Intravenous Alteplase for Stroke
Beyond the Guidelines and in Particular Clinical Situations

Jacques De Keyser, MD, PhD; Zuzana Gdovinová, MD, PhD; Maarten Uyttenboogaart, MD; Patrick C. Vroomen, MD, PhD; Gert Jan Luijckx, MD, PhD

Background and Purpose—Because of the risk of hemorrhage, especially in the brain, thrombolytic therapy with intravenous alteplase is restricted by guidelines, and only a small number of selected patients are being treated. Findings from metaanalyses, post hoc analyses of the randomized trials, and postlicensing experience suggest that more subjects, who otherwise have a poor predicted outcome without treatment, might benefit from intravenous alteplase.

Summary of Review—There is a strong indication that treatment may still be beneficial beyond 3 hours up until 4.5 hours. The risk of symptomatic intracerebral hemorrhage is not increased in patients aged 80 years or older. Excluding patients with severe stroke or with early ischemic changes in more than one third of the middle cerebral artery territory on baseline CT scan is probably not necessary when treatment is started <3 hours of symptom onset. Patients with minor or improving symptoms can also benefit. Intravenous thrombolysis appears appropriate as first line therapy for posterior circulation stroke. Alteplase can be given to patients with cervical artery dissection, seizure at onset and evidence of acute ischemia on brain imaging, and after carefully weighing risk and benefit in pregnancy and during menstruation. There are anecdotal reports on its use in children, patients with recent myocardial infarction, cardiac embolus, intracranial aneurysm or arteriovenous malformation, prior stroke and recent surgery. There appears to be a substantially increased risk of symptomatic cerebral hemorrhage in hyperglycemic stroke patients. The combined intravenous and intraarterial approach to recanalization appears safe and is currently under investigation in a randomized trial.

Conclusions—This document does not intend to change the guidelines but reviews the literature on the use of intravenous alteplase for stroke beyond guidelines and in particular conditions. (Stroke. 2007;38:2612-2618.)

Key Words: acute stroke  ■  alteplase  ■  intravenous thrombolysis  ■  recombinant tissue plasminogen activator

The introduction of intravenous alteplase (recombinant tissue plasminogen activator) as reperfusion therapy has caused a dramatic change in the way acute ischemic stroke is approached. The intervention is simple; alteplase is administered in a dose of 0.9 mg/kg body weight as a bolus (10% of total dose) followed by the remaining dose as an infusion over 1 hour. However, because there is the risk of major bleeding, particularly in the brain, patients need to be carefully selected on the basis of eligibility criteria, which have been largely adopted from the inclusion and exclusion criteria used in the randomized clinical trials.1-5 Contraindications according to the European license guidelines,6 the US license in combination with guidelines of the Stroke Council of the American Heart Association/American Stroke Association,7 and the Canadian license in combination with guidelines of the Canadian Stroke Council,8 are shown in the Table. In many circumstances no evidence-based data are available and recommendations are based on expert judgments. Some restrictions, especially in the European license, lack a scientific basis: for example, diabetes with prior stroke.

Because intravenous alteplase for stroke has become widely used in clinical practice, there have been new insights and experiences in particular settings where its anticipated benefits have to be weighed against the risk of harm. The purpose of this review is to gather the available literature on the use of intravenous alteplase for stroke beyond the guidelines and in situations not well covered by the guidelines.

Beyond 3 Hours
A pooled analysis of data from the National Institute of Neurological Disorders and Stroke (NINDS) trials (parts 1 and 2, 3-hour window),3 the 2 European Cooperative Acute Stroke Study (ECASS) trials (6-hour window),3,4 and the 2 Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials (part A, 6-hour window and part B, 5-hour window),1,2 suggest a potential benefit from treatment beyond 3 hours.9 The odds ratio for a favorable outcome was 1.40 (95% CI, 1.05 to 1.85) for patients treated between 3 to 4.5 hours, and 1.15 (0.90 to

