

# Thrombolytic therapy for acute ischemic stroke

Canadian Association of Emergency Physicians Committee  
on Thrombolytic Therapy for Acute Ischemic Stroke\*

## ABSTRACT

Current evidence suggests that, in a small subset of acute stroke patients who can be treated within 3 hours of symptom onset, the administration of tissue plasminogen activator (tPA) confers a modest outcome benefit, but that this benefit is associated with an increased risk of intracranial hemorrhage that can be severe or fatal. The data show that tPA therapy must be limited to carefully selected patients within established protocols. Further evidence is necessary to support the widespread application of stroke thrombolysis outside research settings. Until it is clear that the benefits of this therapy outweigh the risks, thrombolytic therapy for acute stroke should be restricted to use within formal research protocols or in monitored practice protocols that adhere to the NINDS (the rt-PA Stroke Study Group trial of the National Institute of Neurological Disorders and Stroke) eligibility criteria. All data on protocol compliance and patient outcomes should be collated in a central Canadian registry for the purposes of tracking safety and efficacy.

Stroke thrombolysis should be limited to centers with appropriate neurological and neuroimaging resources that are capable of administering treatment within 3 hours. In such centres, emergency physicians should identify eligible patients, initiate low risk interventions and facilitate prompt computed tomography. Only physicians with demonstrated expertise in neuroradiology should interpret head CT scans used to determine whether to administer thrombolytic agents to stroke patients. Neurologists should be directly involved prior to the thrombolytic administration.

## RÉSUMÉ

Les données actuelles suggèrent que, chez un petit sous-groupe de victimes d'accident vasculaire cérébral (AVC) pouvant être réanimées dans les heures qui suivent l'apparition des symptômes, l'administration d'un activateur tissulaire du plasminogène (tPA) produit un effet bénéfique modeste, mais que cet effet est associé à un risque accru d'hémorragie intracrânienne potentiellement sévère ou fatale. Les données indiquent que la thérapie au tPA doit être limitée à certains patients sélectionnés avec soin en respectant les protocoles établis. Des preuves additionnelles s'imposent afin d'appuyer une application répandue de la thrombolyse chez les victimes d'AVC à l'extérieur d'un cadre de recherche. Jusqu'à ce qu'on ait clairement établi que les avantages de cette thérapie l'emportent sur ses risques, le recours à la thrombolyse pour les victimes d'AVC doit être restreint au contexte de protocoles formels de recherche ou de protocoles d'exercice sous surveillance qui respectent les critères d'admissibilité du NINDS (l'étude du *rt-PA Stroke Study Group* du *National Institute of Neurological Disorders and Stroke* américain). Toutes les données concernant le respect du protocole et le devenir des patients doivent être colligées dans un registre central canadien afin de surveiller la sécurité et l'efficacité des interventions. On devrait limiter la thrombolyse aux centres dotés de ressources neurologiques et d'imagerie neurologique appropriées en mesure d'administrer le traitement dans les 3 heures suivant l'apparition des symptômes. Les médecins d'urgence oeuvrant dans ces centres devraient identifier les patients admissibles, mettre en marche les interventions à faible risque et obtenir rapidement une tomodensitométrie. Seuls les médecins ayant une compétence reconnue en neuroradiologie devraient interpréter les résultats des tomodensitométries crâniennes utilisées pour déterminer la pertinence d'administrer des agents thrombolytiques aux victimes d'AVC. Les neurologues devraient être directement impliqués avant l'administration de la thrombolyse.

\*For a complete list of the Committee members, see Appendix 1.

## Introduction

Emergency physicians across North America are being enjoined to facilitate the delivery of thrombolytic therapy for thromboembolic stroke. The Canadian Association of Emergency Physicians supports continuing research to improve the treatment and outcomes of patients suffering from stroke; however, based on the available evidence, widespread use of thrombolytic therapy for acute stroke remains controversial and problematic.

