Drug Selection Perspectives

Thrombolytic Therapy: A Review of Its Use in Acute Myocardial Infarction

Eric D Bizjak and Vincent F Mauro

OBJECTIVE: To review the literature on the use of thrombolytic agents in the pharmacotherapeutic management of acute myocardial infarction (AMI).

DATA SOURCE: English-language clinical trials, reviews, and editorials derived from MEDLINE (January 1966–September 1997) and/or cross-referencing of selected articles.

STUDY SELECTION: Articles that were selected best represent the clinical trials researching the role for thrombolytics in the therapy of AMI to improve morbidity and mortality.

DATA SYNTHESIS: AMI is one of the leading causes of mortality in the US. Following supportive data that the most common cause of an AMI is an intracoronary thrombus, clinical investigation has demonstrated that intravenous thrombolytic agents improve survival rates in patients who experience an AMI. Several clinical trials have been conducted to determine whether one thrombolytic agent is superior to others with respect to improving mortality. At present, only the first Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial has reported any statistically significant difference in mortality rate. In this trial, "front-loaded" alteplase induced a statistically significant ($p < 0.001$) 1% absolute reduction in 30-day and 1-year mortality compared with streptokinase. This has led to alteplase being the preferred thrombolytic at many US institutions. However, the results of GUSTO-I have been questioned by some on the basis of either study design or clinical significance.

CONCLUSIONS: Thrombolytic agents have secured a place in the treatment of AMI due to their well-proven reduction in mortality rates. In general, comparative trials have demonstrated minimal differences in efficacy among these agents. Probably just as important as choosing which thrombolytic agent to use is ensuring that a patient experiencing an AMI is administered thrombolytic therapy unless a contraindication to receive such therapy exists in the patient and/or the patient is a candidate to receive an emergent intracoronary procedure. Trials also indicate that the sooner thrombolytics can be administered, the greater the benefit to the patient.

KEY WORDS: acute myocardial infarction, thrombolytic agents.

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ACUTE MYOCARDIAL INFARCTION (AMI) continues to be one of the leading causes of morbidity and mortality in the US. It has been estimated that 1.5 million Americans experience an AMI annually, resulting in nearly 500 000 deaths.[1] DeWood et al.[2] demonstrated that greater than 85% of AMIs result from a thrombotic occlusion of the coronary artery that supplied blood to the infarcted area. The results of this discovery unequivocally established a new direction in AMI therapy — the use of thrombolytic agents.

The use of thrombolytic agents to dissolve an occlusive clot has been one of the most significant advancements in the treatment of AMIs. Early reperfusion of the obstructed artery with the use of thrombolytics results in the limitation of infarct size,[3] preservation of left ventricular function,[4-6] and an improvement in overall survival.[7-9] Currently, there are four thrombolytic agents used for AMI in the US: streptokinase, anistreplase, alteplase, and reteplase. Urokinase failed to gain wide clinical interest due to its lack of superior efficacy compared with the far less expensive streptokinase during early clinical investigations.[10] The pharmacology, clinical efficacy (with emphasis on mortality), and safety profile of these four thrombolytic agents are reviewed. A brief discussion of adjunctive agents used concurrently with thrombolytic therapy to enhance their efficacy is also included.

Physiology of the Fibrinolytic System

Coronary artery thrombosis is a pathologic event that results in the obstruction of coronary blood flow. Arterial thrombi are composed primarily of platelets, fibrin, and

plasminogen. The physiologic fibrinolytic system is responsible for the lysis of pathogenic thrombi, but fails to address the initiating pathophysiologic process that led to the development of the thrombi.[11,12]

Thrombi result mostly from rupture of unstable atherosclerotic plaque that leads to a localized hemostatic response characterized by platelet aggregation. The ability of this to occur in a patient is directly related to the number of risk factors present in the patient for coronary artery disease, such as hyperlipidemia and hypertension, and can be reduced by using pharmacotherapeutic measures to remove these risk factors.[13]

The fibrinolytic system, schematically depicted in Figure 1, is composed of plasminogen, plasminogen activators, plasminogen activator inhibitors, and inhibitors of plasmin (α_2-antiplasmin). Plasminogen is a proenzyme that is converted to plasmin by plasminogen activators. Plasmin is the active enzyme that is responsible for the degradation of fibrin, in a process known as fibrinolysis. Fibrinolysis is initiated once plasminogen activators come into contact with fibrin-bound plasminogen. Physiologic examples of plasminogen activators include tissue plasminogen activators, urokinase, and activated clotting factor XII. Overzealous plasminogen activation is prevented by the presence of physiologic plasminogen activator inhibitors.[12,14-17]

Plasminogen activators may also stimulate the conversion of unbound plasminogen to unbound plasmin. The production of unbound plasmin potentially compromises the body's propensity to effectively perform hemostasis. Unbound plasmin degrades fibrinogen (the precursor to fibrin) in a process known as fibrinogenolysis. Unbound plasmin also degrades clotting factors V and VIII. The results of these actions, known as systemic fibrinolysis, induce what is referred to as a fibrinolytic state. α_2-Antiplasmin, present in plasma, inactivates unbound plasmin and, therefore, prevents a fibrinolytic state from occurring during physiologic fibrinolysis. Fibrin-bound plasmin resists inactivation by α_2-antiplasmin, whereas circulating unbound plasmin is rapidly inactivated. This allows prevention of an undesirable fibrinolytic state while permitting lysis of pathogenic thrombi. More detailed reviews of the fibrinolytic system are described elsewhere.[14-17]

Pharmacology

Realization that certain entities contain fibrinolytic activity originated in 1933, when Tillett and Garner[18] recog-

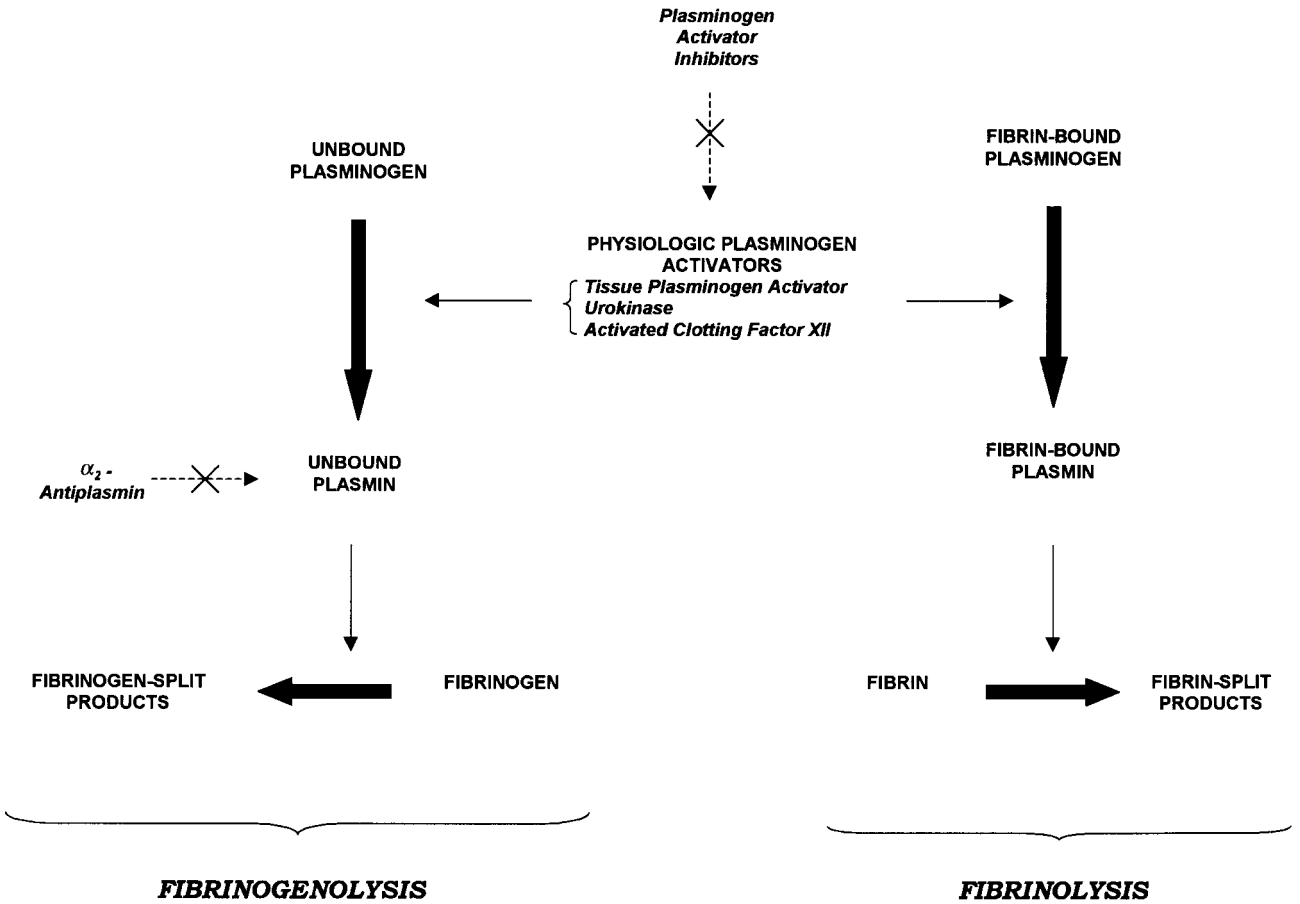

Figure 1. Schematic summary of physiologic fibrinolysis and fibrinogenolysis. Physiologic plasminogen activators catalyze the conversion of both unbound and fibrin-bound plasminogen to plasmin. Physiologic plasminogen activator inhibitors keep this process in check. Fibrin-bound plasmin degrades fibrin within the thrombus, leading to clot lysis (fibrinolysis). Circulating unbound plasmin is capable of degrading fibrinogen (fibrinogenolysis); however, the action of circulating α_2-antiplasmin prevents fibrinogenolysis from being clinically significant during normal physiologic conditions.

