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Review

Issues in the Assessment of the Safety and Efficacy of Tenecteplase (TNK-tPA)

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Summary: While thrombolytic agents have demonstrated improved mortality over the use of placebo, this has come at the expense of bleeding complications such as intracranial hemorrhage (ICH). Tenecteplase (TNK-tPA) is a novel thrombolytic agent engineered to improve upon the ease of use and safety of alteplase (t-PA). Given its longer half-life, TNK-tPA can be administered as a single bolus. The dosing of TNK-tPA has been weight optimized to enhance both safety and efficacy outcomes. Weight-optimized TNK-tPA dosing requires body weight estimation, which may introduce the potential for medication error. However, data from TNK-tPA clinical trials suggest that body weight estimates can err by up to 20 kg (44 lb) without an increased risk of ICH or death. Furthermore, the results of TNK-tPA clinical trials showed that even at the highest weight-optimized dosage of 50 mg, ICH rates were among the lowest reported in clinical trials of thrombolytics for acute myocardial infarction. In elderly female patients of low body weight, the use of weight-optimized TNK-tPA lowered the risk of ICH compared with the use of t-PA, expanding the potential use of thrombolytics to this high-risk patient population. Tenecteplase has demonstrated clinical equivalence to t-PA, but with a wider therapeutic margin of safety.

Key words: tenecteplase, weight-optimized dosing, acute myocardial infarction, r-PA, t-PA, streptokinase

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Introduction

More than 1 million persons in the United States and 7 million patients worldwide sustain an acute myocardial infarction (AMI) each year.[1] While the use of thrombolytic therapy has led to improved survival over treatment with placebo, bleeding complications, such as intracranial hemorrhage (ICH), may offset some of this benefit.[2] Patients who are at higher risk for bleeding complications following thrombolytic therapy include those of increased age, low body weight, female gender, or African ancestry.[3]

Prior to the development of tenecteplase (TNK-tPA), and with the exception of the weight-based infusion of alteplase (t-PA) for patients of low body weight, thrombolytic agents were administered using one dosage for all patients. However, while simple, this fixed dosing of thrombolytic agents can lead to wide variations in serum or plasma drug concentration.[4] Considering the association between the thrombolytic dose and bleeding complications, it seems intuitive that patient outcomes would be optimized with weight-based dosing.

Tenecteplase, recently approved by the Food and Drug Administration, is a novel thrombolytic agent that was engineered to improve upon the characteristics of t-PA. Results of the clinical trials of TNK-tPA for AMI resulted in the refinement of the TNK-tPA dosing regimen. In fact, weight-optimized dosing of TNK-tPA improved both safety and efficacy outcomes. Review of the TNK-tPA clinical trials and comparisons of this agent to other thrombolytics suggest that TNK-tPA is efficacious and exhibits a wide therapeutic margin of safety, particularly with regard to high-risk groups such as low-body-weight women and the elderly.

The Pharmacology of Tenecteplase

Many attempts have been made to improve upon t-PA. In both the case of r-PA and n-PA, large sections or domains of t-PA were completely removed from the molecular structure. More than a thousand mutants of t-PA were tested to arrive at the molecular structure of TNK-tPA. Rather than eliminating large domains of t-PA, TNK-tPA was made by substituting three single amino acids at the T, N, and K domains (Fig. 1).[5–8]

