REVIEW

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New fibrinolytic agents for MI: As effective as current agents, but easier to administer

ABSTRACT

The efficacy and safety of fibrinolytic agents have not dramatically changed since alteplase (Activase), a derivative of tissue plasminogen activator (t-PA), was introduced nearly 2 decades ago. However, newer agents have a longer half-life, making them easier to deliver. Fibrinolytic therapy is underused in many patients, especially in those traditionally thought to be at high risk for complications.

KEY POINTS

Alteplase, in an accelerated dosing regimen, has set the standard against which all other fibrinolytic agents are measured.

The third-generation fibrinolytic drugs reteplase (r-PA; Retavase) and tenecteplase (TNK-t-PA; TNKase) have safety and efficacy profiles similar to that of alteplase, but can be administered in one or two boluses.

Patients older than 75 years derive significant benefit from fibrinolytic therapy, even though their risk of bleeding is higher.

Patients presenting with an ST elevation myocardial infarction experiencing cardiogenic shock should undergo percutaneous coronary intervention, if available.

With current fibrinolytic drugs, about 40% of patients do not achieve epicardial (vessel) patency, and 20% to 50% of those who achieve vessel patency do not achieve myocardial patency.

THE MAIN ADVANTAGE of the latest generation of fibrinolytic drugs for treating acute myocardial infarction (MI) is their ease of administration.

Ease of administration is important. Many patients who might be candidates for fibrinolytic therapy are not getting it, and the complicated regimens of the current, second-generation drugs may partly account for their underuse.

For instance, alteplase (Activase), the gold standard for fibrinolytic therapy, has to be given in an accelerated regimen involving a bolus followed by two timed infusions. New agents can be administered in just one or two boluses.

Thus, although the new, third-generation agents are not associated with higher rates of vessel patency or lower rates of death or serious complications, they may end up being used more.

This review focuses on the fibrinolytic drugs currently approved by the US Food and Drug Administration (FDA) for treating acute MI, with special attention to the new, third-generation agents and to special indications for their use.

INDICATIONS FOR FIBRINOLYTIC THERAPY

MIs are categorized according to whether the ST segment is elevated. ST-elevation MIs are treated with immediate reperfusion therapy if the patient presents within 12 hours of symptom onset. This approach has been shown by multiple trials to reduce morbidity and mortality.[1] Electrocardiographic indications for

The TIMI grading system

Individual clinical measures that are used to evaluate reperfusion include resolution of symptoms, resolution of ST-segment elevation of 70% or more of baseline, and characterization of flow using the Thrombolysis in Myocardial Infarction (TIMI) grading system.

The TIMI flow in the infarct-related artery was evaluated in most of the major trials because it correlates with improvements in mortality and infarct size.

The TIMI system consists of four grades:

- **Grade 0:** Complete occlusion of the infarct-related artery
- **Grade 1:** Some penetration of contrast material beyond the point of obstruction, but without perfusion of the distal coronary artery bed
- **Grade 2:** Perfusion of the entire infarct-related vessel into the distal bed, but with delayed flow compared with a normal artery
- **Grade 3:** Full perfusion of the infarct-related vessel with normal flow.

reperfusion therapy include evidence of ST-segment elevation, new left bundle branch block, or ST depression in V_1 and V_2 suggestive of an acute posterior MI (TABLE 1).

Reperfusion therapy encompasses mechanical percutaneous interventions (such as angioplasty and stenting) and fibrinolytic therapy. Percutaneous interventions are preferred, but they are not readily available in all hospitals. Therefore, fibrinolytic drug therapy is more widely used by far throughout the world.

Major contraindications to fibrinolytic therapy, most of which are related to bleeding complications, are listed in TABLE 2.

FIRST-GENERATION AGENTS

Though fibrinolytic therapy for acute MI was first attempted in the 1950s, significant advances were not made until the 1980s.

Streptokinase

Streptokinase (Streptase, Kabinase; TABLE 3) is a 47-kilodalton protein with a plasma half-life of approximately 25 minutes. It binds to plasminogen, forming a streptokinase-plasminogen complex that converts plasminogen to plasmin, which initiates fibrinolysis.

Streptokinase is not fibrin-specific and activates both circulating and clot-bound plasminogen, which leads to systemic lysis of fibrin. (The more fibrin-specific agents predominantly lyse clot-bound fibrin.) The systemic plasminogen activation with streptokinase results in extensive fibrinogen depletion and concomitant bleeding risks.

Of patients with acute MI who receive streptokinase, approximately 30% achieve TIMI grade 3 flow by 90 minutes, and another 20% achieve TIMI grade 2 flow. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-1 study showed a 30-day mortality rate of 7.3% and an intracranial hemorrhage rate of 0.54% with streptokinase.[1] (Without reperfusion therapy, the mortality rate would be expected to be about 25% higher and the intracranial hemorrhage rate would be about 50% lower.)

