

# Fourth European stroke science workshop

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## Abstract

Lake Eibsee, Garmisch-Partenkirchen, 16 to 18 November, 2017: The European Stroke Organisation convened >120 stroke experts from 21 countries to discuss latest results and hot topics in clinical, translational and basic stroke research. Since its inception in 2011, the European Stroke Science Workshop has become a cornerstone of European Stroke Organisation's academic activities and a major highlight for researchers in the field. Participants include stroke researchers at all career stages and with different backgrounds, who convene for plenary lectures and discussions. The workshop was organised in seven scientific sessions focusing on the following topics: (1) acute stroke treatment and endovascular therapy; (2) small vessel disease; (3) opportunities for stroke research in the omics era; (4) vascular cognitive impairment; (5) intracerebral and subarachnoid haemorrhage; (6) alternative treatment concepts and (7) neural circuits, recovery and rehabilitation. All sessions started with a keynote lecture providing an overview on current developments, followed by focused talks on a timely topic with the most recent findings, including unpublished data. In the following, we summarise the key contents of the meeting. The program is provided in the online only Data Supplement.

The workshop started with a key note lecture on how to improve the efficiency of clinical trial endpoints in stroke, which was delivered by Craig Anderson (Sydney, Australia) and set the scene for the following discussions.

## Keywords

Stroke, small vessel disease, genomics, vascular cognitive impairment, intracerebral hemorrhage, stroke recovery, thrombectomy, stroke therapy

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## **Session I: Acute stroke treatment and endovascular therapy (Bart van der Worp, the Netherlands, and Urs Fischer, Switzerland)**

*Carlos Molina, Spain, discussed reperfusion failure and current challenges in endovascular treatment for ischaemic stroke*

In patients with acute ischaemic stroke caused by occlusion of a proximal intracranial artery of the anterior circulation, endovascular treatment (EVT) strongly increases the chance of a good outcome.<sup>1</sup> As with thrombolysis with alteplase, the benefit of EVT is greater the earlier treatment is started.<sup>2</sup> The initial evidence of benefit of EVT was largely limited to patients in whom treatment could be started within 6 h of symptom onset,<sup>3–7</sup> but recent evidence suggests that in highly selected patients with acute ischaemic stroke who have a considerable mismatch between clinical deficit and infarct volume, EVT is of benefit up to 24 h.<sup>8</sup> Although in recent trials EVT was associated with a 19% absolute reduction in the risk of a poor outcome, 29–67% of the patients randomised to the intervention arm were dead or dependent at three months.<sup>3–7</sup>

This high risk of poor outcome after EVT may be explained by (1) the presence of a large infarct core and lack of salvageable brain tissue before recanalisation; (2) failure to recanalise the occluded artery adequately and (3) incomplete microvascular reperfusion despite adequate recanalisation of the occluded artery. Strategies and research to improve outcomes after intra-arterial therapy should therefore aim at: (1) reducing the time between symptom onset and recanalisation, preferably in combination with treatments preventing irreversible tissue damage before recanalisation; (2) increasing rates, speed and degree of successful recanalisation (first-pass Thrombolysis in Cerebral Infarction scale [TICI] 3) through better treatment techniques and (3) prevention of incomplete microvascular reperfusion, for example with the use of antithrombotic drugs during the procedure. In addition, the access to EVT should be optimised for patients with proximal intracranial artery occlusion.

*Eivind Berge, Norway, gave an overview of thrombolytic agents for the treatment of acute ischaemic stroke*

Thrombolytic agents studied most extensively in patients with acute ischaemic stroke are alteplase, streptokinase, desmoteplase and tenecteplase. Alteplase has been shown to be effective when given within 4.5 h of stroke onset,<sup>9</sup> and is the only drug licensed for the

treatment of acute ischaemic stroke. Streptokinase and urokinase have been associated with a high bleeding risk.<sup>10</sup> Desmoteplase has high fibrin specificity, but was not effective when given 3–9 h after stroke onset.<sup>11</sup> Tenecteplase also has high fibrin specificity, and has a long half-life in plasma. It seems to have comparable effects to alteplase,<sup>12</sup> and has the practical advantage that it can be administered as a bolus injection.

*Philip Bath, United Kingdom, highlighted the potential of nitroglycerin treatment in stroke*

Preclinical studies and small clinical trials suggest that nitroglycerin (glyceryl trinitrate) reduces death and improves outcome after ischaemic stroke or intracerebral haemorrhage.<sup>13</sup> Large ongoing trials (Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 [RIGHT-2],<sup>14</sup> Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch [MR ASAPJ]) are investigating the safety and efficacy of nitroglycerin started in the prehospital setting. Ambulance-based trials create new design issues: (1) limiting recruitment of stroke mimics; (2) tightening trial stopping rules so that trials testing low cost and potentially efficacious interventions can be large; (3) enhancing statistical efficiency through global analysis of ordinal or continuous outcome variables; (4) using hierarchical analysis of the primary outcome, first in the target population of stroke and transient ischemic attack (TIA), and second in all patients, including stroke mimics.

