



ABOUT CAEP ADVOCACY CJEM CME COMMITTEES **POLICIES / GUIDELINES** RESEARCH RESIDENTS

## THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE

The CAEP 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 (t-PA) 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 t-PA 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 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 neuro-imaging 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 CT scanning. 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.

[Introduction](#) | [Relevant Trials](#) | [Recommendations](#) | [References](#)

### Introduction

Emergency physicians across North America are being enjoined to facilitate the delivery 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 thrombolytics for acute stroke demonstrated lack of benefit or worse outcomes with treatment. To date, the NINDS 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 thrombolysis should be limited to physicians with expertise in stroke management, and that centres providing stroke thrombolysis must have access to

immediate CT scanning 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 percent 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 centers. 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 where 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 collated 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\*.**

\*Information in this area is rapidly evolving, and this position statement will be reassessed as new data becomes available.

### Relevant Trials ▲

Prior to NINDS, trials of thrombolytics 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>1-3</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 ECASS study,<sup>4</sup> which compared t-PA (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 t-PA 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>5</sup> was a multicentre, randomized, placebo-controlled trial of intravenous t-PA (0.9 mg/kg) initiated within 3 hours of the onset of stroke symptoms. In this study, t-PA recipients did not suddenly improve, and there were no significant outcome differences at 24 hours. However, patients treated with t-PA were more likely to have a favorable neurological outcome at 90 days (odds ratio 1.7; 95% CI, 1.2-2.6; p=0.008). Compared to controls, t-PA recipients had a 12% absolute (32% relative) increase in the proportion with minimal or no disability. But this benefit came with an attached risk: t-PA 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 t-PA dose, but enrolled patients within 6 hours of symptom onset.<sup>6</sup> In this study, t-PA did not significantly increase the rate of favorable 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 was no significant differences in 30- or 90-day mortality. An ECASS-II subgroup analysis showed a trend towards 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 NINDS.

The PROACT II investigators administered intra-arterial pro-urokinase (vs. placebo) to patients with <6 hours of symptoms.<sup>7</sup> At 90 day follow-up, thrombolytic patients had a higher rate of favorable 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 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 t-PA 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 t-PA. These results, along with those from the ECASS trials, show that, beyond the 3-hour window, the risks of t-PA outweigh its benefits.

## Recommendations ▲

In 1998, the Canadian Stroke Consortium published recommendations concerning the use of thrombolytics in acute stroke.<sup>9</sup> They cautioned that t-PA 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 centers), that expert CT scanning and 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 t-PA was of no benefit or potentially harmful in patients with a normal CT or a large area of hypoattenuation, and that t-PA led to higher rates of favorable 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 invited 38 emergency physicians, 29 neurologists and 36 general radiologists to interpret a series of 15 head-CT scans chosen from a pool of 54 scans with intracerebral hemorrhage, acute infarction, calcifications, old infarction, or normal findings.<sup>11</sup> 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 hemorrhages.

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>5</sup> less than 3% of patients were eligible for thrombolysis. In another 1999 study,<sup>12</sup> only 6 of 208 patients (2.8%) evaluated by a stroke team were eligible for thrombolysis.<sup>12</sup> Therefore, it is likely that the benefit seen with t-PA 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 t-PA eligibility within 3 hours of symptom onset.

Diagnostic accuracy is essential for the safe administration of thrombolytics. 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, et al assessed 70 consecutive patients who presented with acute anterior stroke syndromes and <6 hours of symptoms.<sup>16</sup> All patients underwent magnetic resonance angiography with diffusion-weighted or perfusion-weighted imaging to define the responsible pathologic process. In this series, 49 patients (70%) were correctly diagnosed with large vessel anterior circulation ischemia, while 6 (9%) had non-stroke pathology, 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 occlusions. The authors concluded that 63% of their patients with clinical anterior stroke syndromes were inappropriate for thrombolysis and that current diagnostic strategies are sub-optimal.

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

**Recommendation #2:** Stroke thrombolysis should be limited to centers 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

centers, recently published a cohort study of t-PA 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 t-PA at > 180 minutes of symptoms, administering anticoagulants within 24 hours and administering t-PA to patients with significant hypertension (> 185/110). The STARS investigators reported an intracerebral hemorrhage rate of 11.5% and favorable 30 day outcomes (modified Rankin score = 0-1) in 35% of patients.

Katzan et al reported a one-year stroke thrombolysis experience from 29 Cleveland area hospitals.<sup>18</sup> In this study, 70 of 3,948 presenting stroke patients (1.8%) received t-PA. 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 t-PA recipients than matched patients not treated with t-PA (15.7% vs. 7.2%;  $p < .01$ ). Mortality was also higher in t-PA recipients than in the general population of stroke patients not receiving t-PA (15.7% vs. 5.1%;  $p < .001$ ).

These 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.

