## Second European Stroke Science Workshop
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# Second European Stroke Science Workshop

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The European Stroke Organisation held its second European Stroke Science Workshop in Garmisch-Partenkirchen, Germany (November 21–23, 2013). Stroke experts from 21 European countries were invited to present and discuss their most recent research. The scope of the workshop was to review current findings of selected topics in stroke, to exchange ideas, to stimulate new research, and to enhance collaboration among European stroke research groups. The organization and structure of the workshop was similar to that of the first one in 2011. Seven scientific sessions were held, each starting with a keynote lecture to review the state of the art of a given topic, followed by 4 or 5 short presentations by experts. The meeting was organized by the executive committee of the European Stroke Organisation. The following sections summarize the content of the workshop and offer a useful overview of current knowledge and research activity in stroke.

## Session I: Recent Advances in the Immunology of Acute Stroke (Angel Chamorro, Barcelona, Spain, and Roland Veltkamp, London, UK)

### Michel Mittelbronn, Frankfurt, Germany, Provided an Overview on the Neurovascular Unit as a Selective Barrier to Leukocyte Infiltration Into the Ischemic Brain

It was a well accepted dogma that neutrophils invade the central nervous system (CNS) parenchyma in early stroke events, starting ≈15 hours and ceasing around the 5th day after stroke onset, thereby contributing to blood–barrier breakdown and reperfusion injury. Mittelbronn and coworkers revisited the temporospatial distribution of neutrophils in 25 well-characterized, early human stroke cases (17 stage I and 8 combined stage I/II cases) by means of histology, immunohistochemical, and immunofluorescent staining because currently more precise methods are available to define cellular subtypes and localization. In their cohort, a slight accumulation of CD15-positive neutrophils was observed within blood vessels and the perivascular space. However, virtually no granulocytic infiltration of the CNS parenchyma independent from the localization (ischemic center, penumbra, or remote normal appearing tissue) was seen. The major part of CD15-positive granulocytes passing the endothelium was still localized inside the parenchymal, collagen intravenous-positive basement membrane. Interestingly, at all time points, the number of neutrophils in the CNS parenchyma did not exceed CD68-positive MØs or CD3-positive T cells. A small cellular fraction within the CNS parenchyma histologically appearing as neutrophils could be characterized as cleaved caspase 3-positive cells indicating apoptosis. Their findings in human stroke cases were corroborated in murine transient middle cerebral artery occlusion models with the use of markers for cellular subsets and basement membrane constituents. In the transient middle cerebral artery occlusion model, high-resolution confocal microscopy revealed that neutrophils rarely, if ever, gain access to the CNS parenchyma after the ischemic insult. Furthermore, in vitro studies showed that hypoxia alone failed to induce neutrophil migration across the endothelial monolayer under reestablished flow conditions. In conclusion, their findings shed a new light on the potential role of neutrophils in early stroke events and may at least partly explain several disappointing results in clinical trials that tried to target neutrophils to reduce infarct volume. Their data indicate that the neurovascular unit rather than the CNS parenchyma may be the site of action of granulocytes in ischemic stroke and suggest reappraisal of targets for therapies to reduce reperfusion injury after stroke. The presentation stimulated a lively discussion with some opposing views. There is a substantial body of earlier literature and experimental data demonstrating neutrophil emigration in ischemic infarctions that are typically referred to in textbooks.

### Tim Magnus, Hamburg, Germany, Discussed the Role of T Cells in Acute Stroke

Postischemic inflammation is a dynamic process involving a complicated set of interactions among various inflammatory cells and molecules. Recently, T cells have been shown to be an essential part of the postischemic tissue damage,

and especially, interleukin-17-secreting T cells have been implicated in the pathogenesis of a variety of inflammatory reactions in the brain. Within the T-cell compartment due to the innate abilities, γ/δ T cells are likely to be some of the first responders after an ischemic injury. It has been shown that γ/δ T cells can worsen the outcome after stroke, and eliminating γ/δ T cells with an antibody effectively reduces infarct volumes.[1] Moreover, the data suggest that interleukin-17 secreted by γ/δ T cells is part of a chemokine cascade that eventually attracts neutrophils to the ischemic lesion and interfering with the signals can be beneficial in stroke.[2]

### Álvaro Cervera, Barcelona, Spain, Addressed the Role of the Lectin Pathway of Complement Activation on Stroke Outcome

Álvaro Cervera presented new evidence reinforcing the deleterious role of the mannose-binding lectin (MBL) pathway of complement activation in brain ischemia. In particular, new data were shown describing how MBL impaired the cerebral circulation at reperfusion, due to local intravascular thrombus formation. In patients with acute stroke treated with reperfusion therapies, MBL genotype was not associated with outcome at 3 months, although recovery in the first 24 hours and mortality were lower in MBL-deficient patients, suggesting that MBL inhibition could be beneficial for a short period in the acute phase of ischemic stroke.

