

EDITORIAL

Therapeutic Intervention in Acute Ischemic Stroke: a Paradigm Shift

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ABBREVIATIONS

AHA = American Heart Association
AIS = acute ischemic stroke
CDC = Centers for Disease Control
CT = computed tomography
FDA = Food and Drug Administration
MRI = magnetic resonance imaging
NIHSS = National Institutes of Health
Stroke Scale
NINDS = National Institute of Neurological
Disorders and Stroke
rt-PA = recombinant tissue-plasminogen
activator (alteplase)

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ABSTRACT

In parallel to the situation of acute myocardial infarction, timely restoration of blood flow (reperfusion) using thrombolytic therapy or percutaneous intervention is the key and most effective strategy for salvaging ischemic brain tissue in acute ischemic stroke (AIS). There is a narrow therapeutic window (up to 3-4.5 hours) during which this can be accomplished, since the benefit of reperfusion continually decreases over time. During the acute phase of cerebral ischemia, a rapid determination and triaging of patients who are eligible for reperfusion is key to the success of such a salvaging strategy. Reperfusion in AIS can be effected via thrombolysis, already an FDA approved strategy, while newly emerging endovascular interventional techniques have been added to our therapeutic armamentarium.

INTRODUCTION

Each year, ~795 000 people in the USA and >1 million in Europe experience a new or recurrent stroke.¹ According to data from the Northern Manhattan study (2005), the age-adjusted incidence of first ischemic stroke per 100 000 was 88 in whites, 191 in blacks, and 149 in Hispanics. On average, every 40 seconds, someone in the USA has a stroke, and every 4 minutes, someone dies of a stroke.¹ Stroke ranks third among all causes of death after heart disease and cancer, and is a leading cause of serious, long-term disability. However, on an optimistic note, from 1996 to 2006, the annual stroke death rate decreased 33.5%, and the actual number of stroke deaths declined 18.4%. Although stroke is often considered a disease of the elderly, one third of strokes develop in individuals younger than 65 years of age. Risk of stroke increases with age, especially in patients older than 65 years, in whom 75% of all strokes are observed. One in 6 individuals will have a stroke at some point in their lifetime; approximately 85% of people afflicted by stroke will have risk factors which, if identified, are modifiable and preventable (Table 1).

CLASSIFICATION AND PATHOPHYSIOLOGY

Strokes are classified as ischemic or hemorrhagic.^{2,3} Acute ischemic strokes (AIS) caused by acute cerebral vessel occlusion are more common (80-87%)^{1,2} than hemor-

rhagic and they refer to thrombosis or embolism. They are classified into large (~20%) artery infarctions, small vessel (25%) or lacunar infarctions and cardioembolic (20%) infarctions. Ischemic strokes are commonly caused by atherosclerotic disease of extracranial or intracranial vessels perfusing the brain. Cardioembolic AIS are most frequently caused by atrial fibrillation. Approximately 30% of ischemic strokes are termed cryptogenic, for which the exact cause of stroke remains unknown.

Ischemic stroke develops from acute vascular occlusion which produces regions of ischemia in the affected brain tissue. Local cerebral blood flow is consisted of any residual flow in the major artery and the collateral supply, if any. Regions of the brain with cerebral blood flow <10 ml/100 g of tissue/min are referred to as the *core*, and these brain cells are supposed to die within minutes of the onset of stroke (permanently damaged/necrotic area). Zones of diminished or marginal perfusion (cerebral blood flow <25 ml/100 g of tissue/min) are designated as the (hypoperfused) ischemic *penumbra*. Tissue in the penumbra may remain viable for several hours because of marginal brain tissue perfusion; the ischemic penumbra is present in ≥80% of patients in the first 3 hours, but diminishes rapidly thereafter and it is the target to be salvaged by reperfusion and recanalization. Thus, “time is brain” (analogous to “time is muscle” in acute myocardial infarction) and a race against time should be the top priority of any health care system providing services to patients with AIS. Hemorrhagic transformation (conversion of a necrotic infarction into an area of hemorrhage) is estimated to occur in 5% of uncomplicated ischemic strokes, in the absence of thrombolytics. It occurs within 2-14 days post ictus, usually within the first week. It is more commonly seen with cardioembolic strokes, larger infarct size and following thrombolysis.