*Peter Kelly, Ireland, discussed the acute treatment of TIA and minor stroke*

The TIARegistry.org project gave an insight into the modern natural history of patients with TIA or mild ischaemic stroke treated with state-of-the-art stroke specialist services. In 4789 patients, 87.6% sought attention and 78% were treated by a stroke specialist within 24 h, with very high rates of antiplatelet and other preventive therapies. Recurrence rates were low (e.g. 2.1% at seven days), demonstrating that early treatment is the key priority regardless of clinical setting.<sup>15</sup> Early treatment with alteplase is of benefit in patients with mild ischaemic stroke, defined as National Institutes of Health Stroke Scale (NIHSS) 0–5, with a low risk of symptomatic intracranial haemorrhage.<sup>9</sup>

*Kennedy Lees, United Kingdom, addressed the major challenges in clinical trials*

He contrasted the considerable cost and complexity of generating randomised trial data against the potentially confounded, observational data. Small but

unrecognised advantages of one routine treatment over another could have substantial population benefit, if identified and widely applied. Although registry-based and platform trials offer some streamlining of research, barriers persist around funding, enrolment, regulatory, ethical, consent, monitoring and reporting issues. Research questions could be developed within simple registries by recording topics that generate clinical uncertainty, and then developing these incrementally towards recording of clinicians' treatment choices that were effectively based on complete uncertainty (quasi-randomisation) and of any factors that may have informed their choice. This methodology may reduce confounding and bias associated with interpretation of registry data, while minimising the financial and administrative burden.

## **Session II: Small vessel disease (Joanna Wardlaw, United Kingdom, and Frank-Erik de Leeuw, the Netherlands)**

### *Costantino Iadecola, USA, addressed current mechanistic concepts underlying small vessel disease*

He highlighted key points about control of cerebral blood flow, noting that about 60% of flow regulation occurs in vessels outside the brain (40% in extracranial arteries, 20% in pial arterioles). The other 40% of the regulation is thought to reside in penetrating arterioles, capillaries and venules, the arterioles being the predominant site of flow control and a key target of pathology. The role of capillaries in blood flow regulation is still controversial. He also noted that the innervation of pial arterioles is by autonomic nerves originating outside the brain, but the role of these remains unclear. He highlighted the strong trophic interactions between different cell types, for example neurons produce vascular growth factors and vessels produce neuronal growth factors. He discussed the relevance of perivascular spaces as a route to clearance of brain interstitial fluid and amyloid beta, noting that amyloid beta is produced from synaptic activity. Therefore, failure of neurovascular coupling (NVC), e.g. through dysfunctional neurovascular units, could lead to failure to clear amyloid beta out of the brain, potentially leading to a spiral of amyloid accumulation in microvessel walls and perivascular spaces, further adding to the microvessel dysfunction.<sup>16,17</sup>

He then described the cerebral microvascular dysfunction that occurs in hypertension. This also results in oxidative stress involving the perivascular space.<sup>18,19</sup> Both the neurovascular and cognitive dysfunction are mediated via effects on the blood–brain barrier, entry of angiotensin (Ang) II into the perivascular space to

act on Ang I type receptors on perivascular macrophages, and release of NOX2-derived reactive oxygen species from the latter cells. He described a clear role for similar pathways in genetically induced models of Alzheimer's Disease (AD), which are also worsened by hypertension, where the neurovascular dysfunction is paralleled by cognitive dysfunction, and which can be ameliorated by selective depletion of perivascular macrophages or CD36.<sup>20</sup> Amyloid beta applied to the cortex or administered intravenously results in release of reactive oxygen species and induces profound microvascular dysfunction, indicating a potential vicious cycle of vascular dysfunction accelerating AD pathology and vice versa, explaining the long-observed vascular dysfunction seen in prodromal stages of AD.

### *Joanna Wardlaw, UK, discussed novel risk factors for small vessel disease from early life*

She summarised data from over 5,000,000 subjects showing associations of lower educational attainment, lower childhood IQ and lower socioeconomic status, with increased risk of stroke in later life,<sup>21</sup> and increased risk of small vessel disease (SVD) lesions on imaging.<sup>22</sup> Recent data indicate that the three childhood factors increase risk independently of each other and of adult risk factors (in preparation) and show an inverse relationship between lower childhood IQ and age at stroke;<sup>23</sup> education may modify the impact of IQ on stroke risk by improving reasoning skills and ameliorating adverse effects of exposure to socioeconomic stress. Future studies should, where feasible, adjust for IQ, education and childhood socioeconomic status.