Six grade-one multi-centre randomized controlled trials (RCTs) of thrombolytic agents for acute stroke demonstrated lack of benefit or worse outcomes with treatment. To date, the NINDS trial<sup>1</sup> (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group trial) is the only published RCT of intravenous thrombolytic therapy that has been positive. While NINDS did demonstrate modest benefits, it also revealed significant risks. Based on this, the committee feels that the use of thrombolysis should be limited to use by physicians with expertise in stroke management and that centres providing stroke thrombolysis must have access to immediate computed tomography (CT) and expert CT interpretation. Centres must also have the ability to manage intracranial hemorrhage or arrange emergent transfer to a site with neurosurgical capability. These specialized personnel and resources must be readily available 24 hours a day, 7 days a week, despite the fact that less than 5% of stroke patients are eligible for thrombolytic therapy. At present, the systems and resources necessary to safely administer thrombolytic agents to stroke patients preclude their use in all but specialized tertiary care centres. Future pre-hospital efforts to triage stroke patients to such centres will have significant impact on both emergency department and hospital resources. The implications of making this time-sensitive treatment available to the majority of Canadians are daunting.

Exuberance over the potential development of more effective stroke treatments has raised public expectations, causing anxiety, disappointment and confusion when treatments are not available, not indicated or not effective. Caution is warranted in public pronouncements of the value of thrombolytic therapy for stroke. Such pronouncements should detail the fact that this intervention is not appropriate for the majority of strokes.

***The Canadian Association of Emergency Physicians enthusiastically endorses the promotion of stroke therapies when the benefits clearly outweigh the risks. These include the use of ASA, prevention of aspiration, early rehabilitation, and the establishment of stroke units and protocols. It is the position of the Canadian Association of Emergency***

***Physicians that thrombolytic therapy for acute stroke should be restricted to use in the context of formal research protocols, or in closely monitored programs, until there is further evidence that the benefits of this therapy clearly outweigh the risks. All outcome data should be collected and made available to the medical community. It is important that studies of the safety and effectiveness of this therapy be carried out in community hospitals.\****

## Relevant trials

Prior to NINDS, trials of thrombolytic agents for acute stroke provided very negative results. Three streptokinase studies were prematurely discontinued because of a 1.5- to 2-fold increase in early mortality and a 6- to 10-fold increase in intracranial hemorrhage with active treatment.<sup>2-4</sup> These studies also suggested that patients who survived thrombolysis, particularly those treated within 3 hours of symptom onset, might have reduced disability. In the European Cooperative Acute Stroke Study (ECASS),<sup>5</sup> which compared tissue plasminogen activator (tPA) (1.1 mg/kg) to placebo in patients with <6 hours of symptoms, early intracranial hemorrhage, fatal cerebral edema and early mortality were more common in treated patients than in controls. Like the streptokinase trials, ECASS also showed that surviving tPA recipients were more likely to have minimal or no disability at 3 months. The authors concluded that, while some patients benefit, the rate of negative outcomes was prohibitively high. Subsequently, many encouraged a moratorium on thrombolytic trials until a low risk subgroup more likely to benefit could be identified.

NINDS<sup>1</sup> was a multicentre, randomized, placebo-controlled trial of intravenous tPA (0.9 mg/kg) initiated within 3 hours of the onset of stroke symptoms. In this study, tPA recipients did not suddenly improve and there were no significant outcome differences at 24 hours. However, patients treated with tPA were more likely to have a favourable neurological outcome at 90 days (odds ratio 1.7; 95% confidence interval [CI], 1.2–2.6;  $p = 0.008$ ). Compared with controls, tPA recipients had a 12% absolute (32% relative) increase in the proportion with minimal or no disability. But this benefit came with an attached risk: tPA was associated with a 10-fold increase in symptomatic intracerebral hemorrhage (6.4% vs. 0.6%) and the overall intracerebral hemorrhage rate (symptomatic + asymptomatic) was 10.1%.

In an attempt to replicate the NINDS results, ECASS II applied the same eligibility criteria and used the same 0.9 mg/kg tPA dose but enrolled patients within 6 hours of

\*Information in this area is rapidly evolving, and this Position Statement will be reassessed as new data become available.

symptom onset.<sup>6</sup> In this study, tPA did not significantly increase the rate of favourable 90-day outcomes (40.3% vs. 36.6%,  $p = 0.277$ ) and was associated with a higher incidence of parenchymal hemorrhage (11.8% vs. 3.1%), symptomatic intracranial hemorrhage (8.8% vs. 3.4%), and early death due to intracranial hemorrhage (11 vs. 2 cases). Of note, there were no significant differences in 30- or 90-day mortality. An ECASS II subgroup analysis showed a trend toward improved neurological outcomes in patients with <3 hours of symptoms, but the numbers were small and statistically insignificant. ECASS II therefore failed to reproduce the positive results of the NINDS.

