

# Tenecteplase: Innovative Fibrinolysis for ST-Segment Elevation Myocardial Infarction (STEMI)

Gordon J. Vanscoy, PharmD, CACP, MBA, Thomas L. Rihn, PharmD,  
and Pamela H. Koerner, PharmD

**ABSTRACT** The use of fibrinolytic agents in the early treatment of ST-segment elevation myocardial infarction (STEMI) is known to significantly reduce mortality. Accelerated (“front-loaded”) alteplase is being challenged as the standard of care for pharmacological reperfusion. Alteplase, reteplase, and streptokinase have several limitations. The search for newer agents has focused on developing a fibrinolytic compound with improved safety as well as a pharmacokinetic and pharmacodynamic profile that allows for single-bolus administration, resistance to inactivation by plasminogen activator inhibitor-1, and greater fibrin specificity.

Tenecteplase (TNKase™) has been shown to be equivalent to alteplase in reducing 30-day mortality in patients with STEMI. However, subgroup data analysis reveals less risk of bleeding and superior efficacy in patients treated between four and six hours after the onset of symptoms. Important research into the use of tenecteplase, in combination with potent antiplatelet agents and low-molecular-weight heparins, has demonstrated improved patient outcomes. It is possible that the safest and most effective tenecteplase combinations might redefine the standard of practice for pharmacological reperfusion in patients with STEMI.

## INTRODUCTION

Thrombus formation over a ruptured coronary artery plaque occludes blood flow and can lead to myocardial infarction. Irreversible myocardial necrosis begins in the endocardium shortly after thrombus formation and, over time, progresses to the epicardium.<sup>1</sup> For nearly two decades, rapid dissolution of the thrombus with a fibrinolytic agent has been the pharmacological cornerstone of therapy for patients with ST-segment elevation myocardial infarction (STEMI). Recent practice guidelines recommend that fibrinolytic agents be administered to all qualifying patients who present with ischemic symptoms of less than 12 hours' duration in addition to either ST-segment elevation or left bundle branch block (Table 1).<sup>2</sup> Percutaneous coronary intervention, when available in a timely fashion, is an alternative to fibrinolytic therapy.

Fibrinolytic agents work by catalyzing the conversion of plasminogen to plasmin, which then dissolves fibrin, the thread-like structure that binds clots together. In numerous randomized trials and meta-analyses, fibrinolytic therapy has repeatedly demonstrated an ability to significantly reduce mortality, particularly among patients who are treated early (within 1 to 4 hours) after symptom onset.<sup>3-5</sup>

Four fibrinolytic agents have been approved by the Food and Drug Administration (FDA) and are available for the treatment of STEMI (Table 2).<sup>6,7</sup>

- streptokinase (SK) (Streptase®, AstraZeneca)
- alteplase (t-PA) (Activase®, Genentech)
- reteplase (r-PA) (Retavase®, Centocor)
- tenecteplase (TNK-tPA) (TNKase™, Genentech)

Each agent has its own distinct pharmacological properties and procedures for administration.

## Streptokinase and Alteplase

Streptokinase, a bacterial protein, was the first fibrinolytic agent to be widely used. In the Second International Study of

Infarct Survival (the ISIS-2 trial),<sup>8</sup> mortality in patients who received streptokinase and aspirin was significantly lower than in patients who received no specific treatment (8.0% vs. 13.2%,  $P < .0001$ ) and in patients who received streptokinase or aspirin alone. However, in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study (the GUSTO I trial), streptokinase did not produce as rapid or complete restoration of coronary flow as alteplase, a recombinant version of the naturally occurring tissue plasminogen activator (t-PA) molecule.<sup>5,9</sup> Mortality in the GUSTO I trial was lowest in patients with normal coronary flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3) at 90 minutes (4.4%) and highest in patients with no flow (8.9%,  $P = .009$ ). Overall, mortality in the patients receiving alteplase was an absolute 1% lower than in the patients receiving streptokinase. As a result of the GUSTO I findings, alteplase became the “gold standard” fibrinolytic agent for the treatment of STEMI.

Despite the proven efficacy of alteplase, its success is somewhat limited by its method of administration in patients with STEMI. The accelerated, or front-loaded, dosing regimen requires an initial intravenous (IV) 15-mg bolus injection, followed by a 0.75-mg/kg infusion given over 30 minutes (not to exceed 50 mg), followed by a second infusion of 0.5 mg/kg given over the next 60 minutes (not to exceed 35 mg).<sup>10</sup> All derivatives of natural t-PA carry a slight risk of intracranial hem-

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*Dr. Vanscoy is Assistant Dean for Managed Care and Associate Professor of Pharmaceutical Sciences at the University of Pittsburgh, School of Pharmacy, and Consulting Director of Anticoagulation Services at Veterans Affairs Health Care Systems in Pittsburgh, Pennsylvania. Dr. Rihn is Associate Professor of Clinical Pharmacy at Duquesne University, School of Pharmacy, and Chief Clinical Officer at University Pharmacotherapy Associates, LLC, in Pittsburgh. Dr. Koerner is a Clinical Coordinator at University Pharmacotherapy Associates, LLC, and Adjunct Clinical Instructor at Duquesne University, School of Pharmacy, and at the University of Pittsburgh, School of Pharmacy, in Pittsburgh.*