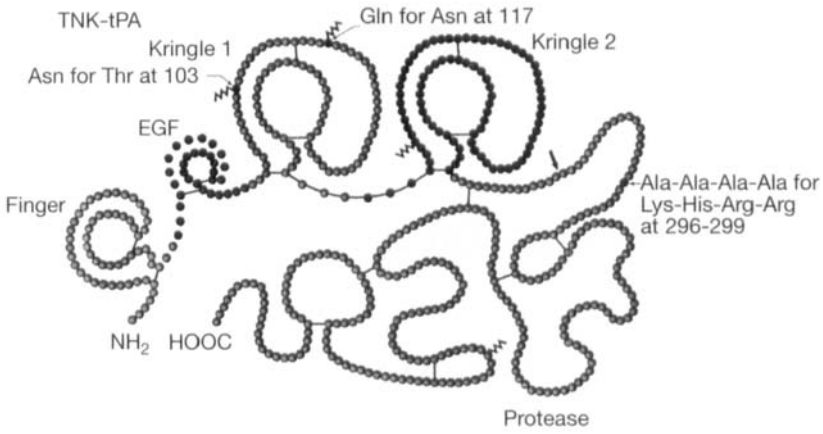

FIG. 1 Distinctive structural elements of tenecteplase (TNK-tPA) provides improved fibrin specificity, reduced clearance, and greater resistance to inactivation of PAI-1. EGF = epidermal growth factor. Source: Product data on file. Genentech, Inc., South San Francisco, Calif., USA.

Tenecteplase was altered at the T domain to achieve clearance from the body four times more slowly than t-PA. This permits convenient, single-bolus administration of TNK-tPA over 5 s. In patients with AMI, TNK-tPA exhibits a biphasic disposition from the plasma when administered as a single bolus.[9] In clinical studies, TNK-tPA was cleared from the plasma with an initial half-life of 20 to 24 min, a much longer half-life than that reported for t-PA (i.e., less than 5 min).[10] The terminal phase half-life of TNK-tPA was 90 to 130 min. In 99 of 104 patients treated with TNK-tPA, mean plasma clearance ranged from 99 to 119 ml/min. Liver metabolism is the major clearance mechanism of TNK-tPA.

At the N domain, an amino acid substitution was made to increase the fibrin specificity of TNK-tPA by a factor of 14 over t-PA. Theoretically, this permits enzymatic activity preferentially at the clot rather than the periphery by minimizing the induction of a systemic fibrinolytic state. In fact, levels of fibrinogen, fibrin degradation products, and other coagulation factors are fairly stable following TNK-tPA administration (Fig. 2).[11] At the K domain on the TNK-tPA molecule, an amino acid substitution was made to enhance its resistance against plasminogen activator inhibitor-1 (PAI-1). Plasminogen activator inhibitor-1 is an enzyme secreted by platelets that interacts with thrombolytics to inhibit their activity. Tenecteplase is 80 times more resistant to inactivation by PAI-1 than t-PA.

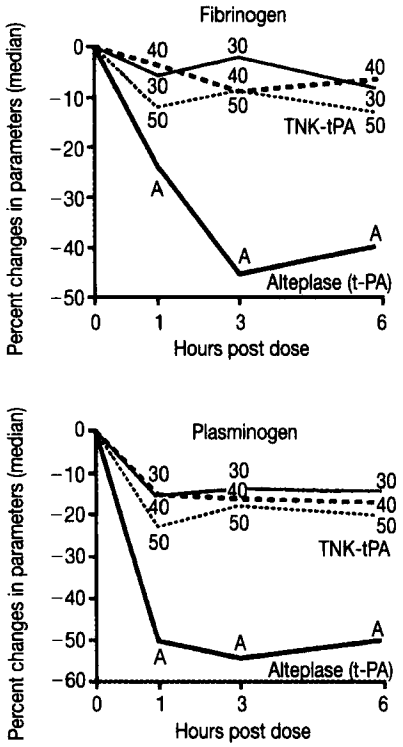

FIG. 2 The benefits of fibrin specificity: There was a 5 to 10% drop in fibrinogen and an 18 to 15% fall in plasminogen after administration of 30 mg, 40 mg, and 50 mg doses of tenecteplase (TNK-tPA) compared with a 40 and 50% drop, respectively, for t-PA in TIMI 10B. Reprinted from Ref. No. 11 with permission.

The Clinical Development of Tenecteplase

TIMI 10A: A Dose-Ranging Study

The Thrombolysis in Myocardial Infarction (TIMI) 10A trial was a small dose-ranging study that enrolled and treated 113 patients with acute ST-segment elevation presenting within 12 h of symptom onset, who had no contraindications to thrombolysis. The goal of this small dose-escalation study was to identify TNK-tPA doses for testing in a second moderate-size angiographic trial.[12] Patients were treated with one of eight doses of TNK-tPA ranging from a single 5 to 50 mg bolus dose of TNK-tPA over 5 to 10 s. Tenecteplase was not administered on a weight-tiered basis in this study. The majority of patients (57–64%) experienced TIMI grade 3 flow at 90 min when treated with the 30 to 50 mg doses. Seven patients (6%) developed a major hemorrhage, but no patients experienced ICH. Hemorrhagic events were distributed across the

doses: one patient at 15 mg; two patients at 20 mg; one patient at 30 mg; two patients at 40 mg; and one patient at 50 mg. Thus, TNK-tPA doses of 30 and 50 mg were identified for further testing.

