N o treatment has had more profound impact on the global management of patients with acute ST-segment elevation myocardial infarction than fibrinolytic therapy. The ability to achieve rapid and effective coronary reperfusion pharmacologically with a systemic intravenous bolus or infusion has truly transformed our therapeutic approach.

Since this subject was last reviewed in 1998 in the New Frontiers Section of Circulation, there have been 2 additional fibrinolytic agents released for clinical application and 1 other that has undergone major and extensive phase 2 and 3 investigation. Although streptokinase (SK), recombinant tissue plasminogen activator (rt-PA), and more recently reteplase (r-PA) are in general clinical use, there remains some dissatisfaction with their overall efficacy. This relates in part to the failure to achieve optimal tissue reperfusion in approximately one half of patients so treated, as well as persistent risks associated with systemic hemorrhagic effects, some of which complicate ancillary vascular interventional procedures in complicated patients. The risk of intracranial hemorrhage, affecting 5 to 10 of 1000 patients treated, remains a dreaded complication.

In this review, we examine (1) the evolution of the development of fibrinolytics; (2) the pharmacology, pharmacokinetics, and pharmacodynamics of available agents; (3) the need for ancillary therapy; (4) the clinical indications, benefits and risks; (5) the therapeutic alternatives to fibrinolysis; and (6) the future developments that are likely to affect the application of this therapy.

**Evolution of Fibrinolysis**

Sherry, 3 one of the pioneers of fibrinolysis, has provided an instructive historical overview of the earliest origins of thrombolytic therapy, beginning with the recognition of the “fibrinolytic” potential of β-hemolytic streptococci, followed by the demonstration of the capacity of SK to dissolve clotted blood and fibrinous exudates in a patient with a hemothorax. It took an additional 25 years for this discovery to culminate in the application of SK treatment in people with acute myocardial infarction and another quarter of a century before the life-saving potential of SK for this common disorder was unequivocally demonstrated. 4, 5 This protracted embryogenesis, which began with the development of a clot-dissolving medicine suitable for intravenous use, was mediated by several factors: (1) concern over the introduction of a foreign bacterial protein into humans and the potential pyrogenic and allergic effects; (2) the risk of hemorrhage induced by a systemic fibrinolytic state; (3) controversy regarding the causative role of coronary thrombosis in acute myocardial infarction; and (4) small, underpowered clinical studies with design features that undermined their general acceptance in the medical community.

Overcoming these obstacles was ultimately achieved by increased confidence garnered from additional clinical experience with progressively better-quality SK preparations; clear demonstration of the importance of epicardial coronary thrombosis in acute myocardial infarction from early in vivo human coronary angiography; angiographic proof that direct intracoronary SK could successfully achieve culprit vessel recanalization and myocardial reperfusion; and convincing evidence that intravenous SK improves survival from a large, well-designed, placebo-controlled, seminal clinical trial. 6– 8 Subsequent developments in this therapeutic area have been characterized as unfolding during the “thrombolytic era.” Given recent understanding of the important role of platelets and other elements that distinctly contribute to the fibrin-linked foundation of coronary thrombosis, it now seems more appropriate to return to the original designation the Tillett and Garner9 applied to the potential of β-hemolytic streptococcal isolate, ie, “fibrinolysin.” Hence, a variation of this terminology is used in the title and text of the current review.

Fibrinolytic therapy confronts formidable anatomic, biochemical, and physiological challenges in achieving its
TABLE 1. Factors Influencing Successful Fibrinolysis

| Depth, complexity, and contents of ruptured plaque | Plaque thrombosis and hemorrhage with potential for extraluminal compression and intraluminal thrombosis | Distal microembolization of plaque content | Small- and large-vessel vasospasm mediated by vasoconstrictor hormones/agent | Endothelial dysfunction mediated in part by oxygen-free radicals |

