PRESS RELEASE

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Remote ischemic conditioning in patients with acute stroke: a multicentre, randomised, patient-assessor blinded, sham-controlled study (RESIST)

Remote ischemic conditioning did not improve the functional outcome in patients with acute ischemic stroke.[1]

The RESIST study is a multicentre, prospective, randomised, patient-assessor blinded, sham-controlled trial that assesses the efficacy of remote ischemic conditioning (RIC) to improve the functional outcome at 90 days in patients with acute stroke.

A total of 1500 patients suspected of having an acute stroke were enrolled in the study. Patients were randomly assigned to RIC or sham that was started in the ambulance and continued during hospital admission. Notably, half of the patients were included in the first hour after symptom onset. After excluding 149 (10%) patients with transient ischemic attack and 382 (27%) patients with a stroke mimic, the target population was represented by 902 patients (436 treated with RIC and 466 with sham) with a confirmed diagnosis of ischemic or haemorrhagic stroke. The treatment with RIC was not associated with a shift toward better functional outcome at 90 days (odds ratio, 1.05; 95% confidence interval, 0.83-1.33, p=0.67), which represented the primary endpoint of the study. RIC was not superior to sham in other key secondary endpoints. There were no safety issues related to the intervention.

The results from the RESIST trial failed to demonstrate the efficacy of early conditioning in acute stroke. However, subgroup analysis of the study is warranted to explore possible subsets of patients that could benefit from RIC and design more individualised trials in the future.

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View a summary presentation by the Principal Investigator here

References:

1. Blauenfeldt R, *et al.* Remote ischemic conditioning in patients with acute stroke: a multicentre, randomised, patient-assessor blinded, sham-controlled study (RESIST). Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.

Efficacy and safety of tenecteplase in patients with late-window acute ischaemic stroke and evidence of salvageable tissue: Results from the phase III TIMELESS trial

New evidence to test the use of Tenecteplase in selected stroke patients with large artery occlusion who presented between 4.5 and 24 hours.[1]

There is increasing evidence that intravenous thrombolytic therapy can improve outcome in selected patients even beyond the traditional 4.5-hour time window. The phase 3 double blind randomised, placebo controlled TIMELESS study sought to investigate if tenecteplase administered in ischemic stroke patients with large vessel occlusion presenting between 4.5 and 24 hours after last known well time would improve clinical outcome as measured by modified Rankin Scale (mRS) at day 90.

Patients meeting eligibility criteria of internal carotid artery occlusion or middle cerebral artery segment 1 or 2 occlusion and presented with salvageable tissue on imaging were randomised 1:1 to either intravenous tenecteplase (0.25mg/kg; maximum, 25mg) or placebo. The study enrolled 458 patients. In addition to the primary endpoint of mRS score at day 90, several secondary endpoints regarding clinical and safety outcomes were analysed.

Among the 458 included patients, 228 patients were included in the Tenecteplase group, and 230 were included in the placebo group. The proportion of patients treated with mechanical thrombectomy were similar between the two treatment arms.

The study completion rate was higher than 96% in both treatment arms. There was no significant difference in baseline demographics or clinical stroke data on vessel occlusion, stroke severity measured by NIHSS or performed diagnostics between the groups.

The primary endpoint analyses showed no significant difference in the odds of a lower mRS at day 90. The common OR was 1.13 (0.81-1.56, p=0.48). The percentage of patients achieving a favourable outcome, defined as an mRS of 0-2 was not significantly different between the treatment groups, 46% vs 42% (nominal p=0.41).

There were no significant safety issues, and the risk of bleeding was not significantly increased in the Tenecteplase group. The secondary endpoint of complete recanalization at 24hours post randomization was higher in the Tenecteplase group with 76.7% compared to 63.9% in the placebo group. (p=0.006).

In conclusion, the primary endpoint of improved clinical outcome in patients treated with Tenecteplase in the 4.5 to 24 hour time window was not met. There were no safety issues, and the number of intracranial hemorrhages and fatal adverse events were low and balanced between the two treatment arms.

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References:

1. Albers G.W, et al. Efficacy and safety of tenecteplase in patients with late-window acute ischaemic stroke and evidence of salvageable tissue: Results from the phase III TIMELESS trial. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany

The PRECIOUS randomised trial: prevention of infections and fever to improve outcome after stroke

Monitoring of body temperature and prevention of aspiration pneumonia are important components of stroke unit care, but it is uncertain whether these contribute to the observed benefit of such organised care. Is there room to implement preventive antibiotic, antiemetic, or antipyretic treatment in clinical practice?