nized that a protein obtained from β-hemolytic streptococci, later to be called streptokinase, resulted in the dissolution of a fibrin clot. In 1954, Sherry[19] definitively identified that the fibrinolytic action of streptokinase was due to streptokinase inducing the conversion of plasminogen to plasmin. In the late 1950s, Fletcher et al.[20] conducted one of the first studies involving the administration of streptokinase in patients with AMI. On appreciating the clinical application streptokinase had in occlusive thrombotic disorders, research began on developing other thrombolytic agents. These subsequent agents, listed in Table 1,[21-28] differ in their pharmacology (schematically depicted in Figure 2), fibrin specificity, pharmacokinetic properties, method of administration, and antigenicity. The doses of these thrombolytic agents used for treatment of AMI are listed in Table 2.[21,23,25,27,29]

Table 1. Pharmacokinetics and Pharmacodynamic Comparison of Thrombolytic Agents

PARAMETER	STK[21,22]	ANST[23,24]	ALTPL[25,26]	RETE[27,28]
Molecular weight (Da)	47 000	131 000	70 000	39 600
Half-life (min)	~23	~88	~5	~15
Fibrin specificity	no	no	yes	yes, but slightly less so than alteplase
Plasminogen activation	indirect	direct	direct	direct
Antigenic	yes	yes	no	no

ALTPL = alteplase; ANST = anistreplase; RETE = reteplase; STK = streptokinase.

STREPTOKINASE AND ANISTREPLASE

Streptokinase is derived from streptococcal proteins produced by group C β-hemolytic streptococci.[21] Streptokinase activates the fibrinolytic system indirectly via a two-step process. First, streptokinase binds with a plasminogen molecule that can either be circulating or located within a thrombus, to form a streptokinase–plasminogen activator complex. Second, this complex converts several other plasminogens, both circulating and fibrin-bound, to plasmin. Production of fibrin-bound plasmin leads to fibrinolysis of the clot within which the plasmin is contained. Production of circulating plasmin leads to systemic fibrinolysis, since the amount of unbound plasmin produced by streptokinase overwhelms α_2-antiplasmin.[22,30,31]

As a result of streptokinase being derived from foreign proteins, it is antigenic in humans.[32] Administration of streptokinase is associated with the production of neutralizing antistreptokinase antibodies, similar to those induced by a streptococcal infection, which are capable of inactivating future doses of streptokinase if it is administered when these antibodies are present in significant amounts.[33] Significant titers of these antibodies have been reported to exist as long as 4 years after a dose of streptokinase was administered[34]; as such, repeat doses of streptokinase (or anistreplase for reasons described below) should not be administered for at least 4 years after streptokinase (or anistreplase) exposure, if not longer. Generally, when used in the treatment of an AMI, streptokinase is infused over 30–60 minutes.[22]

Anistreplase, a direct plasminogen activator, is a complex of streptokinase and plasminogen that, due to the presence of an anisoyl group bound to the complex, is inactive.[24] Once anistreplase is administered into the body, the anisoyl group is cleaved, rendering the complex active.[24,35] Because the deacylation is a slow process, anistreplase differs from streptokinase in that anistreplase has an extremely long half-life, which allows it to be administered as a single bolus infusion.[23,24] When activated, anistreplase exerts similar pharmacologic actions and antigenic responses as streptokinase. Originally, anistreplase was thought to have greater fibrin specificity compared with streptokinase, but this has not been shown to be the case.[36]

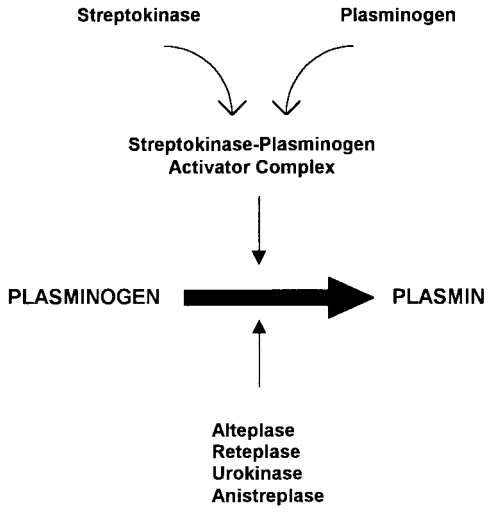

Figure 2. Schematic summary of thrombolytic pharmacology. Alteplase, reteplase, urokinase, and anistreplase are direct-acting plasminogen activators. Alternatively, streptokinase must first bind with a plasminogen molecule to form an activator complex, which is then capable of converting plasminogen to plasmin.

Table 2. Dosing and Administration of Thrombolytic Agents

DRUG	DOSAGE
Streptokinase[21]	1.5 million IU iv over 60 min
Anistreplase[23]	30 IU iv over 2–5 min
Alteplase[25]	accelerated infusion (ACC/AHA's preferred method of administration[29]) >67 kg: 15 mg iv bolus, followed by 50 mg iv infused over 30 min, and then 35 mg iv infused over 60 min ≤67 kg: 15 mg iv bolus, followed by 0.75 mg/kg iv infused over 30 min (not to exceed 50 mg), and then 0.5 mg/kg iv infused over 60 min (not to exceed 35 mg)
Reteplase[27]	10 U iv over 2 min; repeat dose 30 min after initiation of first dose

ACC/AHA = American College of Cardiology/American Heart Association.

ALTEPLASE AND RETEPLASE

Alteplase and reteplase are direct plasminogen activators that have greater fibrin specificity than streptokinase or anistreplase without possessing the antigenic risk.[28,37] Alteplase, which is identical to endogenous tissue plasminogen activator, was developed through recombinant DNA technology using human melanoma cell lines. Alteplase consists of 527 amino acids and has a molecular weight of nearly 70 000 Da. Alteplase is relatively fibrin-specific, meaning the activation of plasminogen by alteplase is greatly enhanced when fibrin is present.[26] Although a degree of systemic fibrinolysis occurs during administration of clinical doses of alteplase, a far lesser degree of fibrinolysis is induced with alteplase than with streptokinase or anistreplase.[37] Alteplase has a relatively short half-life, which necessitates that it be administered as a bolus injection followed by a short continuous infusion, rather than entirely as a bolus injection. When it was first approved for therapy of AMI, the dose of alteplase was approved to be administered over 3 hours.[38] More recent data indicate that greater coronary patency results if the same dose is administered over 90 minutes.[39,40] Subsequently, this accelerated, or front-loaded, dosing regimen is now recommended for routine use.[29]

Reteplase, the newest thrombolytic agent approved for use in AMI, is a variant of tissue plasminogen activator. It is produced in *Escherichia coli* through recombinant DNA technology.[28] Compared with alteplase, reteplase consists of only 355 amino acids and has a lower molecular weight of only 39 600 Da. Reteplase activates the fibrinolytic system in a manner similar to alteplase, but reteplase's structural variation results in a longer half-life than alteplase, allowing for the entire dose to be administered as two bolus doses separated by 30 minutes.[41] Reteplase's structural differences also include the deletion of a fibrin-binding domain. This domain, which is present on alteplase, is responsible for allowing a thrombolytic agent to be able to concentrate on the thrombus surface, thus enhancing the ability of the thrombolytic to be fibrin-specific and less apt to cause systemic fibrinolysis. The absence of this domain on reteplase results in a slightly lower affinity for fibrin and a slightly greater ability to produce systemic fibrinolysis compared with alteplase.[41] Theoretically, the absence of this domain could permit reteplase to be able to produce more rapid coronary patency than alteplase by its ability to reversibly bind to fibrin at different sites on the thrombus surface.[28,41]

Rethrombosis

Paradoxically, the use of thrombolytic therapy can also trigger rethrombosis at the site of the acute occlusion. Explanations of why this process occurs include the fact that fibrinolysis causes the release of thrombin originally bound within the thrombus. The newly released thrombin promotes the activation of clotting factors of V and VIII and stimulates platelet hyperactivity, thus creating an environment at the site of the acute occlusion suitable for thrombogenesis.[42]

Clinical Efficacy

Several trials investigating the use of intravenous streptokinase in AMI were performed in the 1960s and 1970s, but data gathered from these trials failed to conclusively demonstrate that the use of intravenous streptokinase resulted in clinical benefit.[43,44] A number of clinical trials performed in the early 1980s demonstrated a trend in decreasing morbidity and mortality rates when streptokinase was administered via the intracoronary route.[8,11] However, the practical logistics and difficulties of this administration technique led researchers to reinvestigate the clinical utility of using the intravenous route as the preferred means of administering thrombolytic agents during AMI. Several controlled clinical trials[45-52] were conducted that examined the effect of intravenously administered thrombolytic agents on overall mortality, compared with the effect of standard therapy. Five large multicenter, controlled trials, summarized in Table 3,[45-49,51] are reviewed below.

