

# Current management of acute ischemic stroke

## *Part 1: Thrombolytics and the 3-hour window*

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### ABSTRACT

**OBJECTIVE** To help family physicians who care for patients with acute stroke or who are involved in planning service delivery or resource allocation to understand recent developments in acute stroke care.

**QUALITY OF EVIDENCE** A MEDLINE search indicated that most data were derived from well designed, randomized, double-blind, placebo-controlled trials, including all the largest international studies and large systematic reviews.

**MAIN MESSAGE** Treatment of acute stroke with tissue plasminogen activator seems beneficial for certain patients with certain kinds of stroke. Because thrombolytic therapy is not without risk and requires substantial resources, it should be administered only by physicians trained in its use and in centres with the necessary experience and resources. Because time is important, an organized and efficient system of stroke care with collaboration between hospital and prehospital care providers and help from ordinary citizens is essential.

**CONCLUSION** Management of acute stroke is an emerging discipline; many potential therapies are still experimental.

### RÉSUMÉ

**OBJECTIF** Aider les médecins de famille qui prennent soin de patients victimes d'accidents vasculaires cérébraux (AVC) ou qui planifient la prestation des services ou l'attribution des ressources à comprendre les récents faits nouveaux dans la prise en charge de tels patients.

**QUALITÉ DES DONNÉES** Une recension dans MEDLINE a permis de cerner que la majorité des données étaient tirées d'études aléatoires contrôlées contre placebo, à double insu et bien conçues, notamment toutes les plus grandes études internationales et les revues systématiques de grande envergure.

**PRINCIPAL MESSAGE** Le traitement des AVC aigus avec l'activateur tissulaire du plasminogène semble bénéfique chez certains patients et pour certains types d'AVC. Parce que la thrombolyse n'est pas sans risque et qu'elle exige des ressources substantielles, elle ne devrait être administrée que par des médecins formés à cet égard et dans les centres où se trouvent l'expertise et les ressources nécessaires. Le temps étant un facteur crucial, il est essentiel de disposer d'un système structuré et efficace de soins pour les AVC prévoyant une collaboration entre l'hôpital et les dispensateurs de soins préalables à l'hospitalisation, ainsi que d'une assistance des citoyens ordinaires.

**CONCLUSION** La prise en charge des AVC est une discipline émergente; de nombreuses thérapies potentielles en sont toujours au stade expérimental.

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**C**erebrovascular disease remains an important cause of morbidity and mortality in North America.<sup>1</sup> Because incidence of stroke rises with age, the magnitude of this problem will likely increase as life expectancies grow longer. Hill and Hachinski<sup>2</sup> have stated, however, that “nihilistic attitudes about stroke treatment are now archaic, because the future holds much promise for stroke patients.”

I review two aspects of current stroke treatment: thrombolysis and an organized system of emergency treatment. Part 2 of this series will review other aspects of acute stroke treatment, such as use of anti-coagulants and antiplatelets, neuroprotective drugs, and stroke units (page 1795).

Family physicians are usually directly involved in treatment of stroke patients, often in conjunction with specialists, but sometimes by themselves. While thrombolysis should be administered only by physicians and in centres with special expertise and training, patients or their families often turn to their family physicians for guidance. Because family physicians also play an advocacy role, understanding recent developments in treatment of acute stroke will allow them to contribute to the debate about service delivery and resource allocation.

**Quality of evidence**

A MEDLINE search was undertaken using the key words stroke, cerebrovascular accident, thrombolytic agent, and prehospital care. Most data were derived from randomized, double-blind, placebo-controlled trials with a range of sample sizes; all the largest international studies were included. Large systematic reviews and meta-analyses were also consulted. All these trials are cited frequently in the neurology literature and are considered by experts to be the best evidence to date.

**Evidence**

Thrombolysis has a role in treatment of cerebral ischemia and infarction, which accounts for 85% to 90% of all strokes in western countries.<sup>1</sup> The challenge in thrombolytic treatment is to differentiate accurately between nonhemorrhagic strokes and the 5% to 10% of strokes that are hemorrhagic.<sup>3</sup>

Many case reports and non-randomized studies of thrombolysis for acute ischemic stroke have been .....

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published during the last 40 years.<sup>4</sup> Only randomized controlled trials (RCTs) will be discussed in this article.

