
The Role of Thrombolytic Drugs in the Management of Acute Myocardial Infarction and Stroke

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Thrombolytic drugs play a crucial role in the management of patients with thrombotic and thromboembolic complications during pre-, peri-, and postinterventional cardiologic procedures and acute thrombotic stroke, most often in combination with anticoagulants, antiplatelet agents or mechanical procedures, in order to achieve vascular reperfusion. Coronary Heart disease (CHD) is the most common cause of mortality not only in the United States (accounting for 481.287 deaths in 1995) but world-wide^[1,2]. Annually an estimated 1.1 million Americans experience a new or recurrent acute myocardial infarction (AMI) due to CHD and in one-third of individuals the event is fatal^[1]. The age-adjusted mortality rate of CHD has declined dramatically from 2.8% per year in 1965 to 1.5% since 1990^[3]. The reasons for the age-adjusted decline in incidence, case-fatality, and CHD mortality rate are many: The advent of coronary care units with intensive monitoring, aggressive treatment of complications, and reperfusion therapies such as thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft (CABG) surgery^[4-6]. The goal in the care of patients with AMI is to make these effective treatments available in a timely manner.

With the advances in antithrombotic and anticoagulant drugs have come significant developments in the field of thrombolytic therapy. It is now possible to produce recombinant forms of tissue-type plasminogen activator (tPA), urokinase, prourokinase, and staphylokinase etc. by the use of recombinant DNA technology. Recombinant urokinase and prourokinase are expressed from mouse hybridoma cell line, and the latter, a precursor of urokinase, has such advantages as increased potency and increased effectiveness of thrombolytic therapy. The development of longer acting tPAs, fibrin-specific agents, and newer urokinase-type plasminogen activators may be beneficial in new indications of thrombolytic therapy such as thrombotic stroke.

Hemostasis represents a physiologic homeostasis resulting from a dynamic equilibrium between coagulation and fibrinolysis. An intact endothelium (a single layer of cells lining the vascular lumen, estimated to be 1.000-5.000 square meters) is the largest endocrine, paracrine and autocrine organ in the body and serves as a unique hemostatic tool in the regulation of coagulation by synthesizing procoagulant and anticoagulant substances (Table 1)^[7].

Development of antithrombin drugs, glycoprotein (GP) IIb/IIIa inhibitors, and low molecular weight heparins (LMWHs) provide favorable options for use in combination strategies for better long term clinical outcome. The more potent the antithrombotic drug, the more rapid and thorough the thrombolysis^[8]. As a result of enhanced thrombolysis, there is a reduction in the residual mass of mural thrombus, residual stenosis, local shear force and increased platelet deposition and reocclusion. To maximize the extent of thrombolysis, there is a necessity of the simultaneous administration of antithrombotic drugs with the lytic agent because of an increase in thrombin generation^[8,9]. In a recent study [Hirulog Early Reperfusion/Occlusion (HERO) trial] of a randomized double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for AMI, White et al and Chesesbro have shown that hirulog is more effective at achieving early thrombolysis in myocardial infarction (TIMI) 3 flow than heparin does as an adjunct to streptokinase and aspirin in AMI, and that the effect of hirulog may be dose-dependent^[10,11]. The early patency achieved with streptokinase can be improved by adjunctive administ-

ration of the direct-acting thrombin inhibitor, hirulog. The improved antithrombotic effect and the gain in patency were achieved at lower activated partial thromboplastin time (aPTT) levels and were not associated with an increased risk of bleeding^[10,11].

The time from AMI to reperfusion (thrombolytic) therapy is commonly divided into three periods^[12]. The first period is the time from the onset of symptoms to the patient's action to seek treatment, such as going to the hospital or calling emergency medical services (EMS). This delay constitutes 60-70% of the total time to starting reperfusion (thrombolytic) therapy. This delay may be shortened by primary prevention through the education of patients and their families about heart disease and the importance of early response to symptoms. Delay results in cardiac muscle loss. The second component of delay is the time to EMS response and transit time to an emergency care facility (3-8% of the total delay). The third delay is the time from arrival at the hospital to definitive treatment (25-33% of the total delay). Factors contributing to effective, timely reperfusion therapy are patient education, EMS availability and proficiency, and reduced delay in the hospital^[1,2,13,14].

Table 1. Substances secreted by the endothelium

Prothrombotic	Antithrombotic
Stimulation of platelet aggregation and adhesion: von Willebrand factor Platelet activating factor	Inhibition of platelet aggregation: Prostacyclin Nitric oxide ADPase
Procoagulant factors: Tissue factor Binding factors IXa and Xa Factor V	Anticoagulant binding and inhibition of thrombin and tissue factor: Antithrombin Acceleration by heparin like molecules Thrombomodulin activation of protein C and S a-2 macroglobulin Tissue factor pathway inhibitor (TFPI)
Inhibition of fibrinolysis: tPA inhibitor	Fibrinolysis: tPA
Cytokines: Interleukin-1 Tumor necrosis factor (TNF)	

Trials of prehospital thrombolytic therapy have resulted in reduced time to treatment and improvement in mortality rates^[3,15-19].

Table 1 lists the substances secreted by the vascular endothelium. Selection criteria are listed in Table 2. Table 3 lists the thrombolytic drugs currently in use and under development. Distinctive features of the available thrombolytic agents are shown in Tables 4, 5, and 6. Selection of the specific drug for a particular patient must include prior use because antibody-mediated resistance may have developed (see Table 4, 5 and 6 for immunogenicity of each drug). Cost factors also are important, as shown in the above table 4 and 5.

SELECTION CRITERIA for LYTIC THERAPY

Table 2. Selection criteria for thrombolytic therapy

Indications:

- Chest pain for > 30 minutes and < 12 hours
- No congestive heart failure or hypotension
- ST elevation (0.1 mm) in two contiguous leads or new bundle branch block

Absolute contraindications:

- Acute: Active internal bleeding
 - Blood pressure > 200/120 mmHg
 - Suspected aortic dissection
- Subacute or chronic
 - Arteriovenous malformations
 - Tumor involving spinal cord or cranial structures
 - Hemorrhagic retinopathy
 - Pregnancy
 - Active peptic ulcer
 - Warfarin use
 - Bleeding diathesis

In the past 2 months

- Trauma or surgery in the past 2 weeks with a risk of bleeding into closed space
- Spinal or intracranial procedure in the past 8 weeks
- Recent head trauma
- Prolonged or traumatic cardiopulmonary resuscitation
- Prior hemorrhagic stroke or any stroke within the prior year.

* Advanced age is not a contraindication. Elderly patients have increased complications (especially intracranial hemorrhage) but also the highest absolute mortality reduction.

Patients who are candidates for thrombolytic therapy must be identified as soon as possible after presentation, using the National Heart Attack Alert Program Coordinating Committee eligibility criteria^[20]. About 20% of the patients with AMI receive thrombolytic therapy. An additional 15% are eligible but never receive the therapy^[21].