CONTROLLED TRIALS

The Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) study[45] was a double-blind, multicenter trial comparing the effects of intravenous streptokinase with placebo with respect to 21-day mortality. Approximately 1700 patients with symptoms suggestive of AMI and an electrocardiogram (ECG) demonstrating ST segment elevation were randomly assigned to receive either a 60-minute intravenous infusion of streptokinase 1.5 million IU or placebo. To be eligible, patients had to present within 6 hours of the onset of their AMI. More than half of the patients received therapy within 3 hours. The use of streptokinase was not associated with a significant reduction in 21-day mortality (6.3% streptokinase vs. 7.1% placebo). The authors observed that the magnitude of reduction associated with streptokinase was greater in the nearly 55% of the patients who were treated within 3 hours of AMI (5.2% streptokinase vs. 6.5% placebo); however, this difference was still nonsignificant. As these results may be partially explained by the relatively small size of the trial, larger trials need to be conducted to see a difference.

The first Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-I) study[46] was an open, multicenter trial conducted in more than 11 000 patients with symptoms suggestive of AMI and either ST segment elevation or depression. Patients were randomized to receive either intravenous streptokinase 1.5 million IU over 60 minutes or no thrombolytic agent. Patients were enrolled if they presented within 12 hours of the onset of the AMI. The primary end point was 21-day mortality. Approximately half of the patients received therapy within 3 hours. Analysis of data at 21 days revealed a significant 18% decrease ($p = 0.0002$) in overall mortality in patients treated with streptokinase (10.7%) compared with the control group (13.0%). Subgroup analysis of those who presented within 1 hour of their AMI onset demonstrated an even more impressive 47% decrease ($p = 0.0001$) in mortality in the streptokinase group (8.2%) than in the control group (15.4%). Streptokinase did not significantly alter 21-

day mortality of a small portion of patients (n = 451) entered into the trial with ST segment depression (20.5% streptokinase vs. 16.3% control; NS). Overall mortality at 1 year also was significantly decreased (p = 0.008) within the streptokinase group (17.2%) compared with the control group (19.0%). At 21 days, this benefit was even greater in the patients treated with streptokinase within 1 hour of onset (12.9% streptokinase vs. 21.2% control; p = 0.00001). A significant increase in mortality at 1 year was associated with streptokinase use in patients entered with ST segment depression (34.0% streptokinase vs. 24.2% control; p = 0.02).[47]

The investigators in the Second International Study of Infarct Survival (ISIS-2)[48] also compared streptokinase with placebo. In addition, this study investigated the impact of aspirin therapy on AMI survival. ISIS-2 was designed as a double-blind, placebo-controlled trial involving more than 17 000 patients who presented within 24 hours of AMI. ECG alterations were not required for entry into this trial. Patients were randomized to receive one of four therapies: streptokinase infusion plus aspirin therapy, streptokinase infusion plus placebo tablets, placebo infusion plus aspirin therapy, or placebo infusion plus placebo tablets. Streptokinase was given as 1.5 million IU intravenously over 60 minutes. Aspirin was given as an initial 162.5-mg tablet to be chewed immediately on entry into the trial followed by a daily dose for a total of 1 month. The primary end point was vascular death at 35 days. The combination of streptokinase and aspirin reduced cardiovascular mortality by 42% compared with the double-placebo group (8.0% streptokinase + aspirin vs. 13.2% double placebo; p < 0.00001). The combination also provided significantly lower mortality than either streptokinase alone (10.4%; p < 0.0001) or aspirin alone (10.7%; p < 0.0001). Subgroup analysis based on ECGs obtained when patients were entered into the trial revealed that streptokinase had no significant impact on 35-day mortality in 315 patients with normal ECGs (1.9% streptokinase vs. 3.9% control; NS) or in 1137 patients with ECGs demonstrating ST segment depression (18.7% streptokinase vs. 18.6% control; NS).

The APSAC Intervention Mortality Study (AIMS)[49] investigated the effect of anistreplase on mortality. In this multicenter trial, over 1200 patients who presented within 6 hours of symptoms and ECGs with ST segment elevations suggestive of an AMI were randomized to receive either anistreplase 30 IU or a placebo bolus dose as an intravenous injection administered over 5 minutes. Thirty-day mortality was significantly reduced (p = 0.0016) from 12.2% within the placebo group to 6.4% within the anistreplase group. Mortality at 1 year continued to be significantly less (p = 0.0007) within the anistreplase group (11.1%) than within the placebo group (17.8%).[50]

The Anglo-Scandinavian Study of Early Thrombolysis (ASSET) Study Group[51] compared the impact of alteplase on 1-month mortality compared with placebo. Approximately 5000 patients with symptoms suggestive of an AMI were randomized to receive either alteplase (given as 100 mg over 3 h) or a placebo infusion within 5 hours of their infarct. Changes in ECG were not required for entry. Results at 1 month revealed a significant 26% reduction (p = 0.0011) in mortality within the alteplase group (7.2%) compared with the placebo group (9.8%). ECG changes were not present in 874 patients entered into the trial. No significant difference in the mortality rates of these patients was observed (1.6% alteplase vs. 3.0% placebo; NS). Overall mortality at 6 months continued to be significantly lower in patients receiving alteplase (10.4% alteplase vs.

Table 3. Controlled Thrombolytic Trials

TRIAL	TYPE OF STUDY	TREATMENT GROUPS	SIZE OF POPULATION (n)	TIME FROM ONSET OF SYMPTOMS (h)	MORTALITY END POINT	RESULTS (%)	p VALUE	STROKES (%) (total/hemorrhagic)
ISAM[45]	R,DB,MC	streptokinase 1.5 million U over 1 h	859	6	21-d mortality	6.3	NS	NR/~0.5
		placebo	882			7.1		NR/0.0
GISSI-I[46,47]	R,OL,MC	streptokinase 1.5 million U over 1 h	5860	12	21-d mortality	10.7	p = 0.0002	0.7/NR (at 6 mo.)
		control	5852			13.0		0.7/NR
ISIS-2[48]	R,DB,MC	streptokinase + aspirin	4292	24	35-d vascular mortality	8.0	p < 0.0001[a]	0.6/0.1
		streptokinase alone	4300			10.4	p < 0.0001[b]	0.8/0.05
		aspirin alone	4295			10.7	p < 0.00001[c]	0.5/0.0
		double placebo	4300			13.2		1.0/0.0
AIMS[49]	R,DB,MC	anistreplase 30 U over 5 min	502	6	30-d mortality	6.4	p = 0.0016	0.4/NR
		placebo	502			12.2		1.0/NR
ASSET[51]	R,DB,MC	alteplase 100 mg over 3 h	2515	5	1-mo mortality	7.2	p = 0.0011	1.1/0.3
		placebo	2494			9.8		1.0/0.1

AIMS = APSAC Intervention Mortality Study; ASSET = Anglo-Scandinavian Study of Early Thrombosis; DB = double-blind; GISSI-I = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2 = Second International Study of Infarct Survival; MC = multicenter; NR = not reported; NS = nonsignificant difference; OL = open label; R = randomized.
[a]Streptokinase plus aspirin versus streptokinase plus placebo.
[b]Streptokinase plus aspirin versus aspirin plus placebo.
[c]Streptokinase plus aspirin versus double placebo.