Besides the risk of bleeding, other disadvantages of streptokinase are that some patients develop antibodies to it (preventing its reuse), and allergic reactions, hypotension, and bleeding as a result of its nonspecific plasminogen binding.[2]

Percutaneous interventions are preferred, but not always available

Urokinase

Urokinase (Abbokinase) is a serine protease derived initially from urine and later from renal parenchymal cell cultures. It directly activates plasminogen and is not specific for fibrin-bound thrombus. In acute MI patients receiving urokinase, the patency rate at 60 minutes is about 60%.

However, after the manufacturer could not prove there is no risk of transmitting infectious agents in this drug derived from human source material, urokinase was not approved by the FDA and production was suspended.

Nevertheless, the drug is widely used in Korea and the Asian-Pacific area, where the Thrombolysis in Myocardial Infarction in Korea (TIMIKO) trial compared alteplase and

TABLE 1

Guidelines: Indications for reperfusion therapy in acute myocardial infarction (MI)

Class I
Conditions for which there is evidence or general agreement that the treatment is beneficial, useful, and effective
- ST-segment elevation (> 0.1 mV, ≥ 2 contiguous leads), time to therapy ≤ 12 hours, age < 75
- Bundle branch block (obscuring ST-segment analysis) and history suggesting acute MI

Class II
Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of the treatment

Class IIa
Weight of evidence or opinion is in favor of usefulness or efficacy
- ST-segment elevation, age ≥ 75

Class IIb
Usefulness or efficacy is less well established by evidence or opinion
- ST-segment elevation, time to therapy 12–24 hours
- Blood pressure on presentation > 180 mm Hg systolic and/or > 110 mm Hg diastolic associated with high-risk MI

Class III
Conditions for which there is evidence or general agreement that a procedure or treatment is not useful or effective and in some cases may be harmful
- ST-segment elevation, time to therapy > 24 hours, ischemic pain resolved
- ST-segment depression only (not consistent with posterior MI)

BASED ON RYAN TJ, ANDERSON JL, ANTMAN EM, ET AL. ACC/AHA GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION. J AM COLL CARDIOL 1996; 28:1328–1428.

urokinase in patients presenting with acute MI. The 30-day mortality rate was not significantly different between the two treatment groups: 4.6% in the urokinase group and 4.4% in the alteplase group.[3] The incidence of intracranial hemorrhage was 0.3% in the urokinase group and 1.1% in the alteplase group. The risk of major bleeding was 10% with urokinase and 9.7% with alteplase.[3]

SECOND-GENERATION AGENTS

The need for a safer, more effective fibrinolytic drug led to the development of the second-generation agents, which include anistreplase and alteplase. (A third second-generation agent, prourokinase, has not been approved and will not be discussed here.)

Anistreplase

Anistreplase (Eminase) is a 131-kilodalton protein with a plasma half-life of 70 to 120 minutes. Anistreplase results in a combined TIMI grade 2 and TIMI grade 3 flow rate at 90 minutes of 50% to 60%. It has a side effect profile similar to that of streptokinase, but has the advantage of single-bolus administration.

The International Study of Infarct Survival (ISIS)-3 showed a 10.5% mortality rate at 35 days with anistreplase and an intracranial hemorrhage rate of 0.6%.[4]

Alteplase

Alteplase (Activase) is a 70-kilodalton protein with enhanced fibrin specificity and a plasma half-life of approximately 4 to 8 minutes. The naturally occurring form of this molecule, tissue plasminogen activator (t-PA), is a serine protease produced by normal endothelial cells. Serum t-PA levels increase with exercise. Its effect is inhibited by plasminogen activator inhibitor (PAI-1).

Alteplase produces TIMI grade 3 flow in 50% to 60% of patients at 90 minutes. In GUSTO-1, patients who received alteplase had a 6.3% mortality rate at 30 days and a 0.72% incidence of intracranial hemorrhage.[1] Compared with streptokinase, alteplase resulted in a 1% absolute reduction in death or nonfatal stroke.

Alteplase is most effective when given in an accelerated regimen of an initial bolus and two timed infusions (TABLE 4), and it is the benchmark to which all new thrombolytic agents are compared. It accounted for 80% of fibrinolytic therapy in the United States until the of the third-generationdrugs emerged.

THIRD-GENERATION FIBRINOLYTIC AGENTS

The third-generation fibrinolytic agents (TABLE 3) were developed to improve upon the efficacy, safety, and ease of administration of previous generations (TABLE 4).

The newer agents are more specific for fibrin, meaning that they tend to bind to and predominantly activate clot-bound plasminogen, thus avoiding systemic plasminogen activation. Though a completely fibrin-specific agent remains elusive, there is ongoing research in this area. Because they have a longer half-life, the newer drugs can often be administered in a single bolus or two boluses.

Reteplase

Reteplase (r-PA; Retavase) is a deletion mutant of tissue plasminogen activator that preferentially activates fibrin-bound plasminogen. It has a half-life of approximately 11 minutes.[5] Compared with alteplase, it has greater fibrinolytic potency and less affinity for endothelial cells.[6,7]

The RAPID I (Recombinant Plasminogen Activator Angiographic Phase II International Dose Finding Study) compared the efficacy and safety of various doses of reteplase combined with heparin in approximately 600 patients presenting within 6 hours of MI onset.[8] The most effective reteplase regimen was two boluses of 10 million units each, given 30 minutes apart.

