

The history of the TIMI, GISSI, and ISIS trials: the development of thrombolytic therapy in acute myocardial infarction

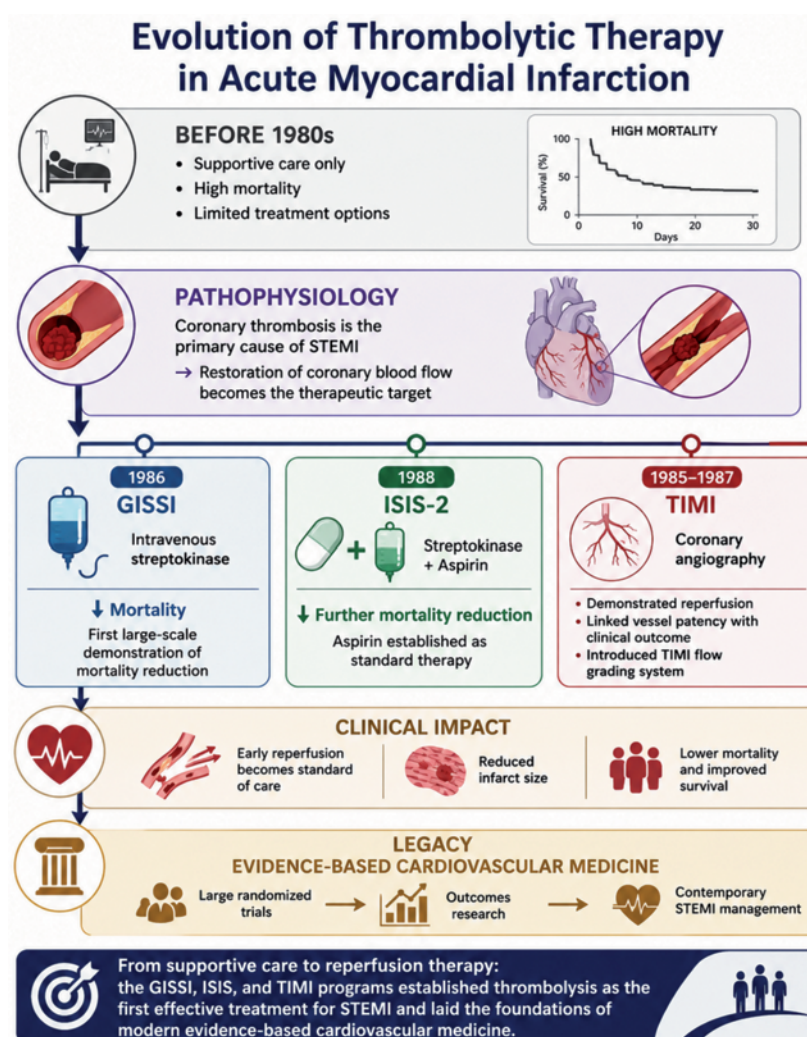
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ABSTRACT

The introduction of thrombolytic therapy represents one of the most important advances in the history of cardiovascular medicine. Before the 1980s, treatment of acute myocardial infarction (AMI) was largely supportive, with limited opportunities to modify the natural course of the disease. The recognition that coronary thrombosis was the principal mechanism underlying ST-segment elevation myocardial infarction led to the development of reperfusion strategies aimed at restoring coronary blood flow and limiting myocardial damage. Among the landmark investigations that established the efficacy of thrombolytic therapy, the GISSI, ISIS, and TIMI trials occupy a central place. GISSI demonstrated for the first time on a large scale that intravenous streptokinase reduced mortality after AMI. ISIS confirmed and expanded these findings by documenting the additive benefits of aspirin, while TIMI advanced the understanding of coronary reperfusion through systematic angiographic assessment. Together, these programs transformed the management of acute myocardial infarction and established many of the principles that continue to guide reperfusion therapy today.

GRAPHICAL ABSTRACT



Key words: acute myocardial infarction; thrombolysis; GISSI; ISIS; TIMI.