Relative contraindications are not included in the table below because the survival benefit for thrombolytic therapy should justify the risks associated with relative contraindications^[22].

More than 90% of patients who present with ST segment elevation have coronary thrombotic occlusion and early thrombolytic intervention reduced the mortality by approximately 30% as per the placebo-control-

Table 3. Three generations of thrombolytic agents

First generation
Streptokinase
Urokinase
Second generation
Recombinant tissue plasminogen activator (rtPA, alteplase, Duteplase)
Anisoylated plasminogen streptokinase activator complex (APSAC, Anistreplase).
Single-Chain urokinase type plasminogen activator (scu-PA, prourokinase)
Third generation
Vampire bat salivary plasminogen activator
Retepase (rPA)
TNK-tPA
Lanoteplase (n-PA)
Staphylokinase
Recombinant glycosylated plasminogen activator
Thrombolytic drugs under development
Antibody-targeting thrombolytic agents
Polyethylene glycol-coupled thrombolytic agents
Mutants and variants of plasminogen activator
Recombinant chimeric plasminogen activator (fibrolase)

Table 4. Characteristics of first generation thrombolytics

Characteristics	Streptokinase	Urokinase
Source	Gr C Streptococci	Recombinant, human fetal kidney
Molecular weight (Kd)	47	35-55
Immunogenicity	Yes	No
Mode of action	Forms an activator complex	Direct
Plasma half-life (min)	18-23	14-20
Metabolism	Hepatic	Hepatic
Dose	1.5 million units	3 million units
Cost per dose	\$300	\$2000

led randomized trials of the 1980s^[23-28].

PHARMACOLOGY and CLINICAL USE

The characteristics and functional properties of thrombolytic agents commonly in current use and summarized in Tables 3-6. These drugs are either direct activators of plasminogen, such as tPA, urokinase, and anisoylated plasminogen-streptokinase activator comp-

lex (APSAC), or indirect activators, such as streptokinase. Average doses are shown in the tables 4-6. APSAC and tPA are “fibrin-specific” in that they bind to fibrin and activate plasminogen at the site, whereas streptokinase and urokinase are not fibrin-specific, lysing both fibrinogen and fibrin. Streptokinase and APSAC (which contains streptokinase) cannot be re-used because they are antigenic and give rise to circu-

Table 5. Characteristics of second generation thrombolytics

Character	APSAC	rtPA	Scu-PA (saruplase)
Source	Gr C Streptococci plasminogen anisoylated	Recombinant human	Prodrug from a naturally occurring physiologic protease
Molecular weight (Kd)	131	63-70	49
Immunogenicity	Yes	No	No
Mode of action	Direct	Direct	Direct
Fibrin specificity	+	++	+
Plasma half-life (min)	70-120	4-6	9
Metabolism	Hepatic	Hepatic	Hepatic
Dose	30 units IV over 2-5 minutes	15 mg bolus + 90 min infusion	20 mg bolus + 60 mg infusion for 1 hour.
Cost per dose	\$2400	\$2200	\$2100

Table 6. Characteristics of third generation drugs

Character	r-PA	n-PA	TNK-tPA	Vam. bat PA	Staphylokinase
Source	Recombinant, human mutant type PA	Chinese hamster ovary cells	Variant of tPA-rearranging gene sequence	Saliva of desmodus rotundus	PA of bacterial origin-strains of <i>Staphylococcus aureus</i>
MW (Kd)	39	39	39	52	15.5
Immunogenicity	No	?	No	Yes	Yes
Mode of action	Direct	Direct	Direct	Indirect	Indirect
Fibrin specificity	Yes	+	+++	+++	+++
Plasma half-life (min)	14	37	20	170	6
Metabolism	Renal	Hepatic	Hepatic	Hepatic	Hepatic
Dose	20 million units	120.000 U/kg single bolus	0.5 mg single bolus	0.5 mg single bolus	1.5 mg + 15 mg double bolus over 30 minutes

lating antibodies. Because urokinase and tPA are of human origin, they do not induce antibodies. As a practical matter, urokinase is rarely used for AMI because of the necessity for intracoronary administration. The two commercially available recombinant forms of tPA, reteplase and alteplase, are given intravenously, as are streptokinase and APSAC. APSAC has not been studied in patients over 75 years of age and may be unsafe in this age group. Theoretically, the longer half-life of a single bolus of APSAC makes it ideal for prehospital

therapy^[29]. All thrombolytic drugs have the potential to cause more bleeding in elderly than in younger patients, and most manufacturers' warnings advise caution. This risk must be weighed against anticipated benefit. A synopsis of thrombolytic therapy in AMI trials is given in the Table 7.

FIRST GENERATION THROMBOLYTIC AGENTS

Streptokinase

Streptokinase is the most extensively studied agent to date. It is not an enzyme and activates the fibrinolytic system by forming a 1:1 stoichiometric complex with plasminogen that in turn converts plasminogen to plasmin. Streptokinase causes systemic conversion of plasminogen to plasmin and depletion of circulating fibrinogen, plasminogen and F V and F VIII. With the usual dose of 1.5 million units streptokinase, the fibrinogen level drops to 20% of the pretreatment level with corresponding higher levels of fibrinogen degradation products that may result in a modest increase in bleeding complications.

CHOICE of AGENT

The type of thrombolytic drug is not as critical and important as the delay to administration (Table 8). The GUSTO-I trial showed that accelerated tPA was better than streptokinase for most patients with AMI^[69]. The GUSTO-III trial showed no mortality benefit of reteplase over alteplase. Both lanoteplase and TNK-tPA (Tenecteplase) can be administered as a single bolus. TNK-tPA was recently approved by the Food and Drug Administration^[70].

PREHOSPITAL THROMBOLYSIS

Several prehospital thrombolytic therapy trials were designed to evaluate time-saving, left ventricular function, infarct size, and differences in mortality rates^[16-19,29,71-74]. The largest trial, the European Myocardial Infarction Project (EMIP) was carried in 15 European countries and Canada. Administration of anistreplase as a bolus in the prehospital setting in 2750 patients was compared with hospital treatment in 2719 patients. The 30-day mortality rate was 9.7% vs 11.1% in the prehospital and hospital groups, respectively (risk reduction= 13%, 95% CI=1-26%, p= 0.08). The cardiac mortality rate was 8.3% vs 9.8%, respectively (risk reduction= 16%, 95% CI= 0-29%, p= 0.049). There was no obvious correlation between the reduction in mortality at 30 days and the interval between the onset of symptoms and the first injection. There were no differences between the groups in the incidence of bleeding, overall incidence of stroke, ventricular fibrillation, or shock during the hospital period. The Gramscian Region Early Anistreplase Trial (GREAT) compared prehospital thrombolytic therapy given by the practitioner in patients' homes with treatment after hospital arrival in 311 patients^[29]. The average time to treat-

ment was 101 vs 240 minutes, respectively. Patients treated in their home had fewer Q-wave myocardial infarctions and improved left ventricular function compared with the group treated in the hospital^[29]. The Myocardial Infarction Triage and Intervention (MITI) trial was the largest randomized trial of pre-hospital thrombolysis in the US. The trial evaluated 360 patients who were initially screened by paramedics using a checklist and electrocardiograms. Because the trial included only patients with a short delay to treatment in both prehospital and hospital settings (92 minutes in prehospital-treated vs 120 minutes in hospital-treated patients), prehospital treatment provided only a modest time saving of 33 minutes.