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2612
1.47) for those treated between 4.5 to 6 hours. In a model estimating global odds ratio for favorable outcome at 3 months at different times from stroke onset, the upper 95% CI remained above 1.0 between 4.5 to 6 hours, suggesting probability of benefit. Additional information is considered necessary to move the maximal time beyond 3 hours. The ongoing ECASS III is evaluating the potential use of alteplase given between 3 and 4.5 hours after the onset of stroke,10 and the Third International Stroke Trial (IST-3)11 studies the efficacy of intravenous alteplase treatment until 6 hours. The apparent reduction in benefit from alteplase beyond 3 hours in the pooled analysis was not explained by an increased rate of intracerebral hematoma.9 It is likely attributable to a progressive disappearance of the ischemic penumbra; therefore, application of penumbral imaging modalities may allow a better selection of patients beyond 3 hours.12 What the pooled analysis clearly demonstrated is that the sooner alteplase is given to stroke patients, the greater the benefit, especially if started within 90 minutes. The adage “time is brain ,” which has now become widely familiar in the

### Contraindications for the Use of Alteplase in Patients With Stroke

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>European Licence</th>
<th>United States Licence and Guidelines</th>
<th>Canadian Licence and Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of intracranial hemorrhage</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &lt; 18 years or adults &gt; 80 years of age</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of symptoms &gt; 3 hours</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor deficit or symptoms rapidly improving</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe stroke (eg NIHSS &gt; 25)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe stroke demonstrated by brain imaging</td>
<td>✓</td>
<td>&gt;1/3 cerebral hemisphere</td>
<td>&gt;1/3 MCA territory</td>
</tr>
<tr>
<td>Heparin = 48 hours and elevated aPTT</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count ≤ 100 000/mm³</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients receiving oral anticoagulants</td>
<td>✓</td>
<td>and INR &gt; 1.7</td>
<td>and INR &gt; 1.7</td>
</tr>
<tr>
<td>Seizure at onset of stroke</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke within the last 3 months</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manifest or recent severe or dangerous bleeding</td>
<td>✓</td>
<td>Prior 21 days</td>
<td>Prior 21 days</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected subarachnoid hemorrhage</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent puncture of a non-compressible blood-vessel</td>
<td>✓</td>
<td>Past 7 days</td>
<td>Past 7 days</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction in the past 3 months</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>✓</td>
<td></td>
<td>Post-myocardial infarction</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Past 3 months</td>
<td>Past 14 days</td>
<td>Past 14 days</td>
</tr>
<tr>
<td>Significant trauma in past 3 months</td>
<td>✓</td>
<td>Head trauma</td>
<td>Head trauma</td>
</tr>
<tr>
<td>Systolic blood pressure &gt; 185 or diastolic &gt; 110 mm Hg or aggressive management necessary to reduce blood pressure to these limits</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>&lt; 2.7; &gt; 22.2</td>
<td>&lt; 2.7</td>
<td>&lt; 3; &gt; 22</td>
</tr>
<tr>
<td>Intracranial neoplasm, arteriovenous malformation, or aneurysm</td>
<td>✓</td>
<td>Any history of CNS damage</td>
<td></td>
</tr>
<tr>
<td>Prior stroke and concomitant diabetes</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (&lt; 10 days) traumatic external heart massage</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm with increased bleeding risk</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrical delivery</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other illness that could limit effectiveness or increase risk of bleeding in the judgment of the physician</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; MCA, middle cerebral artery; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time.
medical community, should be further promoted in the general public.

**Age 80 Years or Older**

Although stroke is more common in old age, elderly patients were excluded or underrepresented in the randomized controlled trials with intravenous alteplase. A systematic review of 6 studies comparing intravenous alteplase in stroke patients of ≥80 versus <80 years of age found no increased risk of symptomatic intracranial hemorrhage in the older age group. However, the 80 plus patients had a 3× higher 3-month mortality and were less likely to regain a favorable outcome, compared with younger patients. It is of interest to mention the case of a 100-year-old woman in whom alteplase rapidly improved stroke symptoms without complications.

From a safety point of view, there seems to be no reason to exclude ischemic stroke patients from thrombolysis based on a predefined upper age limit. However, there are doubts whether this intervention beyond the age of 80 years really improves 3-month outcome. Age itself is the most significant independent risk factor for stroke-associated mortality, mainly because elderly persons are more prone to complications and have more comorbidity than their younger counterparts. It is expected that we will learn more from the randomized, placebo-controlled IST-3, where elderly people are also included.