Introduction

The management of acute myocardial infarction (AMI) underwent a revolutionary transformation during the 1980s. Prior to this period, treatment was largely supportive, focusing on treating the complications such as arrhythmia management, and hemodynamic stabilization. Mortality remained high because the underlying pathophysiology of ST-segment elevation myocardial infarction (STEMI)—acute coronary artery occlusion by thrombus—could not be timely and effectively reversed.

The emergence of thrombolytic therapy fundamentally changed the treatment paradigm. Among the most influential were the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico), ISIS (International Study of Infarct Survival), and TIMI (Thrombolysis in Myocardial Infarction) trials. These studies established the efficacy of fibrinolytic therapy, refined therapeutic strategies, and laid the scientific foundation for modern reperfusion medicine.¹

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The birth of thrombolytic therapy

By the late 1970s and early 1980s, pathological and angiographic studies had demonstrated that acute myocardial infarction was frequently caused by thrombotic occlusion of a coronary artery.² The logical therapeutic implication was that dissolution of the thrombus might restore perfusion and salvage myocardium. A pioneering multicenter study conducted in the early 1970s compared streptokinase with heparin and showed favorable outcomes in patients treated with streptokinase. However, probably because of the relatively small sample size, the findings were not considered sufficiently convincing at the time to change the standard management of patients with AMI.³

Initial investigations employed intracoronary streptokinase delivered directly into the culprit vessel during cardiac catheterization. Although promising, this approach was technically demanding and unavailable to most hospitals. Consequently, attention shifted toward intravenous thrombolytic therapy, which could be administered rapidly and broadly.

The first large-scale randomized studies to test this concept were the GISSI and ISIS trials in Europe and the TIMI trials in the United States.

GISSI-1: the first thrombolytic megatrial

Under the leadership of Fausto Rovelli and Gianni Tognoni with the scientific collaboration of Italian experts in thrombosis (P.M. Mannucci, M.B. Donati, G.G. Neri Serneri), the GISSI program was initiated in Italy in 1983 by a large network of cardiologists seeking to evaluate whether intravenous streptokinase could reduce mortality in patients with AMI.⁴ The resulting GISSI-1 trial enrolled 11,712 patients between 1984 and 1985, making it one of the first cardiovascular megatrials.

Patients presenting within 12 hours of symptom onset were randomized to receive either intravenous streptokinase or conventional therapy. The primary endpoint was in-hospital mortality.

GISSI-1 demonstrated a significant reduction in mortality among patients treated with streptokinase, particularly when therapy was initiated within the first few hours after symptom onset. The study provided convincing evidence that intravenous thrombolytic therapy could save lives in AMI.

The trial also highlighted the importance of treatment timing. Patients treated within three hours from symptoms onset experienced the greatest benefit, introducing the concept that *time is muscle*.

GISSI-1 represented a turning point in cardiology. It was the first prospective megatrial to conclusively demonstrate that thrombolytic therapy reduce mortality after myocardial infarction. The simplicity of its design and the large number of participating hospitals (almost 90% of coronary care units existing in Italy at those times) showed that large-scale collaborative clinical research was feasible and could directly influence patients' care.

Long-term follow-up confirmed that the survival benefit persisted beyond hospital discharge, extending to at least ten years after infarction.⁵

ISIS-2: a very authoritative confirmation

Under the leadership of Peter Sleight, the Second International Study of Infarct Survival (ISIS-2), published in 1988, is widely regarded as one of the most influential clinical trials in medical history.⁶

The study enrolled 17,187 patients with suspected acute myocardial infarction and used a factorial design to evaluate four treatment strategies: Streptokinase, Aspirin, Streptokinase plus aspirin, neither specific therapy (control).

The primary endpoint was vascular mortality at five weeks. ISIS-2 demonstrated that Streptokinase significantly reduced mortality. Aspirin independently reduced mortality. The combination of streptokinase and aspirin produced the greatest benefit. The effects of the two therapies were additive rather than redundant. Patients receiving both therapies experienced approximately a 42% reduction in vascular mortality compared with those receiving neither treatment.

