PRESS RELEASE

Embargoed: Wednesday, 15 May 2024, 10:30am CEST

ESOC 2024 Plenary Highlights: Wednesday, 15 May 2024

PROMOTE Study Reveals Potential of Polypill Intervention in Stroke and Cognitive Impairment Prevention

(15 May 2024, Basel, Switzerland) The PROMOTE study, sponsored by the Program of Support for Institutional Development for the Unified Health System (PROADI-SUS) of the Hospital Moinhos de Vento in partnership with the Ministry of Health of Brazil, was conducted by a collaborative team of researchers from different Institutions, led by Professor Sheila Cristina Ouriques Martins.[1]

The study was designed to prove the World Stroke Organisation's concept of a comprehensive intervention approach in primary prevention to "Cut Stroke in Half", conceived by former World Stroke Organisation President Michael Brainin from Austria, and Professor Valery Feigin from New Zealand. The intervention is based on lifestyle modification utilising the Stroke Riskometer and a polypill containing anti-hypertensive and statin for patients at low to moderate risk of stroke, a population that currently has no recommendation for medication use. The main study will explore the efficacy of intervention in reducing the incidence of stroke and cognitive impairment in this population. The polypill regimen comprised valsartan 80mg, amlodipine 5mg, and rosuvastatin 10mg.

PROMOTE is a Phase III, randomised, double-blinded, placebo-controlled clinical trial recruiting participants aged 50-75 years without a history of hypertension, diabetes, stroke, or cardiovascular disease, yet presenting systolic blood pressure (SBP) levels between 120-139mmHg and at least one lifestyle risk factor (including an unhealthy diet, sedentarism, obesity or smoking). This pilot study aimed to assess the feasibility of this strategy implementation, the tolerability of this new polypill, and the potential impact of this integrated intervention, including as the main outcome a target reduction in 2.5mmHg in SBP and improvement in 0.4 points in the Life's Simple 7 score over a 9-month period. Participants underwent a 28-day run-in phase to evaluate adherence and tolerance to the polypill regimen. Primary Health Care Units in southern Brazil were randomised into clusters to implement Stroke Riskometer-guided lifestyle modification or provide standard care, while individual participants were allocated to the polypill or placebo.

The pilot study enrolled 371 patients, with a mean age of 59 years, 64% were women and 87% white. The mean estimated 10-year cardiovascular risk was 4-5%. The polypill regimen was very well-tolerated, with only 4% of participants excluded after the run-in period because of mild adverse events. In total, serious adverse events occurred only in 1.4% of patients and were not related to the polypill.

Participants receiving the polypill experienced a significant 13 mmHg reduction in SBP throughout the study duration compared to 4 mmHg in the placebo group. Notably, participants in the Polypill+Riskometer group exhibited the most pronounced reduction in SBP. Participants taking the polypill also showed a reduction of 38 mg/dl in LDL cholesterol, with no difference observed in the placebo group. The riskometer did not add benefit in reducing cholesterol but, encouragingly, 71% of participants utilising the Stroke Riskometer reported its efficacy in facilitating lifestyle modifications.

The PROMOTE pilot study demonstrated that the new polypill can already be used for hypertensive population and it is effective and well tolerated in patients with lower blood pressure but still with an increased risk for stroke. The riskometer is a free app, easy to use, and can assist in lifestyle modification. The findings from the PROMOTE pilot may represent a paradigm shift in preventive healthcare based on combined therapies targeting vascular risk factors to reduce the incidence of stroke and cognitive impairment.

The results of the expansion for a large clinical trial with 8,250 participants is now starting across the entire country. This may demonstrate the impact in stroke and cognitive decline in this new target population with low and middle risk of stroke, with the expectation of cutting stroke rates.

