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**Embargoed: 12:30 CEST, Thursday, 25 May 2023**

## ESOC 2023 Plenary Highlights: Thursday 25 May 2023

### The effect of randomisation to tight or less tight blood pressure control, and to intensive or conventional blood glucose control on 44-year incidence of stroke or dementia: the UKPDS Trial

***The effect of intensive blood pressure and glucose lowering on developing dementia in people with diabetes - the long term follow up of the UK Prospective diabetes study.*[1]**

People with diabetes have a two-thirds greater risk of dementia than people without diabetes. Blood-pressure-lowering and glucose-lowering have been suggested as treatments to reduce this risk. However, dementia takes many years to develop and most studies of treatments are not long enough to detect any effect.

The UK prospective diabetes study started in 1977 and tested blood-pressure-lowering and glucose-lowering treatments for up to 10 years in 5102 people with newly diagnosed diabetes.

The study observed what had happened to study participants over the 44 years since the study's inception. Data was collected by the UK National Health Service on hospital admissions and other care, with this approach allowing the researchers to observe study participants without needing to contact them. By the end of the study, approximately 13% of participants had developed dementia.

The study did not show that blood-pressure-lowering or glucose-lowering reduced the risk of dementia. The results were consistent with either a modest increase or a modest reduction in dementia risk with the treatments. A larger participant pool could have provided more conclusive results.

By using records collected by the health system, the researchers were able to test the long-term effects of treatments at a modest cost. It is hoped that this method can be used in future studies in Europe and around the rest of the world.

The study was led by researchers at the University of Oxford and the University of Edinburgh. The study was supported by the original UKPDS funders, the Nuffield Department of Population Health, the Diabetes Trials Unit and the Chief Scientist's Office, Scotland.

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**References:**


1. Whiteley W, *et al.* UKPDS Trial: The effect of randomisation to tight or less tight blood pressure control, and to intensive or conventional blood glucose control on 44-year incidence of stroke or dementia. Presented at the European Stroke Organisation Conference; 25 May 2023; Munich, Germany.

## Early minimal invasive surgery versus medical management in patients with intracerebral haemorrhage: the ENRICH trial

***Is minimal invasive surgery, if started early, effective and safe in patients with spontaneous supratentorial intracerebral haemorrhage (ICH)? Or does standard medical management remain the best care approach for ICH? In the ENRICH (Early MiNimally-invasive Removal of ICH) trial, 300 ICH patients were randomised to undergo minimally invasive trans-sulcal parafascicular surgery (MIPS) for ICH clot evacuation or receive medical management alone within 24 hours after symptom onset. The results of the trial are promising.[1]***

In contrast to ischemic stroke, there are few acute treatment options with proven benefit for patients with ICH. Standard medical care, consisting of admission to a stroke unit, coagulopathy reversal, and blood pressure control, are all recommended by current guidelines. Several large clinical trials have assessed the effect of surgical treatment, including both craniotomy and minimally invasive surgery, but failed to demonstrate a beneficial effect on functional outcome. In part, this may be explained by the long time from symptom onset to start of surgery (>30 hours) and the disadvantages associated with standard craniotomy. Given this equipoise about the role of surgery in supratentorial ICH, several new trials have been set up to compare minimally invasive ICH clot evacuation with standard medical management within different time windows.

The ENRICH trial compared medical management (MM) to minimal invasive trans-sulcal, parafascicular surgical (MIPS) ICH clot evacuation with the BrainPath® and Myriad® devices, started within 24 hours of symptom onset. The study was an adaptive Bayesian design that permitted enrichment of a pre-specified ICH population (anterior basal ganglia [ABG] vs lobar). The primary outcome was a functional outcome (utility-Weighted modified Rankin Scale [uW-mRS]) at 6 months. Patients were block randomised according to ICH location (ABG or lobar) and Glasgow Coma Scale (GCS). After enrolling 175 patients, the population was enriched to focus only on the lobar population.

