Glenzocimab, a Novel Antithrombotic, is Associated with Reduced Intracranial Hemorrhage and Mortality Rates when Combined with Standard-Of-Care Reperfusion Therapies: The ACTIMIS Study

Is glenzocimab associated with reduced intracranial hemorrhage and mortality rates when combined with standard of care reperfusion therapy?

ACTIMIS is a randomized, single parallel escalating dose study to evaluate the ability of glenzocimab to safely improve the efficacy of reperfusion therapy (alteplase +/- mechanical thrombectomy) in acute ischemic stroke patients as an add-on therapy.

Glenzocimab is a fragment of antibody targeting platelet glycoprotein VI with antithrombotic activity and no effect on hemostasis. 166 patients with a median age of 75 years and NIHSS score of 12 points were enrolled. They were randomly assigned to placebo or glenzocimab in an initial escalating dosage scheme from 125 to 1000 mg (Phase 1b), subsequently a 1000 mg dose or placebo under a 1:1 parallel group design (Phase 2a).

Glenzocimab resulted in reduced symptomatic and asymptomatic sICH events compared to placebo (Symptomatic ICH 1% v 8%, non-symptomatic ICH 29% v 47%). Death occurred in 8% of Glenzocimab group and 19% in the placebo group during 90-day follow-up.

These promising results will need to be confirmed in larger studies including ACTISAVE and GREEN.

ENDS

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Treatment of Hyperglycaemia in Acute Stroke: Results from the Trial of Exenatide in Acute Ischaemic Stroke (TEXAIS)

Exenatide is safe and prevents hyperglycaemia in patients with acute ischaemic stroke, according to the results from the phase 2 TEXAIS trial.

High glucose levels in the blood, known as hyperglycaemia, is a poor prognostic factor in patients with stroke and reduces the chance of favourable clinical outcomes in stroke patients receiving reperfusion therapies (thrombolysis and/or mechanical thrombectomy).

Controlling blood glucose levels tightly with conventional treatment such as insulin is challenging in an acute stroke setting and could lead to undesirable and potentially dangerous hypoglycaemia when the blood glucose is too low. Exenatide, a drug that is already used to improve glucose control with a low risk of hypoglycaemia in people with diabetes, could offer better glucose management in patients with an acute stroke.

TEXAIS is a phase 2, international, multicentre, randomised open-label trial comparing the efficacy of short-acting Exenatide (5mg twice daily subcutaneous injection for 5 days, given within 9 hours of stroke symptom onset) to standard care. The study set an ambitious goal of reducing short-term disability (an 8-point improvement in NIHSS score).

Participant recruitment for TEXAIS was unfortunately stopped early due to the Covid-19 pandemic and time constraints. The study included 350 participants (planned sample size 528) with a median age of 71 years and minor stroke severity (median NIHSS 4). 42% of the recruited sample had hyperglycaemia, defined as blood glucose >7.0 mmol/L and the median blood glucose on admission was 6.7 mmol/L.

The primary outcome, defined as the proportion of participants with an 8-point improvement in NIHSS score or NIHSS 0-1 at 7 days, was similar in the Exenatide and standard care groups (61.2% vs 56.7%; aOR 1.22 (95% CI, 0.79-1.88), p=0.38). The frequency of hyperglycaemia was significantly lower in participants receiving Exenatide than in the standard care group, and no episode of hypoglycaemia was reported in either group. Nausea and vomiting occurred in 4% of participants receiving the study drug.

Despite the early trial termination and insufficient power to detect a significant difference in the primary outcome, the results are encouraging for the safety of Exenatide in acute stroke and support the planning for a large phase 3 trial.

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Effects of Intensive Blood Pressure Lowering on Cerebral Ischaemia: Insights from the ENCHANTED Trial

How to treat high blood pressure in patients receiving thrombolysis in acute ischemic stroke has been an important question for many years and new analyses from a trial added some new insights.

