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Questions
1. What is the evidence for using pTA in acute stroke beyond 3 hours?
2. In ED patients presenting within 3 hours of onset of stroke symptoms, are thrombolytics (e.g. tPA) better than heparin in minimizing long-term neurological sequelae?

PICO
1. P= patient with recent onset of stroke symptoms
   I= tPA administered within more than 3 hours of onset
   C= placebo
   O= survival with fewer neurological sequelae

2. P= patients presenting at ED within 3 hours of onset of stroke symptoms
   I= thrombolytic agent like tPA
   C= anticoagulant like heparin
   O= reduction in neurological sequelae

PICO revised for PubMed for Handhelds

Question 1.
P= stroke
I= tpa or tissue plasminogen activator
C= nil
O= neurologic*

Results of Limit to Meta-analysis
Intravenous tissue plasminogen activator for stroke: a review of the ECASS III results in relation to prior clinical trials.
Cronin CA.

Abstract:
BACKGROUND: Intravenous tissue plasminogen activator (IV tPA) is currently approved by the Food and Drug Administration for use in acute ischemic stroke patients up to 3 h from symptom onset, based primarily on the National Institute of Neurological Disorders and Stroke (NIH) tPA trials published in 1995. The most recent trial published with IV tPA in stroke (European Cooperative Acute Stroke Study [ECASS III]) studied patients between 3 and 4.5 h from symptom onset and found a benefit to treatment in the rate of favorable outcome when compared to placebo, with no difference in mortality.

OBJECTIVES: To examine the patient selection criteria and primary outcomes in ECASS III as compared to prior clinical trials and the current practice in the United States to determine how these new data could be applied to clinical practice.

DISCUSSION: With the exception of the longer time from symptom onset to treatment, ECASS III used more restrictive patient selection criteria than is the current practice in the United States to determine patient eligibility for IV tPA.

CONCLUSIONS: Based on the combined data from all trials, the benefits of thrombolysis with IV tPA for acute ischemic stroke outweigh the risks of treatment for selected patients up to 4.5 h from symptom onset. It is already known that thrombolysis is not beneficial for all stroke patients and strict criteria should be applied before treatment. As time from symptom onset increases, the need for careful patient selection likely also increases.


Abstract:
BACKGROUND: Early administration of intravenous recombinant tissue plasminogen activator (rt-PA) after ischaemic stroke improves outcome. Previous analysis of combined data from individual patients suggested potential benefit beyond 3 h from stroke onset. We re-examined the effect of time to treatment with intravenous rt-PA (alteplase) on therapeutic benefit and clinical risk by adding recent trial data to the analysis. METHODS: We added data from ECASS III (821 patients) and EPITHET (100 patients) to a pool of common data elements from six other trials of alteplase for acute stroke (2775 patients).

We used multivariate logistic regression to assess the relation of stroke onset to start of treatment (OTT) with treatment on favourable 3-month outcome (defined as modified Rankin score 0-1), mortality, and occurrence and outcome of clinically relevant parenchymal haemorrhage. The presence of an arterial occlusion was inferred from the patient's symptoms and absence of haemorrhage or other causes of ischaemic stroke. Vascular imaging was not a requirement in the trials. All patients with confirmed OTT within 360 min were included in the analysis.

RESULTS: Treatment was started within 360 min of stroke onset in 3670 patients randomly allocated to alteplase (n=1850) or to placebo (n=1820). Odds of a favourable 3-month outcome increased as OTT decreased (p=0.0269) and no benefit of alteplase treatment was seen after around 270 min. Adjusted odds of a favourable 3-month outcome were 2.55 (95% CI 1.44-4.52) for 0-90 min, 1.64 (1.12-2.40) for 91-180 min, 1.34 (1.06-1.68) for 181-270 min, and 1.22 (0.92-1.61) for 271-360 min in favour of the alteplase group. Large parenchymal haemorrhage was seen in 96 (5.2%) of 1850 patients assigned to alteplase and 18 (1.0%) of 1820 controls, with no clear relation to OTT (p=0.4140). Adjusted odds of mortality increased with OTT (p=0.0444) and were 0.78 (0.41-1.48) for 0-90 min, 1.13 (0.70-1.82) for 91-180 min, 1.22 (0.87-1.71) for 181-270 min, and 1.49 (1.00-2.21) for 271-360 min.

