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## **Stroke Literature Synopsis (Clinical)**

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## Stroke Literature Synopsis

Stroke care has transformed in the last decades with many new interventions for primary and secondary prevention. However, intravenous thrombolysis with alteplase remains the only drug approved by international regulatory authorities for acute ischemic stroke. Although thrombolysis is now a core part of acute stroke, much is still unknown regarding the indications, dosing, and safety.

A potential alternative to alteplase is another tissue plasminogen activator, Tenecteplase (TNK), a drug which is already used in myocardial infarction. TNK has theoretical advantages over alteplase due to its higher fibrin specificity and longer half-life, permitting a single bolus administration. A recent study in Norway aimed to prove the non-inferiority of Tenecteplase in patients with moderate to severe stroke (**CE Kvistad et al. Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A Lancet Neurol.2022 [https://doi.org/10.1016/S1474-4422\(22\)00124-7](https://doi.org/10.1016/S1474-4422(22)00124-7)**). In total 216 patients were randomised to TNK or alteplase. Unfortunately, the study was prematurely terminated because of safety concerns in the TNK arm. The patients receiving TNK were less likely to have a good functional outcome (31% vs. 51%, odds ratio:0.54, 95%CI:0.25-0.8) with higher rates of intracranial haemorrhage and mortality at three months. These findings are in contrast with the outcomes from the previous NOR-TEST investigators trial, which demonstrated more favourable outcomes with TNK with no safety signal. So, why the difference between trials. The dosing schedule may be explanatory, and the NOR-TEST part B trial continues with a reduced Tenecteplase dose (0.25 mg/kg instead of 0.4 mg/kg). Another explanation could be the difference in baseline characteristics in both groups. Patients in the TNK group were older and had higher pre-stroke disability. Other trials of TNK are ongoing and a synthesis of these studies will help us understand the role of TNK in acute stroke.

Intravenous thrombolysis was considered standard of care for ischemic stroke, but mechanical thrombectomy is now proven to be even more effective in selected patients. Yoshimura and colleagues studied whether thrombectomy was still effective in those patients presenting with radiologically large infarcts (**Yoshimura S et al. Endovascular Therapy for Acute Stroke with a Large Ischemic Region. N Engl J Med. 2022 Apr 7;386:1303-1313. doi: 10.1056/NEJMoa2118191.**). Across several centres in Japan, 203 patients with large infarcts (as defined by Alberta Stroke Program Early Computed Tomographic Score [ASPECTS] 3-5) were randomised to best medical care or best medical care and endovascular therapy. The group receiving endovascular therapy were more likely to have good functional outcome at three months, modified Rankin scale 0-3 was 31% vs. 13% (relative risk:2.43, 95%CI:1.35-4.37). This efficacy did not come at a cost of safety. Although in the endovascular group, there were significantly more intracranial haemorrhages (58% vs. 31%, relative risk:1.85, 95%CI:1.33-2.58), there was no significant difference in percentage of patients with symptomatic intracranial haemorrhage.

Although these data are impressively convincing, there are concerns over the applicability of the results in other healthcare settings. Both groups could receive intravenous thrombolysis, but rates of administration were low at around 27% of patients in both groups. The dose of alteplase was also lower than is standard in Europe and North America (0.6 mg/kg in the study vs standard 0.9 mg/kg).

If thrombectomy is good and thrombolysis is good, what happens when the two are combined. This was the question asked in a multicentre Spanish trial, where patients with successful recanalization following thrombectomy were randomised to post procedure intra-arterial alteplase or placebo (**Renú A et al. Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke. JAMA.2022;327:826–835. doi:10.1001/jama.2022.1645**) Giving thrombolysis *after* removal of large vessel occluding thrombus is the reverse of usual practice, where thrombolysis is usually given first. The rationale was that thrombolytic may help clear microthrombi in the distal circulation and thus

further improve cerebral reperfusion. Participants in both arms could still receive intravenous thrombolysis before the thrombectomy procedure.

The COVID-19 pandemic had a negative impact on the trial resulting in limited availability of placebo and slow enrolment. The study was prematurely discontinued with 60% (n=121) of the original sample size recruited. Nonetheless, despite only minor differences in angiographic scores between the treatment groups, treatment with intra-arterial alteplase resulted in improved functional outcome (mRS 0-1 at 90 days achieved in 59% of the alteplase group vs 40.4% of the placebo group). Again, safety was not compromised by the thrombolytic with no significant difference in death or cerebral haemorrhage.

When the first cohort of trials describing successful thrombectomy were presented there was a suggestion that thrombolysis may become obsolete. These three papers show that there is still a role for intravenous thrombolysis, and there is still a lot to learn about these drugs.

**Disclosures:**nil