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References:

1. POLYPILL AND RISKOMETER TO PREVENT STROKE AND COGNITIVE IMPAIRMENT IN PRIMARY HEALTH CARE – FINAL RESULTS OF THE PROMOTE PILOT STUDY. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

Tactical training to revolutionize access to acute stroke treatment in regional Australia: results from the TACTICS Trial

(15 May 2024, Basel, Switzerland) TACTICS, a non-randomised intervention trial that aimed to optimsze workflow and implement specialized imaging, has shown promise in improving access to endovascular thrombectomy (EVT) for patients in regional and rural areas of Australia.[1] EVT is a minimally invasive procedure that removes blood clots from blocked arteries in the brain, significantly improving outcomes for stroke patients.

“While EVT has revolutionized stroke treatment, access remains a challenge for patients outside major urban centers,” explains Dr. Delcourt, the investigator who presented the results of TACTICS today at the European Stroke Organisation Conference (ESOC) 2024. “The TACTICS trial investigated a multi-faceted intervention designed to address this disparity.”

The TACTICS trial involved six regional clusters in Australia, each with a central hub that is able to provide EVT and associated spoke hospitals. Each cluster underwent a three-month pre-intervention period followed by a three-month intervention, and a three-month post-intervention period. During the intervention, hospitals were exposed to a combination of face-to-face, video and virtual reality-based education. Additionally, the hospitals were fitted and trained to use multimodal brain imaging to optimise workflow and pathways, improve diagnosis and aid earlier detection of candidates for EVT.

The study enrolled 1,011 patients across the six clusters and a total of 34 hospitals. Compared to the pre-intervention period, the odds of receiving EVT in the pooled intervention and post-intervention period increased by 44%. Notably, these improvements were consistent across all participating clusters.

Dr Christopher Levi, lead investigator of TACTICS concludes: “These findings suggest that this intervention has the potential to be a valuable tool for healthcare systems worldwide, particularly those grappling with geographic barriers to stroke care.”

Further research is needed to confirm the long-term sustainability and generalizability of the TACTICS approach.

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References:

1. TRIAL OF ADVANCED CT IMAGING AND COMBINED EDUCATION SUPPORT FOR DRIP AND SHIP(TACTICS): PRIMARY RESULTS. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

Results of the TASTE trial support the use of tenecteplase for acute ischaemic stroke within 4.5 hours based on perfusion imaging

(15 May 2024, Basel, Switzerland) In the international TASTE trial, the intention-to-treat analysis narrowly failed to demonstrate non-inferiority of tenecteplase compared to alteplase in patients with acute ischaemic stroke within 4.5 hours of symptom onset selected by perfusion imaging. Non-inferiority was demonstrated in the per-protocol analysis, supporting the growing body of evidence for the use of tenecteplase in acute ischaemic stroke.[1]

Over the past two years, several clinical trials have demonstrated non-inferiority of intravenous tenecteplase as compared to alteplase for acute ischaemic stroke. The Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation with Perfusion Imaging Selection within 4·5 hours of Onset (TASTE) trial, presented today at the European Stroke Organisation Conference (ESOC) 2024, lends considerable weight to this series of studies.

The trial design of TASTE differed to the prior trials, in that all patients in TASTE had modern brain imaging including measurement of salvageable tissue ('target mismatch') on brain perfusion imaging. TASTE was a multicentre, randomised, controlled phase III non-inferiority trial conducted in 35 hospitals in 8 countries. Patients were randomly assigned to intravenous tenecteplase (0.25mg/kg) or alteplase (0.90mg/kg). The primary outcome was the proportion of patients without disability (modified Rankin Scale 0-1) at 3-months. Safety outcomes were all-cause mortality and symptomatic intracranial haemorrhage.

The trial was stopped early following the results of previous tenecteplase trials. 680 patients were randomised. In intention-to-treat analysis, the primary outcome occurred in a numerically higher proportion of patients allocated to tenecteplase (57.0%) as compared to those allocated to alteplase (55.3%). This translated into a standardised risk difference of 0.03 (95% confidence interval: -0.033;0.10), which narrowly missed the pre-defined non-inferiority criteria of a lower boundary of -0.03. In the per-protocol analysis, non-inferiority was demonstrated and safety outcomes were comparable between groups.