INTERPRETATION: Patients with ischaemic stroke selected by clinical symptoms and CT benefit from intravenous alteplase when treated up to 4.5 h. To increase benefit to a maximum, every effort should be taken to shorten delay in initiation of treatment. Beyond 4.5 h, risk might outweigh benefit.

FUNDING: None.

Question 2.
P= stroke
I= thrombolytic* or tpa or tissue plasminogen activator
c= heparin or anticoagula*
O= neurologic* or nervous system or brain

Result of Limit to Practice Guideline


The Bottom Line: For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (Grade 1A). In patients with atrial fibrillation and a recent stroke or TIA, we recommend long-term oral anticoagulation (target international normalized ratio, 2.5; range, 2.0 to 3.0) (Grade 1A). In patients with venous sinus thrombosis, we recommend unfractionated heparin (Grade 1B) or low-molecular-weight heparin (Grade 1B) over no anticoagulant therapy during the acute phase.

Recent Cohort Study

**The Bottom Line:** Preadmission warfarin was not associated with less severe neurological deficits on admittance. However, it was related to both less severe neurological deficits 1 week after the onset of cerebral infarction and larger improvement as to neurological deficits within 1 week of acute cerebral infarction.

**Abstract:**

**BACKGROUND:** We hypothesized that patients with cerebral infarction on preadmission warfarin have less severe neurological deficits on admittance, less severe neurological deficits 1 week after the onset of cerebral infarction and a larger improvement as to neurological deficits within 1 week of acute cerebral infarction. **METHODS:** All patients with cerebral infarction who did not receive thrombolytic treatment were included. Preadmission use of warfarin was registered. The National Institute of Health Stroke Scale (NIHSS) score was obtained on admittance and 7 days after stroke onset. **RESULTS:** In total, 42 patients (8.1%) used warfarin at the time of stroke onset. The mean NIHSS score on admittance was 6.9 among the patients on warfarin and 5.2 among those without warfarin (p = 0.10). The 1-week improvement in the NIHSS score was 3.5 among the patients on warfarin and 0.8 among the participants without warfarin (p < 0.001). Linear regression showed that a low NIHSS score on day 7 was independently associated with a low NIHSS score on admittance (p < 0.001), low age (p = 0.002) and preadmission use of warfarin (p < 0.001). **CONCLUSION:** Preadmission warfarin was not associated with less severe neurological deficits on admittance. However, it was related to both less severe neurological deficits 1 week after the onset of cerebral infarction and larger improvement as to neurological deficits within 1 week of acute cerebral infarction.

**DynaMed Results**

**Question 1:** *Thrombolytics for acute stroke*

- t-PA given 3-6 hours after stroke onset increases risk of symptomatic intracranial hemorrhage (level 1: likely-reliable evidence) but effect on functional outcomes is inconsistent in high-quality randomized trials.
- Alteplase given 3-4.5 hours after non-severe stroke onset reduces disability at 90 days (NNT 14) but increases risk of symptomatic intracranial hemorrhage (NNH 46) (level 1: likely-reliable evidence) patients 65 years old may have increased risk of symptomatic intracranial hemorrhage (NNH 11) without functional benefit (level 2: mid-level evidence)
  - *References*
    - Review comparing ECASS III results to other trials of IV t-PA can be found in *J Emerg Med* 2010 Jan;38(1):99
- Alteplase given 3-5 hours after stroke onset increases rate of symptomatic and fatal intracranial hemorrhage without apparent benefit in functional outcomes (level 1: likely-reliable evidence based on randomized trial)
  - *References:* ATLANTIS trial (JAMA 1999 Dec 1;282(21):2068, commentary can be found in ACP J Club 2000 Jul-Aug;133(1):18)
- t-PA given 3-6 hours after stroke onset does not appear beneficial and may increase mortality (level 2: mid-level evidence based on small randomized trial)

**Question 2:** *Anticoagulation therapy for acute stroke*

- Intravenous heparin started within first 3 hours after symptom onset may improve functional outcome after acute nonlacunar hemispheric stroke (level 2: mid-level evidence: based on randomized trial with allocation concealment not stated)
  - DynaMed commentary: excluded from Cochrane review because of confounding by use of low-dose unfractionated heparin in control group