Weight-Adjusted Dosing of TNK-Tissue Plasminogen Activator and Its Relation to Angiographic Outcomes in the Thrombolysis In Myocardial Infarction 10B Trial

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Fixed doses of thrombolytic agents are generally administered to patients of varying body weights, and the dose-response relation may be confounded by the variability in patient weight. We hypothesized that higher doses of TNK-tissue plasminogen activator (tPA) per unit body weight would be related to improved flow at 90 minutes after thrombolytic administration. A total of 886 patients with acute myocardial infarction were randomized to receive either a single bolus of 30, 40, or 50 mg of TNK-tPA or front-loaded tPA in the Thrombolysis In Myocardial Infaction (TIMI) 10B trial. The dose of TNK-tPA administered was divided by the patient's weight to arrive at the TNK-tPA dose (mg) per unit body weight (kg), and patients were stratified into tertiles based on mg/kg of TNK-tPA: low dose, 0.2 to 0.39 mg/kg; mid-dose, 0.40 to 0.51 mg/kg; high dose, 0.52 to 1.24 mg/kg. Flow in the culprit and nonculprit arteries was analyzed using the TIMI flow grades and the corrected TIMI frame count (CTFC). The median CTFC in culprit arteries differed between the tertiles (3-way p = 0.007), with the CTFC being 7.2 frames faster in high-dose than in low-dose patients (43.1 ± 30.1, median 31.2, n = 171 vs 54.6 ± 34.8, median 38.4, n = 166, 2-way p = 0.002). Patients in the mid- and high-dose tertiles achieved patency more frequently (TIMI grade 2 or 3 flow) by 60 minutes (p = 0.02), and the 90-minute percent diameter stenosis was less severe in patients in the high- versus low-dose tertile (p = 0.03). In nonculprit arteries, the CTFC was faster in high- than in low-dose tertiles (29.6 ± 13.4, median 26.9, n = 130 vs 34.7 ± 16.3, median 32.8, n = 108, 3-way p = 0.03, 2-way p = 0.008). In patients who underwent percutaneous transluminal coronary angioplasty (PTCA), the CTFC in culprit arteries after PTCA was fastest in the high- and mid-dose tertiles than in those receiving low doses (2-way p = 0.05). Thus, higher doses per unit body weight of TNK-tPA result in not only faster culprit artery flow, but also faster nonculprit, global, and post-PTCA flow, which may reflect earlier opening, reduced stunning, or improved microvascular function. The greater effectiveness of thrombolysis must be weighed against any increase in risk.

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In dose-finding thrombolytic trials, several fixed doses of a thrombolytic agent are usually administered.[1–3] Within each dose regimen, however, the body weight may vary significantly among patients which may confound ascertainment of a dose-response relation. For instance, a 50-kg patient administered a 30-mg dose of a thrombolytic agent might respond with greater efficacy to this relatively small dose than a 100-kg patient administered a higher dose of 40 mg because of the higher dose per unit body weight administered to the 50-kg patient (dose/weight = 0.6 vs 0.4 mg/kg). The Thrombolysis In Myocardial Infarction (TIMI) 10B trial was a dose-ranging trial with the new bolus thrombolytic, TNK-tissue plasminogen activator (tPA).[2] To examine the dose-response relation with greater precision, the dose of TNK-tPA per unit body weight (kg) was determined, and patients were stratified into tertiles. We hypothesized that higher doses of TNK-tPA per unit body weight would be related to improved indexes of coronary perfusion such as the corrected TIMI frame

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TABLE I Baseline Characteristics by Weight-Adjusted Dose Tertile

Variable	High Dose (n = 174)	Mid Dose (n = 178)	Low Dose (n = 177)
Age (yr)*	61.9 ± 12.6	60.1 ± 11.5	57.1 ± 10.8
Men (%)†	59.4%	74.3%	90.6%
Left culprit location	55.0%	44.9%	47.4%
Thrombus presence‡	25.0%	29.0%	34.3%
Systolic blood pressure (mm Hg)	132.9 ± 22.5	132.6 ± 22.9	134.5 ± 21.5
Diastolic blood pressure (mm Hg)	77.9 ± 14.5	77.5 ± 17.7	80.6 ± 14.8
Pulse (beat/min)	75.8 ± 18.5	75.3 ± 16.1	75.7 ± 15.3
History of MI (%)	14.0%	18.2%	13.2%
Presence of collaterals	15.6%	13.9%	13.5%
Presence of nonculprit lesion	50.9%	55.5%	52.6%
Disease extent			
1-vessel	13.8%	16.3%	13.0%
2-vessel	37.3%	38.2%	40.1%
3-vessel	48.9%	45.5%	46.9%
Drugs in 24 hours			
Aspirin	96.6%	97.8%	94.9%
β blockers	55.8%	51.7%	61.6%
Calcium channel blockers	6.3%	2.3%	6.8%
ACE inhibitors	6.9%	8.4%	9.6%