These are summarized in Table 1. Together, these factors likely account for the inability to achieve TIMI grade 3 perfusion in at least 40% of instances. Moreover, even when epicardial TIMI grade 3 perfusion is demonstrable, it does not translate into a commensurate increment in distal myocardial perfusion in as many as 15% to 20% of instances, as reflected by myocardial contrast echo studies.12

**Pharmacology and Pharmacokinetics**

**Non–Fibrin-Specific Agents**

SK remains the most common fibrinolytic agent used globally. It is usually used as a short-term infusion (30 to 60 minutes) in doses of 1.5×10⁶ U and has a plasma elimination half-life in man of ≈ 20 minutes.5 Within a few days, the anti-SK titer rapidly rises to 50 to 100 times the preinfusion level, remaining there for many months or even years.13 This makes repeated administration impractical except very early after initial dosing. A new recombinant preparation of SK has recently been demonstrated to possess a similar risk/benefit profile in acute myocardial patients compared with wild-type SK.14

Anisoylated plasminogen streptokinase activator complex (APSAC) or anistreplase was the first bolus fibrinolytic agent developed. Given in a dose of 30 U (1 mg=1 U; 30 mg contains ≈ 100 000 U of SK), its plasma half-life is ≈ 90 minutes, and it produces a similar fall in fibrinogen and increase in neutralizing antibody equivalent to its SK content.15 In aggregate, phase 2 angiographic studies indicate the coronary thrombolytic efficacy of APSAC is comparable to or somewhat higher than intravenous SK but lower than intracoronary SK (1.5×10⁶ U over 60 minutes).16 Although APSAC demonstrated promise on the basis of an initial randomized placebo-controlled trial (APSAC Intervention Mortality Study, AIMS), which was stopped early for reasons of efficacy, when APSAC was administered as a bolus over 3 minutes in the International Study of Infarct Survival (ISIS)-3 study, no mortality advantage was observed over that with SK or rt-PA.17,18 Moreover the intracranial hemorrhage rate with APSAC was closer to that of rt-PA than of SK. Although this agent was approved for general use, it has not been widely accepted in the clinical community.

Urokinase is a naturally occurring 2-polypeptide chain plasminogen activator derived from human urine and human kidney cells in culture. It produces extensive systemic fibrinolysis, is nonimmunogenic, and has achieved coronary patency rates approximating that of SK. In acute myocardial infarction, the dose of urokinase is either 2×10⁶ U as a bolus or 3×10⁶ U over 90 minutes, and it is cleared from plasma with an initial half-life of 6 to 9 minutes.19 Its principal use in North America has been for direct intracoronary infusion.

Prourokinase or single-chain urokinase-type plasminogen activator (scu-PA) is a recombinant form of prourokinase and has 2 formulations: a glycosylated form (Abbott-74187) produced in mouse hybridoma cells that has greater fibrin specificity and stability at similar doses than its nonglycosylated form (saruplase produced in Escherichia coli).20 An initial phase 2 study of glycosylated prourokinase suggested promising coronary patency rates in human infarction, but further randomized studies have not been undertaken.

Nonglycosylated prourokinase or saruplase has a biphasic disappearance with an initial half-life of 6 to 9 minutes in patients with acute myocardial infarction. This preparation was given as a 20-mg bolus with an additional 60 mg over the next 60 minutes in patients with acute myocardial infarction (Prourokinase in Myocardial Infarction [PRIMI] study)21; early TIMI 2 and 3 patency rates at 60 minutes demonstrated a higher rate (71.8%) for scu-PA than for SK (48.0%). In the Study in Europe With Saruplase and Alteplase in Myocardial Infarction (SESAM) conducted 9 years after the PRIMI