RAPID II compared this double-bolus regimen and accelerated alteplase in 324 patients.[9] The primary end point of this trial was TIMI grade 3 flow in the infarct-related artery at 90 minutes, which was achieved in 59.9% of patients treated with reteplase and in 45.2% of patients treated with alteplase (P = .01). There was also a nonsignificant trend toward a lower mortality rate with reteplase (4.1% vs 8.4%). Rates of severe bleeding and hemorrhagic stroke were similar between the two groups. The investigators concluded that reteplase was superior to alteplase.

The INJECT investigators compared reteplase and streptokinase and found a non-

TABLE 2

Contraindications to fibrinolytic therapy

Absolute

- Any history of hemorrhagic cerebrovascular event
- Any other cerebrovascular events within 1 year
- Active internal bleeding, not including menses
- Known intracranial neoplasm
- Suspected aortic dissection

Relative

- Blood pressure > 180/110 mm Hg
- Use of anticoagulants with an international normalized ratio > 2.0
- Noncompressible vascular punctures
- Prolonged cardiopulmonary resuscitation (> 10 minutes)
- Prior gastrointestinal hemorrhage
- Pregnancy
- Menstruation
- Recent trauma (within 2 to 4 weeks)
- Major surgery within 3 weeks

TABLE 3

Fibrinolytic agents

GENERIC NAMES	BRAND NAMES
First-generation	
Streptokinase	Streptase, Kabinase
Urokinase	Abbokinas
Second-generation	
Alteplase (tissue plasminogen activator, t-PA)	Activase
Anistreplase (APSAC)	Eminase
Prourokinase (scu-PA)*	
Third-generation	
Reteplase (r-PA)	Retavase
Tenecteplase (TNK-t-PA)	TNKase
Lanoteplase* (n-PA)	
Staphylokinase* (SAK 42D)	
Antibody-targeted PAs*	
Vampire bat-PA*	
Alfimeprase*	

*Not approved for clinical use

TABLE 4

Characteristics of alteplase compared with the third-generation fibrinolytic drugs

	ALTEPLASE	TENECTEPLASE	RETEPLASE	STAPHYLOKINASE
Molecular weight (kilodaltons)	70	70	39	16.5
Half-life (min)	4–8	20–24	11	6
Fibrin specificity	++	+++	+	++++
Weight-adjusted	Yes	Yes	No	Pending
Dosage	≤ 67 kg: 1.25 mg/kg* > 67 kg: 100 mg†	< 60 kg: 30 mg 60–69.9 kg: 35 mg 70–79.9 kg: 40 mg 80–89.9 kg: 45 mg > 90 kg: 50 mg	10 million units x 2, 30 minutes apart	14–45 mg
TIMI grade 3 flow rate at 90 minutes (%)	50–60	50–64	50–60	60–65
Intracranial hemorrhage (%)	0.62–0.94	0.93	0.77–1.2	Not well studied

*15 mg bolus over 1–2 minutes, then 0.75-mg/kg infusion (50-mg maximum) over 30 minutes, followed by 0.5-mg/kg infusion (35-mg maximum) over 60 minutes
†15 mg over 1–2 minutes, then 50 mg over 30 minutes and 35 mg over 60 minutes

significant trend toward a higher survival rate with reteplase, but no difference in bleeding.[10]

The GUSTO III trial compared alteplase and reteplase in more than 15,000 patients presenting within 6 hours of MI onset.[11] All patients received aspirin 160 mg and heparin in a 5,000-unit bolus followed by a 1,000-unit-per-hour infusion (adjusted to 800 units per hour for patients weighing less than 80 kg).

Rates of mortality, bleeding complications, and stroke were similar in the two treatment groups (FIGURE 1). The 30-day mortality rate was 7.47% with reteplase and 7.24% with alteplase. The incidence of intracranial hemorrhage was 0.91% in the reteplase group and 0.87% in the alteplase group. Reteplase had the advantage of bolus administration and a fixed dose, which tends to reduce errors.[12]

The primary finding of the trial was that reteplase was not superior to alteplase; however, the favorable safety profile of reteplase and its ease of administration resulted in its approval by the FDA.

Tenecteplase

Tenecteplase (TNK-t-PA; TNKase), a triple mutant of tissue plasminogen activator, is more specific than alteplase for fibrin, more resistant to PAI-1, and longer-lasting (with a half-life of approximately 20 minutes).[13–15] Owing to its longer half-life, tenecteplase can be given as a single bolus.

The efficacy and dosing of tenecteplase in the treatment of acute MI were evaluated in the TIMI 10A, TIMI 10B, ASSENT-1, and ASSENT-2 trials.