### *Eric Jouvent, France, discussed the wider effects of SVD on the brain, particularly in the cortex*

He showed that while some morphological aspects of the cortex are preserved during the course of SVD,<sup>24</sup> the cortical mantle undergoes important morphological alterations, including a loss of cortical surface area. In rare occasions, in advanced SVD, this involves some focal areas of cortex disintegration superficial to areas of severe white matter damage.<sup>25</sup> In passing, he insisted on caution when using automated image processing methods that are prone to interpret any cortical change as cortical thinning, since these distort real tissue shapes particularly in diseased brains.

### *Marco Düring, Germany, discussed new markers for characterising brain damage in SVD*

The heterogeneity of mean diffusivity (MD) in skeletonised white matter is proving to be sensitive to altered white matter integrity, is available to download

(www.psm-d-marker.com) and is resistant to between-scanner variation.<sup>26</sup> Bi-tensor diffusion tensor imaging (DTI), being applied in CADASIL and sporadic SVD, demonstrates that increased water content in the brain is the major determinant of the diffusion imaging alterations seen in normal-appearing and abnormal tissues in SVD, rather than presumed demyelination.<sup>27</sup> The level of neurofilament light chains in the blood is related to cognition and is a more sensitive measure than conventional SVD imaging markers.<sup>28,29</sup>

### *Susanne van Veluw, USA, reflected on the benefits of 7T MRI in SVD*

She demonstrated that 7T MRI can assess blood flow velocity in individual perforating arterioles,<sup>30</sup> and topographical associations between cortical microbleeds and perivascular spaces in cerebral amyloid angiopathy (CAA). Next, she focused on (the limits of) microbleed and microinfarct detection in CAA. Microbleeds often escape detection on neuropathology, whereas MRI is very sensitive to microbleeds. In contrast, microinfarcts are commonly observed at autopsy, but vastly under-recognised in vivo even at 7T MRI.<sup>31</sup> Despite the underestimation of total microinfarct burden with MRI, a small proportion can be seen at lower field strengths.<sup>32</sup>

### **Session III: Opportunities for stroke research in the omics area (Stephanie Debette, France, and Bo Norrving, Sweden)**

#### *Nilesh Samani, United Kingdom, provided an overview of clinical applications of genetics to cardiovascular disease*

In the last decade, large-scale genome-wide association studies (GWAS) have started to provide insights into the genetic determinants of complex cardiovascular diseases such as coronary artery disease (CAD), stroke and atrial fibrillation, which have a substantial genetic basis in addition to well-established lifestyle and demographic risk factors.<sup>33</sup> For instance, almost 100 loci associated with risk of CAD have been identified. The association of each locus with risk is modest with a 5–30% increased population risk per copy of the risk allele. However, the risk alleles are very common in the population. What have we learnt from these discoveries and what are the clinical implications? First, only about 40% of the loci for CAD are associated with conventional cardiovascular risk factors such as lipids and blood pressure suggesting that other hitherto unrecognised mechanisms contribute causally to its

pathogenesis.<sup>34</sup> This is illustrated by the first CAD GWAS locus at 9p21, which currently appears to affect CAD risk through the action of a long non-coding RNA (ANRIL). Second, using Mendelian randomisation, the genetic data have allowed researchers to test whether the association of multiple biomarkers with CAD is causal or due to confounding or reverse causation. This is of profound importance in selecting the right biomarkers for therapeutic targeting. These studies have revealed, for example, that the associations of high-density lipoprotein cholesterol (HDL)-cholesterol or C-reactive protein with CAD risk are probably not causal, leading to re-evaluation of these molecules as targets for therapy. On the other hand, the studies have demonstrated that plasma triglyceride, often considered a bystander, is a causal risk for CAD and highlighted the boosting of the activity of lipoprotein lipase as a promising therapeutic target.

Finally, genetic risk scores based on identified loci were found to add to conventional risk scores (e.g. Framingham) in risk evaluation and shown to stratify groups of individuals into very different life-long trajectories of CAD risk.<sup>35</sup> Studies have shown that both lifestyle changes and medication (statins) can ameliorate genetic risk.<sup>33,36</sup> These findings open up the possibility of much earlier screening for CAD risk using genetics and more targeted primary prevention.