MORTALITY AND RISK FACTORS

Strokes incur significant morbidity and mortality and impose an insurmountable emotional and economical burden¹ to patients, families and society. The death rate (per 100 000 population) is estimated at 32.3 for the USA, 32.7 for the UK, 58.4 for Greece, 27.7 for France, 31.9 for Italy and 39.2 for Spain (years 2006-2007).¹ In a study of persons ≥65 years of age, in 4 USA communities, the 1-month case fatality rate was 12.6% for all strokes, 8.1% for ischemic strokes, and 44.6% for hemorrhagic strokes. In a report released by the Centers for Disease Control (CDC), 30-day stroke mortality rate varied by age: 9% in patients 65 to 74 years of age, 13.1% in those 74 to 84 years of age, and 23% in those ≥85 years of age. The cost estimate of stroke for 2010 in the USA culminates to \$73.7 billion.¹ Among the modifiable risk factors for stroke, prominent place is held by coronary heart disease, hypertension, smoking, diabetes mellitus, atrial fibrillation, sickle cell

disease, dyslipidemia, asymptomatic or symptomatic (transient ischemic attacks) carotid stenosis, obesity, physical inactivity, and post-menopausal hormone therapy (Table 1). Although primary prevention of stroke concentrating on these modifiable risk factors would be an ideal approach, it still lacks implementation and efficacy, and thus more effective management strategies are needed to cope with this devastating disease.

REPERFUSION

As timely restoration of blood flow (reperfusion) using thrombolytic therapy or percutaneous intervention is the key and most effective strategy for salvaging ischemic myocardial tissue in acute myocardial infarction, the same principle applies to AIS. There is a narrow therapeutic window during which this can be accomplished, since the benefit of reperfusion

TABLE 1. Modifiable Risk Factors for Ischemic Stroke¹

Factor	Relative Risk
Coronary heart disease	1.6
Hypertension	1.0-4.0 (reverse age-dependent)*
Smoking	1.8
Diabetes	1.8-6.0
Carotid stenosis	2.0
Atrial fibrillation /flutter	2.6-4.5
Sickle cell disease	200-400
Dyslipidemia	1.5-2.5
Obesity	1.7-2.4
Physical inactivity	2.7
Early menopause/Postmenopausal hormone therapy	1.4-2.0
Elevated plasma homocysteine	2.2
Depression	4.0
Pregnancy/Post-pregnancy period	2.4
Structural heart disease: myocardial infarction, LV aneurysm, dilated cardiomyopathy, endocarditis, valvular disease (e.g. mitral stenosis), intracardiac communications (e.g. ASD or PFO)	NA
Illicit drug use	NA

ASD = atrial septal defect; LV = left ventricular; PFO = patent foramen ovale; NA = not available

*Although clearly important even in the elderly, the impact of hypertension, as a risk factor for stroke, may decrease with increasing age; the relative risk (odds ratio) is 4 at age 50, decreasing to 1 by age 90

continually decreases over time. During the acute phase of ischemia, be it myocardial or cerebral, a rapid determination and triaging of patients who are eligible for reperfusion is key to the success of such a salvaging strategy. Reperfusion in AIS can be effected via thrombolysis, already a Food and Drug Administration (FDA) approved strategy, while newly emerging endovascular interventional techniques are added to our therapeutic armamentarium.⁴

THROMBOLYSIS

The initial evidence that thrombolysis was effective in AIS was provided in 1995 with the publication of the National Institute of Neurological Disorders and Stroke (NINDS) trial showing thrombolysis to be beneficial in selected patients, if administered within 3 hours from onset.⁵ This trial initially received considerable scepticism, mostly due to the fact that it was a single randomized trial of 624 patients that proposed a significant change in the management of acute ischemic strokes

with adoption of a potentially dangerous mode of therapy. There followed 3 more studies (ECASS I & II, ATLANTIS) which were negative,⁶⁻⁸ but pooled data from all these 4 trials (NINDS, ECASS I, ECASS II, ATLANTIS),⁹ which included 2775 patients treated up to 6 hours after symptom onset, were positive, supporting the results of the NINDS trial and demonstrating that thrombolysis within 3 hours (and possibly up to 4.5 hours) of symptom onset is associated with a greater chance of a favorable outcome at 3 months. Nevertheless, the paradigm shift in the management of acute ischemic stroke actually started with the ECASS III study,^{10,11} the second positive (after NINDS) randomized trial, which was published in September 2008, and confirmed the effectiveness of thrombolysis with use of alteplase in treating acute ischemic stroke (Table 2). This was a study of 821 patients, randomized to receive alteplase or placebo, between 3 and 4.5 hours after the onset of an acute stroke. Conducted in Europe, the trial had a median time to administration of rt-PA (alteplase) of 4 hours. A total of 52.4%