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**Table 1 Recommendations for the Use of Fibrinolytic Therapy**

- All patients with STEMI who receive fibrinolytic therapy should receive aspirin (165 to 325 mg) on arrival at the hospital and daily thereafter.
- Unless there are contraindications, all patients presenting with ischemic symptoms characteristic of STEMI of 12 hours' duration or less and who have either ST-segment elevation or left bundle branch block should receive fibrinolytic therapy.
- Fibrinolytic therapy should also be considered in patients with symptoms characteristic of STEMI of 12 to 24 hours' duration.
- Patients with prior intracranial hemorrhage, any stroke within the past year, or active bleeding should not receive fibrinolytic therapy.
- The door-to-needle time should not exceed 30 minutes.
- Patients with symptom duration of 12 hours or less should receive streptokinase or alteplase. (Note: Reteplase is equivalent to streptokinase.)
- Patients with symptom duration of six hours or less should receive alteplase. (Note: Tenecteplase is equivalent to alteplase.)
- Patients with a known allergy or sensitivity to streptokinase should receive alteplase, tenecteplase, or reteplase.

STEMI = ST-segment elevation myocardial infarction.

Adapted from Ohman EM, Harrington RA, Cannon CP, et al. Intravenous thrombolysis in acute myocardial infarction. *Chest* 2001;119:253S-277S.<sup>2</sup>

orrhage (ICH). With alteplase, the rate of ICH in the GUSTO I trial was 0.72%, higher than the rate of 0.54% seen with streptokinase ( $P = .03$ ); nevertheless, the net clinical benefit favored alteplase.<sup>5</sup>

### Reteplase

An attempt to improve upon the properties of alteplase came in the form of reteplase, a deletion mutant of wild-type t-PA. Reteplase is administered as a double bolus; each dose consists of 10 units given over two minutes 30 minutes apart. In the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial,<sup>11</sup> reteplase was found to be equivalent to streptokinase in terms of 35-day mortality (9.02% vs. 9.53%). There was no statistically significant difference in the rate of ICH (0.77% vs. 0.37%).

In the later GUSTO III trial,<sup>12</sup> reteplase did not demonstrate superiority over alteplase. The 30-day mortality rate with alteplase was 7.24%; the rate with reteplase was 7.47%. The difference was not statistically significant, and because the trial was powered for superiority—not equivalence—these agents cannot be said to have equivalent efficacy. Instead, the investigators concluded that reteplase provides no survival advantage over alteplase.

### Tenecteplase

Tenecteplase, recently approved for the treatment of STEMI, is a third-generation variant of the t-PA molecule. Unlike its predecessors, tenecteplase can be administered as a single bolus over five seconds. It has also been designed for enhanced fibrin specificity and resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1); these are considered to be desirable features in a fibrinolytic agent. The advantage

**Table 2 FDA-Approved and Available Fibrinolytic Agents for the Treatment of STEMI**

Characteristic	Streptokinase (Streptase®) (SK)	Alteplase (Activase®) (t-PA)	Reteplase (Retavase®) (r-PA)	Tenecteplase† (TNKase™) (TNK-tPA)
Antigenicity	Yes	No	No	No
Plasminogen activation	Indirect	Direct	Direct	Direct
Fibrin specificity	–	++	+	+++
Plasma half-life	18	5	18	20*
Dose/administration	1.5-MU infusion over 60 minutes	15-mg bolus plus 90-minute infusion up to 85 mg	10 + 10 units double bolus given over two minutes 30 minutes apart	0.53 mg/kg single bolus given over five seconds
Resistance to PAI-1	No	No	No	Yes
Activity on platelet-rich clot	–	++	+	+++
Indications	STEMI	STEMI, ischemic stroke, pulmonary embolism, central venous access device	STEMI	STEMI
Cost	+	+++	+++	+++

\*The terminal phase half-life 90 to 130 minutes.

†Data from TNKase™ (tenecteplase) package insert. South San Francisco, CA, Genentech, Inc, June 2000.

FDA = Food and Drug Administration; MU = million units; PAI = plasminogen activator inhibitor; STEMI = ST-segment elevation myocardial infarction. Adapted from Ross AM. New plasminogen activators: A clinical review. *Clin Cardiol* 1999;22:165-171.<sup>6</sup>

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of enhanced fibrin specificity is a reduction in bleeding complications and more effective lysis of older clots than can be accomplished with agents having less fibrin specificity.<sup>2</sup> The longer a clot is allowed to mature, the more resistant it can become to successful lysis. A fibrin-specific agent, compared with an agent without a high degree of fibrin specificity, appears to be more successful in lysing long-standing clots.

