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Scientific Symposium EVER **Acute Stroke Management and Stroke Recovery – New Insights & New Treatment Concepts**

Salzburg, Austria / September 14th, 2018

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Welcome speech and the official opening of the 25th IMMM



Dr. Wilfried Haslauer

Governor of Salzburg, Austria

Dr. Haslauer welcomed the delegates for the anniversary 25th IMMM conference, personally greeting Chairpersons Prof. Eugen Trinka (Medical Director Paracelsus University, Austrian Neurological Society) and Prof. Bettina Pfausler (President of the Austrian Society of Neurocritical Care, Neurointensive Care and Neurosurgical Care Medicine), Prof. Valeria Caso (past President of European Stroke Organisation), Prof. Michael Braining (President Elect of World Stroke Organisation), Prof. Dafin Muresanu (President of The European Federation of The Neurorehabilitation Societies) and Prof. Stefan Kichl (President of the Austrian Stroke Society).

He went on to list the cultural, business and academic hallmarks of Salzburg which make this city a unique and vibrant place in Europe, featuring a high quality of life, and also a place important for the regional development. The term quality of life is intricately related to medicine and major health issues it addresses. This is why the city of

Salzburg is dedicated to support development of internationally recognized life sciences hub in cooperation with local universities. Known for its high quality medical care and intact nature, the region attracts also medical and pharmaceutical businesses, companies like EVER Neuro Pharma, the main sponsor and creator of IMMM. The company contributes strongly to the region's quality of life through its research efforts and business development, especially in the field of neurological diseases, including stroke. Dr. Haslauer thanked the owners, management and employees of the company for their continuous efforts in this field. He also thanked all academic institutions of the Salzburg region for contributing to these highly relevant efforts through collaboration in the clinical research and development. Finally, Dr. Haslauer congratulated EVER Pharma and the participating institutions for the 25th anniversary IMMM and wished all delegates a fruitful meeting and a memorable stay in Salzburg.

Keynote speaker: The burden of stroke: Prevention is the main issue



Michael Brainin

Chair and Director, Department of Neurosciences and Preventive Medicine, Danube University Krems, Austria

ABSTRACT:

Today, there is an increase in stroke mortality which is most dramatic in low and middle income countries. If we include prevalence rates and the overall burden of the disease, dementia and stroke combined are by far the most burdening diseases globally. Moreover, in countries with aging populations the increase is also seen due to demographic changes. More recently, several studies have shown that a decrease of incidence rates is possible by improving modifiable risk factors, mostly of life style. For example, The Global Burden of Disease Study and the Inter-stroke Study both report that the burden of stroke is strongly influenced by modifiable risk factors and up to 90% of stroke occurrence can be explained by these risk factors. Conversely, a major reduction of incidence might be expected if behavioral and metabolic risk factors are managed appropriately. Recently, environmental factors (indoor and outdoor air pollution and lead exposure) have been recognized as major risks. Air pollution alone explains 30% of the stroke risk burden globally.

Prevention on a population scale can only be effective if large programs are established that target not only high-risk persons but aim also at medium risk and low risk persons. The WHO led initiative of reducing the NCDs (non-communicable diseases such as heart disease, cancer, diabetes, stroke and cardiopulmonary disease) can only become effective if the prevention issues are carried across diseases and are not only focused on one specific illness. This NCD Alliance has published a WHO Global Action Plan 2013-2020 which aims at reducing the NCD burden by 30% in 2030 (30 by 30). Regional assessments of the effectiveness of such initiatives show that in some world regions this may be reached, but in others the targets will be missed if additional efforts are not made.

Prof. Brainin started by immediately suggesting a conclusion to the topic of his lecture, which should be the prevention. To answer the question why the prevention is the key issue in stroke, he pointed to the fact that about 70% deaths due to neurological disorders are caused by stroke (about 10 million cases) followed by Alzheimer's disease (20%). Stroke is the second cause of death after cardiovascular diseases worldwide. The indicator of loss of healthy lifespan (DALYs) also points to the leading role of stroke as major neurological burden (50% of all of neurological diseases DALYs). Moreover, both these and other epidemiological parameters are dynamically increasing over the last three decades which indicates that new measures must be considered in the field of prevention (**Fig. 1**).