Although the primary endpoint was not met, the results of TASTE are in line with those from previous trials of tenecteplase for acute ischaemic stroke. When the TASTE results are added to a meta-analysis of the previous trials tenecteplase was, for the first time, demonstrated to be superior to alteplase for excellent recovery at 3 months after stroke. This means that for every 25 patients treated with tenecteplase (rather than alteplase), one more patient will have full recovery at 3 months.

Professor Mark Parsons, the principal investigator of the trial, commented, "TASTE is the largest clinical trial ever in stroke to use modern brain perfusion imaging selection in all patients. Although there were other tenecteplase trials completed before us, we were the only phase 3 clinical trial of tenecteplase that exclusively included patients with a proven tissue target for reperfusion treatment. Thus, the TASTE results increase confidence that tenecteplase is actually a superior agent for stroke thrombolysis."

Intravenous alteplase has been the predominant thrombolytic agent used for acute ischaemic stroke for more than two decades. Currently, the stroke community is facing a transition towards tenecteplase becoming the first choice for intravenous thrombolysis in clinical practice. The results of TASTE will further push forward this movement.

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Watch a recorded summary from the author

References:

1. TENECTEPLASE VERSUS ALTEPLASE FOR STROKE THROMBOLYSIS EVALUATION (TASTE): A MULTICENTRE RANDOMISED CONTROLLED PHASE III TRIAL. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

Glibenclamide, a drug targeting cerebral edema, did not improve functional outcome in patients with severe stroke

(15 May 2024, Basel, Switzerland) Intravenous glibenclamide, a drug capable of reducing cerebral edema, did not improve functional outcome at three months in patients with large hemispheric infarction, a new study shows.[1] The international randomised controlled trial did however confirm that the drug is safe and that there may be a beneficial signal in less severely affected stroke patients.

The CHARM study, presented today at the European Stroke Organisation Conference (ESOC) 2024, was a global, randomised, double-blind, placebo-controlled trial conducted at 141 hospitals. Patients who presented with large hemispheric infarction within 10 hours of last seen well were randomised to intravenous glibenclamide or placebo. The researchers primarily focused on the functional outcomes in both groups at three months, but also studied safety outcomes.

The group of patients who received intravenous glibenclamide (n=217 patients) did not have a lower likelihood of a poor functional outcome (common odds ratio [OR] 1.17; 95% confidence interval [CI] 0.80, 1.71) at three months, when compared to placebo (n=214 patients). The rates of serious adverse events were high in both groups, consistent with critical illness of the large stroke population.

Dr. W. Taylor Kimberly, one of the lead investigators on the study, from Massachusetts General Hospital, Boston, believes there is reason for optimism following CHARM. “We have learned a lot about glibenclamide during our 14-year journey from bench to bedside. When it comes to large hemispheric infarctions, we have wondered about a ceiling effect. How big a stroke is too big? Although we must be cautious in interpreting subgroup analyses, we have seen some promising signals in patients with medium-large stroke volumes (80-130 mL).”

Cerebral edema is a significant complication after ischemic stroke that can lead to neurological deterioration and death, especially in patients with large hemispheric infarction. The damage caused by stroke disrupts the blood-brain barrier and alters the function of ion channels, resulting in excess water accumulation and lesional swelling. Preclinical data and prior clinical trials have shown that glibenclamide can reduce cerebral edema following stroke by regulating the opening of ion channels through certain receptor proteins, the so-called surfonylurea receptor 1 (SUR1) proteins.

Dr Kevin Sheth, also one of the lead authors, from Yale School of Medicine, New Haven, adds, “We know the potential of glibenclamide through our translational research. However, getting everything right in a clinical stroke landscape that is evolving is challenging. It is very exciting to see consistent signals of potential drug effect across these various trial cohorts so that we can inform the next trial.”