ENCHANTED was a large international, multicentre, randomised trial that investigated if intensive blood pressure lowering in thrombolysed acute ischaemic stroke was beneficial. The main trial showed no benefit on functional recovery with intensive lowering of systolic blood pressure (SBP) with a target of <140mmHg when compared with a standard approach with a target of SBP <180mmHg. However, intensive BP lowering significantly reduced symptomatic intracerebral haemorrhage (ICH). Thus, in this new analyses, the authors aimed to investigate if there was an effect of intensive BP lowering on cerebral ischaemia volume and if this had any effect on functional outcome.

They included the participants from ENCHANTED-BP where series of brain images by CT and MRI, at baseline and follow-up were available (N=2196). The images were analysed centrally by expert readers assisted by image computation programs to record volume of cerebral infarction and ICH. The investigators looked at the effect of intensive BP lowering on cerebral infarction, with adjustment for potential confounders.

In 813 (37.0%) patients (mean age 67.9 years; male 59.3%) with sequential scans, the mean highest and lowest between-group SBP difference over 24 hours were 4 and 2 mmHg.

Median (IQR) infarct sizes (mL) in the intensive and control groups were 0.8 (0.0-21.5) and 1.3 (0.0-17.9), and 2.3 (0.6-25.7) and 2.9 (0.6-17.3), in the CT and MRI scans, respectively. No significant effect of intensive BP control was found on infarct size, either on CT (aOR 0.02, 95%CI -0.62 to 0.66, P=0.98) or MRI (aOR -0.42 95%CI -1.34 to 0.49, P=0.36).

The authors concluded that a modest early intensive BP lowering did not increase infarct size in thrombolysed patients with ischaemic stroke.

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Drip-And-Ship vs Mothership Transfer Protocols in Patients with Intracranial Hemorrhage: Secondary Analysis of RACECAT Trial

‘Drip-and-ship’ and ‘mothership’ are two transfer models commonly discussed in managing patients with ischaemic stroke with suspected large vessel occlusion. A new study found no difference in disability and death between these two transfer models in patients with spontaneous intracranial hemorrhage.

Spontaneous intracranial hemorrhage (ICH) is a potential cerebral catastrophe associated with high morbidity and high mortality. A proportion of patients with spontaneous ICH may benefit from specialised treatment only available at comprehensive stroke centres such as neurosurgical interventions and care.

The current study is a secondary analysis of the RACECAT trial which evaluated two different transfer models in the management of patients with large vessel occlusion and ischemic stroke. In the current study, the investigators analysed if patients included in the RACECAT trial with a final diagnosis of spontaneous ICH had improved clinical outcomes from direct transfer to a comprehensive centre, known as the ‘mothership’ transfer model, compared to admittance to the local hospital for initial diagnostics and subsequent transfer to a comprehensive centre, known as ‘drip-and-ship’ transfer model.

The primary outcome measure was disability measured by the modified Rankin scale (mRS) on day 90, evaluated by shift analysis. A secondary outcome measure was 90-day mortality. The investigators also took into account potential confounders such as clinical severity and age in their analyses.

From the 1401 patients included in the RACECAT trial, 314 had a final diagnosis of spontaneous ICH. Of these, 173 (55.1%) patients were assigned to the ‘drip- and-ship’ protocol. They found no statistically significant difference in 90-day disability (mRS score distribution) between two groups (adjusted common odds ratio 0.76 [95% CI, 0.48-1.20]). There was also no statistically significant difference in 90-day mortality (adjusted hazard ratio 1.22 [95%CI: 0.86-1.71]).

A higher frequency of transfer complications (6.4% vs. 23.4%, p<0.001), in-hospital pneumonia (19.7% vs. 35.5%, p=0.002) and a longer time interval from symptom onset to hospital admittance (135 vs. 95) was reported in the ‘mothership’ group.

Overall, the authors concluded that the ‘mothership’ transfer protocol did not result in any difference in terms of 90-day disability or death in patients with ICH when compared to the ‘drip-and-ship’ model. There were also more transfer complications in the ‘mothership’ model.