TIMI 10A evaluated escalating doses of tenecteplase from 5 mg to 50 mg in 113 patients who presented with acute MI within 12 hours of symptom onset.[16] These patients were treated with heparin to maintain the activated prothrombin time (aPTT) between 55 and 85 seconds for 48 to 72 hours. Tenecteplase doses of 30 to 50 mg were the most effective, with 90-minute TIMI grade 3 flow rates of 59% to 64%.

TIMI 10B[17] subsequently compared 30-mg and 50-mg doses of tenecteplase and an accelerated alteplase regimen. However, the 50-mg dose was reduced to 40 mg after a high rate of intracranial hemorrhage was seen. The overall incidence of intracranial hemorrhage was 1.9% in the tenecteplase 40-mg group and also 1.9% in the accelerated alteplase group.

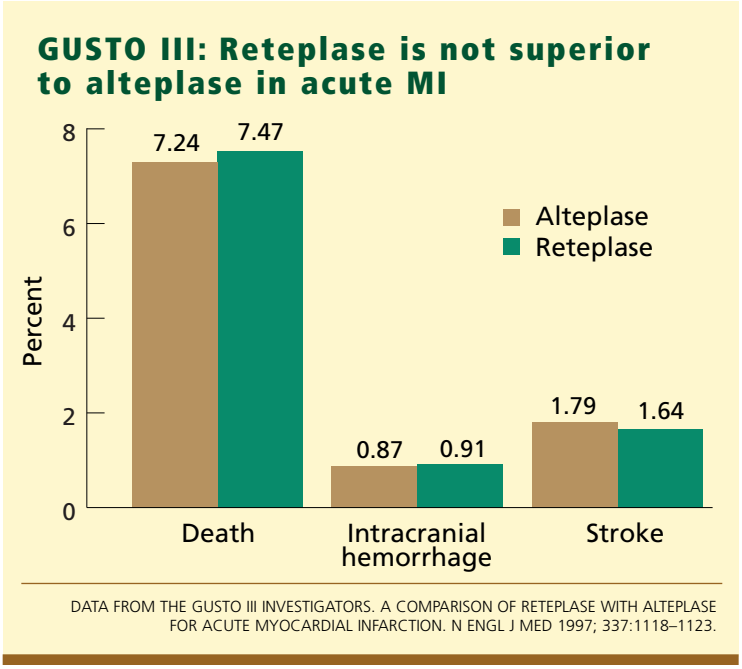

FIGURE 1

Tenecteplase causes fewer bleeding complications than alteplase, and is gaining use

The heparin dose was reduced during the trial, and dose adjustments for heparin were begun at 6 hours.[17]

The primary end point, the rate of TIMI grade 3 flow at 90 minutes, was 62.7% in the accelerated alteplase group and 62.8% in the tenecteplase 40-mg group. In the tenecteplase 30-mg group, the rate was significantly lower.

The ASSENT-1 study (Assessment of the Safety of a New Thrombolytic TNK-t-PA)[18] evaluated the efficacy and safety of tenecteplase 30 mg vs 40 mg in patients presenting within 12 hours of MI onset. The primary end point of this trial was intracranial hemorrhage.

The incidence of intracranial hemorrhage was 0.94% in the 30-mg group and 0.62% in the 40-mg group; the higher rate in the 30-mg group was due to a higher heparin dose given to the first 248 patients, in whom the rate was 1.62%. Those taking lower-dose heparin had a significantly lower incidence of hemorrhagic stroke: 0.82%. Further study led to the development of a weight-adjusted regimen (**TABLE 4**).

ASSENT-2[19] compared alteplase and tenecteplase, both in weight-adjusted doses, in more than 16,000 patients presenting with acute MI. All patients received aspirin 150 mg to 325 mg and heparin in a bolus of 4,000 to 5,000 U followed by an infusion of 800 to 1,000 U/hour, adjusted to maintain the aPTT at 50 to 75 seconds, for 48 to 72 hours.

The primary end point of 30-day all-cause mortality occurred in 6.18% of the tenecteplase group and 6.15% of the alteplase group (**FIGURE 2**). The incidence of noncerebral major bleeding was 4.66% in the tenecteplase group and 5.94% in the alteplase group (P = .0002); the total incidence of noncerebral bleeding was 26.4% in the tenecteplase group and 29% in the alteplase group (P = .0003). There was also a significantly lower incidence of blood transfusions in the tenecteplase group: 4.25% vs 5.49% (P = .0002). The incidence of intracranial hemorrhage was 0.93% and 0.94% in the two groups, respectively.[19]

The investigators concluded that the two drugs were associated with an equivalent 30-day mortality rate, and with lower rates of noncerebral bleeding with tenecteplase.

Lanoteplase

Lanoteplase (n-PA) is also a deletion mutant of tissue plasminogen activator, designed to provide single-bolus administration along with improved fibrin specificity.[20] Its plasma half-life is approximately 30 to 45 minutes.[21] Compared with alteplase, lanoteplase is associated with a lower increase in serum PAI-1 activity and is nine times as potent.[21]

InTIME I. The Intravenous n-PA for Treatment of Infarcting Myocardium Early (InTIME I) investigators compared the efficacy and safety of four escalating doses of lanoteplase: 15, 30, 60, and 120 kU/kg and a weight-adjusted accelerated alteplase regimen.[22,23] The primary end point of the trial was 90-minute TIMI grade 3 flow.

