STROKE: THROMBOLYSIS AND ENDOVASCULAR THERAPY

OBJECTIVE:
To outline the evidence, indications and guidance relating to the use of thrombolytic and endovascular therapy for the early management of acute ischemic stroke (AIS).

BACKGROUND:
Thrombolytic therapy is highly effective in AIS. Recombinant tissue plasminogen activator (rt-PA), the most well-studied agent used in this setting, has demonstrated efficacy in the treatment of AIS in 9 randomized trials involving more than 6,700 patients over more than 20 years. Thrombolytic therapy with rt-PA has been shown to improve the likelihood of favourable outcome in AIS, despite a small increased risk of serious bleeding. Therapy is time-sensitive, with the benefits of therapy decreasing successively with longer delays from onset to treatment. The benefit is greatest when rt-PA is administered within the first 3 hours after symptom onset, with a less robust risk-vs-benefit balance up to 4.5 hours. Treatment benefits of rt-PA are preserved across the spectrum of age and clinical severity of disabling deficits. The most serious risks of thrombolytic therapy are intracranial hemorrhage (ICH, affecting up to 6% with variable trial-dependent definitions), major extracranial hemorrhage, and angioedema (up to 5%). Approximately 2% of rt-PA-associated intracranial hemorrhages are fatal.

Evidence-based guidelines support the use of thrombolytic therapy with rt-PA for carefully selected patients with disabling AIS and its use is considered standard of care in this setting. An effective stroke protocol demands highly coordinated input from paramedics and a pre-notified emergency department team, collaboration from radiology to ensure emergent brain imaging to confirm eligibility, as well as the availability of physicians trained in acute stroke and thrombolytic therapy. If patients may be eligible for thrombolysis, they should have an emergent head CT at the time of hospital arrival. The target median door-to-rt-PA time is less than 30 minutes.

Recent evidence supports the use of advanced neuroimaging to select individuals who may benefit from rt-PA beyond the 4.5 hour window or individuals with unknown time of onset (e.g. those who have a disabling deficit without evidence of established parenchymal ischemic changes, or a small ischemic core on MRI). Current Canadian best practice guidelines recommend consultation with a stroke specialist cases where thrombolysis will be administered past 4.5 hours from known time of onset.

The role of tenecteplase as an alternative to rt-PA (at doses of 0.25 mg/kg or 0.50 mg/kg as a single bolus dose) for thrombolysis in acute ischemic stroke is under active investigation. There are no current Canadian recommendations for use of tenecteplase at this time for individuals with acute ischemic stroke, but multiple clinical trials examining use of the 0.25 mg/kg dose for this indication are ongoing.

Endovascular thrombectomy is indicated in selected patients with a proximal intracranial artery occlusion and may be used both in those who have received rt-PA, as well as in those who are not
eligible for rt-PA. The strongest evidence for benefit exists for treatment within 6 hours of onset of stroke symptoms, although selected candidates who may benefit from late revascularization (i.e. up to 24 hours after onset) may be identified through advanced neuroimaging.

In some regions of the country, a stroke bypass system exists in which patients who may have AIS are transported to the nearest stroke center to facilitate rapid expert treatment, with bypass of the closest hospital if they meet established criteria. In most provinces, Telestroke is a rapidly developing service to connect remote centers with physicians who have expertise in stroke [https://www.strokebestpractices.ca/recommendations/telestroke].

**PATIENT SELECTION FOR THROMBOLYTIC THERAPY IN AIS:**

**Inclusion criteria:** Patients ≥18 years of age with a diagnosis of disabling AIS with time of onset ≤4.5 hours. If rt-PA administration is considered after 4.5 h, consultation with a physician with stroke expertise should be obtained. For adolescents, decision to administer alteplase should be based on clinical judgment, presenting symptoms, and patient age and, if possible, consultation with a pediatric stroke specialist.

**Absolute Exclusion Criteria:**
- Any source of active hemorrhage or any condition that could increase the risk of major hemorrhage after thrombolytic administration
- Any hemorrhage on brain imaging

**Relative Exclusion Criteria** (requiring clinical judgement):

**A. History**
- History of intracranial hemorrhage
- Stroke, serious head injury or spinal trauma in the preceding 3 months
- Recent major surgery, such as cardiac, thoracic, abdominal, or orthopedic in previous 14 days
- Arterial puncture at a non-compressible site in the previous 7 days

**B. Clinical**
- Symptoms suggestive of subarachnoid hemorrhage
- Stroke symptoms due to another non-ischemic acute neurological condition such as seizure with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia
- Hypertension refractory to antihypertensive treatment such that target blood pressure <180/105 cannot be achieved or maintained
- Currently prescribed and taking a direct oral anticoagulant (DOAC). In centres with access to specialized tests of DOAC levels and reversal agents, thrombolysis could be considered, and decisions made based on individual patient characteristics, in consultation with hematology specialists, patients and their families. Otherwise, endovascular treatment should be considered if the patient is otherwise eligible.