### Christoph Kleinschnitz, Würzburg, Germany, Investigated T Cells and Thromboinflammation in Acute Ischemic Stroke

Christoph Kleinschnitz described how ischemic stroke elicits an inflammatory response, which leads to the invasion of different immune cell subsets. Among these, T cells start to enter the ischemic brain around day 1 with a maximum around day 3 in both mice and men. Kleinschnitz's group recently showed that T cells promoted ischemic brain damage and that this detrimental T-cell effect was antigen independent, at least during the early stage.[3] Follow-up studies revealed that regulatory T cells were especially prone to foster acute stroke by interacting with platelets and brain endothelial cells.[4] Importantly, this thromboinflammation might be amenable to specific therapeutic interventions, such as novel immunomodulators.[5]

### Alexander Gerhard, Manchester, UK, Reviewed Brain Imaging of Inflammation in Patients at Risk of Stroke

Alexander Gerhard described microglia as resident macrophages of the brain which become activated after insults to the brain, such as ischemic stroke, and that positron emission tomography (PET) with the tracer [11C](R)-PK11195 is a sensitive in vivo technique to image activated microglia. Using PK11195 PET, it was possible to demonstrate persistent microglia activation in areas distant of the primary ischemic infarct.[6] More recent studies also indicate widespread microglia activation in patients who did not have a manifest infarction but were at risk of stroke.[7]

### Session II: Advances in Neurovascular Imaging (Didier Leys, Lille, France, and Christian Gerloff, Hamburg, Germany)

### Leif Østergaard, Aarhus, Denmark, Provided an Update on Recent Advances in the Imaging of Acute Stroke and Hemorrhage

The pathophysiology of acute stroke and the ischemic penumbra concept are traditionally understood in relation to reductions in cerebral blood flow (CBF).[8] A recent reanalysis of oxygen transport in tissue shows, however, that increased capillary transit time heterogeneity (CTH) can reduce brain oxygenation dramatically for a given CBF.[9] Changes in capillary morphology are common in conditions that predispose to stroke, and disturbances in capillary flow patterns have been observed in animal models of ischemia and have been shown to predict infarction in human stroke.[10] Increasing CTH causes functional shunting of oxygenated blood through the microvasculature. To counteract this oxygen loss, CBF responses, and ultimately resting CBF, must be attenuated to support the metabolic needs of brain tissue.[11] Much like CBF can reach an ischemic threshold of 20 mL/100 mL/min, it seems that CTH can reach an upper limit, at which both small changes in CBF (eg, a hypotensive episode or a minor thromboembolic event) and increases in CTH (eg, dehydration or leukocytosis in relation to infections) can trigger a critical lack of oxygen in brain tissue.[12] Interestingly, the CBF level that provides optimal oxygen extraction at this critical CTH threshold is predicted to coincide with the classical ischemic threshold.[12] The extension of the classical penumbra concept to take both CBF and CTH into account may have implications for the diagnosis and management of acute stroke. First, CTH measurements by either perfusion magnetic resonance imaging (MRI) or computed tomography (CT)[13,14] may provide prognostic information in cerebrovascular disease and acute stroke. Second, therapeutic means of restoring capillary flow patterns (eg, blood rheology) may improve tissue oxygenation (1) prior to hospitalization, (2) after recanalization with incomplete capillary reperfusion, and (3) in patients ineligible for recanalization therapy, possibly improving patient outcome. Third, microcirculatory disturbances may contribute to delayed cerebral ischemia injury after subarachnoid hemorrhage.[15]

### Wilhelm Küker, Oxford, UK, Outlined Current Knowledge on Vessel Wall Imaging

Nonembolic stenoses of intracranial brain-supplying arteries are an important cause of cerebral ischemia, with the underlying disease situated locally within the arterial wall itself. The main underlying conditions are vasculitis[16] and atherosclerosis.[17] MRI technology now allows the direct wall visualization of large- and medium-sized brain vessels on routine clinical scanners. In conjunction with magnetic resonance angiography, T2 and contrast-enhanced T1-weighted high-resolution images can demonstrate focal inflammatory vessel wall activity and hence assist in the initial diagnosis and assessment of treatment response. However, diagnostic accuracy remains limited for small vessel vasculitis and differential diagnosis between inflammatory atherosclerosis and primary vasculitis.

### Christian Riedel, Kiel, Germany, Reviewed the Role of Clot Imaging in Acute Stroke

Although high clot burden in acute ischemic stroke can explain why intravenous thrombolysis (IVT) may fail to recanalize obliterated arteries, the amount of clot is typically not assessed using acute stroke imaging.[18] This is because nonenhanced CT as the most important acute imaging modality is known to be highly specific in displaying clots but only low in sensitivity for clot detection. The most important reason for this low sensitivity results from the low spatial resolution of nonenhanced CT images reconstructed with a typical slice thickness between 5 and 10 mm. However, it is possible to reconstruct the nonenhanced CT raw data with much smaller slice width on modern CT scanners. As the contrast of clots increases compared with the image noise in thin-slice reconstructions (0.6–2.5 mm), these images can be used to assess clot burden with a high sensitivity to predict failing intravenous thrombolysis.[19]