Lanoteplase produced TIMI grade 3 flow in a consistent dose-response fashion: 26.1%, 31.7%, 47.5%, and 57.1% at 90 minutes in each of the four escalating-dosage groups. The rate with alteplase was 46.4%.

InTIME II compared lanoteplase in a 120-kU/kg bolus and alteplase 100 mg over 90 minutes. The 30-day mortality rates were not significantly different between the two groups, 6.77% in the lanoteplase group and 6.6% in the alteplase. The intracranial hemorrhage rate was 1.13% in the lanoteplase group and

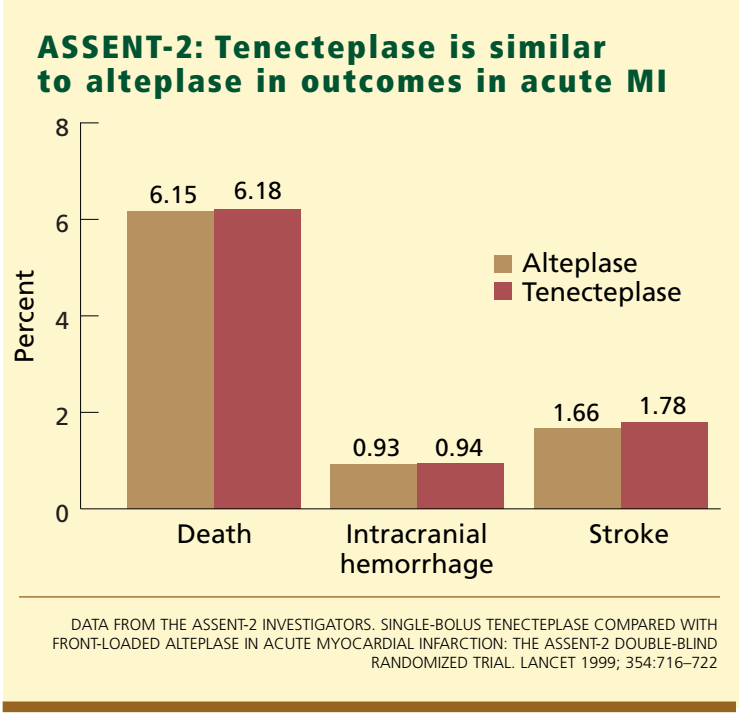

FIGURE 2

0.62% in the alteplase group (P =.003).

Further analysis of patients according to time of first adjustment of heparin infusion revealed that patients having their first adjustment at 3 hours had a significantly lower incidence of intracranial hemorrhage than those having their first adjustment at 6 hours.

Though the overall efficacy of lanoteplase is similar to that of alteplase, its higher incidence of intracranial hemorrhage has stifled its commercial development.

Fibrinolytic drugs reduce mortality in acute ST-elevation MI by about 30%

Staphylokinase

Staphylokinase (SAK 42D) is produced by *Staphylococcus aureus* and was discovered and tested in the 1950s. Staphylokinase is highly fibrin-specific and does not decrease the levels of fibrinogen or alpha-2 antiplasmin. It binds to plasminogen and remains inactive as a staphylokinase-plasminogen complex until it is exposed to fibrin. In the absence of fibrin, it is inactivated by alpha-2 antiplasmin.[24–26]

Initial studies of staphylokinase have been very small. One trial included 100 patients with acute MI who received either staphylokinase 10 mg, staphylokinase 20 mg, or alteplase in a weight-adjusted regimen.[27] TIMI grade 3 flow at 90 minutes was achieved in 62% of the patients treated with staphylokinase and in 58% of the patients treated with alteplase. The rate was higher with the higher staphylokinase dose, 74% with 20 mg vs 50% with 10 mg. No significant difference in bleeding complications was detected between alteplase and staphylokinase.

The CAPTORS study (Collaborative Angiographic Patency Trial of Recombinant Staphylokinase) evaluated staphylokinase 15 mg, 30 mg, and 45 mg given as 20% bolus and 80% infusion over 30 minutes.[28] TIMI grade 3 flow at 90 minutes occurred in 62%, 65%, and 63% of the patients, respectively. There were no cases of intracranial hemorrhage or allergic reactions, which may be a result of the small sample size.

A follow-up study from the CAPTORS investigators suggested that giving staphylokinase as a single 0.05-mg/kg bolus may be most effective.[29] This agent is undergoing further study.

THERAPY IN SPECIAL GROUPS

Fibrinolytic therapy has been shown to reduce the 30-day mortality rate by approximately 30% in patients presenting with ST-elevation MI or bundle branch block.[30] Its benefit has been questioned in certain groups, however, including the elderly, women, people with diabetes, those with prior coronary artery bypass graft surgery or MI, and those presenting in cardiogenic shock or a considerable time after symptoms began.

