ESOC 2017

3rd European Stroke Organisation Conference

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MEDIA RELEASE

Data highlights from the opening plenary of ESOC 2017

- DAWN study – mechanical thrombectomy between 6 and 24 hours from symptom onset significantly prevented disability in patients with severe strokes and 'mismatch' on brain imaging.
- CLOSE and Gore-REDUCE – PFO closure significantly reduces recurrent stroke in younger adults with cryptogenic stroke.
- PICASSO study – Probucol significantly reduces recurrent cardiovascular events in ischemic stroke patients with a high risk of cerebral haemorrhage.
- NOR-TEST study – No significant difference in functional outcome between acute stroke patients who received standard of care, alteplase, and those who received tenecteplase.
- Other highlights came from RATS-3 (benefit of early intensive cognitive linguistic therapy), T3 (nurse-initiated intervention to reduce disability) and ASTER (contact aspiration versus stent retriever).

See video interviews with principle investigators and summary slides at:
http://www.esoc2017.com/conference-information/conference-news

Prague, 16 May 2017 – Presentations during the opening session of the 3rd European Stroke Organisation Conference (ESCO) 2017 offered an encouraging mix of positive results and useful data. From the success of the CLOSE and REDUCE trials showing benefit of PFO closure, to the DAWN trial which expands the population of patients who will benefit from thrombectomy, to the PICASSO study in secondary prevention of stroke, there was plenty of fuel for discussion and debate. In only its third year, ESOC has strengthened its reputation as Europe's premier stroke conference with teaching courses and presentation of results from major clinical trials. Highlights from the morning plenary are outlined below.

Holes in the Heart: To close or not to close?

Two trials aimed to answer the ongoing controversy of whether or not closing a patent foramen ovale (PFO, a small hole in the heart which affects 20-25% of the population) reduces the risk of recurrent stroke in patients with a stroke of unknown origin.

In the **CLOSE Study**, closure of a high-risk PFO was associated with a significantly lower rate of recurrent stroke in patients with a PFO who had experienced a cryptogenic stroke. These results were presented by the Principal Investigator Prof Jean-Louis Mas of the Hôpital Sainte-Anne, Paris, France. This academically-driven, multicentre study (32 study sites in France and 2 sites in Germany) compared whether endovascular closure of PFO reduced

the risk of recurrent strokes compared to blood thinning drugs alone. It included 663 patients who had experienced a stroke of unknown origin.

Key findings from the CLOSE study:

- PFO closure significantly reduced the risk of recurrent stroke compared to anti-platelet therapy (HR 0.03, 95% CI 0 to 0.25, p < 0.001).
- The difference in risk of recurrent stroke with anticoagulants vs. anti-platelet therapy was not significant (HR 0.43, 95% CI 0.1 to 1.5, p=0.17).
- There was an increased risk of atrial fibrillation with PFO closure, mostly periprocedural and of uncertain significance.

"These data will change clinical practice in patients with cryptogenic stroke with atrial septal aneurysm or a large shunt," said Prof Mas. "I also believe the question of whether or not to close a PFO in this subset of patients has been answered by these data – the answer is yes."

In the **Gore-REDUCE Study**, closure of a PFO with a GORE® Helex® or or GORE® CARDIOFORM Septal Occluder device was associated with a significant reduction in risk of recurrent stroke in adults with PFO and cryptogenic stroke. Principal Investigator Prof Scott Kasner of the University of Pennsylvania, Philadelphia, US, presented the findings of this study. PFO closure reduced risk of recurrent strokes in 664 patients across 63 centres in 7 countries, with a previous stroke of unknown origin.

Key findings from the Gore-REDUCE study:

- The study achieved statistical significance with both its primary endpoints with a 77% relative reduction in clinical stroke hazard and a 49% relative risk reduction in new brain infarction.
    - PFO closure with a GORE® HELEX® or CARDIOFORM® device was associated with a reduction in recurrent clinically apparent stroke (HR 0.23, 95% CI 0.09-0.62, p=0.001) and silent ischaemia on brain imaging (RR 0.51, 95% CI 0.29 to 0.91, p=0.024).
- There was a small increase in the periprocedural risk of atrial fibrillation (6.6% vs 0.4%, p<0.001).
- Effective closure was achieved in 94.5% of patients.

"In carefully selected patients with cryptogenic stroke, PFO closure with GORE devices significantly reduced the risk of recurrent stroke…with a number needed to treat of 28 over 2 years," said Dr Kasner. "These data provide clear and definitive evidence that PFO closure is beneficial in this patient population."

CLOSE and Gore-REDUCE are the first studies to independently show benefit from endovascular closure of higher-risk PFOs, associated with a moderate shunt or and atrial septal aneurysm. This has the potential to significantly change clinical practice for a large population of patients in whom an inability to define the cause of their stroke left them without a specific treatment option.

Mechanical thrombectomy: Widening the window?

In the **DAWN Study**, mechanical thrombectomy in patients presenting late (after the standard 6 hours but before 24hrs) or who woke with symptoms reduces disability.

An independent Data Safety Monitoring Board (DSMB) recommended that the study be stopped early based on a pre-planned interim review of data from the first 200 patients (of a planned 500). The review concluded that multiple pre-specified stopping criteria were met. Joint Principal Investigators Dr Tudor Jovin of the University of Pittsburgh School of Medicine and Dr Raul Nogueira from Emory University School of Medicine, USA, presented the data at ESOC 2017 today.

The DAWN study sought to answer whether advanced imaging methods with MRI DWI and CT-perfusion can be used to successfully select patients for endovascular therapy, even though they present late or have an uncertain onset of symptoms. They included patients in whom brain imaging demonstrated a significant area of potentially salvageable brain tissue. Endovascular treatment significantly reduced disability compared to medically managed patients.

