

Should the time window for intravenous thrombolysis be extended?

The ESO GC decides to recommend the following revision of the Guidelines for intravenous thrombolysis after consideration of the presentations at the Karolinska Stroke Update meeting 2008, and the Consensus Statements adopted by the meeting.

ESO guidelines:

Specific treatment

Recommendations

- ~~Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 3 hours of onset of ischaemic stroke (**Class I, Level A**)~~
- Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke (**Class I, Level A**), although treatment between 3 and 4.5 h is currently not included in the European labelling.
- Second Bullet removed

Further bullets unchanged:

- The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended for routine clinical practice (**Class III, Level C**)
- It is recommended that blood pressures of 185/110 mmHg or higher is lowered before thrombolysis (**Class IV, GCP**)
- It is recommended that intravenous rtPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischaemia (**Class IV, GCP**)
- It is recommended that intravenous rtPA may also be administered in selected patients under 18 years and over 80 years of age, although this is outside the current European labelling (**Class III, Level C**)
- Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option (**Class II, Level B**)
- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (**Class III, Level B**). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 hours (**Class III, Level B**)
- It is recommended that aspirin (160–325 mg loading dose) be given within 48 hours after ischaemic stroke (**Class I, Level A**)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours (**Class IV, GCP**)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (**Class III, Level C**)
- The administration of glycoprotein-IIb/IIIa inhibitors is not recommended (**Class I, Level A**)

- Early administration of unfractionated heparin, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischaemic stroke (**Class I, Level A**)
- Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances (**Class I, Level A**)

Thrombolytic therapy

(Please note that the numbered references are in agreement with the ESO Guidelines paper for ischaemic stroke and TIA 2008. New references are indicated by the first author and year of publication. Full details are given in the reference list. The new references will be included in the next revision of the paper, planned for 2013).

Intravenous tissue plasminogen activator

Thrombolytic therapy with rtPA (0.9 mg/kg body weight, maximum dose 90 mg) given within 4.5 h after stroke onset significantly improves outcome in patients with acute ischaemic stroke [126, Hacke 2008]. By contrast, the ECASS (European Cooperative Acute Stroke Study) and ECASS II studies did not show statistically significant superiority of rtPA for the primary endpoints when treatment was given within 6 h [384, 385]. A pooled analysis of individual data of rtPA trials involving a total of 2,889 patients suggested a benefit up to 4.5 h, although, even within a 3-hour window, earlier treatment results in a better outcome (0–90 min: OR 2.11; 95% CI 1.33–3.55; 90–180 min: OR 1.69; 95% CI 1.09–2.62, 180–270 min: OR 1.40; 95% CI 1.05–1.85) [387]. **The recently published trial European Cooperative Acute Stroke Study III (ECASS III) has shown that intravenous alteplase administered between 3 and 4.5 hours (median 3 h 59 min) after the onset of symptoms significantly improves clinical outcomes in patients with acute ischemic stroke compared to placebo [Hacke 2008]; the absolute improvement was 7.2% and the adjusted OR of favourable outcome (mRS 0-1) was 1.42, 1.02-1.98. Mortality did not differ significantly (7.7% versus 8.4%), but alteplase increased the risk of SICH (2.4% vs. 0.2%). Treatment benefit is time-dependent. The number needed to treat to get one more favourable outcome drops from two during the first 90 minutes through seven within 3 hours and towards 14 between 3 and 4.5 hours [387; Hacke et al 2008].**

The SITS investigators compared 664 patients with ischaemic stroke treated between 3 and 4.5 hours otherwise compliant with the European summary of the product characteristics criteria with 11 865 patients treated within 3 hours [Wahlgren 2008a].

In the 3-4.5-hour cohort, treatment was started on average 55 minutes later after symptom onset. There were no significant differences between the 3-4.5-hour cohort and the 3-hour cohort for any outcome measures, confirming that alteplase remains safe when given between 3 and 4.5 hours after the onset of symptoms in ischaemic stroke patients who otherwise fulfil the European summary of product characteristics criteria [Wahlgren 2008a].

European regulatory agencies do not advocate rtPA treatment in patients with severe stroke (NIHSS >25), extended early ischaemic changes on CT-scan, or age above 80 years (unlike the US labelling). However, the NINDS (National Institute of Neurological Disorders and Stroke) Study showed that the extent of early ischaemic changes (using the ASPECT score) had no effect on treatment response within the 3-hour time window [387]. Moreover, observational studies suggest that rtPA given within 3 h of stroke onset is safe and effective in patients over 80 years of age [389–391], but more randomized data are pending.

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise and brain CT is assessed by an

experienced physician [393-395, Wahlgren 2008b]. Whenever possible, the risks and benefits of rtPA should be discussed with the patient and family before treatment is initiated.

Blood pressure must be below 185/110 mmHg before, and for the first 24 hours after, thrombolysis. Management of high blood pressure is required [126]. Protocol violations are associated with higher mortality rates [396, 397].

Continuous transcranial ultrasound was associated with an increased rate of early recanalisation after rtPA in a small randomized trial [398]; this effect may be facilitated by the administration of microbubbles [399]. However, a randomized clinical trial has recently been stopped for undisclosed reasons.

The use of multimodal imaging criteria may be useful for patient selection. Several large observational studies suggest improved safety and possibly improved efficacy in patients treated with i.v. rtPA beyond 3 hours based on advanced imaging findings [131, 160, 400, 401]. However, available data on mismatch, as defined by multimodal MRI or CT, are too limited to guide thrombolysis in routine practice (see also the section on imaging) [153].

Patients with seizures at stroke onset have been excluded from thrombolytic trials because of potential confusion with post-ictal Todd's phenomena. Case series have suggested that thrombolysis may be used in such patients when there is evidence for new ischaemic stroke [389].

Post hoc analyses have identified the following potential factors associated with increased risk of intracerebral bleeding complications after rtPA use [402]:

- elevated serum glucose
- history of diabetes
- baseline symptom severity
- advanced age
- increased time to treatment
- previous aspirin use
- history of congestive heart failure
- low plasminogen activator inhibitor activity
- NINDS protocol violations.

However, none of these factors reversed the overall benefit of rtPA.

References:

New:

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Current text

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The NINDS (National Institute of Neurological Disorders and Stroke) Study showed that the extent of early ischaemic changes (using the ASPECT score) had no effect on treatment response within the 3-hour time window [388]. However, European regulatory agencies do not advocate rtPA treatment in patients with severe stroke (NIHSS \geq 25), extended early ischaemic changes on CT scan, or age above 80 years (unlike the US labelling). Nevertheless, observational studies suggest that rtPA given within 3 h of stroke onset is safe and effective in patients over 80 years of age [389,390,391], but more randomized data are pending. The effect of gender on the response to rtPA is uncertain [392].

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise and brain CT is assessed by an

experienced physician [393,394,395]. Whenever possible, the risks and benefits of rtPA should be discussed with the patient and family before treatment is initiated.

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