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Management of Acute Ischaemic Stroke in the Elderly

Tolerability of Thrombolytics

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Abstract

Stroke and its consequences are of global concern. Although stroke can affect individuals of any age, it primarily affects the elderly. It is among the leading causes of severe disability and mortality. In recent years, acute stroke has become a medical emergency requiring urgent evaluation and treatment. Effective management of patients with acute stroke starts with organisation of the entire stroke care chain, from the community and prehospital scene, through the emergency department, to a dedicated stroke unit and then to comprehensive rehabilitation.

Intravenous thrombolysis with alteplase (recombinant tissue plasminogen activator; rt-PA) 0.9 mg/kg (maximum dose 90mg) was shown to significantly improve outcome of acute ischaemic stroke, despite an increased rate of symptomatic intracerebral haemorrhage, if treatment is initiated within 3 hours after the onset of symptoms to patients who meet strict eligibility criteria. Post-marketing studies have demonstrated that intravenous alteplase can be administered appropriately in a wide variety of hospital settings. However, strict adherence to the published protocol is mandatory, as failure to comply may be associated with an increased risk of symptomatic intracerebral haemorrhage. Intra-arterial revascularisation may provide more complete restitution of flow than intravenous

thrombolytic therapy and improve the clinical outcome if it can be undertaken in patients with occlusion of the middle cerebral artery, and possibly the basilar artery, within the first hours from stroke onset. However, further data are needed.

Although intravenous alteplase is recommended for any age beyond 18 years, elderly patients, in particular patients aged ≥80 years, were often excluded or under-represented in randomised clinical trials of thrombolysis, so that available data on risk/benefit ratio for the very elderly are limited. Small post-marketing series suggest that despite elderly patients over 80 years having greater pre-stroke disability, the use of intravenous alteplase in this patient group does not significantly differ in effectiveness and complications compared with the same treatment in patients aged under age 80 years. Further studies are necessary and elderly patients with acute stroke should be included in future trials of the merits of thrombolytic therapy.

1. Stroke and the Elderly

The incidence of stroke increases greatly with age.[1-5] Half of all strokes occur in people who are aged ≥70 years and nearly one-quarter affect individuals who are >85 years of age.[2,6] Stroke in the elderly is of serious concern not only because of the higher incidence of the disease with increasing age but also because of the increased disability that is associated with a stroke in an older individual.[1,7-9] Age is one of the strongest predictors of functional disability after a stroke. Up to half of patients who survive a stroke do not regain independence, and older age is associated with relatively poorer outcome.[10,11] An older person who survives a stroke is more likely to need assistance in daily living or require placement in an institution. [12,13]

With the aging of the population, stroke will take an increasing toll on individuals and society. Treatment aimed at reducing disability must be a primary concern of physicians involved in the care of elderly stroke patients.

2. Stroke as a Medical Emergency

The introduction of thrombolytic therapy for acute ischaemic stroke has required a dramatic change in clinical practice. Acute stroke is now a treatable condition that deserves urgent specialist attention. Patients should be assessed at a hospital immediately after a stroke.

There are numerous potential barriers to the delivery of thrombolytic therapy. In current clinical practice in the US, where intravenous alteplase (recombinant tissue plasminogen activator; rt-PA) has been approved for use since 1996, it is estimated that only 1 to 2% of patients with ischaemic stroke are being treated with alteplase. This represents only a fraction of the 5 to 20% of stroke patients who present to hospitals within 3 hours after onset of symptoms.[14,15]

A large proportion of stroke patients do not know the signs or symptoms of a stroke.[16] The population at greatest risk for stroke, the very elderly, are in fact the least knowledgeable about stroke warning signs and risk factors.[17] Considerable ongoing public education is needed to increase awareness of the presenting symptoms of stroke, and the potential benefits of obtaining early assessment and treatment.

The role of emergency medical services is of paramount importance in the access to acute stroke care. Ambulance crews can be trained to initiate evaluation with easy-to-administer scales that have been found to be clinically useful.[18,19]

2.1 Neurovascular Imaging

Stroke is a clinical diagnosis, but an urgent computed tomography (CT) of the brain is necessary to differentiate intracerebral haemorrhage (ICH) from an ischaemic stroke, and to exclude other

structural lesions mimicking a stroke. Ischaemic changes may be seen as early as within the first hour of symptom onset, and are valuable for the assessment of risks and prognosis with thrombolysis. Such early ischaemic changes include focal flattening of the cortical sulci, loss of the insular ribbon, and blurring of the interface between the grey and white matter or between the basal ganglia and white matter. These signs make it possible to predict the severity of stroke since the earlier such radiological features appear, and the greater the area of the brain involvement, the more likely it is that a major stroke will develop. Large regions of early ischaemic changes (>33% of the middle cerebral artery territory) possibly indicate an increased risk of haemorrhagic complications after thrombolytic therapy given within 6 hours.[20] However, there is considerable lack of agreement, even among experienced clinicians, in recognising and quantifying early CT changes.[21,22] By using a structured score to systematically quantify early CT ischaemia, it is possible to better predict functional outcome and the risk of symptomatic ICH before alteplase administration.[23]