TIMI 10B: A Dose-Finding Study

The goal of TIMI 10B, a Phase II dose-finding study, was to compare 30 and 50 mg doses of TNK-tPA with front-loaded t-PA. This was a larger study that included 886 patients with acute ST-segment elevation myocardial infarction presenting within 12 h of onset of ischemic symptoms. Patients were randomized to a single bolus of 30 or 50 mg of TNK-tPA or the accelerated regimen of t-PA.[11] Similar to TIMI 10A, patients were not treated with TNK-tPA on a weight-tiered basis.

In all, 78 patients were treated with the 50 mg dosage. Three patients who were treated with TNK-tPA 50 mg plus heparin (10,000 U) experienced ICH; therefore, the 50 mg bolus was eliminated and was replaced with a 40 mg bolus. In fact, these results also prompted a protocol amendment that instituted the use of reduced and weight-adjusted heparin doses. It also specified that no additional heparin was to be given before diagnostic angiography if the patient was already receiving intravenous heparin. This protocol amendment was initiated during the TIMI 10B study and was utilized in subsequent TNK-tPA trials, including Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-1 and ASSENT-2. Following the heparin protocol amendment, ICH rates associated with TNK-tPA treatment were reduced significantly from 1.82 to 0.73% ($p = 0.046$).[13] Notably, the results of this study suggested a relationship between body weight, efficacy, and safety outcomes.[11] For example, with regard to the three patients who experienced ICH on the 50 mg dose of TNK-tPA, all weighed < 90 kg (mean weight 77.2 kg).

At the completion of this angiographic dose-finding trial, a comparison of TNK-tPA and t-PA demonstrated that the 40 mg dose resulted in similar rates of TIMI grade 3 flow at 90 min (62.8 vs. 62.7%, respectively). The 30 mg dose produced a significantly lower rate (54.3%; $p = 0.035$), and the 50 mg dose produced a similar rate (65.8%). Rates of ICH for TNK-tPA were 1.0% for the 30 mg dose, 1.9% for the 40 mg dose, and 3.8% for the 50 mg dose. The ICH rate for t-PA was 1.9%. Serious bleeding rates for TNK-tPA were 1.9% for the 30 mg dose, 5.2% for the 40 mg dose, and 11.5% for the 50 mg dose. The serious bleeding rate for t-PA was 8.5%. These bleeding rates are higher than those generally observed in large-scale safety trials and in clinical practice. This most likely is due to the fact that bleeding rates are generally higher in angiographic trials. Two reasons have been suggested for this fact. The first is the need for vessel instrumentation. The second reason is that higher heparin dosing is used in these trials because many patients undergo adjunctive or rescue percutaneous coronary intervention (PCI). Similar to ICH, the incidence of major hemorrhage was related to body weight. Nine patients who received the 50 mg dose experienced major hemorrhage, but the vast majority of these patients (eight of the nine patients, or 89%) weighed < 90 kg.

Weight-Corrected Dosing Improves Outcomes

These valuable observations led to a formal, objective analysis of the impact of body weight on both safety and efficacy outcomes, and a "weight-corrected" dose was calculated using the TNK-tPA dose divided by the patient's weight (i.e., TNK-tPA dose [milligram] per unit of body weight [kilogram]).[4, 11, 14] This analysis showed that higher doses per kilogram of body weight improved TIMI grade 3 flow until a plateau was reached between 0.5 and 0.6 mg/kg TNK-tPA (Fig. 3).[11] The weight-corrected analysis assisted in the determination of the most appropriate TNK-tPA dosage per kilogram of body weight to maximize efficacy outcomes and minimize bleeding complications. Adjusting the dose of TNK-tPA to approximately 0.53 mg/kg resulted in correcting TIMI frame counts more quickly in both the culprit artery and in uninvolved arteries, achieving earlier vessel patency (by 60 min), reducing thrombus burden, and reducing the severity of residual stenoses compared with other doses/weight.[14] Even after the stenosis is relieved by PCI, this weight-adjusted dose of TNK-tPA "facilitated PCI," in that it resulted in faster flow at the completion of the intervention and improved 2-year outcomes in TIMI 10B.[15]