## References ▲

1. Anonymous. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial--Italy (MAST-I) Group [comment]. *Lancet* 1995;346:1509-14.
2. Anonymous. Thrombolytic therapy with streptokinase in acute ischemic stroke. The Multicenter Acute Stroke Trial; Europe Study Group [comment]. *N Engl J Med* 1996;335:145-50.
3. Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, et al. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA* 1996;276:961-6.
4. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke, the European cooperative acute stroke study (ECASS). *JAMA* 1995;274:1017-25.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581.
6. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998;352:1245-51.
7. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA* 1999;282:2003-11.
8. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. (The alteplase

- thrombolysis for acute noninterventional therapy for ischemic stroke [ATLANTIS] study). JAMA 1999;282:2019-26.
9. Norris JW, Buchan A, Cote R, Hachinski V, Phillips SJ, Shuaib A, et al. Canadian guidelines for intravenous thrombolytic treatment in acute stroke: a consensus statement of the Canadian Stroke Consortium. Can Neurol Sci 1998;25:257-9.
  10. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology 1997;205:327-33.
  11. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA 1998;279:1293-7.
  12. O'Connor RE, McGraw P, Edelsohn L. Thrombolytic therapy for acute ischemic stroke: Why the majority of patients remain ineligible for treatment. Ann Emerg Med 1999;33:9-14.
  13. Zweifler RM, Drinkard R, Cunningham S, Brody ML, Rothrock JF. Implementation of a stroke code system in Mobile, Alabama: diagnostic and therapeutic yield. Stroke 1997;28:981-3.
  14. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department: implications for acute stroke trials. Arch Neurol. 1995;52(11):1119-22.
  15. Leys D, Lucas C, Devos D, Mounier-Vehier F, Godefroy O, Pruvo JP, et al. Misdiagnoses in 1,250 consecutive patients admitted to an acute stroke unit. Cerebrovasc Dis 1997;7(Suppl 5):284-288.
  16. Alder SJ, Moody AR, Martel AL, Morgan PS, Delay GS, Gladman JR. Limitations of clinical diagnosis in acute stroke. Lancet 1999;354:1523-26.
  17. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke. (The standard treatment with alteplase to reverse stroke [STARS] study). JAMA 2000;283:1145-50.
  18. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, et al. Use of tissue-type plasminogen activator for acute ischemic stroke. The Cleveland area experience. JAMA 2000;283:1151-8.

## CAEP Committee on Thrombolytic Therapy for Acute Ischemic Stroke

<p><b>Tim Rutledge MD, CCFP(EM), FCFP</b>            Chair, CAEP CTTAIS            Director of Emergency Services            North York General Hospital            Toronto, Ontario</p>	<p><b>Terence Bergmann MD</b>            Staff Emergency Physician            Salvation Army Grace General Hospital            Winnipeg, Manitoba</p>
<p><b>Dan Cass MD, FRCPC(EM)</b>            Director of Emergency Services            St. Michael's Hospital            Toronto, Ontario</p>	<p><b>Isser Dubinsky MD, CCFP(EM), FCFP</b>            Chief, Emergency Medicine            University Health Network            Toronto, Ontario</p>
<p><b>Jonathan Dreyer MD, FRCPC(EM)</b>            Chief, Emergency Department            London Health Sciences Centre            London, Ontario</p>	<p><b>Jim Ducharme MD, FRCPC(EM)</b>            Emergency Physician            Saint John Regional Hospital            Saint John, New Brunswick</p>
<p><b>Jane Findlater MD, FRCPC(EM), FACEP, MCFP(EM)</b>            Director, Clinical Emergency Services            Everett Chambers Hospital            Fredricton, New Brunswick</p>	<p><b>Harold Fisher MD, FACEP, MCFP(EM)</b>            Assistant Director, Emergency Department            Mount Sinai Hospital            Toronto, Ontario</p>
<p><b>Keith Greenway MD, FRCPC(EM)</b>            Chief, Emergency Services            Brampton Memorial Hospital</p>	<p><b>Roger Hoag MD, FRCPC(EM)</b>            Chief, Emergency Medicine            Queensway-Cartleton Hospital</p>

Brampton, Ontario	Nepean, Ontario
<b>Andrew McCallum MD, FRCPC(EM)</b> Chief, Department of Emergency Medicine Hamilton Health Sciences Corporation Hamilton, Ontario	<b>Michael Murray MD, CCFP(EM)</b> Medical Director, Emergency Department Royal Victoria Hospital Barrie, Ontario
<b>Howard Ovens MD, CCFP(EM), FCFP</b> Director, Division of Emergency Services Mount Sinai Hospital Toronto, Ontario	<b>Michael O'Conner MD, FRCPC(EM)</b> Medical Director, Emergency Department Hotel Dieu Hospital Kingston, Ontario
<b>Wes Palatnick MD, FRCPC(EM)</b> Director, Emergency Services Health Sciences Centre Winnipeg, Manitoba	<b>Rob Robson MD, FRCPC(EM)</b> President/CEO Orleans Urgent Care Clinic Ottawa, Ontario
<b>Doug Sinclair MD,CCFP(EM) FRCPC(EM)</b> Chief, Department of Emergency Medicine Queen Elizabeth II Health Sciences Halifax, Nova Scotia	<b>Jim Squires MD</b> Emergency Staff Guelph General Hospital Guelph, Ontario
<b>Tony Taylor MD, FRCPC(EM)</b> Division Chief, Emergency Medicine Foothills Medical Centre Calgary, Alberta	<b>Jim Thompson MD, CCFP(EM), FRCPC</b> Staff, Emergency Department Queen Elizabeth Hospital Charlottetown, PEI
<b>Claude Topping MD, CCFP(EM), FCFP</b> Emergency Physician Centre Hospital University Quebec Quebec. Quebec	<b>Rudy Vandersluis MD, CCFP(EM), FRCPC</b> Physician Leader, Emergency Services Lakeridge Health, Oshawa
<b>Brian Weitzman, MD, CCFP(EM), FRCPC</b> Department of Emergency Medicine Ottawa Hospital	<b>Harry Zeit MD, DABEM</b> Staff, Emergency Department Cambridge Memorial Hospital Cambridge, Ontario

COPYRIGHT © 2006 CANADIAN ASSOCIATION OF EMERGENCY PHYSICIANS  
[PRIVACY POLICY](#)