The potential role of various neurovascular imaging techniques that may complement noncontrast brain CT is being evaluated. These techniques include CT-based techniques such as CT-angiography and perfusion CT, and ultrasound-based techniques such as transcranial doppler and transcranial colour coded duplex sonography. An alternative emerging neurovascular imaging approach is multimodal magnetic resonance imaging (MRI). MRI provides all 3 critical pieces of information necessary for accurate neurovascular assessment. Diffusion-weighted imaging provides details about tissue status, magnetic resonance angiography provides the location of arterial occlusion, and perfusion-weighted imaging provides relative measures of cerebral blood volume and transit time of contrast. However, the drawbacks of MRI are that it is expensive, less readily available and requires considerable patient cooperation.

2.2 Organised Stroke Units

The benefits of stroke units have been evaluated in an increasing number of studies.[24-26] The Cochrane Collaboration meta-analysis[27] of more than 3500 patients in 20 trials comparing stroke units with general care units indicates that stroke unit care results in significant reductions in death [odds ratio (OR) 0.83; 95% confidence interval (CI) 0.7, 0.97], death or dependency (OR 0.75; 95% CI 0.65, 0.87), and death or institutionalisation (OR 0.76; 95% CI 0.65, 0.90). Compared with conventional care on a general medical ward, care in an organised stroke unit reduces death and dependency with an absolute risk reduction of 5.6%. In addition, among elderly patients with stroke well-organised management was associated with a better outcome. It was also the more economical alternative.[27] In the Goteborg 70+ stroke study,[28] there was a reduction in death or institutional care after 3 months in the stroke unit group compared with the group receiving conventional care among patients with concomitant cardiac disease, but this effect did not remain after 1 year.

The ideal stroke unit provides multidisciplinary care to ensure the best management of physiological variables including temperature, fluid and electrolyte balance, blood glucose levels and blood pressure; to promote early mobilisation, physiotherapy and appropriate nutrition; and to prevent and treat secondary complications. The impact of dedicated stroke units on the stroke population depends on how well these units are staffed, and on their availability and cost. Key elements for operation include acute stroke teams, written care protocols and an integrated emergency response system. Stroke units are designed to improve care for the largest possible number of stroke patients by organising the initial triage and appropriate referral. Stroke units ensure that the recognised benefits of acute stroke care are more readily available and create a necessary setting where thrombolytic treatment can be administered safely to appropriate patients.[25,29,30]

3. Thrombolytic Therapy

3.1 Rationale for Thrombolysis

Acute ischaemic stroke results from the abrupt interruption of focal cerebral blood flow. Angiographically visible embolic or thrombotic occlusions have been identified as the cause of stroke in 70 to 80% of patients with symptoms severe enough to warrant early arteriography.[31,32] Within the first hours after onset of cerebral ischaemia, neuronal death and brain infarction evolves in a time-dependent fashion determined by both the duration and severity of the ischaemic insult. The infarct core may be densely ischaemic and will inevitably die, but there is also tissue with a compromised blood supply balanced on the edge between death and recovery – the ischaemic penumbra.[33] Therapeutic strategies designed to restore cerebral perfusion in a timely fashion have the potential to limit the cellular, biochemical and metabolic consequences of cerebral ischaemia that ultimately lead to irreversible brain injury. Indeed, early spontaneous reperfusion is associated with a favourable outcome in patients with an acute ischaemic stroke.

Thrombolysis is aimed at recanalisation of the acutely occluded arteries thus restoring perfusion to the ischaemic region and limiting the size of the evolving acute infarction. Considerable experimental evidence using thrombolytic agents in rabbit, primate and other animal stroke models show that autologous clots can be effectively lysed by thrombolytics without excessive risk of brain haemorrhage.[34-36]

3.2 Intravenous Thrombolysis

Intravenous thrombolysis for the treatment of acute ischaemic stroke has been the subject of recent intense investigation. Although many intravenous thrombolytic agents exist, the 2 that have been extensively studied are streptokinase and alteplase, as summarised in table I.