ASSENT-1: A Safety Study

The ASSENT-1 trial was the largest safety study ever done on a fibrinolytic. It enrolled a total of 3,235 patients presenting within 12 h of symptom onset; 1,705 received a 30 mg dose of TNK-tPA, 1,457 received a 40 mg dose, and 73 received a 50 mg dose.[16] The TIMI 10B and ASSENT-1 trial were conducted simultaneously; therefore, TNK-tPA was not administered on a weight-tiered basis in ASSENT-1. However, following the observation of bleeding complications associated with the 50 mg dose in the TIMI 10B study, the 50 mg dose of TNK-tPA was discontinued and replaced by a 40 mg dose. The difference between TIMI 10B and ASSENT-1 was that heparin was dosed according to the heparin protocol amendment.

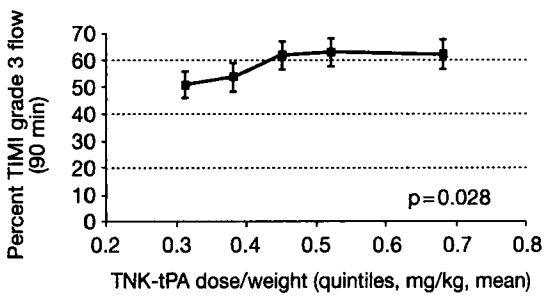

FIG. 3 Weight-corrected dosing analysis in TIMI 10B demonstrated that reperfusion benefit plateaus between 0.5 and 0.6 mg/kg tenecteplase (TNK-tPA). Figure shows TIMI flow grade at 90 min among TNK-tPA-treated patients with dose expressed in TNK-tPA (mg) per patient body weight (kg). Data shown are quintiles of weight-corrected dose of TNK-tPA. P for trend was 0.028 across quintiles. Reprinted from Ref. No. 11 with permission.

The incidence of all strokes at 30 days was 1.5%, and the incidence of ICH was 0.77%. Of the 25 patients who experienced ICH, 16 were treated with 30 mg of TNK-tPA, and 9 were treated with 40 mg. The incidence of ICH was lower in patients treated within 6 h of symptom onset (0.56% for 30 mg TNK-tPA and 0.58% for 40 mg TNK-tPA). Severe bleeding complications were reported in 2.8% of patients, and 30-day mortality was 6.4%.

It is interesting to note that there were no strokes reported among the 73 patients treated with the 50 mg dose prior to the protocol amendment that eliminated this dose from the study. The main difference between this study and the TIMI 10B trial, in which three patients treated with the 50 mg dose experienced ICH, was that none of the patients in ASSENT-1 received high-dose heparin (10,000 U), which was given concomitantly to the three patients who experienced ICH in TIMI 10B. As noted earlier, the elimination of high-dose heparin resulted in a sharp reduction in ICH rates associated with TNK-tPA.[13] These findings further substantiate the need to use weight-optimized heparin dosages when treating patients with thrombolytic agents.

ASSENT-2: An Equivalence Trial

The practical weight-based analyses conducted on data from TIMI 10B refined the dosing regimen for TNK-tPA and permitted the selection of an optimal dosage for study in the Phase III ASSENT-2 trial. Dosing was determined using weight-based calculations and a logistic regression analysis of the TIMI frame count data from TIMI 10B and safety data from ASSENT-1. A TNK-tPA dosage of 0.53 mg/kg was selected as the most appropriate for the ASSENT-2 trial.[4, 16]

ASSENT-2 was a Phase III trial that randomized 16,949 patients with AMI and ST-segment elevation presenting within 6 h to a weight-optimized TNK-tPA regimen or t-PA.[17, 18] The study was designed to demonstrate equivalence between the drugs. In an equivalency trial, the goal is to say with 95% statistical confidence that the mortality rates of the two drugs lie within 1% of each other. Not only were t-PA and TNK-tPA found to be statistically equivalent, but the covariate-adjusted, 30-day mortality rates were almost identical between TNK-tPA- and t-PA-treated patients (6.18 and 6.15%, respectively).

