SMH ST. MICHAEL'S HOSPITAL Cardiology UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

The Present and Future of Fibrinolytic Therapy for Acute Myocardial Infarction

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Satellite Symposium at the 73rd Scientific Sessions of the American Heart Association

November 11, 2000 New Orleans, Louisiana

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Many new fibrinolytic agents have been developed over the last few years. While none of the new strategies have demonstrated greater efficacy than that realized with the current gold standard alteplase (t-PA), the ASSENT-2 trial has shown sustained equivalence of single-bolus tenecteplase (TNK-t-PA) with similar rates of intracranial hemorrhage, but significantly fewer noncerebral bleeding complications. In view of its equivalence to alteplase, coupled with its safer profile and ease of administration, tenecteplase will likely become the new gold standard in fibrinolytic therapy once it becomes commercially available in Canada (estimated to be mid-2001).

Since the first reports on the use of streptokinase for acute myocardial infarction (MI) in 1959, fibrinolytic therapy has evolved as an important reperfusion tool in patients presenting with ST-segment elevation or left bundle branch block. Major advances in biotechnology during the1980s led to the development of recombinant DNA technology, resulting in the production of several recombinant molecules that are now used successfully as therapeutic agents. The recombinant tissue plasminogen activator (rt-PA) alteplase was one of the first human proteins to be successfully administered as life-saving medical treatment.

Comparisons between fibrinolytics

The last decade of the 20th century ushered in a new era of non-placebo-controlled trials of reperfusion strategies: 8 large-scale trials, comparing thrombolytic regimens and involving over 130,000 cases of acute MI presenting with ST-segment elevation, were completed in the 1990s. In contrast to the results from GISSI-2[1] and ISIS-3,[2] in the GUSTO-I trial,[3] a statistically and clinically significant benefit was seen with accelerated/front-loaded alteplase and intravenous heparin as compared with two streptokinase strategies. The benefit of alteplase over streptokinase translated into 10 additional lives saved at 30 days per 1,000 patients treated. For the prevention of death and disabling stroke, this benefit was 9 per 1,000 patients treated, highlighting the precise quantitative trade-off between safety and efficacy, and establishing alteplase as the current gold standard in fibrinolytic therapy.

Rationale for development of new fibrinolytic agents

However, even with the superior strategy of alteplase plus intravenous heparin, only about 50% of patients have optimal (normal or TIMI-3) flow in their infarct-related artery 90 minutes after treatment initiation.[4] Moreover, reocclusion occurs in 5 to 10% of cases and is associated with a significantly worse outcome. Thus, new fibrinolytic agents have been developed in an attempt to improve the efficacy of clot lysis and to facilitate more rapid administration. The main goals underlying the design of newer fibrinolytic agents is to provide better fibrin specificity, greater resistance to plasminogen activator inhibition (PAI), a longer duration of action (increased half-life), and simpler administration.[5] Indeed, first-generation fibrinolytics (eg, streptokinase) are not fibrin-specific and also convert circulating plasminogen to plasmin. Since plasminogen in the thrombus and in the plasma are in equilibrium, the plasminogen within the thrombus is also gradually depleted; this "plasminogen steal" reduces clot lysis. In contrast, second-generation lytics (eg, alteplase) are fibrin selective and were designed to avoid the systemic thrombolytic state that causes depletion of circulating fibrinogen and plasminogen.[5] However, the high doses of these agents required for successful treatment in acute MI produce a mild-to-moderate decrease in levels of circulating fibrinogen and plasminogen.

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The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. *Cardiology Scientific Update* is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which receives educational grants from the pharmaceutical industry for the distribution of this publication.

Third-generation fibrinolytics

The third-generation fibrinolytic agents consist of:

• mutants of t-PA conjugates of plasminogen activators with monoclonal antibodies against fibrin, platelets, or thrombomodulin;

• mutants, variants, and hybrids of alteplase (tenecteplase, reteplase, lanoteplase) and prourokinase (amediplase);

• or new molecules developed from animal origin (vampire bat plasminogen activator) or from bacterial origin (staphylokinase).[5]

