

PRESS RELEASE

## ESOC 2021 Daily Highlights: Friday, 3 September

On the final day of ESOC 2021, we heard about the ongoing quest by investigators of APACHE-AF and SoSTART to answer the question, 'To start or not to start blood thinners in people with a bleed in their brain who also have atrial fibrillation?'. TIMING investigators presented results on the optimal time to start blood thinners after an acute ischaemic stroke. Results of THALES and CSPS.com trials on dual antiplatelet therapies for ischaemic stroke, meta-analysis on short-term BP variability and functional outcome after intracerebral haemorrhage, and the NETS trial--a rehabilitation study using transcranial direct current stimulation were also presented on the last day of ESOC 2021.

### APACHE-AF trial

*Is it safe and beneficial to restart apixaban (an OAC) after an OAC-associated intracranial bleed in patients with AF?*

Oral anticoagulants (OAC), such as apixaban, are drugs to thin the blood and are usually prescribed for patients with atrial fibrillation (AF) to prevent ischaemic stroke or systemic embolism. However, they increase the risk of bleeding, especially bleeding in the brain. Therefore, clinicians usually face dilemmas whether to restart or avoid anticoagulation in patients with AF who just survived anticoagulation-related bleeding in the brain.

The APACHE-AF investigators set to shed light on this question with a randomised, open-label, phase 2 trial including 101 patients recruited from 16 centres in the Netherlands. They were randomly allocated to receive apixaban 5mg twice daily or avoid anticoagulation (i.e., receiving only antiplatelet drug or no antithrombotic treatment). During a mean follow-up of 1.9 years, non-fatal ischaemic stroke, intracranial haemorrhage, subarachnoid haemorrhage or vascular death occurred in 13 participants allocated to apixaban and 12 allocated to avoid anticoagulation. There was no statistical evidence that these risks differed.

The study highlights the need for more extensive phase 3 trials to identify subgroups that may benefit from either approach.

## **SOSTART trial**

***Simultaneous publication in Lancet Neurology at 16:30 CEST on 3 September 2021***

***Is it safe and beneficial to start oral anticoagulation (OAC) in adult survivors of spontaneous (non-traumatic) intracranial haemorrhage who also have AF?***

SoSTART is a pilot randomised controlled trial to evaluate the safety and effect of starting OAC in patients who had AF after an intracranial haemorrhage. 203 participants were recruited from 67 hospitals in the UK. These patients had AF and were 3-4 months after an intracranial haemorrhage. They were randomly allocated to start OAC or to avoid OAC.

At one year follow-up, the event rate of recurrent symptomatic intracranial haemorrhage was low and non-significant between the two groups (8 events including seven fatal /101 in 'start OAC' and 4/102 non-fatal events in 'avoid OAC'). The results suggest that starting OAC might be beneficial in preventing symptomatic major vascular events compared to avoiding OAC, consistent with the known benefits of OAC.

The pilot study did not find evidence that starting OAC was non-inferior to (no worse than) avoiding OAC. There is a possibility that starting OAC might be beneficial in reducing symptomatic major vascular events, but this might come at the cost of having more fatal intracranial haemorrhages.

"This was a small pilot trial intended to precede definitive main phases. We were encouraged to find that the main phase trial was feasible to deliver recruitment in a few years at a large number of sites. Findings from this pilot phase inform recruitment discussions, and our job now is to maximise recruitment to ongoing trials to generate definitive evidence," Al-Shahi Salman, the study PI added.

## **RESTART trial extended follow-up**

***Simultaneous publication in JAMA Neurology on 16:15 CEST 3 September 2021***

***In 2019, RESTART showed us that it was safe to restart antiplatelet therapy in people surviving intracerebral haemorrhage up to 2 years of follow-up. At ESOC 2021, we find out the longer-term effects of the study's extended follow-up.***

Patients with an intracerebral haemorrhage (ICH) are often on antiplatelet therapy for their other vascular diseases (e.g. heart attack, ischemic stroke). Antiplatelet therapy is usually stopped at the time of ICH. The RESTART randomised controlled trial in 2019 showed that restarting antiplatelet therapy was safe and possibly beneficial in reducing all serious vascular events compared to avoiding antiplatelet therapy.

