SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

New directions in thrombolytic therapy: The ASSENT II and InTime-II Trials

Originally presented by: Frans Van de Werf, MD and Karl-Ludwig Neuhaus

Symposium at the 48th Annual Scientific Session of the American College of Cardiology

New Orleans, Louisiana, March 7-10, 1999

Reported and discussed by:
ANATOLY LANGER, MD

Thrombolytic therapy continues to be the most important aspect of the medical management of patients early in the course of acute myocardial infarction (MI). Significant advances have occurred with respect to understanding how best to deliver thrombolytic therapy and use adjunctive therapy. The next generation of thrombolytic agents can now be delivered as a single bolus. Two studies using these new compounds, presented at the Annual Scientific Session of the American College of Cardiology, are reviewed here.

ASSENT II

TNK-tissue plasminogen activator (TNK-tPA) is a biochemically engineered mutation of a naturally occurring tPA molecule. No deletions are made, but there are three substitutions resulting in reduced clearance, and therefore, prolonged half-life, increased fibrin specificity, and greater protection against PAI-I (PAI-I resistance) inhibition. Initial studies with TNK-tPA reveal safety and efficacy with respect to achieving TIMI-3 flow at 60 and 90 minutes with results that are comparable to those achieved with an accelerated regimen of tPA.

Study parameters

The ASSENT II study compared administration of a single bolus of TNK-tPA to that of an accelerated regimen of tPA in patients with acute MI (based on ST-segment elevation) who presented within 6 hours of symptom onset. The study was a multicentre, international, double-blind, double-dummy, randomized study. The primary endpoint was 30-day mortality; the primary hypothesis was that TNK-tPA would be similar to tPA in reducing mortality in patients with acute MI. The sample size was based on the equivalence analysis including the absolute difference in mortality between the two groups being not more than 1% and the difference in relative mortality being not more than 14%.

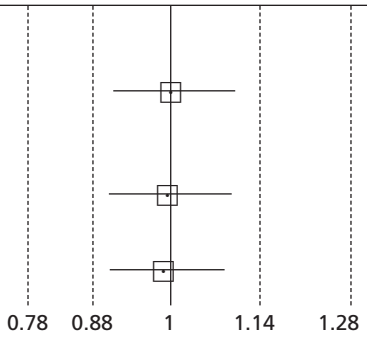
Comparison of baseline characteristics and medical history in the 8,462 patients randomized to the TNK-tPA group and the 8,488 randomized to the tPA group revealed no significant differences with respect to age, gender, history of previous MI, or admission hemodynamics. Approxi-

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

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. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Figure 1: Thirty-day mortality: Relative risk

	TNK-tPA	rt-PA	Relative risk (95% CI)	p-value
Primary analysis				
Nonparametric adjusted rate (*)	6.174	6.154	1.003 (0.913,1.103)	0.0265
Secondary analysis				
Unadjusted rate	6.159	6.176	0.997 (0.904, 1.101)	0.0262
Exploratory analysis				
Logistic regression (*)	6.096	6.146	0.992 (0.903, 1.069)	0.0149



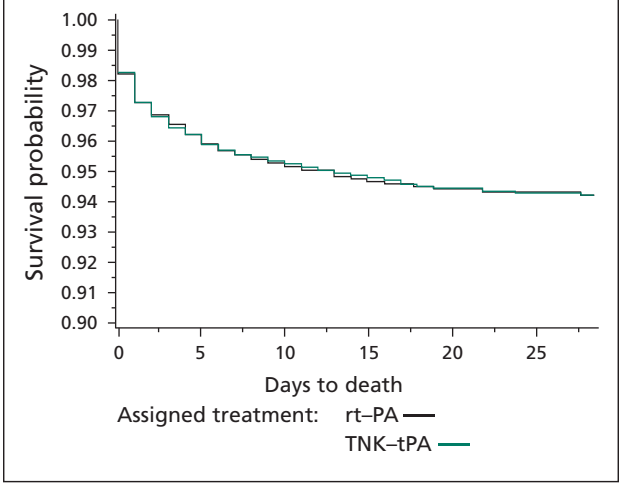
(*) Covariates used are age, infarct location, Killip class, SBP, and heart rate.

mately 12.5% of patients were >75 years old and the average time to treatment was approximately 2.7 hours with no significant differences between the two treatment groups.

