One-shot thrombolysis for the management of acute ischaemic stroke

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Comment on ‘Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomized, controlled, non-inferiority trial’ which was published in Lancet. https://doi.org/10.1016/S0140-6736(22)01054-6.

Key Points

- The Alteplase compared with Tenecteplase (AcT) trial 1 was an investigator-initiated, multicentre, parallel-group, open-label, registry-linked, randomized, controlled trial with blinded outcome assessment that involved patients with acute ischaemic stroke eligible for thrombolysis according to standard-of-care indications in Canada. The aim of the study was to determine whether the efficacy of intravenous tenecteplase, as a single bolus at a dose of 0.25 mg/kg (to a maximum of 25 mg), was non-inferior to alteplase (0.9 mg/kg to a maximum of 90 mg; 0.09 mg/kg as a bolus; and then a 60-min infusion of the remaining 0.81 mg/kg).
- The primary outcome was the proportion of patients who had a modified Rankin Scale (mRS) score of 0–1 at 90–120 days after treatment, assessed via blinded review in the intention-to-treat (ITT) population. The mRS score is a seven-point ordered categorical scale from 0 to 6 for functional neurological outcome, with 0 indicating no neurological symptoms and 6 indicating death. Non-inferiority was met if the lower bound of the 95% confidence interval (CI) for the difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was greater than –5%.
- Between December 2019 and January 2022, 1577 patients were randomized and included in the ITT population. The median age was 74 years, with a balanced representation of both sexes (52% M, 48% F). The median symptom onset-to-randomization time was 2 h (IQR 1.5–3.0). The median follow-up was 97 days (IQR, 91–111). Thirty-seven percent of patients in the tenecteplase group and the 35% in the alteplase group had a mRS score of 0–1 at 90–120 days (unadjusted risk difference, 2.1%; 95% CI, –2.6 to 6.9), meeting the prespecified non-inferiority threshold. However, tenecteplase was not superior to alteplase.
- There were no significant differences between groups in the incidence of 24-h symptomatic intracerebral haemorrhage, 90-day mortality, and other key safety outcomes.

Comment

Acute ischaemic stroke is a common threatening companion of a number of cardiovascular (CV) diseases including atrial and ventricular arrhythmias, myocardial infarction, cardiomyopathies, heart failure, valvular heart disease, and carotid atherosclerosis. 2 Although stroke mortality has declined over the past 50 years, due to increased use of anticoagulants for the management of atrial fibrillation and aspirin for secondary prevention, as well as improvement in structured preventive programmes and better control of risk factors, stroke continues to represent a leading cause of death and disability worldwide. 2

In the last few years, the use of endovascular thrombectomy has revolutionized the treatment of patients presenting with occlusion of a proximal intracranial artery. 3 However, reperfusion of smaller arteries often requires pharmacological thrombolysis, which represents a key strategy in the management of ischaemic stroke for those patients presenting within 4.5 h from symptom onset. 4 Several mechanisms have been proposed to explain why intravenous thrombolysis may add benefit to highly effective endovascular therapy. Thrombolysis allows immediate administration of a potentially beneficial reperfusion therapy before endovascular therapy eligibility is established, thus minimizing ischaemic injury. In patients with vessel tortuosity or resistant to thrombectomy attempts, intravenous thrombolysis may represent the only feasible reperfusion option, potentially lysing non-visualized microthrombi. 5

Based on this evidence, the tissue plasminogen activator, alteplase, currently represents the standard medical therapy for early diagnosed
patients with acute ischaemic stroke. More recently, tenecteplase, a genetically modified variant of alteplase with greater fibrin specificity and longer plasma half-life, has been proposed as a potential alternative to alteplase in view of the promising results of phase 2/3 trials. In patients with acute myocardial infarction, tenecteplase is frequently preferred over alteplase due to the simplified administration schedule and favourable benefit/risk profile in this setting.

In a sizeable cohort of stroke patients recruited with pragmatic eligibility criteria, the AcT trial showed that intravenous tenecteplase was not inferior to alteplase for the primary outcome of excellent functional outcome (defined as an mRS score of 0–1) at 90–120 days. Given the consistency of results across multiple secondary outcomes and subgroups, these findings candidate the ‘one-shot’ strategy with tenecteplase as a reasonable alternative for all patients presenting with acute ischaemic stroke who meet standard criteria for thrombolysis.

However, some limitations of the study should be underlined. First, follow-up was limited to a maximum of 120 days, thus preventing the assessment of long-term benefits and risks of tenecteplase. Secondly, patients were enrolled only from stroke centres in Canada, where symptom onset-to-randomization time of 2 h and door-to-needle times close to 30 min reflect current practice, thus limiting the generalizability of the findings to different clinical settings which may follow different guidelines or practice. Third, the study did not specifically address the influence of endovascular thrombectomy (used in one third of both groups) on the efficacy and safety of the different thrombolysis strategies. Finally, the cost-effectiveness and clinical read-out(s) of the ease of administration of tenecteplase vis-à-vis alteplase remain to be assessed.

A current knowledge gap is represented by the discrepancy between the number of reperfused patients and those who experience a favourable functional outcome. Persistence of peripheral microthrombi despite appropriate thrombolysis and/or thrombectomy may be responsible for incomplete microvascular reperfusion and impaired neurological recovery. In such a context, the efficacy and safety of early antiplatelet or anticoagulant therapy to treat microcirculatory occlusion are currently being evaluated in different studies. Such a strategy might eventually add further benefit in the acute management of stroke, although current guidelines discourage heparin use in combination with intravenous thrombolysis and recommend postponing antiplatelet agents after thrombolytic therapy. A careful evaluation of the balance between the expected benefits of microvascular reperfusion and the additional risk of haemorrhages appear to be of key importance.

Effective stroke management translates into better survival rates and prolonged disability-free life. Although recanalization treatments have advanced in recent years, further efforts are necessary to encourage multidisciplinary approaches aimed at improving clinical efficacy and cost-effectiveness, as well as at better selecting those patients who may benefit from more sophisticated revascularization strategies.

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Data availability
There are no new data associated with this article.

References