### Marwan El-Koussy, Bern, Switzerland, Explained the Role of Susceptibility-Weighted MRI

Marwan El-Koussy explained the role of susceptibility-weighted MRI (SWI) in the management of acute brain ischemia, with or without gadolinium enhancement, and showed that this technique can be incorporated in the routine stroke MRI protocol. SWI allows measurement of the occluding thrombus and distal fragments of the thrombus. The latter are rather rare and can be observed in ≈7% of cases. SWI can be used as a quality control tool after mechanical thrombectomy to look for peripheral emboli related to the interventions. The prominent SWI signal loss in the cortical veins on the side of the occlusion is related to increased deoxyhemoglobin concentration because of increased oxygen extraction and can reflect the extent of the ischemic penumbra. SWI can be performed after gadolinium injection without any loss of information, which is a practical point for the stroke MRI.[20]

### Sergio Amaro, Barcelona, Spain, Investigated the Potential Role of Dual Source CT in the Management of Acute Stroke

Dual source CT is a relatively novel technique that allows accurate differentiation among several preselected materials, such as normal brain parenchyma, brain hemorrhage, calcium, and iodine. In acute ischemic stroke treated with endovascular treatment (EVT), dual source CT is able to differentiate between contrast extravasation and brain hemorrhage and may add relevant prognostic information in an early stage of the disease.[21] Moreover, dual source CT can be used to improve the identification of the underlying pathological mechanism in patients with brain hemorrhage.[22]

### Session III: EVT of Acute Ischemic Stroke (Heinrich Mattle, Bern, Switzerland, and Derk Krieger, Copenhagen, Denmark)

### Heinrich Mattle, Bern, Switzerland, Addressed in His Keynote Lecture the Question Which Stroke Patient Might Benefit From EVT

Catheter-based interventions for acute stroke encompass techniques such as intra-arterial pharmacological thrombolysis,

multiple devices for proximal or distal thrombectomy and thrombus aspiration, and stent recanalization, including stent retrievers. Clinical outcomes depend on multiple factors, such as the severity of the neurological deficit, patient's age, the site of vessel occlusion, time to treatment, the quality of collaterals, and the degree of recanalization and reperfusion. Good collaterals markedly reduce and slow down penumbral tissue loss.[23] Patients with severe neurological deficits and large clot burdens are most likely the patients who will benefit from EVT, but only as long as mismatch on imaging is indicating salvageable tissue. Clinical outcomes are strongly associated with the degree of reperfusion achieved in target mismatch patients.[24] Randomized controlled trials (RCTs) have shown the benefit of intra-arterial pharmacological thrombolysis in proximal middle cerebral artery occlusion compared with placebo. Furthermore, a case–control study of intra-arterial thrombolysis versus IVT in patients with hyperdense middle cerebral artery sign on CT has shown better outcomes after intra-arterial therapy.[25] However, RCTs of intra-arterial thrombolysis versus IVT and EVT after IVT versus IVT alone did not fulfill the expectations of superiority of EVT compared with IVT.[26–28] To obtain positive results in such trials, faster and higher reperfusion rates have to be reached than in the previous studies.

### Thomas Liebig, Cologne, Germany, Gave an Overview of the State of the Art Endovascular Recanalization Techniques

Endovascular stroke treatment by means of mechanical removal of the thrombus is not totally new. Technically, its development can be divided in a pre- and post-stent retriever era because this technique has been proven in many trials and case series to be both more efficacious and, more importantly, less traumatic than previous approaches, independent of clinical results. The superiority of Solitaire and Trevo over the Merci has been shown in Solitaire FR With the Intention for Thrombectomy (SWIFT) and Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO); despite the nonconclusive trials Interventional Management of Stroke 3, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS), and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE), stent retrieval seems to be also a clinically efficient therapy in a subset of patients with stroke. These especially include patients with long segmental occlusions that will most likely not benefit from intravenous fibrinolysis alone.

With regard to access products, there is evidence that the combination of aspiration and mechanical thrombectomy yields higher rates of recanalization than thrombectomy alone. Thus, either balloon occlusion guide catheters or intermediate/distal access catheters should be used whenever possible. Recently, lesional aspiration alone with highly flexible large lumen catheters is under evaluation as a potential alternative. Finally, independent of the technique, patient selection including vessel and perfusion imaging remains an important tool to allocate patients to intravenous only, intravenous bridging, or EVT only.