#### *Martin Dichgans, Germany, summarised data from a recent Genome-Wide Association Study*

This multi-ancestry GWAS in over 65,000 patients with stroke and 450,000 controls revealed numerous novel risk loci for stroke and for aetiological stroke subtypes.<sup>37</sup> The study revealed substantial genetic overlap with related vascular traits at individual loci, and on a genome-wide level. Several of the novel loci have previously not been implicated in stroke pathophysiology and therefore point to novel mechanisms. Prioritisation of relevant risk variants and genes was achieved by integrating data on gene and protein expression amongst other information. The talk further highlighted the potential of GWAS for drug discovery and drug repurposing.

#### *Stephanie Debette, France, provided an update on genomics of imaging-defined cerebrovascular phenotypes*

MRI markers of covert vascular brain injury, mainly reflecting underlying cerebral SVD are highly prevalent in older community persons. They are associated with an increased risk of incident stroke, dementia and death. Recently, large collaborative efforts have enabled the identification of several loci associated



with white matter hyperintensity (WMH) burden, suggesting a possible involvement of glial proliferative pathways,<sup>38</sup> and developmental factors such as mural cell differentiation.<sup>39</sup> Some WMH risk variants are associated with both ischaemic and haemorrhagic stroke.<sup>38–40</sup> No robust associations have been identified yet for other MRI markers of SVD, although some like dilated perivascular space burden appear to be highly heritable.<sup>41</sup>

**David Tregouet, France, discussed recent advances and perspectives of multiomics approaches**

During the last 30 years, the evolution of the genetic epidemiology discipline paralleled the development of high-throughput technologies. For several decades, the research community has been strongly focused on the identification of genetic markers associated with human complex diseases. The recent development of high density DNA/RNA arrays and next generation sequencing technologies strongly boosted the field. From now on, it is time to interrogate other molecular phenotypes in addition to genetic variation, including metabolites and proteins, through new high-throughput techniques,<sup>42,43</sup> and to integrate their analysis with that of epigenetic data,<sup>44</sup> in order to deeply disentangle the complex architecture underlying common diseases. This opens the era of epidemiomics.

**Elisabeth Tournier-Lasserre, France, presented recent data on the genomics of Mendelian cerebral small vessel disease**

Targeted sequencing of known cSVD genes in adult probands with a familial history of cSVD identifies the causative mutation in <15% of patients despite the identification of multiple cSVD genes in the last 20 years. The combination of pan-genomic linkage analysis and whole exome sequencing of well-characterised families led to the recent identification of the causative anomaly in PADMAL (Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy).<sup>45</sup> PADMAL mutations are located in the 3'UTR of *COL4A1*.<sup>46</sup> These non-coding mutations affect a binding site for a microRNA regulating *COL4A1* expression and, in contrast with mutations affecting *COL4A1* glycin residues, they lead only to lacunar infarcts, causing neither cerebral haemorrhage nor systemic manifestations. This led to the hypothesis that other anomalies such as duplications of *COL4A1* may cause cSVD, which was confirmed by copy number analysis in several families.

**Session IV: Vascular cognitive impairment (Martin Dichgans, Germany, and Geert Jan Biessels, the Netherlands)**

**Edo Richard, the Netherlands, discussed multi-domain interventions for dementia prevention from a population perspective**

The prevalence of dementia is expected to rise dramatically over the coming decades, which is mostly attributable to low and middle-income countries (LMIC). Results from observational cohort studies in Europe show a rather stable age-specific prevalence, but a decreasing age-specific incidence across all age strata.<sup>47,48</sup> Registration data show a seemingly contradictory stable age-specific incidence.<sup>49</sup> Although diagnostic drift and increased attention for dementia may inflate incidence rates in registration data, they better reflect the actual burden on healthcare systems.

Thirty per cent of dementia is attributable to seven potentially modifiable risk factors, with their most detrimental effect at different points in life.<sup>50</sup> Complex relationships between risk factors and dementia complicate the design of optimally tailored interventions to prevent dementia. Due to societal changes, the relationships between risk factors and dementia that we know from birth cohorts from the 20s and 30s, may not be applicable in the current generation of people in their 50s and 60s.

