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Evaluation of a Weight-Adjusted Single-Bolus Plasminogen Activator in Patients With Myocardial Infarction

A Double-Blind, Randomized Angiographic Trial of Lanoteplase Versus Alteplase

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Background—Lanoteplase (nPA) is a rationally designed variant of tissue plasminogen activator with greater fibrinolytic potency and slower plasma clearance than alteplase.

Methods and Results—InTIME (Intravenous nPA for Treatment of Infarcting Myocardium Early), a multicenter, double-blind, randomized, double-placebo angiographic trial, evaluated the dose-response relationship and safety of single-bolus, weight-adjusted lanoteplase. Patients (n=602) presenting within 6 hours of acute myocardial infarction were randomized and treated with either a single-bolus injection of lanoteplase (15, 30, 60, or 120 kU/kg) or accelerated alteplase. The primary objective was to determine TIMI grade flow at 60 minutes. Angiographic assessments were also performed at 90 minutes and on days 3 to 5. Follow-up was continued for 30 days. Lanoteplase achieved its primary objective, demonstrating a dose-response in TIMI grade 3 flow at 60 minutes (23.6% to 47.1% of subjects, $P<0.001$). Similar results were observed at 90 minutes (26.1% to 57.1%, $P<0.001$). At 90 minutes, coronary patency (TIMI 2 or 3) increased across the dose range up to 83% of subjects at 120 kU/kg lanoteplase compared with 71.4% with alteplase. Thus, at this dose, lanoteplase was superior to alteplase in restoring coronary patency (difference, 12%; 95% CI, 1% to 23%). The early safety experience in this study suggests that lanoteplase was well tolerated at all doses with safety comparable to that of alteplase.

Conclusions—Lanoteplase, a single-bolus, weight-adjusted agent, increased coronary patency at 60 and 90 minutes in a dose-dependent fashion. Coronary patency at 90 minutes was achieved more frequently with 120 kU/kg lanoteplase than alteplase. In this study, safety with lanoteplase and alteplase was comparable. InTIME-II, a worldwide mortality trial, will evaluate efficacy and safety with this promising new agent. **(*Circulation*. 1998;98:2117-2125.)**

Key Words: plasminogen activators ■ thrombolysis ■ reperfusion ■ myocardial infarction ■ trials

Thrombolytic therapy reduces mortality in acute myocardial infarction (AMI).[1–3] Time to treatment and achievement of complete reperfusion (TIMI grade 3 flow) are critical factors.[4,5] Early treatment and complete TIMI grade 3 flow have been facilitated by faster delivery regimens for accelerated alteplase[3] and double-bolus reteplase.[6–8] Simpler effective regimens, such as a single-bolus injection, may offer additional benefits through earlier achievement of reperfusion and by reduction in the risk of dosing errors.

Efforts to improve thrombolytic efficacy are tempered by the risk of serious bleeding, particularly hemorrhagic stroke. As the use of thrombolytic agents has expanded to include

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*The InTIME investigators are listed in the Appendix.

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more elderly patients, women, and patients with hypertension, there is a suggestion of increased hemorrhagic stroke.[9] Use of a fully weight-adjusted dose may optimize the risk-benefit ratio with thrombolytic therapy.

Lanoteplase (novel plasminogen activator, nPA) is a rationally designed variant of wild-type tissue plasminogen activator (tPA) developed to achieve greater fibrinolytic potency and prolonged plasma half-life. Lanoteplase does not contain the fibronectin fingerlike and epidermal growth factor domains of wild-type tPA, accounting for its slower clearance.[10–12] Like alteplase, lanoteplase has enhanced fibrinolytic activity in the presence of fibrin-related plasminogen. Despite deletion of the fingerlike domain, lanoteplase retains some fibrin specificity relative to streptokinase and urokinase. In addition, an asparagine-to-glutamine change was made at residue 117 to prevent this glycosylation site from being occupied.[13] These modifications allow delivery of effective thrombolytic therapy as a single 2- to 4-minute injection. In human volunteers, the half-life for plasminogen activation activity is ≈37±11 minutes, which permits single-bolus dosing.[14]