## CHEMISTRY AND PHARMACOLOGY

Tenecteplase is a genetically engineered variant of t-PA (alteplase). Modifications to the natural human t-PA molecule were made to increase the plasma elimination half-life, fibrin specificity, and PAI-1 resistance. The longer half-life of tenecteplase is the result of two substitutions on the kringle 1 domain of t-PA (threonine 103 with asparagine, and asparagine 117 with glutamine).<sup>13</sup> Substitution of the amino acids at positions 296–299 with alanine residues in the protease domain increases fibrin specificity and renders tenecteplase relatively resistant to inactivation by PAI-1 (Figure 1).<sup>13</sup>

Like other fibrinolytic agents, tenecteplase produces fibrinolysis by binding to the fibrin-rich portion of a coronary thrombus. This initiates conversion of plasminogen to plasmin,

resulting in fibrinolysis. *In vitro*, tenecteplase and alteplase are equipotent fibrinolytic agents;<sup>14</sup> however, because of the molecular modification of tenecteplase, its fibrin specificity is 14-fold greater than that of wild-type t-PA (wt-tPA).<sup>13,15</sup> Increased fibrin specificity minimizes systemic plasminogen activation, resulting in a lower incidence of bleeding complications.<sup>13</sup>

The fibrin-rich portion of blood clots is dissolved by plasminogen activators, a process that exposes clot-bound thrombin and, in turn, stimulates platelet aggregation. Attached to the platelet surface, to prevent a blood clot from lysing prematurely, is PAI-1. Platelet aggregation and the release of PAI-1 create a rapid, localized accumulation of PAI-1 in the circulatory system;<sup>16</sup> this action inhibits the dissolution of blood clots and limits the effectiveness of fibrinolytic therapy. Clinical studies suggest that inhibition of PAI-1 may improve the outcome of fibrinolysis.<sup>17</sup>

To help reduce the deleterious effect of PAI-1, tenecteplase was bioengineered to possess an 80-fold greater resistance to inactivation than its parent, wt-tPA.<sup>13</sup> This is supported by an *in vivo* study in which tenecteplase lysed platelet-rich clots more effectively than did wt-tPA.<sup>13</sup> In a small clinical trial, a 30-mg IV bolus dose of tenecteplase was shown to lack procoagulant effects.<sup>18</sup> In contrast, after two hours, thrombin