Three large multi-domain intervention trials to prevent cognitive decline or dementia have been performed.<sup>51</sup> In the preDIVA trial, six- to eight-year four-monthly visits to a practice nurse to optimise vascular risk management did not prevent dementia.<sup>52</sup> In those with untreated hypertension, this type of intervention may be effective. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, two-year multi-domain intervention including cognitive training led to improvement of cognitive functioning, which was slightly better in the intervention vs. the control group.<sup>53</sup> There is no evidence for an effect in stroke populations.<sup>54</sup>

It is currently unknown who should be targeted, when an intervention should take place and what the optimal intervention to prevent dementia is. Considering the dramatic increase in LMIC, dementia prevention strategies should be cheap, easy to implement on a large scale, in a variety of healthcare settings. eHealth interventions, such as the Healthy Ageing Trough Internet Counselling in the Elderly (HATICE) intervention, may be one solution to this challenge and can be tested in large pragmatic trials.<sup>55</sup>

*Michael Brainin, Austria, discussed the role of vascular prevention asking “Is there any hope after HOPE-3?”*

The Heart Outcomes Prevention Evaluation (HOPE)-3 study tested antihypertensives and statins in a large cohort of persons with intermediate risk of suffering a vascular event including stroke.<sup>56</sup> While statins were effective in preventing all types of vascular endpoints, the antihypertensive arm showed a preventive effect only in persons with high blood pressure entry values of more than 143 mmHG systolic but not in those with lower values. Of future studies, HOPE-4 is currently ongoing and promises more data on the efficacy of life-style changes and the ‘Cut Stroke in Half’ study of the World Stroke Organisation is in preparation. Overall, multicompartments drugs or ‘Polypills’ hold great promise not only for cardiological endpoints but also for primary prevention of stroke.

*Carole Dufouil, France, provided an overview on the methodological challenges inherent to the study of vascular cognitive decline*

Clinical and population research on dementia and cognitive decline faces several methodological challenges, including right and interval censoring (including non-random dropouts during follow-up), competing risks of death and time-varying covariates. The research literature reflects little consensus on best practices to account for these challenges. Methods were discussed that may optimise the accurate identification of predictors of vascular cognitive decline and dementia, an important pre-requisite to facilitate the development of efficient preventive and therapeutic strategies.<sup>57</sup> This is particularly relevant to the study of clinical, imaging and molecular vascular biomarkers for predicting dementia risk of cognitive decline trajectories.

*Terry Quinn, UK, discussed the concept and clinical implications of transient cognitive impairment*

Classical neurological teaching suggests that transient cognitive symptoms are rarely cerebrovascular in origin. Recent evidence challenges this stance. Ischaemic lesions causing temporary amnesia are described but are infrequent. Much more prevalent is a syndrome of multi-domain cognitive impairment, evident immediately post-stroke and improving over days to weeks. A label of transient cognitive impairment (TCI) has been proposed but this description is potentially misleading as the presence of these ‘transient’ impairments is associated with poor longer-term cognitive outcomes. The clinical picture and natural history of TCI are similar to delirium and the two conditions may be related or even synonymous.<sup>58,59</sup>

*Leif Ostergaard, Denmark, provided an overview on capillary pathways to stroke and cognitive decline*

Changes in capillary morphology and function, so-called capillary dysfunction, may limit oxygen availability in brain tissue by shunting oxygenated blood through the microcirculation, although blood supply is inconspicuous.<sup>60</sup> Capillary dysfunction has now been demonstrated in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarctions and Leucoencephalopathy (CADASIL)<sup>61</sup> and AD,<sup>62</sup> and estimates of tissue hypoxia correlate with cognitive decline in AD.<sup>63</sup> In acute ischaemic stroke, early recanalisation largely restores capillary function, while penumbral infarction is associated with capillary flow disturbances, possibly caused by per-ischaemic capillary occlusions.<sup>64</sup> The talk discussed whether vascular disease pathophysiology represents a continuum between tissue hypoxia caused by limited blood supply at one end (e.g. brief ischemia) and by capillary dysfunction (e.g. AD), at the other.<sup>65</sup>

**Session V: Intracerebral and subarachnoid haemorrhage (Gabriel Rinkel, the Netherlands, and Charlotte Cordonnier, France)**

*Thorsten Steiner, Germany, provided an overview of trials on blood pressure lowering in the acute phase after ICH, and whether we need additional ones after INTERACT-2 and ATTACH-2*

The three large randomised trials on blood pressure lowering in acute intracerebral haemorrhage (ICH) demonstrated that intensive lowering of systolic blood pressure below 140 mmHg may decrease hematoma expansion,<sup>66</sup> but does not improve clinical outcome.<sup>67,68</sup> A meta-analysis including these and 2 smaller randomised trials ( $n < 100$ ) found no effect.<sup>69</sup>

There are two main reasons - among several others - for why trials failed to show a positive clinical effect: First, the baseline hematoma volume was too small with an average baseline volume in the two largest trials (Intensive blood pressure reduction in acute cerebral haemorrhage trial-2 [INTERACT-2] and Antihypertensive Treatment of Acute Cerebral Hemorrhage II [ATTACH-2]) of about 11 mL,<sup>45,46</sup> which might have left too few patients with hematoma expansion. Second, time to start of treatment was too late with an average time to start of treatment of 5.7 h in these trials: The post hoc analyses of the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial on the use of recombinant factor VIIa in spontaneous ICH

revealed that the odds of severe disability or death is increasing beyond 2.5 h after onset.