**TABLE 2. Pharmacology and Pharmacokinetics of Fibrinolytic Agents for Treatment of Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Property</th>
<th>Alleplase</th>
<th>Saruplase</th>
<th>Reteplase</th>
<th>TNK-rt-PA</th>
<th>Lanoteplase</th>
<th>PEG-SAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight, kDa</td>
<td>70</td>
<td>47</td>
<td>39</td>
<td>70</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg/90 min</td>
<td>80 mg/60 min</td>
<td>2×10⁶ U bolus 30 min apart</td>
<td>0.5-mg/kg bolus</td>
<td>120-IU/kg bolus</td>
<td>5-mg bolus</td>
</tr>
<tr>
<td>Plasma t½α, min</td>
<td>4–8</td>
<td>9</td>
<td>15</td>
<td>20</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Fibrin-specificity</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>++(++)</td>
</tr>
<tr>
<td>Antigenicity</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>90-min patency</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>+++(?)</td>
<td>++++</td>
<td>++(+)</td>
</tr>
<tr>
<td>Mortality reduction</td>
<td>++</td>
<td>+ (+)</td>
<td>++</td>
<td>++</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>++</td>
<td>+ (+)</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Clinical development</td>
<td>Established standard</td>
<td>Not approved (EMEA)</td>
<td>Approved for general use</td>
<td>FDA approved; likely to replace rt-PA</td>
<td>Not further developed</td>
<td>Phase 2 ongoing</td>
</tr>
</tbody>
</table>

PEG indicates pegylated. Number of + signs is proportional to efficacy, extent, or frequency.
study, the 90-minute combined TIMI 2 and 3 patency rates were similar for saruplase (79.9%) and a 3-hour infusion of alteplase (81.4%). Most recently, in the Comparison of Saruplase and Streptokinase (COMPASS) trial, an equivalence study of 3089 patients that evaluated 30-day mortality, equivalence was defined as an OR of <1.5 for all-cause 30-day mortality. Mortality rates were not different, ie, 5.7% for saruplase versus 6.7% for SK, but the rate of intracranial hemorrhage was higher for saruplase than for SK (0.9% versus 0.3%; P=0.038). The European Medical Evaluation Agency (EMEA) has rejected saruplase for clinical use.

**Fibrin-Specific Agents**

**Wild-Type rt-PA**

This prototype fibrin-specific plasminogen activator has high affinity for plasminogen in the presence of fibrin and is a serine protease containing a single polypeptide chain of 527 amino acids. Manufactured by recombinant DNA technology, it is converted from a single- to a double-chain form by plasmin. Its pharmacology and pharmacokinetics, along with those of other agents in this class, are depicted in Table 2.

The recommended dose of rt-PA (alteplase) for the treatment of acute myocardial infarction is 100 mg administered “front loaded,” starting with a bolus of 15 mg followed by 50 mg in the next 30 minutes and the remaining 35 mg in the following hour. The initial half-life of rt-PA in plasma is 4 to 8 minutes. In the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) trial, a 15-mg IV bolus of rt-PA was administered, followed by a weight-adjusted regimen of 0.75 mg/kg over 30 minutes (not to exceed 50 mg) and then 0.50 mg/kg over 60 minutes (not to exceed 35 mg). This study conclusively demonstrated that rt-PA, a fibrin-selective molecule, was superior to SK, a non–fibrin selective agent, for both early and 1-year mortality reduction. The angiographic substudy of GUSTO also demonstrated an important relationship between the establishment of early coronary patency and survival.

Further modification of the 90-minute front-loaded rt-PA infusions has also been evaluated. Because of superior patency rates with a double-bolus administration of rt-PA 30 minutes apart, this approach was compared with conventional accelerated rt-PA over 90 minutes. Mortality and intracranial hemorrhage tended to be higher with the double-bolus approach, leading investigators to conclude that this modification could not be recommended for general use. Gulba et al have recently demonstrated that a 60-minute rt-PA infusion in an open-labeled, nonrandomized study yielded an 81% TIMI 3 patency at 90 minutes. Further study of this regimen has not been undertaken.

**Mutants and Variants of rt-PA**

r-PA is a single-chain nonglycosylated deletion variant consisting only of the kringle 2 and the protease domain of human tPA; it contains amino acids 1 through 3 and 176 through 527 or rt-PA (deletion of Val1-Glu53). The Arg275, Ile276 plasmin cleavage site is maintained. Because of the absence of the finger and kringle 2 domains, the fibrin specificity of r-PA is expected to be lower. In patients with acute myocardial infarction, an initial half-life of 14 to 18 minutes was observed for r-PA.