The PROACT II investigators administered intra-arterial prourokinase (vs. placebo) to patients with <6 hours of symptoms.<sup>7</sup> At 90-day follow-up, thrombolytic patients had a higher rate of favourable outcomes (40% vs. 25%;  $p = 0.04$ ), defined as a modified Rankin score of 2 or less. There were also trends toward improvement in the Barthel and NIH stroke scores, but these were not statistically significant. Intracranial hemorrhage with early neurological deterioration was more common in prourokinase patients (10% vs. 2%;  $p = 0.6$ ), and 90-day mortalities were similar between the groups (25% vs. 27%). PROACT II suggests that intra-arterial prourokinase may confer some benefit, but at substantially increased risk of symptomatic intracranial hemorrhage. In addition, the invasive approach used in this study is impractical in most Canadian hospitals.

ATLANTIS was a placebo-controlled, randomized clinical trial addressing the efficacy and safety of tPA administered 3 to 5 hours after stroke onset.<sup>8</sup> The study found no beneficial treatment effect, but a significantly higher rate of asymptomatic (11.4% vs. 4.7%) and symptomatic (7.0% vs. 1.1%) intracerebral hemorrhage with tPA. These results, along with those from the ECASS trials, show that beyond the 3-hour window the risks of tPA outweigh its benefits.

## Recommendations

In 1998, the Canadian Stroke Consortium published recommendations concerning the use of thrombolytic agents in acute stroke.<sup>9</sup> They cautioned that tPA is the only suitable agent, that it should only be administered using the NINDS criteria, that it should only be administered by physicians with expertise in stroke management (generally neurologists in tertiary care centres), that expert CT and CT interpretation must be available on a 24-hour basis and that hospitals should have on-site capability to manage intracranial hemorrhage. These recommendations reflect concerns about CT interpretation, early diagnostic accuracy and community hospital experience.

### *CT interpretation*

Three neuroradiologists performed a retrospective analysis of ECASS data to define CT criteria that would identify patients likely to benefit from thrombolysis.<sup>10</sup> Their analysis suggested that tPA was of no benefit or potentially harmful in patients with a normal CT scan or a large area of hypoattenuation, and that tPA led to higher rates of favourable 90-day outcomes (38% vs. 11%,  $p = 0.001$ ) when patients had small areas of baseline hypoattenuation (33% or less). Unfortunately, these conclusions were limited by the fact that  $\kappa$  values for inter-rater agreement were poor (approximately 0.3–0.4), meaning the neuroradiologists often disagreed on the interpretation of relevant scans.

In another study, Schriger and colleagues<sup>11</sup> invited 38 emergency physicians, 29 neurologists and 36 general radiologists to interpret a series of 15 CT scans of the head, chosen from a pool of 54 scans of patients with intracerebral hemorrhage, acute infarction, calcifications, old infarction or normal findings. The rate of correct CT interpretation was 67% for emergency physicians and 83% for neurologists and radiologists. Only 6 emergency physicians (16%), 11 neurologists (38%) and 19 radiologists (53%) correctly identified all of the scans of patients with hemorrhage.

Safe thrombolysis depends on accurate CT interpretation and the ability to recognize intracerebral hemorrhage. CT findings can be subtle; therefore pre-thrombolysis CT scans should be interpreted by neurologists or radiologists with expertise in neuroradiology.

***Recommendation #1: Only radiologists or neurologists with demonstrated expertise in neuroradiology should provide interpretation of CT scans of the head used for the purpose of deciding whether to administer thrombolytic agents to stroke patients.***

### *Early diagnostic accuracy*

In the NINDS study,<sup>1</sup> less than 3% of patients were eligible for thrombolysis. In another 1999 study<sup>12</sup> only 6 of 208 patients (2.9%) evaluated by a stroke team were eligible for thrombolysis.<sup>12</sup> Therefore, it is likely that the benefit seen with tPA in the NINDS trial is applicable to only 2%–3% of patients who present with acute stroke syndromes. The most common reason for exclusion was inability to make the diagnosis and confirm tPA eligibility within 3 hours of symptom onset.