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The Effects of Long-Term Oral Anticoagulant Agents for Atrial Fibrillation (AF) After Intracranial Haemorrhage (ICH): Prospective Individual Participant Data Meta-Analysis (IPDMA) of Randomised Controlled Trials

Should anticoagulation be restarted in patients with atrial fibrillation after intracranial haemorrhage to prevent recurrent stroke and other vascular events?

A prospective individual participant data meta-analysis (IPDMA) of four randomised controlled trials (SoSTART, APACHE-AF, NASPAF-ICH and ELDERCARE-AF) was performed. Individual participant data were available for analysis in 302 participants (from SoSTART and APACHE-AF).

Starting oral anticoagulantion in patients with AF after ICH may reduce major ischaemic events but increase the risk of major haemorrhagic events. Net effect remains uncertain. Recruitment to large definitive trials e.g. STATICH, A3ICH, PRESTIGE-AF, ASPIR, ENRICH-AF are needed.

ENDS
Association Of Intraventricular Fibrinolysis with Clinical Outcomes in Patients with Intracerebral Hemorrhage: An Individual Participant Data Meta-Analysis

Clot busting treatment in patients with intracerebral haemorrhage and acute blockage of the ventricular system reduced death and disability without any increase in harm.

Bleeding in the brain (intracerebral haemorrhage – ICH) accounts for 10-15% of all strokes and causes the highest disability among all stroke survivors. One of the predictors for worse outcome among patients with ICH is the co-existence of blood in the ventricles of the brain (intraventricular haemorrhage – IVH). IVH is not uncommon and is present in up to 40% of all ICH cases. The clotted blood product can result in blockage of the drainage system in the brain leading to serious consequences (increased intracranial pressure and death due to herniation). Intraventricular fibrinolysis (IVF) has been proposed as a clot buster which can dissolve the blood clots hence reducing death but it is unclear whether this approach also reduces functional disability.

In a new study led by Dr Kuramatsu and Professor Huttner, the investigators analysed individual patient data from two randomised controlled trials and seven observational studies involving 1,501 patients who suffered from acute blockage of the ventricular system caused by the clotted blood product in the ventricular system. All studies compared the clot buster approach (IVF) with routine care (no IVF). They showed patients who received the clot buster treatment did better at 6 month with less disability. The clot buster treatment also halved the chance of dying without any increase in harm. Encouragingly, the effect was most prominent in patients who were given the treatment within 48 hours after the onset of symptoms, which was validated using RCT only data, suggesting a potential target population for future trials.

Whilst there are still remaining uncertainties, such as if we can achieve better clinical outcome by more efficient way of removing the blood product with IVF, we have an important step forward with the potential use of IVF in the routine acute management of ICH in the near future.

The results are also published in full in a simultaneous publication in Stroke

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Intravenous Thrombolysis in Patients with Ischaemic Stroke and Recent Direct Oral Anticoagulants Intake – an International Collaboration

Is withholding clot busting treatment in patients with acute stroke on recent direct oral anticoagulants justified? Novel evidence for a burning clinical dilemma.

Patients with atrial fibrillation (AF) are at increased risk of stroke despite strong blood thinners, such as a family of anticoagulants called DOACs (Apixaban, Dabigatran, Edoxaban and Rivaroxaban). Up to 20% of patients with AF having an ischaemic stroke are on DOAC therapy at the time of stroke onset. Whilst intravenous thrombolysis (IVT) is an effective acute stroke treatment, current ASA/AHA and ESO guidelines recommend against the use of IVT in patients with recent intake of a DOAC due to safety concerns. However, there is a significant lack of data to support it, leaving clinicians with ongoing dilemma.