TABLE 2. Studies of Thrombolysis in Acute Ischemic Stroke

Study	No. of Patients	Mode of Therapy*	Timing of Therapy	Favorable Outcome	Intracerebral Hemorrhage	Mortality
NINDS ⁵	624	IV	<3 h	Yes (32-55%) (OR 1.7)	Higher (10.9% vs 3.5%)	Similar (17% vs 21%)
ECASS I ⁶	620	IV	<6 h	No (14-15%) (OR 1.3)	Similar (42.8% vs 36.8%)	Similar (22.4% vs 15.8%)
ECASS II ⁷	800	IV	<6 h	No (3.7%) (OR 1.2)	Similar (48.4% vs 40.2%)	Similar (10.5% vs 10.7%)
ATLANTIS ⁸	613	IV	3-5 h	No (2%)	Higher (2.6-11.3% vs 0.3-4.2%)	Similar (11% vs 6.9%)
STARS ¹⁶ **	389	IV	<3 h	Yes	10.5%	13%
SITS-MOST ¹⁷ **	6483	IV	<3 h	Yes (15%)	7.3%	11.3%
ECASS III ¹⁰	821	IV	<3-4.5 h	Yes (52.4% vs 45.2%)	Higher (27% vs 17.6%)	Similar (7.7% vs 8.4%)
SITS-ISTR ^{18,19}	664/11865	IV	3-4.5 h vs <3 h	No (58% vs 56.3%)	Similar (14% vs 16.4%)	Similar (12.7% vs 12.2%)
CASES ¹⁴	1112	IV	3-5 h vs <3 h	No (39.4% vs 36.5%)	Similar (7.8% vs 3.8%)	Similar (28.4% vs 21.4%)
EPITHET ²⁸	101	IV	3-6 h	Yes (30%)	Higher (7.7% vs 0%)	Similar (25% vs 14%)
DEFUSE ²⁹	74	IV	3-6 h	Yes (42%) (OR 5.4)	9.5%	4%
PROACT II ²²	180	IA †	<6 h	Yes (40% vs 25%) (OR 2.1)	Higher (10% vs 2%)	Similar (25% vs 27%)
IMS ²⁴	80	IV+IA	<3 h	Yes (30% vs 18%) (OR ≥ 2.0)	Similar (6.3% vs 6.6%)	Similar (16% vs 24%)
EMS ²⁷	25	IV+IA vs IA	<3 h	No (24% vs 24%)	Higher (35.3% vs 11.1%)	Increased (29% vs 5.5%)

h = hours; IA = intraarterial; IV = intravenous; OR = odds ratio, *rt-PA, unless otherwise specified, **prospective observational study, †recombinant pro-urokinase plus IV heparin vs IV heparin / recanalization rate 66% vs 18%

of patients given alteplase compared with 45.2% receiving placebo had a 'favorable outcome' (defined as little or no disability) ($p=0.04$). The incidence of intracranial hemorrhage was significantly higher in the alteplase group compared with the control group, however, mortality did not differ between the two groups (7.7% mortality in alteplase versus 8.4% in control; $p=0.68$). This trial was the second randomized trial after the NINDS trial to show benefit from the administration of a thrombolytic agent in acute ischemic stroke, and extended the time window of thrombolytic therapy up to 4.5 hours after the onset of the symptoms of stroke, and this was endorsed by the AHA and the American Stroke Association guidelines in May 2009.^{12,13}

A recent prospective multicenter study from a Canadian registry (CASES)¹⁴ comprising 1112 patients indicated that patients with acute ischemic stroke had a trend for better outcome if treated early with rt-PA within the 3-hour compared with the 3-4.5-hour treatment window, and cautioned that later time window treatment may result in greater adverse events.¹⁴ However, analysis of data from 66 MRI-selected patients receiving rt-PA 3-6 hours after symptom onset and comparing them with 108 patients presenting within 3 hours and with pooled data from the ATLANTIS, ECASS, and NINDS trials (1085 patients), indicated a favorable outcome in MRI-selected patients similar to those treated within 3 hours and better than those of the pooled analysis.¹⁵ The rate of symptomatic intracerebral hemorrhage in MRI-selected patients (3%) was lower than in the pooled rt-PA group (8%) and comparable to the rate in 1081 patients of the pooled placebo group (2%). This study supports the expansion of the time window for rt-PA administration up to 6 hours in patients with brain tissue at risk as defined by MRI.