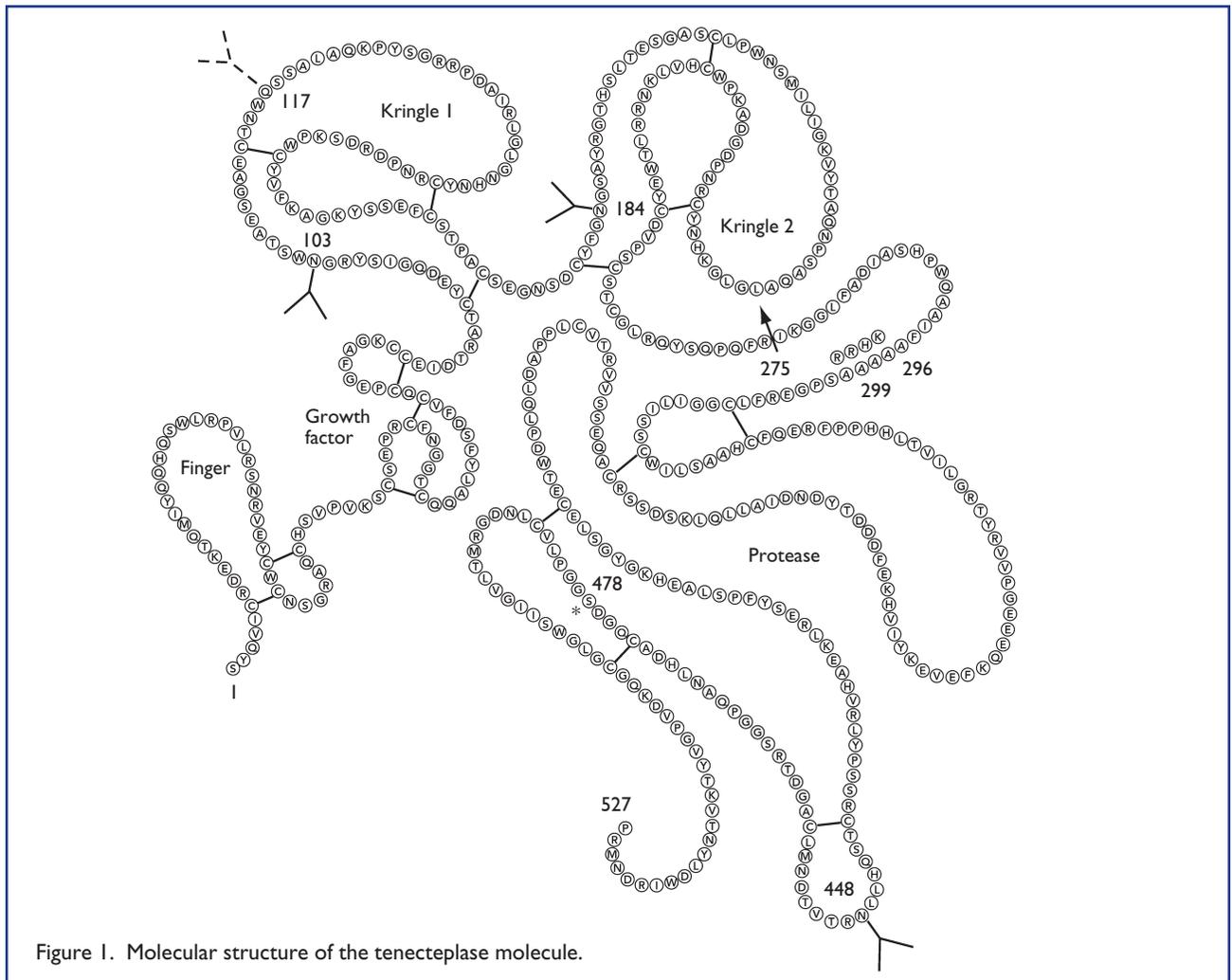


Figure 1. Molecular structure of the tenecteplase molecule.

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formation increased four-fold following streptokinase administration and doubled after alteplase was administered.<sup>18</sup>

### PHARMACOKINETICS

Modi and associates evaluated the pharmacokinetics and pharmacodynamics of single-bolus tenecteplase, compared with alteplase, in a randomized, open-label study of 159 patients.<sup>19</sup> One hundred three patients were randomly assigned to receive 30, 40, or 50 mg of tenecteplase, and 56 patients were assigned to receive 100 mg of accelerated alteplase (Table 3). The mean age of patients was 57 years (range, 31 to 86 years), and the mean weight was 83 kg (range, 48 to 189 kg). Patient demographics were balanced across dose groups except for sex; the 40- and 50-mg groups receiving tenecteplase included three and six women and 23 and 17 men, respectively.

Peak tenecteplase plasma concentrations increased with larger doses and were cleared from the plasma in a biphasic manner. The initial half-life of tenecteplase was 22 minutes, with a terminal phase half-life of 115 minutes. The terminal phase accounted for 66% to 75% of the total area under the curve (AUC) concentration. The initial volume of distribution of tenecteplase was 4.7 liters, and the steady-state volume of distribution was approximately 45% larger, suggesting some extravascular distribution. Mean plasma clearance of tenecteplase was approximately 105 ml/minute across all doses. This clearance rate is four times slower than that of alteplase, thus demonstrating that plasma concentrations of tenecteplase following single-bolus injection provide sustained fibrinolytic concentrations.

### CLINICAL TRIALS

#### TIMI 10A

Tenecteplase has been studied in the treatment of acute myocardial infarction in more than 20,000 patients. An early phase I dose-ranging study, the TIMI 10A trial (n = 113),<sup>20</sup> found that complete reperfusion (TIMI grade 3 flow) was achieved in 59% of patients at a dose of 30 mg and in 64% of patients who received 50 mg of tenecteplase. Patency, defined as TIMI grade 2 or 3 flow, occurred in 85% of patients. Most of these patients (79% to 82%) achieved patency in the occluded vessel within 60 minutes.

The investigators also measured the TIMI frame count, which offers a more quantitative assessment, to assess coronary flow. A TIMI frame count of less than 40, which corresponds with complete reperfusion (TIMI grade 3 flow), was observed in 62% and 68% of patients receiving the 30- and 50-mg doses, respectively.<sup>20</sup> Truly normal coronary flow in the absence of a STEMI, represented by a TIMI frame count of less than or equal to 27, occurred in 45% of patients receiving the 30- and 50-mg doses.

#### TIMI 10B

TIMI 10B, an angiographic and second dose-ranging study, compared a 30-, 40-, or 50-mg single bolus of tenecteplase with front-loaded alteplase.<sup>21</sup> To determine the weight-based dosage, the dose of tenecteplase administered was divided by the patient's weight on admission. Patients were then stratified and evaluated on a milligram-per-kilogram (mg/kg) basis of tenecteplase as follows: (1) low-dose,

0.2 to 0.39 mg/kg; (2) mid-dose, 0.40 to 0.51 mg/kg; and (3) high-dose, 0.52 to 1.24 mg/kg. By 60 minutes, 81% to 82% of patients who received mid-dose to high-dose tenecteplase achieved patency in the occluded artery. Reperfusion (TIMI grade 3 flow) was achieved more often in the patients receiving the high-dose (62.1%) and mid-dose (60.3%) ranges of tenecteplase than in the patients receiving the low-dose range (53.5%), although there was no statistically significant difference among the groups ( $P = .09$ ). The overall efficacy rates observed with tenecteplase were comparable to the reperfusion and patency rates observed with alteplase. Interestingly, flow rates in the non-infarct-related arteries and global flow were significantly improved with high-dose tenecteplase, as measured by the corrected TIMI frame count. Improved global flow rates may yield better outcomes, including lower mortality.<sup>21</sup>

### ASSENT-1

The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-1) trial (Table 4),<sup>23</sup> a major safety study, was conducted in parallel with TIMI 10B. The 30-day mortality rate for tenecteplase was reported to be 6.47% with an ICH rate of 0.77% (Table 4). These results are similar to those reported with front-loaded alteplase in other large clinical trials.<sup>5,12</sup> Data analysis from TIMI 10B, and the phase II safety trial (ASSENT-1) confirmed the safety of tenecteplase and the correlation between body weight, dose, and efficacy.<sup>24</sup> Lower weight-based dosages of tenecteplase were associated with decreased coronary patency, higher rates of reocclusion, and increased mortality.