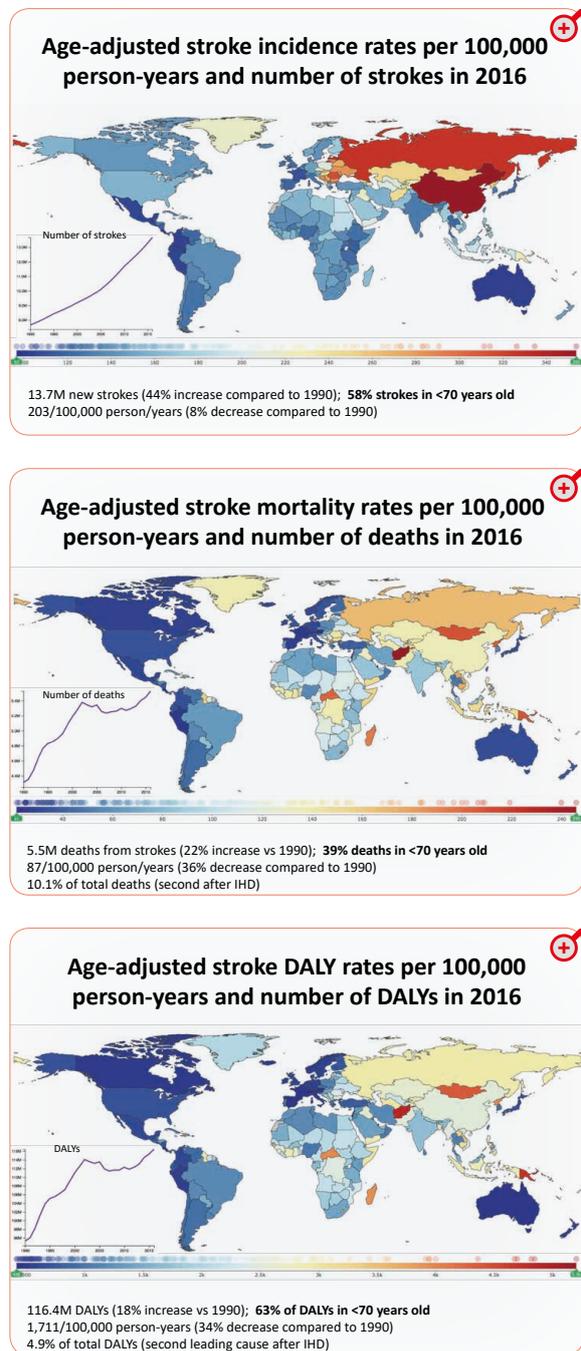


Fig. 1 The worldwide pandemic of stroke must be addressed with dedicated preventive programs

The socioeconomic status at early childhood, BMI, alcohol and drug abuse, physical inactivity, poor diet, current smoking are strong contributors as risk factors, and air pollution appear to be correlated with 30% of stroke incidents. In order to impact the global burden of stroke we have to address the broad population of low to moderate risk of stroke, not the small population at high risk which we deal with currently (**Fig. 2**).

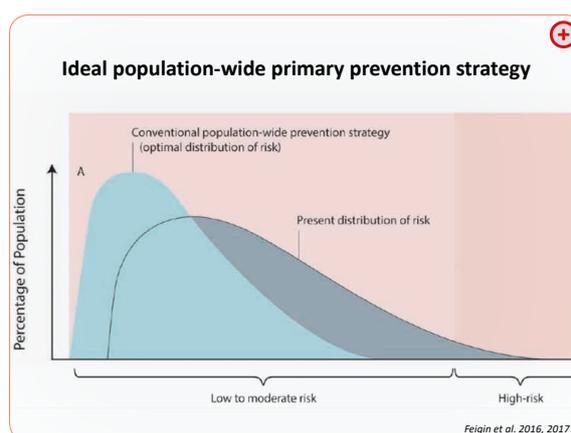


Fig. 2 The target for the preventive measures in stroke is a broad population with low to moderate risk of experiencing stroke

Unfortunately, such an approach to prevention isn't happening anywhere in the world. All countries focus their preventive programs (if they exist) on the high risk groups of NCDs. This is why WSO is particularly focusing on this issue keeping in mind that the data from large population studies indicate that about 90% of all strokes can be attributed to 10 modifiable risk factors, said Prof. Brainin. One of such initiatives is the Hearts Package Partners which created very important healthcare document for teaching interventions that can be used in the community stroke prevention programs by involved doctors (<https://goo.gl/hfbb9f>). The widespread use of mobile stroke prevention applications should also contribute to much needed progress in this field. In the arena of stroke prevention clinical studies, WSO is supporting construction of a trial that is based on usage of multi-compartmental drugs („Polypill“) and additionally targets lifestyle behavior changes („Cut Stroke in Half“: Polypill for primary prevention in stroke. M. Brainin, V. Feigin, S. Martins, et al. Int J Stroke 2018). The project aims at the reduction in incidence of stroke of up to 50% with risk factor modification and Polypill use. It will be a large, international, randomized trial developed under the participation and governance of the WSO and academic institutions. The philanthropic donors will be the core supporters. The project aims at testing the mobile App and Polypill together, and is titled: Overview of the Mobile App and Polypill for Stroke and Cognitive Impairment Prevention trial design WSO: Cut Stroke in Half.



Fig. 3 The Cut Stroke in Half, a large scale stroke prevention study by WSO

This will be phase III, factorial, placebo controlled, international RCT to determine the effectiveness of a Polypill (candesartan 16 mg, amlodipine 2.5 mg and rosuvastatin 10 mg) once daily, alone or in combination with the Stroke Riskometer app in primary prevention of stroke and cognitive decline. The primary outcomes will be measured at 3 year follow-up in more than 12 000 patients from all parts of the world (**Fig. 3**).

Finally, Prof. Brainin mentioned the importance of the work of WHO's High Level Commission on Non-Communicable Diseases which in its June 1 2018 report called for more comprehensive taxation policies towards sugar, added sugar, tobacco and alcohol products (STAX). This should contribute enormously to global efforts for decreasing the pandemic of stroke and other NCDs.