The dose response of r-PA in patients with acute myocardial infarction was evaluated in 2 open, nonrandomized pilot trials. The Recombinant Plasminogen Activator Angiographic Phase II International Dos Finding Study (RAPID) I trial showed that r-PA, when given as a double bolus of 10 +10 × 10^6 U 30 minutes apart, achieves more rapid, complete, and sustained thrombolysis than standard-dose alteplase (100 mg over 3 hours). In the RAPID II trial, the same r-PA dose regimen yielded 90-minute reperfusion rates that were higher than those of front-loaded rt-PA (59.9% versus 45.2%, P=0.01). These promising angiographic findings notwithstanding, r-PA did not achieve superior mortality or clinical outcomes compared with SK (1.5×10^6 U over 60 minutes) in the International Joint Efficacy Comparison of Thrombolytics (INJECT) study.

In the GUSTO III trial, which hypothesized the superiority of r-PA over rt-PA, no difference was demonstrated between these agents in 30-day mortality, hemorrhagic stroke, bleeding complications, and the combined end point of death and stroke. A 1-year follow-up in GUSTO III has recently confirmed similar mortality outcomes in the 2 treatment arms of this trial.

These data underscore the multiplicity of factors beyond epicardial coronary patency that ultimately translate into patient outcomes.

Another significant tPA variant is the triple-substitution mutant tenecteplase (TNK-tPA) in which replacement of Asn117 with Gln (N117Q) deletes the glycosylation site in kringle 1, whereas substitution of Thr103 by Asn (T103N) introduces a glycosylation site but at a different locus; these modifications substantially decrease the plasma clearance rate. In addition, the amino acids Lys206-His207-Arg208 were each replaced with Ala, which confers higher fibrin selectivity and resistance to inhibition by plasminogen activator inhibitor-1 (PAI-1). In phase 2 studies of TNK-tPA, comparable TIMI 3 patency rates to accelerated rt-PA were demonstrated at 90 minutes, as well as a clear dose-response relationship of weight-based TNK-tPA for both coronary patency and systemic and intracranial hemorrhage. Importantly, a 50-mg dose of TNK-tPA was discontinued prematurely because of increased intracranial hemorrhage; with this adjustment and reduced doses of heparin downtitrated earlier, lower rates of serious bleeding and intracranial hemorrhage were evident for both TNK-tPA and rt-PA.

With this information as a foundation, a phase 3 equivalence study of TNK-tPA compared with rt-PA was conducted in 16 949 patients. Thirty to 50 mg of weight-adjusted TNK-tPA was compared with accelerated rt-PA and revealed virtually identical 30-day (6.18% for TNK-tPA; 6.15% for rt-PA) and 1-year mortalities. Although there were fewer systemic bleeding complications and a reduced requirement for blood transfusion with TNK-tPA, intracranial hemorrhage rates remained higher than desirable in both treatment arms, ie, 0.93% for TNK-tPA and 0.94% for rt-PA. The attractiveness of a single bolus given over seconds will likely lead to rapid incorporation of TNK-tPA into the pharmacological armamentarium of clinicians, because it facilitates integration into combination antithrombotic strategies. Moreover, given
the failure of high-profile public education campaigns to abbreviate the time from symptom onset to the beginning of therapy for acute myocardial infarction and the powerful impact of reducing time to treatment, bolus therapy is likely to reenergize the movement toward prehospital therapy.42