There were significantly fewer noncerebral bleeding events and less need for blood transfusion with TNK-tPA than with t-PA (Table I).[18] Improved safety was noted in both major and minor noncerebral bleeding events. These differences may have reflected weight-optimized dosing or the greater fibrin specificity of TNK-tPA, or both. The lower rates of transfusion associated with TNK-tPA therapy may translate into greater cost effectiveness. This high cost is not due to the cost of blood products per se, but rather to all the ancillary costs associated with transfusion, including longer stays in the intensive care unit, the costs of imaging studies to determine the site of bleeding, the cost of therapeutic modalities such as endoscopy, and so forth. In the ASSENT-2 trial, rates of ICH were similar between the treatment groups (i.e., 0.93% for TNK-tPA and 0.94% for t-PA). The rates also were similar to those observed in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-III study, which compared r-PA with t-PA (i.e., 0.91% for r-PA and 0.87% for t-PA).[19] Overall, the ASSENT-2 study confirmed that weight-optimized dosing of TNK-tPA could be utilized effectively and more safely to treat patients with AMI.

TABLE I ASSENT-2: Tenecteplase induced fewer noncerebral bleeding events than t-PA

Event	TNK-tPA (n = 8,461)	t-PA (n = 8,488)	p Value
Total bleeds (%)	26.43	28.95	0.0003
Major bleeds (%)	4.66	5.94	0.0002
Minor bleeds (%)	21.76	22.99	0.0553
Any transfusion (%)	4.25	5.49	0.0002

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Tenecteplase Dosing Regimen for Acute Myocardial Infarction

The TNK-tPA dosing regimen that has received approval from the Food and Drug Administration includes dosing categories that are about 10 kg (22 lb) wide and permits dosing according to the patient's actual or estimated weight (Table II).[20] The wide TNK-tPA dosing range and the requirement of a single bolus of TNK-tPA should minimize the likelihood of dosing error that has been purported to occur with thrombolytic therapy.[21] It is important to note that the three patients who were treated with 50 mg of TNK-tPA and experienced ICH in TIMI 10B would not have received this dose of the agent in either clinical practice or in the ASSENT-2 trial. An analysis of all patients in ASSENT-2, who were treated with the 50 mg TNK-tPA dosage on a weight-optimized basis, demonstrated that there was no increased risk of 30-day mortality or ICH compared with patients who received less than the 50 mg dosage.[22] In fact, the rates of ICH and death were lower among these patients. Thirty-day mortality in this patient population

TABLE II Weight-optimized dosing ranges for tenecteplase (TNK-tPA)

Patient weight (kg)	TNK-tPA (mg)	Volume of TNK-tPA to be administered (ml) [a]
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 80 to < 90	45	9
≥ 90	50	10

[a] From one vial of TNK-tPA reconstituted with 10 mg sterile water for injection, USP.

TNKase(tm) (tenecteplase) prescribing information. Genentech, Inc., South San Francisco, Calif. Available at http:www.gene.com/products/tnkas/insert.html. Accessed August 2000.

was actually slightly lower than that observed in all patients (4.8 vs. 6.2%), suggesting that this weight-optimized dosage maintained efficacy in high-weight patients. Concerning safety outcomes, the risk of ICH in these patients was 0.6% compared with 0.9% for all TNK-tPA-treated patients.[23]

Analyses of High-Risk Patients: A Favorable Safety Profile with Tenecteplase

Elderly female patients are at particular risk for ICH complications associated with thrombolytic therapy, yet such patients represent a substantial proportion of persons presenting with AMI.[3, 24–26] Women aged >75 years have an 8-fold greater risk for ICH compared with men aged <65 years.[25] Concerns about the risk of ICH have limited the use of such thrombolytics in this population despite the potential for substantial survival benefits with treatment.[2] Of interest is the fact that analyses of TNK-tPA clinical trials suggest that the use of weight-optimized dosing may improve safety outcomes in elderly female patients of low body weight.