3.2.1 Streptokinase

Three major randomised trials of streptokinase have been conducted. These were the Multicentre Acute Stroke Trial-Italy (MAST-I), the Multicentre Acute Stroke Trial-Europe (MAST-E), and the Australian Streptokinase Trial (ASK).[37-39] The dose of 1.5 million units used in all 3 trials was the same as that given to patients with acute myocardial infarction (MI) and was not determined by detailed dose-ranging trials. Treatment was initiated within a therapeutic window of 6 hours after the onset of symptoms in both MAST trials and within 4 hours in the ASK trial. A trend toward adverse outcome was noted in the ASK trial for those patients who received therapy after 3 hours but not for those who received therapy earlier.[39] Each of the 3 trials was halted because of an excess rate of poor outcomes or excess mortality among the streptokinase-treated patients. Therefore, intravenous streptokinase cannot be used at present for treating acute ischaemic stroke.

The Thrombolysis in Acute Stroke Pooling Project, an individual patient data meta-analysis of the streptokinase trials, found that only a few factors influenced the response to streptokinase.[51] When patients were categorised according to age, the treatment effect was not shown to be different on death or severe disability. There was a trend toward better outcomes in the patients who received therapy within 3 hours compared with those who received therapy later, and the concomitant use of aspirin was significantly associated with increased death rates.

3.2.2 Alteplase

The results of 4 large-scale phase III trials of intravenous alteplase for the urgent treatment of patients with acute ischaemic stroke have been reported,[41-43] and their design and results reviewed.[52,53] The pivotal trial leading to the US Food and Drug Administration (FDA) approval of this treatment was the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (the NINDS rt-PA Stroke Trial).[42] In this landmark trial, carried out in 2 parts, a total of 624 patients with isch-

Table I. Summary of main randomised, clinical trials and recent post-marketing experience with thrombolysis for acute ischaemic stroke

Series	Thrombolytic agent	Window for treatment (hours)	No. pts	Age (years)	Upper age limit (years)
Randomised clinical trials					
MAST-I[37]	STK	6	622	NK	-
MAST-E[38]	STK	6	310	69	-
ASK[39]	STK	4	340	69	85
ECASS-I[40]	Alteplase	6	620	65	80
ECASS-II[41]	Alteplase	6	800	68	80
NINDS rt-PA Stroke Trial[42]	Alteplase	3	624	67	-
ATLANTIS[43]	Alteplase	3-5	613	66	80
PROACT II[44]	IA proUK	6	180	64	85
Post-marketing series					
Tanne et al.[45] (Multicentre survey)	Alteplase	3	189	65 (30 - 97)	-
Katzan et al.[15] (Cleveland)	Alteplase	3	70	69	-
Hanson et al.[46] (STIC)	Alteplase	3	252	70	-
Grond et al.[47] (Cologne)	Alteplase	3	100	63	80
Grotta et al.[48] (Houston)	Alteplase	3	269	69 (24 - 93)	-
Albers et al.[49] (STARS)	Alteplase	3	389	69 (28 - 100)	-
Hill et al.[50] (CASES)	Alteplase	3	450	69 (29 - 100)	-

ASK = Australian Streptokinase Trial; **ATLANTIS** = Alteplase Thrombolysis for Acute Noninterested Therapy in Ischaemic Stroke; **CASES** = Canadian Activase for Stroke Effectiveness Study; **ECASS** = European Cooperative Acute Stroke Study; **IA proUK** = intra-arterial pro-urokinase; **MAST-E** = Multicentre Acute Stroke Trial – Europe; **MAST-I** = Multicentre Acute Stroke Trial – Italy; **NINDS** = National Institute of Neurological Disorders and Stroke; **NK** = not known; **PROACT** = the Prolyse in Acute Cerebral Thromboembolism; **rt-PA** = alteplase or recombinant tissue plasminogen activator; **STARS** = Standard Treatment with Alteplase to Reverse Stroke; **STIC** = Stroke Treatment in the Community; **STK** = streptokinase.

aemic stroke were treated with alteplase within 3 hours after the onset of stroke symptoms. The dose chosen, based on pilot dose-ranging studies, was 0.9 mg/kg bodyweight, to a maximum of 90mg. Treatment onset was further stratified between the first 90 minutes versus 91 to 180 minutes.

Of the patients treated with alteplase, 31 to 50% had a complete or near-complete recovery at 3 months compared with 20 to 38% of the patients given placebo. Overall, there was an 11 to 13% absolute difference (or a 30 to 50% relative difference) favouring alteplase. The benefit was sustained at 1 year.[54] The main adverse effect of alteplase therapy was symptomatic ICH, which occurred in 6.4% of the patients given alteplase compared with 0.6% of those given placebo. However, the mortality rates in the 2 treatment groups were similar at 3 months (17% in the alteplase group and 21% in the placebo group) and at 1 year (24 and 28%, respectively).

