Alteplase (recombinant tissue Plasminogen Activator, rt-PA)
for the Treatment of Acute Ischemic Stroke.

Application for inclusion of a new individual medicine in the WHO Model List of Essential Medicines (EML)

For the 2019 WHO Expert Committee on the Selection and Use of Essential Medicines

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Alteplase for AIS : WHO EML 2019 application
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIS</td>
<td>Acute ischaemic stroke</td>
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<tr>
<td>ATC</td>
<td>Anatomical therapeutic chemical</td>
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<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>DALY</td>
<td>Disability-adjusted life years</td>
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<td>DOAC</td>
<td>Direct oral anticoagulants</td>
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<td>ECASS</td>
<td>European-Australasian Cooperative Acute Stroke Study</td>
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<td>EML</td>
<td>WHO Model Essential Medicines List</td>
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<td>GOS</td>
<td>Glasgow outcome scale</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratios (ICER)</td>
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<td>INN</td>
<td>International nonproprietary name</td>
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<td>LMIC</td>
<td>Low- to middle-income countries</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>mRS</td>
<td>Modified Rankin scale</td>
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<td>NINDS</td>
<td>National Institute of Neurological Diseases and Stroke</td>
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<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life years</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled clinical trial</td>
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<td>rt-PA</td>
<td>Recombinant tissue Plasminogen Activator</td>
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<tr>
<td>sICH</td>
<td>Symptomatic intracranial hemorrhage</td>
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<td>SITS-MOST</td>
<td>Safe Implementation of Thrombolysis - Monitoring Study</td>
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<td>WSO</td>
<td>World Stroke Organisation</td>
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</table>
1. **Summary statement of the proposal for inclusion, change or deletion.**

Clot-dissolving (thrombolytic) drugs may reduce brain damage from a stroke by restoring the blood flow if given rapidly enough after stroke. On the other side, these drugs may also cause serious bleeding in the brain.

The authors apply for alteplase (recombinant tissue plasminogen activator, rt-PA) to be included in the EML as an *individual medicine* for intravenous thrombolysis. The indication is for patients diagnosed with *acute ischaemic stroke* (AIS) with a potentially handicapping neurological deficit at the time of thrombolysis, and treatment within 4.5 hours after onset of stroke symptoms (or after last proof of good health if unknown onset of symptoms).

With the huge worldwide burden of AIS and increasing numbers, recent trials confirming efficacy and safety of alteplase in various AIS populations, and with the ongoing improvement of stroke services worldwide, the conditions are met for making this cost-effective treatment more available worldwide.

This listing of alteplase is being sought for the EML’s *complementary list* because it requires organized pre- and inhospital care pathways in stroke-ready facilities, clinical training in diagnosing stroke, capacity to perform and interpret acute neuroimaging, continuous surveillance for at least 24 hours, and basic stroke management skills.

2. **Relevant WHO technical department and focal point (if applicable).**

The WSO is a non-state actor (NSA) in official relations with WHO. In this role, it maintains regular contacts with several WHO departments and units, addressing issues such as stroke and NCD prevention, health system issues, and essential technology and interventions for stroke patients. These discussions are held with the following WHO units concerned by stroke prevention and treatment:

- Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVI), in particular:
  - Management of Noncommunicable Diseases (MND)
  - Emergency and Trauma Care Programme
- Department of Essential Medicines and Health Products, in particular:
  - Innovation, Access and Use

For the current application, the main WHO focal point is Management of Noncommunicable Diseases in the NVI.

3. **Name of organization(s) consulted and/or supporting the application.**

The authors submit this application on behalf of the World Stroke Organization (WSO), the world’s leading non-governmental organization active against stroke. WSO’s main mission is to reduce the global burden of stroke through prevention, treatment and long term care. WSO has more than 60 society members and over 4000 individual members from 85 different countries. The society members include professional as well as patient support organizations.

Therefore, the current application by WSO is supported by its individual and societal members, and by its mission to fight against the worldwide burden of stroke.

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4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

The International Nonproprietary Name (INN) of rt-PA is alteplase, and its INN number is 5975 (source: https://mednet-communities.net/inn/, accessed 04.12.2018).

The Anatomical Therapeutic Chemical (ATC) code according to the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health is alteplase, ATC code B01AD02 (http://www.whocc.no/atc_ddd_index, accessed 04.12.2018).

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The dose of alteplase for adults is 0.9 mg per kg of body weight. The maximal dose for a patient is 90 mg. Of the total dose, 10% is given as an intravenous bolus once the indication for acute ischemic stroke thrombolysis is confirmed by the responsible physician, and the other 90% are given immediately thereafter as a continuous intravenous infusion over 60 minutes.

We propose that all three doses of alteplase, i.e. 10, 20 and 50 mg, are listed on the EML, in order to avoid that health care providers have to dispose of unused quantities of the drug.

Alteplase is stored at room temperature and is prepared shortly before its use. It has to be administered as a reconstituted solution for bolus injection, and then as infusion (with 1 mg alteplase per mL). Once mixed, it is stable and useable for several hours without particular risk of degradation.

Efficacy and safety has not been formally tested in the pediatric population and is not recommended below age 16. For this reason, no recommendation for a pediatric dose exists (see also chapter 9 below: “Special considerations: Pediatric population).

A higher alteplase dose of 1.1 mg per kg of body weight (1) and a lower dose of 0.6 mg per kg (2) were not superior with regards to long-term outcome, but symptomatic intracranial hemorrhage (sICH) risk were significantly higher and lower, respectively (see more details in chapter 9 on efficacy, and chapter 10 on harm, of these doses).

Alteplase is currently available in 104 countries. More details on market availability is listed in the chapter 12 below.

6. Is listing requested as an individual medicine or as representative of a pharmacological class?

The current application is for alteplase to be listed as an individual medicine for treatment of AIS if the specific prescribing conditions are met.

