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## 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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3-5</sup> In 1980, DeWood and colleagues used coronary angiography in patients with acute MI and found that 87% of patients had thrombotic occlusion of the infarct vessel.<sup>6</sup> 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.<sup>7-9</sup> In the mid-1980s, a meta-analysis of these early fibrinolytic studies suggested a reduction in mor-

tality with fibrinolytic therapy.<sup>10</sup> 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 I 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 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. S<sub>4</sub> 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 V<sub>2</sub> through V<sub>4</sub> (**Figure 2**). The patient is treated with supplemental oxygen, aspirin, a β-blocker, nitroglycerin, and unfractionated heparin.