13.1% placebo; p = 0.0026). The lack of a significant difference in mortality rates of patients with normal ECGs continued to be present (3.2% alteplase vs. 3.7% placebo; NS).[52]

The results of these large trials demonstrated that thrombolytic agents are of benefit in improving the survival of AMI patients presenting with ST segment elevation, especially when patients received therapy within 6 hours of the onset of the AMI. The benefit of these agents in patients who received therapy 6 hours after the onset of the AMI was not as well delineated. Therapy administered beyond the first few hours was analyzed in the ISIS-2 and GISSI-I trials. ISIS-2[48] demonstrated a significant benefit in mortality in patients treated after 5 hours of the onset of the AMI, whereas only a trend was observed in GISSI-I[46] for patients treated after 6 hours. The Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS)[53] and the Late Assessment of Thrombolytic Efficacy (LATE)[54] studies were designed to further investigate the delayed use of thrombolytics.

EMERAS[53] was a randomized, double-blind, placebo-controlled trial comparing streptokinase 1.5 million IU over 1 hour with placebo in nearly 2000 patients presenting between 7 and 12 hours after the onset of AMI symptoms. The results demonstrated a nonsignificant reduction in mortality prior to hospital discharge with the use of streptokinase (11.7% streptokinase vs. 13.2% placebo). LATE[54] was a randomized, double-blind, placebo-controlled trial that compared alteplase 100 mg over 3 hours with placebo in nearly 5700 patients presenting within 6–24 hours after onset of AMI symptoms. In the 2075 patients who were treated within 6–12 hours, alteplase had a significant 25.6% reduction in 35-day mortality compared with the 3611 patients treated with placebo (8.9% alteplase vs. 12.0% placebo; p = 0.0229). Although the LATE trial extended the window of treatment opportunity beyond 12 hours, the reduction in mortality associated with alteplase did not reach statistical significance in patients treated between 12 and 24 hours (8.7% alteplase vs. 9.2% placebo; NS).

As a result of these trials, it has become so well-established that thrombolytic therapy reduces mortality in patients experiencing an AMI that placebo-controlled trials with reteplase have not been conducted in patients.

COMPARATIVE TRIALS

Given the acceptance that thrombolytic therapy use during an AMI definitively reduces patient mortality, the question arises as to whether one thrombolytic agent is clearly superior to others available, especially with respect to improving survival. This is an extremely important issue, given the acquisition cost difference between thrombolytic agents. For therapy of an AMI, the average wholesale price (AWP) of streptokinase is approximately $550, whereas the AWP of both alteplase and reteplase is approximately $2750.[55] A summary of the five large comparative trials discussed below is presented in Table 4.[56-60]

The first large study to examine comparative mortality between thrombolytic agents was the trial conducted by the International Study Group (ISG)[56] in more than 20 000 patients. The ISG trial incorporated data from nearly 12 000 patients entered into the GISSI-II trial,[61] another large, similarly conducted study as the ISG trial that compared alteplase with streptokinase. The primary end point of GISSI-II was combined mortality and left ventricular dysfunction. The primary end point of the ISG trial was mortality; therefore, the ISG trial was selected for discussion in this article. In the ISG trial, patients with symptoms of an AMI that started within the past 6 hours were randomized to receive either streptokinase 1.5 million IU over 30–60 minutes or alteplase 100 mg over 3 hours. In-hospital mortality was not significantly different between the two groups (8.9% alteplase vs. 8.5% streptokinase; risk ratio [RR] 1.05; 95% CI 0.95 to 1.16). Major hemorrhages (other than strokes) occurred more frequently in the streptokinase group than in the alteplase group (0.9% streptokinase vs. 0.6% alteplase; RR 0.67; 95% CI 0.49 to 0.91). In contrast, strokes were more common in the alteplase group than in the streptokinase group (1.3% alteplase vs. 0.9% streptokinase; RR 1.41; 95% CI 1.09 to 1.83). Six-month analysis also revealed no significant difference in mortality between the two groups (12.3% alteplase vs. 11.7% streptokinase; RR 1.06; 95% CI 0.97 to 1.15).[62]

Although it would appear that these medications were equally effective with respect to mortality, it cannot be ignored that the method of administering heparin in this trial may have had an impact on the results. Half of the patients within each thrombolytic group were randomized to receive subcutaneous heparin 12 500 units every 12 hours until discharge; however, heparin therapy was not initiated until 12 hours after the start of infusing the selected thrombolytic therapy. As discussed above, it has been suggested that successful thrombolysis creates an environment within the coronary artery that encourages thrombogenic activity.[42] Bleich et al.[63] demonstrated that a higher incidence of coronary patency occurred at 48–72 hours when intravenous heparin therapy was administered concurrently with alteplase than when alteplase was used alone. The sixth European Cooperative Study Group (ECSG-6)[64] observed a significantly (RR 0.66; 95% CI 0.47 to 0.93) greater incidence of patency 48–120 hours following alteplase administration when it was given with intravenous heparin therapy compared with alteplase alone. Given these observations, the ironic fact that thrombogenesis may result from thrombolytic use, and the fact that the half-life of alteplase is relatively short (~5 min[25]), the omission of using heparin or the 12-hour delay in instituting heparin may have negatively biased the findings of the alteplase groups by permitting reocclusion to occur during the heparin-free interval. Although the method of administering heparin is also unlikely to have biased the streptokinase findings, the impact may have been of a lesser degree because the half-life of streptokinase is considerably longer (~23 min[21]) and because streptokinase induces more profound systemic fibrinolysis.

A second trial[57] investigating comparative survival benefits among the thrombolytic agents was the third International Study of Infarct Survival (ISIS-3). This double-blind, placebo-controlled trial compared three thrombolytic agents (streptokinase 1.5 million IU over 1 h, anistreplase 30 IU

over 3 min, and duteplase 0.6 million unit/kg over 4 h) in more than 40 000 patients suspected of having an AMI that started within the past 6 hours. The incidence of mortality at 35 days was not significantly different between any of the groups (10.6% streptokinase vs. 10.3% duteplase vs. 10.5% anistreplase). Bleeding (other than strokes) occurred more often with anistreplase (5.4%; 2p < 0.00001) and duteplase (5.2%; 2p < 0.01) than with streptokinase (4.5%). Strokes also occurred more frequently with anistreplase (1.26%; 2p = 0.08) and duteplase (1.39%; 2p < 0.01) than with streptokinase (1.04%). As in the ISG trial, heparin therapy was randomized and given subcutaneously (12 500 units twice daily for 7 d or until the patient was discharged) to half of the patients; however, heparin therapy was initiated 4 hours after the start of thrombolytic therapy. Although this earlier administration of heparin would not be expected to bias the results as much as in the ISG trial, contention still arises as to how to interpret the findings of ISIS-3, since the heparin regimen used was not the standard intravenous method of administration in the US. Further impairing interpretation of these results is the fact that the tissue plasminogen activator used in this trial (duteplase) is not available for use in the US.

The first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial[58] was the third large trial designed to compare effects on mortality rates among thrombolytic agents. More than 40 000 patients were randomized to receive alteplase (using an accelerated weight-based dosing regimen, generally 100 mg over 1.5 h), streptokinase (1.5 million IU over 1 h), or a combination of alteplase and streptokinase (simultaneous 1-h infusions of alteplase 90 mg and streptokinase 1 million IU) within 6 hours of chest pain. Heparin was administered to all patients, generally as

Table 4. Thrombolytic Comparative Trials

TRIAL	TYPE OF STUDY	TREATMENT GROUPS	SIZE OF POPULATION (n)	TIME FROM ONSET OF SYMPTOMS (h)	MORTALITY END POINT	RESULTS (%)	p VALUE	COMMENTS
ISG[56]	R,OL,MC	streptokinase 1.5 million U over 0.5–1.0 h	10 396	6	6-mo mortality	8.5	NS	sc heparin administered 12 h after starting a thrombolytic in half of the pts.
		alteplase 100 mg over 3.0 h	10 372			8.9		
ISIS-3[57]	R,DB,MC	streptokinase 1.5 million U over 1.0 h	13 780	24	35-d mortality	10.6	NS[a]	sc heparin administered 4 h after starting a thrombolytic in half of the pts.
		duteplase 0.6 million U/kg over 4.0 h	13 746			10.3		
		anistreplase 30 U over 3 min	13 773			10.5		
GUSTO-I[58]	R,OL,MC	streptokinase 1.5 million U over 1.0 h	20 173	6	30-d mortality	7.3	0.001[b]	all pts. received heparin; the alteplase and streptokinase + alteplase pts. received iv
		alteplase 100 mg over 1.5 h	10 344			6.3	0.04[c]	heparin; streptokinase pts. were randomly assigned to
		combination streptokinase 1 million U + alteplase 90 mg, administered over 1.0 h)	10 328			7.0	NS[d]	receive either sc or iv heparin
INJECT[59]	R,DB,MC	streptokinase 1.5 million U over 1.0 h	3006	12	35-d mortality	9.5	NS	based on mortality, results indicate that these agents are equivalent
		reteplase (two 10 million-U bolus doses separated by 30 min)	3004			9.0		
GUSTO-III[60]	R,OL,MC	reteplase (two 10-U bolus doses separated by 30 min)	10 138	6	30-d mortality	7.5	NS	due to the statistical design of this study, reteplase was not superior to alteplase based on mortality; however, it cannot
		alteplase 100 mg over 1.5 h	4921			7.2		be concluded that these agents are equivalent

DB = double-blind; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; INJECT = International Joint Efficacy Comparison of Thrombolytics; ISG = International Study Group; ISIS = International Study of Infarct Survival; MC = multicenter; NS = nonsignificant difference; OL = open-label; R = randomized.