An international multi-centre cohort study was coordinated by neurologists from New Zealand (Duncan Wilson and Teddy Wu), Germany (Jan Purrucker) and Switzerland (Thomas Meinel and David Seiffge). The collaboration collected data of patients with ischemic stroke receiving IVT in more than 50 centres to study the safety of IVT in those who were also on prior recent DOAC therapy (last intake <48 hours or unknown). The primary outcome was symptomatic intracerebral haemorrhage (sICH), the secondary outcome functional independence (defined as a mRS 0-2 at 3 months).

In total, 20,448 patients were included, of whom 830 were on DOAC therapy at the time of stroke onset. Among the DOAC users, 252 (30%) received DOAC reversal prior to IVT, 223 (27%) had their DOAC-level measured and 345 (42%) received IVT without reversal treatment or knowledge on DOAC-levels. Compared to the control group (19,618 patients), DOAC users were half as likely to develop sICH, without a significant difference in independent outcome at 3 months between the groups (adjusted OR 1.21; 95% CI: 0.99-1.49). This finding was consistent among different subgroups including different selection methods and for patients with a very recent intake (<12hours).

“The results of our study provide reassuring safety data on the use of IVT in patients with a recent DOAC intake. We did not find any signal of harm” comments PD Dr David Seiffge. “Obviously, this is a highly selected patient population as only experienced centres are currently offering IVT to patients on DOAC therapy. However, we tested different selection approaches (DOAC plasma level based, DOAC reversal agent use or IVT without prior testing or reversing) which all resulted in safe IVT” adds PD Dr Jan Purrucker.

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COMBINE AF: Outcomes of Patients with Atrial Fibrillation and Ischaemic Stroke Despite Receiving Oral Anticoagulation

Patients with atrial fibrillation (AF) who suffer an ischaemic stroke while on a blood thinner e.g. direct oral anticoagulant (DOAC) and warfarin (a vitamin-K antagonist) are at very high risk of recurrent stroke and death.

Blood thinners are known to be effective at reducing the risk of stroke recurrence in people with AF. However, the clinical outcomes of patients with AF who are already treated with oral anticoagulation (OAC) at the time of an ischaemic stroke are incompletely understood.

Dr Benz and colleagues presented the results of an analysis using individual patient data from 5 pivotal RCTs of antithrombotic therapy in AF (COMBINE AF), addressing the risk of stroke recurrence and death in patients with AF who suffer an ischaemic stroke while on OAC.

The analysis included 1,163 patients with an ischaemic stroke while on OAC from a total sample of 74,491 patients who were randomly allocated to receiving DOAC (e.g. apixaban, dabigatran, rivaroxaban) or warfarin. The study aimed to assess the incidence of recurrent stroke and death following the first post-randomisation ischaemic stroke.

The main results showed that recurrent ischaemic stroke occurred in 7.0% (95% CI: 5.2-8.7%) at one year after the index stroke. Further sensitivity analysis showed that this high risk of stroke recurrence was not driven by a lack of anticoagulant treatment following the index stroke event. The analysis on post-stroke death was also alarming, with death occurring in 12.4% at 90 days, and 18.1% at one year.

The authors of this study call attention to the high risk of stroke recurrence and death in patients with AF and ischaemic stroke despite being on OAC—the current best medical therapy for stroke prevention in patients with AF. Their risks of stroke recurrence and death are higher than those of patients with AF on OAC who have not had an ischaemic stroke before (primary prevention).

The results of this study suggest that there is an unmet medical need in this subset of high-risk patients with AF who have an ischaemic stroke despite being on OAC. Future research should focus on strategies aiming at improving secondary prevention of ischaemic stroke in this group of patients.

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TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial)

Do patients with wake-up ischaemic stroke benefit from a new clot busting drug?

Patients who wake up with stroke have previously been excluded from treatment with thrombolytic agent due to the unknown onset of stroke symptoms. However, in recent years this has started to change with previous trials showing benefit of thrombolytic treatment in wake-up stroke patients where Magnetic Resonance imaging (MRI) or Computed Tomography (CT) contrast perfusion imaging identify salvageable tissue.