Quality improvement tools in stroke treatment: An overview about ESO-EAST, ANGELS and QUASC



Valeria Caso

Stroke Unit, Santa Maria della Misericordia Hospital,
University of Perugia, Perugia, Italy

ABSTRACT:

Stroke is a leading cause of death in Europe accounting for 1 million deaths annually. In the past 20 years, there have been significant advances in stroke prevention and treatment. Yet, there are wide disparities in the incidence of stroke and stroke-related morbidity and mortality including the percentage of patients who receive thrombolysis, are treated in stroke units, and have access to mechanical thrombectomy. To address these disparities, the European Stroke Organisation is implementing a continuous quality improvement project which is composed by the following pillars: ESO-EAST (European Stroke Organisation: Enhancing and Accelerating Stroke Treatment): is the first comprehensive program of improving stroke care in Europe. ESO-EAST Programme is initiated by the European Stroke Organisation and implemented in Eastern European countries through participation of stroke professionals, professional organisations and local authorities of all these countries. ESO-EAST Programme is planned for the period 2015 – 2019 (at least). ANGELS aims to increase the number of patients

treated in stroke-ready hospitals and to optimise the quality of treatment in all existing stroke centres. A community is being created of stroke centres and stroke-ready hospitals, working every day to improve the quality of treatment for every stroke patient. QUASC (Quality in Acute Stroke Care): is designed to implement and evaluate nurse-initiated evidence-based stroke care in Europe, to manage fever, hyperglycaemia and swallowing difficulties. Within ESO-EAST, ANGELS, and QUASC quality measures are collected by the RES-Q and SITS registries in order to constantly measure the improvements in European Stroke Care.

The activities of medical community that can be seen as complementary to the preventive efforts described by Prof. Brainin are directed at enhancing and spreading best standards of stroke management and care. Such efforts, as coordinated by European Stroke Organisation, were the theme of Prof. Caso's lecture. She introduced the audience to three major programs: ESO-EAST, ANGELS, and QUASC.

The project for Enhancing and Accelerating Stroke Treatment, The ESO-EAST project (www.eso-stroke.org/eso-east/), is supported by independent and unrestricted educational grants from EVER Pharma and Boehringer Ingelheim. It is a 5-year collaboration uniting selected physicians from Eastern Europe with the aim of optimizing and harmonizing stroke care. The major drivers of the program were underrepresentation of Eastern Europe in memberships and in conference presentations of ESO. The countries of the region also have less developed stroke services as well as the implementation of evidence-based treatment is suboptimal. Finally, health care systems in the region were developed in similar historical context. Prof. Caso presented the organizational milestones of the program as well as its major achievements (**Fig. 1**).

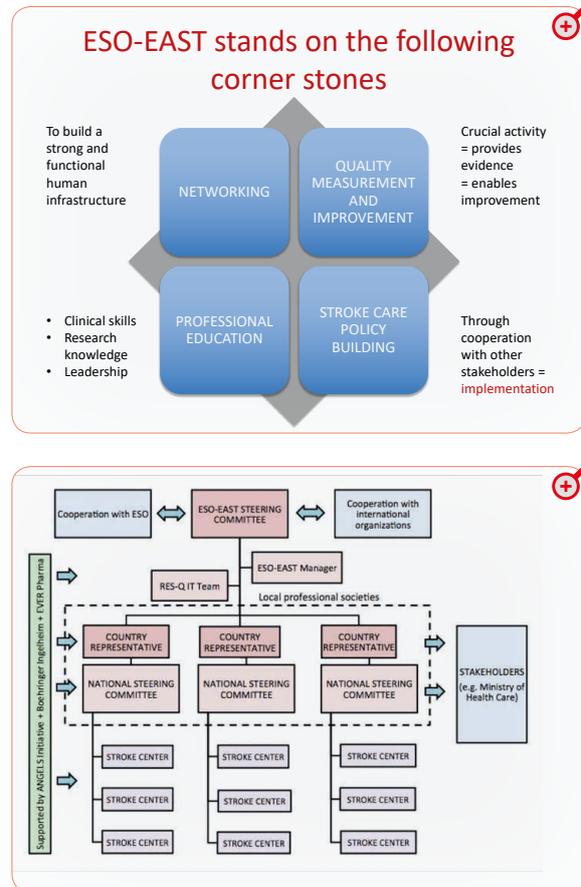


Fig. 1 The ESO-EAST program cornerstones and structure

Prof. Caso mentioned organizational achievements of Austria and Catalunya as blueprints for modeling the stroke management services in Europe and indicated that transfer of these standards and solutions into other countries' practices characterizes the efforts of ESO-EAST.

The European Angels initiative is a non-promotional, pan-European health care initiative by Boehringer Ingelheim, endorsed by the European Stroke Organisation to assist in implementing its main goal, which is to improve the stroke care across Europe. The specific aim of this program is to build 1500 stroke centers and stroke-ready hospitals across Europe. An important quality measure of this effort is achieving 50% of stroke patients treated within 1 hour (Fig. 2).

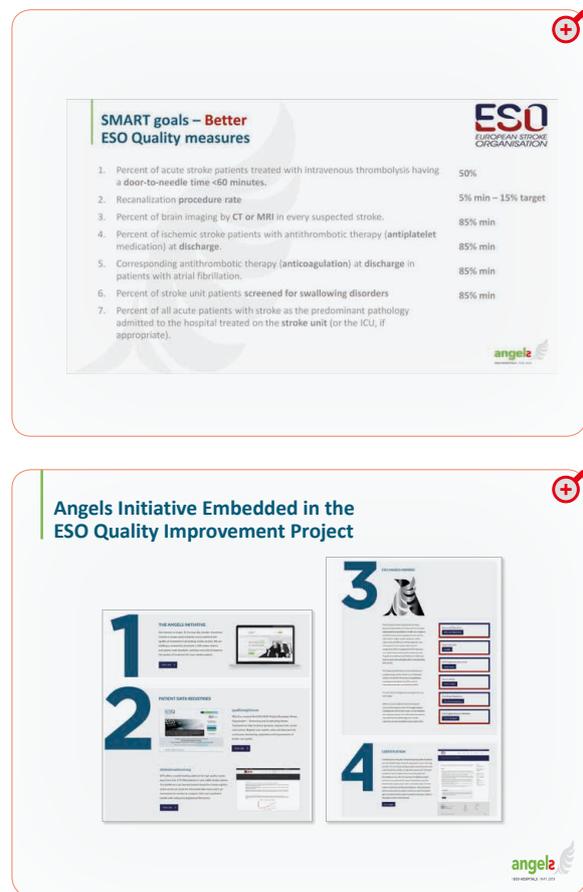


Fig. 2 Smart goals and quality measures of the ANGELS program by ESO

Prof. Caso stressed that the aim of the ANGELS is to improve overall stroke care, not to merely increase the rate of the thrombolysis across Europe. Since its inception, the program surpassed the initial expectations helping to increase access of stroke patients to professional stroke care by about 30%. The reduction of treatment time achieved was by 33%, and the rate of recanalization has been increased by 4%, on average.

