

PRESS RELEASE

ESOC 2022 Plenary Highlights: Wednesday 4 May 2022

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Alteplase compared to Tenecteplase (ACT) Randomized Controlled Trial

Is tenecteplase non-inferior to alteplase when given in routine clinical practice?

For several decades, physicians have been able to treat acute stroke by using clot-busting drugs, so called thrombolytics. The most widely used thrombolytic drug is alteplase, administered as a one-hour infusion. However, there are phase II trials indicating that an alternative thrombolytic agent, tenecteplase, which is administered as a single bolus, might be at least as safe and effective as alteplase.

The ACT trial aimed to test whether tenecteplase is non-inferior to alteplase when given to patients with acute ischemic stroke in routine clinical practice. The trial included 1,600 individuals who were randomised to receive either of the two drugs. The primary outcome was the proportion of subjects achieving a score of 0-1 on the modified Rankin Scale (mRS), i.e., no significant disability and independent in all activities, at 90 days after their stroke. Key safety outcomes were symptomatic intracerebral haemorrhage within 24 hours of treatment and death within 90 days.

Results showed that good outcome (mRS 0-1) occurred in 36.9% in the tenecteplase group, compared to 34.8% in the alteplase group suggesting non-inferiority between the groups.

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The Principal Investigator interview will take place on ESOC TV Studio at 18:30 on 4/5/2022

Tenecteplase versus Alteplase for Management of Acute Ischemic Stroke (NOR-TEST 2 Part A): A Phase 3, Randomised, Open, Label, Blinded Endpoint Trial

Is tenecteplase non-inferior to alteplase in moderate or severe stroke?

Acute ischemic stroke can be treated with clot-busting drugs called thrombolytics. However, there is a significant risk of haemorrhage, and 4,5 hours after onset is a commonly set cut-off for when the risks of treatment are considered to outweigh benefits. The most widely used thrombolytic drug is alteplase, administered as a one-hour infusion. An alternative drug called tenecteplase, which may be administered as a single bolus, is currently being evaluated for safety and efficacy in several ongoing and finished trials.

A previous trial, NOR-TEST, showed effect and safety similar to that of alteplase in minor stroke. The NOR-TEST 2 trial now aims to test whether the tenecteplase, at the dose of 0,4 mg/kg is non-inferior to alteplase in moderate or severe stroke. The primary outcome was a score of 0-1 on the modified Rankin Scale (mRS), i.e., no significant disability and independent in all activities, at 90 days after stroke.

After having included 216 patients, randomised to treatment with either tenecteplase or alteplase, the trial was terminated prematurely due to an increased number of symptomatic intracerebral haemorrhage in the tenecteplase group: 6% as compared to 1% in the alteplase group. Also, mortality was increased (15.6% versus 4.8%) and the proportion with a favourable outcome (mRS 0-1) 90 days after stroke was lower (32.3% versus 51.5%).

Thus, tenecteplase yielded worse safety- and functional outcomes than alteplase in moderate or severe stroke. The authors suggest further assessment of tenecteplase using lower dosages.

[The full results are now published in a simultaneous publication in the Lancet Neurology](#)

ENDS

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The Paramedic Norwegian Acute Stroke Prehospital Project (PARAMASPP): Diagnostics and Triage of Acute Stroke by Paramedics Using the National Institutes of Health Stroke Scale (NIHSS)

Timely prehospital triage to facilitate a common language in the chain of stroke survival – the ParamASPP model of prehospital NIHSS.

Suspected strokes are first handled by the prehospital service, and the first clinical assessment is completed by paramedics at scene. Accurate and speedy identification of the diagnosis, stroke or non-stroke, and a common language between the first responders and stroke physicians could help triage patients to the appropriate hospitals in a timely manner. An accurate and timely prehospital triage system could potentially reduce delay in transferring patients to the appropriate hospitals so they can receive the best level of care.

The Paramedic Norwegian Acute Stroke Prehospital Project (ParamASPP) evaluated a pre-hospital intervention that consists of a structured learning program, a prehospital stroke assessment: National Institutes of Health Stroke Scale (NIHSS), and a mobile application to facilitate stroke communication with the hospital stroke physician.

The ParamASPP intervention was sequentially rolled out to 5 participating ambulance stations in a randomly allocated order (stepped wedge cluster randomised controlled trial).

