Update on Fibrinolytic Therapy: New Treatment Regimens

Series Editor: A. Maziar Zafari, MD, PhD, FACC
Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA,
Staff Cardiologist, Atlanta Veterans Affairs Medical Center, Decatur, GA

Contributors:
Philip R. Huber, MD
Cardiology Fellow, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA,
Atlanta Veterans Affairs Medical Center, Decatur, GA

Mark E. Leimbach, MD
Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA,
Atlanta Veterans Affairs Medical Center, Decatur, GA

Table of Contents

Introduction ........................................... 2
Case Patient 1 ........................................ 2
Next-Generation Fibrinolytic Agents ......... 3
Adjunctive Therapy ................................. 6
Summary Points ...................................... 10
References ........................................... 11

Cover Illustration by Christie Grams

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Endorsed by the Association for Hospital Medical Education

The Association for Hospital Medical Education endorses HOSPITAL PHYSICIAN for the purpose of presenting the latest developments in medical education as they affect residency programs and clinical hospital practice.

Copyright 2002, Turner White Communications, Inc., 125 Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications, Inc. The editors are solely responsible for selecting content. Although the editors take great care to ensure accuracy, Turner White Communications, Inc., will not be liable for any errors of omission or inaccuracies in this publication. Opinions expressed are those of the authors and do not necessarily reflect those of Turner White Communications, Inc.


I. INTRODUCTION

Fibrinolytic therapy emerged from the large “mega-trials” in the 1980s and 1990s as the mainstay of treatment in acute myocardial infarction (MI). It has clearly resulted in a significant reduction in mortality when compared with previous standard therapy (eg, prolonged bedrest, nitrates, and occasional heparin). Despite the success of traditional fibrinolytic agents (ie, tissue plasminogen activator [t-PA] and streptokinase), these agents still have their shortcomings. Unsuccessful reperfusion still occurs in 20% of patients, and restoration of normal coronary artery blood flow is only achieved in about 50% of patients. After successful fibrinolysis, a small subset of patients will experience reocclusion of the infarct-related artery within hours to days. Bleeding complications with fibrinolytic therapy, including intracranial hemorrhage, remain an additional concern. Also, infusion regimens of some of the traditional fibrinolytics are complex.

To address some of these shortcomings, numerous attempts have been made to improve on current therapy. Newer fibrinolytic agents have been developed to ease administration, potentially improve reperfusion rates, and possibly decrease the rate of bleeding complications. The utilization of various agents in combination with fibrinolytic therapy has also been studied in an effort to achieve more complete thrombolysis.

This is the second part of a 2-part review on fibrinolytic therapy. The first part emphasized the early “mega-trials” that laid the groundwork for fibrinolytic use in acute MI (see “Update on Fibrinolytic Therapy: Mega-Trials” in the Hospital Physician Cardiology Board Review Manual, Volume 8, Part 2). This second part discusses the use of newer generation fibrinolytic agents and examines more recent adjunctive therapies to fibrinolytic therapy, including platelet glycoprotein IIb/IIIa inhibitors, low-molecular-weight (LMW) heparins, direct thrombin inhibitors, and thienopyridines. A case patient will be provided to highlight features of adjunctive therapy to fibrinolytic therapy in acute MI.

II. CASE PATIENT 1

PRESENTATION

Patient 1 is a 66-year-old woman who presented to the emergency department 45 minutes after developing severe chest heaviness at work. Except for some mild chest pain that morning (3 hours ago), she has no history of chest pain. Her medical history is significant for type 2 diabetes, diagnosed 6 months ago, and hypercholesterolemia, which is treated with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor. At work, she had taken 2 nitroglycerin tablets (obtained from a colleague) without relief. On physical examination, patient 1 is moderately obese and somewhat anxious. She has a blood pressure of 105/60 mm Hg, a heart rate of 95 bpm, and a respiratory rate of 22 breaths per minute. There is no jugular venous distention. Her chest is clear. The cardiac examination is notable for a II/VI systolic ejection murmur at the upper sternal border. The remainder of the physical examination is within normal limits. An electrocardiogram (ECG) shows normal sinus rhythm with 2 to 3 mm of ST-segment elevation in the inferior leads and 1 to 2 mm of ST-segment depression in leads V1 through V4 (Figure 1). She is treated with aspirin, unfractionated heparin, supplemental oxygen, and a β-blocker.