Using data from ASSENT-2, Barron *et al.* compared ICH rates among elderly, low-weight women (i.e., < 67 kg and aged >75 years) with all other women in the study (Table III).[27] Among low-weight, elderly women, the ICH risk was 1.1% for TNK-tPA-treated patients, compared with 3.0% for t-PA-treated patients. When multivariate analyses were performed, controlling for other confounding factors, this lower rate of ICH for TNK-tPA reached statistical significance within this subgroup ($p < 0.05$).[18] This analysis demonstrated that TNK-tPA was safer for low-weight, elderly women than t-PA, an outcome that may reflect weight-optimized dosing and/or improved fibrin specificity.

At the other end of the spectrum are patients whose body weight exceeds 90 kg. Patients of greater weight may theoretically not receive enough drug. As a result, questions have been raised about drug efficacy in these heavier patients.[28] In ASSENT-2, a total of 1,924 patients weighed more than 90 kg and thus were treated with the 50 mg dosage of TNK-tPA (approximately 11% of patients).[18] It is interesting that mortality in this patient population was actually slightly lower than that observed in all patients (4.88 vs. 6.28%). These findings indicate that weight-optimized dosing of TNK-tPA maintained efficacy in high-weight patients. Likewise, with respect to safety outcomes, the risk of ICH in these patients was 0.57% compared with 0.93% for all TNK-tPA-treated patients. The therapeutic action appears to plateau, and there is no incremental benefit to adding more drug for patients weighing above 90 kg. Thus, weight-optimized dosing of TNK-tPA in high-weight patients can produce safe and efficacious outcomes.[22, 29]

TABLE III ASSENT-2: Low-weight, elderly women are at less risk for intracranial hemorrhage (ICH) when treated with tenecteplase (TNK-tPA) rather than with t-PA[a]

Group	Rates of intracranial hemorrhage (%)	
	TNK-tPA, %	t-PA, %
Low-weight, elderly women (<67 kg and >75 years)[a]	1.1 (3/264)	3.0 (8/265)
All other women	1.5 (25/1,677)	1.6 (27/1,715)
All women	1.4 (28/1,941)	1.8 (35/1,908)

[a] When multivariate analyses were performed, controlling for confounding factors, this lower rate of ICH for TNK-tPA reached statistical significance within this subgroup ($p < 0.05$).
Adapted from Ref. No. 27 with permission.

Safety Outcomes with Other Thrombolytic Agents

Several large clinical trials have examined the impact of various thrombolytic agents on safety and efficacy. A comparison of these trials indicates that weight-optimized dosing with TNK-tPA is associated with a low to moderate incidence of ICH and mortality (Fig. 4).[18, 19, 30–33] Another important observation is that patients who received a 50 mg dosage of TNK-tPA calculated on a body weight basis were at no greater risk for ICH or mortality than patients who received other weight-optimized doses of TNK-tPA given in the ASSENT-2 study, or patients treated with most other thrombolytic agents assessed in large clinical trials (Fig. 4). In fact, the risk of ICH and mortality observed in patients treated with 50 mg of TNK-tPA as a weight-optimized dose was actually lower than the risks observed with TNK-tPA overall and with other thrombolytic agents. Aside from TNK-tPA and the infusion portion of t-PA administration, all thrombolytics are administered as one dosage for patients of all body weights. Clinical trials of r-PA, streptokinase, and t-PA demonstrate that patients with low body weights who receive the non-weight-based thrombolytic dosage are at greater risk for bleeding complications compared with higher-weight patients.[19, 31] In a subgroup analysis of GUSTO-III data, the incidence of bleeding episodes in low-body-weight women was consistently higher in patients treated with r-PA than with t-PA.[34] In the International Joint Efficacy Comparison of Fibrinolytics Trial (INJECT), which compared streptokinase (1.5 MU intravenously over 60 min) and r-PA (2 boluses of 10 MU given 30 min apart), the frequency of bleeding complications and the need for transfusion were greater among patients with low body weight (Table IV).[31] In fact, the incidence of bleeding complications was almost twice as great in the low-weight patients (i.e., ≤65 kg) than the higher-weight patients (i.e., ≥80 kg). The importance of a weight-based dosing strategy for heparin was demonstrated in the GUSTO-I trial, where an analysis of the relationship between the degree of anticoagulation (activated partial thromboplastin time [aPTT]) and 30-day clinical outcomes in nearly 30,000 patients was performed.[24] Low body weight, older age, female gender, and nonsmoking status were associated with significantly higher aPTTs. Furthermore, the degree of mortality risk increased with higher and lower aPTTs. Similar relationships were observed between aPTTs and the risk of stroke and bleeding events.

