Update on Fibrinolytic Therapy: Mega-Trials

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Update on Fibrinolytic Therapy: Mega-Trials

Philip R. Huber, MD, and Mark E. Leimbach, MD

I. INTRODUCTION

The management of acute myocardial infarction (MI) has changed dramatically during the past 20 years. Much of this change has occurred because of a better understanding of the underlying pathophysiology of MI, which involves thrombosis of a coronary artery. Improved understanding of the cause of MI has led to the development and use of treatments designed to restore coronary flow. A mainstay of these treatments is the development of fibrinolytic agents designed to lyse the obstructing coronary thrombus. The use of fibrinolytic agents has brought about a significant reduction in mortality from MI.

Fibrinolysis occurs when plasminogen is converted to plasmin, which then degrades fibrin (Figure 1). Fibrinolytic agents can be fibrin-specific, such as tissue plasminogen activator (t-PA), or relatively nonspecific, such as streptokinase. The fibrin-specific agents activate plasminogen at the fibrin surface, whereas the nonspecific fibrinolytics result in systemic conversion of plasminogen to plasmin with resultant depletion of fibrinogen, plasminogen, factor V, and factor VIII.

The first description of fibrinolytic use in the treatment of acute MI was reported by Fletcher and colleagues. Although the coronary thrombus theory of acute MI was not widely accepted at the time, they reported treating 24 patients with intravenous (IV) streptokinase. A few scattered case series using intracoronary injection of fibrinolytics were reported after this study during the next 2 decades. In 1980, DeWood and colleagues used coronary angioscopy in patients with acute MI and found that 87% of patients had thrombotic occlusion of the infarct vessel. This observation led to widespread acceptance of the coronary thrombus model of MI. In the early 1980s, the use of fibrinolytic agents shifted from intracoronary injection to IV injection, and several small studies were performed. These individual studies failed to show a benefit of fibrinolytic use when compared with standard therapy of prolonged bedrest, nitrates, and occasional heparin. In the mid-1980s, a meta-analysis of these early fibrinolytic studies suggested a reduction in mortality with fibrinolytic therapy. These findings led to large “mega-trials” evaluating fibrinolytics in acute MI.

This is the first part of a 2-part review on fibrinolytic therapy. The first part emphasizes the early “mega-trials” that laid the groundwork for fibrinolytic use. A case patient will be used to highlight features of the use of fibrinolytic therapy in acute MI. The second part will discuss the use of newer fibrinolytic agents and examine more recent adjunctive therapies to fibrinolytic therapy, including platelet glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparins, and direct thrombin inhibitors (see “Update on Fibrinolytic Therapy: New Treatment Regimens” in the Hospital Physician Cardiology Board Review Manual, Volume 8, Part 3).

II. CASE PATIENT 1 PRESENTATION

Patient 1 is a 57-year-old man with a history of hypertension and hypercholesterolemia who presents to an emergency department with chest discomfort that woke him from sleep 4 hours earlier. He describes the discomfort as a “crushing” pressure sensation across the left side of his chest that radiates to his neck, accompanied by shortness of breath. He had been seen by his primary care physician 3 days ago for mild chest discomfort occurring with modest exertion. He was started on a mononitrate at that time. Other cardiac risk factors include a history of smoking (1 pack of cigarettes per day for 30 years, quit 3 years ago) and a strong family history of early atherosclerotic coronary heart disease. He has a history of peptic ulcer disease that was treated 5 years ago with no recurrent symptoms, and he underwent appendectomy 6 months ago. On physical examination, his blood pressure is 122/72 mm Hg in the right arm and 128/76 mm Hg in the left arm. His heart rate is 80 bpm; he is diaphoretic and anxious. S4 is present. The remainder of the physical examination is within normal limits.

Patient 1’s electrocardiogram (ECG) shows 3 mm of ST-segment elevation in leads V2 through V4 (Figure 2). The patient is treated with supplemental oxygen, aspirin, a β-blocker, nitroglycerin, and unfractionated heparin.
• Which of the following is the most appropriate therapy for patient 1 at this point?