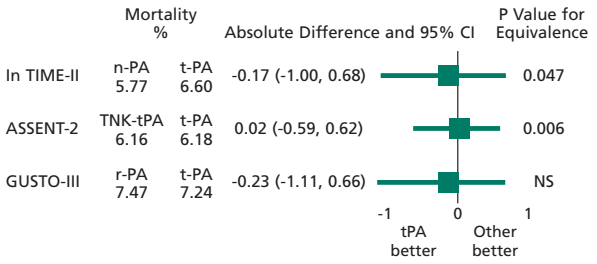
Characteristics of third-generation fibrinolytic agents that have been evaluated in large-scale, randomized, clinical trials are compared with the second generation gold standard alteplase in Table 1.[5]

The INJECT study[6] showed equivalence of double-bolus reteplase and streptokinase and the GUSTO-III trial[7] failed to demonstrate superiority of reteplase over alteplase. Despite the suggestion that this trial supports the "equivalency" of alteplase and reteplase, the GUSTO-III investigators themselves acknowledge that their study "was not designed to assess equivalence, nor did it have adequate power to do so;"[7] others also maintain that the GUSTO-III primary outcome event (30-day mortality) provides no convincing evidence for equivalence between reteplase and alteplase.[8,9]

More recently, the InTIME-II study[10] demonstrated similar 30-day and 6-month mortality rates among n-PA (lanoteplase) and alteplase-treated patients; however, despite apparent equivalence of these two agents with respect to mortality reduction, lanoteplase led to a significantly greater number of intracranial hemorrhages (ICH) and mild-moderate bleeding episodes.

In contrast, the ASSENT-2 trial[11] confirmed the equivalence of TNK-t-PA (tenecteplase) and alteplase (Figure 1), with similar rates of ICH, but significantly fewer mild-moderate bleeding episodes with tenecteplase. The ASSENT-2 study[11] randomised 16,949 patients with ST-elevation MI of less than 6 hours duration to alteplase or single-bolus injection tenecteplase (30-50 mg according to body weight). All patients received ASA and unfractionated heparin (target activated partial thromboplastin time 50-75 seconds). Co-variate adjusted 30-day mortality rates were almost identical for the two treatment groups (6.18% for tenecteplase and 6.16% for alteplase; p=0.0059 based on test for equivalence). Rates of ICH were also similar (0.93% vs. 0.94%), but fewer non-cerebral bleeding complications (26.43% vs. 28.95%, p=0.0003) and less need for blood transfusion (4.25% vs. 5.49%, p=0.0002) were seen with tenecteplase. In view of its equivalence to the current gold standard alteplase, coupled with the safer profile and ease of administration, tenecteplase will likely become the new gold standard in fibrinolytic therapy once it becomes commercially available in Canada (estimated mid-2001).

Figure 1: Equivalency analyses (post-hoc for the GUSTO-III trial, which was designed as a superiority study) for 30-day mortality.



The ASSENT-2 study: One-year follow-up

One-year mortality status available to-date (n=14,203 patients; 84%) reveals that equivalence of tenecteplase and alteplase has been maintained, with an incremental mortality after 30 days of 2.77% and 2.82%, respectively (1 year mortality 10.15% vs. 10.23%, p=0.87). Mortality at one year continued to be higher in female patients, patients older than 75 years of age, and patients with prior MI or anterior infarction, but there was

Table 1: Characteristics of alteplase and selected third-generation thrombolytic agents

	Alteplase*	Tenecteplase	Reteplase	Lanoteplase
Molecular weight, D	70,000	70,000	39,000	53,500
Plasma half-life, min	4-8	11-20	14-18	23-37
Fibrin-selectivity	++	+++	+	+
Inhibition by PAI	Yes	No	Yes	No
Dose (infusion or bolus)†	100 mg/90 min	≈0.5 mg/kg bolus	Two 10 MU boluses 30 min apart	120,000 U/kg bolus
TIMI-3 flow	46%-75% at 90 min	63% at 90 min	60%-63% at 90 min	57%-83% at 90 min
Hemorrhagic stroke	0.6%-0.9%	0.9%	0.8%-0.9%	1.1%

*Alteplase is a second-generation thrombolytic drug.
†Most frequently used/tested.
MU = million units; PAI = plasminogen-activator inhibitor; TIMI = Thrombolysis in Myocardial Infarction trial

Figure 2: One-year mortality in the ASSENT-2 ECG Substudy in all patients and those with non-Q or Q wave MI--stratified by extent of ST segment elevation resolution at 24-36 hours (complete, partial, no) compared to pre-fibrinolysis (baseline). (Adapted from Lockwood et al, *J Am Coll Cardiol* 2001 [in press]).