The TWIST study aimed to investigate if thrombolytic treatment with tenecteplase in a dose of 0.25 mg/kg compared to no thrombolytic treatment in wake-up stroke patients selected by non-contrast CT imaging results in better functional outcome measured by the modified Rankin scale score.

They included patients with wake-up stroke if treatment could be administered within 4.5 hours after time of wake-up and randomised in a 1:1 ratio to either tenecteplase 0.25 mg/kg or no thrombolytic treatment. Blinded follow-up assessment was performed at 90 days. The primary outcome variable was a ordinal shift analyses of the seven leveled ordinal modified Rankin scale score measured after 90 days. A favorable outcome defined as a score of 0 or 1 was also analyzed as a secondary endpoint.

The original plan was to include 600 patients and the final inclusion stopped at 578 patients. Of these, 288 (56.9% men) were randomised to receive tenecteplase and 290 (57.9% men) in the control group. Mean age of patients was similar in both groups, as was the stroke severity as measured by NIHSS on admission. Thrombectomy was more common in the control group than in the tenecteplase group.

No significant difference was found between the two groups on primary outcome (90-day shift analysis of modified Rankin score, mRS) or the secondary outcome—90-day mRS 0-1 (45% in Tenecteplase v 38% in control, not statistically significant).

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Basilar Artery Occlusion CHinese Endovascular Trial (BAOCHE)

Strokes caused by a blockage in the basilar artery are associated with high risk of death and disability, yet they can be difficult to diagnose causing further delays in treatment. Can endovascular treatment (EVT), also known as clot retrieval, improve the outcome of these patients outside the usual 6 hour time window?

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 and the benefit can be seen up to 24h from last seen well in selected patients.

About 1% of all strokes are caused by blockage in the basilar artery, which is in the posterior circulation. These patients usually have very poor outcomes and 50-70% die or are left with severe 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. Moreover, they only randomised patients within 6 and 8 hours from symptom onset respectively.

In BAOCHE, investigators recruited patients from multiple centres in China between August 2016 and June 2021, with a mean age of 64 years and most (73%) were men. They all had a blockage in the basilar artery confirmed on vascular imaging and presented within 6-24 hours from last seen well, a later time window than previous studies. The symptoms were severe with a median NIHSS score of 20. Enrolment was restricted to patients with evidence of small or moderate infarct burden in the posterior circulation assessed by non-contrast CT. The patients were randomly allocated to EVT with the detachable Solitaire device plus BMM versus BMM alone in a 1:1 ratio.

Their primary efficacy outcome was the difference in proportion of patients achieving modified Rankin Scale (mRS) 0-3 (indicating independent walking) at 90 days adjusted for age, stroke severity (NIHSS) and therapeutic window (6-12 hours vs 12-24 hours). Key safety variables were death at 90 days, symptomatic intracranial haemorrhage rates at 24 hours and procedure-related complications.

Enrolment was stopped based on the recommendation of the data safety monitoring board after a pre-planned interim analysis revealed that pre-specified efficacy boundaries were crossed in favour of thrombectomy. In the final analysis including 217 patients, The difference in rates of mRS 0-3 between treatment and control groups were 46.4% vs 24.3% respectively, adjusted OR 2.92, p=0.001. Mortality rates were: 30.9% vs 42.1% respectively, p=0.088 and rates of symptomatic haemorrhage were 5.9% vs 1.1% respectively, p = 0.13.

The results of BAOCHE mirror those of DAWN, a randomized trial of thrombectomy in patients with anterior circulation stroke presenting in the 6-24 hour time window implying that indications for EVT
in late presenting basilar occlusion stroke should be treated similarly to those with late presenting stroke due to proximal large vessel occlusion in the anterior circulation.

To conclude, EVT for basilar artery occlusion confirmed on vascular imaging within 6-24 hours from time ‘last seen well’ resulted in a better functional outcome (Number Needed to Treat: 4.5). A trend towards fewer deaths and higher rates of sICH in EVT group compared to BMM was not statistically significant.

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