[a]Streptokinase versus duteplase and streptokinase versus anistreplase.

[b]Alteplase versus streptokinase.

[c]Alteplase versus combination.

[d]Streptokinase versus combination.

an intravenous bolus dose (5000 units) followed by a continuous infusion (1000 units/h in patients ≤ 80 kg or 1200 units/h in patients > 80 kg) that was initiated with the thrombolytic agent and continued for at least 48 hours with the dosage adjusted to maintain an activated partial thromboplastin time (aPTT) between 60 and 85 seconds. The exception to this occurred in nearly half of the streptokinase patients who were administered subcutaneous heparin, as described in the ISIS-3 trial, rather than intravenous heparin.[57] This was to determine whether the use of subcutaneous heparin, as used in ISIS-3, would produce results different from those of streptokinase patients receiving the standard intravenous heparin regimen. Subsequently, no major differences in deaths, strokes, and bleeding between heparin regimens were found among the streptokinase groups; therefore, the following results of GUSTO-I include the combining of data from the two streptokinase groups.[58] The incidence of mortality at 30 days was 6.3% with alteplase and 7.3% with streptokinase. This absolute difference of 1% in the mortality rate was statistically significant ($p < 0.001$). The combined use of thrombolytic agents did not demonstrate any significant advantages compared with alteplase or streptokinase alone; in fact, the combination regimen was associated with a significantly greater incidence in mortality compared with alteplase alone (7.0% combination vs. 6.3% alteplase; $p = 0.04$). Severe bleeding occurred equally in the alteplase and streptokinase groups. Moderate bleeding tended to be present more frequently ($p = 0.04$) in the streptokinase groups (5.7%) than in the alteplase group (5.1%). Although not statistically different, strokes tended to be more frequent ($p = 0.09$) in the alteplase group (1.55%) than in the streptokinase groups (1.31%), whereas hemorrhagic strokes occurred significantly more often ($p = 0.03$) within the alteplase group (0.72%) than in the streptokinase groups (0.52%). The investigators also analyzed the net clinical benefit (accounting for both deaths and serious complications) of alteplase with that of streptokinase to determine whether the greater incidence of cerebrovascular complications associated with alteplase outweighed its benefit in enhancing survival. The incidence of the combination of nonfatal strokes and all-cause deaths (including fatal strokes) associated with alteplase (7.2%) was still significantly less ($p = 0.006$) than that reported with streptokinase (8.1%). When only disabling nonfatal strokes are added with all-cause deaths, the reported incidence continued to occur significantly less often ($p = 0.006$) in the alteplase group (6.9%) than in the streptokinase group (7.8%). On 1-year follow-up analysis, a statistically significant 1% absolute reduction ($p = 0.003$) in mortality still existed between the alteplase (9.1%) and streptokinase (10.1%) groups.[65]

The GUSTO-I[58] investigators also reported the results of prespecified subgroup analyses. The benefit of alteplase was most favorable in AMI patients younger than 75 years and in patients with an anterior AMI. The investigators also originally reported that patients seeking medical intervention within the first 4 hours of their infarction also received a superior benefit with alteplase, but later refuted this claim subsequent to a follow-up analysis, a fact not widely known among health professionals.[66]

GUSTO-I,[58] which used the tissue plasminogen activator product available in the US and the intravenous heparin regimen typically used in the US, demonstrated that an accelerated infusion of alteplase was significantly superior to streptokinase in improving survival of myocardial infarction patients based on statistical analysis. However, the facts that only 1 death per 100 patients treated is saved by using alteplase over streptokinase, that the acquisition cost of using alteplase to save this 1 life in 100 is nearly $200 000 more than with using streptokinase, and that the incidence of nonfatal stroke is greater with alteplase (~1 of 1000 patients treated) have prevented universal acceptance of alteplase being the thrombolytic agent of choice in patients experiencing an AMI.[67,68]

In an effort to assess alteplase's added expense, Mark et al.[69] have published a cost-effectiveness analysis comparing alteplase with streptokinase from a societal perspective using the results obtained in GUSTO-I. They reported that the total healthcare costs associated with using alteplase was $2845 higher than with streptokinase. However, when the mortality benefit of alteplase was taken into account, the cost per year of life saved associated with using alteplase was $32 678. On subgroup analysis, it was observed that the cost of life saved was most expensive for patients 40 years or younger (>$100 000 per year of life saved) and least expensive for patients older than 75 years (<$20 000 per year of life saved). For each age group studied, the cost of life saved was more expensive with inferior infarctions than with anterior infarctions. Given the overall cost-effectiveness ratio of approximately $33 000 per life saved reported from the study, the question arises as to whether this value is too costly for society. Goldman et al.[70] reported that cost-effectiveness ratio values less than $40 000 per year of life saved should be considered relatively cost-effective, since this value approximates that of renal hemodialysis. Assuming that there are 250 000 patients with an AMI eligible to receive thrombolytic therapy per year in the US, based on their findings, Mark et al.[69] stated that 38 500 years of life can be saved at a cost of $500 million, a price considered to be cost-effective. In this analysis, the costs of patient care were derived from the clinical course of patients who were admitted to select institutions conducting the GUSTO-I trial. It would be of interest to know how these cost-effective analyses extrapolate to the general population whose AMIs are treated in community hospitals. In addition, from an institutional perspective, the site administering alteplase would not directly appreciate the societal economic benefit of using alteplase.

Armentano and Favaloro[71] reported a cost analysis from a different perspective. Using the data from Mark et al. in a simple approach (extra cost of using alteplase divided by each life saved at 1 y), they calculated that using alteplase costs approximately $260 000 for each life saved at 1 year.

Using the data from the subgroup analyses of GUSTO-I, an algorithm has been developed based on patients' age and infarction location to suggest when streptokinase or alteplase may be preferred over the other in treating AMI patients in efforts to maximize efficacy and minimize expense.[72] This manner of adapting the subgroup analyses, as with any subgroup analysis, is not without scientific limita-

tions. Caution should be used when applying this algorithm, since the reproducibility of the GUSTO-I subgroup findings in prospective, randomized trials is lacking.

The results of GUSTO-I have led to alteplase being the preferred thrombolytic agent at many US institutions; however, this trial has not been without criticism. Eisenberg[73] has identified several of the concerns and potential limitations of this study. The study was not double-blind and some patients may not have received a full dose of streptokinase due to the development of hypotension and possible overreaction by health professionals in discontinuing the streptokinase infusion. Coronary intervention procedures may have occurred more frequently in the alteplase group than in the streptokinase group. The issue has also been raised that results obtained in North America tended to differ from results obtained outside North America.

The two most recent trials comparing survival rates of patients receiving thrombolytic agents have included reteplase, the newest thrombolytic agent available in the US. The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial[59] compared reteplase with streptokinase in hopes of proving that reteplase was equivalent to streptokinase with respect to decreasing mortality rates. More than 6000 patients diagnosed with an AMI within 12 hours were randomized to receive either reteplase two 10-unit bolus doses separated by 30 minutes or streptokinase 1.5 million IU over 1 hour. Intravenous heparin was used with both medications (a bolus dose given simultaneously with the initiation of the thrombolytic followed by a continuous infusion initiated 60 min later that was continued for at least 24 h). Mortality at 35 days was 9.0% with reteplase and 9.5% with streptokinase, a small enough absolute difference in mortality rates to statistically support (difference –0.51%; 95% CI –1.98 to 0.96) the conclusion that reteplase is equivalent to streptokinase with respect to their impact on mortality.