- Which of the following would be the most appropriate therapy for patient 1 at this point?

A) Administer a glycoprotein IIb/IIIa inhibitor and transfer to the coronary care unit for close monitoring
B) Administer tenecteplase (TNK-t-PA, 40-mg intravenous [IV] bolus)
C) Order a ventilation-perfusion lung scan and continue current therapy
D) Transfer without further medications to a tertiary care facility 2 hours away for cardiac catheterization
**Discussion**

The correct answer is B. Patient 1 has an acute inferior MI, possibly with posterior involvement, manifested by ST-segment elevation in the inferior leads and ST-segment depression in leads V1 through V3 on the ECG. She is a candidate for reperfusion therapy. Because a catheterization facility is not readily available, the best option is to administer fibrinolytic therapy. TNK-t-PA, a next-generation fibrinolytic agent derived from t-PA, is an acceptable choice. Glycoprotein IIb/IIIa inhibitors, although frequently used in acute coronary syndromes, are never the sole therapy in patients with acute ST-segment elevation MI. A ventilation-perfusion lung scan, performed for evaluation of pulmonary embolism, is not indicated in this setting.

**PATIENT 1 TREATMENT**

Patient 1 is subsequently treated with TNK-t-PA. Her post-MI course is uneventful. She undergoes a cardiac catheterization on hospital day 4 that shows a residual 70% lesion in the middle portion of the right coronary artery as well as a calcified 80% bifurcation lesion involving the left anterior descending coronary artery and the first diagonal branch. Patient 1 undergoes coronary artery bypass grafting (CABG) on hospital day 5 and is discharged from the hospital on day 10.

**III. NEXT-GENERATION FIBRINOLYTIC AGENTS**

Despite its efficacy in treatment of acute MI, front-loaded t-PA has limited uses. First, t-PA has a short half-life, which requires a complex infusion regimen. This regimen theoretically may lengthen the “door to drug” time, increasing the potential for human error in administration. In the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, 12% of patients receiving fibrinolytic therapy (streptokinase or t-PA) had a medication error; those with a medication error had a significantly higher 30-day mortality (7.7% versus 5.5% with t-PA, 11.3% versus 6.4% with streptokinase; \( P < 0.001 \)). Subsequently, newer fibrinolytic agents with longer half-lives have been bioengineered from t-PA. A diagram of t-PA and some of its mutant forms is shown in Figure 2. Alterations in 3 regions (the fibronectin finger, the Kringle-1, and the epidermal growth factor domains) cause the prolongation of the half-life. A longer half-life leads to simpler dosing regimens that let these drugs be given as a single or double bolus. Because of its ease of delivery, bolus fibrinolytic therapy may shorten “door to drug” times and decrease the number of medication errors. However, alterations prolonging the half-life generally decrease fibrin specificity. Less fibrin-specific agents result in systemic conversion of plasminogen to plasmin, which can deplete fibrinogen, plasminogen, factor V, and factor VIII levels. Thus, using less fibrin-specific agents may cause a hypocoagulable state, with the potential for more bleeding.

Another limitation of fibrinolytic therapy is unsuccessful reperfusion. One factor that is known to contribute to unsuccessful reperfusion is the presence of endogenous plasminogen inhibitors. Plasminogen inhibitors, predominantly plasminogen activator inhibitor-1 (PAI-1), counteract the effects of t-PA and contribute to delays in reperfusion or lead to reocclusion after initially successful reperfusion. To overcome the effect of plasminogen inhibitors, t-PA can be altered so that it is less susceptible to these inhibitors. For example, the substitution of 4 amino acids in the protease domain of t-PA leads to enhanced PAI-1 resistance for the t-PA variant, TNK-t-PA.
Three variants of t-PA have been evaluated in clinical trials: reteplase, lanoteplase, and TNK-t-PA. The results of these trials will be discussed in the next 3 sections.

RETEPLASE

Reteplase (also called r-PA) is a single-chain-deletion mutant of t-PA that lacks the fibronectin finger, epidermal growth factor, and Kringle-1 domains. It is administered as a double bolus (30 minutes apart), is both hepatically and renally excreted, and is somewhat less fibrin specific than t-PA. The INJECT (International Joint Efficacy Comparison of Thrombolytics) trial demonstrated the equivalence of reteplase to streptokinase. More than 6000 patients with acute MI within 12 hours of symptom onset were randomly assigned either to double-bolus reteplase (2 doses of 10 million units, 30 minutes apart) or to streptokinase (1.5 million units over 1 hour). Mortality at 6 months was similar between the 2 groups.