Several other thrombolytic agents from the same pharmacological class as alteplase are potential candidates for treating AIS, but none scientific evidence for them is currently insufficient in our eyes for an application for a class (square box) application. The following thrombolytic drugs have been considered or tested for treatment of AIS:

- Streptokinase (ATC code B01AD01)
- Desmoteplase (no ATC code)
- Urokinase (ATC code B01AD04)
- Tenecteplase (ATC code B01AD11)

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Whereas too little data exist for urokinase, streptokinase is currently listed on the EML as powder for injection: 1.5 million IU in vial on the complementary list for intravenous thrombolysis in acute myocardial infarction. It has not been been shown to be sufficiently safe for AIS (3, 4). Desmoteplase has not been further developed despite encouraging results in randomized trials (5-8), and tenecteplase is currently being tested in phase III RCT (9). Before such trials have shown therapeutic equivalence with, or superiority to alteplase, these drugs cannot be considered as valid alternatives alteplase for IV thrombolysis.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Dosing and administration of alteplase
The recommended alteplase dose for adults is 0.9 mg per kg body weight. The maximal dose for a patient is 90 mg. Of the total dose, 10% is given as an intravenous bolus once the indication for acute ischemic stroke thrombolysis is confirmed by the treating physician, and the other 90% are given immediately thereafter as a continuous intravenous infusion over 60 minutes. Therefore, an adult of 70 kg would require a total dose of 0.9 x 70 = 63 mg, of which 6.3 mg are given as a bolus, and the remaining 56.7 mg as an infusion over 60 minutes.

In the occasional situation of an ischemic stroke recurrence within three months, alteplase should not be re-utilized because of the potentially increased intracerebral hemorrhage risk after a recent stroke (10).

Guidelines on alteplase use in acute ischemic stroke
The WHO supports treatment of acute ischemic stroke with intravenous thrombolytic therapy in the Appendix 3 to the “Global Action Plan for the prevention and control of Noncommunicable Diseases 2013-2020” (11).

Most national and international guidelines on AIS treatment recommend intravenous alteplase treatment up to 4.5 hours if other conditions are met. Such examples are the European , American (10), Canadian (12), Indian (13), South African (14), Chinese (15), Swiss (16)and South Korean guidelines (17).

Additional requirements for effective use of alteplase in AIS
Several conditions are usually needed in order to allow treatment of appropriate patients with AIS within the early time window. If such additional requirements are met, this will increase the proportion of patients receiving acute treatment, decrease the number of patients where treatment is likely futile (too late, or treatment of stroke mimics) or dangerous (risk of intracranial or systemic hemorrhage), and shorten the delay between onset and thrombolysis. All these elements will increase the efficacy and safety of alteplase thrombolysis, resulting in reduction of early mortality and long-term handicap, i.e. a reduction of disability-adjusted life years (DALY).

Such additional requirements concern prehospital, emergency room, acute clinical assessment, acute neuroradiology, drug availability and appropriate dosing, and subsequent patient monitoring. Ideally, a region or country sets up a comprehensive chain of stroke care for potential patient that integrated primary prevention, acute stroke care, designed and trained hospitals and health care workers, stroke center care, and structured follow-up (18, 19). Even is some ore many elements of such a system are lacking, basic stroke services should be made available to the population which at some point will include provision of early thrombolysis, a measure with a significant impact on the patient’s chance of living without long term handicap (20, 21).

Additional basic requirements for delivering early thrombolysis in AIS include the following elements:

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1) An effective prehospital organization that allows patients with suspected stroke and clinical indications (i.e. a new neurological deficit that is potentially handicapping) to reach a thrombolyzing hospital within a short time (10),(19). This includes the availability of a centralized emergency call number, an effective transport system usually consisting of a coordinated an ambulance system (emergency medical system) with trained professionals, training of paramedics in recognizing stroke symptoms (triage) and stroke scores, defined and rapid referral patterns for patients with clinical criteria for thrombolysis and thrombectomy, and a prenotification system (“stroke alert code”) in collaboration with thrombolysing hospitals in this region.

2) Availability of stroke-ready hospitals (18, 22) or primary stroke units (23, 24). Such hospitals have a predefined pathway to assess potential thrombolysis candidates on a 24h/24h basis in their emergency room, and provide immediate thrombolysis for appropriate patients. These hospitals should provide immediate clinical and neurological assessment by qualified nurses and physicians, availability of rapid imaging to differentiate AIS from other conditions causing neurological symptoms (in particular acute intracranial bleeds), and fast access to basic laboratory tests (glucose, simple chemistry, simple blood count, basic coagulation tests) for patients with potential laboratory abnormalities.

3) Rapid clinical and neurological assessment upon hospital arrival by trained medical staff using stroke severity scores such as the National Institute of Health Stroke Scale (NIHSS) (25, 26) which is shown below in table 1. Online instruction and certification for the NIHSS is available (27).

This clinical assessment will allow to triage the patient for emergent imaging and to detect potential imitators of stroke and contraindications for thrombolysis. The clinical evaluation and the medical expertise for thrombolysis decision may also be provided remotely by telemedicine systems (Highashida Stroke 2013; TEMPIS) in remote facilities or institutions without the necessary qualified medical staff.

4) Immediate availability of basic neuroradiology services in the thrombolyzing institution (28). A simple non-contrast computed tomography scan (CT) suffices for thrombolysis within 4.5 hours in a standard situation. Alternatively, basic magnetic resonance imaging (MRI) sequences designed to identify AIS and exclude intracranial hemorrhage can be used.

Although addition of arterial sequences of the neck and brain arteries during acute neuroimaging is desirable (CT-angiography or MR-angiography), this additional imaging is not mandatory for performing intravenous thrombolysis. The same is true for perfusion imaging (CT-perfusion or MR-perfusion) for thrombolysis within 4.5 hours.

5) Before, during and after thrombolysis, the patient’s status should be monitored and documented frequently for the first 24 hours in a dedicated surveillance part of a Stroke Unit in order to detect complications of stroke (neurological worsening, bronchopneumonia, epileptic seizure, cerebral mass effect, etc.) and of thrombolysis (intracranial hemorrhage, lingual edema) (10, 29). Such monitoring consists of frequent checks of the neurological status (for example using the NIHSS or parts of it) and vital signs, including heart rate, systolic and diastolic blood pressure measurement by an inflatable cuff, and respiratory rate, and non-invasive blood oxygen saturation.