InTIME (Intravenous nPA for Treatment of Infarcting Myocardium Early) was a multicenter (Europe and North America), double-blind, randomized, double-placebo dose-ranging study comparing 4 doses of lanoteplase with accelerated alteplase. The primary objective of InTIME was to determine whether single-bolus lanoteplase restored complete coronary blood flow (TIMI grade 3) in a dose-related fashion at 60 minutes after initiation of therapy in patients presenting within 6 hours of suspected AMI. The preliminary safety and tolerability profile of lanoteplase was also evaluated. Additional objectives of the study included evaluation of TIMI grade 3 flow, of coronary patency (TIMI grade 2 and TIMI grade 3 flow) at 90 minutes after initiation of therapy, and of angiographic reocclusion on days 3 to 5 after initiation of therapy. The predefined composite end point of unfavorable clinical outcome at 30 days was also evaluated.

Methods

Study Population

Men and postmenopausal or surgically sterile women between the ages of 18 and 80 years, presenting within 6 hours of suspected AMI, were eligible for the study if the following criteria were met: ischemic symptoms lasting ≥20 minutes, ST-segment elevation of ≥0.1 mV in 2 contiguous limb leads or ≥0.2 mV in 2 contiguous precordial leads or new left bundle-branch block, and ability to receive study medication within 6 hours of symptom onset and to undergo coronary angiography within 60 minutes after starting study medication.

Patients were excluded if any of the following conditions were present: bleeding diathesis; active or recent internal bleeding; history of cerebrovascular accident; intracranial neoplasm, arteriovenous malformation, or aneurysm; systolic blood pressure ≥180 mm Hg; diastolic blood pressure ≥110 mm Hg; recent major surgery, trauma, or cardiopulmonary resuscitation; likelihood of left heart thrombus; acute pericarditis or subacute bacterial endocarditis; significant liver or renal disease; oral anticoagulation; Killip class IV heart failure; recent revascularization; history or symptoms of aortic dissection; or any other medical condition that would interfere with study participation or produce significant risk to the patient. The protocol was

TABLE 1. Demographic Characteristics of 602 Patients Who Received Lanoteplase or Accelerated Alteplase

	Lanoteplase Dose (kU/kg)				
Characteristic	15	30	60	120	Alteplase
No. of patients	123	109	123	123	124
Mean age, y±SD	59.4±11.0	59.7±10.2	59.2±11.3	58.3±10.4	59.1±11.3
Men, %	80	78	85	79	84
Mean delay before treatment, h±SD	3.1±1.5	3.1±1.3	3.0±1.3	3.1±1.3	3.2±1.3
Prior MI, %	13.0	10.1	21.1	15.4	14.5
Killip class, %					
I	93	93	93	93	92
II–IV	8	7	7	8	8
MI location, %					
Anterior	25	24	21	15	23
Inferior	31	40	31	35	31
Multiple	37	30	42	43	39
IRA location, %					
LAD	37	38	36	35	43
RCA	44	50	41	50	45
LCx	15	10	19	11	8
Multiple	0	0	1	1	0
None	2	1	1	1	0
Other	3	1	3	2	4

MI indicates myocardial infarction; IRA, infarct-related artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; and LCx, left circumflex artery.