Patients older than 75 years derive significant benefit from fibrinolytic therapy, even though their risk of bleeding is higher. The use of fibrinolytic agents in this population results in 18 lives saved per 1,000 patients treated.[30] Though one should be cautious when treating elderly patients because they have higher rates of intracranial hemorrhage, they do better with fibrinolytic therapy than without it.

Women. Fibrinolytic therapy is used less often in women than in men, even though 18 lives are saved per 1,000 women treated.[30] This discrepancy is believed to be due to the combination of women presenting at an older age and the presence of more comorbid conditions.

Patients with diabetes. Fibrinolytic therapy has also been underused in patients with diabetes, possibly because physicians fear causing bleeding complications, specifically in those with proliferative retinopathy. Yet 37 lives are saved per 1,000 diabetic patients treated, an absolute benefit exceeding that in patients without diabetes.[30]

An analysis of the GUSTO-I data base showed that the risk of ocular hemorrhage following fibrinolytic therapy in patients with diabetic retinopathy was minimal and concluded that diabetic retinopathy is not a contraindication to fibrinolytic therapy.[31]

Patients with a prior MI are at particular risk if they have a second MI. Fibrinolytic therapy saves 15 lives per 1,000 patients treated who have had a prior MI.[30]

Patients in cardiogenic shock. The *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico* (GISSI)-1 and GUSTO-1 trials included patients in cardiogenic shock who received fibrinolytic therapy. There was no benefit of streptokinase over placebo[32] or over alteplase.[33] Given that most patients with cardiogenic shock were excluded from large randomized trials of fibrinolytic therapy, the data are limited. The data that are available have been obtained from subgroup analyses. The only therapy shown to definitively reduce mortality in the setting of cardiogenic shock is percutaneous coronary intervention or immediate coronary artery bypass grafting.[34]

Thus, patients presenting with an ST elevation MI experiencing cardiogenic shock should be treated with percutaneous coronary intervention, if it is available.[34] If percutaneous coronary intervention is unavailable, fibrinolytic therapy remains an acceptable alternative.

Patients with coronary artery bypass grafts. There is little information on the use of fibrinolytic therapy in patients with coronary artery bypass grafts, because most of these patients have been excluded from the large randomized trials. In this group of patients, the vein graft rather than a native vessel is the infarct vessel in approximately 80% of cases. Patency rates in the vein graft after fibrinolysis are in the range of 25%. Therefore, patients with prior grafting should ideally be treated with percutaneous coronary intervention.[35]

Cardiopulmonary resuscitation. The use of fibrinolytic therapy after cardiopulmonary resuscitation has not been well studied either, as these patients have been excluded from large trials. However, a study in 90 patients who experienced an out-of-hospital cardiac arrest showed that fibrinolytic therapy may be safe and improve outcome in this setting.[36] Another recent trial comparing alteplase and placebo in patients presenting with cardiac arrest and pulseless electrical activity found no beneficial effect of fibrinolysis.[37]

This subgroup of patients will require more research before a definitive answer can be obtained.

Hypertensive patients derive benefit from fibrinolytic therapy, though a blood pressure greater than 180/110 mm Hg is considered a relative contraindication.

In ISIS-2,[2] among patients with a systolic blood pressure greater than 175 mm Hg on presentation, the mortality rate was 4.8% with fibrinolytic therapy vs 7.5% without it.

A large meta-analysis[30] showed that fibrinolytic therapy saved 15 lives per 1,000 patients treated who presented with a systolic blood pressure of 150 to 174 mm Hg.[30] The mortality rate was also lower with fibrinolytic therapy than without it in patients who presented with a systolic blood pressure of 175 mm Hg or higher, but the trend was not statistically significant.

Nevertheless, the risk of intracranial hemorrhage with fibrinolytic therapy increases directly with the blood pressure. The GISSI group[32] found a fivefold increase in intracranial hemorrhage when the diastolic blood pressure was greater than 110 mm Hg. The meta-analysis[30] showed an increase in intracranial hemorrhage associated with a systolic blood pressure greater than 150 mm Hg.

Therefore, in patients with even one systolic blood pressure measurement greater than 180/110 mm Hg, percutaneous revascularization should be considered.

The risk of intracranial bleeding due to fibrinolytics increases directly with the blood pressure

PREHOSPITAL FIBRINOLYSIS IN THE GOLDEN HOUR

One of the key determinants of the success of fibrinolytic therapy is the interval between symptom onset and treatment. Early therapy,

within 1 hour of MI onset, can save as many as 50 lives per 1,000 patients treated, while later therapy is associated with an increasingly smaller benefit.[30]

Prehospital fibrinolytic therapy is gaining recognition. A randomized study[38] demonstrated that emergency medical services (EMS) crews could start fibrinolytic therapy a median of 31 minutes after their arrival. The time from EMS arrival to in-hospital administration of fibrinolytic therapy was 63 minutes; therefore, 32 minutes were saved by letting the EMS crew start the fibrinolytic therapy.