Modulation of Endogenous Fibrinolytic Activity

TAFI is a latent carboxypeptidase B like enzyme that is activated by thrombin-thrombomodulin complex and attenuates fibrinolysis by cleaving carboxyterminal lysine residues from fibrin^[75,76]. The fibrinolytic process is retarded by removal of these lysine residues which decreases the plasminogen or plasmin binding to thrombin. It has been shown in dogs and rabbits that a potato-derived carboxypeptidase B inhibitor increases tPA-induced thrombolysis^[77,78].

Factor XIIIa Inhibitors

The Laki-Lorand F XIIIa, a thrombin-activated transglutaminase, crosslinks the a and g-chains of fibrinogen to form a-polymers and g-dimers, respectively. As the fibrin polymer is stabilised due to crosslinking, it is rendered more refractory to degradation by plasmin^[79]. It is therefore thought that inhibition of F XI-IIa makes the thrombus susceptible to lysis. Tridegin, a peptide isolated from the giant Amazon leech, *Hemeteria ghiliani*, is a specific F XIIIa inhibitor and has been shown to enhance fibrinolysis in vitro when added prior to clotting of fibrinogen^[80,81]. Destabilase, a leech enzyme that hydrolyses g-g crosslinks also inhibits F XIII action^[82,83].

PAI-1 Inhibitors

Inhibition of PAI-1, which is a major physiologic inhibitor of tPA and uPA, results in increased endogenous fibrinolytic activity. PAI-1 synthesis is decreased in vitro by lipid lowering drugs, such as niacin and fibrates^[84,85]. Similarly, peptides that block PAI-1 activity

Table 7. Synopsis of thrombolytic therapy in AMI trials

Trial name (Ref. #)	Design	Population, n, age	Drug procedure	Major endpoints	Results
GISSI-1 ^[30]	R, OL, PC, MCS	11, 712; no age limit	IV SK vs no lytic therapy	Mortality benefits at 21 days and 1 year	Reduction in mortality of 10.7% at 21 days and of 17.2% at 1 year
GISSI-2 ^[31]	MCS, R, OL, 2 X 2 factorial	12, 381; no age limit	IV SK vs tPA	Mortality rate, rate of reinfarction, stroke rate, incidence of post infarction angina	SK and tPA were equally effective within 6 hours of the onset of symptoms
ISIS-2 ^[32]	MCS, PC, R, DB, 2 X 2 factorial	17, 187; no age limit	IV SK + aspirin vs placebo	Mortality and stroke risk	SK & aspirin independently reduced mortality in patients with AMI. The combination of two drugs had a synergistic effect on mortality without increase in rates of stroke.
ISAM ^[33]	P, R, DB, PC, MCS	1.741; < 75 years	SK vs placebo	21-day mortality rate	Nonsignificant reduction in 21-day mortality rate; significantly higher LVEF
White HD et al ^[34]	R, DB	219; no age limit	SK vs placebo	LVEF; mortality rate	Increased LVEF and significantly lower mortality rate in SK group
TIMI-1 ^[35]	R, DB, MCS	290; < 75 years	IV SK or placebo vs IV rtPA or placebo	Coronary angiography to assess reperfusion at 90 min	Higher reperfusion rate with rtPA; no difference in mortality rate, bleeding complications or LVEF
ASSET ^[36]	R, MCS, DB, PC	5013; 18-75 years	TPA vs placebo	Mortality rate	TPA treatment within 5 hr of onset of symptoms reduced mortality sustained to 1 year but not rates of recurrent infarction or development of heart failure compared with placebo

Table 7. Synopsis of thrombolytic therapy in AMI trials (continuation)

Trial name (Ref. #)	Design	Population, n, age	Drug/procedure	Major endpoints	Results
TAMI-6 ^[37]	P, R, DB, PC, MCS	197; < 75 years	TPA vs placebo	Vessel patency at 6-24 hrs.	Better early patency with tPA but similar rate for late patency, in-hospital mortality rate, LVEF
LATE ^[38]	R, MCS, DB, PC	5711; > 18 years	RtPA vs placebo; 6-24 hr from onset of symptoms	Mortality rate	Reduces 35-day mortality rate even if given up to 12 hr after onset of symptoms
GREAT ^[29]	P, R, DB, PG, MCS	311; no age limit	Anistreplase at home vs in hospital	Mortality rate	52% lower 1-year mortality rate in home-treated group
TEAM-2 ^[39]	R, DB, MCS	370; < 76 years	Anistreplase (APSAC) or SK	Early patency and reocclusion rates	Both agents were equally effective and safe
AIMS ^[40]	R, MCS, DB, PC	1004; < 70 years	APSAC or placebo	Mortality	IV APSAC within 6 hr of onset of symptoms reduced mortality in AMI
Meinertz T et al ^[41]	R	313; no age limit	APSAC vs heparin	28-day mortality rate	Less cardiogenic shock and 56% lower 28-day mortality rate in APSAC Group
ISIS-3 ^[42]	MCS, PC, R, DB, OL, 3X2 factorial	41,299; no age limit	IV SK, APSAC, rtPA	Mortality and reinfarction rate at 35 days and 6 months	No difference in 35-day mortality rates
TIMI-4 ^[43]	R, DB, MCS	382; < 80 years	Front-loaded r-PA or APSAC or combination of r-tPA and APSAC	Coronary angiographic estimation of infarct-related artery patency and TIMI grade 3 flow at 90 min	TIMI grade 3 flow at 90 min: rTPA 60.2%, APSAC 42.9%, combination 44.8%
GUSTO-1 ^[44]	R, OL, MCS	41,021; no age limit	IV SK + SC heparin, IV SK + IV heparin, accelerated tPA + IV heparin, SK + tPA + IV heparin	Mortality, hemorrhagic stroke	Reduced mortality rate in tPA + IV heparin group
GUSTO-III ^[45]	R, MCS, OL	15,059; no age limit	Alteplase vs reteplase	Mortality and stroke risk	Both agents were identical
INJECT ^[46]	R, DB, MCS	6010; >18 years	Reteplase vs SK	Mortality at 35 days and 6 months	Reteplase is safe and effective thrombolytic agent

Table 7. Synopsis of thrombolytic therapy in AMI trials (continuation)