In contrast to INJECT,[59] the primary goal of GUSTO-III[60] was to prove that reteplase reduced 30-day mortality rates to a greater extent than did alteplase. In GUSTO-III, more than 15 000 patients with an AMI that started within the past 6 hours were randomized (in 2:1 fashion favoring reteplase) to receive reteplase two 10-unit bolus doses separated by 30 minutes or alteplase at the dose used in GUSTO-I. Intravenous heparin was administered concurrently with both thrombolytic agents as follows: 5000-unit bolus dose followed by a continuous infusion (800 units/h in patients <80 kg and 1000 units/h in patients ≥80 kg) with the dosage adjusted to maintain an aPTT between 50 and 70 seconds. At 30 days, the mortality was 7.47% in the reteplase group and 7.24% in the alteplase group, a trend favoring alteplase but a nonsignificant difference (odds ratio 1.03; 95% CI 0.91 to 1.18). According to the authors, the rates of overall strokes and hemorrhagic strokes did not differ significantly. As a result, this trial failed to demonstrate that reteplase was superior to alteplase. Since the aim of this study was to prove that reteplase was superior to alteplase, one cannot take for granted that the lack of proving this point allows one to assume that the medications are equivalent.[74] It may be that a difference does exist between treatments, but in a direction opposite that expected by investigators (i.e., alteplase being superior to reteplase).

Open-Artery Hypothesis

Before discussion of the open-artery hypothesis, a review of a generally accepted system used to grade coronary patency is warranted. The Thrombolysis in Myocardial Infarction (TIMI) study[75] developed a scale (using integers ranging from 0 to 3) based on coronary blood flow to evaluate the degree of patency acquired in previously obstructed arteries following the use of thrombolytic agents. The scale is described in Table 5.[75] Until recently, TIMI grade 2 flow attainment was considered to lead to outcomes similar to those of TIMI grade 3 flow, and as a result, the attainment of TIMI grade 2 flow was often categorized collectively with the attainment of TIMI grade 3 flow as end points in clinical trials. However, meta-analysis data indicate that patients achieving TIMI grade 2 flow actually have outcomes that are more similar to those of patients achieving TIMI grade 0 or grade 1 flow.[76] As a result, many investigators now accept only the attainment of TIMI grade 3 flow as achievement of successful patency.

When a patient experiences an AMI, it has been postulated that the earlier reperfusion occurs within the occluded coronary artery, the more apt the acutely ischemic myocardial tissue will be salvaged (versus becoming infarcted), thus leading to decreased morbidity and mortality rates for the patient. This thinking has become known as the open-artery hypothesis.[9,77] This hypothesis appears to be supported by several of the clinical trials described above documenting the effectiveness of thrombolytic therapy in AMI. In these trials,[45,46,48] the earlier a thrombolytic agent was administered to patients, the greater the magnitude of mortality benefit. This would appear to suggest that, if a given thrombolytic agent could induce coronary patency earlier than other thrombolytic agents, it would be associated with greater survival. However, not all clinical trials have been able to definitively validate this premise.

In GUSTO-I, angiographic investigation was performed in a subgroup of patients.[78] In patients angiographed 90 minutes after the start of thrombolytic therapy, the achievement of TIMI grade 3 flow occurred in 54% of 292 patients receiving alteplase compared with 31% of 576 patients receiving streptokinase alone ($p < 0.001$). This difference in patency rates between the two groups

Table 5. Thrombolysis in Myocardial Infarction (TIMI) Coronary Patency Scale[75]

TIMI GRADE OF CORONARY BLOOD FLOW	CLINICAL DESCRIPTION
0	failure to reestablish any degree of coronary blood flow
1	achievement of minimal coronary blood flow
2	partial reestablishment of coronary blood flow
3	nearly complete or complete reestablishment of normal coronary blood flow

disappeared in patients who were angiographed at 180 minutes (38% of 203 streptokinase patients vs. 43% of 93 alteplase patients) and at 5–7 days (54% of 189 streptokinase patients vs. 58% of 83 alteplase patients) after thrombolytic therapy. In addition, the magnitude of improved survival associated with alteplase over that with streptokinase was only an absolute difference of 1%, not as great as one might expect, given the 20% absolute difference between therapies with respect to 90-minute patency rates.[73,79] In the Reteplase versus Alteplase Patency Investigation During Acute Myocardial Infarction (RAPID-2) study,[80] more than 300 patients were randomized to receive either front-loaded alteplase or reteplase (two 10-unit bolus doses separated by 30 min). Although TIMI grade 3 flow was achieved with reteplase in a significantly greater number of patients at 60 minutes (51% reteplase vs. 37% alteplase; $p < 0.05$) and at 90 minutes (60% reteplase vs. 45% alteplase; $p < 0.05$), patency rates determined 5–14 days into the trial were similar in the two groups (75% reteplase vs. 77% alteplase; NS). In addition, as described above, GUSTO-III[60,80] failed to observe a mortality difference between these two therapies despite the fact that the smaller RAPID-2 trial suggested that reteplase was capable of achieving a greater incidence of early patency than was alteplase. These observations may indicate that producing a marginal benefit in opening the culprit coronary artery earlier with one thrombolytic agent versus others may not be enough for that agent to proclaim clinical superiority. Such an agent may also need to prove that it is far more effective in both inducing and sustaining complete patency.

On the other hand, early patency may be important in determining clinical outcomes, but at a time earlier than the 90-minute patency that has been traditionally studied. In the RAPID-2 study, 30-minute patency rates obtained in approximately 100 patients were not significantly different between the two treatment groups.[80] This observation along with knowledge that mortality rates did not differ significantly in GUSTO-III leads to the possibility that 30-minute patency rates should be studied to determine their impact on clinical outcomes.

Adjunctive Therapy

The acute use of agents such as intravenous nitroglycerin and β-blockers have been shown to improve the survival of AMI patients independent from the use of thrombolytic therapy. The chronic use of oral agents such as β-blockers, angiotensin-converting enzyme inhibitors, aspirin, and antihyperlipidemic agents has also been proven to improve the survival of patients with AMI. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines for the management of AMI discuss in detail the proper use of these therapies.[29] An additional clinical benefit to that of thrombolytic therapy may be seen when aspirin, heparin, or other anticoagulant or antiplatelet agents are coadministered with thrombolytic agents during an AMI.[81] A brief discussion of the use of these agents follows below.

The role of aspirin in AMI was clearly defined by the ISIS-2 trial in which patients receiving both aspirin and streptokinase had a lower incidence of vascular deaths than those receiving streptokinase alone.[48] As aspirin therapy also has been shown to reduce strokes and nonfatal reinfarctions in patients with an AMI, it is recommended that aspirin 160–325 mg be immediately administered on recognition of an AMI and be continued daily in patients who have no absolute contraindication to its use.[29]

The role of heparin as an adjunctive agent is not as clearly defined as that for aspirin. As discussed earlier, Bleich et al.[63] and ECSG-6[64] observed greater clinical patency when heparin was used concurrently with alteplase. The results of ISG[56] and ISIS-3[57] failed to demonstrate that heparin had any significant impact on survival or total strokes. In ISG[56] and ISIS-3,[57] more bleeding was observed with the use of heparin. In ISIS-3,[57] cerebral hemorrhage was significantly ($2p < 0.05$) more frequent; however, as discussed above, the heparin dosing protocols used in these trials are subject to critique. Current ACC/AHA guidelines[29] state that patients receiving alteplase should receive intravenous heparin dosed to maintain an aPTT between 1.5 and 2.0 times control for 48 hours. The manufacturer[27] also recommends that heparin be used with reteplase in similar fashion. The infusion should be continued for longer than 48 hours only if patients have an anterior MI, congestive heart failure (CHF), previous embolus, or atrial fibrillation. Based on ACC/AHA guidelines,[29] patients receiving streptokinase or anistreplase should not routinely receive intravenous heparin for reasons described above. Exceptions are patients who present with an anterior MI, CHF, previous embolus, or atrial fibrillation, in which case it is suggested that heparin be initiated when the patient's aPTT is less than 2.0 times control following the use of streptokinase or anistreplase, but no earlier than 4 hours after starting the selected thrombolytic agent. Patients not receiving intravenous heparin should at least receive subcutaneous heparin 7500 units every 12 hours for deep-venous thrombosis prophylaxis until full ambulation is achieved.

Given the inconclusive role for concurrent heparin use with thrombolytic agents, hirudin, a direct thrombin inhibitor, has been compared with heparin in patients receiving thrombolytic therapy in hopes that hirudin would provide a more defined clinical benefit beyond that of heparin.[82] At present, hirudin has failed to clearly demonstrate any significant superiority over heparin when used in combination with thrombolytic agents. In TIMI-9b,[83] no significant difference in 30-day mortality was observed when hirudin was compared with heparin in 3000 patients concurrently receiving thrombolytic therapy. In the GUSTO-IIb study[84] conducted in 12 000 patients, the 30-day mortality when hirudin was used in conjunction with thrombolytic therapy was 8.9% compared with 9.8% when heparin was used ($p = 0.06$). Further studies are needed to more clearly define the role for hirudin in patients experiencing an AMI.