**C. Laboratory**
- Blood glucose concentration below 2.7 mmol/L or above 22.2 mmol/L
- Elevated activated partial-thromboplastin time (aPTT)
• International Normalized Ratio (INR) > 1.7

D. CT or MRI Findings
• CT showing early signs of extensive infarction

THROMBOLYTIC AGENT DOSING IN AIS:
The recommended dose of rt-PA for AIS is 0.9 mg/kg (maximum 90 mg) infused over 60 minutes, with 10% of the total dose administered as an initial IV bolus over 1 minute. Anticoagulants and antiplatelet agents may increase the risk of bleeding complications and are not recommended within 24 hours of rt-PA administration.

MONITORING OF PATIENTS WHO RECEIVED THROMBOLYTIC THERAPY FOR AIS:
The patient should be observed in a monitored setting with frequent neurologic and vital signs assessments as well as cardiac monitoring. The clinician must be ready to recognize and manage possible complications. Complications include systemic and intracranial bleeding, angioedema and rarely serious anaphylaxis reactions. There is insufficient evidence to support the use of fresh frozen plasma, prothrombin complex concentrates, or platelets for rt-PA related bleeding; however, cryoprecipitate and tranexamic acid are recommended in addition to supportive care.

ENDOVASCULAR THERAPY:
Endovascular therapy (EVT) may be used in eligible patients alone or in combination with thrombolysis. There is very strong evidence from multiple randomized trials demonstrating benefit of EVT in individuals with proximal intracranial occlusions in the anterior circulation (internal carotid artery and proximal middle cerebral artery as well as individuals with tandem cervical carotid and intracranial occlusions) with moderate-to-severe neurological deficits. The majority of patients from contemporary EVT trials were treated within 6 hours of stroke onset, and shorter times from onset to recanalization are associated with better functional outcomes. Most participants in these trials also received rt-PA. Two trials have demonstrated benefit of EVT in individuals treated up to 24 hours from time of last seen well who are carefully selected individuals based on small ischemic cores with advanced CT or MR perfusion imaging. Individuals with larger branch anterior occlusions and significant neurological deficits also benefit from EVT, though the evidence is less robust and treatment decisions are individualized in this group. The benefit of EVT in individuals with milder neurological deficits and proximal large artery occlusions is the subject of ongoing clinical trials; treatment decisions also remain individualized in this group at present. Trials examining EVT for basilar occlusions, which are associated with high rates of death and dependence, have not demonstrated as robust a benefit for EVT as in anterior circulation occlusions. However, interpretation of existing data is complicated by both enrolment biases and crossover to treatment from control participants. Current guidelines recommend EVT for basilar occlusions.

Treatment decision-making regarding suitability for EVT is generally a collaborative effort between the neuro-interventionalist and stroke physician. Decision-making takes into account the patient’s pre-morbid status, current neurological deficits, burden of ischemic core on neuroimaging, and vascular access. Transport logistics are also often germane to treatment decisions as EVT is performed only at comprehensive stroke centres. Success of EVT requires the coordination of pre-
hospital and hospital systems, rapid neurovascular imaging and expertise in neurointervention, and access to stroke unit care.

**SPECIAL CONSIDERATIONS:**

**Pediatrics:** There are little safety and efficacy data in patients under 18 years of age with AIS. Physicians with expertise in pediatric stroke should manage these patients where possible. When this is not possible, a combination of a neonatologist/pediatrician and an adult neurologist, supported by consultation with an experienced specialist in pediatric stroke, is recommended.

**Pregnancy:** There have been no empiric studies of IV rt-PA in pregnant women presenting with AIS; however, it is reasonable to consider giving rt-PA to a pregnant women with disabling AIS who meets existing criteria for treatment and pregnancy should not be considered to be a contraindication for EVT. Although there are fetal risks to these interventions, given the very high morbidity and mortality associated with AIS due to large vessel occlusion, maternal care for disabling stroke should not be delayed or deferred on the basis of pregnancy. **Treatment options for pregnant women with AIS should promptly be considered in consultation with an interdisciplinary team with expertise in neurology, obstetrics and gynecology, maternal-fetal medicine, and interventional radiology where possible and available.**

**REFERENCES:**


**Date of version:** 06September2020

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