A) Administration of a glycoprotein IIb/IIIa inhibitor and transfer to the coronary care unit for close monitoring
B) Administration of IV front-loaded t-PA (alteplase, 15 mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour)
C) Administration of indomethacin 50 mg orally every 8 hours
D) Transfer to a tertiary care facility 1 hour away without further medications for cardiac catheterization

**DISCUSSION**

The correct answer is B. Patient 1 has an acute anterior MI manifested by ST-segment elevation in leads V_2 through V_4 on the ECG. Based on current data, patient 1 would benefit from fibrinolytic therapy. Although glycoprotein IIb/IIIa inhibitors are increasingly common in acute coronary syndromes, they are never the sole therapy in patients with acute MI. Indomethacin is one of the nonsteroidal anti-inflammatory agents (NSAIDs) used in the treatment of pericarditis. Pericarditis also can be associated with ST-segment elevation, but this is generally widespread when present and the ST-segments are concave-upward. A careful patient history and characterization of the chest pain are useful in distinguishing pericarditis from acute MI. Some data suggest that the use of NSAIDs in the setting of acute MI may be associated with ventricular free-wall rupture; therefore, NSAIDs are generally avoided in the acute setting after MI. Although primary percutaneous coronary intervention is the best option, this is only possible if the patient can be quickly treated (ie, rapid “door to balloon” time), preferably within the first hour. If patient 1 could be taken to the catheterization laboratory immediately, this would be the treatment of choice. Transferring patient 1 to another facility for coronary intervention would take 1 hour; therefore, it is not a feasible option at this time.

Patient 1 has no definite contraindications to fibrinolytic therapy (see Section IV. “Complications of Fibrinolytic Therapy”) and is subsequently treated with t-PA. His hospital course is uneventful. He undergoes a cardiac catheterization 3 days after being admitted to the hospital that shows a residual 70% proximal lesion on the left anterior descending coronary artery. This lesion is stented with an excellent result, and patient 1 is discharged from the hospital on day 5.

### III. GENERAL PRINCIPLES OF FIBRINOLYTIC THERAPY

The development of systemic fibrinolytic therapy brought about a revolution in the treatment of acute MI. Extensive clinical data comparing various agents, their doses, and timing have demonstrated clear benefits.
INITIAL STUDIES: FIBRINOLYTIC THERAPY VERSUS PLACEBO

Streptokinase

The GISSI-1 (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico) trial was the first major randomized study to compare treatment with a fibrinolytic agent versus placebo in the setting of acute MI. More than 11,000 patients with suspected MI who presented within 12 hours of the onset of symptoms were randomly assigned either to IV streptokinase (1.5 million units over 1 hour) or to placebo. Adjunctive therapy was left to the discretion of the physician; only 14% of patients received aspirin and only 21% received IV heparin. In-hospital mortality was reduced by 18% in the streptokinase group (10.7% versus 13.0%; \( P = 0.002 \)), and the mortality reduction of streptokinase was still apparent after 1 year (17.2% versus 19%; \( P = 0.008 \)). The mortality benefit was greatest in patients receiving early therapy, ranging from a 47% reduction in those treated within the first hour, to 23% for those treated within 3 hours, and to 17% in patients treated within 6 hours. No mortality benefit was observed in patients treated after 6 hours.14,15

Subsequently, ISIS-2 (Second International Study of Infarct Survival Collaboration Group) confirmed the mortality benefit of streptokinase when compared with placebo in large trials including anisoylated plasminogen-streptokinase activator complex (APSAC or anistreplase) and t-PA. APSAC was compared within 24 hours of symptom onset were randomly assigned to IV streptokinase alone (1.5 million units over 1 hour), aspirin alone (162.5 mg daily for 1 month), both, or neither in a 2 \( \times \) 2 factorial design. At 35 days, a 25% reduction in vascular (cardiac, hemorrhagic, or other vascular) mortality was observed in the streptokinase group (9.2% versus 12.0%; \( P < 0.001 \)). A 23% reduction in vascular mortality was observed in the aspirin group (9.4% versus 11.8%; \( P < 0.001 \)), a benefit nearly equal to that of streptokinase itself. Figure 3 provides a different presentation of the data in which the effects of aspirin are compared with streptokinase. The effects of aspirin and streptokinase were synergistic, resulting in a 42% reduction in vascular mortality in the combination group (8.0% versus 13.2%; \( P < 0.001 \)). Similar to GISSI-1, patients receiving earlier therapy had a greater mortality benefit.16 One other smaller placebo-controlled trial with streptokinase, the ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) study, demonstrated a 16% reduction in early mortality with streptokinase.17