A list of major trials on use of thrombolysis, mostly with rt-PA, in AIS is furnished in Table 2.^{5-11,16-31} They provide consistent evidence of efficacy of thrombolysis in selected patients who present within 3 hours after AIS or even up to 5-6 hours in certain patients. *Intracranial hemorrhage* constitutes a major hindrance to wider adoption and questions the safety of thrombolytic therapy (Table 2), albeit it only contributes to approximately 20% of deaths.^{10,20} Predictors of such a potentially catastrophic complication may include older age, hypertension, hyperglycemia and diabetes, baseline stroke severity (National Institutes of Health Stroke Scale-NIHSS score >20), baseline CT abnormalities, site and persistence of vascular occlusion, atrial fibrillation, concurrent heparin use and concomitant intake of antiplatelet agents.³²⁻³⁷ Measuring certain biomarkers, e.g. matrix metalloproteinase-9 indicating increased permeability of the blood brain barrier that leads to edema formation and hemorrhagic transformation, has been suggested as a means to predict this hemorrhagic complication of thrombolysis.³³

The most common reason for ineligibility of administration of a thrombolytic in acute ischemic stroke is time delay; pa-

tients arrive too late and do not call emergency services in time. Education of the public, and targeted education of patients at high risk of stroke by their primary care physicians, could increase the number of stroke patients who arrive to emergency rooms within the time window for assessment and life-saving therapy. Family physicians should emphasize that patients presenting with or calling in with symptoms and signs suggesting a stroke should be immediately directed to the closest emergency room. Acute stroke in the emergency room should be triaged and treated with the highest priority and urgency. Ideally, emergency room staff and stroke teams should be notified, if possible, by ambulance staff, prior to patient arrival. Prompt assessments should be made upon arrival and stroke patients should rapidly be taken to the CT scanner with the objective to determine whether the stroke is ischemic or hemorrhagic.³⁸ Alternatively, magnetic resonance imaging (MRI) may be used as the initial imaging modality for acute assessment.³⁸ Most commonly an immediate unenhanced (noncontrast) head CT scan is obtained and still considered the gold standard in the management of AIS. Recent technology has ushered in more sophisticated perfusion-based imaging modalities, such as CT or MRI perfusion and CT angiography which provide a map of cerebral blood volume, cerebral blood flow, and mean transit time, able to identify the ischemic core and penumbra that can distinguish patient subgroups that will or will not benefit from reperfusion therapies and also guide the decision for applying additional interventional techniques.^{4,28,29,38} Of course, other diagnostic tests may be in order in AIS patients, such as carotid duplex scanning to screen for cervical vessel stenosis, cerebral angiography to accurately delineate the degree and site of vessel lesion and guide interventional therapy when such a decision is made, and finally transthoracic and transesophageal echocardiography to seek cardioembolic sources and define cardiac anatomy and function.

The decision to thrombolysate patients should be a shared decision among patients, referring and treating physicians. The recombinant tissue plasminogen activator (rt-PA) is the only treatment for AIS approved by the US FDA, and it ideally should be administered within 3-4.5 hours of symptom onset. The rt-PA dose for AIS is 0.9 mg/kg (up to 90 kg) (less than the dose given in myocardial infarction or pulmonary embolism), administered in divided doses: 10% as a bolus over 1 minute, and the remaining 90% as a continuous infusion over the next 60 minutes (Table 3). Alternatively, the use of intra-arterial thrombolysis, performed by interventionalists, aims at delivering the thrombolytic agent at higher concentrations directly into the thrombus.^{24,26} In selected cases, intra-arterial thrombolysis extends the window of intervention to 6 hours after the onset of AIS symptoms. Furthermore, combined therapy with intravenous thrombolysis and then intra-arterial thrombolysis is occasionally proposed, e.g. with low-dose intravenous (0.6 mg/kg) rt-PA followed by 22 mg of intra-arterial rt-PA.²⁷ Some investigators have examined the combined approach to lysis