Infections and fever frequently occur following stroke, particularly in older patients. These post-stroke complications are associated with an increased risk of death and poor functional outcome. Whether or not preventive antibiotic or antipyretic treatment can improve functional outcome in patients with acute stroke has been the subject of previous studies, including three large randomised clinical trials. In these trials, preventive antibiotic or antipyretic treatment did not improve functional outcomes, but these were performed in broad populations that encompassed patients with a low risk of post-stroke complications, thereby reducing the potential for benefits from these interventions. The PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke (PRECIOUS) trial was the first large-scale, randomised trial to assess both the effect of the prevention of infections and that of fever in patients with acute stroke.

The PRECIOUS trial was an international, multi-centre, 3 × 2 factorial, randomised, controlled, open-label clinical trial with blinded outcome assessment.[1] Eligible patients were aged 66 years or older with moderately severe to severe ischaemic stroke or intracerebral haemorrhage. The trial tested if prevention of infections or fever with metoclopramide, ceftriaxone, paracetamol, or any combination of these, in the first 4 days after stroke onset improved functional outcome at 90 days.

From April 2016 to June 2022 PRECIOUS enrolled 1493 patients from 67 European sites. After excluding patients who withdrew consent or were lost to follow-up, 1471 patients were included in the intention-to-treat analysis. Preventive use of the medication mentioned above did not reduce the risk of a poor functional outcome at 90 days.

The results of PRECIOUS do not support preventive use of anti-emetic, anti-pyretic or anti-biotic drugs in older patients with acute stroke.

Professor Bart van der Worp commented, “Contrary to what I had expected, medication to prevent infections and fever after stroke did not lead to better functional outcomes. This is unfortunate because the widely available, safe, and inexpensive drugs we tested could without any problem have been prescribed to tens of thousands of stroke patients worldwide.”

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References:

1. de Jonge J, *et al.* Prevention of complications to improve outcome in elderly patients with acute stroke (PRECIOUS): A randomised, open, phase III, clinical trial with blinded outcome assessment. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.

Study suggests starting anticoagulation early after an ischemic stroke may be as safe and better at preventing further events than delaying

An international clinical trial demonstrates that in people with ischemic stroke and atrial fibrillation, anticoagulation can safely be started earlier than currently recommended by guidelines. The chances of suffering a recurrent ischemic stroke with earlier treatment are likely to be lower, without any increased risk of bleeding complications.[1]

Around 80% of all strokes are caused by occlusion of an artery in the brain. Up to 20% of these are caused by blood clots, which form in the heart in people with atrial fibrillation. Atrial fibrillation is an irregular heart rhythm that affects as many as 5% of people over the age of 65 years. Blood thinners called direct oral anticoagulants (DOACs) are used to prevent blood clots in people with atrial fibrillation but it is unclear how early after stroke they should be started. There is a potential increased risk of bleeding into the stroke which may be highest in the first few days. However, the potential benefit of these drugs may also be highest in these first few days. In the presence of this uncertainty, international guidelines recommend a delay before starting DOACs.

Can DOACs be safely started early after an ischemic stroke?

A new international clinical trial led by the Stroke Center, Inselspital, University Hospital Bern, and the University of Bern has addressed this controversy. The results of the ELAN (Early versus Late initiation of direct oral Anticoagulants in post-ischemic stroke patients with atrial fibrillatioN) trial were published in the latest issue of the renowned medical journal "The New England Journal of Medicine".[2] The study shows that the chances of suffering a recurrent event with early treatment are likely to be lower compared to a later start, without an increase in risk of complications.

The study included 2013 participants with an acute ischemic stroke and atrial fibrillation recruited from 103 different stroke units in 15 different countries in Europe, the Middle East and Asia between 2017 and 2022. Based, on the size and location of the infarct on imaging (i.e. a minor, moderate or major stroke) participants were randomly assigned to an early treatment start or a later, guideline recommended, treatment start. An early start was defined as within 48 hours of a minor/moderate stroke or day 6–7 following a major stroke. A late start was defined as day 3–4 following a minor stroke, day 6–7 following a moderate stroke, or day 12–14 following a major stroke. The primary outcome was a composite of recurrent ischemic stroke, symptomatic intracranial hemorrhage, extracranial bleeding, systemic embolism, or vascular death within 30 days after randomisation.