### Perttu Lindsberg (Department of Neurology, Helsinki University Central Hospital), Helsinki, Finland, Addressed Futile Recanalization

IVT yields approximate recanalization rates in the internal carotid artery only of 10%, of 40% in the middle cerebral artery, and of 60% in the basilar artery. Endovascular thrombectomy devices will substantially improve these rates to roughly 65%, 80%, and 80%, respectively. Will these improved rates translate into superior outcomes? The concept of futile recanalization computes the fraction of poor outcomes among recanalized occlusions. If futility is defined according to the poor outcome trial definitions, modified Rankin Score (mRS) 3 to 6, and recanalization as thrombolysis in cerebral infarction (TICI) 2a-3, in the recent RCTs of EVT, the futile recanalization rates reach 60%. Many still advocate mRS 3 to represent a meaningful stroke outcome and that TICI 2b-3 correlates better with outcome. The use of futile recanalization index will become important, and this requires uniform criteria in defining recanalization and poor outcome. He suggests that TICI 2b-3 and mRS 4 to 6 should be used for this purpose.

### Alfonso Ciccone, Milano, Italy, Responded to the Question Did We Do Anything Wrong With the SYNTHESIS Trial?

Among trials on EVT, SYNTHESIS Expansion is the prototype pragmatic approach. Explanatory trials study whether a specific intervention works in the ideal condition, whereas pragmatic trials study whether a specific intervention works in the real world and address treatment effectiveness over efficacy.[29] Here, the option of the best EVT was left to each interventionalist's discretion, and there were no prespecified criteria, such as an National Institutes of Health stroke scale (NIHSS) score cutoff or the demonstration of arterial occlusion, to further select a patient already eligible for intravenous recombinant tissue-type plasminogen activator. SYNTHESIS Expansion did not provide support for the use of EVT over intravenous recombinant tissue-type plasminogen activator.[26]

### Antoni Dávalos, Barcelona, Spain, Opened the Discussion Is There Still Equipoise on Endovascular and Intravenous Treatment of Acute Stroke?

EVT achieves a higher rate of revascularization than IVT, but equipoise between these 2 strategies is anticipated on the grounds that good collateral circulation may sustain clinical recovery without revascularization, IV tissue-type plasminogen activator may work even 6 to 12 hours after infusion, and distal occlusions may have favorable natural outcome, whereas futile revascularization and procedure-related adverse events often occurs after EVT. Recent RCTs have shown that favorable outcome was similar in patients with IVT and in those with IVT + EVT or EVT alone although revascularization was higher in the combined group.[26,27] Equipoise was also shown regarding safety variables. Although many drawbacks in EVT methodology have been argued to justify these neutral results, EVT meets the equipoise concept of disagreement within the medical community about the best acute stroke treatment and it is not the standard of care.[30] Furthermore, we should recognize several biases in our local experience and admit that our decisions are fallible and that society demands a utilitarian approach. Consecutive enrollment of every eligible patient is the only way to maximize the generalizability of trials results, and so we should offer to our patients' unproven therapies such as EVT only within trials.[31]

## Session IV: Carotid Artery Disease (Patrik Michel, Lausanne, Switzerland, and László Csiba, Debrecen, Hungary)

### Martin Brown, London, UK, Summarized in His Keynote Lecture on Advances in Carotid Artery Disease

Randomized trials conducted many years ago established the benefit of carotid endarterectomy (CEA) for symptomatic carotid stenosis. However, a risk prediction model showed that only patients with a high risk of stroke under medical therapy benefited from CEA. Medical therapy for stroke prevention has improved and the risk profile of patients with carotid stenosis has changed since these original trials, leading to a decline in the risks of stroke with medical treatment alone in both symptomatic and asymptomatic stenosis. However, new evidence shows that the risks of CEA have also declined. There is, therefore, a need for new randomized trials comparing medical treatment against revascularization. New information about whether revascularization should be performed by carotid stenting (CAS) or CEA is available from the International Carotid Stenting Study (ICSS). In this trial, there was an increase in the procedural risk of stroke with CAS compared with CEA. However, the impact of this on disability measured by mRS after CAS was balanced by the impact of myocardial infarction, cranial nerve palsy, and severe wound problems after CEA. A recent analysis from ICSS has also shown that a greater than average number of white-matter lesions were associated with an excess of procedural stroke after CAS, whereas patients without excessive white-matter lesions had similar stroke. Older age has been shown to be a predictor of increased risk with CAS, whereas patients <70 years had a similar outcome after CAS and CEA. There was also no difference in mRS scores at the end of long-term follow-up in ICSS. Thus, the current evidence suggests that choice of CAS or CEA for patients with symptomatic stenosis should be made on the basis of the known risks for periprocedural complications and the patients' suitability for either procedure. The ongoing carotid trials, including European Carotid Surgery Trial (ECST)-2, Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs Endarterectomy (SPACE)-2, Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)-2, and Asymptomatic Carotid Surgery Trial (ACST)-2, address the remaining uncertainties. These trials will also provide an opportunity for suprastudies investigating whether carotid plaque imaging can be used to identify vulnerable plaque.

### Marcel Arnold, Berne, Switzerland, Provided an Update on Cervical Artery Dissection: Pathogenesis and Future Direction of Research

Mechanical factors and inflammation have been reported to play an important role in the pathogenesis of cervical artery dissection. However, precise pathogenic mechanisms and the

role of underlying predisposing factors remain largely widely unknown. Ongoing projects on cervical artery dissection focus on biomechanic properties of the carotid artery using modern ultrasound, MRI, and computer technology. Several studies aim to identify inflammatory biomarkers and to visualize inflammation by multimodal vessel imaging. Moreover, results of a large-scale whole-genome analysis in patients with cervical artery dissection are expected soon. In the light of the rarity of this disease, a multicenter, multidisciplinary, and multifactor approach is mandatory.