The RAPID (Reteplase Angiographic Phase II International Dose-finding) trials were angiographic trials comparing reteplase with t-PA. The RAPID-1 trial examined 3 dosing strategies for reteplase compared with t-PA conventional dosing (10-mg bolus, then 50 mg over 1 hour followed by 40 mg over 2 hours) in 606 patients within 6 hours of MI. The double-bolus reteplase regimen (2 doses of 10 million units, 30 minutes apart) was associated with higher TIMI (Thrombolysis in Myocardial Infarction) grade-3 patency (ie, achievement of normal coronary artery blood flow determined by coronary angiography using criteria from the TIMI trial) at 90 minutes than t-PA (63% versus 49%; \( P = 0.019 \)).

The double-bolus regimen of reteplase (2 doses of 10 million units, 30 minutes apart) from RAPID-1 was then compared to front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour) in the RAPID-2 trial. More than 300 patients within 12 hours of acute MI were evaluated with serial angiograms. Similar to RAPID-1, reteplase was associated with higher TIMI grade-3 patency at 90 minutes than t-PA.
front-loaded t-PA (60% versus 45%; \(P = 0.011\)). Transfusion rates and hemorrhagic stroke were similar between the 2 groups.\(^{10}\)

The GUSTO-III trial assessed whether the improvement in TIMI grade-3 patency demonstrated with reteplase over front-loaded t-PA would translate into improved mortality. More than 15,000 patients with acute Ml within 6 hours of symptom onset were randomly assigned either to double-bolus reteplase (2 doses of 10 million units, 30 minutes apart) or to front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour) in a 2:1 fashion (ie, 2 patients randomized to reteplase for every patient randomized to t-PA). However, the 30-day mortality was equivalent for reteplase and t-PA (7.47% for reteplase versus 7.24% for t-PA; \(P = \text{not significant} [\text{NS}]\)). Stroke rates were similar between the 2 groups (1.64% with reteplase, 1.79% with t-PA; \(P = \text{NS}\)).\(^{11}\) The GUSTO-IV trial demonstrated that the relationship between infarct-vessel patency and mortality was more complex than initially perceived.

**TENECTEPLASE**

TNK-t-PA results from the modification of t-PA at 3 sites (Figure 2): threonine is replaced by asparagine in position 103, which adds a glycosylation site in Kringle-1; asparagine is replaced by glutamine in position 117, which removes a glycosylation site from Kringle-1; and 4 amino acids in the protease domain are replaced by alanines (this enhances fibrin-specificity and increases resistance to PAI-1). TNK-t-PA is administered as a single bolus, is heparically excreted, and is the most fibrin-specific of the t-PA variants.\(^{12}\)

The TIMI-10B trial was an angiographic trial of more than 800 patients comparing various doses of TNK-t-PA (30-mg or 50-mg bolus) with front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour). The 50-mg dose of TNK-t-PA was discontinued because of an increased rate of intracranial hemorrhage and was replaced by a 40-mg dose. The 40-mg bolus of TNK-t-PA achieved similar rates of TIMI grade-3 patency at 90 minutes when compared with front-loaded t-PA (62.8% versus 62.7%; \(P = 0.99\)).\(^{12}\)

Because of the increased bleeding complications associated with the 50-mg dose in the TIMI-10B trial, the ASSENT-1 (Assessment of the Safety and Efficacy of a New Thrombolytic: TNK-t-PA) was set up as a safety trial to further assess the risk of intracranial hemorrhage with TNK-t-PA. This trial led to a weight-based dosing regimen of TNK-t-PA and to alterations in heparin dosing, which were associated with lower rates of intracranial hemorrhage (0.77% overall; 95% confidence interval, 0.50%-1.14%).\(^{13}\)

The ASSENT-2 trial was designed to assess whether mortality was equivalent between TNK-t-PA and t-PA. More than 16,000 patients who presented within 6 hours of MI symptom onset were randomly assigned either to TNK-t-PA (0.53 mg/kg bolus, ranging from 30 to 50 mg) or to front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour). Thirty-day mortality was equivalent between the 2 groups (6.17% for TNK-t-PA and 6.15% for front-loaded t-PA). Similar rates of stroke and intracranial hemorrhage were observed in the 2 treatment groups, but fewer noncerebral bleeding complications occurred with TNK-t-PA (26.4% versus 29.0%; \(P < 0.001\)) and fewer blood transfusions (4.25% versus 5.49%; \(P < 0.002\)).\(^{14}\)