At 30 days, the primary outcome occurred in 29 (2.9%) people in the early and 41 (4.1%) in the late treatment group (risk difference -1.2%, 95% confidence interval for risk difference -2.8% to 0.5%). At 90 days the difference in rate of the composite outcome was -1.9% (95% CI -3.8% to -0.02%). Recurrent ischemic stroke at 30 days occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the late-treatment group and symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups.

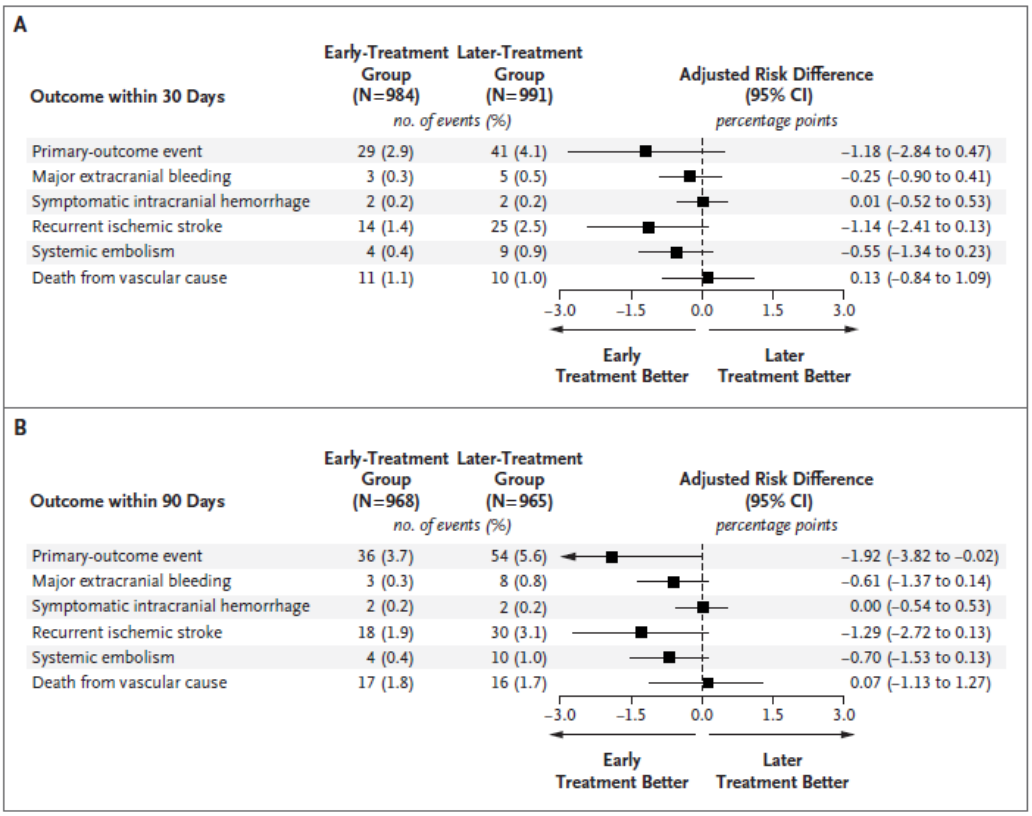

Figure 2. The Primary Composite Outcome and Its Components at 30 and 90 Days.

Shown are point estimates (squares) and two-sided 95% confidence intervals (horizontal bars) for the treatment effect, which was defined as a risk difference between the trial groups (early initiation of DOAC minus later initiation of DOAC). The absolute and relative numbers of events in each group are shown. The risk difference is derived from a penalized logistic regression adjusted for stratification factors. The widths of the confidence intervals were not adjusted for multiple comparisons, and the reported confidence intervals should not be used for hypothesis testing.

"Our study finally brings scientific evidence for a common dilemma in early secondary prevention after an ischemic stroke. In view of our results, early treatment initiation is reasonable if indicated or if desired for logistic or other reasons. It is probably better and is unlikely to cause harm", commented the study leader Prof. Dr med. Urs Fischer from the University Hospitals of Bern and Basel. Prof. Dr med. Jesse Dawson from the University of Glasgow added. "The study also suggests that the incidence of symptomatic intracerebral hemorrhage is low with early anticoagulation if imaging based classification is used ".