Thus, a positive effect of blood pressure lowering on clinical outcome has not been excluded, and further trials are needed. The corner stone of the design should be to lower blood pressure as soon as possible, meaning start of treatment instalment within 2.5 h, and use of fast-acting anti-hypertensives with short half-life time. Baseline volume needs to be limited by an upper threshold, as in ICH the target is prevention of clinical deterioration, and in patients with large ICH there is little room for deterioration, and also by a lower threshold as too small volumes have little chance of deterioration.

*Jürgen Beck, Switzerland, discussed the question whether interventional strategies for ICH are still an option*

Previous trials on interventional strategies for ICH, including two recent, carefully performed trials (Surgical Treatment for Intracerebral Hemorrhage [STICH and STICH II])<sup>70</sup> found no clinical benefit of surgical removal of the hematoma. Surgical removal of the hematoma is thought to be ineffective due to the additional trauma to the brain. Decompressive craniectomy decreases intracranial pressure without further damage to the vulnerable brain, is a well-established treatment for large ischaemic strokes and is therefore a potential effective treatment for patients with ICH. A randomised trial (SWITCH) is currently running.

*Hanne Krarup Christensen, Denmark, reviewed the relation between ICH and statins, asking the question: No need to worry?*

Some new evidence has emerged within the last two years. In a pharmaco-epidemiological study, the risk of ICH in patients after ischaemic stroke or TIA was not higher in patients on statins.<sup>71</sup> Based on a nationwide Swedish sample, the risk of ICH was not higher in statin users.<sup>72</sup> Data from patients after stroke exposed to PCSK9-inhibitors and resulting massive LDL-reductions in the FOURIER trial have not documented any increased risk. It is hard to rule out any interaction between statins and risk of ICH, however, new high-quality data do not support that statins increase risk of ICH after stroke.

*Roland Veltkamp, United Kingdom, reviewed the question: Why don't we use antithrombotics regularly after ICH?*

Patients with ICH are at risk of recurrent ICH, but also of myocardial and cerebral infarction. According to a

systematic review examining the effect of antiplatelet therapy after ICH, there is insufficient evidence to either support or withhold antithrombotic therapy.<sup>73</sup> The ongoing randomised controlled REstart or STOP Antithrombotic Randomised Trial will provide essential information for best management in this setting. For ICH patients with atrial fibrillation (AF), evidence from meta-analyzed recent large observational studies suggests a much higher annual rate of ischaemic stroke than for recurrent ICH,<sup>74</sup> but randomised trials, preferably with Direct Oral AntiCoagulants (DOACs), are needed to resolve the uncertainty. Several such trials are currently ongoing.

*Arthur Liesz, Germany, in a spotlight talk unrelated to the session topic discussed the inflammatory response and atheroprogession after stroke*

Stroke induces a multiphasic systemic immune response but the consequences of this response on atherosclerosis – a major source of recurrent vascular events – are barely investigated. Among the hallmarks of post-stroke systemic immunity is a low-grade chronic inflammatory response. The Liesz group tested whether stroke-induced systemic inflammation promotes atherosclerosis in a murine model. They observed that stroke exacerbated atheroprogession via alarmin-mediated propagation of vascular inflammation.<sup>75</sup> The prototypic brain-released alarmin HMGB1-induced monocyte and endothelial activation and increased plaque load and vulnerability. Neutralisation of circulating alarmins or knockdown of the key receptors attenuated atheroprogession. Their findings identify the stroke-induced sterile inflammation – which is driven by brain-released alarmins – as a critical mechanism of exacerbated atheroprogession after stroke.

## **Session VI: Alternative treatment concepts (Valeria Caso, Italy, and Heini Mattle, Switzerland)**

*Krassen Nedeltchev reviewed recent trials on PFO closure and addressed the question whether it is time to close the discussion*

