- European cooperative acute stroke study (ECASS) trial - was one of the first large RCTs to test tPA administered within 6 hours of stroke onset. Patients with clinically severe hemispheric strokes were excluded & CT was allowed to show no or early signs of ischemia only. No difference in outcome and increased risk of bleeding. Subgroup analysis of target population showed statistically significant in favour of tPA for good outcome.

- ECASS-II: designed with strict exclusion of patients with greater than 1/3rd MCA infarct on CTB. Also failed to demonstrate benefit - NINDS to cause haemorrhage was 18.

- NINDS was designed to assess very early tPA (<3 hours). Total of 624 patients in 2 parts. Demonstrates NNT to have minimal or no disability at 3 months is 8. NINDS to cause symptomatic ICH is 14. No significant difference in mortality (24 vs 28% respectively). No difference in outcomes at 24 hours.

- Canadian ATEPE for stroke effectiveness study which is a cohort study of all patients receiving t-PA in Canada over a 2 and half year period shows similar benefit to NINDS with a lower risk of ICH (only 4.6%). This study includes at total of 1135 patients. Another meta-analysis of 15 publications from post NINDS era were all achieved a very favourable outcome (similar to NINDS but a lower risk of bleeding (5.2%). This study includes 2639 patients and results were achieved despite protocol deviations in 19.8% of patients.

- ATLANTIS part A was another North American study of tPA which enrolled patients up to 6 hours stopped early because of safety concerns. Study showed increased risk of haemorrhage and no favourable outcome.

- ATLANTIS part B aimed to assess efficacy within 5 hours - results indicated no significant benefit. Subgroup of patients treated within 3 hours of onset had better outcome but this only constituted 62 patients.

- Analysis of all the above studies (and others) with total of 5216 patients shows significant improvement in good outcome at 3 months and significant increase in ICH:
  - 3 large double blind placebo controlled trials of streptokinase in stroke (multicentre acute stroke trial - Europe MAST-E; Australian Streptokinase Trial (AST) & the multicentre acute stroke trial - Italy MAST-I) - all three demonstrate a significant increase in risk of haemorrhage NNH to cause death or disability = 5

- general:
  - Further analysis of the NINDS study did not identify any specific subgroup with a greater or lesser likelihood of responding to tPA, however, clinical experience has raised questions about treatment of several subgroups:
    - elder patients have a higher incidence of cerebral amyloid angiopathy which might predispose to haemorrhage after tPA - in the NINDS study, older patients were less likely to have a favourable outcome but fared better with tPA without it - in ECASS II, older patients had a greater risk of haemorrhagic transformation - advanced age is not a contraindication to thrombolysis but requires consideration of a lower probability of good outcome and higher risk of haemorrhage

- CT findings on baseline scan:
  - before RCT tPA trials, several studies suggested that the presence of early changes on CT predicted a greater risk of haemorrhagic transformation - in ECASS II early hypodensity was an independent risk factor for intracranial haemorrhage - in the NINDS study the odds ratio of symptomatic haemorrhage was increased (2.9 vs 1.5) with hypodensity of >1/3rd the MCA territory; however, few patients had this finding on baseline scan and the increased risk of haemorrhage did not reach statistical significance.

- mechanical:
  - mechanical devices have been shown to increase recanalisation rates (MERCI trial); however, clinical data are lacking at present

- general:
  - alternative approach to intravenous thrombolytics is direct delivery of thrombolytic agents by a microcatheter embedded in the clot - the advantage is direct visualisation of the occluded artery and knowledge of the recanalisation status as thrombolytic proceeds; while the disadvantage is the additional time required
  - the rationale for acute ischaemic stroke treatment is that when arterial occlusion occurs there is an area of infarcted brain the is surrounded by a region of that has reduced blood flow impeding function but not sufficiently severe to result in irreversible infarction.
  - this is the 'ischaemic penumbra' and if adequate blood flow can be restored within a critical time frame this area may return to normal function.

- ischaemic strokes are generally classified as:
  - (i) large vessel thrombotic
  - (ii) small vessel thrombotic
  - (iii) embolic

- large vessel thrombotic strokes are often preceded TIA's - clinical deficits typically correspond to the territory of a major cerebral artery or their border zones

- several clinical syndromes are attributable to small vessel or lacunar strokes including pure motor stroke, pure sensory stroke, ataxic hemiparesis and dysarthria/clumsy hand syndrome.

- clinical determination is unreliable and imaging is required

- general assessment:
  - emergent assessment of the stroke patient begins prehospital and mechanisms are required for early notification if aggressive early therapies are feasible
  - initial assessment should be performed rapidly and targeted towards ensuring airway and ventilation (particularly in obtunded or comatose patients)
  - hypoxaemia should be corrected (aspiration is a major cause of morbidity in these patients)
  - arrhythmias are common in stroke patients (particularly AF) and bradycardia may signal increased intracranial pressure
  - hypoglycaemia may mimic stroke and should be treated

- blood pressure management:
  - hypertension commonly accompanies stroke & in most cases treatment is not recommended due to the risk of causing further impairment of perfusion to ischaemic penumbra
  - hypothermia reduces stroke severity in animal models of stroke but no randomised trials to date include trials of low molecular weight heparin & heparin
  - with thrombolytic therapy is considered, SBP should be controlled to less than 185mmHg or diastolic less than 110mmHg

- imaging studies:
  - immediate concern for the emergency department after initial stabilisation is confirming the diagnosis of stroke, excluding stroke mimics & establishing whether acute intervention is warranted

- mechanical:
  - mechanical devices have been shown to increase recanalisation rates (MERCI trial); however, clinical data are lacking at present