Other Fibrinolytic Agents

Streptokinase is not the only agent to stimulate the fibrinolytic system. Other fibrinolytic agents also were compared with placebo in large trials including anisoylated plasminogen-streptokinase activator complex (APSAC or anistreplase) and t-PA. APSAC was compared
with placebo in the AIMS (APSAC Intervention Mortality Study) trial. More than 1000 patients presenting within 6 hours of acute MI were randomly assigned to IV APSAC (30 units over 5 minutes) versus placebo. Additional therapy included IV heparin in the acute setting followed by warfarin for at least 3 months. A 43% reduction in mortality was observed in the APSAC group at 1 year (11.1% versus 17.8%; \(P < 0.001\)). In the ASSET (Anglo-Scandinavian Study of Early Thrombolysis) trial, more than 5000 patients presenting within 5 hours of suspected MI were randomly assigned either to t-PA conventional dosing (10 mg IV bolus, 50 mg infusion over 1 hour, then 40 mg infusion over 2 hours) or to placebo. Patients also received a 5000-unit bolus of IV heparin followed by an infusion of 1000 units per hour for 21 hours. At 1 month, a 26% reduction in mortality was noted in the t-PA group (7.2% versus 9.8%; \(P = 0.0011\)) that was sustained at 1 year (13.2% versus 15.1%; \(P < 0.05\)). Although the incidence of stroke was similar in both groups, major bleeding (requiring transfusion) was more common in the t-PA group. The results of these early placebo-controlled trials of fibrinolytic therapy are summarized in Figure 4.

Analysis of Trials

Early placebo-controlled trials provided solid evidence that fibrinolytic therapy reduces mortality in patients after acute MI. Collective data from 9 trials, each of which enrolled more than 1000 patients, were evaluated by the Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group. The pooled data from nearly 60,000 patients treated with various fibrinolytics (streptokinase, t-PA, APSAC, or urokinase) demonstrated an 18% reduction in mortality (9.6% versus 11.5%) when compared with placebo. Survival benefit was noted across various subgroups, including both male and female patients; patients with prior MI or diabetes; patients in age groups younger than 75 years; patients receiving therapy within 12 hours of symptom onset; and patients with relative hypotension (systolic blood pressure < 100 mm Hg, but the patient is not in shock).

In addition, early trials showed that the mortality benefit derived from fibrinolytic therapy depends on the amount of time from onset of symptoms to delivery of a drug. Rapid treatment is associated with decreased mortality, which is termed “time is muscle.” Several studies demonstrate a greater than 50% reduction in mortality when fibrinolytic therapy is initiated within the first hour after symptom onset (data from GISSI-1 and ISIS-2, together with later studies of pre-hospital administration of fibrinolytic therapy [MlTI [Myocardial Infarction Triage and Intervention]] and EMIP [The European Myocardial Infarction Project Group]). After the first hour, however, the mortality benefit dwindles to about a 25% reduction when treatment is initiated 12 hours or less after symptom onset. Studies evaluating delayed treatment of patients up to 24 hours after symptom onset (LATE [Late Assessment of Thrombolytic Efficacy] and EMERAS [Estudio Multicéntrico Estreptoquinasa Reúnicas de América del Sur]) have failed to demonstrate a benefit of fibrinolytic therapy when initiated 12 hours or more after symptom onset.