Other novel antithrombotic medications besides hirudin currently being studied as adjunctive agents to thrombolytic therapy include low-molecular-weight heparins and platelet glycoprotein IIb/IIIa–receptor antagonists (e.g., abciximab).[85,86] It has been hypothesized that the use of these

antithrombotic agents concurrently with thrombolytic medications may provide clinical benefit that exceeds that of current practice. In fact, it has been speculated that these agents, especially the glycoprotein IIb/IIIa–receptor antagonists, may prove to be of equal or greater importance than the thrombolytic agents themselves in the pharmacotherapy of patients with an AMI.[42]

Adverse Effects

The concern for severe debilitating or fatal adverse events resulting from thrombolytic use is the most likely reason for physician hesitancy in prescribing these agents routinely.[87] The risk for severe adverse effects, such as a cerebral hemorrhage, systemic bleeding that results in the need for a major transfusion, severe hypotension, and allergic reactions, is relatively low.[88] Results from large comparative trials best reflect any variation in the incidence of these adverse effects among agents. These results, however, need to be evaluated carefully, since differences in the inclusion/exclusion criteria, concomitant adjunctive agents used, and/or the criteria that define an adverse event may differ in each trial.

BLEEDING/STROKE

Based on the pharmacologic profile of thrombolytic agents, it is expected that bleeding would be the most significant adverse event. To best gain a perspective on the actual relative incidence of bleeding between thrombolytic agents, one needs to review data from trials that administered thrombolytics along with adjunctive agents in a manner similar to current practice. Moderate bleeding requiring transfusion appears to occur equally among streptokinase, alteplase, and reteplase, with an incidence of approximately 5–6%.[58,60] As mentioned above, the risk for such bleeding may be enhanced somewhat with concurrent heparin use.[63]

The overall incidence of strokes ranges from approximately 1% to 2% regardless of the choice of thrombolytic agent.[56,57,89] However, the risk for hemorrhagic stroke, the most feared adverse reaction associated with thrombolytic use due to its resultant high morbidity and mortality, is not universal among thrombolytic agents.[48] Clinical trials have demonstrated that the incidence of hemorrhagic stroke associated with the use of alteplase (0.5–0.9%[57,58,60]), reteplase (0.8–0.9%[59,60]), or anistreplase (0.7%[57]) is greater than the incidence associated with streptokinase (0.2–0.5%[57-59]). The risk for hemorrhage strokes with any of these agents is further enhanced in the presence of hypertension, with the concurrent use of heparin, and/or when used in patients of advanced age.[89-91]

HYPOTENSION

Hypotension observed early during an AMI can be a result of decreased left ventricular function, involvement of the inferior myocardium, or from using medications with hypotensive properties.[92] Hypotension has also been attributed to the use of thrombolytic therapy.[88] It is theorized that increasing serum plasmin concentrations activate kallikrein and stimulate bradykinin production, leading to vasodilation.[93] Anistreplase and streptokinase appear to be implicated more frequently than is alteplase or reteplase.[57-59] In GUSTO-I,[58] the incidence of hypotension associated with streptokinase (12.9%) was significantly greater ($p < 0.001$) than with that of alteplase (10.1%). Streptokinase was also associated with inducing hypotension more frequently than was reteplase in the INJECT trial (17.6% streptokinase vs. 15.5% reteplase; $p < 0.05$).[59] In ISIS-3, the incidence of hypotension associated with anistreplase use (12.5%) and streptokinase use (11.8%) was significantly more frequent ($2p < 0.00001$) than with that of duteplase (7.1%).[57] The ability of streptokinase and anistreplase to cause hypotension more frequently is probably a result of their ability to elevate systemic plasmin concentrations to a greater extent than do alteplase and reteplase, due to their enhanced ability to induce systemic fibrinolysis.[94] The increased frequency of hypotension associated with streptokinase or anistreplase may also be related to their antigenicity.[95] In patients who develop hypotension while receiving streptokinase, slowing the infusion rate and/or careful administration of fluids should be considered prior to discontinuing the streptokinase infusion.

ALLERGIC REACTIONS

As was elucidated earlier, streptokinase and anistreplase are derived from bacterial products and, as such, are capable of stimulating the production of neutralizing antistreptokinase antibodies (of the immunoglobulin G and M types) or activating immunoglobulin E antibodies.[32,92] Neutralizing antistreptokinase antibodies, produced upon initial exposure to streptokinase or anistreplase (or recent streptococcal infections), are not involved in acute allergic responses, but are capable of inactivating streptokinase or anistreplase and, thus, can induce treatment failure if these thrombolytics are readministered later when these antibodies are still present in high titers.[33] This concern can be an issue for at least as long as 4 years after initial exposure to streptokinase or anistreplase.[34] The fact that one never knows how long these high titers remain present in an individual has led to the suggestion that streptokinase or anistreplase not be readministered to patients previously exposed to these products.[29] Stimulation of immunoglobulin E antibodies by streptokinase or anistreplase can result in immediate allergic reactions.[88] These reactions may range from a mild presentation, such as fever, urticaria, myalgia, flushing, and chills, to a more severe episode such as anaphylactic shock. The overall incidence of these allergic reactions is remarkably low for streptokinase and anistreplase, and is even lower for alteplase and reteplase. Experience from clinical trials indicates that the incidence of allergic reactions is approximately 1.8–5.7% with streptokinase,[57-59] 5.1% with anistreplase,[57] 0.8–1.6% with alteplase,[57,58] and 1.1% with reteplase.[59] Routine prophylactic steroid administration prior to streptokinase or anistreplase use for the purpose of preventing allergic reactions from occurring is not recommended, since such therapy did not demonstrate a reduction in the incidence of allergic reactions during the ISIS-2 trial.[48]

Agents Under Development

Further research into developing newer agents is generated by the need to create an agent that possesses all desired properties: rapid and sustained patency of an occluded artery, low incidence of adverse events, minimal antigenicity, convenient administration, and economic feasibility.[96]

Most newer agents under development have been designed in an attempt to improve on the pharmacologic properties of currently available agents.[97] TNK-tissue plasminogen activator is a variant of alteplase that purportedly has increased fibrin specificity, a longer plasma half-life, and resistance to inactivation by plasminogen activator inhibitors. Its method of administration is currently being investigated as a single bolus dose.[98-101] n-Plasminogen activator, a mutant of wild-type tissue plasminogen activator, is another plasminogen activator being investigated that also has a long half-life allowing for single bolus administration; however, its affinity for fibrin may be less than that of other tissue plasminogen activators.[101]

Saruplase is a direct plasminogen activator identical in structure to endogenous urokinase-type plasminogen activator. In addition to being studied alone, saruplase has been studied concurrently with alteplase to determine whether it provides a synergistic effect, thus allowing alteplase to be administered in lower doses.[102] Staphylokinase, like streptokinase, needs to bind with a plasminogen molecule before it becomes active. Although it is immunogenic like streptokinase (but to a lesser extent), the fact that staphylokinase is more fibrin-specific than streptokinase may lead to future use of this agent.[103] The plasminogen activator with possibly the most interesting origin is *Desmodus* salivary plasminogen activator, a relatively fibrin-specific product derived from the saliva of vampire bats.[104] These and other agents currently under investigation need further evaluation to identify their clinical attributes and place in the treatment of AMI.

Primary Percutaneous Transluminal Coronary Angioplasty

In recent years, percutaneous transluminal coronary angioplasty (PTCA) has been studied as an alternative therapy to thrombolytics in the acute management of patients with an AMI. Potential benefits of performing PTCA during the acute phase of an AMI (primary PTCA) include a greater probability of achieving reperfusion of the involved coronary artery, earlier identification of patients requiring cardiac surgery, and a reduced incidence of causing a stroke. Primary PTCA would also be useful for patients in whom thrombolytic therapy is contraindicated or concern exists that thrombolytic therapy may cause a cerebral hemorrhage. Potential disadvantages include the fact that this procedure is invasive and requires many more hospital personnel than are required to administer thrombolytic therapy. In addition, the personnel and the cardiac catheterization room need to be available within minutes of recognizing that PTCA is required in a patient. Weaver et al.[105] performed a meta-analysis using 10 smaller trials that compared primary PTCA with thrombolytic therapy. They concluded that primary PTCA results in a reduction in short-term mortality, nonfatal reinfarction, and stroke rates; however, before primary PTCA can be widely recommended, larger trials reporting long-term outcomes need to be performed. Currently, the ACC/AHA guidelines[29] propose that primary PTCA be considered as an alternative to thrombolytic therapy when it can be performed by an experienced individual within a short time of the patient arriving at the hospital.