**LANOTEPLASE**

Lanoteplase (also called n-PA) lacks the fibronectin finger and epidermal growth factor domains; it also lacks a glycosylation site in the first Kringle domain as a result of a glutamine substitution for asparagine in position 117 (Figure 2). Lanoteplase has a substantially longer half-life than t-PA and is administered as a single bolus. It is heparically excreted and is less fibrin-specific than t-PA.\(^{15}\)

Similar to reteplase and tenecteplase, lanoteplase also was tested against front-loaded t-PA in an angiographic trial to assess infarct-vessel patency. More than 600 patients in the InTIME-1 (Intravenous n-PA for Treatment of Infarcting Myocardium Early) trial received lanoteplase (doses ranged from 15 to 120 kilo units [kU]/kg) or front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour). The primary endpoint, TIMI grade-3 flow in the infarct-related artery at 60 minutes, was increased in the group receiving 120 kU/kg of lanoteplase (47% versus 37%; \(P = 0.001\)). Major and moderate bleeding were similar between lanoteplase and t-PA.\(^{16}\)

The InTIME-2 trial evaluated more than 15,000 patients with suspected MI with lanoteplase (120 kU/kg single bolus) or front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour). The 30-day mortality data were similar between the 2 groups (6.75% for lanoteplase and 6.61% for t-PA), demonstrating equivalence of lanoteplase and t-PA. Of concern, although the overall incidence of stroke was similar in the 2 groups, the lanoteplase group had a significantly higher incidence of intracranial hemorrhage (1.12% versus 0.64%; \(P = 0.004\)).\(^{17}\) As a result, further development of lanoteplase has been halted.

To summarize, improved TIMI grade-3 patency rates at 60 and 90 minutes (with reteplase and lanoteplase)
have not translated into decreased mortality when compared with front-loaded t-PA. All 3 variants of t-PA (reteplase, lanoteplase, and TNK-t-PA) are similar to front-loaded t-PA in regard to mortality; however, the increased rate of intracranial hemorrhage with lanoteplase has halted further development of this agent. Reteplase and TNK-t-PA appear to be as safe as front-loaded t-PA; given their ease of administration, these next-generation fibrinolytic agents are becoming an integral part of modern fibrinolytic therapy.

### IV. ADJUNCTIVE THERAPY

Aspirin and unfractionated heparin have been the mainstay of adjunctive therapy in fibrinolytic trials. Although traditional regimens are undoubtedly beneficial, they are unable to establish optimal reperfusion in a number of patients. In recent years, several trials have evaluated the adjunctive use of various agents in an attempt to improve on current fibrinolytic therapy (Table 1).

#### PLATELET GLYCOPROTEIN IIb/IIIa INHIBITORS

Coronary thrombus is comprised of so-called platelet-rich “white” thrombus and fibrin-rich “red” thrombus. Thrombolytics only address part of the problem; they break up the fibrin-rich red thrombus, but they do not target the white thrombus (this is why fibrinolytics is a more accurate term). By breaking up fibrin strands, fibrinolytics leave thrombin exposed, which in turn induces a prothrombotic state. Exposed thrombin leads to the production of more thrombin and is a powerful stimulant of platelet aggregation. By using platelet glycoprotein IIb/IIIa inhibitors together with reduced doses of fibrinolytics, both platelets and fibrin are targeted, conceptually leading to a more complete thrombolysis.

Several small studies have evaluated platelet glycoprotein IIb/IIIa inhibitors and fibrinolytic agents in combination therapy. In the TIMI-14 trial, the combination of abciximab (0.25 mg/kg bolus followed by 12-hour infusion of 0.125 µg/kg per min) and half-dose t-PA (15-mg bolus, then 35 mg over 1 hour) was associated with improved TIMI grade-3 patency rates at 90 minutes (77% versus 62%; \( P = 0.02 \)) compared with front-loaded t-PA.\(^{10}\) Improvement in TIMI grade-3 patency at 90 minutes also was seen with Integrifil (eptifibatide, 180 µg/kg bolus, followed by 0.75 µg/kg per min infusion) and front-loaded t-PA (15-mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour) when compared with front-loaded t-PA alone (66% versus 39%; \( P = 0.006 \)) in the IMPACT-AMI (Integrifil to Manage Platelet Aggregation to Combat Thrombosis in Acute MI) trial.\(^{19}\)