Three-way p values; *p = 0.0006; †p <0.001 (2-way p values [low- vs high-dose tertile]): *p = 0.0002; †p <0.001; ‡p = 0.06. All other p values are NS.

count (CTFC). In addition to the CTFC in the culprit artery (which has been related to mortality after thrombolytic administration),[4] we also examined the flow in nonculprit arteries, the global flow in all 3 epicardial arteries, and the flow in the culprit artery after percutaneous transluminal coronary angioplasty (PTCA) as indirect indexes of microvascular function.

METHODS

Study population: The data are drawn from the TIMI 10B trial in which 886 patients with acute ST-segment elevation myocardial infarction were randomized to receive either a single 30-, 40-, or 50-mg bolus of TNK-tPA or front-loaded tPA.[2] Front-loaded tPA was administered to 312 of the 886 patients. Coronary angiography was performed at 60, 75, and 90 minutes after thrombolytic administration. Nitroglycerin (intravenous, intracoronary, or sublingual) was administered every 15 minutes if the systolic blood pressure exceeded 110 mm Hg.[2]

Weight-adjusted doses: The dose (mg) per unit body weight (kg) (i.e., weight-adjusted dose) was determined by dividing the dose of TNK-tPA administered by the patient's weight on admission. Patients were stratified into tertiles based on the mg/kg of TNK-tPA: high dose, 0.52 to 1.24 mg/kg (n = 174); mid-dose, 0.40 to 0.51 mg/kg (n = 178); and low dose, 0.20 to 0.39 mg/kg (n = 177). The weight-adjusted dose of tPA was also calculated as above in patients who weighed >67 kg by dividing the tPA dose (100 mg) by the patient's weight on admission. In patients weighing ≤67 kg, the dose of tPA was as follows: a bolus of 15 mg followed by 0.75 mg/kg infused for 30 minutes (not to exceed 50 mg), and then 0.5 mg/kg infused for 60 minutes, not to exceed 35 mg. The total dose administered over 90 minutes to these lighter weight patients was calculated (bolus plus weight-adjusted maintenance dose), and then divided by the patient's weight.

Angiographic analysis methods: The TIMI flow grade was assessed at the TIMI Angiographic Core Laboratory as previously defined.[5] To evaluate coronary flow as a continuous variable, the number of cine frames required for contrast to first reach standardized distal coronary landmarks in the infarct-related artery was measured using a frame counter on a cine viewer (corrected TIMI frame count, CTFC).[4,6–13] In patients without acute myocardial infarction, the frame count of the left anterior descending artery is 1.7 times greater than that of the right coronary artery and the circumflex, and the left anterior descending frame count was therefore divided by 1.7 to correct for its longer length[4,6–13]; occluded vessels were imputed a value of 100 frames (99th percentile of patent vessels) as described previously.[4,6–13] Data presented here have been converted to and are reported using the most common cine filming speed in the United States: 30 frames/s.

Statistical analysis: All analyses were performed using Stata version 6.0 (StataCorp. Stata Statistical Software, College Station, Texas). Continuous variable values are reported as mean ± SD, along with median values. The Student's *t* test or analysis of variance were used for the analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank-sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) were used when the data were not normally distributed or when data were imputed to an occluded vessel. The chi-square test was used for the analysis of categorical variables.

RESULTS

Baseline and angiographic characteristics: The baseline characteristics of the tertiles differed by age (3-way p = 0.0006) and gender (3-way p <0.001), while other characteristics were similar. There was a trend for the high-dose tertile to have a lower incidence of angiographically apparent thrombus (Table I).