Many RCTs were published before 1995. These earlier trials used a variety of agents and protocols and varied in size and time to treatment. There was also marked heterogeneity among trials for the outcomes assessed. For most patients included in these early trials, thrombolysis did reduce risk of dependence after stroke, but it also increased risk of death.<sup>4</sup>

Three RCTs of streptokinase (SK) were published in the mid-1990s.<sup>5-7</sup> These trials each enrolled more than 300 subjects and used 1.5 million units of SK over 1 hour. Patients were treated within 4 hours and within 6 hours of symptom onset and received concomitant acetylsalicylic acid or heparin.<sup>5-7</sup> These trials had one other thing in common: all were stopped early because of increased hemorrhage or mortality in the treatment group.<sup>4</sup> There has been little further work on SK for acute ischemic stroke. It is not licensed for this indication in North America.

Four major RCTs of tissue plasminogen activator (TPA) have been published to date.<sup>8</sup> Unfortunately, only one of these trials demonstrated substantial improvement in outcome without much increase in mortality.<sup>9</sup> A brief summary of each trial follows (Table 1<sup>9-12</sup>).

**National Institute of Neurological Disorders and Stroke (NINDS) trial.**

The NINDS trial, carried out from 1991 to 1994, randomized 624 patients to receive either 0.9 mg/kg of TPA or placebo. Among the strict inclusion and exclusion criteria, the most notable was that treatment had to be initiated within 3 hours of symptom onset. Computed tomography was undertaken before treatment to exclude intracranial hemorrhage (ICH), and blood pressure (BP) was rigorously controlled according to a strict protocol. At the end of the study, treated patients were 30% more likely to have minimal or no disability at 3 months, as measured by four different outcome parameters.<sup>9,13</sup>

Symptomatic ICH at 36 hours was more frequent in the treated group, but there was no significant difference in mortality at 3 months.<sup>13</sup> Despite the 10-fold greater risk of ICH with treatment, overall incidence of neurologic deterioration from all causes during the first 24 hours was similar in both groups.<sup>9</sup> It has been postulated that those whose risk of symptomatic ICH was greatest had the most severe strokes and the highest risk of death without treatment.<sup>9</sup> On the basis of this single, albeit convincing trial, TPA has been licensed in both the United States (1996) and Canada (1998) for use for acute ischemic stroke if given within 3 hours of symptom onset according to the NINDS protocol.<sup>4</sup>

**Table 1. Summary of randomized controlled trials using tissue plasminogen activator (TPA) for acute stroke**

TRIAL	N	TIME TO TREATMENT (H)	FOR TREATMENT GROUP COMPARED WITH PLACEBO GROUP
NINDS <sup>9</sup>	624	3	30% more likely to have little or no disability Similar mortality (17% vs 21%)
ECASS <sup>10</sup>	620	6	18% more likely to have minimal or no disability* Greater mortality (22% vs 16%)
ECASS II <sup>11</sup>	800	6	8% more patients alive and independent† Similar mortality (10.5% vs 10.7%)
ATLANTIS <sup>12</sup>	613	5	No benefit to treatment Greater mortality (11% vs 7%)

NINDS—National Institute of Neurological Disorders and Stroke,  
ECASS—European Cooperative Acute Stroke Study.

Adapted from NINDS study,<sup>9</sup> Hacke et al,<sup>10</sup> Hacke et al,<sup>11</sup> and Clark et al.<sup>12</sup>

\*Excluding protocol violations.

†Not the primary end point.

### European Cooperative Acute Stroke Studies (ECASS).

The first ECASS was released about the same time as the NINDS trial. Carried out from 1992 to 1994, it enrolled 620 patients. It differed substantially from the NINDS trial in that the dose of TPA was 1.1 mg/kg, treatment was initiated up to 6 hours after symptom onset, prophylactic subcutaneous heparin was administered, and strict BP control was not part of the protocol.<sup>10</sup> Scanning with CT before treatment was also part of the protocol. It was done to identify the exclusion criterion of early hypodensity in more than one third of the middle cerebral artery territory.<sup>10</sup> This finding has been previously recognized as predicting poor outcome<sup>14</sup> and the possibility of subsequent hemorrhage.<sup>15</sup>

This study was marked by a high proportion of protocol violations (17.4%), predominantly misread CT scans. In an intention-to-treat analysis including these violations, there was no difference between treatment groups in terms of primary outcome measures, but there was some benefit with treatment in terms of some secondary end points.<sup>10</sup> In a target population

analysis where these violations were excluded, there was an 18% greater likelihood of little or no disability at 3 months with treatment.<sup>10</sup> There was a significantly greater risk of ICH and death in the treated group, yet the rate of hemorrhagic infarction was lower in this group.<sup>10</sup> The authors of this study concluded that thrombolytic therapy was effective at improving some functional and neurologic parameters in some patients with moderate-to-severe clinical deficits and no signs of extended infarct on CT.<sup>10</sup> They acknowledged that identification of these patients could be difficult, but that there was an unacceptably higher risk of ICH and death among ineligible patients.<sup>10</sup>

Steiner et al<sup>16</sup> carried out a post-hoc analysis of the 3-hour cohort from ECASS, using NINDS outcome parameters. Despite interstudy differences in dose of TPA, BP control, and heparin prophylaxis, outcomes were similar to the NINDS trial for the 87 patients treated within 3 hours of symptom onset.