In the extended follow-up, 537 participants that were randomly allocated to restart or avoid antiplatelet therapy were followed up for a median of 3.4 years.

The results showed no significant difference between the two groups on recurrent ICH or serious vascular events. The trend towards fewer serious vascular events in the 'restart' group compared to 'avoid' is seen once again in the extended follow-up, although it did not reach statistical significance.

Al-Shahi Salman, who led the RESTART study, added, "By recruiting larger sample sizes in ongoing trials, we will stand a much better chance of being much more certain about the effects of antiplatelet therapy. Given that there is a possibility that patients may benefit from fewer vascular events with restarting antiplatelet therapy, the best way to resolve this dilemma is to conduct a definitive main phase trial of around 4000 patients."

## **TIMING study**

### ***When is the optimal time to start anticoagulants after an acute ischemic stroke?***

The optimal time-point to start non-vitamin K antagonist oral anticoagulants (NOAC) after acute ischemic stroke in AF patients is unknown. The TIMING study aimed to investigate the efficacy and safety of NOAC treatment initiated early, within the first four days after stroke, compared with delayed treatment initiation, between 5-10 days after the stroke event.

TIMING was a registry-based, randomised study using the Swedish Stroke Register—Rikstroke. 888 patients with acute ischemic stroke and AF were randomly allocated to early (within the first four days after stroke) or delayed (5-10 days) NOAC initiation and were followed up for at least 90 days.

The study found that early NOAC initiation was non-inferior to (no worse than) delayed NOAC initiation after acute ischemic stroke on the combined outcome of recurrent ischemic stroke, symptomatic intracerebral haemorrhage or all-cause mortality. No symptomatic intracerebral haemorrhages were seen in either study group.

Asberg and Oldgren, the study authors, concluded, “Whether early start of NOAC offers clinical benefit over delayed start remains to be established. Ongoing randomised controlled trials such as OPTIMAS, ELAN and START will contribute further information on the efficacy and safety of early versus delayed start of NOAC treatment”.

## **THALES trial—secondary analysis**

***Simultaneous publication in Stroke on 3 September 2021, 17:10 CEST***

***The ischemic benefits of a ticagrelor-aspirin combination therapy outweigh the bleeding risks in patients in specific stroke subgroups***

The THALES trial (Acute STroke or Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death) in 2020 demonstrated a reduction in risk of the composite of stroke or death for the ticagrelor-aspirin combination compared to aspirin alone. However, severe bleeding complications were more frequent with ticagrelor. Johnston and colleagues re-analysed the THALES data to identify patient subgroups with disproportionate risk or benefit under ticagrelor-aspirin combination therapy.

The THALES trial was a randomised placebo-controlled study in patients with mild to moderate ischemic stroke of non-cardioembolic origin or high-risk transient ischemic attack (TIA). 11,016 patients were randomised to 30 days of therapy with either ticagrelor plus aspirin or placebo and aspirin within 24 hours of symptom onset.

Major ischemic events occurred in 5.3% of patients in the ticagrelor-aspirin group and 6.5% in the aspirin group. Major haemorrhages occurred in 0.4% of patients in the ticagrelor-aspirin group and 0.1% in the aspirin group. The net clinical impact favoured the ticagrelor-aspirin combination.

Study author Johnston concluded that in patients with acute ischemic stroke or high-risk TIA, “Benefit-risk analysis of the THALES trial suggests that the benefit of a 30-day treatment with ticagrelor-aspirin instead of aspirin alone outweighs the risk 4:1.”

## **CSPS.com trial**

***When should dual antiplatelet therapy with cilostazol be initiated for secondary prevention in high-risk ischemic stroke? According to the CSPS.com study, dual therapy with cilostazol is more effective in***

## ***secondary stroke prevention than monotherapy when treatment is initiated after a waiting period of 2 weeks.***

Combination therapy with cilostazol and aspirin or clopidogrel is effective in secondary prevention in patients at high risk for stroke recurrence with a bleeding risk comparable to aspirin or clopidogrel alone.