Relation between weight-adjusted dose and coronary blood flow: The CTFC in culprit arteries differed between the tertiles (3-way p = 0.007), with the median CTFC in high-dose patients being 7.2 frames lower (i.e., faster) than in low-dose patients (p = 0.002) (Figure 1). Likewise, more patients in the high (62.1%) and mid-dose tertiles (60.3%) tended to achieve TIMI grade 3 flow than those receiving low doses (53.5%; p = 0.09). The CTFC in nonculprit arteries differed between the tertiles (3-way p = 0.03), with the fastest flow in the high-dose tertile and slowest in the low-dose tertile (2-way p = 0.008)

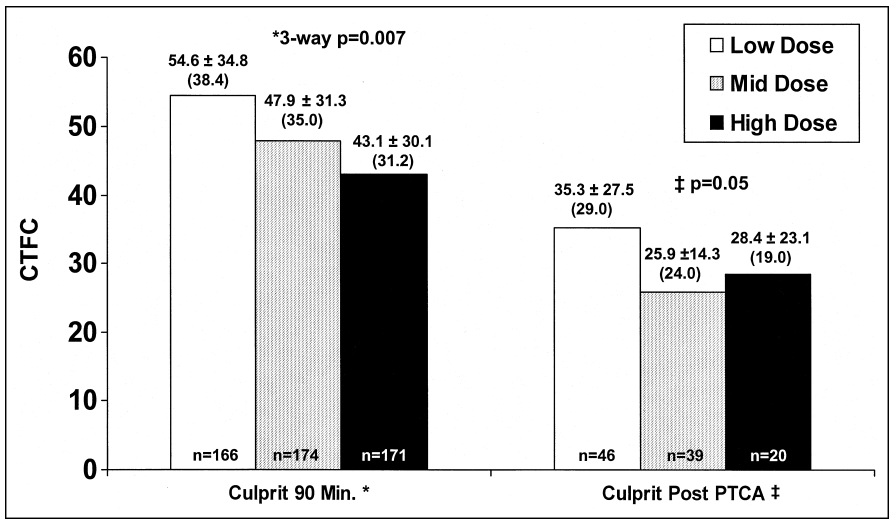

FIGURE 1. CTFCs divided into weight-adjusted tertiles (low, mid, and high doses) for culprit arteries at 90 minutes after thrombolytic administration and after PTCA. Faster flow (lower CTFCs) is seen in the culprit artery at 90 minutes after thrombolytic administration and after PTCA in patients who received the highest doses per unit body weight.

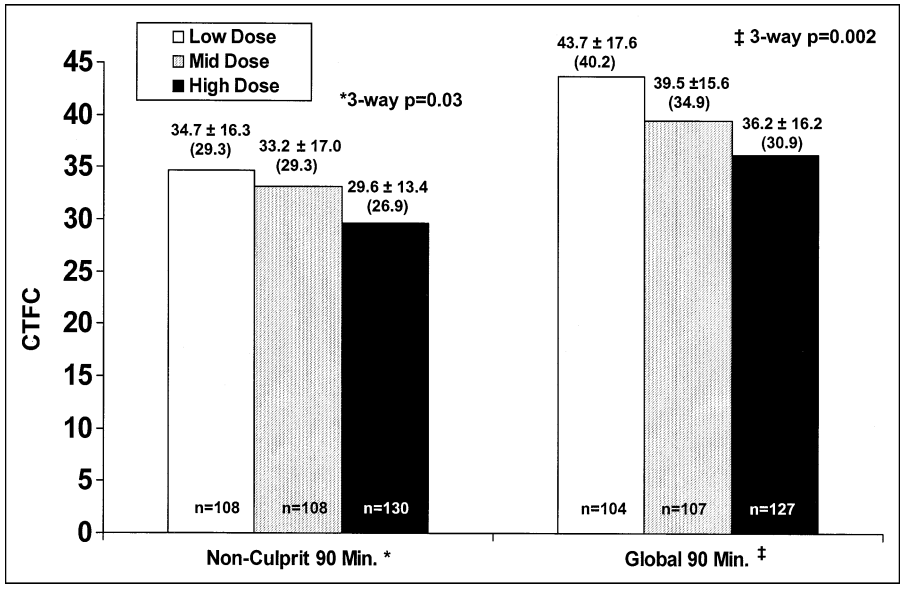

FIGURE 2. CTFCs divided into weight-adjusted tertiles (low, mid, and high doses) for nonculprit arteries, as well as the global CTFCs (average CTFC in all 3 arteries). Patients who received the highest doses per unit body weight achieved the fastest flow in their nonculprit arteries (lowest CTFCs) as well as the fastest flow globally.