TABLE 2. TIMI Grade at 60 Minutes in Patients Randomized to Receive Lanoteplase or Accelerated Alterplase

	No. of Patients (%)				
	Lanoteplase Dose (kU/kg)				
TIMI Grade	15 (n=110)	30 (n=95)	60 (n=109)	120 (n=102)	Alteplase (n=107)
Failure*	0 (0)	0 (0)	1 (0.9)	1 (1.0)	0 (0)
0	40 (36.4)	36 (37.9)	23 (21.1)	22 (21.6)	27 (25.2)
1	10 (9.1)	3 (3.2)	10 (9.2)	6 (5.9)	9 (8.4)
2	34 (30.9)	28 (29.5)	27 (24.8)	25 (24.5)	31 (29.0)
3	26 (23.6)	28 (29.5)	48 (44.0)	48 (47.1)	40 (37.4)
Difference [95% CI] from					
15 kU/kg	NA	5.8 [−6.3, 18.0]	20.4 [8.2, 32.6]	23.4 [10.9, 35.9]	NA
Alteplase	−13.7 [−25.9, −1.6]	−7.9 [−20.9, 5.1]	6.7 [−6.4, 19.7]	9.7 [−3.7, 23.0]	NA

NA indicates not applicable.
*Failure because of death or cardiovascular reason.

approved by local ethics committees, and informed consent was obtained from all patients.

Treatment Protocol

Patients were randomized to receive 1 of 4 doses of lanoteplase and the alteplase placebo or accelerated alteplase and the lanoteplase placebo in a 1:1:1:1:1 ratio. All patients received only 1 active thrombolytic. The sequence of the lanoteplase (or placebo) single bolus or alteplase (or placebo) bolus was also randomized. The 30- and 60-minute infusions of alteplase or placebo were always given last. Lanoteplase was administered as a weight-adjusted dose of 15, 30, 60, or 120 kU/kg (not to exceed 12 000 kU). Lanoteplase or its matching placebo was administered as a split single bolus (due to provision of drug in 2 vials to allow full dose range) over 2 to 4 minutes. Alteplase or its matching placebo was administered according to the accelerated regimen from GUSTO[3]; 15 mg was given by intravenous bolus followed by doses of 0.75 mg/kg (not to exceed 50 mg) over 30 minutes, then 0.5 mg/kg (not to exceed 35 mg) over 60 minutes.

Aspirin 150 to 325 mg/d and heparin 5000 U by intravenous bolus followed by 1000 U/h for at least 48 hours and adjusted to activated partial thromboplastin time of 60 to 85 seconds were initiated before study medication. Conventional antianginal therapy, long-acting nitrates, calcium channel blockers, β-blockers, and standard care were also initiated. Investigational treatments and devices were not permitted within 30 days before or during the study. Other thrombolytic agents were not permitted during the study.

Study End Points

Primary and secondary end points were prospectively determined. Angiographic evaluations of TIMI grade flow in the infarct-related artery were obtained 60 minutes (primary end point) and 90 minutes (secondary end point) after initiation of study medication. Another coronary angiogram was required between days 3 and 5, unless revascularization was performed or the initial TIMI grade was 0 or 1. The Angiographic Core Laboratory (Cleveland Clinic, Cleveland, Ohio) evaluated all angiograms in a blinded fashion. Patency of the infarct-related artery was classified according to TIMI criteria.[15]

Brief physical examinations, laboratory tests, and 12-lead ECGs were performed daily during hospitalization to monitor patients for myocardial reinfarction, heart failure, recurrent ischemic symptoms, coronary revascularization, bleeding, and other adverse events. The presence of these events was also assessed on day 30 by brief physical examination or telephone interview. Composite clinical outcome was defined as death, reinfarction, major bleeding, or heart failure within 30 days.

Myocardial reinfarction was defined by the presence of 2 of the following conditions occurring >18 hours after index AMI: chest pain lasting ≥20 minutes not relieved by nitroglycerin, new ST-segment elevation of ≥0.1 mV or new abnormal Q waves, and serum creatinine kinase (CK) that was more than twice the upper limit of normal and >50% above the lowest CK level from the index AMI. Heart failure was defined as congestion on chest radiograph without evidence of noncardiac cause, plus at least 2 of the following: midlung rales not cleared by coughing, mean pulmonary capillary wedge pressure ≥18 mm Hg and cardiac index ≤2.4 $L \cdot min^{-1} \cdot m^{-2}$, and new use or increased dose of furosemide or bumetanide. Recurrent ischemic symptoms were defined as chest, neck, or arm discomfort lasting ≥1 minute, which was relieved by nitroglycerin and was associated with new horizontal or downsloping ST-segment depression. Stroke was diagnosed by investigators on clinical grounds.