**Children**

The clinical trials did not enroll persons under the age of 18 years. Alteplase has been used in many settings in the pediatric population, but experience in stroke is very limited. Only a few cases, ranging in age from 12 to 16 years, have been reported. There were no complications and all had a good outcome.

**Posterior Circulation Stroke**

The randomized trials with intravenous alteplase focused on patients with anterior circulation stroke, and this was a formal inclusion criterion in the ECASS trials. However, approximately one fifth of ischemic strokes occurs in the posterior circulation, where basilar artery occlusion causes the most desolate strokes. Based on earlier pioneering work, thrombolytic therapy for basilar thrombosis is commonly delivered with an invasive endovascular approach to the occlusion site. However, there are indications from open studies that intravenous alteplase may be equally beneficial. Lindberg and colleagues reported their experience on 50 consecutive patients with angiographically proven basilar artery occlusion treated with intravenous alteplase. They found rates of survival, recanalization, and independent functional outcome comparable with those reported with endovascular approaches. A metaanalysis comparing intravenous (76 patients) versus intraarterial (344 patients) thrombolytic treatment found that survival and outcome were roughly equal; a total of 24% of patients treated with intraarterial thrombolysis and 22% treated with intravenous thrombolysis reached good outcomes. Thus, there is no good reason why for posterior circulation stroke invasive endovascular procedures should be preferred above intravenous therapy. The intravenous approach prevents the unavoidable delays incurred by invasive endovascular procedures and is the best option in centers lacking endovascular interventional expertise.

**Severe Stroke**

Patients with severe strokes (National Institute of Health Stroke Scale score >20) have a poor prognosis whether or not they are treated with alteplase. Because the risk of hemorrhage is higher among this population, caution should be exercised. However, these patients may still benefit from treatment, as shown in a post hoc analysis of the NINDS, ECASS and ATLANTIS trials.

**Early Ischemic Signs in More Than One Third of the Middle Cerebral Artery Territory**

The importance of early ischemic changes (loss of gray/white matter distinction, hypointensity, and sulcal swelling) involving more than one third middle cerebral artery territory on baseline brain CT in the decision to thrombolysate a patient with ischemic stroke is controversial. This concept was introduced by ECASS (6-hour window) and adopted by subsequent stroke trials with intravenous alteplase. However, a systematic review of the CT scans in the NINDS, and a study on 1205 patients with acute ischemic stroke treated in “routine” clinical practice, both found that early ischemic changes more than one third of the middle cerebral artery territory were not independently associated with increased risk of adverse outcome. These findings suggest that early ischemic changes on brain CT scan are not critical to the decision to treat otherwise eligible patients with alteplase within 3 hours of stroke onset. There is insufficient information beyond the 3-hour window.

**Mild or Rapidly Improving Symptoms**

Many patients do not receive intravenous alteplase because of mild or improving stroke symptoms and the uncertain risk-benefit ratio. However, a substantial part of these patients have poor outcomes and cannot be discharged home. A post hoc subgroup analyses of the NINDS could not detect a difference in the beneficial effects of alteplase in patients with minor stroke syndromes compared with the overall treatment effects in the entire cohort. About one third of acute stroke patients with rapid improvement of neurological deficit on arrival at the hospital develop severe subsequent deterioration. In 19 patients with rapidly improving symptoms, treatment with intravenous alteplase was associated with good outcome. These preliminary data suggest that withholding intravenous thrombolysis because of mild or improving symptoms may not always be justified.

**Seizure**

Because it may be difficult to differentiate ischemic stroke from postictal Todd paralysis by clinical examination and brain CT scan, current guidelines exclude patients with seizure at stroke onset for thrombolytic therapy. Magnetic resonance diffusion and perfusion-weighted images or angiography, perfusion CT, or CT angiography can be used to...
confirm the diagnosis of an acute ischemic process in the presence of concurrent seizures, and these patients can be treated.32,33

**Prior Stroke in Previous 3 Months**

Recent prior stroke was often an exclusion criterion for trials of thrombolytic therapy in patients with acute myocardial infarction, so information on the prevalence of prior stroke and the associated risk for brain hemorrhage is limited.34,35 We found 1 case report of a 50-year-old man who improved significantly after intravenous alteplase for acute stroke and who was successfully treated again with intravenous alteplase for a recurrent stroke on the fourth day.36

**Recent Myocardial Infarction**

Pericarditis is a contraindication to thrombolysis. Pericardial effusion is a common event in acute myocardial infarction.37 Acute stroke patients with recent myocardial ischemia pose a risk for hemopericardium and life-threatening tamponade after treatment with thrombolytic drugs.38-41 Recent myocardial infarction, however, is not included as contraindication in the European guidelines.