A subanalysis of the CSPS.com trial, which randomised 1,879 patients between 8 and 180 days after high-risk non-cardioembolic ischemic stroke to receive aspirin or clopidogrel alone or in combination with cilostazol, was used to address the question of the optimal timing for initiation of long-term dual antiplatelet therapy with cilostazol and aspirin or clopidogrel. Patients were divided into three groups according to the time of treatment initiation. The primary endpoint was a recurrent ischemic stroke. Safety endpoints included major bleeding events.

Dr Kazunori Toyoda, deputy director of the National Cerebral and Cardiovascular Center in Osaka and coordinator of the study, concluded, “Long-term DAPT [dual antiplatelet therapy] using cilostazol was more effective for secondary prevention of non-cardioembolic stroke than monotherapy in high-risk patients who started the medication at 15 days or later after stroke onset without increasing haemorrhage risk, but not in those starting medication between 8 and 14 days.”

## **BASC collaborators: Short-term systolic BP variability and functional outcome after acute ICH: analyses of pooled individual participant data**

Previous research found an association between higher systolic BP variability (SBPV) in the acute phase after acute intracerebral haemorrhage (ICH) and poor functional outcomes. However, there remained uncertainty about the potential for confounding from the interventions used to lower BP after acute ICH. To investigate, the study group pooled individual participant data (IPD) from randomised controlled trials in the Blood pressure in Acute Stroke Collaboration (BASC). Short-term SBPV was defined as the standard deviation (SD) of SBP measures during 1-24 hours after randomisation. The primary outcome was function measured on the modified Rankin scale (mRS) 90-180 days after randomisation.

5,463 of 6,221 (88%) patients in the BASC IPD dataset provided the minimum required data for adjusted analyses. A linear association existed between short-term SBPV during 1-24 h after acute ICH and functional outcome: for every 10 mm Hg increase in SD of SBP during 1-24 hours, there was a corresponding 18% increase in the odds of poor functional outcome (adjusted OR [95%CI] for unfavourable shift in ordinal mRS scores per 10 mm Hg increase in SD of SBP 1.18 [1.11-1.27],  $p < 0.001$ ). Significant heterogeneity in the association existed according to several aspects of the BP-lowering interventions (strategy, agent and degree of SBP reduction).

In conclusion, early variation in SBP after acute ICH was associated with worse functional outcomes, especially in patients receiving intensive, targeted BP reductions with  $\alpha$ - and  $\beta$ -adrenoreceptor blockers and calcium channel blockers.

### **NETs trial: Neuroregeneration enhanced by transcranial direct current stimulation (TDCS)**

Transient direct current stimulation (TDCS) involves passing a small electric current from the scalp to the brain, with the aim of stimulating neuroplasticity and reorganisation of the motor cortex to aid recovery of motor function. It is not clear whether this treatment is effective in improving upper limb function in stroke patients.

NETs is a double-blind, randomised placebo-controlled trial, which randomly allocated 123 mild-to-moderate stroke patients to active TDCS or placebo during the subacute phase after a stroke event (mean 20 days). The study was carried out in 11 centres in Germany, Italy and Austria over ten years (2009 – 2019). This study did not find a significant difference in upper extremity function between the two groups.

There could be a number of potential reasons for the lack of effect of TDCS in this study. Stimulation intensity might be too low, time of intervention might be too late or early, and the degree of deficit tended to be mild. Reassuringly, no safety concerns were reported with the use of TDCS.

This study paves the way for future randomised clinical trials to evaluate the effect of TDCS definitively in upper-extremity recovery after stroke.

### **ENDS**

#### **Notes to Editors:**

A reference to the European Stroke Organisation (ESO) Conference must be included in any coverage or articles associated with this study and research.

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# 7<sup>th</sup> European Stroke Organisation Conference

1-3 SEPTEMBER 2021  
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## **About ESO:**

The European Stroke Organisation (ESO) is a pan-European society of stroke researchers and physicians, national and regional stroke societies, and lay organisations, founded in December 2007. The ESO is an NGO comprised of individual and organisational members. The aim of the ESO is to reduce the burden of stroke by changing the way that stroke is viewed and treated. This can only be achieved by professional and public education and making institutional changes. ESO serves as the voice of stroke in Europe, harmonising stroke management across the whole of Europe and taking action to reduce the burden.