Bleeding was classified according to GUSTO criteria.[3] Major bleeding was defined as documented hemorrhagic stroke or bleeding resulting in hemodynamic compromise and requiring transfusion of packed red blood cells or other intervention. Moderate bleeding was defined as an event requiring transfusion of packed red blood cells, but one that was not accompanied by hemodynamic compromise. Mild bleeding did not require transfusion of packed red blood cells and was not accompanied by hemodynamic compromise.

Statistical Analysis

Calculations of sample size revealed that 107 patients were needed in each group to detect a 20% increment in complete reperfusion (from 40% to 60%) across the 15- to 120-kU/kg dose range at a power of 85% and significance level (2-tailed) of 0.05. This calculation was based on logistic regression and on the assumption of a linear relationship to dose. To accommodate missing data and a planned

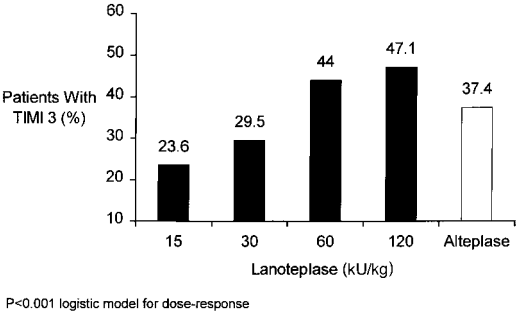
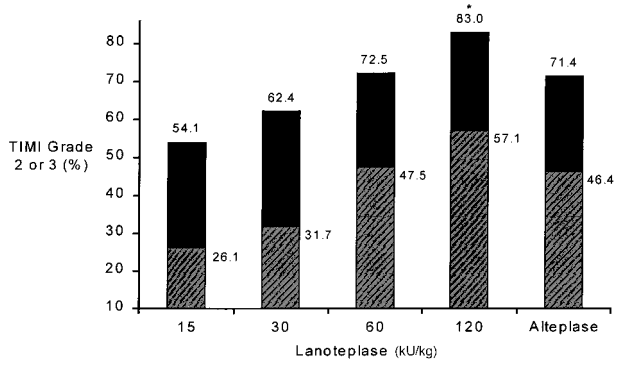


Figure 1. Dose-response effect of lanoteplase (15, 30, 60, and 120 kU/kg) and accelerated alteplase on normal coronary perfusion (TIMI grade 3) at 60 minutes in patients with suspected AMI.



* 95% CI for difference from alteplase:
TIMI 3: (-2.3, 23.7)
TIMI 2 or 3: (0.7, 22.5)
P<0.001 logistic model for dose-response for both TIMI 3 and for TIMI 2 or 3

Figure 2. Dose-response effect of lanoteplase (15, 30, 60, 120 kU/kg) and accelerated alteplase on TIMI grades 2 (shaded bars) and 3 (solid bars) flow at 90 minutes in patients with suspected AMI.

interim analysis, the sample size was adjusted to 118 per group, for a total of 590 patients.

All patients who received study medication were included in the safety analysis. Patients were included in the efficacy analysis whenever possible on the basis of the availability of complete angiographic data. For the day 3 to 5 angiographic assessment, patients were also included if the assessment was performed on day 6. (Day 1 was defined in the protocol as the day the study treatment was given. To capture data in cases in which investigators interpreted day 5 as the fifth day after treatment [day 6], the angiographic analysis was expanded to include angiographic assessments on day 6.) If angiographic data were missing because of death or cardiovascular reasons (eg, revascularization), patients were considered to be treatment failures. If data were missing for other reasons (eg, usually failure to obtain assessment within the specified time window after initiation of study medication or to indicate time of assessment), patients were excluded from the efficacy analysis.