**Cervical Artery Dissection**

Cervical arterial dissection accounts for 10% of strokes in young people. Thrombolytic drugs might theoretically enlarge the wall hematoma, but the available information suggests that it should not be a contraindication. More than 50 patients treated with intravenous thrombolysis for acute stroke attributable to spontaneous cervical carotid artery dissection have been reported.42-45 The intervention appears safe and effective. Importantly, no new or worsening focal deficits, subarachnoid hemorrhage, or rupture of the internal carotid artery were observed.

**Intracranial Aneurysm or Arteriovenous Malformation**

A previously treated aneurysm, an incidentally discovered unruptured aneurysm, or the presence of a cerebral arteriovenous malformation may put the patient at greater risk of intracranial hemorrhage with thrombolysis. Only a few cases have been reported. Uncomplicated thrombolysis with intravenous alteplase was reported in 2 stroke patients with unruptured cerebral aneurysms, and in another 2 patients with myocardial infarction who had previously been treated for cerebral aneurysm (1 clipped and 1 coiled).46 Five cases have been described with an intracranial aneurysm detected after intraarterial thrombolysis for stroke; 2 had a fatal intracranial hemorrhage.46 There are 2 reports of intracranial hemorrhage resulting from an arteriovenous malformation detected after receiving alteplase for myocardial infarction.47,48 On the other hand, 1 patient underwent successful and uncomplicated intraarterial thrombolysis with alteplase for ischemic stroke before embolization of an arteriovenous malformation,49 and another patient with a known cerebral arteriovenous malformation was successfully treated with intravenous alteplase for massive pulmonary embolism.50

**Cardiac Embolus**

Cardiac thrombus is not an established contraindication to intravenous alteplase, but the drug could potentially accelerate break-up of the cardiac thrombus and cause embolism. Thromboembolic complications have been observed in 1.5% of patients receiving systemic thrombolysis for acute myocardial infarction, who were believed to have a preexisting clot.51 Very few data are available to evaluate the risk to benefit ratio of thrombolysis in stroke patients with cardiac thrombus. One study reported 5 patients with a cardiac thrombus who were given intravenous alteplase for stroke.52 No early systemic or cerebral embolism occurred. Two patients made a complete recovery, 2 others had a moderate outcome at 3 months, and 1 patient had late recurrent cerebral embolism and died. However, cases subjected to intravenous alteplase therapy for ischemic stroke with recurrent cerebral embolus, embolic myocardial infarction, and lower limb embolism have also been reported.53-55 Thus, the administration of intravenous alteplase to patients with known intracardiac thrombosis could represent a particular risk situation in the presence of which this therapy should be carefully evaluated.

**Pregnancy**

The major concern regarding the use of thrombolytics during pregnancy is their effect on the placenta, possibly resulting in premature labor, placental abruption, or fetal demise. The number of women reported in the literature who received alteplase during pregnancy is around 30; of these 6 were treated intravenously for stroke.56-60 Complication rates were similar compared with nonpregnant patients and child outcome appeared not affected. Alteplase does not cross the placenta, and studies on rats and rabbits did not find teratogenicity.56 The best level of evidence we have suggests that intravenous alteplase should not be withheld in pregnant patients with ischemic stroke, but because experience is limited risks and benefits must be carefully weighed.

**Menstruation**

Active bleeding is a contraindication against the use of thrombolytic therapy. However, a review of the limited literature concluded that intravenous alteplase can be administered relatively safely in women who are menstruating and should not be withheld or delayed.61 Patients may have an increased rate of menstrual flow and may require transfusion, especially if treatment is necessary during the first day of menses or in women with a history of dysfunctional uterine bleeding.