In total, 300 patients from 37 centres in the United States were randomised to early MIPS ICH clot evacuation or medical management, with complete follow-up in 286 patients. Of patients randomised to clot evacuation (150), the Bayesian primary analysis compared the mean UWmRS at 6 months between treatment groups, with an estimated mean UWmRS of 0.374 for the MM and 0.458 for the MIPS group, with a difference of 0.084. The Bayesian posterior probability of superiority of the intervention was 0.9813, which exceeded the pre-specified 0.975 threshold to claim superiority of MIPS versus MM. The overall benefit of MIPS appears to be from the strong positive effect observed for participants with lobar ICH.

“This is the first trial to demonstrate functional benefit in surgical clot evacuation among patients with supratentorial ICH,” says Alex Hall, co-investigator at Emory University. “As we continue to understand the data collected in the ENRICH trial, we are excited at the possibilities and future ICH management.”

“We are grateful to the dedicated teams from the 37 participating centres. MIPS was safe, resulted in substantial clot evacuation, and improved functional outcome at 6 months. The

data from this trial will help inform future ICH research and practice," says Jonathan Ratcliff, co-investigator at Emory University.

**ENDS**

**References:**


1. Hall A, *et al.* Very early minimally invasive removal of intracerebral hemorrhage: the ENIRCH trial. Presented at the European Stroke Organisation Conference; 25 May 2023; Munich, Germany.

## The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT3)

***Does the implementation of a goal-directed care bundle incorporating protocol for early intensive blood pressure lowering and management algorithms for hyperglycaemia, pyrexia, and abnormal anticoagulation improve outcomes for patients with acute spontaneous intracerebral hemorrhage?***

INTERACT3 was a pragmatic, international, multicentre, blinded endpoint, stepped wedge cluster (hospital) randomised controlled trial conducted at sites in 9 low- and middle-income countries and 1 high-income country.[1] The care bundle protocol included early intensive lowering of systolic blood pressure, strict glucose control, antipyrexia treatment, and rapid reversal of warfarin-related anticoagulation within 1 hour in patients where these parameters were abnormal.

A total of 7036 patients from 121 hospitals were enrolled in the modified intention-to-treat population. Among them, 3221 patients were assigned to the 'care bundle' group, while 3,815 patients were assigned to the 'usual' care group. The care bundle group demonstrated a significantly lower likelihood of a poor functional outcome (common odds ratio of 86). The favourable shift in modified Rankin scale scores in the care bundle group was consistent across a range of sensitivity analyses that included additional adjustments for country and patient variables, as well as different approaches to multiple imputations for missing data. Patients in the care bundle group experienced fewer serious adverse events than those in the usual care group (16% vs. 20%; p=0.01).

Professor Anderson, the study author from The George Institute for Global Health, concluded that implementation of a care bundle protocol for intensive blood pressure lowering and other management algorithms for physiological control within several hours of the onset of symptoms resulted in improved functional outcome for patients with acute intracerebral haemorrhage. He recommended that hospitals should incorporate this approach into clinical practice as part of active management for this serious condition.

**ENDS**

View a summary presentation by the Principal Investigator here

**References:**


1. Anderson C, *et al*. The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT3). Presented at the European Stroke Organisation Conference; 25 May 2023; Munich, Germany.

# Immediate revascularization versus optimized medical therapy alone in patients with carotid stenosis at low to intermediate risk of stroke: interim results of ECST-2

***Will patients with carotid stenosis >50% at low or intermediate risk of stroke benefit from additional carotid revasculatisation when treated with optimised medical therapy?***

The 2nd European Carotid Surgery Trial (ECST-2) hypothesised that in patients with carotid stenosis ≥50% at low to intermediate risk of stroke, there will be no benefit from additional carotid revascularisation when treated with optimised medical therapy (OMT).[1]

Based on randomised trials that started over 30 years ago, carotid endarterectomy is currently recommended for patients with recently symptomatic carotid stenosis ≥50%. Since these original trials, medical treatment has improved significantly.