Trial name (Ref. #)	Design	Population, n, age	Drug/procedure	Major endpoints	Results
RAPID [47]	R, MCS, OL	606; 18-75 years	r-PA (reteplase bolus vs infusion of standard-dose alteplase	Artery patency and LVF	r-PA given as double bolus of 10 MU + 10 MU 30 min apart resulted in more rapid and complete reperfusion than standard dose tPA and was associated with improved global and regional LV function at discharge
RAPID-II [48]	R, MCS, PG, OL	324; >18 years	Double bolus reteplase or front-loaded accelerated alteplase	Artery patency and TIMI grade 3 flow at 90 min	Double bolus dose of reteplase was associated with higher rates of reperfusion at 60 and 90 min after initiation of therapy than front-loaded alteplase infusion, without increase in risk of complication
COBALT [49]	R, MCS, OL	7169; no age limit	Accelerated infusion of alteplase or double bolus of alteplase	Mortality and stroke risk	Accelerated infusion alteplase remains preferred regimen
TAMI-7 [50]	R, MCS	219; 18-76 years	5 different regimens of tPA	Patency rate, reocclusion rate, LVEF, death, bleeding	Accelerated tPA administration according to protocol 3 is relatively safe, achieving high 90-min patency rate and low rates of reocclusion and complications
Carney RJ et al ^[51]	R, OL	281; no age limit	Standard vs accelerated tPA regimen	TIMI grade 3 flow at 60 min and 90 min	Better patency at 60 min but not at 90 min. Similar rates of recurrent ischemia, reinfarction, stroke and bleeding

Table 7. Synopsis of thrombolytic therapy in AMI trials (continuation)

Trial name (Ref. #)	Design	Population, n, age	Drug/procedure	Major endpoints	Results
COMPASS [52]	R, MCS DB	3089; > 20 years	Saruplase vs SK	Efficacy, safety and mortality	Similar mortality rate, but more hemorrhagic stroke in Saruplase group
PERM ^[53]	Retrospective	481; no age limit	SK vs tPA	TIMI grade 3 flow at 90 min	SK, but not tPA, was found to be less effective when administered after 3 hr, regardless of whether TIMI flow grades 2 and 3 were poled or grade 3 flow was considered alone
In TIME ^[54]	R, MCS, DB, DP	602	Lanoteplase or alteplase	TIMI grade 3 at 60 and 90 min	Increased coronary patency in lanoteplase group
PACT ^[55]	R	606; no age limit	Precatheterization tPA or placebo	Predischarge EF	No significant difference between two groups in predischarge EF
GUSTO Angiographic Investigators ^[56]	P, R, MCS, OL	2.431; no age limit	IV SK + SC heparin, IV SK + IV heparin, accelerated tPA + IV heparin, SK + tPA + IV heparin	TIMI grade 3 flow at 90 min	Highest patency at 90 min with tPA and IV heparin: 81% vs 54% with SK and SC heparin; 73% combination
In TIME-II ^[57]	R, MCS, DB	17.078; no age limit	Lanoteplase vs tPA	30-day mortality rate	Similar 30-day mortality rate; higher incidence of intracranial hemorrhage in tPA group
TIMI-10A ^[58]	Phase I, dose-ranging pilot trial	113; no age limit	Dose ranging of TNK-tPA	Coronary angiography at 90 min and hemorrhage	TIMI grade 3 flow at 90 min in 64% of patients; major hemorrhage 6.2%
TIMI-10B ^[59]	R, MCS	886; no age limit	Single bolus of TNK-tPA vs front-loaded tPA	Coronary angiography at 90 min and hemorrhage	TIMI grade 3 flow is similar
ASSENT-2 ^[60]	P, R, DB, OL, MCS	16.949; no age limit	TNK-tPA (tenecteplase) vs front-loaded alteplase	All cause mortality at 30 days	Nearly identical all cause mortality rate at 30 days and similar intracranial hemorrhage rate

Table 7. Synopsis of thrombolytic therapy in AMI trials (continuation)

Trial name (Ref. #)	Design	Population, n, age	Drug/procedure	Major endpoints	Results
TAPS ^[61]	R	421; no age limit	APSAC vs front-loaded r-tPA	TIMI grades 2 and 3 at 90 min	Higher 90-min patency (TIMI grade 2 or 3 flow) was achieved with rtPA (84% vs 70%; p= 0.0007), as were fewer inhospital deaths (2.4% vs 8.1%; p< 0.01).
TEAM-3 ^[62]	R	325; no age limit	Anistreplase vs alteplase	LVF, morbidity, 1-day patency	Higher EF before discharge and at 1 month in r-tPA group; similar patency rate; no difference in mortality rate
PATENT ^[63]	R, OL	1011; no age limit	Sequential combination of r-tPA and prourokinase	TIMI grade 3 flow at 90 min; mortality rate	60% TIMI grade 3 flow at 90 min; 1 in-hospital death
STAR ^[64]	R, OL	100	Staphylokinase vs r-tPA	TIMI grade 3 flow at 90 min	
DUCCS-II ^[65]	R	162	Front-loaded tPA-IV heparin; anistreplase without heparin	Patency, reinfarction, heart failure, shock, stroke, death	Similar patency rate; 19% fewer end-points in tPA group
TIMI-11B ^[66]	R, OL, MCS	2948, < 76 years	Immediate IV beta blockade (metoprolol) vs beta blockade after r-tPA	Ventricular function, mortality	No difference in clinical outcome at 6 weeks or 1 year
GISSI-3 ^[67]	MCS, OL, R, 2 X 2 factorial	18.895; no age limit	Lisinopril or open control nitrate or placebo 72% of patients received thrombolytic therapy	Effect of ACE inhibition (lisinopril), transdermal nitrate, or combination on survival and LVF after MI	ACE inhibitor reduced mortality (6.3% vs 7.1% for no ACE inhibitor or nitrate at 6 weeks
ISIS-4 ^[68]	R, DB, PC, OC, MCS	58.050; no age limit	Captopril or placebo, mononitrate or placebo, IV magnesium or placebo 70% of patients received thrombolytic therapy	Mortality benefit	Magnesium and oral nitrates had no mortality benefit, but captopril reduced 5-week mortality by 7%.

AMI: Acute myocardial infarction, OL: Open label, P: Prospective, R: Randomized, PC: Placebo-controlled, DB: Double-blind, MCS: Multicenter study, SK: Streptokinase, tPA: Tissue plasminogen activator, ACE + angiotensin converting enzyme, LVF: Left ventricular function, EF: Ejection fraction, APSAC: Anisoylated plasminogen-streptokinase activator complex, PG: Parallel group, GISSI: Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardio, ISIS: International Study of infarct Survival, GUS-

TO: Global Utilization of Streptokinase and tissue Plasminogen activator for Occluded Coronary Arteries, ASSET: Anglo-Scandinavian Study of early Thrombolysis, COMPASS: Comparison Trial of Saruplase and streptokinase, LATE: Late assessment of Thrombolytic Efficacy, AIMS: APSAC Intervention Mortality Study, In TIME: Intravenous nPA for treatment of infarcting myocardium Early, TEAM: Second Thrombolytic Trial of Eminase in AMI, RAPID: Reteplase Angiographic Patency International Dose-ranging Study, INJECT: International Joint Efficacy Comparison of Thrombolytics, COBALT: Continuous infusion versus Double Bolus Administration of Alteplase Investigators, SESAM: Study in Europe with saruplase and Alteplase in AMI, AIMS: APSAC Intervention Mortality Study, TAMI: Thrombolysis in Angioplasty in Myocardial Infarction, GREAT: Grampian Region Early Anistreplase Trial, PERM: Prospective Evaluation of Reperfusion Markers Study Group, PACT: Plasminogen Activator-Angioplasty Compatibility Trial, DUCCS: Duke University Clinical Cardiology Group Study, PATENT: Prourokinase and tPA Enhancement of Thrombolysis, TAPS: rt-PA-APSAC Patency Study, ASSENT: Assessment of the Safety and Efficacy of a New Thrombolytic: TNK-tPA.