**Recent Surgery**

Recent major surgery is a contraindication for intravenous thrombolysis because the drug could disrupt hemostasis in the surgical bed and cause significant bleeding. However, it may be feasible in patients who had a relatively small or low-risk procedure with a site that is accessible and amenable to conservative management of bleeding complications. A patient has been reported who was treated with intravenous alteplase for acute stroke 24 hours after rhytidectomy and blepharoplasty.62 The patient developed hematomas that were
evacuated, but no life-threatening complications occurred. The facial flaps remained viable and she was discharged neurologically and cosmetically intact. The treatment of choice for carefully selected patients with postoperative strokes is intraarterial thrombolysis or mechanical clot disruption/embolectomy.63

Hyperglycemia
Hyperglycemia may not only hamper the fibrinolytic process, delaying alteplase-induced reperfusion of the ischemic penumbra,64 but treatment is also associated with increased cerebral hemorrhage and worse outcome.65–68 In the NINDS trial, patients with blood glucose levels above 22.2 mmol/L were excluded. Hyperglycemia is not considered a contraindication in the guidelines of the Stroke Council of the American Heart Association/American Stroke Association.7 However, the risk of symptomatic intracranial hemorrhage may already be substantially increased in patients with a blood glucose >11.1 mmol/L at stroke onset. A retrospective analysis of 138 consecutive alteplase treated patients showed that the rate of hemorrhage already sharply increased above a glucose level >8.4 mmol/L. Levels >11.1 mmol/L were associated with a 25% symptomatic hemorrhage rate.67

In the PROACT II trial with intraarterial recombinant prourokinase, patients with baseline glucose 11.1 mmol/L experienced a 36% risk of symptomatic intracranial hemorrhage compared with 9% for those with ≤11.1 mmol/L.68 From the available evidence, it may be prudent for safety reasons to restrict the upper limit of blood glucose to a level of 11.1 mmol/L. Hyperglycemia induces a variety of biochemical changes within endothelial cells that accelerate damage of the vasculature in the ischemic area,69 and this may be primarily responsible for the increased incidence of intracerebral hemorrhages after reperfusion. It remains to be determined whether hyperacute glycemic control before reperfusion may improve the efficacy and safety of thrombolytic therapy in these patients.

Combined Intravenous and Intraarterial Thrombolysis
When early recanalization with intravenous thrombolysis is not achieved, rescue thrombolytic treatment with local application at the site of the thrombus is still possible.70–75 This method may especially apply to ischemic strokes with large clot burden, as occurs with proximal middle cerebral artery, carotid terminus, and basilar artery occlusions. The rescue therapy provides higher rates of recanlization and appears relatively safe in experienced centers. The result of the randomized Interventional Management of Stroke III trial that compares combined therapy with standard intravenous thrombolysis is required before this method can be adopted into clinical practice.76

Conclusions
A conservative interpretation of the guidelines for intravenous thrombolysis in acute ischemic stroke may eliminate a number of otherwise eligible subjects. The intervention appears safe in patients aged 80 years or older, during pregnancy and menstruation, and in cervical artery dissection. Patients with mild symptoms, rapidly improving symptoms with residual deficit, and severe stroke may benefit from treatment. The pooled analysis of the randomized trials emphasizes the benefit of timely treatment but also shows that there may still be therapeutic efficacy up to 4.5 hours after stroke onset. It is hoped that the results from ECASS III will allow us to obtain consensus about the 3 to 4.5-hour window. The importance of early ischemic signs on baseline CT scan of the brain affecting more than one third of the middle cerebral artery territory, as an exclusion criterion for thrombolysis, is uncertain. The available information suggests that it has no prognostic value when treatment is given within 3 hours of symptom onset.

Thrombolysis in stroke patients with hyperglycemia represents a major safety concern that is not appropriately dealt with in the guidelines. The potential use of emergent blood glucose control before intravenous thrombolysis should be further investigated. We need clinical trials to find out whether and in whom local intraarterial thrombolysis provides clinical advantage over intravenous alteplase. In patients with posterior stroke, intravenous thrombolysis may be underused. The combined intravenous and intraarterial approach to recanalization in patients with ischemic stroke appears relatively safe and is currently investigated in a randomized clinical trial.

Disclosures
None.

References


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