Results

Comparison of 30-day mortality revealed a virtually identical result (Figures 1 and 2), with the primary analysis adjusted for age, infarct location, Killip class, systolic blood pressure (SBP), and heart rate. Mortality was 6.17% in the TNK-tPA group and 6.15% in the tPA group; the p value was highly significant for equivalence. Prespecified subgroup analysis did not reveal any significant differences based on age or infarct location; however, patients treated beyond 4 hours of symptom onset appeared to benefit from administration of TNK-tPA, as compared to tPA, with an almost 2% absolute reduction (Figure 3). Similar observations with respect to superiority of fibrin specificity have been demonstrated in the comparison of tPA versus streptokinase (SK) (TIMI 1[1] [Figure 4]) and in the comparison of tPA versus reteplase (GUSTO III[2] [Figure 5]).

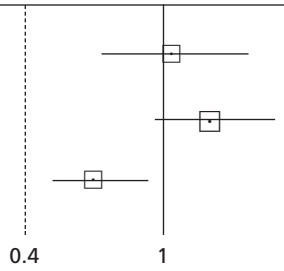
Figure 2: Kaplan-Meier curve for mortality intent-to-treat population



With respect to safety parameters, no difference was seen between the TNK-tPA and tPA groups in the total occurrence of stroke (1.78% vs 1.66%, p=NS), and while the overall incidence of intracranial hemorrhage was higher than expected, there was no difference between the two groups (0.93% vs 0.94%, p=NS). The overall incidence of intracranial hemorrhage was higher in patients >75 years old, and in this subpopulation there was a somewhat lower incidence of intracranial hemorrhage with TNK-tPA (1.72%) versus that seen with tPA, (2.62%, p=0.18). No difference was seen between TNK-tPA and tPA treated groups with respect to severe bleeding (0.83% vs 1.05%, p=0.15); however, mild and moderate bleeding was significantly less frequent with TNK-tPA (26.02% vs 28.12%, p=0.002). Similarly, the overall number of units transfused

Figure 3: Thirty-day mortality subgroups

Time to treatment (hours)	TNK-tPA (n=8462)	rt-PA (n=8488)	Relative risk (95% CI)	p-value
0-2	125/2518 (4.96)	125/2564 (4.08)	1.018 (0.000, 1.297)	0.8969
>2-4	256/4035 (6.34)	214/3901 (5.49)	1.157 (0.970, 1.379)	0.1061
>4	129/1833 (7.04)	181/1969 (9.19)	0.766 (0.616, 0.951)	0.0176

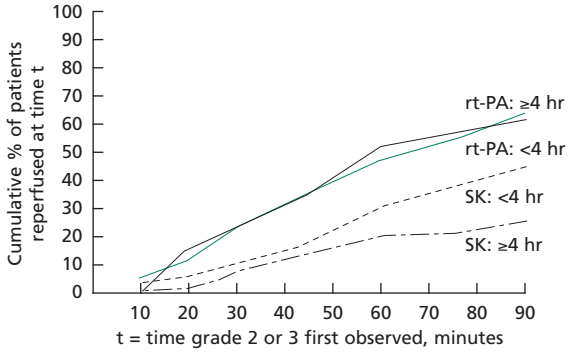


was smaller in TNK-tPA-treated patients than in tPA-treated patients (p=0.001).

Conclusion

The results of the ASSENT II study indicate that the primary hypothesis was supported, namely that TNK-tPA is similar to tPA in reducing 30-day mortality in patients with acute MI. It is worth noting that the overall incidence of mortality was virtually identical between the two groups, leaving little doubt as to the efficacy of these two compounds. The significantly lower incidence of mild-to-moderate bleeding complications seen in TNK-tPA-treated patients suggests that the fibrin specificity associated with this compound may afford greater safety with its administration.