The QUASC is about managing fever, sugar and swallowing (FeSS) and it is an educational program supporting the nursing care. The underlying rationale of the QUASC is the realization that significant reduction in stroke mortality can be achieved by controlling these vital parameters (Fig. 3).

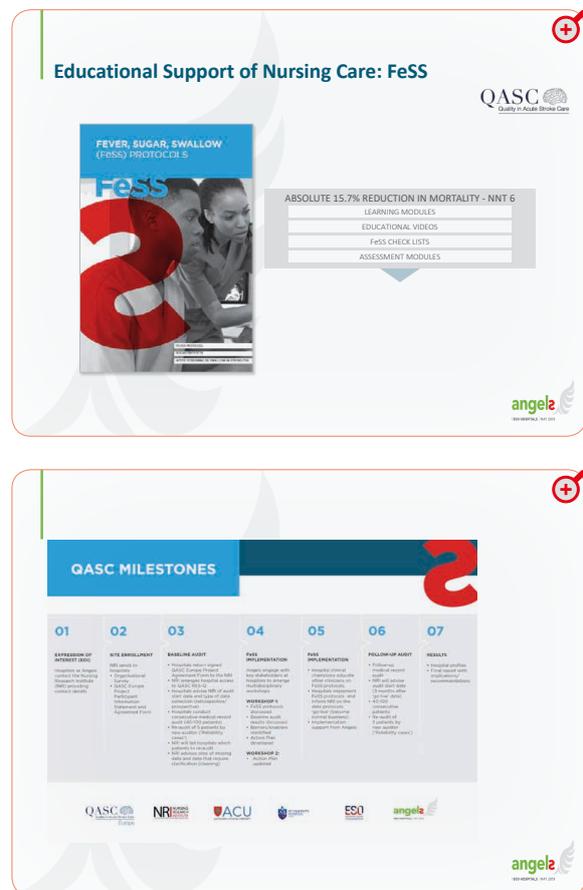


Fig. 3 The QUASC and FeSS program developed for reducing the mortality rate after stroke

Finally, Prof. Caso mentioned the importance of quality control for successful implementation of the presented programs. This measure is based on the international registries: RES-Q and SITS. The registries allow for objective evaluation of these efforts and show that the programs presented are indeed working. The 17 ESO ANGELS awards were for the first time presented to European stroke centers during 2018 ESO Congress in Goteborg. Prof. Caso warmly invited the delegates to participate in the ESO programs and registries.

Severe disorders of consciousness – modern approach to diagnosis and therapy



Andreas Bender

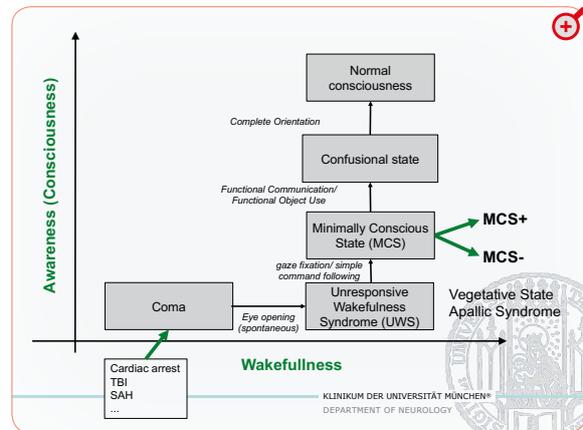
Therapy center Burgau, Germany & Department of Neurology, Ludwig-Maximilians University of Munich (LMU), Germany

ABSTRACT:

Coma, unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS) are frequent consequences of severe brain injury, such as anoxic-ischemic encephalopathy (AIE), traumatic brain injury (TBI), or stroke. Neurorehabilitation of patients with such severe disorders of consciousness (DOC) is a challenge, ranging from the correct diagnosis, the choice of neurorehabilitation techniques, management of frequent complications to prognostication and expectation management. The first major obstacle are high misdiagnosis rates of up to 40% of patients. It is important to use standardized clinical rating scales, such as the CRS-R, to establish the appropriate level of consciousness. Modern neuroimaging and electrophysiological tools to probe for consciousness may enhance diagnostic accuracy as well as prognostication. In addition, the lecture will

provide an evidence-based overview of interventions, which are tailored to improve consciousness and the outcome in DOC patients, such as pharmacological stimulation, music therapy, or tilt table therapy. Also, novel interventions and study protocols with the potential to improve the outcome will briefly be introduced. Prognostication of the long-term outcome of DOC patients is a challenge with only limited prospective data having been published. Current practice parameters for prognostication may carry the risk of too pessimistic assumptions, therapeutic nihilism, and self-fulfilling prophecies. In order to provide the audience with a realistic view on possible outcomes of DOC patients, results of a multicentre clinical trial with 3-year long-term outcome data will be presented.