The benefits of alteplase were consistent regardless of patient age, stroke subtype, stroke severity or prior use of aspirin. Earlier treatment with alteplase within the 3-hour window was associated with better outcome.[55] Patients treated 0 to 90 minutes from stroke onset had an increased odds of improvement at 24 hours and favourable 3-month outcome compared with patients treated later than 90 minutes. Although patients with severe neurological deficits at baseline were less likely to have a good outcome regardless of treatment, a subgroup analysis of patients older than 75 years with an initial National Institutes of Health stroke scale (NIHSS) of >20 (implying a severe stroke) demonstrated a slight reduction in death or severe disability with alteplase compared with placebo.[56]

Intravenous alteplase was approved for use in North America and recommended by authoritative bodies based on the strict NINDS rt-PA Stroke

Table II. Eligibility criteria for intravenous alteplase (recombinant tissue plasminogen activator; rt-PA) treatment for acute ischaemic stroke

Eligibility for intravenous alteplase treatment[a]
Age 18 years or older
Diagnosis of ischaemic stroke causing clinically apparent neurological deficit
Onset of symptoms (or time patient last seemed normal) well established to be <3 hours before possible beginning of drug infusion
No evidence of intracranial haemorrhage on pretreatment CT
No stroke or head trauma during the preceding 3 months
No major surgery or serious trauma during the preceding 14 days
No history of intracranial haemorrhage
No symptoms suggestive of subarachnoid haemorrhage
No known arteriovenous malformation or aneurysm
No gastrointestinal or urinary tract haemorrhage within the preceding 21 days
No arterial puncture at a noncompressible site within the preceding 7 days
No known bleeding diathesis, including but not limited to:
platelet count <100 000/mm^3
heparin administered within preceding 48 hours and prolonged aPTT
concurrent use of oral anticoagulants and PT >15 sec (or INR ≤1.7)
No rapidly resolving symptoms or only minor symptoms of stroke
No seizure at the onset of stroke
Systolic blood pressure ≤185mm Hg and diastolic blood pressure ≤110mm Hg at time of treatment; no need for aggressive measures to lower blood pressure to within the above-specified limits
Blood glucose level >50 and <400 mg/dl
Caution advised for patients with extensive early infarct signs on CT or severe stroke (NIHSS> 22)[b]

a Data based on Adams et al. [59] and the NINDS rt-PA Stroke Study Group.[42,57]

b Not integral part of the NINDS rt-PA Stroke Trial protocol.

aPTT = activated partial thromboplastin time; **CT** = computed tomography; **INR** = international normalised ratio; **NINDS** = National Institute of Neurological Disorders and Stroke; **NIHSS** = National Institutes of Health Stroke Scale; **PT** = prothrombin time.

Trial protocol for patients aged 18 years or older meeting inclusion and exclusion criteria.[42,57-60] The eligibility criteria and main protocol guidelines for intravenous alteplase administration for acute ischaemic stroke are summarised in tables II and III, respectively. Based on the results of this trial, Fagan and colleagues have demonstrated that alteplase therapy is likely to result in a net cost savings to the healthcare system.[61]

The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischaemic Stroke (ATLANTIS) trial, assessed alteplase administered 3 to 5 hours after stroke onset in patients up to 80 years of age. The trial was terminated prematurely when it was decided that treatment was unlikely to prove beneficial. No differences in mortality were seen between the treatment and placebo groups, although the risk of symptomatic ICH (7%) did not appear to be higher than in patients treated within 3 hours in other trials, suggesting that treatment within 5 hours is not associated with increased risk.[43]

Two other large placebo-controlled, randomised clinical trials were the European Cooperative Acute Stroke Study (ECASS)-I and -II.[40,41] Both assessed intravenous alteplase administered within a time window of 6 hours and used a CT radiological exclusion criterion of extensive early ischaemic changes. Both studies also applied an age limit of 80 years. In ECASS-I, the dose of alteplase was higher (1.1 mg/kg up to a total of 100mg) than in the NINDS rt-PA Stroke Trial. Besides an intention-to-treat analysis, a target population analysis excluded results in 109 of the 620 patients treated despite protocol violations, in particular the >1/3rd of middle cerebral artery CT criterion. Intention-to-treat analysis showed no significant differences in the primary outcome measures. However, in the target population analysis the modified Rankin scale (a 5-point scale) was 1 point lower in the al-

teplase treated group, implying better functional outcome with treatment. In addition, some of the secondary end-points were in favour of the alteplase-treated arm. Yet mortality was somewhat higher among alteplase-treated patients in both analyses. Excess mortality was mostly due to haemorrhage, and intracerebral haematoma was significantly more frequent among patients given alteplase than among those given placebo (19.8 *vs* 6.5%).