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References:

1. INTRAVENOUS GLIBENCLAMIDE FOR LARGE HEMISPHERIC INFARCTION: RESULTS FROM THE CHARM PHASE 3 TRIAL. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

New ANNEXa-I secondary analysis demonstrates the importance of limiting hematoma growth in order to improve mortality and functional outcomes in anticoagulant-related intracerebral haemorrhage patients

(15 May 2024, Basel, Switzerland) A secondary analysis of ANNEXa-I, presented today at the European Stroke Organisation Conference (ESOC) 2024, showed the clinical consequences of hematoma growth and of the less commonly occurring thromboembolic events.[1] Data pooled from both treatment arms of ANNEXa-I demonstrated that hematoma expansion and thromboembolic events are independently associated with 30-day mortality. Hematoma expansion was also associated with poor functional outcomes 30 days post-event.

The ANNEXa-I trial investigated the effect of a new reversal agent (Andexanet alfa) in the treatment of oral Factor Xa (FXa) inhibitor in patients experiencing an intracerebral haemorrhage (ICH) versus usual care. The drug was shown to reduce the occurrence of hematoma growth, but also resulted in more thromboembolic events than in the standard of care group.

In this secondary analysis the authors used a time-dependent regression analysis combining the data from both trial arms and found that the occurrence of hematoma growth and of thromboembolic events were associated with increased 30-day mortality with a Hazard Ratio of 2.98 and 3.33, respectively.

In a second analysis using a landmark approach, which included all events of haematoma expansion and thromboembolic events across both trial arms occurring up to day 5, haematoma expansion was significantly associated with worse functional outcome. There was no association between thromboembolic events and functional outcome, but the interpretation of this result is limited given the low event rate of thromboembolic complications in the first 5 days. Overall, haematoma expansion was four times more frequent than thromboembolic complications.

Professor David Seiffge, one of the lead authors of the study from Bern, Switzerland commented, “One in three anticoagulant-related intracerebral haemorrhage patients will experience haematoma expansion, which is in turn associated with a three-fold increase in mortality and survivors suffer from significant disability. This new analysis demonstrates that prevention of haematoma expansion is a priority for treatment of these patients, and will help to support clinicians in their benefit/risk analysis.”

ICH, a subtype of stroke, accounts for 10-15% of strokes across Europe, but is responsible for half of the stroke-related morbidity and mortality. Advancements in treatment have been slower than for ischemic stroke. Anticoagulant-related ICH becomes increasingly common with increasing prescription of anticoagulants drugs in the community. Factor Xa inhibitors, the most prescribed anticoagulant type, has up to now been lacking an effective antidote. A drug that convincingly prevents hematoma expansion is a breakthrough for anticoagulant-related ICH treatment. A downside of the treatment is the increased risk of thromboembolic complications, the clinical consequences of which were previously unknown.

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1. CLINICAL CONSEQUENCES OF HAEMATOMA EXPANSION AND THROMBOEMBOLIC EVENTS IN PATIENTS WITH FACTOR XA-INHIBITOR ASSOCIATED ICH IN ANNEXA-I. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

Flipping the SWITCH on intracranial haemorrhage

(15 May 2024, Basel, Switzerland) SWITCH, a landmark international, randomised clinical trial, has provided new insights into the treatment of severe intracerebral hemorrhage.[1] Conducted across 42 leading stroke centers in Europe, the study explored the potential benefits of decompressive craniectomy in improving outcomes for patients suffering from spontaneous severe deep intracerebral hemorrhage.

Recent studies suggest some benefits from early minimally invasive surgical evacuation for selected patients with superficial brain hemorrhages. However, effective treatment of deep brain hemorrhages has remained a major unresolved issue and up to now surgical evacuation has not shown to decrease disability or death.

In patients with malignant brain infarcts, decompressive hemicraniectomy – a surgical procedure during which part of the skull on the affected side is lifted – has been shown to improve long-term outcomes by preventing secondary brain damage. However, prior to SWITCH, the effect of decompressive hemicraniectomy on long-term outcome in patients with deep brain hemorrhages was uncertain.

SWITCH enrolled adults aged 18 to 75 with severe deep intracerebral hemorrhage affecting critical areas of the brain and assigned patients to decompressive craniectomy plus optimal medical treatment or optimal medical treatment alone. The primary outcome assessed the proportion of patients who were bedridden or deceased at 6 months. Despite being halted prematurely due to funding constraints, the trial enrolled 201 individuals.