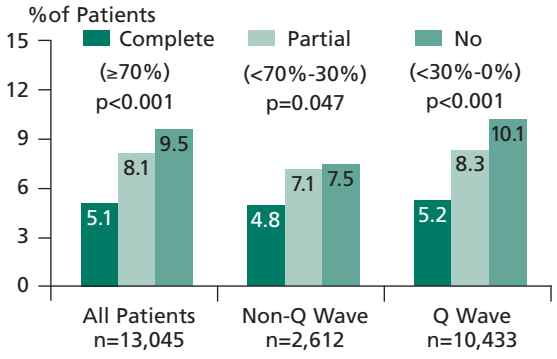
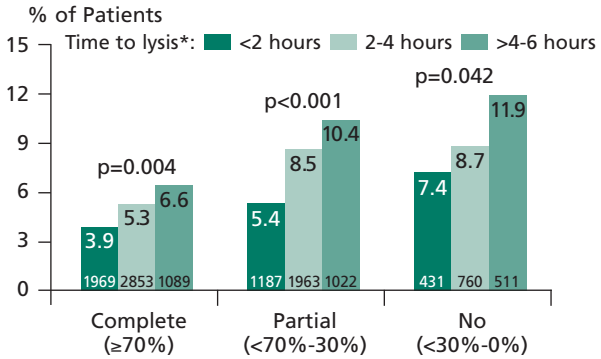


Figure 3: One-year mortality in the ASSENT-2 ECG Substudy – stratified by extent of ST segment elevation resolution at 24-36 hours (complete, partial, no) compared to pre-fibrinolysis (baseline) and according to time to fibrinolytic therapy (<2, 2-4, and >4-6 hours from symptom onset*). (Adapted from Fu et al, *J Am Coll Cardiol* 2001 [in press]).



no significant difference between the two treatments in these subgroups. In patients randomized after 4 hours of symptom onset, 30-day mortality was lower in patients who received tenecteplase (7.0% vs. 9.2%, p=0.018) and this absolute difference of 2% was maintained at one year (12.1% vs. 14.4%, respectively) although this was no longer statistically significant (relative risk 0.84; 95% confidence intervals 0.70-1.01, p=0.069).

In the ASSENT-2 ECG substudy, 13,045 patients surviving for at least 24 hours who had ECGs free of confounding factors, underwent systematic core ECG analysis performed at baseline and at 24-36 hours. For the 80% of patients with Q-wave infarction, the one-year mortality rate was 7.0%; in contrast, for the 20% of patients with non-Q-wave infarction, the one-year mortality was lower at 5.9%. Of note, among patients with a pre-discharge ECG available (n=8,979), those receiving tenecteplase were less likely to evolve to a Q-wave MI (31.8% vs. 33.8%, p=0.024).

ST-segment elevation resolution was evaluated by comparing the sum of ST elevation at 24-36 hours to that initially seen at baseline. One-year mortality rates were lower among those with complete ST resolution (>70%) compared to those with partial (30%-70%) or no ST resolution (<30%) as seen in Figure 2. The extent of ST resolution by 24-36 hours was a further discrimination parameter for one-year mortality within the non-Q-wave and the Q-wave cohorts. In addition, the extent of ST-segment resolution was related to the time to fibrinolytic treatment (from symptom onset) with a greatest number of patients who were treated early (less than 2 hours) achieving complete ST resolution. Not surprisingly, this was associated with the lowest one-year mortality rate (Figure 3). The results of this one-year follow-up of the ASSENT-2 study support the concept of improved prognosis in those who are treated early, who have more complete ST segment elevation resolution, and less Q wave evolution.

