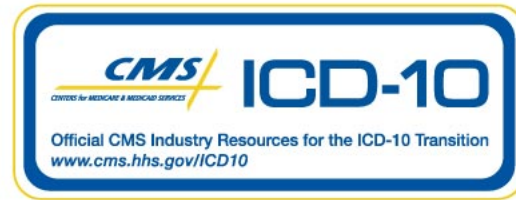


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*Editorial Comment***Is Time Running Out on Streptokinase?***

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It is now clear that the early restoration of vigorous (Thrombolysis in Myocardial Infarction [TIMI] grade 3) flow to the infarct-related artery during an acute myocardial infarction (MI) maximizes patient survival and clinical outcome (1,2). In this issue of the Journal, Steg et al. (3) report that the reperfusion efficacy of streptokinase (SK), but not tissue-type plasminogen activator (t-PA), drops considerably when the interval from the onset of pain to drug administration exceeds 3 h. Although the numbers of patients treated at the later time points are small, the rapid drop in recanalization rate by SK (to <20% at 6 h after pain onset) is striking and concerning. These results are consistent with previous observations (4-8) that there is progressive resistance of the thrombus to lysis with SK (as well as anistreplase and urokinase-type plasminogen activator [u-PA]). Based on data from the TIMI-1 and PAIMS trials, Sherry and Marder (8) concluded that t-PA and SK are equivalent in restoring reperfusion during the first 2 h after onset of symptoms, but thereafter SK is less effective. By their estimate, t-PA is twice as effective at reperfusion as SK at 4 to 5 h after the onset of pain during an acute MI. This duration is still well within the 6-h time limit that most physicians in the United States use for thrombolytic therapy administration.

Why is the thrombus progressively resistant to lysis by SK? An increased interval may allow for persistent propagation of the thrombus, so that the total clot burden is increased. Uncontrolled thrombus extension could be especially significant when a large vein graft is the infarct-related vessel. In addition to quantitative differences, there are qualitative differences in the aged thrombus, probably mediated by the platelet. The platelet alpha-granule contains plasminogen activator inhibitor (PAI)-1, the major inhibitor of t-PA and u-PA, which is released by platelet activation (9). PAI-1 binds to fibrin, where it is concentrated up to 1,000-fold over the plasma PAI-1 concentration (10). However, PAI-1 deposition contributes to only a portion of the platelet-mediated resistance of thrombi to thrombolysis (11,12). Activated platelets provide

prothrombinase complex activity for the generation of thrombin, which may be shielded from inactivation within the thrombus (13). Platelets are a major source of Factor XIII, which when activated by thrombin stabilizes fibrin by forming cross-linked homopolymers and heteropolymers of alpha- and gamma-chains (14). Factor XIIIa also couples an inhibitor of plasmin (alpha-2-antiplasmin) directly to the alpha-chain of fibrin (15). Finally, clot retraction, an energy-consuming process involving the platelet glycoprotein (Gp) IIb/IIIa receptor interacting with fibrin in the extracellular domain and cytoskeletal contractile proteins in the cytoplasm, may contribute to thrombolytic resistance. The retraction or shrinkage of the thrombus is associated with reduced lysis, reduced t-PA binding and a more compact clot, with reduced perfusion by thrombolytic agents (12). The reduced clot permeation could be especially deleterious for agents that lack fibrin binding (e.g., SK) because these agents are usually able to diffuse farther into the unretracted clot than t-PA, the penetration of which is limited by its fibrin affinity (16).

It is possible that some of the factors that reduce SK efficacy at longer intervals to treatment reside in the patient rather than in the thrombus. As myocardial necrosis proceeds, the left ventricle may have progressively less ability to maintain the baseline blood pressure. In the most extreme cases, cardiogenic shock ensues, a condition with a high mortality and poor response to all thrombolytic agents (17). However, even in less severe cases, a drop in blood pressure could affect thrombolytic efficacy. The rate of blood flow through experimental clots in vitro influences their rate of dissolution by thrombolytic agents (18), and augmentation of coronary diastolic pressure with vasopressors (19) or with intraortic pumping (20) increases coronary thrombolysis in canine models. These considerations may explain the finding that survival in the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO)-1 trial (for patients treated with both t-PA and SK) declined when systolic blood pressure was <120 mm Hg, a surprisingly high threshold (21). SK infusion, unlike t-PA therapy, is associated with a significant fall in systolic and diastolic blood pressure in ~50% of patients (22,23), and up to 30% of patients have a nadir systolic blood pressure <80 mm Hg (24). Furthermore, hypotension during SK infusion may portend a poorer prognosis (24). Because a longer interval from onset of pain to treatment increases the rate of cardiogenic shock (25), it is also likely these patients, as a group, have a lower blood pressure and reduced ability to compensate in response to vasodepressing medications. Thus, it is possible that SK, when administered to a patient who presents after 3 h of pain with a large infarct and marginal blood pressure, may cause a pronounced decline in blood pressure that could adversely affect coronary perfusion pressure and reduce thrombolysis. This hypothesis is consistent with the finding that lower blood pressure at presentation is associated with an incremental mortality benefit for patients who are treated with t-PA versus those treated with SK (26).

The time-dependent decline in reperfusion efficacy with SK

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Abbreviations and Acronyms

Gp	= glycoprotein
GUSTO	= Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries
MI	= myocardial infarction
PAI	= plasminogen activator inhibitor
SK	= streptokinase
TIMI	= Thrombolysis in Myocardial Infarction
t-PA	= tissue-type plasminogen activator
u-PA	= urokinase-type plasminogen activator

but not t-PA would be expected to produce a progressive increase in the relative mortality benefit for t-PA as the time to treatment lengthens. Instead, this margin *narrows*. Patients treated at >6 h in the GUSTO-1 trial had equal survival statistics with t-PA and SK (27). The most likely explanation for this finding is that there is little benefit with either thrombolytic agent as the time to treatment interval increases (28). Another explanation for this discrepancy is that time to treatment is a less potent predictor of mortality than previously thought, with age, blood pressure, heart rate, Killip class and location of infarction being more closely tied to mortality (21). Thus, one could argue that the decline in reperfusion efficacy of SK after the 2- to 3-h interval of equivalence is of little clinical consequence. However, this is a risky conclusion because determining the precise onset of pain at the onset of an MI can be difficult, even during rigorous clinical trials (27). Patients may have intermittent occlusions causing cyclic pain syndromes early in the course of a coronary thrombosis. Thus, when timing is in doubt, and perhaps even when it is not, it would seem preferable to administer an agent that has no time limitations to its reperfusion efficacy.

Although thrombolysis will continue to be an important treatment for acute MI despite the attractiveness of primary angioplasty, the role of SK as a first-line agent for thrombolytic therapy is being increasingly challenged. This challenge comes not only from t-PA, but also from reteplase which was recently shown (29) to be nearly equivalent to t-PA in benefit, but with the benefit of a simpler dosing regimen. A variety of other thrombolytic agents (TNK-t-PA, lanoteplase, staphylokinase) are in various stages of clinical trials and have potential advantages over t-PA as well as SK. Because platelets may have a pivotal role in mediating thrombolytic resistance, trials using combinations of Gp IIb/IIIa inhibitors with thrombolytic agents are planned. This combination has shown early promise (30). Thus, as we enter a new era of genetically modified plasminogen activators and approach the 65th anniversary of the discovery of SK (31), the secure position of this venerable thrombolytic agent may be coming to an end.

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