In ECASS-II, a lower dosage of alteplase was used, similar to the NINDS rt-PA Stroke Trial (0.9 mg/kg), and there was stricter adherence to the exclusion of patients with extensive early infarct signs on the baseline CT scan. A total of 800 patients were enrolled and approximately 80% were treated 3 to 6 hours after stroke onset. ECASS-II failed to demonstrate a significant difference between treatment groups in the primary outcome measure of the modified Rankin scale (score 0 or 1) 3 months after treatment. A *post hoc* analysis revealed a lower rate of death or dependency among those treated with alteplase than among those treated with placebo. Treatment with alteplase did not increase mortality or morbidity, despite a 2.5-fold increase in symptomatic ICH (8.8% of patients treated with alteplase and 3.4% of those given placebo), so the safety data were consistent with those of the NINDS trial.

A meta-analysis of the NINDS rt-PA Stroke Trial and both ECASS trials includes over 2000 randomised patients.[62] Among patients treated within 3 hours of stroke onset (n = 866) a significant reduction in the rate of death or dependency was found, from 71.6% in placebo-treated patients to 57.7% with intravenous alteplase (OR 0.55; 95% CI 0.41, 0.72). The number needed to treat to prevent 1 additional patient from being dead or disabled was 7 for a time window of 3 hours and a alteplase dose of 0.9 mg/kg.

3.2.3 Post-Marketing Experience with Alteplase

The successful use of alteplase in the NINDS rt-PA Stroke Trial required strict selection criteria, accurate diagnosis of stroke, precise determination of stroke onset (time when patient was last seen normal) and careful reading of CT scans, all performed on an urgent basis. The first 24-hour period of monitoring occurred in an acute stroke unit or an intensive care unit setting, blood pressure was strictly managed, and neurological assessments and vital signs frequently monitored. Over the following years, post-marketing ('phase IV') data on the use of intravenous alteplase became available from multiple sources, encompassing different

Table III. Main protocol guidelines for intravenous alteplase (recombinant tissue plasminogen activator; rt-PA) for acute ischaemic stroke

Main Protocol Guidelines[a]
1. Consider treatment if diagnosis of stroke and assessment of brain CT by physician with appropriate expertise, and patient can be admitted to an acute stroke unit (or intensive care unit)
2. Review carefully patient selection criteria
3. Discuss potential benefits and risks with patient and/or family
4. Infuse alteplase at a dose of 0.9 mg/kg (maximum dose 90mg) over a 60-minute period; first 10% of the total dose given as a bolus over a 1-minute period
5. Perform neurological assessments every 15 minutes during infusion of alteplase, every 30 minutes for the next 6 hours and every 60 minutes for the next 16 hours
6. If an intracranial haemorrhage is suspected, discontinue the alteplase infusion and obtain an emergency CT scan
7. Monitor blood pressure every 15 minutes for 2 hours, every 30 minutes for 6 hours, and every 60 minutes for 16 hours; repeat measurements more frequently if systolic pressure is >180mm Hg or diastolic pressure is >105mm Hg; administer antihypertensive drugs (such as intravenous labetolol) as needed to maintain blood pressure ≤ those levels
8. No concomitant anticoagulants or antiplatelets during first 24 hours
9. No central venous access or arterial puncture, and if possible, no insertion of nasogastric tube within first 24 hours; no insertion of indwelling bladder catheter within drug infusion or 30 minutes after

a Data based on Adams et al.[59] and the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.[42,57]

CT = computed tomography.

clinical settings ranging from expert tertiary care stroke centres to rural community hospitals. These data made it possible to critically assess the tolerability and effectiveness of this novel treatment in routine clinical use.

Treatment with alteplase stimulates the fibrinolysis of blood clots by converting plasminogen to plasmin. The most critical risk of alteplase therapy, hampering widespread endorsement by clinicians, is symptomatic ICH. Risks of symptomatic ICH following administration of alteplase in routine clinical practice were assessed in different clinical settings and are summarised in figure 1. Comparison of results reported in different settings should be interpreted with caution because differences in patient characteristics and stroke severity, as well as differences in study methodology and data collection, may affect reported rates of ICH and outcome.

Rates of alteplase related symptomatic ICH in most phase IV studies ranged between ≈3 and 7%, and were comparable with the NINDS rt-PA Stroke Trial experience. The mean age was nearly 70 years in most series and, rarely, patients even up to ≈100 years of age were treated. The rate of symptomatic ICH was 6% in a multicentre retrospective survey among 13 medical centres in the US[45] and 5% in the single academic centre in Cologne, Germany.[63] However, the general applicability of alteplase is uncertain as reflected by the recent audit from the Cleveland, Ohio, US, metropolitan area.[15] In an historical prospective cohort study Katzan et al.[15] found a rate of symptomatic ICH as high as 16% among the 70 patients treated with alteplase in the 29 hospitals audited. Two recent large post-marketing studies are the Standard Treatment with Alteplase to Reverse Stroke (STARS) study[49] and CASES (the Canadian Activase for Stroke Effectiveness Study).[50] STARS was a prospective monitored, multicentre study (57 medical centres: 24 academic and 33 community) in the US mandated by the FDA. The rate of symptomatic ICH in this study of 389 patients was 3.3%.[49] CASES is an ongoing comprehensive post-marketing registry in Canada mandated by Health Canada, as part of the conditional Canadian licensure.[50] Interim analysis of 450 patients revealed a 4% rate of symptomatic ICH. The median age of treated patients was 71 years and 40% were aged ≥75 years.

