The rationale of tissue plasminogen activator (tPA) treatment is the restoration of blood supply to ischemic brain areas by clot lysis and subsequent arterial recanalization. With view to the high vulnerability of brain tissue, early restoration of blood supply will have a better chance of regaining neurological function than delayed restoration. Brain tissue survival is, however, clearly not guaranteed for 3 hours, the currently accepted time window for thrombolysis, if cerebral blood flow falls below 10 mL per 100 g × min. Under such conditions, it survives for not more than 15 to 30 minutes. Time is only one condition among others for the success of thrombolysis. This treatment will work if the clot is dissolvable by tPA, (containing fibrin, not calcified, small), if reperfusion is accelerated compared with the spontaneous course, and if reperfusion of the ischemic brain tissue will result in recovery of neurological function. Fortunately, stroke can have a beneficial spontaneous course, and no treatment is necessary. Conversely, stroke in others may be caused by conditions that cannot be treated with tPA. These conditions are arterial wall dissection or inflammation, arteriosclerotic stenosis, and long-standing extracranial carotid occlusion in combination with a drop in arterial blood pressure. Again, time may play a crucial role: arterial recanalization by 0.9 mg/kg tPA may be too slow and too late. Under unfortunate circumstances (e.g., embolic occlusion of the distal internal carotid artery), the major portion of the affected arterial territory is already dead, when tPA treatment is initiated and when the agent achieves recanalization. Reperfusion of severely injured brain tissue may then further enhance ischemic edema.

Methods are available that can more specifically identify the patients who may benefit from treatment with tPA than the often unreliable assessment-of-stroke-onset method. Computed tomography (CT) detects brain tissue water content and thus ischemic edema in stroke patients. Edematous ischemic brain tissue means irreversible injury from severe hypoperfusion. It is logical, then, to hypothesize that hypoattenuating brain tissue on CT represents irreversible ischemic injury that may be prone to further water uptake or hemorrhagic transformation in case of reperfusion. The risk from irreversibly injured brain tissue is associated with its extent. A patient may benefit from the recanalization of the middle cerebral artery (MCA) trunk, if only the basal ganglia are irreversibly injured, but the remaining portions of the MCA territory are still viable. This patient will not benefit from tPA treatment, if the entire MCA territory or major portions are already irreversibly injured when treatment is initiated irrespective of the time point.

Other CT findings such as brain tissue swelling or hyperdense segments of arteries indicating occlusion are not closely associated with brain tissue damage. From a pathophysiological point of view, it makes no sense to mix these findings with tissue hypodensituation, then measure the extent of this mixture of early “CT changes” or “CT signs” and study whether the extent is associated with the response to tPA treatment.

The hypothesis that the extent of hypoattenuating ischemic brain tissue is associated with poor prognosis and lack of benefit from tPA was first used for a careful selection of patients in ECASS and is now supported by clinical evidence: patients with MCA trunk occlusions and hypoattenuation of more than one half of the MCA territory had a mortality of 85%. Patients with hypoattenuating brain tissue in more than one third of the MCA territory did not benefit from tPA in ECASS I. In ECASS II, the extent of hypoattenuating brain tissue on baseline CT was identified as an independent risk factor for parenchymal hematoma. The quantitative grading of early CT findings in tPA treated patients showed a threshold beyond which the clinical outcome of patients was considerably impaired. A study of 1205 tPA-treated stroke patients identified “early ischemic CT changes, in particular if exceeding one third of the MCA territory” as an independent risk factor for symptomatic brain hemorrhage. In a recent analysis with re-evaluation of CT scans by a single observer, the risk for symptomatic hemorrhage was odds ratio (OR, 95% CI) = 2.9 (0.3 to 32.4) in patients with hypodensity in >33% of the MCA territory and OR = 1.5 (0.3 to 7.2) in patients with hypodensity in ≤33% of the MCA compared with patients with normal early CT. These data demonstrate a low statistical power because only a few patients with
hypothesis were identified. The CT reader in this study had a sensitivity of only 31% for early ischemic changes in contrast to a sensitivity of 75% in a comparable study.8

In summary, based on pathophysiological considerations and increasing evidence from clinical trials, “early major ischemic changes on CT” should preclude the use of tPA. Patients with ischemic edema as detected by CT as hypodense cortical tissue in the major portion of an arterial territory, or presenting >33% of the MCA territory, or >100 mL, or an ASPECTS <8, should not be treated with tPA, because a benefit of this treatment is not proven for these patients.

References

Key Words: brain ischemia • computed tomography • tissue plasminogen activator

Early Major Ischemic Changes on Computed Tomography Should Not Preclude Use of Tissue Plasminogen Activator

Patrick Lyden, MD

Early major ischemic changes on CT should not preclude use of tPA. In 1997, Prof von Kummer and his colleagues in ECASS greatly advanced stroke neurology by showing us the importance of early ischemic changes (EIC) on computed tomography.1 They devised the so-called one third rule and taught us to estimate whether EIC subsumed more or less than one third of the territory of the middle cerebral artery (MCA). In the NINDS study, we missed this important finding. In our trial, we focused on treating half our patients within 90 minutes, and the remainder within 3 hours; there was only time to review the scans for hemorrhage, perform a history and physical, and obtain informed consent prior to mixing up the drug.2 Following the regulatory approval of intravenous (IV) thrombolysis in the United States, physicians have tried to implement CT reading and to learn to read EIC and use the one third rule.1 Although FDA approval was based primarily on NINDS, the approval language and package insert incorporated the ECASS warning about EIC and the one third rule. Listening to neurologists and emergency medicine physicians debate the importance of EIC, I would guess that no single aspect of hyperacute stroke therapy has produced more physician angst, and excluded more patients from IV thrombolysis, unless it might be the time window. Yet this angst is ultimately needless, and these patients could be treated, for 3 very simple reasons.