Three randomised control trials (RCTs) published in 2012/2013 failed to demonstrate the superiority of patent foramen ovale (PFO) closure over medical treatment in secondary prevention of cryptogenic stroke (CS).<sup>76–78</sup> In 2017, the long-term results of the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Standard of Care Treatment (RESPECT) study<sup>79</sup> and two subsequent RCTs reported less recurrent CS after PFO



closure than with antithrombotic treatment alone.<sup>80,81</sup> Why was that? First, we now better understand PFO's pathogenic role. PFO is more frequent in CS patients, compared to healthy persons, but not all PFOs in CS are pathogenic. The PFO-attributable fraction depends on factors like age, hypertension, diabetes, previous stroke, smoking and stroke location.<sup>82</sup> Second, the definition of CS needs standardisation. For example, the definition of ESUS (embolic stroke of undetermined source) is an attempt to narrow down the population of CS including only embolic strokes. Third, up to 87% of recurrent strokes after PFO closure are due to alternative causes that either had been missed at initial workup or had emerged after randomisation. Fourth, improvements in closure device technology have resulted in lower complication rates. Finally, the risk of stroke recurrence appears to be driven by both PFO-intrinsic (large PFO, atrial septal aneurysm, shunt at rest) and PFO-extrinsic factors (age, CAD, diabetes). The attributable risk of PFO-extrinsic factors is even higher than that of PFO-intrinsic factors (91% vs. 35%, Kahles T et al., manuscript in preparation).

The preventive role of PFO closure in patients older than 55 years remains unclear. Theoretically, the risk of paradoxical embolism increases with advancing age due to the accumulation of prothrombotic conditions such as hypercoagulability, chronic inflammation and venous stasis. However, PFO-related risk is obfuscated by more potent vascular risk factors in older patients and the benefit of closure is difficult to be proven.

#### ***Jean Claude Baron reported on sensory stimulation, a novel paradigm for treating acute stroke?***

Sensory stimulation (SS) increases perfusion via the NVC. As NVC is not abolished after middle cerebral artery (MCA) occlusion (MCAo), SS might increase penumbral perfusion more than neuronal activity, affording neuroprotection. In rat models, contralateral forepaw or whisker stimulation started early after MCAo reduced infarct volume (12/13 studies; one temporary MCAo study only), sometimes spectacularly, but benefits vanished with 2 h SS-start, while 3h SS-start induced larger infarcts.<sup>83</sup> Both mice MCAo studies showed no benefit or worse outcome, possibly reflecting poorer collaterals in mice. Regarding clinical translation, SS could easily start in the ambulance and may benefit patients with good collaterals and extensive penumbra, but the time-window seems narrow while potential harmful effects would require close monitoring. A safety and feasibility study in imaging-based selected patients appears feasible.

#### ***Christine Roffe discussed normobaric oxygen in acute stroke: Dead or still alive?***

She reported on the results of the Stroke Oxygen Study, which randomised 8003 patients with acute stroke to supplemental oxygen or control (room air) failed to detect benefit on early neurological recovery, mortality and functional outcome at 90 days.<sup>84</sup> This lack of benefit was also observed in subgroups, which were considered most likely to benefit (enrolment within 6 h of onset, severe strokes, reduced level of consciousness, comorbid heart and lung disease).<sup>84</sup> It may be argued that low dose oxygen is not sufficient to affect neurons in the ischaemic penumbra. This concept is being tested in the PROOF trial, which will randomise patients within 4.5 h of severe acute ischaemic stroke to oxygen at a rate of 45 L/min.<sup>85</sup>

#### ***Daniel Strbian summarised developments in targeting brain oedema in stroke, in a preclinical and clinical setting***

He discussed the pathophysiology of brain oedema after ischaemic stroke and summarised development in the field during the last 2.5 years in the preclinical and clinical setting. He reviewed data on targeting beta1-integrins, vascular-endothelial growth factor (a possible target for therapy with hypertonic saline), aquaporin channels (including a monoclonal antibody for treatment of neuromyelitis optica), the arginine-vasopressin pathway, glitazone receptor, lithium, oxidative stress and interleukins, Ephrinb2-EphB4R guidance molecules pathway, and with no lysine=K - Ste20/SPS1-related proline-alanine-rich protein kinases (WNK-SPAK kinase) pathway. He further presented preclinical and clinical data on the sulfonylurea receptor, the intravenous inhibitor (glyburide). After a Phase IIb study,<sup>86</sup> intravenous glyburide is ready to be tested in a Phase III trial (CHARM).

#### ***George Ntaios provided an update on ESO Guidelines***

Several European Stroke Organisation (ESO) Guidelines are expected in, 2018 as a continuation of the series of ESO Guidelines already available.<sup>87-90</sup> The ESO Guideline app<sup>91</sup> aims to enhance the accessibility of stroke physicians to the ESO Guidelines. To date, six ESO Guideline Development Workshops have been organised aiming to introduce stroke physicians to the ESO Guideline Standard Operating Procedure. A dedicated ESO Guideline session is regularly included in the program of the ESO Conference. To support these expanding activities and serve the dedication of ESO to improve stroke management and education, the ESO



Guideline Committee was recently turned into the ESO Guideline Board.