6) After this initial 24 hours period, basic stroke management and care are required in order to identify, prevent and treat potential complications. Repeat brain imaging at this point will help to choose the appropriate antithrombotic regimen and prevent early stroke recurrences. Early mobilization and physio/ergo/logotherapy, search for the stroke mechanism and risk factors, assessing the patients handicap and rehabilitation needs, and educating patients and next of kin are continued. This should preferably occur in a dedicated Stroke Unit (18, 23, 24), given its evidence-based favorable long-term impact on many clinical outcomes (30).
<table>
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<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
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<td><strong>1a. Level of Consciousness:</strong> The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, otorrhoeal trauma, or bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</td>
<td>0 = Alert, keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend; or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and anephelic.</td>
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<td><strong>1b. LOC Questions:</strong> The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close.</td>
<td>0 = Answers both questions correctly. 1 =Answers one question correctly. 2 =Answers neither question correctly.</td>
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<td><strong>1c. LOC Commands:</strong> The patient is asked to open and close the eyes and then to grip and release the non-paralysed hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</td>
<td>0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.</td>
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<td><strong>2. Best Gaze:</strong> Only horizontal eye movements will be tested. Voluntary or reflexive (oculorreflexic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV, or VI), score a 1. Gaze is testable in all aphasic patients. Patients with oculor trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</td>
<td>0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculorreflexic maneuver.</td>
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<td><strong>3. Visual:</strong> Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at the point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.</td>
<td>0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).</td>
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<td><strong>4. Facial Palsy:</strong> Ask — or use pantomimis to encourage — the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma, bandages, otorrhoeal trauma, tape or other physical barriers obscure the face, these should be removed to the extent possible.</td>
<td>0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Complete paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower faces).</td>
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<td><strong>5. Motor Arm:</strong> The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</td>
<td><strong>0</strong> = No drift; limb holds 90 (or 45) degrees for full 10 seconds.&lt;br&gt;<strong>1</strong> = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds, does not hit bed or other support.&lt;br&gt;<strong>2</strong> = Some effort against gravity; limb cannot get to or maintain (if curved) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.&lt;br&gt;<strong>3</strong> = No effort against gravity; limb fails.&lt;br&gt;<strong>4</strong> = No movement.&lt;br&gt;UN = Amputation or joint fusion, explain:</td>
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<tr>
<td><strong>5a. Left Arm</strong></td>
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<td><strong>5b. Right Arm</strong></td>
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<td><strong>6. Motor Leg:</strong> The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</td>
<td><strong>0</strong> = No drift; leg holds 30-degree position for full 5 seconds.&lt;br&gt;<strong>1</strong> = Drift; leg falls by the end of the 5-second period but does not hit bed.&lt;br&gt;<strong>2</strong> = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.&lt;br&gt;<strong>3</strong> = No effort against gravity; leg fails to bed immediately.&lt;br&gt;<strong>4</strong> = No movement.&lt;br&gt;UN = Amputation or joint fusion, explain:</td>
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<tr>
<td><strong>6a. Left Leg</strong></td>
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<td><strong>6b. Right Leg</strong></td>
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<td>Table 1: The National Institute of Health Stroke Scale (NIHSS) with detailed instructions (26). Online instruction and certification is available (27).</td>
<td>7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untastable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</td>
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<td></td>
<td>0 = Absent.</td>
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<td></td>
<td>1 = Present in one limb.</td>
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<td>2 = Present in two limbs.</td>
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<td>UN = Amputation or joint fusion, explain:</td>
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<td>8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms, not hands), legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, “severe or total sensory loss,” should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 0 or 2. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a-3) are automatically given a 2 on this item.</td>
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<td>0 = Normal; no sensory loss.</td>
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<td>1 = Mild to moderate sensory loss: patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick, but patient is aware of being touched.</td>
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<td>2 = Severe to total sensory loss: patient is not aware of being touched in the face, arm, and leg.</td>
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<td>9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The inattentive patient should be asked to write. The patient in a coma (item 1a-3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</td>
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<td>0 = No aphasia; normal.</td>
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<td>1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient’s response.</td>
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<td>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient’s response.</td>
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<td>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untastable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</td>
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<tr>
<td></td>
<td>0 = Normal.</td>
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<td>1 = Mild to moderate dysarthria; patient slurs at least some words and, if worst, can be understood with some difficulty.</td>
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<td>2 = Severe dysarthria; patient’s speech is so slurred as to be unintelligible in the absence of or out of proportion to any aphasia, or is mutism/anarthria.</td>
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<td>UN = Intubated or other physical barrier, explain:</td>
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<td>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untastable.</td>
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<td>0 = No abnormality.</td>
</tr>
<tr>
<td></td>
<td>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</td>
</tr>
<tr>
<td></td>
<td>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or oriented to only one side of space.</td>
</tr>
</tbody>
</table>
8. Information supporting the public health relevance.

Burden of stroke, and public health need of alteplase

Globally, stroke is the second leading cause of death and disability, with the bulk of the burden (almost 80%) residing in low to middle-income countries (LMIC) (31, 32). On average, stroke occurs 15 years earlier in LMIC compared to those in high-income countries (33). In 2016, there were almost 14 million new cases of stroke, 5.5 million deaths associated with stroke and about 81 million stroke survivors (32). 30% of strokes are fatal in the first year and a further 70% of survivors are left with some level of disability. Although stroke incidence, mortality and disability burden rates have declined since 1990, in 2016 the absolute number of people who died from stroke, remained disabled from stroke, were affected by stroke (as measured by incidence of new strokes), or survived stroke had almost doubled largely due to aging of the population and population growth (32). If the current trend in stroke burden continues, by 2050 we can expect almost 200 million stroke survivors, over 12 million deaths from stroke and about 30 million new strokes annually.

Despite the huge and increasing stroke burden, there are significant unmet needs of acute stroke patients. The lack of prevention and undertreatment results in a huge burden of disease, with stroke being in second place worldwide for disability-adjusted life years (DALY) (34, 35), and in the first place in many LMICs (36, 37).

Assessment of current use

In well a well-developed stroke system, about 25% of all AIS patients arriving within 24 hours are eligible for intravenous thrombolysis within 4.5 hours (38). In Europe the current true rate is only 7.3% for all AIS patients (39), in the USA this number is probably similar (40). The situation in LMIC is fare worse, however, with very few patients receiving thrombolysis (36, 37).

Target population

The target population for thrombolyse by alteplase is the adult population above age 18 years (and likely above 16 years, potentially lower). These patients need to have an acute neurological deficit that is potentially handicapping and that is attributed by trained physicians to AIS after a rapid clinical, basic neuroradiological, and laboratory evaluation. There is currently no upper age limit for thrombolysis, but the benefit of this treatment has not been established in populations with an important preexisting handicap.

Likely impact of treatment on the disease

The number needed to treat (NNT) within 3 hours to reduce long-term handicap is about one in four patients (one in six if treated within 4.5 hours) (41). The NNT to avoid a long-term handicap is about one in 10 over the whole 4.5 hour range (20). The risk of sICH is already integrated in this gain.

The magnitude of the thrombolysis benefit is therefore somewhat larger than the other evidence-based stroke intervention used on a large scale, which is admission to an organized Stroke Unit (30). It seems about as large as neurorehabilitation after stroke (42). Both Stroke Unit care and neurorehabilitation are rather labor intensive and require important financial investments. When compared to EVT, absolute effect of thrombolysis is not as powerful. Its population effect may be at least as large; however, as it can be offered to about three times more patients (38).