As a next step, the researchers plan to explore whether the risk and benefit is similar in different subgroups of the ELAN trial population, especially in people more severely affected.

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View a summary presentation by the Principal Investigator here

References:

1. Fischer U and Dawson J, *et al.* Early vs late anticoagulation in stroke patients with atrial fibrillation. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.
2. Fischer U, *et al.* Early versus Late Anticoagulation for Stroke with Atrial Fibrillation. N Engl J Med. 2023; doi: 10.1056/NEJMoa2303048.

Primary results of the AtRial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) randomised trial

Does anticoagulation reduce future stroke in patients with atrial cardiopathy and cryptogenic stroke compared to current treatment with antiplatelet therapy?

One in three ischaemic strokes do not have any cause identified after standard investigations and they are called cryptogenic strokes. A large proportion of cryptogenic strokes are embolic strokes of undetermined source (ESUS). Current clinical practice is to treat these patients with a blood thinner such as aspirin, a type of antiplatelet therapy. However, this treatment might not be adequate, as a significant proportion of patients with cryptogenic stroke will have another stroke whilst taking this treatment. Anticoagulants are a stronger type of blood thinner and have been shown to be better at preventing recurrent stroke in patients with atrial fibrillation (AF) (i.e. an irregular heartbeat) despite a higher risk of bleeding. However, only a minority of patients with cryptogenic strokes ultimately show any evidence of AF. How best to treat patients with cryptogenic stroke without AF remains a big clinical challenge.

Emerging data suggest atrial cardiopathy (an abnormal left atrium) might also cause clots in the absence of AF. Some patients with cryptogenic strokes might have atrial cardiopathy and may therefore benefit from anticoagulation due to the shared pathophysiology between atrial cardiopathy and AF.

ARCADIA is an investigator-initiated, multicentre trial and is the first trial to shed light on treatment options in patients with atrial cardiopathy but no known AF and otherwise cryptogenic strokes.[1] The primary objective of the trial is to test if oral anticoagulation (i.e. apixaban) is better than aspirin (an antiplatelet therapy used in current practice) for the prevention of recurrent strokes in this patient population.

In the study, all patients had cryptogenic stroke and markers of atrial cardiopathy, defined using a blood biomarker, an electrocardiogram (ECG) marker or a marker on echocardiogram. AF was ruled out at baseline with a 12-lead ECG and ≥24h continuous heart-rhythm monitoring. Patients received either apixaban 5mg twice a day or aspirin 81mg four times a day in a double-blind fashion.

Overall, 1015 participants were recruited from 185 centres in the US and Canada between 2018 and 2022 when the trial was halted after a planned interim analysis (target number of participants was 1100). The mean age was 68 years, 54% were female and the average follow-up was 1.8 years.

Compared to aspirin, apixaban did not reduce the risk of the primary outcome of recurrent stroke (HR, 1.00; 95% CI, 0.64-1.55) or the secondary outcomes of ischemic stroke or systemic embolism (HR, 0.92; 95% CI, 0.59-1.44) or recurrent stroke or death (HR, 1.08; 95% CI, 0.76-1.52). The rates of the primary safety outcomes of symptomatic intracranial haemorrhage were not higher with apixaban (0 cases) than with aspirin (7 cases), and apixaban did not increase the risk of major haemorrhage (HR, 1.02; 95% CI, 0.29-3.51) or all-cause mortality (HR, 1.53; 95% CI, 0.63-3.74).

“ARCADIA is the first randomized trial to test the concept of atrial cardiopathy as a risk factor for stroke. Our findings may mean that there is no thrombogenic atrial cardiopathy in the absence of AF, that our biomarkers or thresholds were suboptimal, or that the trial lost power due to inadequate study drug adherence or high rates of crossover after AF detection. Further analyses of the ARCADIA data will shed light on these potential explanations. In the meantime, clinicians should be aware that no successful strategy of anticoagulation has yet been found for secondary stroke prevention after ESUS,” commented Dr Kamel, one of the principal investigators of ARCADIA along with Drs. Elkind, Longstreth, and Tirschwell.

ENDS

View a summary presentation by the Principal Investigator here

References:

1. Kamel H, *et al.* Primary results of the AtRial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) randomised trial. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.

SECRET: Study of rivaroxaban in CeREbral venous Thrombosis

Are direct oral anticoagulants (DOACs) a suitable choice for anticoagulation for cerebral venous thrombosis (CVT)?