801 participants were included, 354 in the ParamASPP intervention group and 447 received standard care. Participants were representative of a general stroke population; mean age was 71 years and half were women. Upon discharge 42% were discharged with an ischaemic stroke/TIA diagnosis, 5% with intracerebral haemorrhage and 53% with a stroke mimic condition.

The ParamASPP (intervention group) correctly identified the diagnosis in 48.1% of participants (positive predictive value) and 45.8% in the control group. Median NIHSS at admission was 2 and similar in both groups.

Prehospital on-scene time (i.e., ambulance arrival at the patient to departure from the patient) was significantly longer in the intervention group compared with the control group (median 30 versus 25 minutes). Median time from hospital arrival to first CT was significantly shorter in the intervention group, with 18 minutes versus 20 minutes in the control group. Door to first CT-time for patients arriving within 4 hours from symptom onset was 17 minutes in the intervention group vs 19 minutes in the control group, a significant difference. Median door to first CT-time for the patients treated with thrombolysis was 15 minutes in the intervention group vs 16 minutes in the control group, also a significant difference. Median door-to-needle time was shorter in the intervention group with 25.5 minutes in the intervention group vs 27 minutes in the control group, however this was not significant.

The Chain of Stroke Survival needs a common language. By using prehospital NIHSS in the ParaNASPP model we found that in-hospital time was reduced, but time was not saved in the prehospital phase in our study. Given time and practice, prehospital time may improve as well.

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[View the ParaNASPP Press video](#)

The Principal Investigator interview will take place on ESOC TV Studio at 18:30 on 5/5/2022.

The Melbourne Mobile Stroke Unit Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in The Ambulance (TASTE-A)

Will the use of tenecteplase improve patient outcomes in Mobile Stroke Unit setting compared to alteplase?

For decades now, stroke patients have been treated successfully with clot-busting, thrombolytic, drugs. These need to be administered as fast as possible as for each minute that passes, there is irretrievable neuron loss. To further reduce the time to treatment, Mobile Stroke Units (MSU) were introduced and have been shown to shorten the time to treatment as well as improving patient outcomes. The thrombolytic drug alteplase is commonly used but is administered as a one-hour infusion which poses practical difficulties in the MSU setting.

TASTE-A, a phase II randomized controlled trial set out to test if treatment with an alternative thrombolytic drug, tenecteplase, which is administered as a single bolus, would result in superior outcome compared to alteplase.

The study included 104 patients presenting within 4.5 hours of symptom onset to the MSU in Melbourne, Australia. The primary outcome was the extent of perfusion lesion on computed tomography perfusion imaging upon arrival at the receiving hospital. In addition, secondary outcomes included time for MSU arrival to treatment, NIHSS change from MSU to emergency department assessments and 90 day modified Rankin Score.

Stroke patients treated with tenecteplase had a significantly smaller perfusion lesion compared to those treated with alteplase. For secondary outcomes, patients treated with tenecteplase also had a significantly higher chance of ultra-early clinical improvement (NIHSS change) and were treated significantly faster (median of 7 minutes) than those treated with alteplase. There was no difference in the incidence of symptomatic cerebral haemorrhage or other safety concerns.

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Secondary Prevention by Structured Semi-Interactive Stroke Prevention Package in India (SPRINT INDIA): A Randomized Controlled Trial

To achieve a 30% relative reduction in premature death due to non-communicable diseases (NCDs) worldwide by 2030, we should address the increase in NCDs, including stroke, in low- and middle-income countries. The SPRINT INDIA trial investigated the role of stroke education to prevent recurrent strokes in India.

Recurrent stroke rates remain substantial in low- to middle-income countries, attributing to the global increase in stroke-related morbidity and mortality. This is also true for India, where stroke recurrences occur in up to 20% of stroke survivors. Apart from effective treatment strategies, stroke education programs may improve awareness about risk factors and healthy lifestyle modifications, as well as adherence to existing guidelines.

The SPRINT INDIA, a multicentre randomized trial, assessed the role of a structured semi-interactive stroke prevention package to reduce recurrent strokes, myocardial infarction, and death in patients with first-ever stroke. Eligible patient had to be able to receive an educational intervention by mobile phone. The intervention consisted of an educational workbook, short messages, and videos about risk factors. The primary outcome was a composite of recurrent stroke, high-risk TIA, acute coronary syndrome, and death at one year. Key secondary outcomes included medication compliance, glucose and lipid levels, and smoking and alcohol cessation at one year.

