Creation of the Recombinant Tissue Plasminogen Activator (rt-PA) Image and Its Influence on Practice Habits*

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American physicians have commonly practiced thrombolytic therapy for acute myocardial infarction with the recombinant form of tissue plasminogen activator (rt-PA), although its cost is much higher than that of streptokinase. The greater popularity of rt-PA is based on the belief that it is a more effective and a safer drug for achieving myocardial salvage and mortality reduction. However, a series of studies testing this assumption have not substantiated its greater efficacy or safety with respect to not only streptokinase but also urokinase and anisoylated plasminogen-streptokinase activator complex (APSAC).

This editorial reviews the sequence of events that led to the creation of the rt-PA image, the mistaken premises on which it was based and the questions that need to be addressed if we are to strengthen the scientific method for evaluating similar types of drugs and its influence on practice habits including the costs to the health system.

(J Am Coll Cardiol 1991;18:1579–82)

During 1990, approximately 75% of the patients treated in the United States with thrombolytic agents for an acute myocardial infarction received recombinant tissue-type plasminogen activator (rt-PA), 15% received streptokinase and a small proportion received anisoylated plasminogen-streptokinase activator complex (APSAC) (1). Considering the expense of rt-PA in its recommended dose (100 mg), sales of rt-PA could amount to $220 million as compared with $4 million for the relatively inexpensive streptokinase, a 55-fold difference.

rt-PA versus streptokinase. This discrepancy between rt-PA and streptokinase usage and its cost to hospitals—and the even greater ultimate charge to patients and third party agencies, which we estimate at $0.5 billion for the former agent—is remarkable for two reasons. First, there is a lack of evidence that rt-PA therapy has greater clinical benefit or improved safety over streptokinase, as has been shown by trial results (2–9) and pointed out in editorials (10–12) and reviews (13–15). Second, European physicians, who use thrombolytic therapy more extensively than their counterparts in the United States and who are apparently more cost conscious and less impressed with the rt-PA data, prescribe streptokinase 80% of the time and rt-PA only 10%, the opposite of the experience in the United States.

As of March 1991, compelling evidence has been provided against the superiority of rt-PA over other agents. The ISIS-3 (International Study on Infarct Survival-3) study (9) randomized patients with acute myocardial infarction to receive either streptokinase, APSAC or the double-stranded form of rt-PA, the type used in the original TIMI (Thrombolysis in Myocardial Infarction) Phase I trial (16). The mammoth ISIS-3 study involved approximately 46,000 patients, more than those in all previous thrombolytic trials combined, and it failed to demonstrate a therapeutic advantage in survival for rt-PA over streptokinase or APSAC (9). Ironically, ISIS-3 documents that rt-PA causes a significantly higher rate of hemorrhagic stroke than does streptokinase, contrary to expectations that the "fibrin specificity" of rt-PA would serve to avert or minimize hemorrhagic complications (17–19). On the basis of more limited studies, rt-PA is also unlikely to prove superior to urokinase or to single-chain urokinase (prourokinase) (20–23).

The TIMI Phase I trial. Since the data do not justify the current preference for rt-PA by physicians (primarily cardiologists) in the United States treating myocardial infarction, in terms of cost, efficacy or safety, it is necessary to examine the events that led to the current situation. The process can reasonably be traced to the very first comparative studies in humans, the TIMI Phase I trial (16) and the confirmatory European Cooperative Study Group trial utilizing a comparable design (24). The primary end point of reperfusion in the TIMI Phase I trial (not function or mortality) provided data that favored rt-PA by a striking 2:1 superiority over streptokinase. This study began well enough, serendipitously undertaken in lieu of a planned trial by the National Heart, Lung, and Blood Institute that was to have compared intravenous versus intracoronary streptokinase. This course correction whereby the standard therapy with intravenous

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streptokinase served as a trial horse for intravenous rt-PA was reasonable and timely. The trial presented a unique opportunity to significantly increase our understanding of thrombolytic therapy in general and of the comparative benefits of individual agents specifically, and to apply new insights into the treatment of a huge number of patients suffering from acute myocardial infarction (approximately 500,000 each year in the United States alone). Unfortunately, expectations for a new understanding of fundamental mechanisms and for their dramatic application to the public good have not been fully realized. Worse still, the current debate over the choice of agent to be used in the treatment of acute myocardial infarction appears to be taken by many physicians as an argument against the value of thrombolytic therapy in general, further threatening the full application of this important medical treatment.