### László Csiba, Debrecen, Hungary, Reviewed Carotid Wall Imaging Using Ultrasound

The risk of stroke is <1% per year in asymptomatic carotid stenosis, but carotid ultrasound may identify patients with unstable plaque, who are at higher risk. The size of hypoechoic area or number of ulcers also correlates with the stroke risk. The combined presence of microemboli and echolucency is associated with a stroke risk of 8% per year.[32] Contrast-enhanced ultrasound visualizes the pre-, intra-, and poststenotic flow with fewer artifacts and identifies neovascularization that correlates with plaque instability. Additional contrast-enhanced magnetic resonance angiography and CT angiography may add further information on plaque morphology, brain perfusion, and intracranial collateralization and may be helpful for the individual management of carotid stenosis.

### Jean-Claude Baron, Paris, France, Covered the Current Knowledge on PET Imaging of Carotid Plaques

Carotid fludeoxyglucose (FDG) PET reflects plaque embolic potential and inflammation, independent of stenosis and hemorrhage, and could complement plaque MRI and transcranial Doppler to detect unstable plaques/high-risk patients. Given the availability and low cost of PET/CT, is carotid PET now ready for widespread use? Preliminary studies suggest that it helps to identify the culprit in situations of multiple plaques/embolic sources, predict clinical events in recently symptomatic carotid stenosis, and denote plaque inflammation in drug trials.[33] However, it is technically complex and not ready for routine use yet. Future studies should assess its value against simpler methods and search for improved markers.

### Tobias Saam, Munich, Germany, Highlighted the Advances of Vessel Wall Imaging With Magnetic Resonance

Imaging of the carotid atherosclerotic plaque black-blood carotid MRI is able to reliably detect complicated American Heart Association lesion type VI plaques, which are characterized by intraplaque hemorrhage, thrombus formation, and fibrous cap rupture. Cross-sectional MRI studies have shown a higher prevalence of intraplaque hemorrhage, fibrous cap rupture, and thrombus in symptomatic arteries. A recent meta-analysis showed that subjects with carotid artery stenosis of 30% to 99% and intraplaque hemorrhage at baseline had an almost 6-fold increased risk of cerebrovascular symptoms compared with subjects without intraplaque hemorrhage.[34]

MRI is a promising tool to identify patients with carotid atherosclerotic disease at risk for ischemic events and ongoing prospective studies, such as the Carotid Plaque Imaging in Acute Stroke (CAPIAS) and the Plaque At Risk (ParisK) trial will provide us new insights on the role of complicated plaques on recurrent symptoms on patients with <70% stenosis.

### Patrik Michel, Lausanne, Switzerland, Reviewed Carotid Artery Disease and Neuropsychological Findings

Although recent studies have confirmed that patients with asymptomatic carotid stenosis have worse cognitive function than age-matched controls, it remains open whether silent infarcts, chronic hypoperfusion, or shared mechanisms between cognition and atherosclerosis are responsible for this. Decreased cerebral vascular reserve seems to be an independent marker for progression of cognitive decline.[35] Carotid revascularization in unselected patients does not seem to improve cognition. In patients with severe preoperative hypoperfusion, however, several uncontrolled studies have shown possible improvement of cognition, but a well-designed small RCT did not show any benefits.[36] Further RCTs will have to confirm or refute this observation. When comparing different revascularization methods, the ICSS showed a strong cognitive trend in favor of endarterectomy over stenting. During endarterectomy, high-intensity transient signals on Doppler and postoperative hyperperfusion, but not perioperative diffusion-weighted imaging lesions, predict worse cognitive outcome. When comparing different revascularization methods, the ICSS showed a strong cognitive trend in favor of endarterectomy over stenting.

## Session V: Small Vessel Disease (Martin Dichgans, Munich, Germany; Co-Chair: Domenico Inzitari, Florence, Italy)

### Franz Fazekas, Graz, Austria, Gave an Update in His Keynote Lecture on the Epidemiology and Clinical Implications of Cerebral Small Vessel Disease