The medical field of diffuse brain injuries and severe brain injuries while not always related to stroke, also represent important medical challenge. Prof. Bender decided to contribute to IMMM through discussing current state of the art in diagnosis, evidence based therapy and prognosis of severe disorders of consciousness which result from such serious brain injuries. The diagnostic challenge is great (**Fig. 1**), with UWS-misdiagnosis ranging between 37-43%. In many patients it takes months to correct misdiagnosis. About 65% of patients with misdiagnosis are blind which makes the diagnosis very difficult to conduct. Prof. Bender indicated that using mirror (or a selfie camera of a smartphone) appears to be best working means of assessment of visual pursuit. The patients switch between consciousness and unconsciousness quite often. Therefore, the assessment must be done frequently.



The image shows a screenshot of the Coma Recovery Scale Revised (CRS-R) form. A red box highlights the text 'most MCS patients > 9 CRS-R points'. The form includes several sub-scales:

- AUDITORY FUNCTION SCALE:** 4 - Consistent Movement to Command *, 3 - Reproducible Movement to Command *, 2 - Localization to Sound, 1 - Auditory Startle, 0 - None
- VISUAL FUNCTION SCALE:** 4 - Object Recognition *, 4 - Object Localization: Reaching *, 3 - Visual Pursuit *, 2 - Fixation *, 1 - Visual Startle, 0 - None
- MOTOR FUNCTION SCALE:** 6 - Functional Object Use †, 5 - Automatic Motor Responses *, 4 - Object Manipulation *, 3 - Localization to Noxious Stimulation †, 2 - Flexion Withdrawal, 1 - Abnormal Posturing, 0 - None/Flaccid
- OROMOTOR/VERBAL FUNCTION SCALE:** 3 - Intelligible Verbalization †, 2 - Vocalization/Oral Movement, 1 - Oral Reflexive Movement, 0 - None
- COMMUNICATION SCALE:** 2 - Functional: Accurate, 1 - Non-Functional: Intentional †, 0 - None
- AROUSAL SCALE:** 3 - Attention, 2 - Eye Opening w/o Stimulation, 1 - Eye Opening with Stimulation, 0 - Unarousable

 The 'TOTAL SCORE' is indicated at the bottom left. A small note at the bottom says 'Determine emergence from MCS? Determine MCS?'. The form is attributed to 'KLINIKUM DER UNIVERSITÄT MÜNCHEN DEPARTMENT OF NEUROLOGY'.

Fig. 1 The challenge of UWS and MCS diagnosis and the Coma Recovery Scale Revised (CRS-R)

The Cognitive-Motor-Dissociation (CMD) which probably affects up to 20% of patients also contributes to misdiagnosis, as patients cannot follow our tests' orders even if they are conscious. In such cases, the methods based on EEG (passive, active ERPs), fMRI and FDG-PET should be used. These help to identify conscious patients who otherwise would never be recognized as such (**Fig. 2**).

fMRI as a communication method



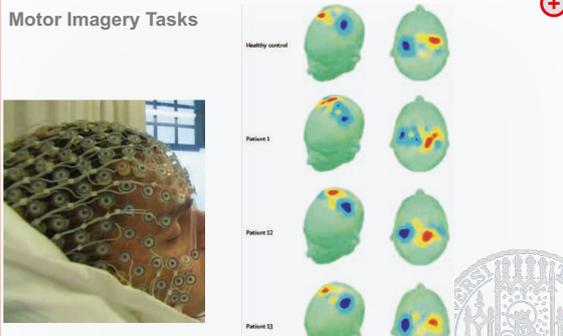
„Is your father´s name John?“
 → „If yes, imagine playing tennis, if no, imagine going through your house!“

Scott Routley (BBC 2012)

The NEW ENGLAND JOURNAL of MEDICINE
 FEBRUARY 16, 2012

Willful Modulation of Brain Activity in Disorders of Consciousness
 Martin M. Monti, Ph.D., Audrey S. Horvath, M.Sc., Martin R. Coleman, Ph.D., Mircea Balci, M.D., John D. Howard, M.D., Michael S. Hirsch, M.D., Adam M. Cheem, Ph.D., and Steven Laureys, M.D., Ph.D.

Motor Imagery Tasks



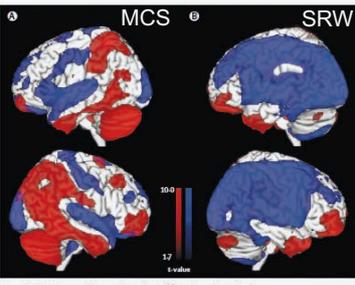
Healthy control
 Patient 1
 Patient 2
 Patient 3

KLINIKUM DER UNIVERSITÄT MÜNCHEN*
 DEPARTMENT OF NEUROLOGY

Cruse D, Chemru S, Chatelle C, et al. Lancet. 2011 Dec 17;378(9809):2088-94.

Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study

Lancet 2014



Correct diagnosis: **85%**
 Correct prediction (1yr): **74%**

IVERSITÄT MÜNCHEN* NEUROLOGY

Fig. 1. Statistical parametric mapping-analysis of fluorodeoxyglucose PET scans (A) Minimally conscious state. (B) Unresponsive wakefulness syndrome. Areas where central glucose metabolism is decreased and preserved in individual patients in a minimally conscious state and/or vegetative state (unresponsive wakefulness syndrome), compared with 39 healthy patients. Blue=areas with significantly lowered metabolism. Red=areas with preserved metabolism (p<0.05).