This strategy has also been associated with a 17% reduction in the odds of death compared with the in-hospital administration of fibrinolytic therapy.[38,39]

The Comparison of Angioplasty and Pre-Hospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study group compared prehospital fibrinolysis and emergent angioplasty for acute MI. The primary end point was a composite of death, nonfatal reinfarction, and nonfatal disabling stroke within 30 days. The event rate for the primary composite end point was 8.2% in the fibrinolytic group and 6.2% in the primary angioplasty group, $P = .29$. The authors concluded that primary angioplasty was not better than prehospital fibrinolysis.[40]

At the other extreme, fibrinolysis has been shown to be effective up to 12 hours from symptom onset, beyond which the risks of bleeding surpass the benefit.[41]

Fibrinolytics are underused, despite their impact on MI outcomes

LIMITATIONS OF FIBRINOLYTIC THERAPY

Fibrinolysis is associated with an early hazard of intracranial hemorrhage, which usually occurs in the first 24 hours and is fatal in nearly two thirds of patients who develop this complication.

An even more important limitation of this therapy has been termed "the illusion of reperfusion."[42] Although fibrinolytic therapy achieves TIMI grade 3 flow in the epicardial vessel in nearly 60% of patients at 60 to 90 minutes from the start of administration, at least 20% of patients with TIMI grade 3 flow do not have tissue-level perfusion. The lack of tissue-level perfusion is demonstrated by persistence of ST-segment elevation and no reflow by angiography or contrast echocardiography.[42]

Gibson et al[43] showed that approximately 50% of patients who achieved TIMI grade 3 epicardial flow after receiving tenecteplase did not achieve myocardial perfusion. The degree of myocardial perfusion was directly related to outcome.

Strategies focusing on tissue-level perfusion such as optimal dosing and timing, adjunctive antiplatelet therapy, and more potent fibrinolytic agents will likely lead to further reductions in mortality.

GIVING FIBRINOLYTIC THERAPY TO MORE PATIENTS

Despite the survival benefit of these agents, data have suggested that many potential candidates for fibrinolytic therapy are not receiving it. These agents should be considered in all patients presenting with ST-elevation MIs, and they should be considered as a therapeutic modality in patients with diabetes, those older than 75 years, and those presenting within 12 hours of symptom onset. The underuse of fibrinolytic therapy likely is due to fear of causing harm and to the relatively limited amount of data accrued in patients at high risk.

Further improvement in patient education and a better understanding of the risks associated with fibrinolytic therapy should lead to earlier presentation for therapy and more widespread use. Because of their profound impact on MI outcome, the emphasis should be on giving these agents to most patients with acute MI.

REFERENCES

1. **The GUSTO Angiographic Investigators.** The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615–1621.
2. **ISIS-2 Collaborative Group.** Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349–360.
3. **Park S.** Comparison of double bolus urokinase versus front-loaded alteplase regimen for acute myocardial infarction. Thrombolysis in Myocardial infarction in Korea (TIMIKO) Study Group. Am J Cardiol 1998; 82:811–813.
4. **ISIS-3 (Third International Study of Infarct Survival) Collaborative Group.** A randomised comparison of streptokinase vs. tissue plasmino-