TIMI risk score for ST-elevation MI

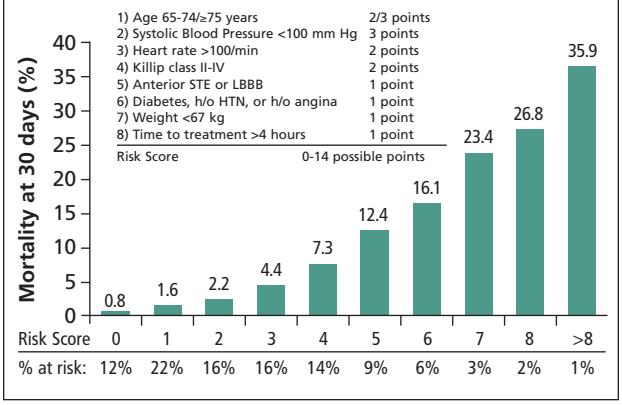
A convenient bedside clinical risk score for predicting 30-day mortality at presentation of fibrinolytic-eligible patients with ST-elevation MI has been recently developed.[12] The Thrombolysis in Myocardial Infarction (TIMI) risk score was created as the simple arithmetic sum of independent predictors of mortality weighted according to the adjusted odds ratio from logistic regression analysis in the InTIME II trial (n=14,114). Ten baseline variables, accounting for 97% of the predictive

Table 2: The impact of fibrinolytic dose on outcome

Weigh-optimized dose of TNK improves angiographic outcome	Low dose (0.20-0.39 mg/kg)	Medium dose (0.40-0.51 mg/kg)	High dose (0.52-1.24 mg/kg)	*P* value
Culprit artery flow (CTFC)	38	35	31	0.007
Mean flow, all 3 arteries (CTFC)	40	35	31	0.002
% of patients with thrombus	34	29	25	0.06
% stenosis, culprit vessel	76		71	0.03
Flow after angioplasty (CTFC)	29	24	19	0.05

CTFC = corrected TIMI frame count, number of frames/second to reach distal landmarks

Figure 4: TIMI risk score for ST elevation (STE) MI for predicting 30-day mortality. (h/o = history of; HTN = hypertension)



capacity of the multivariate model, constituted the TIMI risk score (Figure 4). This simple risk assessment tool can be utilized in the triage and management of fibrinolytic-eligible patients with ST-elevation MI.

The impact of fibrinolytic dose on clinical outcome

When fibrinolytic dose is not adjusted for weight, patients who weigh less may be relatively "overdosed," while patients who are heavier may be "underdosed." The excess dose administered to lightweight patients may account for the well-known risk of ICH which is evident with several fibrinolytic agents such as streptokinase, alteplase, lanoteplase, tenecteplase, and reteplase. Thus, in addition to the improved fibrin specificity of newer agents, weight-optimized dosing may help improve outcomes. Studies to address this issue have demonstrated that weight optimization of the dose of tenecteplase improved TIMI frame counts and increased the rates of TIMI grade 3 flow.[13] The flow was improved, not only in the culprit artery, but also in the uninvolved artery and throughout all three arteries. Weight-optimization of fibrinolytic dose also reduced thrombus burden and improved the percent diameter stenosis; flow was also improved following percutaneous intervention (Table 2).[13]

Weight optimization of fibrinolytic dose may also lead to less bleeding risk, especially among high-risk groups of patients such as lightweight (<67 kg), elderly (>75 years old), women. A sub-analysis of the ASSENT-2 study indicated that ICH rates were reduced by almost 2% among these high-risk patient populations.[14] Nevertheless, the possibility of dosing errors may still occur despite the demonstrated advantages of administering weight-optimized doses with an agent such as tenecteplase. A safety analysis of ASSENT-2 revealed that overdose occurred in 2.7% of patients (n=218, median weight error 8 kg) and underdose in 4.0% (n=326, median weight error 1 kg). Underdosing of 1-2 dosing intervals (up to 20 kg or 44 pounds in error) was not associated with ICH or death in a multivariate model accounting for weight; neither was overdosing. Thus, weight-optimized dosing of tenecteplase is safe and effective, and with the limited number of dose errors reported so far, tenecteplase appears to display an acceptable margin of safety in the treatment of acute ST elevation MI.

Conclusion

Fibrinolytic agents have become an important pharmacological tool for the treatment of acute MI. Several strategies have been employed to improve fibrinolytic therapy, resulting in the design of variants of the human recombinant tissue plasminogen activator (rt-PA, alteplase), such as r-PA (reteplase), n-PA (lanoteplase), and TNK-t-PA (tenecteplase). To date, tenecteplase appears to be the best example of a fibrinolytic drug that combines enhanced fibrin specificity, ease of administration (single bolus), and a better safety profile (including reduced risk of bleeding complications). Tenecteplase (TNK-t-PA) has demonstrated equivalent and sustained (one-year follow-up) efficacy compared to the current gold standard fibrinolytic therapy, alteplase.

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