Many stroke care systems have shown increasing rates of thrombolysis (40). The European Stroke Organisation has recently set a goal to double their thrombolysis rate from currently 7.3% (39) to at least
15% by 2030 (43). Increasing thrombolysis rates and adding its benefits to the other effective acute stroke interventions will decrease the long term handicap and disease burden substantially.


Identification of relevant clinical evidence

Regarding clinical efficacy and safety, the authors searched the Medline database for articles in English language, using the search terms “thrombolysis”, “fibrinolysis”, “alteplase”, “rt-PA”, “stroke”, “ischemic stroke”, “brain infarct”, “symptomatic intracranial hemorrhage”, “systemic hemorrhage”, and “lingual edema”. The references of the retrieved articles were also searched for further relevant articles.

Retrieved articles were considered relevant for assessing efficacy and safety if they presented results of single RCT with at least 200 patients, pooled results of such RCT (including analyses applying the GRADE methodology), and large case series in prospective registries containing >500 patients.

The articles identified are cited in the text and in the references (1, 20, 21, 25, 44-51).

Appraisal of quality of clinical efficacy studies, and of outcome measures

The quality of existing data is good, given the availability of several phase III RCT using comparable outcome measures. The main difference in these RCT is the time window in which thrombolysis was given, allowing for assessment of treatment delay on longterm outcome. Most these RCT were entered in an comprehensive analysis using Cochrane collaboration methodology (21, 50).

In addition the comparative data, efficacy and safety data are available from a large, prospectively designed, European Medical Agency (EMA) mandated phase VI registry (Safe Implementation of Thrombolysis - MOnitoring STudy, SITS-MOST) (52).

The most frequently used outcomes to assess effectiveness of alteplase thrombolysis is a handicap scale, applied several months after the acute stroke treatment. The most frequent scale used for this evaluation is the modified Rankin scale (mRS) as shown in table 2 (53, 54), usually at 3 months. The mRS has 7 values (0 to 6) for assessing handicap, 0 being free of any handicap or sequelae from stroke, and 6 being dead.

| 0: No symptoms | at all. |
| 1: No significant disability | despite symptoms; able to carry out all usual duties and activities. |
| 2: Slight disability | unable to carry out all previous activities but able to look after own affairs without assistance. |
| 3: Moderate disability | requiring some help, but able to walk without assistance (by a person). |
| 4: Moderately severe disability | unable to walk without assistance (by a person), and unable to attend to own bodily needs without assistance. |
| 5: Severe disability | bedridden, incontinent, and requiring constant nursing care and attention. |
| 6: Death |

Table 2: modified Rankin scale (mRS), a handicap scale used to assess long term outcome after stroke (53, 54)

Alteplase for AIS: WHO EML 2019 application
Outcomes using mRS can be analyzed in a dichotomized fashion, for example considering the longterm outcome as being “independent” if mRS is between zero and two at a predefined follow-up date. The outcome “death” is therefore included in the “dependent or death” outcomes, but it can also be used as a separate effectiveness outcome after thrombolysis. Alternatively, the late mRS may be analysed in an ordinal way, called the “Rankin-shift analysis”. The latter method pays more attention to any degree of improvement (or worsening), whereas the dichotomized approach is a more absolute measure. The Rankin-shift approach seems to be more sensitive for detecting differences in treated vs. non-treated patients (55), but it has been used less often, likely because its meaning is more difficult to communicate to patients and physicians.

As alternative handicap scale to the mRS, one large recent trial used the (48). The GOS is similar in structure and contents to mRS, and pooling of results of studies using mRS and GOS is possible (21).

Other outcomes such as cognitive function, psychological and psychiatric sequelae, or care-giver burden have received little attention as an outcome in large comparative studies of thrombolysis. Therefore, they are not reported here.

Summary of alteplase effects in non-clinical studies

Alteplase is a serine protease that catalyses the conversion of plasminogen to plasmin. The high thrombolytic action of alteplase, which essentially acts locally on the thrombus (in contrast to streptokinase and urokinase), was demonstrated convincingly and reproducibly by experiments in the rabbit atherosclerosis model, in the dog coronary thrombosis model and in the dog femoral vein thrombosis model.

Basic kinetic properties of alteplase were studied in rat, mice, dogs, monkey and in humans following single i.v. doses. Pharmacokinetics of alteplase in all species studied is characterized by intravascular distribution, rapid hepatic elimination and a short dominant half-life. The kinetic animal data were comparable to human results. Non-clinical toxicity studies are presented below in chapter 10.

In summary, all nonclinical studies presented are considered to support the effectiveness of intravenous alteplase as a treatment for thrombolytic treatment of AIS.

Comparative effectiveness regarding dependency and death in large phase III clinical studies

Using the Cochrane methodology, a comprehensive analysis has assessed the comparative trials of alteplase and other thrombolytics with different ways of administration (21).

In the effectiveness analysis of the 6886 patients in 10 trials assessing intravenous alteplase up to 6 hours, the OR for dependency or death at 3-6 months was 0.84 (95% CI 0.77 to 0.93, \( P = 0.0006 \)), equivalent to 40 (95% CI 20 to 65) fewer patients being dead or dependent per 1000 treated. There was significant heterogeneity of treatment effect among the trials using alteplase (I² = 63%, \( P = 0.004 \)).

If the time window of the analysis was restricted to 0 – 3 hours in 1779 patients, there was no more heterogeneity of results, and 59.3% of those allocated alteplase were dead or dependent compared with 68.3% of those allocated to control, OR 0.65 (95% CI 0.54 to 0.80, \( P < 0.0001 \)), equivalent to 90 per 1000 fewer (95% CI 46 to 135) dead or dependent patients with alteplase. There was a non-significant reduction of death in the long-term follow-up of patients treated within three hours, with an OR of 0.91 (95% CI 0.73 to 1.13, \( P = 0.39 \)), with no statistically significant heterogeneity (\( P = 0.22 \)) and 14 fewer per 1000 deaths (95% CI 26 fewer to 55 fewer) (Figure 1).

In the time window of 3-6 hours, the OR for this outcome was 0.97 (95% CI 0.85 to 1.09). Therefore, early treatment seems clearly more effective than late treatment.