How did medical opinion arrive at the current state, in which rt-PA is strongly favored over streptokinase despite the results of clinical trials? In our view, the problem arises from three aspects of the highly influential TIMI-Phase I trial (16) relating to 1) weaknesses in the study design, 2) interpretation of data, and 3) decisions about the succeeding (Phase II) studies.

1. The primary end point of the trial. It is now clear that this end point, the incidence of coronary artery reperfusion at 90 min after treatment induction, biased the results. Thus, follow-up coronary angiography was performed 30 min after the termination of infusion of streptokinase, at a time when the clot-dissolving activity of this agent was rapidly diminishing and reclotting and rethrombosis could be taking place. In contrast, the 90 min end point occurred at the mid-point of a 3-h rt-PA infusion when rapid lysis was continuing. Furthermore, early rethrombosis (within 1 h) after the termination of rt-PA therapy was known to be a significant problem with rt-PA (25), one that would negate the potential benefits of early reperfusion in a given patient, but it was not documented in this study because follow-up angiography was limited to the 90-min and predischarge views. Thus the arbitrary 90-min end point of TIMI Phase I would bypass the short (1 h) post-treatment coronary vessel status, which would have documented reocclusion more frequently after rt-PA than after streptokinase (26) whereas the predischarge follow-up only in patients with an open vessel would not have shown an increasing proportion of open vessels in the streptokinase group (27). Furthermore, the trial design was such that a disparity in 90-min reperfusion rates between patients treated with rt-PA and streptokinase was likely to be predictive of striking differences in function and clinical benefits on follow-up study. We now know that the results were quite different: namely, no such difference in ventricular function (2–4) or survival (6,7,9) exists between streptokinase and rt-PA–treated patients.

2. The interpretation of the 90-min reperfusion results. This proved to be simplistic and misleading for reasons that are fully developed elsewhere (15) but can be summarized as follows. First, because increasing clot age (>2 h) influenced

lysis rates with streptokinase but not with rt-PA (8,15,26,28), the mean delay of 4.8 h before treatment strongly favored the rt-PA group. Second, the rate of reperfusion at 90 min did not represent a maximum or stable end point because approximately 20% of rt-PA–treated patients had early reocclusion (29) whereas streptokinase-treated patients tended to show progressive coronary thrombolysis (15,30). Third, the primary end point was the demonstration of reperfusion at approximately 6.3 h after symptom onset, a time when significant myocardial salvage was unlikely (31,32), thereby eliminating the influence of late reperfusion on subsequent functional or clinical end points (15).

The stress on the superiority of rt-PA therapy in terms of the rate of reperfusion at 90 min diverted attention from other outcomes and interpretations: 1) a higher rethrombosis rate with rt-PA (2,26); 2) the possibility that patency rates with streptokinase and rt-PA would be equivalent after a longer observation period—for example, at 3 to 24 h after treatment (15,30); 3) the irrelevance for salvage of myocardium of a subsequent higher rate of reperfusion in coronary vessels subjected to >3 h of thrombosis before thrombolytic therapy (15); and 4) the lack of functional or clinical superiority of rt-PA in the TIMI-I trial itself (2,3), including the absence of any hemostatic advantage (5,16) despite its fibrinogen-sparing effect (5,33).

3. Choice of agents for the TIMI Phase II trial. The third aspect of TIMI Phase I that contributed to rt-PA's favored status has to do with the choice of agents for the Phase II trial. With the data of TIMI Phase I in hand, the National Heart, Lung, and Blood Institute and the TIMI Steering Committee had the following options. A, A trial comparing rt-PA with streptokinase in terms of clinical benefit and to determine whether the patency rate at 90 min is a reliable surrogate end point for myocardial function or mortality, or both. B, A trial comparing rt-PA not only with streptokinase, but also with other promising thrombolytic agents such as APSAC (34) or urokinase. C, A trial based on the "winner" concept in which only rt-PA would be utilized (35) assuming that the advantage in reperfusion rate obtained in TIMI Phase I would be translated into an equally impressive functional and clinical advantage.