Abciximab (0.25 mg/kg bolus followed by 12-hour infusion of 0.125 µg/kg per min) and half-dose reteplase (2 doses of 5 million units, 30 minutes apart) showed similar improvement in 60-minute TIMI grade-3 patency (62% versus 48%) when compared with reteplase alone (2 doses of 10 million units, 30 minutes apart) in the GUSTO-IV pilot study, SPEED (Strategies for Patency Enhancement in the Emergency Department).\(^{20}\)

The GUSTO-V trial was the first large-scale trial to evaluate the combination of a platelet glycoprotein IIb/IIIa inhibitor with a reduced dose of a fibrinolytic agent in the treatment of acute MI. The trial randomly assigned more than 16,000 patients presenting within the first 6 hours of MI either to standard-dose reteplase (2 doses of 10 million units, 30 minutes apart) or to half-dose reteplase (2 doses of 5 million units, 30 minutes apart) plus full-dose abciximab (0.25 mg/kg bolus followed by 12-hour infusion of 0.125 µg/kg per min). The primary endpoint of 30-day mortality was 5.9% in the standard-dose reteplase group and 5.6% in the reteplase/abciximab combination group (\( P = 0.43 \)); the combination group with abciximab was thus shown to be equivalent to standard-dose reteplase. Secondary outcomes (such as reinfarction, ventricular fibrillation, and third-degree heart block) were significantly reduced in the abciximab group. Although the overall rate of stroke was similar between the 2 groups, a trend towards increased intracranial hemorrhage was noted in the abciximab group in patients older than 75 years (2.1% versus 1.1%; \( P = 0.069 \)). Overall bleeding was markedly increased in the abciximab group (24.6% versus 13.7%; \( P < 0.001 \)). Also, thrombocytopenia was increased with abciximab (2.9% versus 0.7%; \( P = 0.001 \)).\(^{21}\)

The ASSENT-3 trial randomly assigned more than 6000 patients presenting within 6 hours of MI to 1 of 3 treatment arms: (1) full-dose TNK-t-PA (30 to 50 mg, based on patient weight) with enoxaparin (30 mg IV followed by 1 mg/kg subcutaneously [SC] every 12 hours for 7 days); (2) half-dose TNK-t-PA (15 to 25 mg, based on patient weight) with abciximab (0.25 mg/kg bolus followed by 12-hour infusion of 0.125 µg/kg per min) and unfractionated heparin; or (3) full-dose TNK-t-PA with unfractionated heparin (control group). The primary efficacy endpoint was a composite of 30-day mortality, in-hospital reinfarction, and in-hospital refractory ischemia. Compared with the control group (full-dose TNK-t-PA with unfractionated heparin, 15.4%), significantly fewer adverse events were observed in the enoxaparin (11.4%) and abciximab (11.1%) arms (\( P = 0.0001 \)). This finding was attributable to less reinfarction and less refractory ischemia in the
enoxaparin and abciximab groups. No difference was noted in the rate of intracranial hemorrhage among the 3 groups. Major bleeding was highest in the abciximab arm (4.3%), was 3.0% in the enoxaparin arm, and was lowest in the control group (full-dose TNK-t-PA with unfractionated heparin, 2.2%; \( P = 0.0005 \)). In patients older than 75 years, major bleeding complications were 3 times as likely in the abciximab group when compared with the unfractionated heparin control group. The abciximab group was also associated with more thrombocytopenia (3.2%) than the enoxaparin group (1.2%) and the control group (full-dose TNK-t-PA with unfractionated heparin, 1.3%; \( P < 0.0001 \)).

Tables 2 and 3 respectively review the efficacy endpoints and bleeding complications from the ASSENT-3 trial.