Based on these data, a weight-adjusted dosing regimen of 0.53 mg/kg was designed for tenecteplase. A schedule, in-

**Table 3 Pharmacokinetics of Tenecteplase and Alteplase in Patients with STEMI**

	Tenecteplase Dose			Alteplase Dose
	30 mg (n = 48)	40 mg (n = 31)	50 mg (n = 20)	100 mg (n = 53)
c(0) (mcg/ml)	10.0 ± 7.3	10.9 ± 11	15.2 ± 12	—
Cl (ml/min)	98.5 ± 42	119 ± 49	99.9 ± 32	435 ± 170
Vc (L)	4.22 ± 2.6	5.43 ± 2.7	4.70 ± 2.6	7.24 ± 4.1
Vss (L)	6.34 ± 3.3	8.01 ± 5.9	6.12 ± 2.4	28.9 ± 22
MRT (min)	62.1 ± 15	63.1 ± 22	60.3 ± 12	61 ± 39
$t_{1/2\alpha}^*$	21.5 ± 8.2	23.8 ± 5.5	20.1 ± 10	—
$t_{1/2\beta}^*$	116 ± 63	129 ± 87	90.4 ± 35	144 ± 100
% AUC $\alpha^*$	72 ± 22	75 ± 16	66 ± 29	—

\* Half-life and % AUC are based on data for patients exhibiting bi-exponential pharmacokinetics.

% AUC = area under the curve associated with the initial phase; c (0) = estimated initial plasma concentration; Cl = plasma clearance; MRT = mean residence time; STEMI = ST-segment elevation myocardial infarction; Vc (L) = initial volume distribution; Vss (L) = steady-state volume of distribution.

From Modi NB, Fox NL, Clow FW, et al. Pharmacokinetics and pharmacodynamics of tenecteplase: Results from a phase II study in patients with acute myocardial infarction. *J Clin Pharmacol* 2000;40: 508-515.<sup>19</sup>

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**Table 4 Adverse 30-Day Drug Events in the ASSENT-1 and ASSENT 2 Trials**

	Mortality	Intracranial Hemorrhage	Total Stroke	Bleeds	
				Major*	Minor
ASSENT-1 (n = 3,325)	6.4%	0.77%	1.5%	1.6%	1.0%
ASSENT-2					
Tenecteplase (n = 8,461)	6.18%	0.93%	1.78%	4.66%	21.76%
Alteplase (n = 8,488)	6.15%	0.94%	1.66%	5.94%	22.99%

\* Major noncerebral bleeding complications were defined as those requiring blood transfusion, intervention because of hemodynamic compromise, or both.

ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic trial.

Data from Van de Werf F, Cannon CP, Luyten A, et al. *Am Heart J* 1999;137:786–791;<sup>23</sup> and the ASSENT-2 Investigators. *Lancet* 1999;354:716–722.<sup>27</sup>

corporating five increments, was devised to assist with dosing (Table 5).<sup>7</sup> Tenecteplase is administered according to the patient's estimated weight—not the patient's actual weight. Dosages are calculated in 10-kg increments. For example, patients weighing less than 60 kg receive a 30-mg dose of tenecteplase.

Determining the correct dosage of tenecteplase in this fashion has been found to be accurate and safe. In the TIMI 10B trial, the total number of errors that changed the dose of tenecteplase (i.e., an incorrect estimate of more than 10 kg) occurred in 2.1% of patients.<sup>25</sup> However, subsequent analysis of the dosing errors revealed that miscalculations of up to 20 kg, or two dosing tiers, did not increase the risk of death or ICH, suggesting that tenecteplase has a wide therapeutic margin.<sup>25</sup> In the larger ASSENT-2 trial, more than 96% of tenecteplase-treated patients received the correct dose, based on their estimated weight.<sup>26</sup>

### ASSENT-2

The ASSENT-2 study was a large, multicenter equivalence trial that compared the efficacy and safety of weight-based tenecteplase dosing with that of accelerated alteplase.<sup>27</sup> All patients received aspirin 150 to 325 mg orally and a weight-adjusted heparin infusion: a 4,000-unit bolus, followed by an infusion of 800 units/hour for patients weighing less than 67 kg and a 5,000-unit bolus and infusion of 1,000 units/hour for patients weighing more than 67 kg (see Table 5).

The ASSENT-2 investigators found overall 30-day mortality rates with tenecteplase (6.18%) and alteplase (6.15%) to be equivalent. The rate of ICH was comparable in the two treatment groups (0.93% with tenecteplase and 0.94% with alteplase), as was the rate of total stroke (1.78% with tenecteplase and 1.66% with alteplase) (see Table 4).