SUBSEQUENT STUDIES: COMPARING VARIOUS FIBRINOLYTIC REGIMENS

The previously described placebo-controlled trials paved the way for comparative trials assessing various fibrinolytic regimens (Table 1). In the TIMI-1 (Thrombolysis in Myocardial Infarction) trial, 290 patients with acute MI underwent diagnostic coronary angiography and then were treated with IV streptokinase (1.5 million
units over 1 hour) or IV alteplase (10 mg bolus, 50 mg infusion over 1 hour, then 40 mg infusion over 2 hours, conventional dosing). The primary endpoint of angiographic patency (ie, of an initially occluded coronary artery after 90 minutes) was achieved in 62% of patients treated with alteplase versus 31% of those treated with streptokinase (P < 0.001).25

To assess whether increased angiographic patency translated into improved survival and to better evaluate the role of heparin, the GISSI-2 trial evaluated more than 20,000 patients who presented within 6 hours of acute MI. Patients were treated either with alteplase conventional IV dosing (10 mg bolus, 50 mg infusion over 1 hour, then 40 mg infusion over 2 hours) or with streptokinase (1.5 million units over 1 hour). In addition, patients were assigned either to subcutaneous heparin (12,500 units beginning 12 hours after fibrinolytic therapy and continuing twice daily for 1 week). At 6 months, no difference was noted in survival among patients receiving any of the 3 fibrinolytic agents. Compared to streptokinase, less reinfarction was noted in the t-PA group (2.93% versus 3.47%; P < 0.02); however, this benefit was offset by a higher rate of stroke with t-PA (1.39% versus 1.04%; P < 0.01).27

Whereas GISSI-2 and ISIS-3 failed to demonstrate a mortality benefit of t-PA when compared with streptokinase or APSAC, changes in both t-PA dosing and heparin administration led to a reduction in mortality with t-PA in the GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) and TIMI-4 trials.28,29 A front-loaded approach was used for t-PA dosing, which delivers the same dose in a shorter amount of time. The systemic activation of plasminogen by streptokinase leads to the depletion of fibrinogen, factor V, and factor VIII; therefore, streptokinase produces a systemic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name</th>
<th>Deaths/Patients</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Reduction (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>GISSI</td>
<td>495/4865</td>
<td>623/4878</td>
<td>23% ± 6%</td>
</tr>
<tr>
<td></td>
<td>ISAM</td>
<td>50/842</td>
<td>61/868</td>
<td>16% ± 18%</td>
</tr>
<tr>
<td></td>
<td>ISIS-2</td>
<td>471/5350</td>
<td>648/5360</td>
<td>30% ± 5%</td>
</tr>
<tr>
<td>APSAC</td>
<td>AIMS</td>
<td>32/502</td>
<td>61/502</td>
<td>50% ± 16%</td>
</tr>
<tr>
<td>t-PA</td>
<td>ASSET</td>
<td>182/2516</td>
<td>245/2495</td>
<td>28% ± 9%</td>
</tr>
<tr>
<td>Overall: any fibrinolytic</td>
<td></td>
<td>1230/14,075</td>
<td>1638/14,103</td>
<td>27% ± 3%</td>
</tr>
</tbody>
</table>

Figure 4. Results of the 5 major placebo-controlled trials of fibrinolytic therapy showing reductions in the risk for early death among patients treated within 6 hours. AIMS = APSAC Intervention Mortality Study; APSAC = anisoylated plasminogen streptokinase activator complex; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; CI = confidence interval; GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2 = Second International Study of Infarct Survival; SD = standard deviation; t-PA = tissue plasminogen activator. (Adapted with permission from Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction. A review. Drugs 1992;44:293–325.)
hypocoagulable state. However, t-PA is fibrin-specific and lysed fibrin strands, leaving thrombin exposed. Thus, t-PA induces a hypercoagulable state and is dependent on therapeutic heparinization to overcome this state. GISSI-2 and ISIS-3 used subcutaneous heparin, which has a slower and more unpredictable effect; however, GUSTO-1 and TIMI-4 switched to IV heparin, yielding better outcomes.