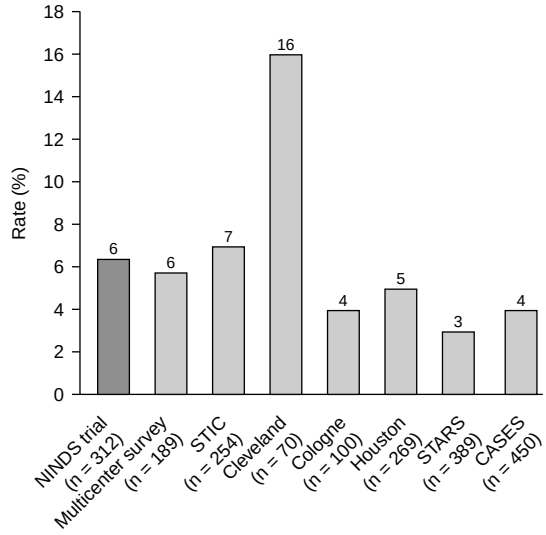

Fig. 1. Rates of symptomatic intracerebral haemorrhage in the alteplase (recombinant tissue plasminogen activator; rt-PA) arm of the NINDS rt-PA Stroke Trial, and in the main post-marketing series administering intravenous alteplase within 3 hours of stroke onset. **CASES** = Canadian Activase for Stroke Effectiveness Study; **NINDS** = National Institute of Neurological Disorders and Stroke; **STARS** = Standard Treatment with Alteplase to Reverse Stroke; **STIC** = Stroke Treatment in the Community.

Some of the variability in rates of ICH between studies is probably a result of chance. However, there are multiple stages in the process of treatment with alteplase where insufficient knowledge, experience or rigor may potentially lead to a higher risk of ICH. It is conceivable that some of the variability in rates of ICH observed may be as a result of differences in expertise and experience of the treating physicians, nurses and other personnel involved in the management of patients with an ischaemic stroke treated with alteplase. In the Houston, Texas, US, experience,[48] the overall risk of symptomatic ICH with the use of intravenous alteplase during the years 1996 to 2000 was 4.5%. Risk of alteplase-related symptomatic ICH decreased from 1996 to 2000, demonstrating that safety of al-

teplase therapy depends on the expertise of the treating team.[48]

Deviations from NINDS protocol guidelines have been reported in nearly one-third and up to half of patients treated with alteplase.[45,46] In the Cleveland area experience that reported the highest risk of ICH, rates of protocol deviations were as high as 50%,[15] while rates were considerably lower in the Canadian experience[50] and at the academic centre in Cologne.[47] Deviations from protocol guidelines are a heterogeneous group. However, overall, deviations are by no means benign. Risk of symptomatic ICH was found to be 4% if protocol guidelines were strictly followed but more than 10% when deviating from protocol guidelines.[45] Similarly, some other studies, but not all, found increased risk of ICH when deviating from protocol guidelines.[64,65] These observations should caution against deviating from recommended treatment guidelines when screening and treating patients with acute stroke with alteplase in routine clinical practice.

Phase IV data may also be useful at the bedside for risk stratification and prognostication of patients who present with acute ischaemic stroke and are being considered for thrombolytic therapy in clinical practice. Most currently available individual series are limited by insufficient statistical power. Demchuk et al.[66] have found that serum glucose levels at baseline and diabetes mellitus are predictors of ICH in alteplase-treated patients. The Multicenter Acute Stroke Survey[67] centrally collected data from multiple series of over 1200 patients treated with intravenous alteplase in order to assess prediction of ICH and of favourable outcome. These data have corroborated some previous observations, and it was shown that early ischaemic changes on CT, especially if extensive, severe strokes and high baseline serum glucose levels predict development of ICH after treatment with alteplase.[67] An inverse relationship was identified between baseline platelet counts and risk of symptomatic ICH.