Logistic regression was used to test for the presence of a linear relationship between the log odds of a TIMI grade 3 response and lanoteplase dose, expressed on the natural log scale. Departures from linearity were assessed by comparing (at the 0.10 significance level) the difference in log likelihood obtained from this linear model and from a model not including the linearity assumption. Estimates of pairwise differences (and 95% CIs) were calculated for the difference in response rates for each lanoteplase dose group versus the low-dose lanoteplase group and versus the alteplase group.

Results

A total of 613 patients were enrolled by 88 investigators from 13 countries between March and November 1996. Eleven patients were not included in the efficacy analysis because treatment was not received. Demographic characteristics of the remaining 602 patients, shown in Table 1, were similar among treatment groups. One patient experienced a second AMI 161 days after the index AMI and was randomized and treated a second time; data from the second exposure (lanoteplase 120 kU/kg) are included in the safety analysis as a separate case but are excluded from the efficacy analysis.

Efficacy

Primary Efficacy Outcome Measure

There was a statistically significant increase in the proportion of subjects with TIMI grade 3 flow at 60 minutes with increasing lanoteplase doses ($P<0.001$) (Table 2, Figure 1). The proportion of subjects with TIMI grade 3 flow at 60 minutes with lanoteplase treatment increased from 23.6% in the 15-kU/kg group to 47.1% in the 120-kU/kg group.

In addition, the proportion of patients who achieved TIMI grade 3 flow at 60 minutes with alteplase was 37.4%. The proportion of subjects with TIMI grade 3 flow was higher in the 120-kU/kg lanoteplase group than in the alteplase group. However, the 95% CI for the difference in rates included zero (9.7%; 95% CI, −3.7% to 23%).

Secondary Efficacy and Other Outcome Measures

Similar to the results at 60 minutes, at 90 minutes there was a statistically significant increase in the proportion of subjects with TIMI grade 3 flow with increasing lanoteplase dose ($P<0.001$) (Figure 2). The proportion of patients who

TABLE 3. Summary of 30-Day Composite Clinical Outcome in Patients Randomized to Receive Lanoteplase or Accelerated Alteplase

	No. of Patients (%) [95% CI]				
	Lanoteplase Dose (kU/kg)				
Clinical Outcome	15 (n=122)	30 (n=108)	60 (n=122)	120 (n=122)	Alteplase (n=124)
Composite clinical outcome*	15 (12.3)	7 (6.5)	15 (12.3)	11 (9.0)	27 (21.8)
	[7.0, 19.5]	[2.6, 12.9]	[7.0, 19.5]	[4.6, 15.6]	[14.9, 30.1]
Death	3 (2.5)	1 (0.9)	6 (4.9)	5 (4.1)	8 (6.5)
	[0.5, 7.0]	[0, 5.1]	[1.8, 10.4]	[1.3, 9.3]	[2.8, 12.3]
Reinfarction	4 (3.3)	1 (0.9)	4 (3.3)	0 (0)	8 (6.5)
	[0.9, 8.2]	[0, 5.1]	[0.9, 8.2]	[0, 3.0]	[2.8, 12.3]
Major bleeding	3 (2.4)	0 (0)	2 (1.6)	2 (1.6)	7† (5.6)
	[0.5, 7.0]	[0, 3.4]	[0.2, 5.8]	[0.2, 5.8]	[2.3, 11.3]
Heart failure	8 (6.6)	5 (4.6)	7 (5.7)	6 (4.9)	11 (8.9)
	[2.9, 12.5]	[1.5, 10.5]	[2.3, 11.5]	[1.8, 10.4]	[4.5, 15.3]

*Composite outcome indicates at least one unfavorable event.
†Includes 1 hemorrhagic stroke.