Table 8. Thrombolytic agents approved by the food and drug administration

Streptokinase (streptase)
Urokinase (abbokinase)
Alteplase (activase)
APSAC (eminase)
Reteplase (retevasc)
TNK-tPA (tenecteplase)

are also identified which prevent insertion of the reactive centre loop upon cleavage by the target protease or by converting PAI-1 into a latent conformation^[86,87]. Development of small molecule PAI-1 inhibitors, some of which may have antithrombotic activity in vivo may provide a more promising alternative strategy^[88].

Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors block the final common pathway of platelet aggregation^[89]. Abciximab during percutaneous coronary interventions has reduced 30-day ischaemic outcomes by approximately 35-50%^[90-92]. The clinical development of peptide and peptidomimetic GP IIb/IIIa inhibitors has shown less consistent benefits^[93-95]. The oral GP IIb/IIIa inhibitors have demonstrated approximately 30% increase in mortality^[96]. A safe and effective level of GP IIb/IIIa inhibition and rapid platelet function testing will allow the optimisation of doses in all patients.

The GP IIb/IIIa inhibitors can be used in combination with the thrombolytic agents in patients with AMI. Activase (alteplase, recombinant) in combination with GP IIb/IIIa inhibitors or TNKase in combination with GP IIb/IIIa inhibitors can be used in patients with

AMI. The thrombi in the coronary arteries causing AMI comprise of a platelet core in a fibrin-thrombin matrix. Following successful thrombolysis, reocclusion is caused by excessive platelet activation which makes the thrombi difficult to lyse. In these situations, adjunctive use of thrombolytic agents with GP IIb/IIIa inhibitors will prevent platelet activation and aggregation^[97]. Platelets bind to the walls of the vessel by attachment at Ia or Ib receptors on the platelet surface. Platelet-platelet binding is a result of interaction between GP IIb/IIIa receptors involving the fibrinogen and vWF^[98].

The Integrelin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) Trial which was designed to the hypothesis that eptifibatide and reduced-dose tPA enhances infarct artery patency at 60 minutes in patients with AMI. The investigators concluded that double-bolus eptifibatide (10 minutes apart) with a 48-hour infusion and half-dose tPA was associated with improved quality and speed of reperfusion, when compared to the standard tPA regimen^[99]. Polymorphisms in the GP Ia/Ia, one of the major collagen receptors on platelets and GP IIb/IIIa genes may by influencing the platelet activation process could modify the thrombogenicity of platelets^[100]. Although recent studies reported an association between GP Ia C807 T polymorphism and myocardial infarction, and GP IIIa PI A1/A2 polymorphism with premature myocardial infarction, Benze et al reported that these polymorphisms had no major effect on premature myocardial infarction risk^[101]. It remains to be seen whether these polymorphisms could play a direct or indirect role linked to other mutations in causing premature myocardial infarction. GP IIb/IIIa receptor inhibitors may be beneficial in the prevention of no-reflow phenomenon

during percutaneous intervention, since platelet and fibrin plugging contributes to the pathophysiology of this phenomenon^[102-104]. Although no-reflow phenomenon may be seen during thrombolytic therapy and more so in percutaneous coronary interventions, thrombolytic agents do not have a direct effect on the no-reflow phenomenon^[105,106].

Antman et al recently reported that enoxaparin is superior to unfractionated heparin for preventing Thrombolytic drugs and LMWHs: Antman clinical events at 1-year follow-up of TIMI 11B and ESSENCE trials^[107]. It was demonstrated that there was a 20% reduction in clinical events with enoxaparin during the acute phase of management of unstable angina/non-ST segment myocardial infarction. These results are favorably compared with the transitory benefits of intravenously administered direct thrombin inhibitors and dalteparin^[108,109]. The beneficial results of a combination of enoxaparin with intravenously administered GP I-Ib/IIIa inhibitor should be considered before selecting other drugs for the acute phase management of unstable angina/non-ST segment elevation myocardial infarction^[110].

CONCLUSION

Thrombolytic therapy for AMI is highly effective when applied early, preferable within 1 hour but not longer than 6 hours after the onset of symptoms. A number of effective agents are available; newer ones are in development. The quest for an ideal thrombolytic drug will continue. With the advancement of thrombolytic agents have come significant developments in the field of antithrombotic agents. The ideal thrombolytic agent should have the characteristic features of, increased circulating half-life, increased fibrin-specificity, increased resistance to PAI-1, rapidity in establishment of TIMI-3 flow, no effect on blood pressure, no antigenicity, low reocclusion rates and compatibility with other intravenous agents. An ideal thrombolytic and an ideal antithrombotic agent will be a perfect combination for use in acute coronary syndromes. An ideal antithrombotic agent should have characteristics such as, less expensive and more affordable, oral as well as parenteral effectiveness, rapid onset of action, < 1 hour, large benefit to risk ratio, rapid neutralization of the effect by non-toxic antagonists; satisfactory the-

rapeutic index, absence of side-effects or adverse effects, no cumulative or toxicity from prolonged usage, predictable dose-response, no need for laboratory monitoring, and no or limited interaction with commonly used agents. Several new antithrombotic agents are being introduced. ARIXTRA (fondaparinux sodium) (Organon Sanofi-Synthelabo, West Orange, NJ), is a synthetic and specific inhibitor of activated factor Xa. It has been indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip fracture surgery, hip and knee replacement surgeries. Carefully dose-titrated combination of an antithrombotic agent and a thrombolytic agent might prove beneficial in acute coronary syndromes. TNKase, a new genetically engineered variant of tPA, produced by recombinant DNA technology is a fibrin-specific agent. Its fibrin specificity decreases systemic activation of plasminogen and the resulting breakdown of the circulating fibrinogen when compared to a molecule lacking this feature. The ASSENT-2 was a phase III, randomized, double-blind trial that compared TNKase activase. The safety and efficacy in combination with GP IIb/IIIa receptor inhibitors or fondaparinux needs to be evaluated in large clinical trials^[111-117].