The second ECASS, conducted from 1996 to 1998, attempted to reconcile some of the differences between the NINDS and the first ECASS trials.<sup>11</sup> A total of 800 patients were randomized. Like the NINDS trial, dose of TPA was 0.9 mg/kg, no antithrombotics were administered for the first 24 hours, and BP was strictly controlled by protocol. Again, a CT scan was obtained for all patients before treatment, and signs of extended infarct were grounds for exclusion. Unlike the NINDS trial, however, patients were treated up to 6 hours after symptom onset. More treated patients had minimal or no disability at 3 months, compared with the placebo group, but absolute difference was only 3.7% and was not statistically significant ( $P = .277$ ). When the secondary end point of death or dependence at 3 months was examined, however, 8.3% more patients in the treatment group were alive and independent at the end of the study, and this was statistically significant ( $P = .024$ ). This study found little difference whether patients were treated within 3 hours or within 6 hours.<sup>11</sup>

**ATLANTIS trial.** In the ATLANTIS trial, which began in 1991, patients were randomized to receive either alteplase (TPA) at 0.9 mg/kg or placebo. The design was similar to that of the NINDS trial.<sup>12,17</sup> In 1993, after recruiting 142 patients,<sup>17</sup> the protocol was amended to exclude patients with CT evidence of > 33% involvement of the middle cerebral artery due to the recognition from ECASS of the higher rate of hemorrhage in this group.<sup>10</sup> Initially, as in the ECASS studies, patients were treated up to 6 hours after onset of stroke. The protocol was also amended to include only patients

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treated within 5 hours,<sup>12</sup> due to the higher risk of ICH in later-treated patients.<sup>8</sup> The trial was terminated prematurely in 1998 after recruiting 613 patients<sup>12</sup> because no substantial treatment benefits were found for any of the end points, and there were higher ICH and mortality rates with alteplase,<sup>12,17</sup> especially in patients treated 5 to 6 hours after stroke onset.<sup>17</sup>

Because only 22 out of 122 patients in part A<sup>17</sup> and 39 out of 613 patients in part B<sup>12</sup> were treated within 3 hours of stroke onset, the negative results of this study could be applied only to those treated after 3 hours.<sup>17</sup> The authors concluded that their results did not support use of TPA for treatment beyond 3 hours after stroke onset.<sup>12</sup>

**Meta-analysis.** Wardlaw et al<sup>18</sup> examined the 17 major thrombolysis RCTs published between 1981 and 1999. These studies, which involved more than 5200 patients, differed substantially in many aspects of design, including agent and dose of agent used, time to treatment, and use of adjunctive antithrombotics. Even outcome parameters showed marked heterogeneity. Some conclusions can be reached, however. The various trials showed that, with thrombolytic treatment, the odds ratio (OR) for late death is 1.31 (95% confidence interval [CI] 1.13 to 1.52), while the OR for death or dependence is 0.83 (95% CI 0.73 to 0.94).

If we look at trials of therapy with TPA given within 3 hours, results are more striking. The OR for late death is 1.11 (95% CI 0.84 to 1.47) and the OR for death or dependence is 0.58 (95% CI 0.46 to 0.74). The authors concluded that the data "... suggest that TPA may be associated with less hazard and more benefit..." and "... may justify the use of thrombolytic therapy with TPA in experienced centers in selected patients. ..."<sup>18</sup>

**Postmarketing data.** Postmarketing data from the United States and Canada support the efficacy and safety of TPA for acute ischemic stroke.<sup>19,20</sup> The rate of independent recovery has been reported at 43% to 57% with thrombolytic therapy, compared with a historical rate of 26% without thrombolysis. Mortality rates have been reported at 13% to 19.7%, compared with as much as 30% with conventional stroke treatment. Rate of ICH with treatment has been reported at less than 4%.