Despite their equivalence in terms of overall 30-day mortality, tenecteplase demonstrated several safety advantages over alteplase. Fewer major bleeding complications (necessitating blood transfusions, intervention because of hemodynamic compromise, or both) were seen with tenecteplase than with alteplase (4.66% vs. 5.94%, respectively,  $P = .0002$ ). The lower number of bleeding complications also fostered a reduced need for blood transfusions in the tenecteplase group

**Table 5 Dosing for Tenecteplase**

Patient Weight (kg)	Tenecteplase (mg)	Volume of Tenecteplase* To Be Administered (ml)
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 80 to < 90	45	9
≥ 90	50	10

\*From one vial of TNKase™, reconstituted with 10 ml of Sterile Water for Injection, USP.

Data from TNKase™ (tenecteplase) package insert. South San Francisco, CA, Genentech, Inc, June 2000.

**Table 6 Noncerebral Bleeding Complications in the ASSENT-2 Trial**

	Tenecteplase (n = 8461)	Alteplase (n = 8488)	P
Bleeding episodes			
Total	26.43%	28.95%	.0003
Major*	4.66%	5.94%	.0002
Minor	21.76%	22.99%	.0553
Units of transfused blood			
Any	4.25%	5.49%	.0002
1–2	2.59%	3.24%	
> 2	1.66%	2.24%	

\*Major noncerebral bleeding complications were defined as those requiring blood transfusion, intervention because of hemodynamic compromise, or both.

ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic trial.

Adapted from ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–722.<sup>27</sup>

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(4.3% vs. 5.5%,  $P = .0002$ ) (Table 6).<sup>27</sup>

Weight-adjusted dosing may also have contributed to lower rates of ICH among at-risk patients, such as older and lightweight women. In tenecteplase-treated women older than age 75 years ( $n = 476$ ), the rate of ICH was 1.3% and 2.5% in the same alteplase-treated subgroup ( $n = 485$ ). Lightweight, elderly women (weighing less than 67 kg and older than age 75) who received tenecteplase ( $n = 264$ ) also experienced fewer ICHs than patients receiving alteplase ( $n = 265$ ) (1.1% vs. 3.0%, respectively).<sup>28</sup>

Subgroup analysis of tenecteplase and alteplase also revealed a significant difference in patients who were treated four hours or more after symptom onset. In these “late presenters,” tenecteplase, compared with alteplase, significantly decreased 30-day mortality rates by an absolute 2%. The investigators suggest that better dissolution of older clots by tenecteplase is attributable to the drug’s high fibrin specificity.<sup>27</sup>

One-year follow-up data from the ASSENT-2 trial confirmed the equivalence of tenecteplase and alteplase. The mortality rates associated with both agents did not differ significantly at one year (10.15% vs. 10.23%).<sup>29</sup>

### FOUNDATION FOR INNOVATION

The goal of improving outcomes in myocardial infarction has led to the development of newer fibrinolytic agents, such as tenecteplase, and the routine use of adjunctive drugs, such as aspirin and heparin, that improve outcomes by accelerating reperfusion and preventing reocclusion.<sup>30</sup> Newer adjunctive antithrombotic agents, such as low-molecular-weight heparins (LMWHs), glycoprotein (GP) IIb/IIIa inhibitors (GPBs), and direct thrombin inhibitors (DTIs), are being investigated.

In the ASSENT-2 equivalence trial, tenecteplase was found to be at least as safe and as effective as alteplase in STEMI patients with respect to 30-day mortality and ICH and to be superior to alteplase in relation to the incidence of major noncerebral bleeding episodes and transfusions.<sup>27</sup> In the Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and TIMI 11B trials, enoxaparin (Lovenox®, Aventis) was shown to be superior to unfractionated heparin in patients with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI).<sup>31,32</sup> The Heparin and Aspirin Perfusion Therapy (HART-2) trial demonstrated that enoxaparin was also safe and effective when combined with alteplase in patients with STEMI.<sup>33</sup> These trials supported the hypothesis that combining these two unique antithrombotic agents had the potential to improve both efficacy and safety outcomes in STEMI patients.

### ASSENT-3

In the ASSENT-3 trial, 6,095 patients with STEMI of less than six hours’ duration were randomly assigned to receive one of three regimens.<sup>34</sup> The specific dosing of the antithrombotic therapy in each arm was as follows:

- *Full-dose single-bolus tenecteplase plus unfractionated heparin.* Patients who were assigned to weight-adjusted IV unfractionated heparin received a bolus of 60 units/kg and a maximum infusion of 1,000 units/hour, adjusted to maintain an activated partial thromboplastin time (aPTT) of 50 to 70 seconds for 48 hours, with

subsequent heparin administration left to the discretion of the treating physician.