The rate of major systemic haemorrhage was 1.6% in the alteplase arm of the NINDS rt-PA Stroke Trial,[42] whereas in the STARS study it was 1.5%[49] and in CASES <1%.[50] Rare cases of haemopericardium and life-threatening tamponade were reported after treatment with alteplase in patients with acute ischaemic stroke with mild or indistinct cardiac symptoms prior to thrombolysis. These cases probably represented undetected myocardial or pericardial disease.[68] Other potential complications are development of orolingual angioedema and rarely anaphylaxis.[69-71] It has been suggested that lingual and pharyngeal weakness caused by the stroke may worsen the effects of orolingual angioedema, and that patients who are taking an ACE inhibitor may be at increased risk for angioedema with concomitant alteplase therapy. Angioedema was observed in 0.9% of patients in CASES, and in each case the patient was taking an ACE inhibitor.[50]

3.3 Intra-Arterial Thrombolysis

Intra-arterial thrombolytic therapy may be delivered either by regional infusion or by local infusion directly into the thrombus using supraselective catheters. These approaches have the potential advantage of delivering higher concentrations of drug directly to the clot and thus minimising potential systemic complications. Disadvantages include the limited availability of facilities and of personnel who are capable of performing intra-arterial therapy, and the inherent delays in drug administration related to the logistics of assembling an appropriate team and performing an angiogram.

Different methods of intra-arterial thrombolysis are being employed. The type and administration of the thrombolytic agents have varied greatly. In previous studies the agent most commonly studied was urokinase. Intra-arterial recombinant alteplase and pro-urokinase have mainly been used in recent investigational studies. The location of delivery of the thrombolytic drug may be proximal to the clot in the parent vessel of the thrombosed artery, directly into the affected artery, into the thrombus itself or a combination of these methods. The infusion process has been variable, ranging from con-

tinuous to pulsed infusion. Mechanical clot disruption by the microcatheter is sometimes used.[72] Approximately 40% of the patients who undergo this treatment have complete arterial recanalisation and approximately 35% have partial recanalisation. These rates of recanalisation are higher than those that have been reported for patients who undergo intravenous thrombolytic therapy.

The larger of the 2 randomised trials, the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial, included patients aged up to 85 years, with arteriographically confirmed occlusion of the middle cerebral artery or one of its trunks.[44] Of over 12 000 patients who were screened, 474 underwent arteriography and 180 were enrolled. Of those, 121 received local intra-arterial pro-urokinase and low dose intravenous heparin within 6 hours after the onset of symptoms, and 59 received only low dose intravenous heparin during this period. At 2 hours, there was partial or complete lysis in 67% of the patients in the pro-urokinase group compared with 18% of those in the heparin-only group. The primary outcome of the PROACT II trial was the ability to live independently at 3 months after the stroke; this outcome was attained by 40% of the patients treated with pro-urokinase and heparin compared with 25% of those treated with heparin alone ($p = 0.04$). After treatment, ICH with neurological deterioration occurred in 10% of the patients in the pro-urokinase group and in 2% of those in the heparin-only group.

PROACT II was the first randomised trial in which intra-arterial thrombolysis was shown to have a benefit in patients who have had a stroke caused by occlusion of the middle cerebral artery and in patients whose treatment is initiated more than 3 hours after the onset of symptoms. The results of case studies comparing intra-arterial urokinase with intra-arterial alteplase and the preliminary results of a study of intravenous alteplase in combination with intra-arterial alteplase suggest that early intra-arterial therapy with urokinase or alteplase may be effective.

Intra-arterial thrombolysis has not been directly compared with intravenous thrombolysis, so the relative merits of these two routes of therapy in patients with acute ischaemic stroke are unknown. Important limitations of using intra-arterial techniques are the major investments in personnel and equipment required, and the additional time delay to initiate drug delivery. A small pilot study has found that combined intravenous and intra-arterial treatment with alteplase is feasible and may provide better recanalisation.[73] This will be further studied in an ongoing NINDS funded trial – IMS (International Management of Stroke).

3.4 Specific Considerations of Thrombolysis Tolerability in the Elderly

The main determinants of symptomatic ICH in the NINDS rt-PA Stroke Trial were greater severity of the initial neurological deficit (as measured by the NIHSS) and evidence of oedema or a mass effect on the baseline CT scan.[74] Increasing age was not an independent predictor of symptomatic ICH in the NINDS rt-PA Stroke Trial but emerged as a predictor for parenchymal haemorrhage in *post hoc* analysis in the ECASS I trial,[75] and for parenchymal haemorrhage and symptomatic ICH in a secondary analysis of the ECASS-II trial.[76]

There are no randomised clinical trials that assess the role of thrombolytics specifically in an elderly population. Patients aged >80 years are often excluded or under-represented in experimental acute stroke trials and in clinical stroke protocols. In a post-marketing observational study of 189 patients with acute ischaemic stroke, an overall age effect on risk of ICH was observed. Patients aged <60 years exhibited an especially low risk of ICH, but the rate of ICH was not higher in those ≥80 years compared with counterparts <80 years of age.[77] Likelihood of favourable outcome, defined as modified Rankin score 0 to 1 and NIHSS ≤5, was comparable between groups (37 and 54% *vs* 30 and 54%, respectively). Elderly patients were discharged more often to nursing care facilities. In logistic regression models there were no differences in OR for favourable or poor outcome, other than tendency for higher in-hospital mortality in elderly patients.