Fig. 2 Diagnosis of patients suffering form Cognitive-Motor-Dissociation (CMD)

Before deciding on a therapy one must remember about basics, including: positioning/PT (e.g. LIN, Bobath), traditional techniques to further awareness (e.g. Affolter therapy), being aware of complications (e.g. hydrocephalus, epilepsy, pneumonia) and of avoiding complications (e.g. neuroleptic drugs). Among the therapies supported by evidence are: verticalization, tDCS, Zolpidem, auditory stimulation/music therapy, and Amantadine (with the strongest positive evidence). Prof. Bender suggested that preliminary results for Cerebrolysin indicate need for further studies as this agent might have beneficial effects on various levels in the severe brain injury patients. The idea of pilot trial has been developed by his center together with EVER Pharma in order to better understand potential impact of Cerebrolysin in these patients (**Fig. 3**).

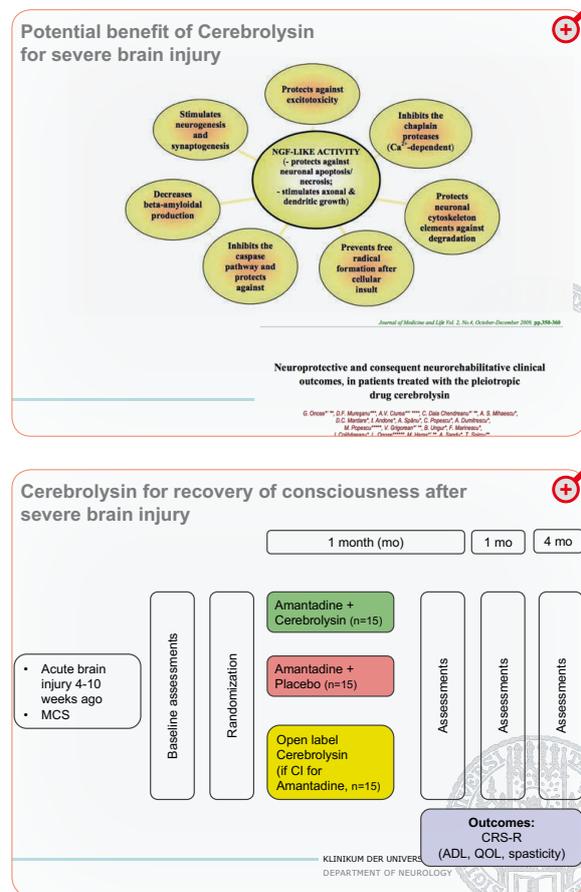


Fig. 3 Potential benefits of Cerebrolysin in patients with severe disorders of consciousness and a pilot trial investigating this therapy

Prof. Bender addressed finally the issue of outcome and prognosis by introducing the audience to the results of the prospective KOPF registry of UWS/MCS patients at admission to neurorehabilitation. The study included 246 patients with 3 year follow up and showed that after 1 year the probability of recovery in communication was 70% for TBI patients but only 5% for HIE (hypoxic ischemic encephalopathy) while only 16% of TBI and 0% of HIE patients regained functional independence. These results confirm that diagnosis of consciousness in the severe brain injury patients is indeed an important matter.

Minimally conscious state – potential advances in treatment



Jongmin Lee

Konkuk University Medical Center, Seoul, South Korea

ABSTRACT:

Severe acquired brain injury has profound impacts on alertness and cognition. A certain portion of survivors fail to fully recover and develop a disorder of consciousness ranging from a comatose state or vegetative state to a minimally conscious state. In addition to the devastating results on the quality of life of the patients, the families and caregivers are struck by the emotional and financial consequences of these conditions. Minimally conscious state (MCS) is a clinical condition characterized by markedly diminished consciousness with minimal reproducible signs of awareness of oneself or the environment. Although there is no definitive treatment options for MCS, advances in pharmacological and non-pharmacological treatments have been made with the growing understanding of the condition. The best studied pharmacological treatments are amantadine and zolpidem, which showed effectiveness in several

case series and randomized controlled studies. Other drugs such as apomorphine, levodopa and methylphenidate have also shown some beneficial effects. Examples of non-pharmacological treatments include deep brain stimulation, transcranial direct current stimulation and multimodal sensory stimulation. A combination of pharmacological or non-pharmacological treatments is another option for consciousness recovery. Cerebrolysin is a neuropeptide preparation with neurotrophic as well as neuroprotective effects. Combination treatments with Cerebrolysin and amantadine showed better recovery when compared with amantadine alone treatment, in MCS patients, and may be a promising treatment option.

Prof. Lee continued the topic of severe brain injuries with focus on MCS and the overview of available proven and new therapies, including his new data on using Cerebrolysin in this group of patients.

In his overview of the topic he indicated that severe acquired brain injury has profound impacts on alertness and cognition and that a certain portion of survivors fail to fully recover and develop a disorder of consciousness ranging from a comatose state or vegetative state to a minimally conscious state. Approximately 0.3% of severe TBIs may result in disorders of consciousness. A vegetative state is defined as a dissociative state of wakefulness without awareness, while minimally conscious state as a severe impairment of consciousness with wakefulness and partial preservation of awareness. Prof. Lee addressed some hypotheses explaining the mechanisms underlying MCS (a mesocircuit model) and went on to list most important diagnostic tools. He supplemented the information given by Prof. Bender with additional behavioral scales in use, such as: Sensory Modality and Rehabilitation Technique (SMART), Western Neurosensory Stimulation Profile (WNSSP), Wessex Head Injury Matrix (WHIM), Sensory Stimulation Assessment Measure (SSAM), Coma Near Coma Scale, Disorders of Consciousness Scale (DOCS). Further on, Prof. Lee elaborated on the therapeutic measures reiterating that the primary goal of therapeutic programs for DOC is to promote arousal while preventing secondary medical complications. In addition to confirming Prof. Bender's message, he pointed to the hypothesis that pharmaco-