First, von Kummer and I agree on some simple definitions of terms that others seem unwilling to accept; once the terminology is clarified, much of the debate evaporates. The term “subtle EIC” should be confined to the very indistinct signs that can be reproducible until they are mastered: obscuration of the insular ribbon, blurring of the gray-white matter margin, and a relative paucity of sulci over the affected hemisphere. The signs are hard to teach, and hard to read unless clinical information is provided.3 These signs may reflect mild, reversible tissue edema, but this is not certain. Von Kummer teaches that these findings indicate increased water content, likely early ischemic edema, and that such findings may precede more ominous findings of irreversible tissue damage.4 In contrast to the subtle signs, obvious, frank hypodensity—manifest as attenuated signal on CT—reflects more severe injury. Von Kummer and I concur: here lies severe tissue injury, and there is greater likelihood of hemorrhage if this region is reperfused. Such hypodensity is not subtle: if large, do not treat; if small, recheck the onset time; if <3 hours, consider treating, but note that even some of the NINDS investigators hesitate to treat patients with frank...
hypodensity. The issue, to me, is that the onset time is likely ≥3 hours, and the patient has obvious evidence of severe tissue injury. We do not yet know for sure, but reperfusion may be hazardous.

Second, subtle EIC has never been shown to correlate with any differential outcomes, either death/disability or hemorrhage. In the original ECASS articles, the outcomes in patients with subtle EIC greater than one third were not statistically significantly different from those with EIC less than one third or those with no EIC. Although von Kummer has been rigorous and consistent in this regard, he is frequently misquoted. The mantra that subtle EIC greater than one third predicts hemorrhage or death has been drummed into review papers, national guidelines, and book chapters.

We examined the NINDS data set to try to prove it, but failed.6 Greater than one third is not true: it was never significant in ECASS and there is not even a trend in NINDS. As confirmation, an analysis showing no relationship to outcome in the Australian Streptokinase Trial data set was reported recently.6 There is no relationship between subtle EIC greater than one third of the MCA territory and outcome. I would not go so far as to say that subtle findings indicate an even greater likelihood of response to tPA, but others have, and the data support this proposition as a testable hypothesis.

Finally, we in the stroke community agree on much more than we acknowledge, but the wider medical world observes and frets over our public squabbling. Consider that intravenous tPA yields an absolute risk reduction for stroke disability of 11%, compared with absolute risk reduction for cardiac disability of 2% in TIMI and 1% mortality in GUSTO. We have an effective therapy that is seldom used because—among other problems—emergency medicine physicians witness us criticizing each other more than we support a proven therapy. In proposing alternatives or improvements to IV tPA, we all feel compelled to indict it as unwieldy or inadequate. I believe that first we must use it, inadequate and difficult as it is, and then build improvements on a successful foundation. It is time to publicize the agreement we all take for granted: IV thrombolytic therapy is the first choice for patients who present within 3 hours, using the NINDS inclusion and exclusion criteria. Imaging modalities—such as ECASS CT criteria, angiography, or MRI perfusion/diffusion mismatch—may be useful in selecting patients beyond the 3-hour window, but all that is experimental. Our goal should be to boost the frequency of IV therapy in the 3-hour window from the current 2% of all strokes to over 12%. This goal is eminently feasible and has been achieved in communities with a unified medical commitment to acute IV therapy. After that, we may begin trials designed to extend the therapeutic window using new imaging modalities. The first step is to identify our profound areas of extensive agreement, isolating our disagreements for the future.

**References**


Key Words: brain ischemia  computed tomography  tissue plasminogen activator

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**CT Screening for Thrombolysis: Uncertainties Remain**

Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

When the landmark NINDS trial was published in 1995, there was no reference to early ischemic change (EIC) on CT. The concept of increased hemorrhagic risk with tPA in patients with EIC was popularized by von Kummer and the ECASS investigators, based substantially on longer time window data (mainly 3 to 6 hours). Interestingly, a further analysis of the NINDS data set, adjusting for confounding variables, did not substantiate a relationship between EIC and symptomatic hemorrhage. The Australian Streptokinase Trial was the only other thrombolytic trial to use a comparatively short time window (4 hours). Interestingly, the investigators also found no link.1 One might therefore conclude that the time window is the important factor to be considered. We agree with Lyden that CT has some value as a “tissue clock” and that major ischemic change may suggest earlier stroke onset than realized.

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Then came ASPECTS. In this phase IV Canadian study in which a semi-quantitative scoring system was used, the investigators found a strong relationship among sub-3 hour tPA, EIC, and hemorrhage. How do we reconcile these findings, when confronted with a potential candidate for tPA in the emergency room? As both our contributors mention, subtle or undefined EIC should not necessarily preclude use of tPA. We certainly endorse the view of Lyden that tPA is too often not administered because of doubtful exclusion criteria.

Given the ASPECTS findings, we consider that enough doubt now remains to err on the side of caution and to continue to exclude patients for thrombolytic therapy based on early CT findings of major ischemia (more than one third of MCA territory) or an ASPECTS score of \( \leq 7 \). We consider that with any area of uncertainty, more evidence is required from both randomized trials and phase IV studies. Certainly, the presence of early CT changes is likely to reflect the severity of ischemia (a product of the duration and level of hypoperfusion) and should alert the clinician to re-evaluate the time of stroke onset.\(^2\)

**References**


**Key Words:** computed tomography □ ischemia □ thrombolytic therapy
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