The GUSTO-1 trial enrolled more than 41,000 patients within 6 hours of acute MI to 1 of 4 treatment regimens: (1) front-loaded t-PA (alteplase, 15 mg bolus, then 0.75 mg/kg over 30 minutes, followed by 0.5 mg/kg over 1 hour) with IV heparin, (2) streptokinase (1.5 million units over 1 hour) with IV heparin, (3) streptokinase with high-dose subcutaneous heparin, or (4) combination t-PA (1 mg/kg over 1 hour) and streptokinase (1 million units over 1 hour) together with IV heparin. Thirty-day mortality was significantly lower (14% relative reduction) in the front-loaded t-PA arm compared with each of the other 3 arms (6.3% for t-PA, 7.0% for the combination group, 7.2% for streptokinase with subcutaneous heparin, and 7.4% for streptokinase with IV heparin; P = 0.001) (Figure 5). This difference in mortality rate translates into 10 lives saved per 1000 patients treated with t-PA. Other endpoints also were reduced with t-PA, including cardiogenic shock, congestive heart failure, and ventricular arrhythmias. A subset of the GUSTO-1 patients underwent serial angiographic studies to assess whether mortality outcomes correlated with early and sustained infarct-vessel patency. A greater than 50% increase was noted in TIMI grade-3 patency (normal coronary artery flow) with t-PA at 90 minutes, which translates into a 20% decrease in mortality after 24 hours. These results demonstrated the association of early and complete infarct-vessel patency with a reduction in mortality.

The TIMI-4 trial further validated the superiority of front-loaded t-PA when compared with other fibrinolytic regimens. Nearly 400 patients were randomly assigned to front-loaded t-PA (alteplase), APSAC, or a combination of these 2 agents. A significant reduction in mortality was noted in the front-loaded t-PA arm at 6 weeks (2.2% for t-PA, 8.8% for anistreplase, and 7.2% for the combination group), which remained significant at 1 year. With the results of GUSTO-1 and TIMI-4, front-loaded t-PA became the accepted standard of fibrinolytics in the United States. Many clinicians around the world, however, argue that the small absolute benefit (1%) does not outweigh the tremendous cost difference.

### IV. POSSIBLE COMPLICATIONS OF FIBRINOLYTIC THERAPY

#### GENERAL PRINCIPLES

The main complications associated with fibrinolytic therapy relate to bleeding, and intracranial hemorrhage is the worst bleeding complication. The GUSTO investigators were first to provide detailed information on the

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**Table 1. Comparison of Selected Trials Evaluating Various Fibrinolytic Regimens**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Fibrinolytics Studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-1</td>
<td>290</td>
<td>Streptokinase vs. t-PA</td>
<td>Improved 90-minute patency with t-PA (62% vs. 31%; P &lt; 0.001)</td>
</tr>
<tr>
<td>GISSI-2</td>
<td>20,768</td>
<td>Streptokinase vs. t-PA; 50% of patients received SC heparin</td>
<td>No difference in in-hospital mortality</td>
</tr>
<tr>
<td>ISIS-3</td>
<td>41,299</td>
<td>Streptokinase vs. t-PA; 50% of patients received SC heparin</td>
<td>No difference in mortality at 6 months; less reinfarction with t-PA (2.9% vs. 3.5%; P &lt; 0.02)</td>
</tr>
<tr>
<td>GUSTO-1*</td>
<td>41,021</td>
<td>Streptokinase (with IV or SC heparin) vs. t-PA vs. combination of both</td>
<td>Decreased 30-day mortality with t-PA (6.3% vs. 7.0% for SK with SC heparin; 7.4% for SK with IV heparin, 14% reduction; P = 0.001)</td>
</tr>
<tr>
<td>TIMI-4</td>
<td>382</td>
<td>Anistreplase vs. t-PA vs. combination of both</td>
<td>Increase in 90-minute patency with t-PA (60% vs. 41% and 45%; P = 0.02)</td>
</tr>
</tbody>
</table>

*Four treatment regimens were assessed (see text). Three regimens used IV heparin, and one regimen used SC heparin.

GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISIS = International Study of Infarct Survival; IV = intravenous; SC = subcutaneous; SK = streptokinase; TIMI = Thrombolysis in Myocardial Infarction; t-PA = tissue plasminogen activator; vs. = versus.
The incidence of intracranial hemorrhage. Of the patients who had hemorrhagic strokes, nearly 60% died. The incidence of intracranial hemorrhage was higher with t-PA than with streptokinase (0.7% in the t-PA group versus 0.5% in the streptokinase group with IV heparin; \( P = 0.03 \)). Most of these hemorrhagic strokes occurred in elderly persons. In patients older than 75 years, the fatality rate from intracranial hemorrhage exceeded 90%.33 Pooled data from the FTT Collaborative Group demonstrated that the risk of stroke increases with advanced age. The risk of stroke was 0.75% for patients younger than 65 years, with no difference among fibrinolytic agents. In patients older than 65 years, the incidence of stroke increased to 1.4% with streptokinase and 2.1% with t-PA.3 Bleeding from either gastrointestinal or retroperitoneal sites occurs in less than 5% of patients but requires rapid diagnosis and treatment. The most common source of bleeding occurs around vascular access sites and is usually self-limited.28