The epidemiology of small vessel disease (SVD) is complicated by a diversity in underlying etiologies (ranging from arteriosclerosis related to age and vascular risk factors to genetic disorders like cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or cerebral amyloid angiopathy), multiple appearances on neuroimaging (recent small subcortical infarcts, lacunes of presumed vascular origin, white-matter hyperintensities, microbleeds, enlarged perivascular spaces, and brain atrophy), and a multitude of clinical manifestations. Apart from being a harbinger of both ischemic and hemorrhagic stroke, SVD propagates slowly evolving (chronic) brain damage which affects cognition, gait, sphincter functions, and mood and accelerates the development of disability.[37] SVD has recently been recognized as an important cause of ischemic stroke already in the young with an alarmingly high rate of silent brain damage.[38] The recently published Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) standards for a common terminology and for standards of image acquisition and analysis represent an important step forward.[39] The new standards will

facilitate a unified approach toward the complexity of SVD and its interactions with degenerative brain diseases. Additional progress can be expected from new pathophysiologic concepts, novel structural and functional MRI techniques, and ultra-high-field MRI. The recently completed Secondary Prevention of Small Subcortical Strokes (SPS3) trial represents a major step toward targeted therapeutic approaches and optimized preventive strategies in SVD. Major challenges ahead include the improvement of diagnostic tools and the development of novel therapeutic targets that need to be informed by pathomechanistic studies.

### Martin Dichgans, Munich, Germany, Reviewed Recent Mechanistic Insights in SVD From Basic Science

Recent ex vivo and in vivo studies in genetic models of SVD provide converging evidence for a role of the extracellular matrix in mediating vascular dysfunction: (1) autosomal dominant mutations in COL4A1 and COL4A2 result in profound thickening of the vascular basement membrane most likely through interference with proper assembly of collagen fibers; (2) proteomic studies in CADASIL transgenic mice demonstrate that TIMP3 and vitronectin, 2 functionally important components of the extracellular matrix, are sequestered into Notch3 aggregates with major consequences on the activity of matrix metalloproteinases[40]; (3) recessive mutations in HTRA1, the gene mutated in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) patients, interfere with transforming growth factor-β signaling.[41] Transforming growth factor-β is released from the extracellular matrix via various stimuli and has been shown to have strong vascular effects. The extracellular matrix represents a highly dynamic and biologically active component of the vasculature, and understanding its role in SVD seems mandatory for the development of novel therapeutic approaches. Although unrelated to these discoveries, another important observation comes from MRI studies in patients with genetically proven SVD. By following a large number of incident lacunes over time, it was recently shown that incident lacunes typically develop at the edge of white-matter hyperintensities and proximal with regard to the orientation of perforating vessels.[42] These findings offer mechanistic insights into SVD-related lesions.

### Marco Düring, Munich, Germany, Highlighted the Role of Brain Atrophy in SVD

Recent studies have highlighted the role of brain atrophy as an important manifestation of SVD and a strong predictor of cognitive impairment. MRI studies in Notch3 mutation carriers and patients with sporadic SVD have provided first insights into how subcortical pathology induces cortical changes. Apparently, a major mechanism driving regional atrophy is secondary neuronal degeneration after damage to connecting fiber tracts: incident lacunes and acute ischemic infarcts have been shown to induce regional thinning specifically in connected cortical regions.[42] Moreover, recent evidence suggests that the cognitive deficits in SVD are mediated by the cortical pathology rather than the burden of subcortical lesions.

### Frank-Erik de Leeuw, Nijmegen, The Netherlands, Discussed the Cognitive Consequences of SVD

Individuals with SVD are at risk to develop dementia, and there is growing evidence that SVD also plays a role in parkinsonism. How SVD relates to these disorders is increasingly better understood by realizing that SVD consists of lesion(s) in the wiring of the brain that disrupts connections between areas of the brain, which for a proper function depend on this connectivity.[43,44] Accordingly, when possible (cognitive or motor), consequences of SVD are studied, and this should be done by especially taking the changes of the connected and disconnected brain structures (including cortical thickness and atrophy) into account. New studies indicate an important role for these gray-matter structures in incident dementia and parkinsonism, which remains significant even when adjusting for classical MRI markers of SVD.

### Geert Jan Biessels, Utrecht, The Netherlands, Provided an Overview on High-Resolution MRI of SVD at 7T

Autopsy studies report vascular pathology in the majority of patients with dementia, even when the clinical diagnosis is Alzheimer disease. Conventional MRI scans do not fully capture this vascular burden in dementia, most of which relates to SVD. Ultra-high-field 7T MRI now allows exploring novel markers of SVD, stroke, and dementia. The 7T MRI depicts small intracranial arteries and veins in great detail, including the arterial wall and surrounding perivascular spaces.[45] Microbleed counts at 7T MRI are much higher than at regular field strength. Using this technique it has been shown, for example, that microbleeds are likely to be present in >75% of patients with Alzheimer disease.[46] A recent study that included verification in postmortem material demonstrated that 7T MRI also allows depiction of cortical microinfarcts in vivo.[47] The next steps will be to link these novel markers to specific disease conditions, etiologic processes in SVD, and cognition.