Some investigators have proposed the combination of PTCA, when feasible, with reduced-dosage thrombolytic therapy in the prehospital setting or early after the event. Combination with GP IIb/IIIa inhibitors and PTCA with or without stent also may be useful. However, a number of studies using a combination of thrombolysis followed by angioplasty, immediate or delayed, have shown no benefit or even reduced benefit when it is done on a routine basis. The cost of combined therapy is much higher than thrombolytic therapy alone^[118-120]. Nevertheless assessment by angiography after thrombolytic therapy provides evidence of failed thrombolysis, which is an indication for angioplasty. Additional studies are needed to assess its value compared with conservative therapy. The results may be influenced by the choice of adjuvant drugs and the use of stents.

Novel approaches for developing agents to dissolve clots or prevent thrombosis are antibody targeting. First a single molecule that contain both an effector molecule and the part of the antibody molecule that contains the antigen-binding site are created by recom-

binant DNA technology. An antibody specific for a platelet receptor has been used to target a plasminogen activator, to enable it to dissolve platelet-rich thrombi resistant to plasminogen activators. Similarly, hirudin has been targeted to fibrin to obtain a local rather than a systemic anticoagulant effect. Bifunctional antibodies capable of bridging an antigen on a clot and an antigen on a plasminogen activator or an anticoagulant now await clinical trials.

THROMBOLYTICS in ISCHEMIC STROKE

Streptokinase

The three studies utilizing streptokinase, namely MAST-I, MAST-E and ASK were prematurely stopped because of excess risk of death and intracranial bleeding in the streptokinase treated group^[121-123]. In these studies the entry criteria for the severe patients were up to 6 hours and the doses of streptokinase were not previously tested for safety in dose escalation studies.

Recombinant Tissue Plasminogen Activator (rt-PA)

Four major trials were conducted on intravenous rt-PA in ischemic stroke. The three negative trials were ECASS I, ECASS II, ATLANTIS and the one positive trial was the NINDS study^[124-127]. After dose escalation studies the NINDS trial enrolled 624 patients who received rt-PA 0.9 mg/kg or placebo within 3 hours of stroke onset. The part 1 of the study evaluated early neurological recovery while the part 2 assessed the percentage of patients who had minimal or no disability at 3 months as measured by various stroke scales as primary end point. A statistically significant difference was found with rt-PA with absolute increase in overall benefit of 11-13% and a relative increase of 30% in the number of patients with excellent outcome. However, in the NINDS and three other trials, there was a significant increase in symptomatic intracerebral bleeding with no change in mortality. If death and dependency are combined, rt-PA showed a significant benefit. Based on the results of this trial, the FDA approved the use of rt-PA for the treatment of ischemic stroke if given within 3 hours of stroke onset. Due to the inherent hemorrhagic risk with the use of rt-PA in ischemic stroke, studies are needed to allow stratification of patients according to the bleeding risk.

Intraarterial Prourokinase

Based on the cerebral angiogram, intra-arterial pro-urokinase is delivered directly into the clot. Patients with documented middle cerebral artery occlusion were treated within 6 hours of stroke onset. The PROACT I study demonstrated an acceptable safety profile and a recanalization rate of 58% in the treated group compared to 14% in the placebo group^[128]. The PROACT II study besides showing the same pattern of results as intravenous rt-PA, demonstrated a significantly better functional recovery at 90 days, a significant increase in symptomatic intracerebral hemorrhage and no difference in mortality^[118].

Defibrinating agent, anecrod: Hossmann et al showed the beneficial role of anecrod in patients with acute ischemic stroke in a small study^[129]. Pollak et al described thrombolysis with anecrod in patients with ischemic stroke^[130]. The STAT trial provided the same results as seen with thrombolytic agents and reinforced the concept that early reperfusion is essential to the treatment of acute ischemic stroke^[131]. The ESTAT included patients up to 6 hours after onset of neurological symptoms. This study was terminated because of lack of efficacy at interim analysis. A recent study was conducted to investigate the effect of anecrod treatment on plasma levels of tissue plasminogen activator activity and plasminogen activator inhibitor-1 (PAI-1) as well as indicators of prothrombin activation^[132]. Anecrod forms desAA-fibrin, which serves as a cofactor in tPA activity-induced plasminogen activation. Subcutaneous injection of anecrod leads to fibrinogenolysis caused solely by providing tPA with soluble fibrin as its cofactor in plasminogen activation.

PREHOSPITAL and EMERGENCY DEPARTMENT DELAYS AFTER ACUTE STROKE

Patient delays in reaching the hospital and delays within the emergency department are the major reasons in the lack of use of thrombolytic therapy for stroke. Recent study reported the efficacy of thrombolytic therapy with recombinant tissue plasminogen activator rt-PA and its direct relation to the time from the onset of symptoms to time of treatment, even within the 3 hour window^[133]. Several small studies have examined the factors that lead to delays before and after arrival at the emergency department^[133]. The Genentech Stroke Presentation Survey (GSPS), a large multicentered study examined prehospital and emergency department

delays in a large and geographically diverse group of patients^[134-140]. This study confirmed that a majority of patients do not arrive at the (ED) early enough to diagnose and treat acute stroke with rt-PA or other therapies. It further confirms that arrival by ambulance is associated with markedly shorter prehospital and ED delay times. Since "time is brain", intervention programs to cut short the delay in reaching the hospital and ED delays will enable early stroke diagnosis and treatment with thrombolytic agents to salvage the ischemic penumbra. The ATLANTIS trial reassured that 3 hour time window is good in selecting thrombolytic treatment and that earlier treatment with intravenous tPA appears better^[141].

FACTORS INFLUENCING EARLY ADMISSION in FRENCH STROKE UNIT

The admission delay of acute stroke patients in a French Stroke Unit during a 12-month period was studied. The study showed that hospital arrival within the first hours of stroke is possible in a French Stroke Unit. About 75% of the patients are admitted within the first 6 hours of stroke onset. It was demonstrated that stroke unit admission in France is fastest in patients brought to the hospital by emergency medical services or fire department ambulances. It was suggested that French stroke patients should be encouraged to seek immediate medical attention by using emergency telephone system and stroke management reprioritized in French EMS, as a time dependent medical emergency, to achieve the same level of organization as applied to myocardial infarction^[142].

The TLL Temple Foundation Stroke Project, organized to determine whether an aggressive, scientifically based behavioral intervention could increase the proportion of stroke patients treated with FDA-approved acute stroke therapy. It was concluded that an aggressive, multilevel stroke educational intervention program increases delivery of acute stroke therapy^[143].

MAJOR ONGOING STROKE TRIALS

Australian Urokinase Stroke Trial (AUST)

This is a randomized, multicentered study, designed to test the hypothesis that the administration of intraarterial urokinase plus anticoagulants in patients with acute posterior circulation ischemic stroke and a lyse-

able lesion seen angiographically will reduce morbidity and mortality assessed at 6 months compared with the administration of anticoagulation alone. Two hundred eligible patients will be enrolled. An initial pilot study of 15 patients was performed.