Alteplase for AIS : WHO EML 2019 application
Figure 1. Effect of alteplase versus control on death or dependency if treated within 3 hours (analysis 1.19 in reference (21))

It is worth mentioning the largest alteplase thrombolysis RCT, the International Stroke Trial 3 (IST-3) (48)(ref). Here, 3035 patients were randomized and within 6 hours who were mostly excluded in previous RCT because of higher age, time windows, or stroke severity (very mild or very severe). This trial confirmed that all such subgroups of patients benefit, but that the main treatment effect modifier is time, i.e. that patients treated earlier had clearly more benefits than patients treated later.

In another meta-analysis of large thrombolysis RCT using alteplase (20), the authors find similar results as the Cochrane analysis. In particular, the highlight a similar benefit of thrombolysis in multiple subgroups of patients. Furthermore, they calculated that the beneficial effect of alteplase becomes non significant beyond approximately 5 hours (Figure 2).

Figure 2: Effect of timing of alteplase treatment on excellent long-term outcome (mRS 0−1) after alteplase thrombolysis for AIS (from reference (20))

Alteplase for AIS : WHO EML 2019 application
A Rankin-shift analysis combining all major alteplase RCT is currently not available.

In summary, intravenous thrombolysis with alteplase reduces the combination of death and dependency in the long-term assessment, despite an initial increase of sICH and systemic fatal hemorrhage. Despite an increased risk of early death, alteplase treatment has not significant impact on the cumulative death rate in the long-term follow-up. This favorable effect of early thrombolysis is present in multiple subgroups of patients including the elderly. It decreases, however, rapidly with each hourly delay, with an absolute increase in disability free survival of about 10% for patients treated within 3 hours, about 5% for patients treated between 4 and 4.5 hours, and no significant benefit thereafter.

Comparative effectiveness of different thrombolytic doses

A higher alteplase dose of 1.1 mg per kg of body weight showed an unacceptable increase of hemorrhagic complications and early death in an early phase III randomized controlled clinical trial (RCT) of AIS (1). This dose was therefore abandoned in further clinical testing in favor of the 0.9 mg per kg of body weight, the current standard dose.

A Cochrane analysis of a limited number of RCT comparing different thrombolytic agents and doses in 1433 patients concluded that there was no difference in the number of patients who were dead or dependent at the end of follow-up between those allocated higher or lower doses of thrombolytic drug (OR 0.86, 95% CI 0.62 to 1.19). However, there was an approximately three-fold increase in fatal sICH in patients allocated to higher than to lower doses of the same thrombolytic drug (odds ratio (OR) 2.71, 95% CI 1.22 to 6.04) (50).

A lower alteplase dose of 0.6 mg per kg of body weight was not non-inferior to the usual 0.9 mg per kg dose in a phase III non-inferiority RCT, despite the reduced risk of early hemorrhage (2). This dose can therefore not be routinely recommended for thrombolysis in AIS.

In conclusion, the currently recommended dose of alteplase 0.9mg per kg of body weight for intravenous thrombolysis seems to have the best benefit to risk ratio.

Special consideration: thrombolysis in the 3.0 – 4.5 hours window

The ECASS III study, a phase III comparison of the efficacy and safety of alteplase compared with placebo in the 3 - 4.5 hour window, showed benefit with regards to long-term handicap. The increased initial sICH rate was comparable to the one in thrombolysis below 3.0 hours (45). Additional randomized data from the ATLANTIS (44), EPITHET (47), and IST-3 (48) studies were integrated in a meta-analysis of alteplase thrombolysis, showing long-term benefit up to approximately 5 hours (20).

Similarly, the phase IV SITS registry of this population showed similar beneficial effects on handicap in early (<3.0h) and late (3.0-4.5h) thrombolysis, despite a mildly elevated initial sICH and 3 months mortality risk (56).

Given these favorable data, the standard thrombolysis window is now 0 to 4.5 hours after stroke onset by most regulatory agencies and national and international stroke treatment guidelines. Still, earliers treatment is more beneficial than later within this time window, and treatment should not be delayed even if the available treatment window is up to 4.5 hours.

Special consideration : elderly patients

Data from recent RCTs (48), a meta-analysis (20) and a Cochrane analysis (21) showed similar efficacy of early thrombolysis in patients above age 75-80 years, despite age being a risk factor for sICH (57, 58). These data were confirmed by analyses of a large alteplase thrombolysis registry (59).

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The results confirm the positive benefit-risk of thrombolysis, as compared to absence of thrombolysis, in all AIS patients including patients above 80 years of age, despite the generally poorer outcome in this age group. Therefore, treatment of AIS in the elderly (>80 years) is now recommended when administered in strict accordance to the approved indication in AIS.

Special consideration: pediatric population
As mentioned in the previous chapters, efficacy and safety has not been formally tested in the pediatric population (60). Following a review of pediatric cases of alteplase for the indication AIS in the literature:
- The contraindication for children under 18 years of age for the indication AIS has recently been replaced by a warning for children 16 - 17 years.
- For children < 16 years, alteplase is officially contraindicated.

Special considerations: pregnancy
Several cases of alteplase thrombolysis during pregnancy have been reported, with limited risk for the mother and the fetus (61).

American guidelines recommend that alteplase may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding (10). Therefore, an individual assessment and decision has to be made and discussed, if possible, with the patient or, if unable, with her next of kin.

Special consideration: thrombolysis for patients with unknown onset and late presentations
Recently, and MRI-based study in patients with stroke symptoms when waking up or being found has shown similar efficacy of alteplase thrombolysis as standard thrombolysis < 4.5 hours (Thomalla). For patients to be treatable, an mismatch between two different MRI sequences had to be present (FLAIR-DWI Mismath), indicating that the stroke onset was likely less than 4.5 hours before imaging.

Similarly, perfusion-imaging (CT-perfusion or MR-perfusion) based selection for thrombolysis of such patients seems to be beneficial if a significant mismatch between established infarct ("core") and salvageable hypoperfused tissue ("penumbra") is present. The results of these studies are not yet published, however (62, 63).

All these studies with highly selected patients showed good safety, with sICH rates and early/late mortality similar or below the ones observed in standard thrombolysis up to 4.5 hours.

Therefore, thrombolysis with alteplase beyond the 4.5 hours window should only be considered if advanced neuroimaging as used in these studies indicates potential benefit. Training and experience in performing and interpreting such imaging is required.