**Summary.** Despite the controversy, treatment of acute stroke with TPA seems beneficial for certain patients with certain types of strokes, both in terms of clinical outcome and mortality.<sup>18</sup> These patients

have moderate-to-severe neurologic deficits, are very early in the course of their events, and are without contraindications to a potent lytic agent. Stroke types are those without evidence of hemorrhage or extended infarct on CT scan and those not otherwise rapidly improving. Generally speaking, patients should be advised that thrombolytic therapy gives a 30% to 40% chance of achieving full recovery and a 40% to 60% chance of achieving independent living.<sup>19,20</sup> Risk of symptomatic ICH and fatal ICH is approximately 4% and 2%, respectively, yet the mortality rate might not be substantially different with treatment.<sup>13,11</sup>

**Table 2** lists inclusion criteria for thrombolytic therapy for acute stroke. **Tables 3** and **4** list exclusion criteria, often referred to as NINDS criteria, and physicians must keep in mind that TPA is licensed only for stroke treatment and only when used as per these criteria.<sup>4</sup>

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**Table 2. Inclusion criteria for thrombolytic therapy for acute ischemic stroke**

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Acute ischemic stroke with *clearly definable time of onset*

Patient presents early enough to be treated within 3 hours of symptom onset

Age > 18 years

NIHSS\* score  $\geq 4$  and  $\leq 22$

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*\*The National Institute of Health Stroke Scale (NIHSS) is a 15-item inventory that assesses level of consciousness, speech, sensation, and neglect, as well as visual, motor, and cerebellar function. Scores can range from 0 to 42: a score > 22 indicates increased risk of intracranial hemorrhage with thrombolytic therapy; a score of < 4 indicates a minor lesion and less chance of benefit. Some stroke deficits, such as aphasia, however, might be so disabling to particular patients that a neurologist would recommend treatment despite a low numerical score.*

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**Table 3. Absolute contraindications to thrombolytic therapy for acute ischemic stroke**

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Evidence of intracranial hemorrhage, edema, mass effect, tumour, or arteriovenous malformation on computed tomography scan

Only minor or resolving symptoms

Suspected subarachnoid hemorrhage, even with normal CT scan result

Blood pressure > 185/110 mm Hg after two attempts at reduction

Major surgery or trauma within 14 days

Active internal bleeding

Arterial puncture at non-compressible site within 7 days

Hematologic abnormality, coagulopathy, or anticoagulation therapy

**Table 4. Relative contraindications to thrombolytic therapy for acute ischemic stroke**

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Decreased level of consciousness
Seizure at stroke onset
Early evidence of extensive infarction on computed tomography scan (>33% middle cerebellar artery territory)
Intracranial or intraspinal surgery within 2 months
Stroke or head injury within 3 months
Gastrointestinal or genitourinary hemorrhage within 21 days
History of central nervous system hemorrhage
Serum glucose level <2.7 mmol/L or >22.2 mmol/L
Pregnancy
Serious underlying medical condition

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### Three-hour window

All currently available evidence suggests that TPA must be administered within 3 hours of stroke onset to give patients the best risk-benefit ratio.<sup>11,12,17</sup> In many of the large RCTs of thrombolytic therapy, only between 3.6% and 4.4% of patients screened were eligible for thrombolytic treatment.<sup>5,13</sup> The most common reason for ineligibility for this treatment is that the interval from symptom onset to treatment is more than 3 hours.<sup>21</sup>

Borrowing from the National Heart Attack Alert Program four-step emergency cardiac care chain of survival, Hazinski has proposed a seven-step stroke care chain of survival and recovery<sup>22</sup> (Table 5<sup>23</sup>). At every step, care must be organized and coordinated for maximum efficiency so that avoidable delays can be minimized. Hill et al<sup>23</sup> have also proposed a similar strategy for streamlining administration of thrombolytic therapy to their stroke patients. The aim of these and other approaches is to create an organized, coordinated system of care delivery.

The public must be educated to recognize potential stroke symptoms and activate local emergency services systems. Pancioli et al<sup>24</sup> showed through a telephone survey of a random sample of 1880 respondents that only a few elderly patients could correctly identify even one stroke warning sign and only 18% of respondents cited their physicians as the source of that information. Kothari et al,<sup>25</sup> in a retrospective analysis of a convenience sample of 151 patients ultimately diagnosed as having acute strokes, found that only 30% presented within 3 hours of symptom onset, 40% were advised by

**Table 5. Stroke chain of survival and recovery**

**Detection** of onset of stroke symptoms and signs

**Dispatch** through activation of emergency services system and prompt emergency services response

**Delivery** of patient to receiving emergency department while providing appropriate prehospital assessment and care and prearrival notification