logical and non-pharmacological modulation of mesocircuit may lead to a recovery of circuitry-level function. This is also the important field to explore in the clinical investigations of new candidate drugs. The therapeutic interventions include pharmacological treatments like Amantadine, Zolpidem, Bromocriptine, Levodopa, Apomorphine, Methylphenidate, modafinil as well as non-pharmacological treatments, like neurorehabilitation, multimodal sensory stimulation, deep brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation (tDCS). There is no definite consensus regarding treatment. Overall, the evidence concerning Amantadine, Zolpidem and tDCS is the most convincing.

Regarding new therapeutic approaches, Prof. Lee focused on Cerebrolysin, the agent with long known neuroregenerative properties. Cerebrolysin is a neuropeptide preparation with neuroprotective and neurotrophic properties. It is known to improve cell survival and neurogenesis through stimulation of neurotrophic factors in damaged brain tissues. Recent studies indicate that Cerebrolysin has a beneficial effect on recovery of motor and cognitive dysfunction in patients with stroke, TBI, and Alzheimer's disease. However, the effect of Cerebrolysin on disorders of consciousness in patients with acquired brain injury has not been systematically studied. Prof. Lee investigated the additive effect of Cerebrolysin and Amantadine treatment and the factors that affect the degree of response to Cerebrolysin in patients with disorder of consciousness (**Fig. 1**).

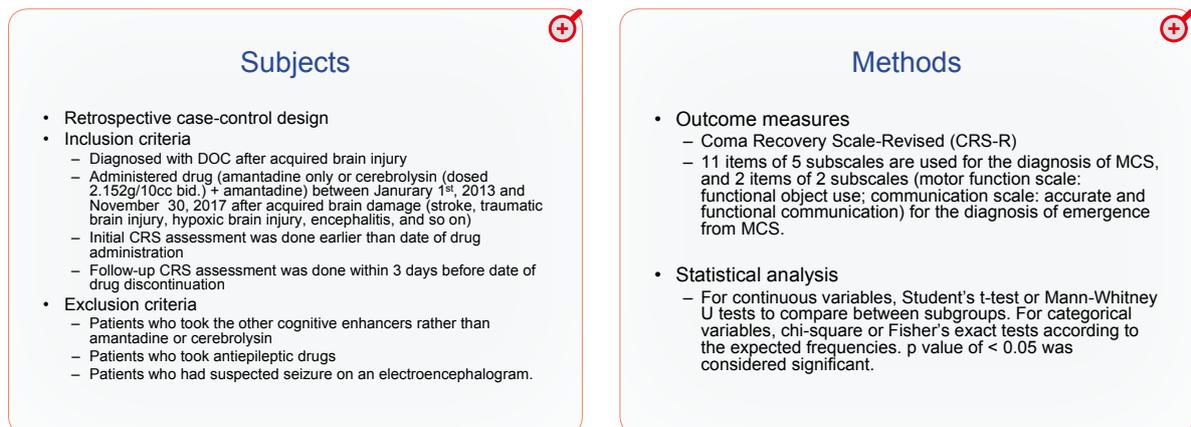


Fig. 1 The design and characteristics of Cerebrolysin plus Amantadine study conducted by Prof. Lee

The results showed that both treatment groups improved in the follow-up period with slight advantage of the combination therapy (Fig. 2).

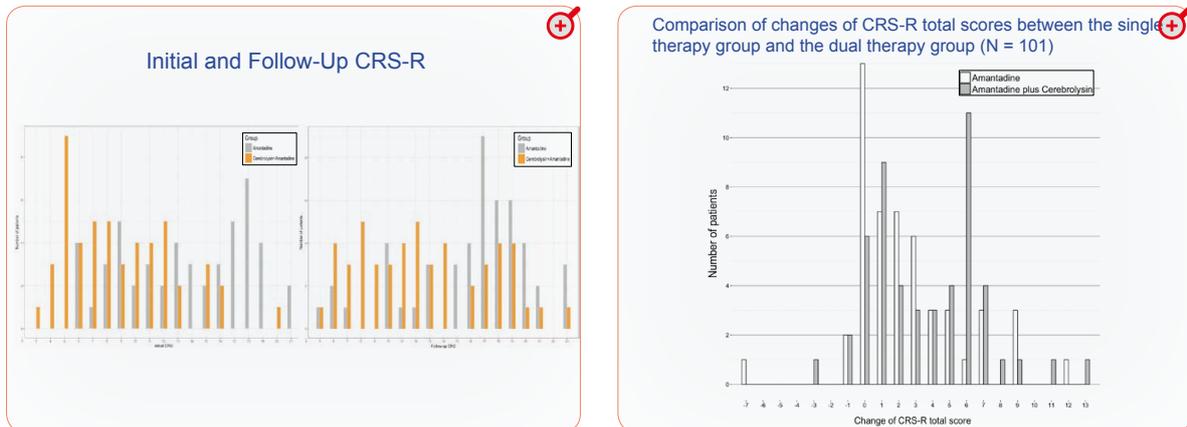


Fig. 2 The results of the study investigating the role of Cerebrolysin in treatment of patients with disorder of consciousness