Key findings from the DAWN study:

- There was a significant relative risk reduction (73%) in disability in 107 patients receiving mechanical thrombectomy compared to 99 with medical management (OR 2.1, 95% 1.20 – 3.12, p<0.001), with a number needed to treat of 2.8 to reduce disability.
- There was a 35% increase good functional outcome defined as mRS score of 0-2.
- There was no significant difference in safety outcomes between groups.

“This study shows that for every 100 patients treated with endovascular therapy, 49 will have a less disabled outcome as a result of treatment, including 36 who will be functionally independent,” said Dr Jovin. “These results greatly expand the population of patients who can significantly benefit from mechanical thrombectomy for stroke, to significantly reduce severe functional impairment in the mostly severely affected patients. However, the shorter the time frame to treatment, the better the outcome, so the mantra ‘time is brain’ still stands.”

In the **PICASSO trial,** the lipid-lowering and anti-oxidant drug probucol significantly reduced recurrent cardiovascular events in patients with ischaemic stroke and a high risk of cerebral haemorrhage. The principal investigators, Prof Sun U Kwon and Prof Eun-Jae Lee of the Asan Medical Center, Seoul, Republic of Korea presented study results at ESOC 2017 today.

The PICASSO trial was a 2 by 2 factorial randomised trial of cilostazol or probucol compared to placebo in 1512 patients with a non-cardioembolic ischaemic stroke or TIA at an increased risk of intracerebral haemorrhage due to previous haemorrhage or multiple microhaemorrhages on brain imaging.

Key findings from the PICASSO study:

- The primary efficacy endpoint of stroke, myocardial infarction or cardiovascular death was significantly reduced by probucol (HR 0.69 (95% CI, 0.50−0.97), p = 0.031).
- There was no significant difference in the primary safety endpoint of recurrent cerebral haemorrhage.

In this population, probucol significantly reduced the risk of recurrent cardiovascular events, offering a potential new treatment for secondary prevention of ischaemic stroke in patients at an increased risk of cerebral haemorrhage. Although this requires confirmation in other clinical populations, it offers an exciting new treatment approach in these difficult patients at risk of both major forms of stroke.

“Probucol treatment in addition to standard lipid regimen may be more efficacious than standard lipid treatment, although more further research is needed,” commented Prof Lee.

A new clot-buster for acute stroke?

In the **NOR-TEST study**, a new clot-buster (tenecteplase) was compared to standard treatment (alteplase) after acute stroke. Dr Nicola Logallo, Haukeland University Hospital, Neurology, Bergen, Norway presented the findings at ESOC 2017 today.

Alteplase is the standard clot-busting drug used for intravenous thrombolysis up to 4.5 hours after onset of an ischaemic stroke. The NOR-TEST study compared standard treatment with alteplase with 0.4mg/Kg of the newer clot-busting drug tenecteplase in 1100 patients with acute ischaemic stroke.

Key findings from the NOR-TEST study:

- There was no significant difference between groups in disability at 3 months (mRS 0-2).
- There was no significant difference in rates of symptomatic intracerebral haemorrhage.

“Based on these findings, physicians may choose to use tenectaplase because of its convenience,” commented Dr Logallo. “Its single administration is easier and you can be sure the patient gets the full dose”.

In the **RATS-3 study,** intensive cognitive linguistic therapy was not beneficial in most patients early after acute stroke. Prof Femke Nouwens, Speech and Language Therapist, Erasmus Medical Centre, The Netherlands presented the findings.

Aphasia remains one of the most significant causes of disability after stroke and there are few effective treatments. Early intensive cognitive linguistic therapy (CLT) is a potential novel treatment. Prof Nouwens reported the results of the RATS-3 trial, testing whether intensive CLT within 4 weeks after stroke in 152 patients was effective.

Key findings from the RATS-3 study:

- Only 29% of patients in the intervention group were able to receive the targeted amount of therapy
- There was no significant difference in language function between groups with no clinically or statistically significant difference between treatment groups.

"In this population, early intensive CLT was neither feasible or effective for the majority of patients," concluded Prof Nouwens.

In the **T3 study**, a nurse-initiated, evidence-based care bundle to improve Triage, Treatment and Transfer of acute stroke patients did not reduce disability at 90 days. Prof Sandy Middleton, Australian Catholic University, Nursing Research Institute, Sydney, Australia presented the results at ESOC 2017 today. The study included 1879 participants in 26 Australian Emergency Departments.

Key findings from the T3 study:

- There was no significant difference between groups for the primary outcome of 90-day modified Rankin Scale score.
- There was no significant difference between groups for 11 secondary quality of care outcomes.

The care bundle did not significantly affect outcomes in this population and there was no evidence of a significant impact on quality of care delivered in Australian Emergency Departments.

Are there alternative methods of mechanical clot removal for acute ischaemic stroke?

From the **ASTER study,** Professor Lapergue from the Foch Hospital, University of Versaille, France, reported that there was no significant difference in safety or efficacy with contact aspiration compared to the standard method of mechanical stent retriever for clot retrieval after acute stroke, demonstrating its as potential as an alternative treatment approach.

Key findings from the ASTER study:

- There was no significant difference between groups for the primary outcome of 3 month mRS OR for 1 point improvement (0.76, 95%CI 0.53 – 1.10, p=0.15).
- Rates of reperfusion were similar in the intervention group (TICI 2b/3 85.4% vs 83.1%).

The ASTER trial demonstrated no significant difference between the current accepted method of clot retrieval in acute stroke and the new method of contact aspiration. Further research will be required to help us decide which approach to use.

"The ASTER trial opens the door to add a new tool (ADAPT) to remove clots," commented Prof Lapergue. "We have reached a milestone in terms of strategic approach."

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