Complications related to streptokinase and APSAC include hypotension, which may require fluid resuscitation or vasopressor support in up to 10% of cases.34 Also, these agents can be associated with allergic reactions (4%) and anaphylaxis (0.5%).36 Given the theoretical risk of serious allergic reactions with re-exposure, second exposure to streptokinase or APSAC is generally avoided for the first 2 years.35 If patients require fibrinolysis during the 2-year period, they may be given t-PA instead. Unlike streptokinase, allergic reactions to t-PA are exceedingly rare and are not considered clinically relevant.

Another potential complication of fibrinolytic therapy is unsuccessful reperfusion. In the GUSTO angiographic sub-study, initial reperfusion using the accepted standard of front-loaded t-PA was unsuccessful in 20% of patients, and restoration of TIMI-3 flow was only achieved in 50% of patients.36 Studies have demonstrated that up to one third of patients may experience intermittent opening and closing of the infarct-related artery in the first few hours after therapy.22 After successful fibrinolysis, 5% to 15% of patients will experience reocclusion of the infarct-related artery within hours or days; this reocclusion is associated with increased mortality.38 Risk factors for reocclusion include initial complete occlusion of the coronary artery, residual stenosis in the infarct-related artery, and slow coronary blood flow after successful fibrinolysis.37

PATIENT 1

- If patient 1 had emergency surgery 2 weeks ago for a perforated ulcer and now presents with acute MI, what is the most appropriate therapy?
  A) Administration of a glycoprotein IIb/IIIa inhibitor and transfer to the coronary care unit for close monitoring
  B) Administration of IV front-loaded t-PA (alteplase, 15 mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour)
  C) Administration of indomethacin, 50 mg orally every 8 hours
  D) Transfer to a tertiary care facility 1 hour away without further medications for cardiac catheterization

Discussion

The correct answer is D. Strong data support primary coronary intervention in MI.25,38 In a patient with a contraindication to fibrinolytic therapy, primary angioplasty is a good choice despite the increased time delay. Given the recent surgery, the best option is to transfer patient 1 to a facility where he could undergo primary angioplasty. Fibrinolytic therapy has few absolute contraindications; these include active internal bleeding (not including menses), history of hemorrhagic stroke at any time, other strokes or cerebrovascular events within 1 year, known intracranial neoplasm, and suspected aortic dissection. Relative contraindications include uncontrolled
hypertension on presentation (> 180/110 mm Hg); a history of chronic, severe hypertension; a history of stroke or known intracerebral pathology not covered under absolute contraindications; current use of anticoagulants in therapeutic doses (international normalized ratio [INR] > 2); a known bleeding diathesis; non-compressible vascular punctures; recent trauma (within 2–4 weeks); recent major surgery (within 3 weeks); traumatic or prolonged cardiopulmonary resuscitation (> 10 minutes); recent internal bleeding (within 2–4 weeks); pregnancy; active peptic ulcer; and prior exposure to streptokinase and APSAC—especially within 5 days to 2 years—or prior allergic reaction.

If patient 1 had presented with a left bundle branch block on his ECG, which was absent from the ECG obtained at his physician’s office 3 days ago, which of the following would be the most appropriate immediate treatment?