### Session VI: Cerebral Hemorrhage (Kennedy Lees, Glasgow, UK; Co-Chair: Thorsten Steiner, Frankfurt, Germany)

### Christian Stapf, Paris, France, Gave an Excellent Keynote Lecture on Bleeding From Cerebral Cavernous and Arteriovenous Malformations

Among the many anomalies of the brain vasculature, cerebral cavernous malformations (CCMs) and arteriovenous malformations (AVMs) constitute the only malformation types of clinical relevance. Because of the increasing availability of magnetic resonance brain imaging, the majority of CCMs (>80%) and more than half of AVMs (60%) are diagnosed without symptomatic rupture. Observed average annual bleeding rates are high in malformations with symptomatic hemorrhagic presentation (≈6% per year for either type) but seem low for untreated lesions that have been diagnosed unruptured (CCM, 0.5%; AVMs, 1% per year).[48,49]

The recommended treatment for symptomatic CCMs is neurosurgical excision (estimated crude treatment–associated

morbidity, 8%; mortality, 2%), whereas stereotactic radio-therapy remains highly controversial because of potentially higher complication rates. Interventional management of brain AVMs is at times complex and includes neurosurgery, endovascular embolization, and stereotactic radiotherapy, either alone or in any combination. A recent systematic meta-analysis suggests that the treatment-associated risk may be up to 30%, including an observed risk of severe long-term disability in 7% of treated patients.[50] Because of their relatively benign natural history, the risk/benefit ratio of preventive eradication seems controversial for both malformation types, especially if diagnosed unruptured. For patients with AVM, A Randomised trial of Unruptured Brain AVMs (ClinicalTrials.gov NCT00389181) was organized to compare the risk of death and symptomatic stroke in those undergoing preventive interventional therapy as compared with those receiving symptomatic medical management alone. After 3 years of follow-up, recruitment was halted by the Data and Safety Monitoring Board, as patients randomized to the interventional group showed a significantly higher risk of death and stroke (hazard ratio, 3.70; 95% confidence interval, 1.85–7.14), as well as a significantly higher risk of death and neurological disability (mRS≥2; relative risk, 3.03; 95% confidence interval, 1.52–6.25).[51]

A similar pragmatic multidisciplinary clinical trial seems justified to compare surgical to noninterventional management of patients with CCM, but—similar to A Randomised trial of Unruptured Brain AVMs—a randomized controlled trial would have to overcome personal convictions, ethical concerns, and financial incentives in fee-for-service health systems.[52]

### Charlotte Cordonnier, Lille, France, Provided an Overview on Recent Progress in Amyloid Angiopathy

Although intracerebral hemorrhage (ICH) incidence has remained stable during the past 30 years, the profile of patients with ICH has evolved. Patients suffer their ICH at an older age with a higher proportion of lobar ICH associated with antithrombotic drugs.[53] These data suggest a strong implication of cerebral amyloid angiopathy. After brain microbleeds, cortical superficial siderosis observed on MRI has been described as a potential marker of cerebral amyloid angiopathy.[54] Interestingly, neuropathological data suggest that cortical superficial siderosis may arise both from hemorrhagic and ischemic lesions.[55] Besides a well-known hemorrhagic expression, this vasculopathy has also a strong occlusive expression (leukoaraiosis, small cortical infarcts). Although analysis of structural lesions in the brain parenchyma remains of interest, to understand pathophysiology, functional MRI associated with visual evoked potential may give clues on early changes of vascular reactivity.[56]

### Thorsten Steiner, Frankfurt, Outlined Current Knowledge on the Spot Sign in Acute Cerebral Hemorrhage

The spot sign has been studied in various small retrospective and prospective trials, one being a RCT.[57] Yet, the original objective, to predict hematoma expansion and outcome, has not been achieved.[58] Reasons are differences in frequency of presence of the spot sign, low sensitivity in all studies, lack of consistency in interpretation of imaging patterns, and differences in imaging acquisition.[58,59] The spot sign should be conceived as a pattern of dynamic change.[60] Future studies should take into consideration timing of spot sign detection and physical–chemical changes of hematoma over time.

### How Reliable Are Animal Models for Cerebral Hemorrhage? Was Addressed by Ulrich Dirnagl, Berlin, Germany

A multitude of rodent models have been developed to study cerebral hemorrhage. Choice of model depends on whether one is exploring mechanisms or trying to develop novel therapeutic strategies. In addition, many approaches exist to include etiologies for cerebral hemorrhages into the model because this may affect pathophysiology of effectiveness of treatment. Such factors include hypertension, cerebral amyloid angiopathy, and anticoagulation. Considering that there does not exist proof of concept that therapeutic principles studied in these models can lead to effective human therapies, the predictiveness of these models seems to be low. However, this may partly be explained by the fact that to date most experimental studies had low internal and external validity, exceedingly low statistical power, and that there was strong negative publication bias.