TABLE 4. Adverse Events Occurring in ≥7% of Patients Within Any Treatment Group up to Hospital Discharge, Excluding Revascularizations

	Percent of Patients				
	Lanoteplase Dose (kU/kg)				
Adverse Event	15 (n=123)	30 (n=109)	60 (n=123)	120 (n=124)	Alteplase (n=124)
Cardiovascular					
Heart failure	7.3	6.4	8.9	8.1	8.9
Rhythm disturbance					
Ventricular	15.4	17.4	17.9	15.3	17.7
Atrial	10.6	9.2	8.1	7.3	11.3
Bradycardia	8.9	3.7	2.4	6.5	4.0
Angina pectoris	14.6	11.9	8.9	10.5	12.1
Hypotension	12.2	12.8	5.7	12.1	8.1
Coronary artery disease	4.1	8.3	9.8	4.8	3.2
Neurological					
Musculoskeletal pain	16.3	18.3	19.5	17.7	17.7
Headache	14.6	10.1	13.8	13.7	16.1
Anxiety/nervousness	10.6	11.0	14.6	13.7	12.9
Sleep disturbance	8.1	12.8	10.6	9.7	12.1
Gastrointestinal					
Nausea/vomiting	19.5	15.6	9.8	12.1	14.5
Constipation	8.1	8.3	9.8	8.9	8.1
Other					
Fever	14.6	12.8	11.4	10.5	13.7
General pain	7.3	10.1	4.9	6.5	8.9
Any adverse event	95.9	95.4	92.7	95.2	87.9

achieved TIMI grade 3 flow 90 minutes after lanoteplase increased from 26.1% after the 15-kU/kg dose to 57.1% after the 120-kU/kg dose. The corresponding proportion of patients in the alteplase group who achieved TIMI grade 3 flow at 90 minutes, 46.4%, was lower than the proportion in the 120-kU/kg lanoteplase group (difference, 10.7%; 95% CI, −2.3% to 23.7%).

Proportions of patients with TIMI grade 2 or 3 flow 90 minutes after lanoteplase increased from 54.1% after the lowest dose to 83.0% after the highest dose ($P<0.001$, Figure 2). At the 120-kU/kg dose, lanoteplase was superior to alteplase (71.4%) in restoring coronary patency at 90 minutes (difference, 11.6%; 95% CI, 0.7% to 22.5%).

The proportion of subjects with TIMI grade 3 flow on days 3 to 6 ranged from 29.3% in the 15-kU/kg lanoteplase group to 50.4% in the 120-kU/kg group. The proportion in the alteplase group was 41.2%.

Tertiary Efficacy and Other Outcomes

The proportions of subjects with unfavorable composite clinical outcomes ranged from 6.5% in the 30-kU/kg lanoteplase group to 21.8% in the alteplase group without evidence of a relationship between lanoteplase dose and outcome (Table 3).

Safety

The numbers and percentages of subjects with adverse clinical events before hospital discharge were comparable among the lanoteplase and alteplase groups (Table 4). Bleeding events were reported in 40.7% of subjects receiving any dose of lanoteplase and in 54.0% of subjects receiving alteplase. Major bleeding, defined as hemorrhagic stroke or bleeding associated with hemodynamic compromise requiring transfusion, occurred in 1.5% (7/479) of the lanoteplase-treated subjects and in 5.6% (7/124) of subjects receiving alteplase (Table 5). One intracranial hemorrhage and 1 thromboembolic stroke occurred in 2 subjects receiving alteplase and in no subject in any lanoteplase group. Twenty-three deaths occurred within 30 days of treatment, 15 (3.1%) in the lanoteplase-treated groups and 8 (6.5%) in the alteplase group.