- *Full-dose single-bolus tenecteplase plus enoxaparin.* Patients who were assigned to enoxaparin co-therapy received an IV bolus of 30 mg immediately, followed by the first subcutaneous (SQ) dose of 1 mg/kg. This SQ dose was repeated every 12 hours up to hospital discharge or revascularization, with a maximum duration of therapy of seven days. The first two SQ doses could not exceed 100 mg.
- *Half-dose single-bolus tenecteplase plus abciximab plus unfractionated heparin.* Patients who were assigned to abciximab (ReoPro®, Eli Lilly) co-therapy received a 0.25-mg/kg bolus and 0.125 mcg/kg/minute (maximum, 10 mcg/minute) for 12 hours. Because abciximab also exerts an anticoagulant effect, a lower dose of unfractionated heparin was given: 40 unit/kg-bolus (maximum, 3,000 units) followed by 7 units/kg per hour (maximum, 800 units/hour) to achieve a partial thromboplastin time (PTT) between 50 and 70 seconds.

Aspirin (150–325 mg) was given to all patients. IV boluses of unfractionated heparin, enoxaparin, and abciximab were given before the bolus of tenecteplase.

There were two primary endpoints in the trial:

- the composite of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia (*efficacy endpoint*)
- the efficacy endpoint plus in-hospital ICH or in-hospital major bleeding complications at 30 days (*efficacy plus safety endpoint*)

The trial and these endpoints were specifically designed to demonstrate clinical relevance but were not an indication for FDA label enabling. Statistical analysis was by intention to treat, but a statistical hypothesis was not defined *a priori*.

As shown in Table 7, the rates of the primary composite endpoints were lower in patients receiving enoxaparin or abciximab than in those receiving unfractionated heparin. Statistical analysis for full-dose TNK-tPA plus enoxaparin versus full-dose TNK-tPA plus unfractionated heparin resulted in  $P$  values of .0002 and .0037, respectively, for the primary efficacy and the efficacy plus safety composite endpoints. The half-dose TNK-tPA plus abciximab vs. full-dose TNK-tPA plus unfractionated heparin comparisons for the same primary endpoints yielded  $P$  values of less than .0001 and .0142. After correcting for multiple testing (the Bonferroni procedure), conventional significance was reached for the primary efficacy endpoint in the abciximab group ( $P = .0002$ ) but not for the efficacy plus safety endpoint ( $P = .057$ ). Statistical significance was reached in the enoxaparin group for both the efficacy and efficacy plus safety endpoints ( $P = .0009$  and  $P = 0.0146$ , respectively).

Table 8 summarizes the ASSENT-3 trial results in terms of individual endpoints. Although the 30-day mortality was lowest for the enoxaparin group (5.4%), the study was not powered for mortality and did not differ significantly from the findings in the patients receiving abciximab or unfractionated heparin.

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**Table 7 Primary Endpoints in the ASSENT-3 Trial**

Endpoint	Enoxaparin (Lovenox®)	Abciximab (ReoPro®)	Unfractionated Heparin	P
Primary efficacy: 30-day mortality/in-hospital re-infarction or refractory ischemia	11.4%	11.1%	15.4%	.0002 (enoxaparin) <.0001 (abciximab)
Primary efficacy and safety: 30-day mortality/in-hospital re-infarction or refractory ischemia/ in-hospital intracranial hemorrhage or other major bleeding episodes	13.7%	14.2%	17.0%	.0037 (enoxaparin) .01416 (abciximab)

Adapted from ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–722.<sup>27</sup>

In-hospital re-infarction and in-hospital refractory ischemia were significantly lower in the enoxaparin and abciximab groups in contrast to the unfractionated heparin group. From a safety standpoint, the incidence of ICH was 0.9% in all three treatment arms.

Notably, the incidence of other major bleeding was significantly higher (4.3%) in the abciximab group than in the enoxaparin group (3.0%) and in the unfractionated heparin group (2.2%). Overall, the reductions in ischemic complications in the patients receiving enoxaparin were similar to those seen in the patients receiving abciximab, but they were more consistent. There was no increase in the rate of ICH and no excess in thrombocytopenia, but there was a nonsignificant increase in major bleeding complications in the patients receiving enoxaparin. A degree of group crossover in each of the three treatment arms might have affected the efficacy and safety results slightly.

Convenience is a major advantage of using enoxaparin plus full-dose tenecteplase. In the abciximab arm, two infusions (abciximab plus unfractionated heparin) had to be started and three IV boluses (tenecteplase, abciximab, and heparin) had

to be given. The enoxaparin arm involved two simple injections: one of tenecteplase and one of enoxaparin, with no infusions needed. As a result, there were three times as many dosing errors in the abciximab group than in the enoxaparin group. The time-to-lytic was also increased in the abciximab group because of the complexity of the regimen, although the number of composite ischemic events in the primary endpoint was the same without abciximab. The ease of the enoxaparin/tenecteplase regimen also potentially lends itself to use in a pre-hospital setting.