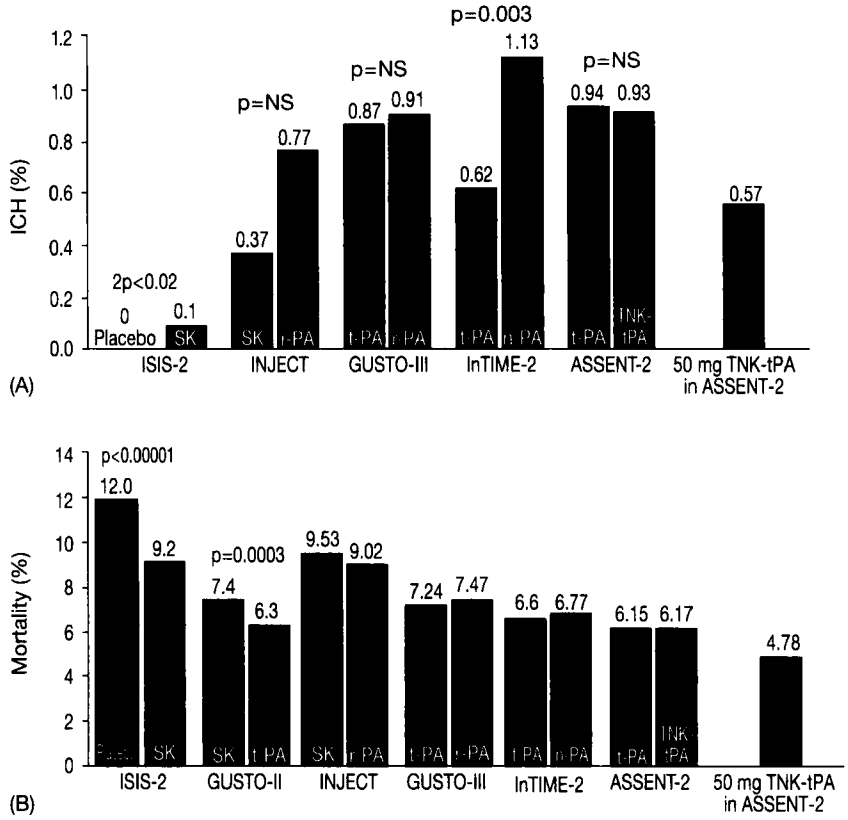

FIG. 4 Comparison of intracranial hemorrhage (ICH) (A) and mortality (B) among major clinical trials of thrombolytics revealed that tenecteplase (TNK-tPA) was associated with low to moderate ICH and mortality rates. SK = streptokinase.

Concerns About Medication Error with Weight-Optimized Dosing

A recent report from the Institute of Medicine established that medication errors are a serious and costly problem in the US healthcare industry.[35] Multiple factors contribute to medication error. For emergency cardiac care, drugs must be selected and dosing regimens must be administered under extreme time pressures, potentially increasing the likelihood of error. Furthermore, error can be introduced by complicated drug administration regimens that require bolus dosing plus infusion or multiple bolus doses.[21] The latter is the case for thrombolytic agents such as t-PA and r-PA. The timing of drug administration also is critical. The duration of the t-PA infusion may be either too long or too short. The timing of the second bolus of r-PA at 30 min may occur too early or too late, or may be missed entirely. The bolus of r-PA may be given more or less rapidly than over 2 min. As a single-bolus agent to be administered over 5 s, TNK-tPA reduces these sources of medication error. Finally, TNK-tPA is compatible with a broad range of other medications, while r-PA and t-PA may precipitate with the administration of heparin, a drug commonly used in treating AMI.