Based on these 2 large trials (GUSTO-V and ASSENT-3), the role of combination therapy with platelet glycoprotein IIb/IIIa inhibitors and fibrinolytics remains unclear. Although mortality seems to be equivalent when this combination is compared with standard fibrinolytic therapy, this comes at the expense of increased bleeding and increased thrombocytopenia. At the very least, the combination of platelet glycoprotein IIb/IIIa inhibitors and fibrinolytic agents should be avoided in elderly persons. When compared with standard fibrinolytic therapy, given the lack of benefit and the increased bleeding risk, questions remain whether this combination in acute MI using current dosing is worthwhile in any patient group.
LOW-MOLECULAR-WEIGHT HEPARIN

LMW heparins (eg, enoxaparin, dalteparin) are worthwhile to assess in combination with fibrinolytic agents given their ease of administration; after a subcutaneous injection, no infusion is needed and activated partial thromboplastin times (aPTT) do not need to be monitored. Several small trials have evaluated the use of LMW heparin with fibrinolytic therapy. The HART-2 (Second Trial of Heparin and Aspirin Reperfusion Therapy) trial was an angiographic study that demonstrated the equivalence of enoxaparin (30-mg IV bolus, then 1 mg/kg SC every 12 hours) with unfractionated heparin in 90-minute patency rates when used as adjunctive therapy to front-loaded t-PA in 400 patients. The 90-minute patency rates were 80.1% with enoxaparin and 75.1% with unfractionated heparin. A trend toward less reocclusion in the enoxaparin group was noted.23

The AMI-SK (Acute Myocardial Infarction—Streptokinase) trial evaluated enoxaparin (30-mg IV bolus, then 1 mg/kg SC every 12 hours) and streptokinase (1.5 million units over 1 hour) compared with streptokinase and placebo in nearly 500 patients with acute MI. The primary endpoint, TIMI grade-3 flow at 5 to 10 days, was significantly improved in the enoxaparin group (70% versus 58%; \( P = 0.01 \)). A 36% reduction in the composite endpoint of death, reinfarction, and recurrent angina was observed at 30 days (13.4% versus 21%; \( P \) value not reported) in the enoxaparin group. A trend toward increased bleeding was noted in the enoxaparin group (4.8% versus 2.8%; \( P = 0.2 \)).25 This is the first study to report an improvement in clinical outcomes by adding LMW heparin to streptokinase in patients with acute MI. Two other small trials, the FRAMI (Fragmin in Acute Myocardial Infarction) study and the BIOMACS-II (Biochemical Markers in Acute Coronary Syndromes) study have demonstrated a trend toward improved clinical outcomes with dalteparin and streptokinase; however, in the FRAMI study, bleeding complications significantly increased with dalteparin.26,27 Prior data have failed to show an improvement when

### Table 2. Frequency of Composite and Single Endpoints at Hospital Discharge and at 30 Days from the ASSENT-3 Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Enoxaparin ( (n = 2040)^* )</th>
<th>Abciximab ( (n = 2017)^† )</th>
<th>Unfractionated Heparin or Control ( (n = 2038)^‡ )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy endpoint (30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia)</td>
<td>233/2037 (11.4%)</td>
<td>223/2017 (11.1%)</td>
<td>314/2038 (15.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Efficacy plus safety endpoints (efficacy + in-hospital ICH or in-hospital major bleeding [other than ICH])</td>
<td>280/2037 (13.8%)</td>
<td>287/2016 (14.2%)</td>
<td>347/2036 (17.0%)</td>
<td>0.0081</td>
</tr>
<tr>
<td>Death at 30 days</td>
<td>109/2037 (5.4%)</td>
<td>133/2017 (6.6%)</td>
<td>122/2038 (6.0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>In-hospital reinfarction</td>
<td>54/2040 (2.7%)</td>
<td>44/2017 (2.2%)</td>
<td>86/2038 (4.2%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>In-hospital refractory ischemia</td>
<td>93/2040 (4.6%)</td>
<td>64/2017 (3.2%)</td>
<td>132/2038 (6.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>In-hospital ICH</td>
<td>18/2040 (0.9%)</td>
<td>19/2017 (0.9%)</td>
<td>19/2038 (0.9%)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Note that this group was given full-dose TNK-t-PA with enoxaparin, see text for specific doses.
†Note that this group received half-dose TNK-t-PA with abciximab and unfractionated heparin, see text for specific doses.
‡Note that this control group received full-dose TNK-t-PA with unfractionated heparin, see text for specific doses.

Adapted with permission from The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-3) Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:608.
unfractionated heparin plus streptokinase is compared with streptokinase alone;28 thus, current guidelines do not recommend the use of unfractionated heparin with streptokinase.29 In contrast to unfractionated heparin, these results suggest that LMW heparin may be beneficial when used in combination with streptokinase; more data are needed to resolve the issue.