Since the 90-min snapshot of the coronary artery suggested a twofold advantage of rt-PA over streptokinase, option 3 was chosen and streptokinase was dropped from further study by the TIMI program. This decision was taken despite concern over Phase II plans expressed by members of the Policy Advisory and Data Monitoring Board (subsequently replaced under a reorganization plan in May 1985). In dramatic fashion, the TIMI Phase I trial was stopped short in February 1985 because of "substantial, statistically significant differences in recanalization rates" (16). As reported in a preliminary report of the TIMI Phase I data published by *The New England Journal of Medicine* (16) in April 1985 and the accompanying editorial (36), the investigators implied or concluded that streptokinase was so much less effective than rt-PA that it should not be studied further. Specifically, the

"Phase I findings" in the preliminary report (16) considered that ". . . the incidence of recanalization 90 min after intravenous streptokinase is quite low; therefore, intravenous streptokinase appears to be of limited value in the treatment of acute myocardial infarction. Indeed, an early recanalization rate of only about one-third in patients with total occlusion raises concern about whether treatment with an agent with substantial side effects is justified on a routine basis." The editorial stated that ". . . tissue-type plasminogen activator holds more promise as an intravenous thrombolytic agent in acute myocardial infarction than does streptokinase and clearly deserves further study . . ." (36), but it did not recommend further trials to evaluate the clinical efficacy of streptokinase.

Detailed analyses of the Phase I data were not published until 1987 and 1988. These showed, for example, a twofold higher reocclusion rate for rt-PA than for streptokinase (26), equal total and major bleeding events with both agents (5), no difference in ventricular functional changes (2) and no difference in subsequent clinical events or 1-year mortality (3). The decision to drop streptokinase from further study proved to be the greatest flaw in subsequent TIMI investigations, for, instead of a continuing comparison of physiologic and clinical benefits of rt-PA and streptokinase (or other agents), Phase II studies focused only on overcoming the major weakness of rt-PA—its propensity for reocclusion—and on maximizing the vascular response. The TIMI Phase II trial evaluated early elective angioplasty as a means of preventing reocclusion or reinfarction, or both (37), and other TIMI studies evaluated measures such as high dose rt-PA (38), while independent studies especially by the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) group evaluated prolonged infusions of rt-PA (29), prostacyclin administration (39) or a combination of plasminogen activators (40,41). None of these studies has solved the rethrombosis problem with rt-PA therapy. Not only have these approaches not increased the stable patency rate significantly, but early angioplasty has proved to be a detriment rather than a benefit in comparison with clinically indicated angioplasty (37,42), and the attempt to administer high doses of rt-PA exceeded the safety level with respect to intracranial hemorrhage (43).

Other trials. By virtue of the decision to exclude streptokinase from further study, rt-PA seemed to have received a stamp of approval from the National Heart, Lung, and Blood Institute. The latter part of 1985 and the beginning of 1986 saw the end of the process for determining the drug of choice for thrombolytic therapy in the United States, and rt-PA was hailed as a wonder drug ("heart Drano") by the lay press (44,45). Left unsettled was the extent to which reperfusion or patency rates at 90 min truly or accurately reflected clinical benefit and whether other agents might have attributes equal to or even superior to those of rt-PA for clinical efficacy or safety, despite the expenditure of multimillions of dollars of federal funds on behalf of rt-PA therapy in the various TIMI trials from 1985 to 1990. Fortunately,

excellent comparative trials organized in other countries, for example, the GISSI-2 trial (6), the ISIS-3 trial (9) and the New Zealand comparison (4), provided critical data. The information from all of these trials does not support the image originally promoted by the TIMI investigators (and the media) on the basis of mistaken predictions (15).

Implications. There are important questions raised by this scenario describing the creation of the rt-PA image, for not only has it affected health care costs, but it has raised serious ethical and scientific concerns. For example, 1) to what extent has bias influenced decision making in trial design (46); 2) are there adequate safeguards in the mechanism by which decision making occurs in the sponsorship of trials by the government; 3) how much do commercialization, politics, financial interests and aggrandizement interfere with the scientific method; and 4) should safeguards be instituted to assure that public money is spent wisely. One hopes that the questions raised by the events leading to the precipitous but unfounded popularization of rt-PA therapy in the United States will be addressed properly.

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