### Martin Koehrmann, Erlangen, Germany, Addressed Management of Blood Pressure in Acute Hemorrhage

Lowering of elevated blood pressure is a promising treatment target ICH. Previous studies have shown that aggressive blood pressure lowering is safe and may attenuate early hematoma growth. Recently, a larger RCT Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)-2 compared intensive (target <140 mm Hg) and guideline treatment (target <180 mm Hg) in 2839 patients with spontaneous ICH.[61] Although the primary efficacy end point (dichotomized mRS, 0–2 versus 3–6) just missed statistical significance (odds ratio, 0.87; 95% confidence interval, 0.75–1.01; *P*=0.06), mRS shift analysis showed improved outcome in the intervention group (odds ratio, 0.87; 95% confidence interval, 0.77–1.00; *P*=0.04). No safety concerns were seen. Additional studies like the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial are ongoing and will provide more evidence for antihypertensive treatment in the acute phase of ICH.[62]

### Session VII: Unresolved Issues With Antiplatelet Agents and Anticoagulants (Michael Brainin, Krems, Austria, and Matthias Endres, Berlin, Germany)

### Matthias Endres, Berlin, Germany, Discussed Unresolved Issues With Antiplatelet Agents and Anticoagulants

Ischemic stroke is a heterogeneous disease: although antiplatelet agents are used for the secondary prevention of atherothrombotic large vessel strokes and also for small vessel and lacunar stroke, anticoagulation is the treatment of choice

for cardioembolic stroke in stroke patients with atrial fibrillation (AFib). Unresolved issues involve specific aspects of the respective classical indications (ie, atherothrombotic versus cardioembolic strokes) but also additional indications.

*Antiplatelet Agents*

Open issues with regard to antiplatelet agents in atherothrombotic stroke relate to the following questions: Which is the preferred agent? What is the ideal dose? Should we use loading doses when initiating clopidogrel? How should we treat patients with recurrent strokes while on antiplatelet medication? Should we routinely perform platelet function testing to identify resistance for antiplatelet drugs? Recent and ongoing trials test novel antiplatelet agents as alternative monotherapy (eg, terutroban, cilostazol, ticagrelor, and possibly also prasugrel or voraxapar). There is mounting evidence that aspirin plus clopidogrel (double platelet inhibition) may be superior to monotherapy for early secondary prevention (ie, up to day 90 post stroke), whereas it is not beneficial for long-term secondary prevention according to the Management of Atherothrombosis With Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) and SPS3 trials (the latter performed in patients with lacunar strokes).

*Anticoagulants for AFib*

In contrast, ever since the publication of the European Atrial Fibrillation Trial some 20 years ago, it is clear that anticoagulation is the treatment of choice for stroke patients with AFib while aspirin is less effective. Despite the introduction of new direct oral anticoagulants, undertreatment of stroke patients with AFib remains a huge challenge. Clearly, side effects of anticoagulation include bleeding events with intracranial hemorrhage being the most feared complication. Reasons for not anticoagulating patients frequently include high age, dementia and cognitive deficits, frequent falls, and SVD with or without cerebral microbleeds. Importantly, although intracerebral bleeding risk might be increased in these conditions, the net clinical benefit is expected to outweigh those risks in most patients. Hence, most stroke patients with AFib should be anticoagulated despite these relative contraindications. The new direct oral anticoagulants offer the advantage of a smaller risk for intracranial hemorrhage compared with warfarin which is of particular advantage for patients with previous stroke. However, many open issues remain with regard to these drugs: (1) compliance and adherence are not studied in real life, (2) there is no antidote available, (3) specific coagulation tests are not available because point-of-care tests and interpretation of routine parameters are complex, (4) it is unclear when it is safe to initiate treatment after an acute stroke, (5) combination with platelet inhibitors clearly increases bleeding risk and mortality, (6) patients with severe renal failure cannot be treated, and (7) overall costs are much higher than for vitamin K antagonists.

*Other Indications for Anticoagulants*

Moreover, there are several indications where it is not clear whether antiplatelet agents or anticoagulation would be the better therapy. These indications include arterial dissection,

heart failure with sinus rhythm, stroke with patent foramen ovale, and cryptogenic stroke. Recently, a working group has introduced a new definition of Embolic Stroke of Undetermined Source, which differentiates likely (cardio)-embolic strokes from other pathologies within the large group of cryptogenic strokes. For example, a RCT to test the efficacy of new direct oral anticoagulants versus aspirin in Embolic Stroke of Undetermined Source patients would be attractive.

*Antithrombotic Treatment After Intracranial Hemorrhage*

In addition, open issues relate to the question whether antiplatelet medication or anticoagulation can be reinitiated after intracranial bleeds. Although anticoagulation may be safe after an intervention because of subdural hematoma or clipping or coiling an aneurysm following subarachnoid hemorrhage, bleeding risk is clearly increased with antithrombotic medication following ICH. According to current recommendations, anticoagulation may be started 4 weeks after deep ICH (ie, loco typico) as long as blood pressure and additional risk factors are controlled, whereas lobar hemorrhage constitutes a contraindication for anticoagulation.

*Antithrombotic Treatment and Thrombolysis*

Thrombolysis in patients taking antithrombotic medication remains a challenge. Current recommendations indicate that thrombolysis is beneficial in patients on antiplatelet drugs although bleeding risk increases. Anticoagulation, however, is a clear contraindication for thrombolysis unless the patient is not effectively anticoagulated. Emergency coagulation testing may help to identify those patients.

## Disclosures

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