Discussion

Lanoteplase is a rationally engineered derivative of tPA that offers the combination of high potency, long half-life, and prolonged clearance. Single-bolus, weight-adjusted lanoteplase establishes complete perfusion (TIMI grade 3 flow) at 60 minutes in a dose-related fashion up to 120 kU/kg in patients with suspected AMI. Early, complete infarct artery reperfusion at 60 minutes was chosen as the primary end point on the basis of evidence that achievement of TIMI grade 3 flow in the infarct-related artery improves survival.[4,16]

Lanoteplase at 120 kU/kg was as effective as alteplase in establishing TIMI grade 2 or 3 flow at 60 minutes and

TABLE 5. Number and Percentage of Subjects With Bleeding Events by Severity

Treatment	No. of Subjects	No. (%) of Subjects Who Experienced Bleeding				
		None	Mild	Moderate	Hemodynamic Compromise	Hemorrhagic Stroke
Lanoteplase, kU/kg						
15	123	82 (67)	34 (28)	4 (3)	3 (2)	0 (0)
30	109	72 (66)	29 (27)	8 (7)	0 (0)	0 (0)
60	123	74 (60)	43 (35)	4 (3)	2 (2)	0 (0)
120	124*	56 (45)	58 (47)	8 (6)	2 (2)	0 (0)
Alteplase	124	57 (46)	53 (43)	6 (5)	6 (5)	1 (0.8%)†

*Includes second exposure of twice randomized subject.
†A thomboembolic stroke also occurred in this group.

superior in restoring TIMI grades 2 or 3 flow at 90 minutes. The 30-day composite clinical outcome suggests that lanoteplase was at least as effective as alteplase in reducing major morbidity and mortality after AMI.

Major bleeding, particularly hemorrhagic stroke, is an important safety issue with thrombolytics. In this trial, >90% of patients experienced no bleeding or mild bleeding, usually at the puncture site. Moderate and major bleeding was seen in 4.9% to 8.1% of patients in the lanoteplase groups and in 10.5% of alteplase subjects. Major bleeding occurred in 1.5% of lanoteplase patients and 5.6% of alteplase patients (including 1 hemorrhagic stroke).

The trend in recent trials toward inclusion of more elderly and female patients, who tend to weigh less, has further focused attention on appropriate dosing of thrombolytics.[9] Early experience with alteplase suggested excessive bleeding in light (<60 kg) patients and a trend toward decreased thrombolytic efficacy in heavy individuals (>90 kg).[17,18] Lanoteplase was administered as a weight-adjusted dose to achieve optimal efficacy with minimal risk of bleeding.

Despite their efficacy in the treatment of AMI, thrombolytic agents are underused. An additional 15% to 25% of patients could receive thrombolytic therapy.[19] The reasons for undertreatment are numerous, but they fall into 2 categories: presentation delay (time from onset of symptoms to arrival at hospital) and treatment delay (time for the medical care team to provide treatment).[20] A single-bolus thrombolytic agent should have an immediate impact on treatment delay. Drug preparation and administration times are cut to a minimum, with little conflict in the coadministration of other drugs through the same intravenous line. In addition, a simple regimen reduces dosing error. Single-bolus administration has also reactivated interest in prehospital treatment with thrombolytics. Improvements in technology are likely to support more aggressive treatment outside of the hospital setting.[21]

Conclusions

Lanoteplase restores complete perfusion in the infarct-related artery at 60 minutes in a dose-related manner in patients presenting within 6 hours of suspected AMI. Although InTIME was not large enough to completely define the safety profile, in this study lanoteplase was well tolerated at 15 to 120 kU/kg. As expected with all thrombolytics, overall bleeding was dose-related, with the incidence at the highest dose, 120 kU/kg, comparable to that of alteplase. Serious bleeding, which occurred in a small number of patients, and other adverse events were not dose-related. At a dose of 120 kU/kg, lanoteplase produced early and sustained patency more frequently than alteplase, with an encouraging trend toward improvement in a 30-day composite clinical outcome.