The ASSENT-3 trial was the first large-scale trial evaluating the combination of a LMW heparin with fibrinolytic therapy. As mentioned previously, this trial randomly assigned patients to 1 of 3 treatment groups: full-dose TNK-t-PA with enoxaparin, half-dose TNK-t-PA with abciximab and unfractionated heparin, or full-dose TNK-t-PA with unfractionated heparin (control group).

### Table 3. Rate of In-Hospital Thrombocytopenia and Noncerebral Bleeding Complications from the ASSENT-3 Trial

<table>
<thead>
<tr>
<th>Complication</th>
<th>Enoxaparin (n = 2040)*</th>
<th>Abciximab (n = 2017)†</th>
<th>Unfractionated Heparin or Control (n = 2038)‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20,000 cells/µL</td>
<td>2/2040 (0.1%)</td>
<td>10/2017 (0.5%)</td>
<td>3/2038 (0.2%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>20,000–50,000 cells/µL</td>
<td>4/2040 (0.2%)</td>
<td>13/2017 (0.6%)</td>
<td>4/2038 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>50,000–100,000 cells/µL</td>
<td>18/2040 (0.9%)</td>
<td>41/2017 (2.0%)</td>
<td>20/2038 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Any thrombocytopenia</td>
<td>24/2040 (1.2%)</td>
<td>64/2017 (3.2%)</td>
<td>27/2038 (1.3%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Bleeding episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>522/2040 (25.6%)</td>
<td>801/2017 (39.7%)</td>
<td>429/2038 (21.1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Major</td>
<td>62/2040 (3.0%)</td>
<td>87/2016 (4.3%)</td>
<td>44/2035 (2.2%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minor</td>
<td>460/2040 (22.6%)</td>
<td>713/2016 (35.3%)</td>
<td>381/2035 (18.7%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>70/2040 (3.4%)</td>
<td>84/2017 (4.2%)</td>
<td>47/2038 (2.3%)</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic: TNK-t-PA; TNK-t-PA = tenecteplase.

*Note that this group was given full-dose TNK-t-PA with enoxaparin, see text for specific doses.

†Note that this group received half-dose TNK-t-PA with abciximab and unfractionated heparin, see text for specific doses.

‡Note that this control group received full-dose TNK-t-PA with unfractionated heparin, see text for specific doses.

Adapted with permission from The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-3) Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:611.

Whereas unfractionated heparin was used in the abciximab arm of the ASSENT-3 trial, the combination of a LMW heparin together with a glycoprotein IIb/IIIa inhibitor and a fibrinolytic agent was recently reported in the phase-2 ENTIRE-TIMI 23 (Enoxaparin and TNK-t-PA with or without glycoprotein IIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation MI) trial.30 More than 450 patients were randomly assigned to full-dose TNK-t-PA or to half-dose TNK-t-PA plus abciximab. Patients were then further randomized to various regimens of unfractionated heparin or enoxaparin. Similar efficacy was observed in the primary endpoint of TIMI grade-3 patency at 60 minutes, which was approximately 50% in all treatment groups. Although rates of major hemorrhage were higher among those receiving abciximab, no difference in bleeding rates was noted between enoxaparin and unfractionated heparin.30

Given the current efficacy and safety data as well as the ease of administration, use of LMW heparins with fibrinolytics is expanding into large phase-3 trials.
• Which of the following combination therapies has shown benefit when compared with standard fibrinolytic therapy in recent clinical trials?

A) Administration of full-dose TNK-t-PA (30 to 50 mg based on weight) with enoxaparin (30 mg IV then 1 mg/kg SC every 12 hours) substituted for unfractionated heparin

B) Administration of half-dose TNK-t-PA (15 to 25 mg based on weight) with enoxaparin (30 mg IV then 1 mg/kg SC every 12 hours) substituted for unfractionated heparin

C) Administration of full-dose abciximab (0.25 mg/kg bolus then 12-hour infusion of 0.125 µg/kg per min) and full-dose reteplase (2 doses of 10 million units, 30 minutes apart)

D) Administration of half-dose abciximab (0.125 mg/kg bolus then 12-hour infusion of 0.0625 µg/kg per min) and full-dose reteplase (2 doses of 10 million units, 30 minutes apart).