Diagnostic accuracy is essential for the safe administration of thrombolytic agents. Given time for observation and investigation, physicians can diagnose ischemic stroke with a high degree of accuracy, but making a diagnosis within limited time constraints is more difficult. Studies suggest

that diagnostic accuracy for stroke within 3 hours of symptom onset ranges from 70%–85%.<sup>13–15</sup>

In a 1999 study, Allder and colleagues<sup>16</sup> assessed 70 consecutive patients who presented with acute anterior stroke syndromes and <6 hours of symptoms. All patients underwent MRI with diffusion-weighted or perfusion-weighted imaging to define the responsible pathologic process. In this series, in 49 patients (70%) large vessel anterior circulation ischemia was correctly diagnosed, while 6 (9%) had non-stroke conditions, including metabolic encephalopathy, hemiplegic migraine, alcohol withdrawal and hysteria. Fifteen patients (21%) were misclassified, including 7 with hemorrhage, 5 with small vessel occlusion and 3 with posterior circulation occlusion. Of 49 patients with confirmed anterior circulation strokes, only 26 had persistent occlusion. The authors concluded that 63% of their patients with clinical anterior stroke syndromes were not suitable for thrombolysis and that current diagnostic strategies are suboptimal.

The problem of limited early diagnostic accuracy indicates the need to proceed with caution. Rushed decisions to administer tPA within the 3-hour window will mean that a subset of patients will be exposed to a substantial risk of hemorrhage without any potential for benefit.

**Recommendation #2: Stroke thrombolysis should be limited to centres with appropriate neurological and neuro-imaging resources that are capable of administering this therapy within 3 hours. In such centres, emergency physicians should identify potential candidates, initiate low risk interventions and facilitate prompt CT scanning. They should not be the primary decision-makers concerning the administration of thrombolytic agents to stroke patients. Neurologists should be directly involved prior to the administration of thrombolytic therapy.**

### Community hospital experience

The STARS investigators, representing a subgroup of ATLANTIS trial centres, recently published a cohort study of tPA stroke thrombolysis.<sup>17</sup> At 57 centres they treated 389 patients over approximately 2 years — roughly 3.4 patients per year per centre. Protocol violations occurred in 32.6% of patients. The most common violations were administering tPA at >180 minutes of symptoms, administering anticoagulants within 24 hours and administering tPA to patients with significant hypertension (>185/110 mm Hg). The STARS investigators reported an intracerebral hemorrhage rate of 11.5% and favourable 30-day outcomes (modified Rankin score = 0–1) in 35% of patients.

Katzan and coworkers<sup>18</sup> reported a 1-year stroke thrombolysis experience from 29 Cleveland area hospitals. In this study,

70 of 3,948 patients presenting with stroke (1.8%) received tPA. Of those who did, deviations from national treatment guidelines occurred in 50%, 15.7% had symptomatic intracerebral hemorrhage and 6 treated patients (9%) had fatal intracerebral hemorrhages. In-hospital mortality was higher among tPA recipients than matched patients not treated with tPA (15.7% vs. 7.2%;  $p < 0.01$ ). Mortality was also higher in tPA recipients than in the general population of stroke patients who did not receive tPA (15.7% vs. 5.1%;  $p < 0.001$ ).

These data demonstrate that eligible patients are rare and that protocol violations are common when this thrombolysis is provided outside of controlled research settings. The Cleveland experience suggests that stroke thrombolysis may be more dangerous and patient outcomes worse in community settings than they were in the NINDS stroke trial.

**Recommendation #3: Administration of thrombolytic agents to stroke patients should be carried out only in the setting of an approved research protocol or a formal clinical practice protocol. These protocols should adhere to the NINDS eligibility criteria. All data on adherence to protocols and patient outcomes should be collated in a central Canadian registry for the purposes of tracking the safety and efficacy of this intervention.**

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