Alternative treatments to IV thrombolysis: comparative benefits and risks
1. Acetylsalicylic acid (ASA)

Rapid administration of ASA (usually in oral form; or intravenously if the enteral route is not accessible) has shown some long term benefit after AIS when using the Cochrane methodology in an analysis of 41’483 patients (64). With ASA, there was a significant decrease in death or dependency at the end of follow-up (OR) 0.95, 95% CI 0.91 to 0.99). For every 1000 people treated with aspirin, 13 people would avoid death or dependency (number needed to treat 79).
ASA as previous standard therapy for AIS was used as the comparator in most RCT where alteplase thrombolysis was tested, and clear superiority of alteplase has been shown in these trials as discussed above. Whereas ASA alone has a small but definite excess of sICH, this risk is clearly increase by alteplase thrombolysis (for magnitude, see next chapter 10 below). This additional early risk of harm by alteplase does not, however, eliminate the alteplase long-term benefits, as shown above. Therefore, thrombolysis by alteplase rather than ASA should be offered whenever a thrombolysis indication exists. ASA should, however, be given rapidly after onset of AIS whenever thrombolysis cannot be performed, and when no other contraindication to ASA are present.

2. Other thrombolytic drugs with intravenous administration

As mentioned in chapter 6, several other thrombolytic agents are potential candidates for intravenous thrombolysis in AIS.

- Streptokinase has been shown in early AIS thrombolysis trials to associated with an unacceptable risk of hemorrhage and early mortality, without significant long-term benefit (3, 4, 50, 65). It has therefore been abandoned in testing or treatment for AIS. Streptokinase is currently listed on the EML as a thrombolytic medicine on the complementary list for the indication of myocardial infarction (powder for injection: 1.5 million IU in vial.)

- Desmoteplase, given as an intravenous bolus, which was only tested in later time (5-8).

- Urokinase (ATC code B01AD04) as not been tested in large-scale trial of intravenous thrombolysis for AIS. Because its unknown efficacy and safety, it can therefore not be recommended for acute treatment of AIS. Recombinant pro-urokinase (no ATC code) has, however, been used with some success for intra-arterial thrombolysis in AIS (66), but intraarterial thrombolysis has in the meantime been replaced by the more effective mechanical endovascular treatment (EVT), using specifically developed thrombectomy devices such as stentretrievers (67) or aspiration devices (68-70).

- Tenecteplase, given as an intravenous bolus, has shown equivalent or superior efficacy when compared with alteplase in phase II RCT (9). It’s safety profile (i.e. hemorrhage risk) seems similar to alteplase. Large phase III randomized clinical trials are now ongoing. Before such trials have shown therapeutic equivalence with alteplase, tenecteplase cannot be recommended as a first line drug for AIS. If proven effective and safe, it would be an interesting alternative to alteplase, however, given its easier way of intravenous administration (bolus only).

3. Percutaneous vascular interventions (or endovascular treatment, EVT)

EVT uses an intra-arterial, mechanical approach for thrombus disruption or removal (thrombectomy). Given that this treatment is only applicable and indicated in the presence of proximal intracranial occlusions causing AIS, it is estimated that about one third of all AIS patients who should receive intravenous thrombolysis are also candidates for EVT (38). Several recent RCT showed clear superiority of EVT when added to intravenous thrombolysis (67). However, intravenous thrombolysis was usually given in both arms of the trial, and there is a lack of data on direct comparison of percutaneous vascular interventions with intravenous thrombolysis. In such a recent comparative Cochrane analysis of 450 patients (71), the quality of evidence was found to be low, and EVT did not improve the proportion of patients with good functional outcome when compared to thrombolysis (modified Rankin Scale score 0 to 2, risk ratio 1.01, 95% CI 0.82 to 1.25, P = 0.92). Several large phase III RCT are now under way to test the value of performing thrombolysis before EVT. Given the current knowledge, direct EVT (without preceding thrombolysis) can therefore not routinely be recommended as an alternative to thrombolysis, but it is considered a valid option in patients with condraindications to thrombolysis, either because of increased bleeding risk (10, 72), or late presentation (73, 74).

Alteplase for AIS : WHO EML 2019 application

The methods of identifying relevant clinical evidence and the appraisal of quality of clinical efficacy studies is described in chapter 9 above.

The exact worldwide exposure of AIS patients to intravenous alteplase is unknown. Assuming current thrombolysis rates of about 7% in Europe and the USA (39, 40), more than 1 million patients must have been receiving alteplase worldwide since the first positive RCT in 1995 (25).

Appraisal of safety outcome measures

The most frequent safety concern is early symptomatic intracranial hemorrhage (sICH), occurring usually within the first 24 hours to 10 days after thrombolysis. The most frequent definition of sICH is the one used in the ECASS-II study (75, 76) which requires a clinical deterioration on the NIHSS score of \( \geq 4 \) points, blood at any site in the brain on the CT scan, and the assessment that hemorrhage was likely to be the cause of the clinical deterioration. Alternative definitions of sICH have been proposed but have found little acceptance in clinical trials (Heidelberg classification (ECASS-3 2008, SITS Wahlgren Lancet 2007, von Kummer Stroke 2015).

Other important safety outcomes are death from systemic (extracranial) hemorrhage, early death from any cause (within 7-10 days), and death any time up to 3 or 6 months after thrombolysis (21).

Lingual edema shortly after intravenous alteplase administration has mainly been recognized in large case series (77, 78); therefore, the evidence for this complication is lower than for other safety issues.