Discussion

The correct answer is A. Full-dose TNK-t-PA (30 to 50 mg depending on weight) with enoxaparin (30 mg IV followed by 1 mg/kg SC every 12 hours) was one of the treatment arms in the ASSENT-3 trial.22 Whenever fibrinolytic agents are used with heparin (unfractionated or LMW heparin) or with direct thrombin inhibitors, the full dose of the fibrinolytic agent is given. In contrast, when used with platelet glycoprotein IIb/IIIa inhibitors, the dose of the fibrinolytic agent is halved to decrease the risk of bleeding complications. Although combination therapy in fibrinolysis has been evaluated extensively (ie, use of LMW heparin or platelet glycoprotein IIb/IIIa inhibitors together with fibrinolytic agents), at this point none of the combination therapies is approved by the Food and Drug Administration.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors (such as hirudin, bivalirudin) may be useful because they directly bind to thrombin without requiring other cofactors. Initial studies with these agents when used together with fibrinolytics showed excessive bleeding complications, including intracranial hemorrhage.31,32 Subsequently, doses were adjusted for completion of the trials.

GUSTO-IIb evaluated hirudin (0.1 mg/kg IV bolus, then 0.1 mg/kg per hr) versus unfractionated heparin in combination with fibrinolytic use (streptokinase or t-PA). In more than 1000 patients receiving streptokinase, a reduction in a 30-day composite endpoint of death or reinfarction was noted in those receiving hirudin (8.6% versus 14.4%; P < 0.004).33

In contrast to GUSTO-IIb, TIMI-9b did not show that hirudin was better than heparin when combined with fibrinolytic therapy (streptokinase or t-PA). The combined primary endpoint of death, recurrent MI, severe heart failure, or cardiogenic shock occurred in 11.9% with heparin versus 12.9% with hirudin (P=NS).34

The HERO-1 (Hirulog Early Reperfusion/Occlusion) trial was an angiographic trial that showed improved infarct-vessel patency with Hirulog (bivalirudin) compared with heparin as adjunctive therapy to streptokinase.35 These results prompted the HERO-2 trial, which randomly assigned more than 17,000 patients either to unfractionated heparin or to bivalirudin in combination with streptokinase. Whereas the primary endpoint of 30-day mortality was similar in both groups (10.8% with bivalirudin and 10.9% with unfractionated heparin; P = 0.876), significantly less reinfarction was noted in the bivalirudin group (3.5% versus 4.5%; P < 0.001). A trend toward increased bleeding also was observed with bivalirudin, but this did not reach statistical significance.36

THIENOPYRIDINES

The thienopyridines, clopidogrel and ticlopidine, inhibit ADP-dependent platelet activation. Although their use in non-ST-segment-elevation acute coronary syndromes37 and in secondary prevention of MI38,39 is encouraging, minimal data are available regarding their use in the setting of acute MI.40 The Second Chinese Cardiac Study (CCS-2) is a large-scale trial that is currently evaluating the addition of clopidogrel to aspirin in patients with acute MI.40

V. SUMMARY POINTS

• Newer fibrinolytic agents have been developed to simplify dosing regimens and to potentially improve reperfusion rates.

• The improved TIMI grade-3 patency rates at 60 and 90 minutes with bolus-fibrinolytic agents have not translated into improved mortality when compared with front-loaded t-PA.

• Given their ease of administration and comparable efficacy to t-PA, bolus-fibrinolytic agents (such as reteplase and tenecteplase) are becoming an integral part of modern fibrinolytic therapy.

• Coronary thrombus is comprised of platelet-rich “white” thrombus and fibrin-rich “red” thrombus; fibrinolytic agents break up the fibrin-rich red thrombus but do not specifically target the white thrombus.
• Adjunctive therapy targeting the white thrombus, when used with fibrinolytic agents, could theoretically lead to more complete thrombolysis.
• Although the combination of platelet glycoprotein IIIb/IIIa inhibitors and fibrinolytic agents appears to be equivalent to standard fibrinolytic therapy in terms of mortality, this improvement comes at the expense of increased bleeding and increased thrombocytopenia; thus, the role of this combination therapy remains unclear.
• The combination of a LMW heparin and a fibrinolytic agent appears to reduce the ischemic complications of acute MI without increasing the rate of intracranial hemorrhage or thrombocytopenia.
• When used with fibrinolytic agents in acute MI, direct thrombin inhibitors have failed to show a mortality benefit when compared with unfractionated heparin.
• Further adjunctive therapies to fibrinolytic agents in acute MI, such as thienopyridine use, continue to be explored.

REFERENCES