Recommendations for Thrombolytic Therapy

Debating which thrombolytic agent is preferred for use during an AMI has been a continuous and exhausting exercise. Anistreplase has not experienced widespread use, probably because of its high cost compared with streptokinase and its high antigenicity compared with alteplase. It may be difficult for reteplase to readily find a niche in the treatment of AMI at this time, given the experience of health professionals with alteplase, the lack of data at present to support superiority over alteplase, and the fact that the cost of reteplase is currently similar to that of alteplase. The roles for anistreplase and reteplase, if any, appear reserved for unique situations in which the bolus administration of a thrombolytic can provide a considerable improvement in the care of an AMI patient, such as a patient in transit.[106,107]

As a result, the selection of which thrombolytic to use once the patient has reached the hospital is generally between alteplase and streptokinase. The selection between these two agents by health practitioners has been based on how the major comparative trials discussed above, especially GUSTO-I,[58] have been interpreted.[73,108,109] ISG and ISIS-3 observed no difference in mortality.[56,57] Although GUSTO-I demonstrated that alteplase was associated with a statistically significant relative reduction in mortality rate of 14%, this translated into an absolute reduction in mortality of only 1% compared with streptokinase.[58] From a drug acquisition perspective, this extrapolates into a cost of approximately $200 000 to save one life with alteplase; however, cost-effective analysis from a societal perspective indicates that the cost per year of life saved associated with using alteplase was approximately $33 000, a value that is currently considered cost-effective.[69]

The subgroup analysis results from GUSTO-I have been used by some to assist in selecting between streptokinase and alteplase. One proposal that has been made suggests that alteplase may be preferred over streptokinase in patients younger than 75 years, in patients with prior exposure to streptokinase or anistreplase, or in patients with an anterior MI.[72]

The greater frequency of hypotension associated with streptokinase use and the need to be concerned about neutralizing antistreptokinase antibodies present in patients using streptokinase while several comparative studies have demonstrated that tissue plasminogen activators are no less effective than streptokinase in reducing mortality rates makes it understandable why alteplase has become the preferred thrombolytic agent at many institutions.

Regardless of which agent is selected, the most important issue is to give a thrombolytic agent and to give it early in the course of therapy.[110] Delays in treatment, due to

either the initial presentation to the hospital or the time it takes for patients to receive thrombolytics once they reach the hospital ("door-to-needle time"), needs to be reduced to improve mortality. The goal of an emergency department should be to have a door-to-needle time within 30 minutes. When a transportation delay of greater than 90 minutes is expected, prehospital administration of a thrombolytic agent should be considered. A collaborative overview indicates that relative mortality is reduced by approximately 25% when a thrombolytic agent is administered within 3 hours of the onset of an AMI, 20% when administered between 4 and 6 hours of the onset, and 15% when administered between 7 and 12 hours of the onset.[110] These data indicate that patients without any contraindication should receive a thrombolytic agent early during an AMI if no other coronary invasive procedures are being considered.[29,111] Contraindications to thrombolytic use are listed in Table 6.[29]

Even with this knowledge, thrombolytics still remain underused in patients without an absolute contraindication.[112-115] In the past, reports have indicated that less than 50% of eligible patients in the US actually receive thrombolytic agents.[112] More recently, this number has improved to approximately 70%.[115] Eligible elderly patients had been receiving thrombolytics even less often due to concerns that these individuals are more susceptible to the complications of thrombolytic therapy, specifically hemorrhagic strokes; however, this trend in practice is changing as physicians now recognize that the elderly have the most to gain from thrombolytic use.[113-116]

When administering thrombolytics, a risk for inducing cerebral hemorrhage exists, but this risk can be minimized by avoiding the initiation of a thrombolytic in a hypertensive patient with an AMI until the blood pressure is controlled, by closely monitoring concurrent heparin therapy to avoid excessive elevations of the aPTT, and, when using alteplase, by correct dosing based on weight in patients weighing 67 kg or less.

The addition of aspirin to thrombolytic therapy is well established in providing additional clinical benefit. In fact, aspirin alone can be of value to patients experiencing an AMI, even if no thrombolytic is administered.[48] As discussed above, the role of heparin use with thrombolytics other than alteplase or reteplase is not as clear.[81]

Table 6. Contraindications for Thrombolytic Use[29]

Absolute
previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 y
cerebral neoplasm
active bleeding
aortic dissection
Relative
hypertension on presentation (blood pressure >180/110 mm Hg)
currently using anticoagulants
recent trauma or major surgery
noncompressible vascular punctures
internal bleeding within the past 2–4 wk
pregnancy
active peptic ulcer
history of chronic severe hypertension
for streptokinase or anistreplase: prior exposure or allergic reaction

Summary

Thrombolytic agents have a secure place in AMI treatment because of a significant reduction in mortality rates. In general, comparative trials have demonstrated minimal difference in efficacy among these agents. Although the clinical superiority of alteplase presented in the GUSTO-I trial was questioned by some, it is the thrombolytic of choice at many US institutions. Results of trials confirm that the sooner a thrombolytic can be administered to patients, the greater the benefit the patient will receive from these agents. Unfortunately, not all patients who are eligible to receive thrombolytic therapy in the face of an AMI are being given these agents; however, this is becoming less of an issue. Educating the community on the importance of seeking medical attention when symptoms of AMI present, along with streamlining protocols in the emergency department, should further improve the benefit that these agents can provide to patients.

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EXTRACTO

OBJETIVO: Revisar la literatura sobre el uso de agentes trombolíticos en el manejo farmacoterapéutico de un infarto agudo del miocardio (IAM).

FUENTES DE INFORMACIÓN: Estudios clínicos, revisiones, y editoriales publicados en el idioma inglés derivados de MEDLINE (1996 al presente) y/o referencias cruzadas de artículos seleccionados.

SELECCIÓN DE FUENTES DE INFORMACIÓN: Se seleccionaron los artículos que representan mejor los estudios clínicos que investigaron el papel de los agentes trombolíticos en la terapia de IAM para mejorar la morbilidad y mortalidad.

SÍNTESIS: IAM es una de las principales causas de muerte en Estados Unidos (E.U.). Siguiendo los datos que apoyan que la causa más común de un IAM es un trombo intracoronario, las investigaciones clínicas han demostrado que los agentes trombolíticos intravenosos mejoran las tasas de supervivencia en pacientes que experimentan un IAM. Se han conducido varios estudios clínicos para determinar si un agente trombolítico es superior al otro con relación a mejorar la mortalidad. Sólo el estudio GUSTO-I ha reportado al presente alguna diferencia estadísticamente significativa en la tasa de mortalidad. En este estudio, alteplasa administrada en dosis cargada frontalmente "front-loaded" produjo una reducción absoluta de 1% estadísticamente significativa en la mortalidad. Esta diferencia se mantuvo a los 30 días y al año cuando se comparó con estreptoquinasa. Debido a esto alteplasa se ha convertido en el trombolítico preferido en muchas instituciones de E.U. Sin embargo, los resultados de GUSTO-I han sido cuestionados por algunos basándose tanto en el diseño del estudio como en su significado clínico. El seleccionar qué agente trombolítico se va a usar es probablemente tan importante como asegurarse que un paciente con IAM se le administre terapia trombolítica, a menos que exista en el paciente una contraindicación para recibir esta terapia. Es igualmente importante asegurarse si el paciente es candidato a recibir un procedimiento intracoronario de emergencia. Los estudios indican que mientras más pronto se puedan administrar los trombolíticos mayor será el beneficio al paciente.

JUAN F FELIU

RÉSUMÉ

OBJECTIF: Reviser la littérature sur l'utilisation des agents thrombolytiques dans la pharmacothérapie de l'infarctus du myocarde (IM).

REVUE DE LITTÉRATURE: Les études cliniques de langue anglaise, les articles de revue, et les éditoriaux furent identifiés par recherche informatique MEDLINE (1996–présent).

SÉLECTION DES ÉTUDES: Les articles sélectionnés représentent les études sur le rôle de la thrombolyse dans la thérapie de l'IM en fonction de la morbidité et al mortalité.

RÉSUMÉ: L'IM représente une des causes majeures de mortalité aux États-Unis. Puisque la cause de l'IM a été associée à la présence d'un thrombus intracoronarien, les études cliniques ont démontré que la thrombolyse intraveineuse améliore le taux de survie chez les patients avec un IM. Plusieurs études ont évalué les divers agents thrombolytiques en terme d'efficacité relative par rapport à la mortalité. Seule, l'étude GUSTO-I a rapporté une différence significative de la mortalité. Les patients recevant le t-PA ont démontré une réduction absolue de mortalité de 1% à 30 jours et à 1 an lorsque comparé à la streptokinase. Ceci a justifié l'utilisation préférentielle du t-PA sur la streptokinase auprès de plusieurs institutions. Cependant, les résultats de GUSTO-I ont été questionnés en fonction du devis expérimental et de la signification clinique des résultats. Le choix de l'agent thrombolytique est probablement aussi important que le fait de décider de thrombolyser un patient à moins de contre-indications et/ou de procédures intracoronariennes d'urgence. Les études indiquent que plus tôt la thrombolyse est débutée, meilleurs sont les résultats.

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