In total, 4298 patients were randomized between 2018 and 2021, of whom 2148 received the stroke prevention package. Although the number of vascular events were comparable in the intervention (119; 5.5%) and control (106; 4.9%) groups (OR 1.12; 95% CI: 0.85-1.47), patients who received stroke education were more likely to quit smoking and alcohol and adhered better to medications.

Dr Jeyaraj Durai Pandian comments: “Such an improvement in lifestyle factors and medication compliance is promising and may have long-term benefits which we did not yet find during the short-term follow-up of this trial.”

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Apixaban for Treatment of Embolic Stroke of Undetermined Source - ATTICUS Randomised Trial

Embolic stroke of undetermined source (ESUS) is when the origin of a blood clot causing an ischemic stroke is uncertain. ATTICUS is the third randomized trial testing the hypothesis of whether patients with ESUS benefit more from treatment with direct oral anticoagulants (blood thinners) than with aspirin. What new insights will ATTICUS bring us?

Approximately 20% of patients with ischemic stroke are categorized as ESUS. The high rate of stroke recurrence and the possibility of different stroke mechanisms in ESUS make the prevention of stroke recurrence challenging. Two prior trials (RE-SPECT ESUS and NAVIGATE ESUS) showed that anticoagulation (blood thinning) was not superior to aspirin in the overall ESUS population. However, further analyses have pointed to a potential benefit of anticoagulation in some subgroups, such as patients ≥ 75 years and those with impaired function of the left ventricle (a chamber in the heart).

ATTICUS, a multicentre randomized controlled trial, compared apixaban (a blood thinner) to aspirin for stroke prevention after ESUS. Eligible participants had to have at least one risk factor for atrial fibrillation (AF), an irregular heart rhythm, or cardiac thromboembolism. Following enrolment, all participants received remote cardiac monitoring and the study drug (apixaban or aspirin) was initiated within one-month after ESUS. The primary outcome was the occurrence of new ischemic lesions on a 12-month follow-up MRI scan.

The trial was stopped due to futility. In total, 352 patients were screened, of whom 178 were allocated to apixaban and 174 to aspirin. 13.6% in the apixaban group developed new ischemic lesion on MRI during 12-month follow up, compared to 16.0 % in the aspirin group. This difference did not reach statistical significance.

AF was common (overall 26%) in the study sample. Findings suggest apixaban was not superior to 'aspirin with switch to apixaban in case of AF detection by mandatory cardiac monitoring' in preventing new ischemic lesions during 12 months of follow up. Early apixaban initiation after ESUS (median 8 days) seems a safe alternative to aspirin with only small increase in minor bleeds.

Dr Sven Poli, co-PI of ATTICUS: "Continuous ECG monitoring will shed new light on the role of (undetected) AF in patients with ESUS. For ESUS and prevention of stroke recurrence, we are still in a phase where we are looking for answers."

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ATTICUS received financial support from Bristol Myers Squibb-Pfizer Alliance and Medtronic and was a collaboration between Neurology (Dr Poli, co-PI) and Cardiology (Dr Geisler, co-PI)

Early vs standard tracheostomy in ventilated patients with severe stroke: results of the randomized, multicenter, international trial (SETPOINT2)

Does early tracheostomy lead to a better outcome in invasively ventilated patients with severe stroke?

A tracheostomy is an opening, created surgically or by intervention, through the front of the neck and into the windpipe, providing a secure airway. This is often necessary in severe stroke causing impaired protective reflexes and/or need for prolonged invasive mechanical ventilation. However, there is uncertainty regarding the optimal timing for tracheostomy. Earlier studies have suggested benefits of early tracheostomy such as less need for sedation, earlier liberation from the ventilator, better de-escalation of ICU measures, earlier transfer to rehabilitation and lower mortality. However, most of these previous studies were small, retrospective and had imbalanced patient groups.

The SETPOINT2 trial aimed to test whether early versus standard tracheostomy improved functional outcome in invasively ventilated patients with severe acute ischemic or haemorrhagic stroke. In this multicentre, randomised controlled trial, 382 patients from 25 US and German neurocritical care centres were randomised either to early tracheostomy (within five days of intubation) or ongoing ventilator weaning with standard tracheostomy if needed (i.e., no prior extubation) from day ten. The primary outcome was survival without severe disability at six months.