TABLE 3. Thrombolysis in Acute Ischemic Stroke

Regimen
<ul style="list-style-type: none"> ● rt-PA/alteplase (Actilyse, Boehringer Ingelheim) 0.9 mg/kg (up to 90 kg), administered intravenously in divided doses with 10% as a bolus over 1 minute, and the remaining 90% as a continuous infusion over the next 60 minutes*
Indications
<ul style="list-style-type: none"> ● Acute ischemic stroke with definite neurologic deficit ● Onset of symptoms <3-4.5 hours** ● Age ≥18 years ● Patient/family consent (accepting a ~6% risk of intracerebral hemorrhage)
Contraindications
<ul style="list-style-type: none"> ● Head injury / previous stroke within the last 3 months ● Hemorrhagic stroke / subarachnoid hemorrhage or history thereof ● Markedly elevated BP (≥185/110 mm Hg) poorly controlled with medical therapy ● Puncture of noncompressible arterial site within the previous 7 days ● Any active bleeding ● Known bleeding diathesis or platelet count ≤100,000/mm³, heparin administered within 48 hours with overshooting aPTT, or receiving oral anticoagulant with INR >1.7 ● Blood glucose concentration ≤50 mg/dl ● Multilobar (large area) infarction on head CT (fear of hemorrhagic transformation)
Relative contraindications
<ul style="list-style-type: none"> ● Minor or rapidly improving stroke symptoms ● Seizure at onset with postictal residual neurologic impairments ● Major surgery or severe trauma within the preceding 2 weeks ● GI or GU tract bleeding over last 3 weeks ● Acute myocardial infarction within the last 3 months
<p>aPTT = activated partial thromboplastin time; BP = blood pressure; CT = computed tomography; GI = gastrointestinal; GU = genitourinary; IV = intravenous; rt-PA = recombinant tissue-plasminogen activator</p> <p>* No anticoagulants/antithrombotics for the first 24 hours; later permitted in absence of hemorrhage on CT scan. After IV rt-PA, a CT angiogram may be considered to examine for persistent arterial occlusion and guide intraarterial intervention with thrombolysis or mechanical thrombectomy or both.</p> <p>** timing may be extended to ~8 hours for endovascular interventions (mechanical revascularization)⁴</p>

with use of a platelet glycoprotein IIB/IIIa inhibitor and rt-PA and found it to be a safe approach.³⁹ Finally, however, despite this apparent progress over the recent years in AIS management, in the US, in 2009, the rate of thrombolytic therapy for AIS doubled (3.4% - 5.2%) compared to 2005,⁴⁰ but remained well below desired rates.

INTERVENTIONAL TECHNIQUES

Endovascular interventional techniques for clot retraction in AIS patients have recently been introduced for those who are not candidates for rt-PA or who have failed intravenous therapy.^{4,41-49} Also, such devices have been used in combination with intravenous or intra-arterial therapy. For mechanical thrombectomy, two FDA-approved devices have become available,^{46,47} the Merci retriever (Concentric medical, Mountain View, CA, USA) and the Penumbra system (Penumbra, Inc., Alameda, CA, USA), with the former placed distally to the thrombus for clot retrieval and the latter proximally for clot disruption and aspiration. Initial results from trials employing these systems indicate that mechanical thrombectomy may be safe and effective for clot removal from large brain vessels after AIS.⁴ A recent review presented data on successful recanalization with varying rates with these two approved devices (43% - 78% with the Merci retriever and 83% - 100% with the Penumbra system).⁴¹ Rates of harms were also variable, including symptomatic (0% - 10% with the former and 0% - 11% with the latter device) or asymptomatic (28% - 43% and 1% - 30%, respectively) intracranial hemorrhage and vessel perforation or dissection (0% - 7% and 0% - 5%, respectively). Older age, history of stroke, and higher baseline stroke severity scores were sorted out as predictors of harm, whereas successful recanalization was a predictor of good outcome. However, in the accompanying editorial, great caution is advised in adopting neurothrombectomy over thrombolysis, before the completion of appropriately designed randomized studies establishing a clinical benefit from the use of such devices.⁴²

For cases of failure of arterial thrombolysis or mechanical thrombectomy or both, self-assisted revascularization with use of self-expanding stents have been used with promising results.⁵⁰ However, in a very recent study, use of these stents in patients with transient ischemic attack or stroke attributed to stenosis 70-99% of a major intracranial artery failed to demonstrate any benefit over aggressive medical management.⁵¹

CONCLUSION

There is currently a paradigm shift in the management of acute ischemic stroke (AIS) similar to that of acute myocardial infarction. Thrombolysis and endovascular interventional techniques have been introduced and have ushered in a new era in more effective treatment strategies in these long-neglected patients. Data are compelling that treatment with intravenous

rt-PA, in the time window of <3.0-4.5 hours after onset of AIS, is better than standard care and should be offered to appropriately selected patients.^{10-13,52} Significant progress has been achieved in this front, however penetration of these promising therapies into the medical community has been slow, albeit much slower than that noted during similar endeavors in shifting gear in the management of acute myocardial infarction initially with thrombolysis and then with primary percutaneous coronary angioplasty. Advances in reperfusion techniques of AIS and in brain and vascular imaging will expand the number of patients who may benefit from such therapies. Until then, we have to work within a limited therapeutic window (≤ 3 hours; or up to 6 hours in select patients), inform and educate the public about the warning signs for stroke, convince the authorities to establish and/or increase the number of stroke centers able to administer thrombolysis on a 24-hour basis or to provide advanced interventional perfusion techniques, and surpass our excessive fear of hemorrhagic complications.

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