TABLE IV The INJECT study: Patients with lower body weight were more likely to experience bleeding complications and require transfusion than patients of higher body weight

	r-PA	Streptokinase
All bleeds		
≤65 kg (%)	20.4	21.3
65 to 80 kg (%)	15.8	15.3
>80 kg (%)	12.4	13.2
Bleeds requiring transfusion		
≥65 kg (%)	1.1	1.6
65 to 80 kg (%)	1.0	1.0
>80 kg (%)	0.1	0.7

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Drugs that require weight-based dosing and body weight estimations also may introduce medication error. Nonetheless, weight-based dosing is essential for drugs that possess a narrow therapeutic window, such as thrombolytics and other emergency cardiac medications. Indeed, many drugs used in emergency cardiac care require weight-based dosing, including heparin and the low-molecular-weight heparinoids, abciximab, amiodarone, dobutamine, dopamine, eptifibatide, nitroprusside, and procainamide, among others. The American College of Cardiology/American Heart Association guidelines have recently been revised to reflect the importance of weight-based heparin dosing.[36–38]

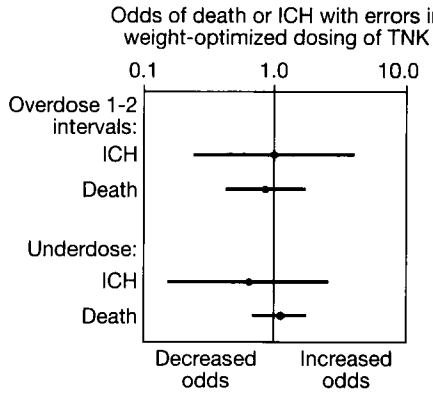

FIG. 5 Overdosing or underdosing tenecteplase (TNK-tPA) for one or two dosing intervals—that is, by up to a 20 kg or 44 lb weight error—was not associated with intracranial hemorrhage (ICH) or death in ASSENT-2. This was determined using a multivariate model accounting for body weight. Source: Ref. No. 29.

In the case of TNK-tPA, the results of clinical studies indicate that most errors in TNK-tPA dosing do not increase the risk of either ICH or mortality. In ASSENT-2, overdosage occurred in 2.7% of patients (n = 218; median weight error 8 kg) and underdosage in 4.0% of patients (n = 326; median weight error 1 kg); underdosing or overdosing of one to two dosing intervals—that is, up to a 20 kg or 44 lb weight error—was not associated with ICH or death in a multivariate model accounting for body weight (Fig. 5).[29] In short, weight-optimized dosing of TNK-tPA provides a broad therapeutic margin of safety.

Finally, concerns have been raised about the higher mortality rate among patients treated with TNK-tPA who were not weighed. However, data from the INJECT study show that there also is a higher rate of mortality among patients who received fixed doses of either streptokinase or r-PA who were not weighed. Failure to weigh a patient and higher mortality are clearly associated. The question relates to causality: Does failure to weigh the patient lead to mortality or does a patient's failure to survive AMI lead to failure to weigh a patient? Given that the same observation is seen among fixed-dose lytic agents, the second possibility appears more likely, namely, that patients who die early during their hospital course are more likely not to have a weight recorded. Thus, the relationship is confounded by both survival bias and selection bias.

Conclusions

Thrombolytic agents are widely used in the management of AMI. Recent improvements such as the development of TNK-tPA and the implementation of weight-optimized dosing have resulted in greater safety and efficacy outcomes. Weight-tiered dosing can prompt concerns about medication error stemming from the need to estimate patient body weight. It is important to note that analyses of data from clinical trials of TNK-tPA suggest that there is no excess risk of death or ICH with dose errors when estimating a patient's weight of up to 20 kg (44 lb). The attributes of TNK-tPA, including biochemical improvements, the potential for a decreased risk of medication error, and refined safety and efficacy outcomes subsequent to weight-optimized dosing make this agent a preferred thrombolytic for the treatment of AMI, particularly in high-risk patients such as low-weight elderly women. Further study of this agent will likely expand its clinical use into the prehospital setting.

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