Figure 4: Successful reperfusion (TIMI patency grade 2 or 3) of infarct artery in the first 90 minutes



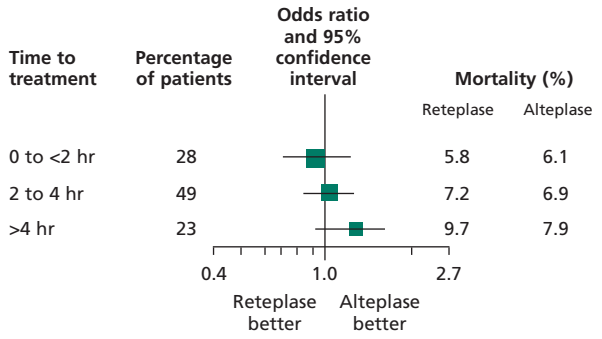
InTime-II Study

Lanoteplase (nPA) is a deletion mutant of the tPA molecule with lesions of epidermal growth factor and finger regions, resulting not only in decreased clearance and therefore increased half-life, but also in diminished fibrin specificity. Initial phase II studies with this molecule have clearly demonstrated an excellent fibrinolytic efficacy based on 60- and 90-minute angiographic TIMI-3 flow rates. The Intravenous nPA for Treatment of Infarcting Myocardium Early (InTime-II) study compared a single bolus administration of nPA to that of an accelerated regimen of tPA.

Study parameters

The study was a multicentre, international, double-blind, double-dummy approach with randomization in a 2:1 ratio between nPA and tPA. The primary endpoint was 30-day mortality, the primary hypothesis being equivalency between nPA and tPA in reducing the 30-day mortality of patients with acute MI. Among the 15,078 patients enrolled, 10,051 were randomized to nPA, and the remaining 5,027 received tPA. No significant differences were observed in patients with respect to age, gender, other baseline variables, or medical history. Time to treatment was somewhat longer than that observed in ASSENT II, with an average of 3.1 hrs; no differences were observed between the two treatment groups.

Figure 5: Odds ratios and 95 percent confidence intervals for death within 30 days, according to time from onset of symptoms to treatment[2]



Results

Thirty-day mortality was similar between the two groups with 6.7% mortality observed in nPA-treated patients and 6.6% mortality observed in tPA-treated patients. Twenty-four hour data was also presented and appeared to be quite similar (2.39% and 2.49%, p=NS respectively). Importantly, the incidence of intracranial hemorrhage was higher in nPA-treated patients (1.13% vs 0.62%, p=0.003). Frequency of ischemic stroke was similar and the overall incidence of stroke was not significantly different between nPA- and tPA-treated patients (1.89% vs 1.52%, p=0.103). There was no difference in the incidence of major bleeding between the two groups (0.6%) and moderate bleeding was also observed with similar frequency (2.4% in nPA-treated patients and 2.3% in tPA-treated patients); however, mild bleeding was more frequent in nPA- treated patients (19.6%) than in tPA-treated patients (14.7%, p=0.0001).

Conclusion

The results of InTime-II Study suggest a similar reduction in 30-day mortality between nPA- and tPA-treated patients, however, a more frequent observation of intracranial hemorrhage, perhaps on the basis of lesser fibrin specificity, raises safety concerns.

Summary

The results of the ASSENT II and InTime-II studies suggest that the efficacy of single bolus administration is similar to that of gold-standard thrombolytic therapy with an accelerated regimen of tPA. The convenience and ease of single bolus administration may be associated with additional benefits when administered to a patient population at large. Safety continues to be a concern, especially with respect to the occurrence of intracranial hemorrhage, particularly in elderly patients. The greater fibrin specificity associated with TNK-tPA, in comparison to tPA, is associated with a safer administration than that seen when comparing nPA to tPA.

Time to treatment from symptom onset continues to be almost 3 hours, suggesting that further reduction in the mortality associated with acute MI in thrombolytic-eligible patients may come from earlier administration, including a pre-hospital phase period.

References

1. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in myocardial infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987;76:142-154.
2. 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.