The findings showed that both treatment and control groups had a better survival and functional outcome than previously reported in this patient population. The need for tracheostomy can be predicted well by a score, and tracheostomy is both feasible and sufficiently safe irrespective of timing. Early tracheostomy did not result in better long-term functional outcome compared to standard weaning with extubation or later tracheostomy. This strongly suggests that postponing tracheostomy and a standard approach of weaning with the aim to extubate is reasonable and may spare about 20% of patients an invasive procedure without functional disadvantages.

[The results are also published in full in a simultaneous publication in JAMA](#)

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[View a recorded presentation from the Principal Investigator](#)

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Procedural Sedation Versus General Anaesthesia in Anterior Circulation Large Vessel Occlusion Thrombectomy: The Anaesthesia management in Endovascular Therapy for Ischemic Stroke (AMETIS) Randomized Controlled Trial

Mechanical thrombectomy can be done under general anaesthesia or sedation, but which approach is superior?

During mechanical thrombectomy the patient is either put under general anaesthesia or given sedatives and pain-reducing medication. Superiority of one approach compared with the other has not been scientifically established and conflicting results have been previously published.

This randomized multicenter study used a pragmatic approach with open label treatment of either general anaesthesia or procedural sedation during mechanical thrombectomy for large vessel occlusion stroke in the anterior circulation. The assessment of the outcome was blinded. The primary outcome was a composite of functional independence, defined as a 0-2 on the modified Rankin scale after three months, and absence of any major procedural complications.

During the study period 135 received general anaesthesia and 138 received procedural sedation. The primary composite outcome occurred in similar frequencies in both groups. They reported no difference in mortality or periprocedural complications. There was a statistically significant lower frequency of hypotension in the group receiving procedural sedation compared to the general anaesthesia group. This difference did not affect the outcome. The authors concluded that their study found no difference in functional outcome after three months or periprocedural complications from anterior circulation mechanical thrombectomy managed with general anaesthesia or procedural sedation.

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Endovascular Treatment for Acute Basilar Artery Occlusion - A Multi-centre Randomised Controlled Trial (ATTENTION)

Stroke caused by a blockage in the basilar artery can be extremely devastating to the patient. Can endovascular treatment (EVT), also known as clot retrieval, improve the outcome of these patients?

It is now well recognised that EVT (clot retrieval) in addition to thrombolysis (clot-busting medication) is superior to best medical management (BMM) alone in patients who have a stroke caused by a blockage of a proximal major artery in the anterior circulation.

About 5% of patients receiving thrombolysis suffer from strokes that are caused by blockage in the basilar artery, which is in the posterior circulation. These patients usually have very poor outcome and up to 70% die or are left with disability. Effective treatment is therefore urgently needed but results from previous studies were conflicting. Two recent randomised trials including 431 patients (BASICS - Basilar Artery International Cooperation Study and BEST - Basilar Artery Occlusion Endovascular Intervention Versus Standard Medical Treatment) demonstrated equivocal benefit between EVT and BMM.

In ATTENTION, investigators recruited patients from 36 comprehensive stroke centres in China between February 2021 and January 2022. They were adult patients with a blockage in the basilar artery confirmed on vascular imaging within 12 hours from stroke onset. They all had severe symptoms at presentation with an NIHSS score ≥ 10 . The patients were randomly allocated to EVT plus BMM versus BMM alone in a 2:1 ratio. Their primary efficacy outcome of this trial was a favourable outcome defined as modified Rankin scale of 0-3, indicating independent walking.

Overall 340 patients (226 EVT; 114 BMM) were included in the final analysis. The mean age was around 67 years and the median NIHSS was 24. About one third of the patients also received intravenous thrombolysis. Comorbidities were balanced between the two groups and were broadly consistent with what would be expected for the population. The primary outcome was achieved in 46% of the EVT group and 23% of the BMM group, resulting in a significant absolute difference of 24% (Numbers Needed to Treat=4). In addition, there was also lower mortality in the EVT group, suggesting that EVT not only reduced disability but also death.

Despite some limitations recognised by the investigators including the inclusion of Asians only, this is a big step forward in terms of management for patients with basilar artery occlusion. “The overwhelming efficacy of EVT persists in the posterior circulation too!” Commented by Raul Nogueira, the PI of ATTENTION.

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