Risks of alteplase administration in non-clinical studies

In general pharmacological studies, alteplase had no adverse effects on CNS functions, the cardiovascular system and the renal performance. Alterplase toxicity was tested i.v. in rodents and monkeys in single- and repeat-dose studies in rats (up to 13 weeks), in dogs (14 days) and in Marmosets (4 weeks). Although the acute toxicity was low, on account of its potent pharmacodynamic effect at low doses the possibility of intoxication following overdosage should be borne in mind by the prescribing physician. From the repeat-dose toxicity studies it can be concluded that alteplase was well tolerated in the rat and monkey at pharmacologically relevant doses. Dogs were more sensitive to the pharmacological action of alteplase. Doses were selected from the therapeutic level (1 mg/kg/day) to toxicologically significant high doses. Doses above 10 mg/kg/day in all species were usually associated with high plasma alteplase levels (non-linear) and adverse systemic effects including deaths due to extensive internal hemorrhaging as well as bleeding associated-anaemia. Although plasma concentration measurements were lacking for most studies, the toxicity data are considered adequate to support the clinical dose in humans. Antibody titres observed in rats and marmosets were much lower than in hyperimmunised control animals (5.2 log units), suggesting that human alteplase is relatively weakly immunogenic in rats and marmosets. No target organ was identified. The high dose findings generally reflected exaggerated pharmacological activity of alteplase, inducing no histopathological changes and being fully reversible. There were no sex-related differences following administration of alteplase. The repeat-dose toxicity studies demonstrated an adequate safety profile of alteplase. Except for exaggerated pharmacodynamics effects the no observed adverse effect level (NOAEL) in the 13-week i.v. study in rats was 3 mg/kg/day and in the 4-week i.v. study in Marmoset monkeys the NOAEL was 4 mg/kg/day. The corresponding Cmax values of 10.3 and 11 μg/mL, respectively, are about 9- to 10-fold above the plasma levels in AMI patients of 1.2-1.0 ng/mL, treated with an i.v. dose of 0.75 mg/kg (79). Reproductive toxicity studies were carried out in rats and rabbits. Embryofetal development studies with doses of up to 10 mg/kg/day, revealed no external, visceral or skeletal abnormalities. Rabbits treated with 10 mg/kg/day exhibited occult bleeding and anaemia after repeated administration of alteplase (10-fold the
recommended human dose), leading to an increased rate of resorption (post implantation loss) and abortion. No effects on peripostnatal development or on fertility parameters were observed in rats with doses up to 10 mg/kg/day. Nevertheless, alteplase should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Alteplase was not mutagenic in in vitro genotoxicity screening studies and did not show clastogenic activity in genotoxicity assays conducted in vivo in mice. The tumouriguric potential of alteplase was examined in the immunosuppressed neonatal rat. The test provided no indication for a carcinogenic potential of alteplase. Alteplase solutions were moderately to well tolerated after single i.v. and i.a. administration in rabbits and paravenous administration in rats. In vitro, the stock solution did not induce haemolysis in marmoset or human blood.

Risk of symptomatic intracranial hemorrhage (sICH) in large clinical studies

In the Cochrane analysis of eight RCT using alteplase in 6683 patients (21), there were 30 (95% CI 20 to 40) extra fatal intracranial haemorrhages per 1000 patients treated (OR 4.18, 95% CI 2.99 to 5.84, P < 0.00001) (Figure 3).

![Table](image)

**Figure 3.** Effect of alteplase versus control on sICH if treated within 6 hours (analysis 2.28 in reference (21))

When trying to identify risk factors for sICH after alteplase in RCT and large registries, the following variables were found to increase the risk: higher age, more severe stroke deficits, higher serum glucose levels, and more early ischemic changes on pretreatment imaging (57, 58).

The risk of sICH in comparative treatments and different alteplase doses have been discussed in the previous chapter 9.

Alteplase for AIS : WHO EML 2019 application
Risk of systemic (extracranial) hemorrhagic death in large clinical studies

In the Cochrane analysis of RCT using alteplase in patients (21), there were 264/3752 (7.0%) non-intracranial haemorrhage deaths in the thrombolysis-treated patients and 234/3474 (6.7%) in the control patients (OR 1.08, 95% CI 0.90 to 1.30, P = 0.39). This results was not significant, but there was significant between-trial heterogeneity (I² = 53%, P = 0.02).

Risk of early death in large clinical studies

In the Cochrane analysis of RCT using alteplase in 5535 patients (21), there was a significant excess of early deaths: the OR was 1.44 (95% CI 1.18 to 1.76, P = 0.0003) with no significant heterogeneity; the absolute effect was 25 more (95% CI 11 to 40 more) deaths per 1000 patients treated (Cochrane 2014). Most of these early death can be attributed to fatal sICH.

Risk of death from all causes during extended follow-up

In the Cochrane analysis of RCT using alteplase in 7012 patients (21), there was no net effect on deaths in the 3-6 months follow-up (OR 1.06, 95% CI 0.94 to 1.20;). This number is equivalent overall to seven more (two fewer to 25 more) deaths per 1000 patients treated. The heterogeneity of treatment effect among the trials of alteplase was not quite statistically significant (I² = 38%, P = 0.09).

Risk of lingual edema following alteplase administration

Lingual edema either during or shortly after starting intravenous alteplase occurs in 1% – 3% of treated stroke patients (77, 78). Its presumed mechanism is intralingual liberation of bradykinin. A risk factor for lingual edema is chronic pretreatment of the patients with antihypertensives of the angiotensin-converting-enzyme inhibitor (ACE inhibitor) class.

Although potentially life-threatening because of rapidly progressive upper airway obstruction with the threat of respiratory arrest, this condition only rarely needs intubation or urgent cricotomy, and is self-limiting. Whether inhibitors of bradykinin release decrease this phenomenon needs to be established.

Safety of simultaneous use of intravenous alteplase and other antithrombotic agents

Patient who take antiplatelet monotherapy (such as ASA) before the AIS have no or only mildly increased risk of hemorrhagic complications after alteplase thrombolysis (57, 58). Even in chronic use of the combination of ASA and clopidogrel before the AIS, the hemorrhagic risk seems not be increased significantly (80). However, the combination of de novo administration of ASA at the same time as thrombolysis has been shown to increase the hemorrhage substantially, without adding long term benefit (49).

In patients on vitamin-K antagonists, thrombolysis in the face of an internationalized ratio (INR) ≤ 1.7 seems safe (Xian JAMA 2012). Safe plasma levels of the direct oral anticoagulants (DOAC) are not known, although no major risk has been identified in limited case series (81). Patients on therapeutic doses of parenteral heparin or low-molecular weight heparin are also considered contraindications to thrombolysis. Therefore, thrombolysis is contraindicated in such patients unless sufficient time has elapsed to allow complete clearance of the DOAC.
Special considerations regarding safety

The following situations where safety of thrombolysis may be of concern have been addressed in the previous chapter. There, both efficacy and safety were addressed on these issues:

- Elderly patients > age 80 years
- Pediatric population < age 16 years
- During pregnancy
- Patients treated in the 3.0 – 4.5 hours window
- Patients with unknown onset and late presentations
- Higher or lower alteplase doses than standard recommended treatment

Other special situations with potentially increased hemorrhage risk after IV alteplase

Clinical trials have used a certain number of exclusion criteria for patients considered to be at increased hemorrhage risk with thrombolysis. Some of these precautions were later proven unsubstantiated (see “Special considerations” in chapter 9). Based on pathophysiological considerations and published case series, some situations continue to be regarded as absolute, and others as relative contraindications for alteplase thrombolysis. In the latter situation, the treating physician has to make a decision whether possible benefits of thrombolysis outweigh potential risks, either based on his knowledge and experience, or after consultation with other specialists. An incomplete list of absolute and relative contraindications is presented in table 3, based on current recommendations (10).