A) Administration of a glycoprotein IIb/IIIa inhibitor and transfer to the coronary care unit for close monitoring
B) Administration of 0.5 to 1 mg of atropine
C) Administration of IV front-loaded t-PA (alteplase, 15 mg bolus, then 0.75 mg/kg over 30 minutes followed by 0.5 mg/kg over 1 hour)
D) Transfer to a tertiary care facility 1 hour away without fibrinolytic therapy for cardiac catheterization

Discussion

The correct answer is C. The 2 electrocardiographic criteria associated with improved mortality after fibrinolytic therapy include ST-segment elevation (> 0.1 mV in 2 or more contiguous leads) and new bundle branch block. However, patients with normal ECGs, T-wave changes, or ST-segment depression have not been shown to benefit from fibrinolytic therapy, and in the case of those with ST-segment depression, may even have a worse outcome. Given the new left bundle branch block, patient 1 is a candidate for either fibrinolytic therapy or primary percutaneous coronary intervention. Therapy should be initiated as promptly as possible. Because primary angioplasty is 1 hour away, the appropriate choice would still be to administer fibrinolytic therapy.

Acute MI presenting with bundle branch block at admission occurs approximately 4% of the time. It is associated with substantially increased in-hospital mortality, more related to extensive myocardial damage than to heart block. These patients are at higher risk of developing complete heart block, and placement of transcutaneous pacing patches as a precautionary measure is warranted. The presence of first-degree atrioventricular block together with either a new bifascicular block (eg, right bundle branch block with a left anterior fascicular block or a left posterior fascicular block) or a new left bundle branch block is an indication for temporary transvenous pacing. Atropine is not indicated for those with left bundle branch block because atropine exerts its effects at the atrioventricular node.

One hour after the initiation of t-PA, patient 1 develops a wide-complex rhythm at 95 bpm. His blood pressure is 115/68 mm Hg. Which of the following is the most appropriate immediate therapy?

A) Continue to monitor closely and observe
B) Immediate, synchronized, electrical cardioversion with 200 joules
C) Administer 100 mg of IV lidocaine and initiate a lidocaine drip
D) Insert a temporary transvenous pacemaker

Discussion

The correct answer is A. Accelerated idioventricular rhythm frequently occurs during the first 12 hours after MI, but this rhythm is not a risk factor for development of ventricular fibrillation. Markers of reperfusion after fibrinolytic therapy include accelerated idioventricular rhythm, resolution of ST-segment elevation, and resolution of chest pain, but these markers are relatively insensitive. In the absence of hemodynamic compromise, accelerated idioventricular rhythm is best managed by observation and should not trigger initiation of antiarrhythmic prophylaxis against ventricular fibrillation. This idioventricular rhythm needs to be distinguished from ventricular tachycardia and ventricular fibrillation, which also occur frequently in the first 48 hours after acute MI and require prompt therapy. Overdrive pacing, which is sometimes attempted with incessant ventricular tachycardia, is generally not used to treat accelerated idioventricular rhythm.

V. SUMMARY POINTS

- Myocardial infarction (MI), in most instances, occurs when an atheromatous plaque ruptures within a coronary artery, leading to thrombus formation and vessel occlusion.
- Fibrinolytic therapy is the mainstay of treatment in acute MI. It has clearly brought about a significant reduction in mortality when compared with previous standard therapy (ie, prolonged bedrest, nitrates, and occasional heparin).
• Fibrinolysis occurs when plasminogen is converted to plasmin, which then degrades fibrin within a coronary thrombus.
• Fibrinolytic therapy is most effective (ie, associated with the greatest mortality benefit) with early therapy, but benefit persists up to 12 hours. Thus, the greatest predictor of mortality benefit from fibrinolytic therapy is the time from vessel occlusion to delivery of drug.
• Although front-loaded tissue plasminogen activator with IV heparin is technically the accepted standard for fibrinolysis in the United States, many areas of the world use streptokinase as the accepted standard because of the decreased cost and nearly similar outcomes.
• Clinical markers of reperfusion after fibrinolytic therapy (including reperfusion arrhythmias, resolution of ST-segment elevation, and resolution of chest pain) are relatively insensitive but can be of diagnostic value when present.
• Although the use of fibrinolytics is a highly effective therapy, there are potential complications, the most serious of which is intracranial hemorrhage.
• After MI, primary catheter-based intervention remains the best option, when available, but only if there is a rapid “door to balloon” time, preferably within the first hour.

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23. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6 to 24 hours after onset of acute myocardial infarction. Lancet 1993;342:759–66.