Lanoteplase, a novel plasminogen activator (nPA), is a deletion mutant of rt-PA lacking the fibronectin fingerlike and epidermal growth factor domains, leading to slower clearance. Deletion of the fingerlike domain contributes to lesser fibrin specificity.1,43 A phase 2 study of nPA, Intravenous nPA for Infarcting Myocardium Early (InTIME), evaluated nPA administered as a split, single bolus over 2 to 4 minutes in doses varying between 15 and 120 kU/kg compared with accelerated rt-PA.44 Although a clear dose response on 60-minute TIMI 3 patency was evident over the first 3 doses, no incremental patency advantage was evident between 60 and 120 kU/kg, and neither of the 2 top doses exceeded that achieved with rt-PA. The 120-kU/kg dose was subsequently chosen for a large phase 3 comparative study (InTIME-2) with a 2-to-1 randomization of nPA compared with accelerated rt-PA.44 Although the 30-day mortality rates for nPA (6.77%) and rt-PA (6.60%) were similar, there was an unacceptable excess of intracranial hemorrhage with nPA (1.13% versus 0.62%, P = 0.003) and an increase in the composite of mild and moderate bleeding with nPA (22% versus 17%, P = 0.0001). Because of the absence of an internationally accepted measurement standard to facilitate direct comparison of fibrinolytic agents, interagent comparisons are challenging. Hence, each plasminogen activator must be treated as a unique agent with its unit of measurement being related to its own international standard preparation.45 It may well be that both the dose of nPA and the heparin dosing strategy—to be discussed subsequently—contributed to the InTIME 2 result.

Other novel modifications of rt-PA include E6010 in which cysteine 84 in the epidermal growth factor domain has been replaced by serine, resulting in a plasma half-life of 23 minutes, making it suitable for single bolus injection.46 A second agent, YM866 (pamiteplase), in which the first kringle domain is deleted and a point mutation (arginine for glutamine) is present at the site of the second kringle (K2) domain linkage to the L-chain has a pronounced affinity for fibrin with the same specific activity as native rt-PA in vitro.47 It too is suitable for single bolus injection and shows promise on the basis of experimental in vivo phase 2 acute myocardial infarction studies.

Another pharmacological approach involves a recombinant chimeric plasminogen activator, MEW 9036 (amediplase). This agent consists of a fusion of the N-terminal part of rt-PA with the C-terminal section comprising the urokinase catalytic domain and is characterized by fibrin specificity like rt-PA and lack of inhibition by protease inhibitors such as PAI-1.48 Phase 1 and 2 studies in humans demonstrate that amediplase has a half-life of ~12 minutes, making it suitable for bolus injection.49 Early experience suggests that it has effective coronary fibrinolytic capacity, and phase 2 dose-finding studies are now underway.

Staphylokinase (SAK) is a protein produced by selected strains of staphylococcus aureus and has been known since 1948 to have profibrinolytic properties.50 It is a protein of 136 amino acids without disulfide bridges and forms a SAK-plasmin complex that efficiently transforms plasminogen to plasmin at the surface of a thrombus. Being bound to fibrin, this plasmin is protected from inhibition by α2 antiplasmin but once liberated is rapidly inhibited by this agent. This has the effect of marked fibrin specificity and efficient activation of plasminogen to plasmin at the clot surface. Through recombinant technology, this agent has been made available for clinical use. In patients with acute myocardial infarction treated with an infusion of 10 mg IV SAK over 30 minutes, SAK-related antigen disappeared from plasma in a biphasic manner with a t1/2α of 6.3 minutes and a t1/2β of 37 minutes, corresponding to a plasma clearance of 270 mL/min.51 The vast majority of patients developed neutralizing antibodies to SAK, albeit after a long lag phase of 7 to 12 days, that remained elevated well above pretreatment levels for several months after administration.51,52

Promising TIMI 3 patency, ie, >60% at 90 minutes with a bolus and 30-minute infusion of SAK, has also been observed without systemic fibrinolysis.53–54 Most recently, this molecule has been substituted with a single, linear, polyethylene glycol linked to a cystein residue substituted in amino acid position 3 of the mature protein, which reduces the clearance 5-fold. This molecule has been given as a single bolus injection at reduced dose (with high TIMI 3 patency at 60 minutes) and is now the subject of ongoing phase 2 angiographic evaluation.55

References


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Paul W. Armstrong and Désiré Collen

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