SWITCH revealed a notable difference in outcomes between the groups. 42% of participants receiving the new, combined treatment were bedridden or deceased after 6 months, compared to 58% in the group receiving only medical treatment. Notably, adverse events did not significantly differ between the groups.

SWITCH provides weak evidence that decompressive surgery plus optimal medical treatment might be superior to optimal medical treatment alone. Although statistical significance was not reached, possibly due to the early termination, the study highlights a substantial estimated effect size compared to previous research, and a high degree of certainty of benefit of the intervention.

It's important to recognise that these findings may not universally apply to all types of intracerebral hemorrhage, such as superficial hemorrhages and smaller hemorrhages of the deep brain areas. Moreover, both treatment groups still exhibited high rates of severe disability and death.

SWITCH shows that decompressive craniectomy in people with severe deep intracerebral haemorrhage is a potential treatment option for people with otherwise no other evidence-based treatment option. Furthermore, SWITCH underscores the urgent need for further research to optimise treatment strategies for severe deep intracerebral hemorrhage, a condition with significant morbidity and mortality.

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References:

1. SWISS TRIAL OF DECOMPRESSIVE CRANIECTOMY VERSUS BEST MEDICAL TREATMENT OF DEEP SUPRATENTORIAL INTRACEREBRAL HAEMORRHAGE (SWITCH). Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

New evidence for the use of anti-inflammatory therapy in the prevention of recurrent vascular events in stroke

(15 May 2024, Basel, Switzerland) In the international CONVINCE trial, presented today at the European Stroke Organisation Conference (ESOC) 2024, anti-inflammatory treatment with long-term colchicine did not reduce rates of recurrent stroke and cardiovascular events in patients with non-cardioembolic stroke in the primary intention-to-treat analysis.[1] Reduced event rates in secondary analyses, and in the subgroup of patients with coronary artery disease, support trials which reported benefit in coronary disease and may inform future secondary prevention trials in stroke.

Inflammation plays an important role in the pathophysiology of atherosclerosis. Over the past years, several trials have shown that anti-inflammatory treatment reduces recurrent vascular events in coronary artery disease, while no such evidence is available for stroke. Colchicine is an established drug to reduce inflammatory response and widely available at low-cost.

CONVINCE was an international, randomised, open-label trial designed to test whether long-term colchicine (0.5 mg/day) in addition to standard of care reduces recurrent stroke or cardiovascular events in patients with non-cardioembolic ischaemic stroke or high-risk transient ischaemic attack (TIA). The primary endpoint was a composite of first recurrent ischaemic stroke, myocardial infarction, cardiac arrest or hospitalisation for unstable angina. Over period of almost 6 years and despite constraint imposed by the COVID-19 pandemic, 3,154 patients were randomised and followed for a median of 34 months.

In the intention-to-treat analysis, the primary endpoint occurred in 153 patients randomised to colchicine (9.8%) compared with 185 on usual care (11.8%), which translated into incidence rates of 3.32 versus 3.92/100 person-years. The adjusted hazard ratio was 0.84 (95% confidence interval 0.68-1.05, p=0.12). Reduced levels of CRP in the colchicine group showed the anti-inflammatory effect of treatment with colchicine. In the pre-specified on-treatment analysis, as well as in the subgroup of patients with a history of coronary artery disease, significantly reduced rates of recurrent stroke or cardiovascular events were observed.

Professor Peter Kelly, the principal investigator of CONVINCE, commented, “Although the primary analysis was neutral, the signals of benefit of colchicine on secondary analyses are in line with findings from previous trials and indicate the potential of colchicine in prevention after stroke. In CONVINCE, the COVID pandemic reduced the planned follow-up time, which led to under-powering for the primary analysis by 8%. Further trials are needed in all stroke subtypes, but with particular focus on patients with objective evidence of atherosclerosis.”