(Figure 2). The global CTFC (average of all 3 arteries) differed between the tertiles (3-way $p = 0.002$), with fastest flow in the high-dose tertile and slowest flow in the low-dose tertile (2-way $p = 0.0008$) (Figure 2). Because of differences observed by tertile at baseline, the culprit, nonculprit, and global CTFCs were stratified by gender and similar trends were observed (Table II).

Although 81% and 82% of patients in the mid- and high-dose tertiles, respectively, achieved patency (TIMI grade 2 or 3 flow) by 60 minutes, only 70% of patients in the low-dose tertile achieved early patency ($p = 0.02$ for low vs mid- and high tertiles combined). The percent diameter stenosis was less severe among patients in the high-dose tertile than among those in the low-dose tertile (71.4 ± 18.9 [$n = 173$] vs 75.7 ± 18.2 [$n = 173$]; $p = 0.03$). In patients who underwent PTCA, the mean post-PTCA culprit artery CTFC was faster in both the high and mid-dose tertiles than in those receiving low doses (mid- and high-dose tertiles combined to achieve adequate power [$n = 59$], $p = 0.05$) (Figure 1). The post-PTCA percent diameter stenosis did not differ significantly among the tertiles.

Administration of the highest tertile dose per unit body weight was independently associated with 5.6 frame faster CTFC than the low-dose tertile ($p = 0.03$; overall model $p < 0.0001$) in a multivariate model that controlled for other variables related to improved CTFCs: achievement of patency early, by 60 minutes ($p < 0.001$), non–left anterior descending artery location ($p < 0.001$), absence of thrombus ($p < 0.001$), and residual percent diameter stenosis ($p < 0.001$).

Relation between weight-adjusted dosing and bleeding complications: There was a statistically nonsignificant trend toward a higher risk of intracerebral hemorrhage (ICH) among patients in the highest dose

TABLE II Gender-Stratified CTFC and TIMI Flow Grade by Weight-Adjusted Dose Tertile

	High Dose (n = 101)	Mid Dose (n = 130)	Low Dose (n = 155)
Men			
90-min CTFC (frames)*	43.9 ± 29.6 Median 34 (n = 99)	47.6 ± 30.1 Median 35.5 (n = 126)	53.6 ± 34.8 Median 28 (n = 147)
Global CTFC (frames)†	37.9 ± 15.3 Median 33.7 (n = 77)	39.9 ± 16.0 Median 37.2 (n = 80)	43.7 ± 17.5 Median 40.2 (n = 94)
Grade 3 TIMI Flow‡	62.4% (63/101)	60.3% (76/126)	55.3% (84/152)
Women	(n = 69)	(n = 45)	(n = 16)
90 min CTFC (frames)§	41.9 ± 31.9 Median 27.5 (n = 68)	49.8 ± 35.3 Median 34 (n = 45)	56.1 ± 35.1 Median 38 (n = 14)
Global CTFC (frames)‖	33.4 ± 17.8 Median 25.9 (n = 46)	39.3 ± 14.8 Median 34.6 (n = 25)	34.3 ± 10.9 Median 33.6 (n = 7)
Grade 3 TIMI Flow¶	62.3% (43/69)	57.8% (26/45)	50.0% (7/14)

The p values for low- versus high-dose tertile: *p = 0.05; †p = 0.03; ‡p = NS; §p = 0.08; ‖p = NS; ¶p = NS.

TABLE III CTFC and TIMI Flow Grade by Weight-Adjusted Dose Tertile of tPA*

	High Dose (n = 100)	Mid Dose (n = 29)	Low Dose (n = 101)
Early patency (60 min)	78.3%	79.0%	77.0%
TIMI grade 3 flow	56.4%	68.9%	60.6%
90-min CTFC (frames)	49.8 ± 34.3 Median 38.5	42.5 ± 29.4 Median 29	47.2 ± 29.7 Median 35
Post-PTCA CTFC (frames)	22.1 ± 9.4 Median 19.4 (n = 21)	27.9 ± 17.7 Median 24.5 (n = 16)	32.5 ± 30.5 Median 22 (n = 17)

*High-dose tertile = 1.40 to 1.59 mg/kg; mid-dose tertile = 1.20 to 1.39 mg/kg; low-dose tertile = 0.63 to 1.19 mg/kg. Three-way p = NS for each variable.