**Door:** emergency department triage as a priority

**Data:** emergency department evaluation as a priority, including prompt computed tomography scanning

**Decision** about potential therapies, including thrombolysis

**Drug** administration (various therapies)

*Adapted from Hill et al.<sup>23</sup>*

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others to seek help, and only 11% initially thought they were having a stroke. They also found that patients presented in a much more timely fashion if they accessed the local emergency services system.<sup>25</sup>

To achieve timely treatment for stroke, in-hospital providers must coordinate their activities with those of prehospital providers. Emergency services systems are, by design, well-suited to rapid deployment and delivery of stroke victims to hospital-based care. Dispatch staff must, in some instances, change their mind-set to give potential stroke victims highest priority. Also, some stroke patients are unstable, at least initially, and careful attention to vital functions (the so-called ABCs of critical care) and vital signs could affect ultimate outcome.<sup>26</sup>

Complications, such as seizures, severe hypertension, or hyperglycemia, can be effectively treated before patients reach hospital. Evidence also suggests that notifying hospital staff (using the so-called code-stroke) can improve time to treatment in hospital.<sup>25,27</sup> If effective and safe neuroprotective agents become available in the future, it is likely these would be administered by emergency services personnel before arrival at hospital.<sup>28</sup> This potentially prolongs the therapeutic window for thrombolysis.

Once a patient arrives at an emergency department, his or her evaluation must be given high priority.<sup>27</sup> In the past, the limited treatment available for stroke victims often meant they were not given as high a priority as victims of trauma or patients with chest pain. For thrombolytic therapy to be administered within the 3-hour window, all hospital-based

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health care providers must adapt to evaluating stroke victims as efficiently as possible, even if thrombolysis will be an option for only a few patients.

The NINDS investigators have recommended time targets for evaluation of potential stroke victims that should be reasonable for most patients. These targets are assessment by a physician within 10 minutes, CT scanning within 25 minutes, and treatment within 60 minutes of arrival.<sup>29</sup> Neurologic and neurosurgical expertise must be readily available, and a monitored bed must always be available.<sup>29</sup> Kothari et al<sup>25</sup> showed that, among their patients, only 30% were evaluated within 10 minutes, and only 17% had a CT scan within 25 minutes of arrival. Hill et al<sup>23</sup> were able to achieve their goals by developing a so-called brain attack team that used designated resources and dedicated staff.

### Conclusion

Despite controversy, treatment of acute stroke with TPA seems to be beneficial for certain patients with certain types of strokes, in terms of both clinical outcome and mortality. For stroke victims to be able to realize this benefit, thrombolysis must be administered within 3 hours of symptom onset. To achieve this, organized and efficient systems of stroke care are essential. Systems must include prompt recognition of symptoms by the general public; rapid deployment of emergency services and delivery of patients to hospital; and efficient evaluation, including priority CT scanning, in emergency departments.

Hospital-based professionals must coordinate their efforts with the public and with emergency services personnel. At present, thrombolysis is an option for a few stroke victims in certain urban centres and requires mobilization of substantial medical resources. Part 2 of this series will discuss other developments in acute stroke care that could benefit many more patients, especially with earlier and enthusiastic intervention. We are just beginning the journey. Everyone involved must abandon the old nihilistic attitudes about stroke.<sup>2</sup> ❖

### Competing interests

None declared

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### Editor's key points

- Evidence from several randomized controlled trials in the 1990s indicates that thrombolysis is effective for patients with acute stroke. It helps reduce dependence and increase the likelihood of independent living after stroke.
- Only the few patients treated within 3 hours of onset of stroke and with no evidence of major hemorrhage or involvement of the middle cerebral artery and only moderate-to-severe neurologic deficits benefit, however. There are numerous contraindications to this therapy.
- Thrombolysis must be carried out in centres prepared for neurosurgical intervention if it is required.

### Points de repère du rédacteur

- Des données probantes tirées de plusieurs études aléatoires contrôlées, réalisées durant les années 1990, indiquent que la thrombolyse est efficace chez les patients victimes d'accidents vasculaires cérébraux aigus (AVC). Elle aide à réduire la dépendance et augmente la probabilité de vivre de manière autonome après l'AVC.
- Par ailleurs, seuls en bénéficient les quelques patients traités dans un délai de trois heures après l'apparition de l'AVC et qui ne présentent pas de signes d'hémorragie majeure ou d'atteinte à l'artère cérébrale moyenne et qui souffrent de déficience neurologique de modérée à grave. Il existe de nombreuses contre-indications à cette thérapie.
- La thrombolyse doit être administrée dans des centres où il est possible, au besoin, de procéder à une intervention chirurgicale neurologique.

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