In conclusion, although the primary endpoint was neutral, the results CONVINCE support the hypothesis that long-term anti-inflammatory therapy with colchicine may reduce recurrent stroke and cardiovascular events specifically in stroke patients with atherosclerosis.

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References:

1. Kelly P, Weimar C, Lemmens R, et al. COLCHICINE FOR PREVENTION OF VASCULAR INFLAMMATION IN NON-CARDIOEMBOLIC STROKE (CONVINCE). A RANDOMISED CONTROLLED TRIAL. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.

Perispinal administration of etanercept, an anti-inflammatory drug, did not improve quality of life in chronic stroke patients

(15 May 2024, Basel, Switzerland) An international study has found no evidence to support use of an arthritis medication sometimes prescribed 'off-label' to patients living with the long-term disabling effects of stroke.[1]

Etanercept, an anti-inflammatory drug targeting tumor necrosis factor, received attention from the stroke survivor community after previous studies pointed towards drastic decreases in post-stroke disability.

However, in presenting its findings today at the European Stroke Organisation Conference (ESOC) 2024, the Perispinal Etanercept to improve STroke Outcomes (PESTO) study found no evidence of any benefit.

PESTO was a phase 2b, international, randomised, placebo-controlled trial, patients with a stroke 1 to 15 years prior to enrollment and a current functional outcome score of at least 2 on the modified Rankin scale, were randomised to a perispinal injection of etanercept or placebo. The researchers primarily focused on the quality of life (QoL) as measured using the Short Form 36 Health Inventory (SF36-HI) at 28 days after injection, but also assessed safety outcomes, functional outcome, fatigue, anxiety and depression, and the effects of an additional dose of etanercept.

In total, 63 patients were randomized to perispinal etanercept and 63 patients to placebo. By 28 days, 53% of the patients in the etanercept group experienced an improvement with 5 points on the SF36-HI versus 58% in the placebo group. (Adjusted Odds Ratio: 0.82; 95% Confidence Interval 0.40-1.67). The rates of serious adverse outcomes were low with 1 reported in each group by day 28. No signals of benefit or harm were seen in the secondary outcome measures, including the second dose analysis.

Professor Thijs, one of the lead investigators, from The Florey and the University of Melbourne, Australia, said PESTO provided important evidence for clinicians. "We can give the stroke survivor community a scientific answer to the question they raised themselves. The trial was very clear in showing no signal at all. That is also an important take-to-the-clinic message."

Improving life after stroke is a key priority according to the Stroke Action Plan for Europe 2018-2030, but very few medical post-stroke treatment options are available. Etanercept targets tumor necrosis factor, a pro-inflammatory factor which may remain elevated in the central nervous system following stroke due to activated microglia.

Unfortunately, as etanercept has a high molecular weight, it does not cross the blood brain barrier when given systemically. A proposed solution for this problem is to inject it perispinally, followed by a supine, head down position. Although this strategy remains controversial, perispinal etanercept has received a lot of attention from the stroke survivor community because of previous studies pointing towards drastic increases in post-stroke disability.

Professor Thijs said the trial had a unique design. "First of all, this trial was patient-driven, as many stakeholders believe in the potential of etanercept. Second, as the drug is already being applied for a diverse group of stroke survivors, we aimed to mimic this real-world experience by including patients up to 15 years after their stroke and applying the exact same method of perispinal injection as is done in private clinics."

Ms Brooke Parsons, the consumer member of the PESTO Steering Committee adds: “The trial's consumer-driven approach highlights the demand for innovative healthcare solutions. However, the neutral findings offer clarity, addressing the anticipation for answers and emphasising the significance of scientific rigor in assessing potential treatments amidst previous uncertainty."

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References:

1. THIJS V, CLOUD G, GILCHRIST N, *ET AL.* A MULTICENTER RANDOMIZED PLACEBO-CONTROLLED TRIAL, TO DETERMINE SAFETY AND EFFICACY OF PERISPINAL ETANERCEPT ON QUALITY OF LIFE. Presented at the European Stroke Organisation Conference; 15 May 2024; Basel, Switzerland.