However, this study was retrospective and non-randomised, and particular caution was exercised by treating physicians in selection of elderly patients for treatment. Treating physicians were more often stroke specialists, and the NINDS rt-PA Stroke Trial inclusion and exclusion criteria were followed with greater accuracy in the elderly. Recently, comparable experience was observed in the prospective London Canada registry (62 patients). Despite the patients over 80 years having greater pre-stroke disability, alteplase did not significantly differ in effectiveness and complications compared with the same treatment in patients <80 years of age.[78]

Several factors may theoretically increase the risk of ICH in elderly patients with acute ischaemic stroke. Cerebral amyloid angiopathy is characterised by amyloid deposition in cortical and leptomeningeal vessels.[79] Its prevalence increases with age and it is associated with development of lobar ICH.[80] Cerebral amyloid angiopathy was identified in pathological specimens of patients developing ICH after thrombolytic therapy for acute MI.[81] Cerebral vasculature may be frail in the elderly, yet this may not be visible on brain imaging. White matter changes or leukoaraiosis are more frequent in the elderly and related primarily to small vessel disease.[82-84] Leukoaraiosis and age >65 years were found to be independent risk factors for bleeding in patients receiving long term anticoagulation because of cerebral ischaemia of presumed arterial origin.[85] In addition, liver blood flow is a major determinant of the rate of clearance of alteplase[86,87] and that may expose elderly patients receiving alteplase to higher blood concentrations over time.[87,88]

3.5 Lessons from Thrombolysis for Acute Myocardial Infarction

Thrombolytic therapy has revolutionised the care of patients with acute MI over the past 2 decades. However, the efficacy of thrombolytic therapy in elderly patients has not been evaluated to the same extent as it has in younger groups. In a meta-analysis of the 9 largest randomised trials conducted between 1982 and 1992 and involving 58 000 patients, thrombolytic treatment was shown to reduce 35-day mortality, particularly in patients younger than 75 years who had evidence of ST-segment elevation or bundle branch block and who were treated within 12 hours of the onset of symptoms.[88]

Among the 5754 patients in these trials who were aged >75 years, thrombolytic therapy was associated with an absolute reduction in mortality of 1% (1 life saved for every 100 patients treated), a reduction that did not reach statistical significance. Since older patients have the highest mortality risk after MI, they have the greatest potential gain from thrombolytic treatment, assuming a uniform treatment effect across age. Given the powerful evidence of benefit in younger patients (including those aged between 65 and 74 years) and the potential benefit in older patients, guidelines for the care of acute MI from the American Heart Association and the American College of Cardiology have supported the use of this treatment for patients aged >75 years. Thrombolysis was also found to be a cost-effective therapy for the treatment of elderly patients with acute MI.[89,90]

Contrary to this perspective, provocative findings from a recent observational study suggested that thrombolytic therapy in the elderly is not beneficial and could actually be harmful in patients aged >75 years.[91] The risk of ICH is higher among elderly patients treated with thrombolytics for acute MI.[92-94] An alternative strategy for reperfusion in patients with acute MI is primary angioplasty. Recent analyses comparing primary angioplasty with thrombolytic therapy among the elderly have suggested a survival benefit with early coronary intervention.[95] Leading experts have called for randomised trials of thrombolysis in the elderly.[96,97] In the meantime, it seems that some older patients certainly benefit from thrombolytic therapy, but some face an increased risk of ICH and other complications that can be disabling or fatal.

4. Conclusions

Effective treatment is now available for selected patients presenting with an acute ischaemic stroke. Intravenous thrombolytic therapy with alteplase improves outcome if treatment is initiated within 3 hours of the onset of stroke symptoms, despite an increased risk of ICH. When initiated 3 to 6 hours after stroke onset, trials did not reveal overall efficacy. Post-marketing data suggest that low complication rates and high rates of favourable outcome can be achieved with proper use of this therapy. Strict adherence to the published protocol is mandatory, since the risk of alteplase may potentially outweigh the benefits in some circumstances. Data on the risk/benefit ratio in the very old is limited. Future trials of thrombolytic therapy for acute ischaemic stroke should consider including patients meeting selection criteria, irrespective of their age. In the meantime, discerning physicians should recognise that age *per se* does not cause positive or negative outcomes of thrombolytic therapy, but rather that it is a marker for underlying pathophysiological factors and comorbid illnesses that may influence treatment effects.

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