**Session VII: Session VII: Neural circuits, recovery, and rehabilitation (Daniel Strbian, Finland, and Mathias Endres, Germany)**

*Christian Grefkes, Germany, delivered a keynote lecture on 'Non-invasive brain stimulation after stroke: Hope or hype?'*

A large fraction of patients remain disabled despite optimal medical and rehabilitative treatment in the acute stroke phase. Currently, the only approved interventions to support recovery of function are training-based methods like physical therapy or language training. Functional neuroimaging experiments have demonstrated dynamical changes of brain activity in both hemispheres, which can be detected already in the first days after stroke. Here, the best predictor for successful functional recovery is the reappearance of the original network architecture, e.g., a lateralised activity pattern in the motor system for hand motor recovery.<sup>92</sup> Therefore, non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) aim at supporting cortical reorganisation by either enhancing activity in hypoactive regions in the lesioned hemisphere, or suppressing activity in hyperactive regions of the structurally intact hemisphere.<sup>93,94</sup> For motor recovery, primary motor cortex (M1) has been a frequent stimulation target in patients suffering from hemiparesis. In the past few years, a number of studies have been published in which motor cortex stimulation has been paired with motor training in order to boost intervention effects. These protocols (10 Hz rTMS/iTBS over ipsilesional M1, 1 Hz rTMS over contralesional M1) induce a significantly better recovery of motor functions compared to sham stimulation. Neuroimaging data obtained from these studies revealed that patients receiving verum stimulation featured not only changes of brain activity in the stimulated region, but also in connected areas in both hemispheres, leading to a more physiological network architecture compared to sham-stimulated patients.<sup>95</sup> Therefore, non-invasive brain stimulation is capable of inducing network-level effects which seem to facilitate recovery of function after stroke. RCTs with large sample sizes are now needed in order to test these promising stimulation protocols in the clinical routine.<sup>96</sup>

*Ulf Ziemann, Germany, reported on therapeutic network modulation by individualised non-invasive brain stimulation*

Rapidly changing excitability states in oscillating brain networks may explain variability and limited effect size of open-loop therapeutic brain stimulation. When millisecond-resolution electroencephalography-triggered transcranial magnetic stimulation (EEG-TMS) was applied in healthy subjects to target specific phases of the sensorimotor  $\mu$ -rhythm in one study, it was shown that the negative vs. positive EEG peak of the  $\mu$ -rhythm represented high- vs. low-excitability motor states. Moreover, identical repetitive TMS triggered consistently at this high-excitability vs. low-excitability state led to long-term potentiation-like plasticity vs. no change.<sup>97</sup> This efficacy control of plasticity induction by real-time information of brain state can open new opportunities in therapeutic brain stimulation, e.g., to enhance recovery after stroke.

**Keith Muir, United Kingdom, gave an update on stem cell therapy in stroke: Fiction or future**

Two recent multicentre Phase 2 clinical trials have investigated early subacute treatment with intravenously delivered cells,<sup>98,99</sup> a mode of delivery that does not lead to CNS engraftment<sup>100</sup> and may be neuroprotective. Further trials of the 'multistem' allogeneic bone marrow derived cells line are underway in Japan and the US/Europe. In chronic stroke, three completed trials have investigated intracerebral implantation of stem cells. The PISCES-1<sup>101</sup> trial of the human neural stem cell CTX line and SanBio<sup>102</sup> trial of Notch1 transfected bone marrow-derived mesenchymal stem cells (SB623) both observed neurological improvement plateauing three months after implantation, and associated imaging changes. Twelve-month outcome data in Pilot Investigation of Stem Cells in Stroke Phase II Efficacy (PISCES-2) are awaited, and further trials of both cell types are underway.

*Lonneke de Lau, The Netherlands, discussed what we can offer to patients suffering from post-stroke aphasia after the RATS3 trial*

Aphasia occurs in about 25% of acute stroke patients and severely affects quality of life. There is evidence for a beneficial effect of speech and language therapy (SLT), and evidence that intensive therapy is more effective, but it is unknown whether efficacy of SLT is influenced by timing of treatment. In the Rotterdam Aphasia Therapy Study (RATS)-3 multicenter RCT, 153 patients with first ever aphasia due

to stroke were allocated within two weeks to either four weeks of intensive SLT or no language therapy for four weeks. Primary outcome was the score on the Amsterdam-Nijmegen Everyday Language Test (ANELT), four weeks after randomisation.

Median treatment intensity in the intervention-group ( $n=80$ ) was 24.5 h. The adjusted difference in mean ANELT scores at four weeks was non-significant (0.39, 95% confidence interval [CI]:  $-2.70$  to  $3.47$ ), suggesting that early intensive SLT is not more effective than no SLT in the acute phase after stroke.<sup>103</sup>

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