The guideline-recommended therapy for CVT is vitamin K antagonist anticoagulation. Emerging data suggest that DOACs may be a suitable choice for anticoagulation for CVT, but adequately powered randomised trial data are lacking. The Study of rivaroxaban in CeREbral venous Thrombosis (SECRET) trial evaluated the feasibility of recruitment for a trial of a rare disease, safety of anticoagulation with rivaroxaban compared to standard-of-care therapy, and functional outcomes following CVT.[1]

SECRET is a Phase II, prospective parallel arm, open-label, blinded endpoint trial.[1] Individuals aged >18 with a neuroimaging-confirmed diagnosis of CVT within the last 14 days were randomised 1:1 to receive rivaroxaban 20 mg daily versus standard-of-care anticoagulation (warfarin or low molecular-weight heparin) for 180 days, with optional extension up to 365 days.

Fifty-five participants were randomised (27 rivaroxaban; 28 standard-of-care). Median age was 48 years and 66% were female. There was one primary event (symptomatic intracranial haemorrhage), two clinically relevant non-major bleeding events, and one recurrent CVT by day 180, all in the rivaroxaban group. Despite 72% of participants having a modified Rankin Scale score of 0 to 2, at enrolment, both groups on average reported reduced quality of life, low mood, fatigue, and headache with impaired cognitive performance. All metrics improved markedly by day 180.

The study author, Dr. Field, concluded that engagement of multiple sites across Canada led to effective recruitment of trial participants for a rare stroke type. There were numerically more bleeding events in patients taking rivaroxaban compared to standard of care, but rates of bleeding and recurrent venous thromboembolism were low overall and in keeping with previous studies. Participants had symptoms affecting their well-being at enrolment, but they improved over time.

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References:

1. Field T, *et al*. SECRET: Study of rivaroxaban in CeREbral venous Thrombosis. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.

Isosorbide mononitrate, cilostazol and their combination for one year: Effect on cognitive outcomes in patients with small vessel stroke – the LACunar Intervention trial-2 (LACI-2)

Isosorbide mononitrate (ISMN) alone or in combination with cilostazol improved cognitive functions in the follow-up of patients with a lacunar stroke.[1]

LACI-2 was a randomised, open-label, blinded-endpoint, 2x2 factorial trial assessing ISMN and/or cilostazol in patients with clinical lacunar ischaemic stroke compatible with brain imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]), which demonstrated to be feasible in the primary analysis. Cognitive outcomes were assessed centrally by telephone call and blinded to drug at one-year follow-up. The cognitive tests included Montreal Cognitive Assessment (MOCA), Cognitive Status (TICS), and animal naming that were mapped to a 7-level ordinal scale reflecting Diagnostic and Statistical Manual of Mental Disorders (DSM-5) neurocognitive categories.

LACI-2 recruited 363 patients at 26 UK hospitals from 5 February 2018 to 31 May 2021. Notably, almost all the patients recruited (99%) were evaluated at one-year follow-up and 86% provided data usable for 7-level cognition assessment, of whom 184 (60%) had mild or worse cognitive impairment. Treatment with ISMN alone (aOR 0.55, 0.36-0.86, p=0.008), and ISMN+cilostazol (aOR 0.44, 0.23-0.85, p=0.015) reduced 7-level cognitive impairment. ISMN+cilostazol also improved MOCA scores (aMD 1.14, 0.24-2.04, p=0.013).

The results of LACI-2 suggest that ISMN, alone or with cilostazol, may improve cognition in the follow-up of patients who had a lacunar stroke. A definitive multicentre phase-3 trial in lacunar stroke (LACI-3) to confirm the efficay of ISMN and cilostazol on clinical outcomes is planned.

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View a summary presentation by the Principal Investigator here

References:

1. Wardlaw J, *et al.* Isosorbide mononitrate, cilostazol and their combination for one year: Effect on cognitive outcomes in patients with small vessel stroke – the LACunar Intervention trial-2 (LACI-2). Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.

The structured ambulatory post-stroke care program (SANO) – A cluster-randomised interventional trial to enhance outpatient aftercare for stroke patients in Germany.

Can post-stroke care program improve risk factor control and reduce future risks of cardiovascular events?