Additionally, aspirin significantly reduced reinfarction and ischemic stroke, establishing antiplatelet therapy as a cornerstone of AMI management. The impact of ISIS-2 was immediate and global. The study transformed routine clinical practice by demonstrating that two inexpensive and widely available therapies could dramatically reduce mortality.

Ten-year follow-up confirmed that the early survival advantage persisted over time.⁷

The TIMI trials: origins of the TIMI program

In 1984, the United States National Heart, Lung, and Blood Institute established the TIMI Study Group to evaluate emerging reperfusion therapies in AMI. Under the leadership of Eugene Braunwald, recently passed away, TIMI became one of the most influential cardiovascular research organizations in the world. Unlike GISSI and ISIS, which primarily focused on mortality outcomes, TIMI focused the research also on detailed angiographic assessment of coronary reperfusion.

TIMI compared intravenous recombinant tissue plasminogen activator (rt-PA) with streptokinase in patients with AMI.⁸ The principal objective was to determine which agent achieved more effective coronary artery reperfusion. The trial demonstrated that rt-PA produced higher rates of coronary artery patency than streptokinase, although early clinical outcomes were similar.⁶

Subsequent TIMI trials explored increasingly sophisticated reperfusion strategies, including comparison of different fibrinolytic agents, adjunctive anticoagulant therapies, platelet inhibition and therapeutic strategies also for unstable angina and non-ST elevation myocardial infarction.

The TIMI program gradually expanded beyond thrombolysis and became a major platform for studying acute coronary syndromes across the entire spectrum of disease.

Complementary contributions of GISSI, ISIS, and TIMI

Although all three trial programs focused on thrombolytic therapy, their contributions were complementary. The GISSI trial provided the first convincing demonstration that intravenous

streptokinase reduced mortality in AMI.^{4,5} The ISIS trials established the combined use of fibrinolysis and aspirin, proving that simple, inexpensive therapies could dramatically improve survival on a global scale.^{6,7}

The TIMI trials advanced understanding of coronary reperfusion mechanisms, with the introduction of angiographic assessment of reperfusion.⁸ Together, these programs transformed AMI from a condition managed primarily with supportive care into a disease treated actively. The success of thrombolytic therapy fundamentally altered cardiovascular medicine. By the early 1990s, fibrinolysis had become the standard treatment for STEMI worldwide.⁹

Subsequent developments in primary percutaneous coronary intervention (PCI) eventually demonstrated superior outcomes compared with thrombolysis when timely catheterization was available. Nevertheless, the principles established by GISSI, ISIS, and TIMI remain central to modern care. Even today, thrombolytic therapy remains an important reperfusion strategy when timely PCI cannot be performed.^{10,11}

Beyond reperfusion: the lesson of large simple trials

Beyond their direct contribution to the treatment of acute myocardial infarction, the GISSI and ISIS trials profoundly influenced the methodology of clinical research.^{4-7,12} These studies demonstrated that large-scale randomized trials could be conducted efficiently across broad healthcare networks and could provide reliable answers to clinically relevant questions within a relatively short time frame.

GISSI and ISIS, in particular, pioneered the concept of the *large simple trial*, characterized by broad inclusion criteria, clinically meaningful endpoints, streamlined data collection, and extensive participation of hospitals outside major academic centers. This approach allowed investigators to enroll tens of thousands of patients and to generate results that were immediately applicable to routine clinical practice.

Conclusions

The GISSI, ISIS, and TIMI trials collectively represent one of the greatest achievements in the history of cardiovascular medicine.⁴⁻⁸ Conducted during a period of rapid scientific progress, these studies established for the first time the possibility to treat actively acute myocardial infarction with thrombolytic therapy, clarified the role of aspirin and adjunctive antithrombotic treatment, and advanced the understanding of coronary reperfusion.

The success of these programs contributed to the development of modern evidence-based cardiovascular medicine. Many of the methodological principles first adopted in these trials subsequently became standard practice in cardiovascular outcomes research and continue to influence the design of contemporary clinical studies.

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