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of symptomatic intracranial hemorrhage</td>
<td>&gt; 10 asymptomatic cortical microbleeds on MRI</td>
</tr>
<tr>
<td>Prior ischemic stroke within 3 months</td>
<td>Asymptomatic intracranial aneurysm ≥ 10 mm, including giant aneurysm</td>
</tr>
<tr>
<td>Severe head trauma within 3 months</td>
<td>Intracranial arterial dissection</td>
</tr>
<tr>
<td>Intracranial/spinal surgery within 3 months</td>
<td>Asymptomatic arterio-venous malformation, dural fistulas, venous angiomas, developmental venous anomaly</td>
</tr>
<tr>
<td>Intracranial intra-axial malignant tumor</td>
<td>Unruptured cavernoma</td>
</tr>
<tr>
<td>Active gastrointestinal malignancy</td>
<td>Recent major systemic trauma without severe head trauma</td>
</tr>
<tr>
<td>Platelet count &lt; 100,000/mm³</td>
<td>Systemic malignancy</td>
</tr>
<tr>
<td>Gastrointestinal or urinary bleed within 21 days</td>
<td>History of bleeding diathesis or coagulopathy</td>
</tr>
<tr>
<td>Acute aortic dissection</td>
<td>Hemorrhagic ophthalmic conditions</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Post-partum period</td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td>Recent major surgery within 14 days</td>
</tr>
</tbody>
</table>

Table 3. Absolute and relative contraindications to intravenous thrombolysis based on reference (10)
11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Pricing examples for representative countries

For a single IV dosis for a patient of 70 kg (i.e. 63 mg of alteplase)

- USA: 6400 US$ (average billing amount)
- United Kingdom: 435 £
- Poland : 2875 PLN (670 Euros)
- Switzerland : 1000 CHF
- Italy: 367 EUR (public hospitals), 809 Euros (private hospitals)
- China 5400 CNY (~1130 US$)
- Brazil : 1002 Reais (~260 US$) (public hospitals), 2333 Reais (~610 US$) (private hospitals)

Source of information: references (82) (83), and personal information by the authors.

Considering all nonclinical and the broad clinical data showing excellent tolerance of alteplase in human clinical experience, alteplase at therapeutic doses can be considered as a safe drug if used in strict accordance to the approved indication in AIS.

Cost effectiveness

Implementing and administering alteplase within the recommended 4.5 hours requires some initial investments in prehospital and intrahospital services (see “additional requirements” in chapter 7). Many of these investments (such as stroke unit surveillance and care) will benefit stroke patients anyway, independently of thrombolysis being offered or not. These additional costs have to be balanced by generally shorter hospital stays, lesser rehabilitation needs, and lesser long-term care (including nursing homes and home care), given the reduction of handicap from thrombolysis (see chapter 9) (84).

Cost-effectiveness is usually measured in incremental cost-effectiveness ratios (ICER). If the ICER is below a certain amount per quality-adjusted life years (QALY) gained, an intervention is considered cost-effective. Such limits for ICER depend on how much a health system or country is willing to pay for a QALY gained. Typical ICER threshold are about 10,000 £ for the UK (83), 50-100’000 US$ for the USA, 105’000 CNY (16’200 USD) for China (85), and 29’000 USD for Brazil (86).

In the UK, the National Institute for Health and Care Excellence (NICE) concluded the cost for all treatment windows up to 4.5 hours were well below accepted willingness to pay thresholds for alteplase (83). In another UK-based model, the authors concluded that any strategy that increases thrombolysis rates will result in cost savings and improved patient quality of life (87).

A Dutch study found that thrombolysis saves short- and long-term health care costs due to lower hospital admission and residential costs (84)

A Chinese analysis showed that alteplase treatment is cost-effective in 98.7% of the simulations at a usual ICER for this country (85).

An assessment of the Brazilian situation concluded that therapy with alteplase within the first three hours was cost-effective in national Public Health System (86).

A review of 16 studies from China and Western countries including Australia, Canada and the USA for alteplase thrombolysis up to 6 hours concluded that all of them but one were cost-effective at a level of 50’000 US$ per QALY (88).

Absolute financial gains of thrombolysis vary from country to country due to variable costs of each element of stroke care, including pricing of thrombolysis. Therefore, absolute gains for single patients and
for a country are difficult to calculate, but may be estimated based on the above mentioned published examples.

**Special pricing arrangements**
The authors are not aware of special pricing arrangements for alteplase.

12. **Summary of regulatory status and market availability of the medicine.**

Alteplase is marketed under the name Actilyse® in a total of 104 countries. In all of them, it is authorized for the indication of *acute ischemic stroke*.

In the following countries, alteplase is marketed *with registration* by the respective authorities: Algeria, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Brunei Darussalam, Bulgaria, Chile, China, Colombia, Costa, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Jamaica, Jordan, Kazakhstan, Korea, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Mexico, Moldova, Mongolia, Montenegro, Myanmar, Namibia, Netherlands, New Zealand, Nicaragua, Norway, Oman, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Republic of Macedonia, Rica, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Syrian Arab Republic, Taiwan, Thailand, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Ukraine, United Arab Emirates, United Kingdom, Uruguay, Uzbekistan, Venezuela, Viet Nam, Yemen.

In these countries, alteplase is available *without registration*, given that these countries do not require registration: Albania, Angola, Bahamas, Barbados, Bermuda, Botswana, Cayman Islands, Liechtenstein, Libya and Morocco.

Whereas the 10mg and 20mg doses of alteplase is only available in some of the preceding countries, the 50mg dose is available in all of them.

Alteplase has no existing or planned listing on the WHO List of Prequalified Medicinal Products.

Marketing rights for alteplase are worldwide with Boehringer-Ingelheim (from Genentech/Roche) with the exception of USA, Canada (marketed by Genentech/Roche), and Japan (marketed by Kyowa Hakko and Mitsubishi Tanabe Pharma Corporation).

To our knowledge, neither Boehringer-Ingelheim nor any other company is producing an alteplase generic drug (biosimilar).

13. **Availability of pharmacopoeial standards**

Alteplase is included in the following two Pharmacopoeias:

- The European Pharmacopoeia ([https://extranet.edqm.eu/4DLink1/4DCGI/Query_SW?vSelectName=2&vContains=1&vtsubName=alteplase&SWTP=1&OK=Search](https://extranet.edqm.eu/4DLink1/4DCGI/Query_SW?vSelectName=2&vContains=1&vtsubName=alteplase&SWTP=1&OK=Search)), European Pharmacopoeia, accessed 06.12.2018

Alteplase is not included in the International Pharmacopoeia nor in the United States Pharmacopoeia.

Alteplase for AIS : WHO EML 2019 application
14. Reference list


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