ECST-2 was designed as a prospective, randomised, controlled, open, multicentre, clinical trial with blinded outcome adjudication. Patients were randomised between immediate carotid revascularisation plus optimised medical therapy versus optimised medical therapy alone. Suitable patients were those with an asymptomatic or symptomatic carotid stenosis ≥50% with an estimated 5-year risk of stroke of less than 20%, calculated using the Carotid Artery Risk score. Recruitment was stopped after inclusion of 428 patients. For the composite endpoint, the 2-year rate of any stroke, myocardial infarction or periprocedural death, the hazard ratio of optimised medical therapy alone in comparison to optimised medical therapy plus revascularization was 0.96 (95% CI 0.53-1.76).

From this interim analysis, ECST-2 investigators concluded that in patients with carotid stenosis ≥50% and a low to intermediate predicted risk of stroke, treated with optimised medical therapy, there was no evidence of benefit from additional carotid revascularization at two years. A complete 2-year analysis including MRI endpoints, and longer clinical follow-up (planned up-to 5 years), will follow.

**ENDS**

View a summary presentation by the Principal Investigator here

**References:**


1. Nederkoorn P, *et al.* Immediate revascularisation versus optimised medical therapy alone in patients with carotid stenosis at low to intermediate risk of stroke: interim results of ECST-2. Presented at the European Stroke Organisation Conference, 25 May 2023; Munich, Germany.

## Effects of amlodipine and other blood pressure lowering agents on microvascular function in small vessel diseases: Results of TREAT-SVD

***In patients with cerebral small vessel disease (SVD), blood pressure (BP) lowering may differentially affect cerebral vascular reactivity depending on the BP lowering drug used.***

Professor Martin Dichgans, from the Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Germany, presented the main results of the TREAT-SVD trial, which aimed to determine whether antihypertensive drug classes differentially affect microvascular function in people with small vessel diseases (SVDs).

TREAT-SVDs - an EU Horizon 2020 project, was a multicentre, randomised, open-label, three-period-crossover phase-3 trial with blinded endpoint assessment (PROBE).[1] From February 2018 to April 2022 101 participants (75 with sporadic SVD, 64. 9±9.9years; 26 with CADASIL, a hereditary type of SVD, 53.1±7.0years) with an indication for antihypertensive treatment were enrolled.

Participants were randomly assigned (1:1:1) to one of three sequences of antihypertensive treatment: a two-week washout period followed by three four-week periods of amlodipine, losartan, or atenolol. The primary endpoint was change in cerebrovascular reactivity determined by BOLD-MRI response to hypercapnic challenge (ΔCVR) in normal appearing white matter from end of washout to the end of each treatment period. ΔCVR in CADASIL patients improved with amlodipine compared with atenolol and with losartan compared with atenolol, whereas there was no significant treatment effect in the overall group of sporadic patients.

In an exploratory subgroup analysis, there was a statistically significant treatment effect in sporadic participants aged < 60 years which was similar to that observed in CADASIL patients. ΔCVR in participants with sporadic SVD aged < 60 years improved with amlodipine compared with atenolol and with losartan compared with atenolol. The secondary endpoints were changes in mean systolic blood pressure (BP) and BP variability from end of washout to the end of each treatment period. All drugs lowered BP to a similar extent. BP variability decreased with amlodipine compared with atenolol and with losartan compared with atenolol in both sporadic and CADASIL patients.

Aside from demonstrating an antihypertensive drug class effect on cerebral microvascular function, the trial highlights the importance of including patients with rare hereditary subtypes of common diseases in clinical trials of sporadic disease and of performing separate analyses for these patients. Whether antihypertensive drug classes differentially affect clinical outcomes in people with SVDs requires further research.

**ENDS**

View a summary presentation by the Principal Investigator here

**References:**


1. Dichgans M. *et al.* Effects of amlodipine and other blood pressure lowering agents on microvascular function in small vessel diseases (TREAT-SVDs): Main trial results. Presented at the European Stroke Organisation Conference; 25 May 2023; Munich, Germany.