gen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction: ISIS-3. Lancet 1992; 339:753–770.
5. **Martin U, van Mollendorff E, Akpan W, et al.** Pharmacokinetic and hemostatic properties of the recombinant plasminogen activator BM 06.022 in healthy volunteers. Thromb Haemost 1991; 66:569–574.
6. **Hu CK, Kohnert U, Wilhelm O, et al.** Tissue-type plasminogen activator domain-deletion mutant BM 06.022: modular stability, inhibitor binding, and activation cleavage. Biochemistry 1994; 33:11760–11766.
7. **Martin U, Sponer G, Strein K.** Evaluation of thrombolytic and systemic effects of the novel recombinant plasminogen activator BM 06.022 compared with alteplase, anistreplase, streptokinase and urokinase in a canine model of coronary artery thrombosis. J Am Coll Cardiol 1992; 19:433–440.
8. **Smalling RW, Bode C, Kalbfleisch J, et al.** More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID Investigators. Circulation 1995; 91:2725–2732.
9. **Bode C, Smalling RW, Berg G, et al.** Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. Circulation 1996; 94:891–898.
10. **The INJECT Investigators.** International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. Lancet 1995; 346:329–336.
11. **The GUSTO III Investigators.** A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997; 337:1118–1123.
12. **Cannon CP.** Thrombolysis medication errors: benefits of bolus thrombolytic agents. Am J Cardiol 2000; 85:17C–22C.
13. **Paoni N, Keyt B, Refino C, et al.** A slow clearing, fibrin-specific, PAI-1 resistant variant of t-PA. (T103N, KHRR 296-299 AAAA). Thromb Haemost 1993; 70:307–312.
14. **Refino C, Paoni N, Keyt B, et al.** A variant of t-PA (T103N, KHRR 296-299 AAAA) that, by bolus, has increased potency and decreased systemic activation of plasminogen. Thromb Haemost 1993; 70:313–319.
15. **Collen D, Stassen JM, Yasuda T, et al.** Comparative thrombolytic properties of tissue-type plasminogen activator and of a plasminogen activator inhibitor-1-resistant glycosylation variant, in a combined arterial and venous thrombosis model in the dog. Thromb Haemost 1994; 72:98–104.
16. **Cannon C, McCabe C, Gibson M, et al.** TNK-tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 10A dose-ranging trial. Circulation 1997; 95:351–356.
17. **Cannon CP, Gibson CM, McCabe CH, et al.** TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Circulation 1998; 98:2805–2814.
18. **Van de Werf F, Cannon CP, Luyten A, et al.** Safety assessment of single-bolus administration of TNK tissue plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. Am Heart J 1999; 137:786–791.
19. **The ASSENT-2 Investigators.** Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999; 354:716–722.
20. **Hansen L, Blue Y, Barone, K, Collen D, Larsen GR.** Functional effects of asparagine-linked oligosaccharide on natural and variant human tissue-type plasminogen activator. J Biol Chem 1988; 263:15713–19.
21. **Ogata N, Ogawa H, Ogata Y, et al.** Comparison of thrombolytic therapies with mutant tPA (lanoteplase/SUN9216) and recombinant tPA (alteplase) for acute myocardial infarction. Jpn Cir J 1998; 62:801–806.
22. **den Heijer P, Vermeer F, Ambrosioni E, et al.** Evaluation of a weight-adjusted single-bolus plasminogen activator in patients with myocardial infarction: a double-blind, randomized angiographic trial of lanoteplase versus alteplase. Circulation 1998; 98:2117–2125.
23. **The InTIME II Investigators.** Intravenous nPA for Treatment of Infarcting Myocardium Early-II. Eur Heart J 2000; 21:2005–2013.
24. **Collen D, Lijnen HR.** Staphylokinase, a fibrin-specific plasminogen activator with therapeutic potential? Blood 1994; 84:680–686.
25. **Schlott B, Hartmann M, Guhrs KH, et al.** High yield production and purification of recombinant staphylokinase for thrombolytic therapy. Biotechnology 1994; 12:185–189.
26. **Collen D, Van de Werf F.** Coronary thrombolysis with recombinant staphylokinase in patients with evolving myocardial infarction. Circulation 1993; 87:1850–1853.
27. **Vanderschueren S, Barrios L, Kerdsinchai P, et al.** A randomized trial of recombinant staphylokinase versus alteplase for coronary artery patency in acute myocardial infarction. Circulation 1995; 92:2044–2049.
28. **Armstrong PW, Burton JR, Palisaitis D, et al.** Collaborative Angiographic Patency Trial of Recombinant Staphylokinase (CAPTORS) [abstract]. Circulation 1999; 100:I-650.
29. **Armstrong PW, Burton JR, Pakola S, et al.** Collaborative Angiographic Patency Trial of Recombinant Staphylokinase (CAPTORS II) [abstract]. J Am Coll Cardiol 2002; 40:281A.
30. **Fibrinolytic Therapy Trialists Collaborative Group.** Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311–322.
31. **Mahaffey KW, Granger CB, Toth CA, et al.** Diabetic retinopathy should not be a contraindication to thrombolytic therapy for acute myocardial infarction: review of ocular hemorrhage incidence and location in the GUSTO-I trial. J Am Coll Cardiol 1997; 30:1606–1610.
32. **Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI).** Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1:397–401.
33. **Holmes DR, Bates ER, Kleiman NS.** Contemporary Reperfusion Therapy for Cardiogenic Shock: The GUSTO-1 Trial Experience. J Am Coll Cardiol 1995; 26:668–674.
34. **Hochman JS, Sleeper LA, Webb JG, et al.** Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. N Engl J Med 1999; 341:625–634.
35. **Grines CL, Booth DC, Nissen SE, et al.** Mechanism of acute myocardial infarction in patients with prior coronary artery bypass grafting and therapeutic implications. Am J Cardiol 1990; 65:1292–1296.
36. **Bottiger BW, Bode C, Kern S, et al.** Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinic trial. Lancet 2001; 357:1583–1585.
37. **Abu-Laban RB, Christenson JM, Innes GD.** Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 2002; 346:1522–1528.
38. **Morrow DA, Antman EM, Sayah A.** Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction. Results of the Early Retavase-Thrombolysis In Myocardial infarction (ER-TIMI) 19 trial. J Am Coll Cardiol 2002; 40:71–77.
39. **Morrison LJ, Verbeek PR, McDonald AC.** Mortality and prehospital thrombolysis for acute myocardial infarction: a meta analysis. JAMA 2000; 283:2686–2692.
40. **Bonnefoy E, Lapostolle F, Leizorovicz A.** Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet 2002; 360:825–829.
41. **The Late Study Group.** Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. Lancet 1993; 342:759–766.
42. **Lincoff AL, Topol EJ.** Illusion of reperfusion. Circulation 1993; 88:1361–1374.
43. **Gibson CM, Cannon CP, Murphy SA.** Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000; 101:125–130.

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