PILOT STUDY in STROKE CURRENTLY FUNDED by NINDS

Pilot Study of TNK-tPA in Acute Ischemic Stroke and New MRI Techniques prior to tPA therapy after stroke: These are the recently introduced programs funded by NINDS, allowing investigators to develop the data and the organization, leading to better, more efficient phase III clinical trials^[144].

Merino et al reported on extending tissue plasminogen activator use to community and rural stroke patients^[145]. This prospective case series evaluated the safety of tPA use in patients referred from rural communities to a tertiary center. This study showed that it is feasible and safe to treat rural patients referred to a tertiary care center with tPA, thereby extending the benefits of thrombolysis for acute stroke to a wider population.

Intravenous alteplase may be ineffective for patients with severe ischemic stroke due to large vessel occlusion. Hill et al studied the safety and feasibility of intravenous followed by intraarterial alteplase therapy^[146]. It was concluded that the combined intravenous and intraarterial alteplase therapy was a promising approach to the treatment of severe ischemic stroke. Immediately after the intravenous alteplase therapy with a standard dose of 0.9 mg/kg, intensive patient selection was performed using early neurovascular and neurometabolic imaging. Intraarterial alteplase therapy was then delivered. There was no incidence of symptomatic intracerebral hemorrhage or significant extracerebral hemorrhage^[146].

NEWER IMAGING TECHNIQUES and THROMBOLYTIC THERAPY

The National Institutes of Health Stroke Scale (NIHSS) is predictive of thrombus presence^[147]. This scale is not predictive of thrombus presence in the anterior circulation. Higher NIHSS scores are correlated with thrombi located in the M1 middle cerebral artery (MCA) and internal carotid artery (ICA)^[148]. Intravenous tPA may lyse some of these thrombi in MCA and ICA, however, it fails to recanalize the proximal ICA

occlusion^[149,150]. El-Mitwalli et al described clinical and sonographic patterns that are associated with tandem ICA and MCA occlusions on transcranial doppler (TCD) in 17% of tPA treated patients^[151].

Symptomatic hemorrhagic transformation (HT) occurs in 6%-10% of patients treated with thrombolytic therapy and remains a significant contraindication to thrombolytic therapy^[152,153]. These clinically silent microbleeds are only detected with advanced MRI sequences such as gradient echo (GRE) and echo planar susceptibility-weighted imaging (EPI-SWI). Previous studies have demonstrated that clinically silent microbleeds most commonly caused by hypertension, cerebral amyloid angiopathy or other causes of small-vessel vasculopathy, occur in up to 6% of healthy elderly subjects and 26% of patients with poor ischemic stroke^[154,155]. New MRI sequences such as T2-weighted GRE and EPI-SWI are highly accurate in the detection of previous microbleeds or petechial hemorrhages, and may alert the physician to avoid thrombolytic therapy^[154,156]. Kidwell et al have reported on magnetic resonance imaging detection of microbleeds before thrombolysis with T2-weighted MRI sequences, which may be a marker of increased risk of hemorrhagic transformations^[157]. Hence, pretreatment screening of thrombolytic candidates with these MRI sequences may be useful to identify these patients and avoid thrombolytic treatment in them.

REDUCTION of tPA-INDUCED INTRACEREBRAL HEMORRHAGE AFTER THROMBOEMBOLIC STROKE

Lapchak et al have demonstrated that the nonpeptide GP IIb/IIIa receptor antagonist SM-20302 reduced tPA-induced intracerebral hemorrhage after thromboembolic stroke^[158]. Platelet activation and deposition in cerebral microvessels produces ischemia-induced neuronal degeneration and behavioral deficits. It has been hypothesized that activated platelets in combination with polymorphonuclear leukocytes and fibrin causes vessel reocclusion leading to the “no-reflow” phenomenon after tPA administration. This study demonstrated that treatment of thromboembolic stroke with the combination of SM-20302 and tPA may have a beneficial outcome. Administration of this platelet antagonist did not significantly increase hemorrhage rate. In combination with tPA, SM-20302 reduced tPA-induced intracerebral hemorrhage. Lapchak et al hypothesized that the increased rate of intracerebral he-

morrhage observed after tPA administration may be partly due to increased reocclusion of the cerebral vessels following lysis of the emboli. Furthermore, the reocclusion can be controlled by the administration of a platelet inhibitor^[158].

PROTECTIVE EFFECT of FACTOR IXa INHIBITION in THROMBOEMBOLIC STROKE

Toomey et al in a rat model of thromboembolic stroke investigated the use of an inhibitory antifactor IXa monoclonal antibody (SB 249417) and compared its efficacy to that of tPA^[159]. It was shown that the inhibition of factor IXa within 4 hours of thromboembolic stroke produced a more favorable outcome than tPA. This suggests that cerebral ischemia and the resultant perfusion deficit are exacerbated by the activation of coagulation and that anticoagulants like SB 249417 may have a role in the treatment of ischemic stroke^[159].

SOME INTERESTING FINDINGS: PRESENTED at the RECENT STROKE MEETING

1. Early arterial recanalization often begins within a few minutes after tPA bolus and may predict the likelihood of clinical recovery. Failure to initiate recanalization during the 60 minutes of tPA infusion is considered a poor prognostic sign and additional interventional treatment should be given to these patients^[160].

2. Persons with previous stroke or MI and inadequate risk factor control are at four-fold higher risk for fatal stroke and ischemic heart disease. Secondary prevention is essential to reduce the cardiovascular mortality^[161].

3. Off-pump coronary artery bypass (OPCAB) revascularization decreases the incidence of cerebrovascular accidents^[162].

4. Emergency physicians can rapidly learn the skill of CT scan interpretation for acute stroke. This increases the confidence of emergency physicians in treating acute stroke patients^[163].

5. Following partial or complete vessel recanalization with intraarterial thrombolytic therapy, persistent hypoperfusion occurred in 3/4 of patients that resulted in infarction. Recovery in patients with or without

hypoperfusion was similar. Hence, following intraarterial thrombolysis, persistent hypoperfusion is a common phenomenon and often represents benign oligemia^[164].

6. Molina et al evaluated the relationship between the timing of rt-PA-induced recanalization and hemorrhagic transformation (HT) risk and investigated the relationship between HT subtype, total infarct volume (TIV) and 3-month clinical outcome. It was concluded that unlike PH1 and PH2, HI (HI 1 and HI 2) is associated with early neurological improvement, reduced infarct size and improved clinical outcome^[165].

7. Stroke teams and organized care increased the proportion of treated patients from 3% to 9%^[166].

8. Early reocclusion occurs in 27% of tPA treated patients and more often in patients with early and partial recanalization leading to deterioration of neurological deficit and higher mortality^[167].

9. CLOTBUST phase I data on transcranial doppler enhanced thrombolysis for stroke was presented^[168].

10. Diffusion and perfusion-weighted MRI rapidly provides important information in acute brain ischemia. Acute PWI > DWI mismatch pattern indicates the presence of at risk but potentially salvageable tissue. The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) demonstrates that the natural evolution of acute PWI > DWI mismatch tissue is altered by thrombolysis with resultant improved stroke outcome. This index is useful in the selection of patients for thrombolytic therapy^[169].