Advances in acute stroke care have made tremendous impact on reducing stroke-related death and disability. However, risks of recurrent vascular events after the acute phase remain high, with some studies suggesting a one-year risk of having another stroke being up to 10%. Therefore, more effort to improve post-acute phase care is urgently needed.

The structured ambulatory post-stroke care program (SANO) is a parallel-arm cluster-randomised controlled trial in Germany which tested whether a comprehensive post-stroke care programme reduces the frequencies of recurrent stroke, myocardial infarction and death as well as optimising control of cardiovascular risk factors (CVRFs, such as hypertension, diabetes, smoking, hypercholesterolaemia and physical activity) after a first ever ischaemic stroke.[1]

Thirty participating clusters were randomised either to the intervention group with a one-year behavioural, organisational and patient-centred intervention within a cross-sectoral multidisciplinary network or to routine care. The multidisciplinary network involves general practitioners, specialists, therapists as well as social workers, sports groups, support groups and providers of smoking cessation programs. There are also several patient-centred elements including education on management of cardiovascular risk factors, target setting, motivational interviewing, dietary counselling and regular hospital follow-up visits.

Overall, 2791 patients were enrolled between January 2019 and December 2020 with 1396 in the intervention group and 1395 in the control group. At 12 months, patients in the intervention group had better control of their cardiovascular risk factors compared to the control group. However, this did not translate into any significant reduction of recurrent stroke, myocardial infarction or death after one year (5.3% in the intervention arm vs. 6.2% in the control group and adjusted odds ratio of 0.95, 95%CI 0.54-1.67).

Dr Christopher Schwarzbach, who will present the results of the SANO trial on behalf of the investigators, stated, “The SANO program has shown positive effects in optimising control of CVRFs in stroke patients. Unfortunately, this did not translate into a reduction of the rate of major cardiovascular events one year after ischaemic stroke. However, all-cause mortality within one year after the index stroke was lower in the intervention-group in the crude analysis, an effect already observed in the STROKE CARD trial.[2] As a one-year follow-up period might be too short to demonstrate a positive effect on recurrent cardiovascular events, longer-term effects still need to be considered. Furthermore, other potentially favourable effects of the structured intervention on stroke-related sequelae and quality of life require further evaluation.”

ENDS

View a summary presentation by the Principal Investigator here

References:

1. Schwarzbach C, *et al.* The structured ambulatory post-stroke care program (SANO) – A cluster-randomised interventional trial to enhance outpatient aftercare for stroke patients in Germany. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.
2. Willeit P, *et al.* STROKE-CARD study group. STROKE-CARD care to prevent cardiovascular events and improve quality of life after acute ischaemic stroke or TIA: A randomised clinical trial. EClinicalMedicine. 2020 Jul 28;25:100476.

Ayurvedic treatment in the rehabilitation of ischemic stroke patients in India: results of the randomized controlled RESTORE trial

RESTORE trial – A randomised controlled trial (RCT) of Ayurvedic rehabilitation therapy vs. conventional physiotherapy found no differences in upper limb performance measured at day 90 after ischemic stroke. This is the first RCT on Ayurveda treatment in stroke rehabilitation in ischemic stroke.[1]

Despite the growing number of treatment options which improve functional outcome after stroke, many stroke survivors need physical rehabilitation. Conventional physiotherapy remains the mainstay for rehabilitation in patients with a physical disability resulting from ischemic stroke. Ayurveda is an alternative system of medicine that offers a holistic approach to rehabilitation after stroke.

In the multicentre RESTORE trial, 140 patients with a first ischemic stroke 1–3 months prior were randomised to either 1 month of Ayurvedic rehabilitative treatment (ART) or conventional physiotherapy. The primary outcome measure was the upper limb performance at day 90 after stroke, measured by the Fugl-Meyer Assessment-Upper extremity (FMA-UE) test. The secondary outcome measures were Barthel Index, Berg Balance Scale and quality of life assessment using SF-36. All outcome measures were blinded from treatment allocation.

The RESTORE trial found no differences in upper limb performance 90 days after ischemic stroke between the Ayurveda and physiotherapy treatment groups. No difference was noted in the secondary outcome measures between both the groups.

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View a summary presentation by the Principal Investigator here

References:

1. Sylaja P.N, *et al*. Ayurvedic treatment in the rehabilitation of ischemic stroke patients in India: A randomized controlled trial (RESTORE) study. Presented at the European Stroke Organisation Conference; 24 May 2023; Munich, Germany.