InTIME was an angiographic dose-ranging trial that was not designed to evaluate relative effects on mortality. A larger study is necessary to determine whether single-bolus, weight-adjusted, lanoteplase will achieve survival benefits, preserve left ventricular function, and prevent heart failure. These issues are being addressed in a 15 000-patient mortality study, InTIME-II, comparing lanoteplase (120 kU/kg) with accelerated alteplase.

Appendix

Participating Clinical Centers Listed by Country

Belgium

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References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;1:397–401.
2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349–360.
3. Global Utilization of Streptokinase, and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.
4. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med*. 1993;329:1615–1622.
5. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311–322.
6. Smalling RW, Bode C, Kalbfleisch J, Sen S, Limbourg P, Forycki F, Habib G, Feldman R, Hohnloser S, Seals A, the RAPID Investigators. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation*. 1995;91:2725–2732.
7. Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, Chernoff R, Christie LG, Feldman RL, Seals AA, Weaver WD, the RAPID II Investigators. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation*. 1996;94:891–898.
8. International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet*. 1995;346:329–336.

9. 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.
10. Larsen GR, Timony GA, Horgan PG, Barone KM, Henson KS, Angus LB, Stoudemire JB. Protein engineering of novel plasminogen activators with increased thrombolytic potency in rabbits relative to activase. *J Biol Chem*. 1991;266:8156–8161.
11. Collen D, Stassen J-M, Larsen G. Pharmacokinetics and thrombolytic properties of deletion mutants of human tissue-type plasminogen activator in rabbits. *Blood*. 1988;71:216–219.
12. Larsen GR, Metzger M, Henson K, Blue Y, Horgan P. Pharmacokinetic and distribution analysis of variant forms of tissue-type plasminogen activator with prolonged clearance in rat. *Blood*. 1989;73:1842–1850.
13. Hansen L, Blue Y, Barone K, Collen D, Larsen GR. Functional effects of asparagine-linked oligosaccharide on natural and variant human tissue-type plasminogen activator. *J Biol Chem*. 1988;263:15713–15719.
14. Liao W-C, Beierle FA, Stouffer BC, Dockens RA, Abbud ZA, Tay LK, Knaus DM, Raymond RH, Chew PH, Kostis JB. Single bolus regimen of lanoteplase (nPA) in acute myocardial infarction: pharmacokinetic evaluation from InTIME-I study. *Circulation* 1997;96(suppl I):I-260–I-261. Abstract.
15. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation*. 1987;76:142–154.
16. Simes RJ, Topol EJ, Holmes DR Jr, White HD, Rutsch WR, Vahanian A, Simoons ML, Morris D, Betriu A, Califf RM, Ross AM, for the GUSTO-I Investigators. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. *Circulation*. 1995;91:1923–1928.
17. Califf RM, Topol EJ, Stump D, George BS, Boswick JM, Abbottsmith C, Candela R, Kereiakes D, O'Neill W, Stack RS, and the TAMI Study Group. Hemorrhagic complications associated with the use of intravenous tissue plasminogen activator in treatment of acute myocardial infarction. *Am J Med*. 1988;85:353–359.
18. Topol EJ, George BS, Kereiakes DJ, Candela RJ, Abbottsmith EW, Stump DC, Boswick J, O'Neill WW, Stack RS, Califf RM, and the TAMI Study Group. Comparison of two dose regimens of intravenous tissue plasminogen activator for acute myocardial infarction. *Am J Cardiol*. 1988;61:723–728.
19. Muller DW, Topol EJ. Selection of patients with acute myocardial infarction for thrombolytic therapy. *Ann Intern Med*. 1990;113:949–960.
20. Califf RM, Newby LK. How much do we gain by reducing time to reperfusion therapy? *Am J Cardiol*. 1996;78(suppl 12A):8–15.
21. Aufderheide TP, Kereiakes DJ, Weaver WD, Gibler WB, Simoons ML. Planning, implementation, and process monitoring for prehospital 12-lead ECG diagnostic program. *Prehospital Disaster Med*. 1996;11:162–171.