tertile: 3.45% (95% confidence interval [CI] 1.3% to 7.4%) for the high-dose tertile, 0.56% (95% CI 0.01% to 3.1%) for the mid-dose tertile, and 1.13% (95% CI 0.1% to 4.0%) for the low-dose tertile (3-way p = 0.09). There was no difference in the rate of nonhemorrhagic stroke between the tertiles (1.15%, 0.56%, and 0.56% in the high-, mid-, and low-dose tertiles, respectively; 3-way p = NS). When adjustments were made for differences in baseline characteristics related to outcomes (age, gender, anterior myocardial infarction), no significant differences between tertiles were observed in the incidence of 30-day death, reinfarction, or shock.

Weight-adjusted dosing of tissue plasminogen activator: Patients assigned to treatment with tPA were stratified into the following 3 tertiles: high dose, 1.40 to 1.59 mg/kg; mid-dose, 1.20 to 1.39 mg/kg; and low dose = 0.63 to 1.19 mg/kg. Although the weight-adjusted doses of TNK-tPA showed a clear relation to angiographic outcomes, the weight-adjusted dose of tPA (dose per unit weight mg/kg) did not show such a relation to angiographic outcomes (Table III).

DISCUSSION

Despite varying body weights, patients often receive the same dose of a medication, and consequently the serum or plasma concentration after drug administration may vary widely. These data demonstrate that higher doses of the single bolus thrombolytic agent TNK-tPA are associated with improved indexes of coronary blood flow at both 60 and 90 minutes after administration. The mechanism for this improvement in culprit flow may be related to the less severe residual stenoses and the greater proportion of high-dose patients achieving patency early, by 60 minutes. Early opening of arteries has been related to improved flow at 90 minutes after thrombolysis.[14] Vessels that had been open for at least 30 minutes had significantly faster flow than vessels that were open <30 minutes (32 vs 58 frames, p = 0.004).[14]

Whereas improved lumen geometry and early opening may play a role in the improved efficacy of the high-dose arm, the multivariable model indicates that the 5-frame benefit of the high-dose arm was also mediated by factors above and beyond percent diameter stenosis, the achievement of early patency, and the reduced incidence of thrombus. Although the critically narrowed epicardial stenosis is obviously a major determinant of flow in the culprit artery in acute myocardial infarction, it is notable that higher doses per unit body weight also improved flow in nonculprit arteries (3-way p = 0.03). Likewise, after relief of the stenosis after adjunctive PTCA, flow was faster in culprit arteries. Global flow in all 3 arteries was also improved (3-way p = 0.002), which may have important prognostic implications since we have recently demonstrated that improved global flow is related to improved outcomes including mortality.[15] Gregorini et al[16] recently confirmed our initial observations, demonstrating that nonculprit flow is delayed in the setting of acute myocardial infarction.[6] The cause of this improved flow in multiple vascular beds (both culprit and nonculprit) in the absence of a critical stenosis is not well understood, one could speculate that it may be due in part to reduced stunning, improved microvascular function, reduced demands, or neural reflexes.

The coronary flow benefits of higher weight-adjusted doses of TNK-tPA must be carefully balanced with any potential increased risk of bleeding, particularly intracranial hemorrhage. There was a statistically nonsignificant trend toward a higher risk of ICH among patients in the highest dose tertile. The sample

sizes were very small, and the variable rates of ICH may have been due to the play of chance. Indeed, the 95% CI for the odds ratio for ICH in the high-dose group (relative to the low-dose group) extended below a value of 1.0, and could have been as low as 0.62 (i.e., indicating a lower risk in the high-dose group). The larger proportion of women in the high-dose group may have also accounted for the observed trend.

There was no clear dose-response relation in patients treated with tPA. This may reflect the fact that at the doses tested, the dose-response curve for tPA had reached a plateau, while the dose-response curve for TNK-tPA remained on the ascending limb of the relation. It could also be speculated that TNK-tPA acts to lyse microthrombii in the microvasculature in a dose-dependent fashion at the doses tested while tPA does not. The lack of a dose-response relation may also result from differing pharmacokinetics between a continuous infusion and a front-loaded bolus.

These analyses are post hoc and the study groups are small. Administration of aspirin, β blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors were not controlled for; however, their administration was balanced across the tertiles.

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