Other fibrinolytic combinations, such as half-dose fibrinolytic plus full-dose GPB in the GUSTO V trial, have been investigated (Table 9).<sup>35</sup>

A study by the World Health Organization found that 28% of all patients with an acute myocardial infarction died within one hour of onset of symptoms.<sup>36</sup> Analysis of the same data noted that more than 50% of all deaths occurred outside the hospital.<sup>37</sup> Treating patients in the prehospital setting has been facilitated somewhat by the advent of double-bolus reteplase, although the second bolus must be administered exactly 30 minutes after the first). Single-bolus tenecteplase, with its even greater ease and speed of administration, may further facilitate the growth of pre-hospital thrombolysis. This approach is currently being studied in the ASSENT-3 Plus substudy, in which another 1,000 patients (not in the U.S.) are to receive either the enoxaparin regimen or the unfractionated heparin regimen in the ambulance. The abciximab arm was not included in the pre-hospital part of the trial because not enough was known about the safety of combining a GPB with a fibrinolytic agent. The results from such trials may provide further insight into how to optimize the early treatment of STEMI.

### DRUG INTERACTIONS

In the tenecteplase clinical trials, heparin and aspirin were routinely administered. In addition, a high proportion of patients in the ASSENT-2 study concomitantly received beta blockers and angiotensin-converting enzyme (ACE) inhibitors. Other medications, including LMWHs, GPBs, ticlopidine, clopidogrel, and statins—although not included in the clinical trial protocol—nevertheless were administered by some physicians.<sup>27</sup> Because data are currently inconclusive regarding the use of tenecteplase in conjunction with adjunctive

**Table 8 Individual Endpoints in the ASSENT-3 Trial**

Endpoint	Enoxaparin (Lovenox®)	Abciximab (ReoPro®)	Unfractionated Heparin	P
30-day mortality	5.4%	6.6%	6.0%	.25
In-hospital re-infarction	2.7%	2.2%	4.2%	.0009
In-hospital refractory ischemia	4.5%	3.2%	6.5%	<.0001
In-hospital intracranial hemorrhage	0.9%	0.9%	0.9%	.98
Other major bleeding	3.0%	4.3%	2.2%	.0005

ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic trial.

Adapted from ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–722.<sup>27</sup>

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Table 9 Other Pharmaceutical Combination Trials

Drug Combination	Trial
GPB + LMWH	A2Z, NICE, ACUTE, TETSTEMI, SINERGY
GPB + LMWH + Lytic	STEMI-SK, ASSENT-3, HART 2
GPB + LMWH + Lytic	ENTIRE, ASSENT-3
GPB + Lytic	TIMI 14, GUSTO V, FASTER, ENTIRE, INTEGRITI
GPB + Lytic + DTI	HERO-2
GPB + DTI	REPLACE
(Pre-hospital) Lytic	ER-TIMI 19, ASSENT-3 PLUS

DTI = direct thrombin inhibitor; GPB = glycoprotein IIb/IIIa inhibitor; LMWH = low-molecular-weight heparin; Lytic = fibrinolytic agent.

agents, such as LMWHs and GPBs, and because of the unpredictability of drug interactions, it is advisable to avoid using untested combinations outside of an investigational trial. Indeed, these agents are not interchangeable; just because one LMWH or GPB works with one fibrinolytic agent does not mean that other agents in the class can work with that fibrinolytic agent.

### DOSAGE AND ADMINISTRATION

The recommended dose of tenecteplase is based on the patient's estimated weight (see Table 5), and the total dose should not exceed 50 mg. A single bolus is administered over five seconds. Tenecteplase is packaged in a 50-mg vial as a lyophilized powder, together with a 10-ml vial of Sterile Water for Injection, USP. Lyophilized tenecteplase can be stored at room temperature or refrigerated. If tenecteplase is not used immediately after it is reconstituted, the solution can be refrigerated and used within eight hours.

The tenecteplase package kit contains a needleless injection system, designed to comply with recent directives to reduce the risk of needle-stick injuries. The enclosed syringe is also compatible with a conventional needle.

### FORMULARY CONSIDERATIONS

Tenecteplase is the first third-generation fibrinolytic agent to be approved by the FDA. It offers the advantage of easy, weight-adjusted, single-bolus administration as well as increased fibrin specificity and PAI-1 resistance. Its 30-day mortality rate is equivalent to that of alteplase, but the safety profile of tenecteplase is better, demonstrating fewer instances of serious noncerebral bleeding and less need for blood transfusions.

The incidence of ICH and total stroke is similar for both alteplase and tenecteplase. The ASSENT-3 trial demonstrated a significant decrease in ischemic events with tenecteplase-combination therapy. In-hospital reinfarction and refractory ischemia occurred less frequently in patients who received enoxaparin or abciximab; these patients also experienced a lower rate of in-hospital deaths and urgent percutaneous coronary interventions.

All of these positive findings support the consideration of tenecteplase-combination therapy, although the trial did show an increase in non-intracranial major bleeding in the abciximab group. Additional phase III combination trials are planned and might enable FDA labeling.

Unlike alteplase, tenecteplase has not yet been extensively investigated for additional indications such as acute ischemic stroke, pulmonary embolism, central venous access device occlusion, or peripheral arterial occlusive disease. The average wholesale price of a tenecteplase kit is approximately equivalent to a 100-mg vial of alteplase or to 20 units of reteplase.

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