11. Diffusion and perfusion changes have been observed after thrombolytic therapy in acute ischemic stroke. Chalela et al investigated changes of MRI parameters two hours after intravenous rt-PA for acute ischemic stroke of less than 3 hours duration^[170]. Tissue reperfusion by mean transit time (MTT) or magnetic resonance angiography (MRA) approximately two hours after rt-PA administration was observed in 64% of patients and decrease in lesion volume was seen in 45% of patients^[170].

12. Schaefer et al reported on the comparison of initial DWI lesion volume with final infarct volume and assessment for areas of reversibility in patients with acute ischemic stroke who underwent thrombolytic

therapy. In a majority of patients who received thrombolytic therapy, there is growth from the initial DWI lesion to the final infarct size. However, in a minority of patients, there are relatively small peripheral regions with DWI hyperintensity which do not progress to infarction. Relative DWI and ADC values may help differentiate from tissue destined to infarct from that which is potentially salvageable^[171].

13. Early treatment with intravenous and intraarterial rt-PA may lead to improved outcomes in major ischemic stroke patients compared to IV rt-PA treatment alone^[172].

14. The combined use of IV integrilin and intraarterial rtPA appears safer in acute ischemic stroke, and may achieve better revascularization and clinical outcomes than IA-rt-PA alone^[173].

15. Diffusion-perfusion MRI in patients with acute basilar artery occlusions treated with IA thrombolysis, detected significant mismatch on pretreatment studies, suggesting that large volumes of salvageable tissue were present. Final volumes were shorter than pretreatment perfusion volumes, suggesting large volumes of tissue were salvaged^[174].

16. Ischemic parenchyma injury seen by early changes on DWI can be reversed in part by intravenous rt-PA therapy in some patients. Reduction in lesion volume of 50% or more was associated with clinical recovery^[175].

17. Gradient echo magnetic resonance imaging might be a useful tool for the study of variations in thrombus composition and characteristics. Thrombus evolution can be detected by serial exam. Thrombus presence, location and composition may have implications in acute stroke therapy^[176].

18. Catheter-based thrombolysis may have a serious risk of intracerebral hemorrhage. Hypoattenuation on initial perfusion weighted CT images (PW-CT) reflects oligemia and may predict hemorrhage in patients with stroke treated with IA-tPA alone or in combination with IV eptifibatid or IV-tPA^[177].

19. There are circadian variations in the success of rt-PA-induced recanalization. Thrombotic processes and cardiovascular mortality are influenced by circadian variations^[178].

20. Anticoagulation with factor Xa inhibitor might limit the extent of ischemic brain damage and neurological deficit following thromboembolic event in cerebral vessels, possibly by enhancing clot dissolution and early reperfusion^[179].

21. The time to symptom onset of stroke to hospital arrival was 85.1 minutes (SD 50.6; range 10-263). The time to call neurologist from hospital arrival was 24.7 minutes (29.5; range 0-128). Time to get to bedside after neurologist was called was 13.6 minutes (13.7, range 0-55). Time to image done after hospital arrival was 51.2 minutes (25.3, range 7-120), and an additional 15.8 minutes (18.6, range 0-80) to have the image read by a qualified person. In a study 72 patients arrived within 3 hours of signs and symptoms of ischemic stroke were treated with IV tPA with a delay of 93.7 minutes (SD 24.2, range 48-140) from arrival to treatment. Five patients were treated IA-tPA with a delay time from hospital arrival of 102.2 minutes (32.7, 67-151). These intrahospital delay times can be improved^[180].

22. ASPECT score has both prognostic value in predicting symptomatic hemorrhage and overall outcome among patients treated with tPA. The baseline ASPECT score predicts both neurological outcome and symptomatic hemorrhage among patients in the 3-5 hour window regardless of treatment assignment^[181].

23. Leukoaraiosis (LA) was not associated with an increased risk of parenchymal hemorrhage among acute ischemic stroke patients enrolled in ECASS trials. LA patients on oral anticoagulants have been associated with an increased risk of brain parenchymal hemorrhage among patients on oral anticoagulants^[182].

24. Admission via ambulance dialing "112" is encouraged because of its being a strongest determinant for early admission^[183].

25. Dramatic recovery after early recanalization is sustained at 3 months in 70% of patients during IV tPA therapy^[184].

26. The Heart and Stroke Foundation of Ontario, Canada, initiated the Coordinated Stroke Strategy (CSS) which brought about a dramatic increase in treatment rate. At least 50% of the current recruitment rate is attributable to internal reorganization, and also a

significant influence of advertisement, an individual dedicated to facilitating system reorganization. A large group of specialized physicians had a significant influence. Treatment of at least 25% of the patients with thrombolytic therapy is possible^[185].

27. Perfusion CT may be helpful for patients who will benefit from thrombolytic therapy^[186].

28. Sequential combination of intravenous recombinant tissue plasminogen activator and intraarterial urokinase in acute ischemic stroke is safe and feasible^[187].

29. Presence of a stroke team positively affects the rate of administration of thrombolytic therapy^[188].

30. Patients with prethrombolysis hyperglycemia have increased infarct volumes and high mortality^[189].

31. Intravenous rt-PA for acute ischemic stroke may have a substantial effect on long term stroke outcome^[190].

32. N-Methyl-D-Aspartate (NMDA) antagonist, MK 801, protects tPA mediated neuroexcitotoxicity in permanent focal ischemia^[191].

CONCLUSIONS

Patient delays in reaching the hospital and delays within the emergency department are the major reasons in the lack of use of thrombolytic therapy for stroke. An aggressive, multilevel stroke educational intervention program can increase delivery of acute stroke therapy. The presence of a stroke team positively affected the rate of administration of thrombolytic therapy. Admission via ambulance dialing "112" is encouraged because of its being a strongest determinant for early admission. Intravenous tPA given within 3 hours of symptom onset to patients who have met strict inclusion and exclusion criteria, is the only approved treatment for acute ischemic stroke. Only 2% of patients with acute ischemic stroke receive IV-tPA nationally^[192]. Coordinated Stroke Strategy (CSS) similar to the one initiated by the Heart and Stroke Foundation of Ontario, Canada, should be initiated in United States. The CSS of Ontario, Canada, brought about a dramatic increase in treatment rate. If such a strategy works in the United States, as predicted by CSS in Ontario, treatment of at least 25% of the patients with

thrombolytic therapy could be possible. Newer MRI sequences such as T2-weighted gradient echo (GRE) and echo-planar susceptibility-weighted imaging (EPI-SWI) can detect microbleeds and petechial hemorrhages to alert physicians of thrombolytic use. Pretreatment screening of thrombolytic candidates with these MRI sequences may be useful to identify these patients with microbleeds and avoid thrombolytic treatment in them. Since "time is brain", intervention programs to cut short the delay in reaching the hospital and ED delays will enable early stroke diagnosis and treatment with thrombolytic agents to salvage the ischemic penumbra.

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