In summary, change of CRS-R in the dual therapy (Cerebrolysin plus Amantadine) group tends to be higher than in the single therapy (amantadine only) group, albeit without reaching the statistical significance. The ratio of patients with change of DOC category in the dual therapy group was higher than in the single therapy group; here with a statistically significant difference. The proportion of patients with traumatic brain injury was higher in the subgroup which responded to dual therapy than in the non-response subgroup, albeit without statistically significant difference. Also the proportion of patients who received the drug before 6 months from onset was higher in the subgroup which responded to the dual therapy

than in the non-response subgroup, albeit without statistically significant difference. This was a retrospective study (therefore, vulnerable to selection bias) which included a small sample size and relatively low dose of Cerebrolysin. Additionally, the patients included in the study presented a heterogeneous population (stroke, traumatic brain injury, hypoxic brain injury, encephalitis) as well as a heterogeneous state of cognitive state. However, the results of this explorative study were interesting and warrant further investigations in the framework of a properly designed RCT. Especially, earlier treatment (before 6 months) and focus on TBI patients appear to be relevant areas of future controlled investigations.

Post-Stroke seizures and status epilepticus



Eugen Trinka

Department of Neurology, Christian Doppler Klinik,
Paracelsus Medical University, Salzburg, Austria

ABSTRACT:

Stroke and associated cerebrovascular disorders are one of the leading causes of death and disability in developed countries. Acute seizures and status epilepticus are increasingly recognized as relevant clinical factors, which are associated with a poor outcome. Whether acute seizures reflect the severity of the underlying stroke or contribute independently to poorer outcome has to be determined. Among stroke survivors the development of post stroke epilepsy increases morbidity and has a severe impact on the quality of life of the already disabled persons. Recognition and treatment of the post-stroke epilepsy syndromes is not always straightforward due to the oligo-symptomatic presentation and complicated by the cardio-vascular comorbidity. Moreover the altered metabolism and pharmacokinetic properties of the most often elderly population suffering from stroke also poses clinical problems to the treatment of post stroke epilepsy. Good tolerability of anti-epileptic drugs and lack of

interactions with other medications are of highest importance in these patients. Seizures, epilepsy and stroke have also common or shared risk factors. It has been shown, that a seizure increases the risk of a consecutive stroke by a factor 2 to 3, indicating, that the pathophysiology leading to cerebrovascular accidents and to seizures share some common pathways. Unfortunately, current anti-epileptic drugs have not been successful in preventing epilepsy or modifying the disease. *Sensu stricto*, they are not truly anti-epileptic drugs, but only anti-seizure drugs. There is an unmet need to develop better tolerated drugs and disease modifying treatments after acute brain insults like stroke, to prevent the further disabling course of post stroke epilepsy. The presentation will highlight principles of treatment in post-stroke epilepsy, management of acute symptomatic seizures and status epilepticus, as well as critically assess the potential of anti-epileptogenic treatments.

Prof. Trinka began his lecture by stating that seizures are inevitably associated with most impactful, high-burden-neurological disorders. Among stroke patients, 25% have seizures within 1 year after stroke. In Alzheimer's disease population, there is a prevalence of 5% of seizures within 3,6 years after diagnosis. This situation

is aggravated by the shift in aging with elderly population being most vulnerable to stroke and AD. The new prevention strategies for seizures must be urgently developed and are still missing. When classifying the seizures post stroke we are talking about early and late events (Fig. 1).

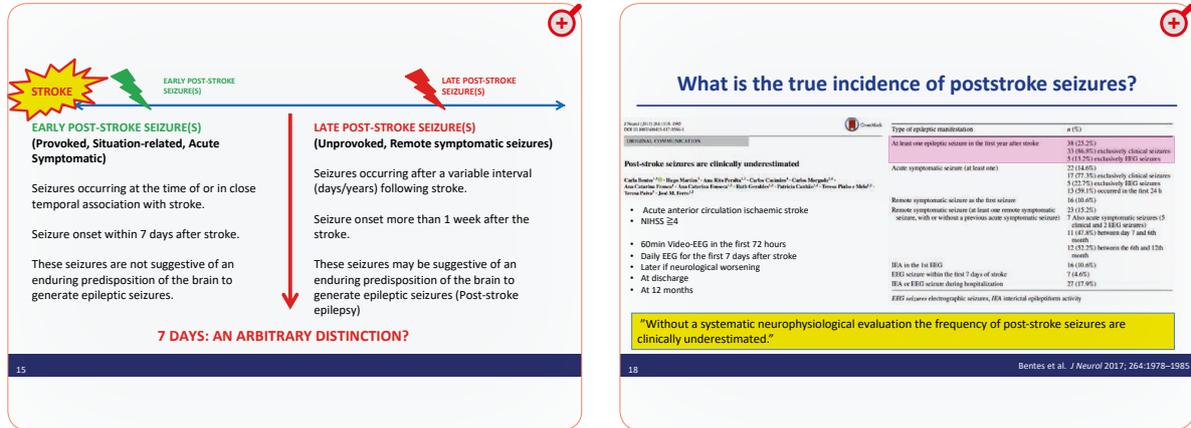


Fig. 1 The classification and incidence of post-stroke seizures

The cortical involvement, intracerebral hemorrhage, hemorrhage transformation, stroke severity and alcohol are risk factors related directly to both early and late seizures. The presence of an early seizure appears to exacerbate also the late seizures, as is the younger age. The incidence depends strongly on how we measure the often subtle and difficult to identify seizures. The continuous EEG appears to be the most precise way of deciphering this matter (Fig. 1). There is

an interesting link between post-stroke seizures and development of dementia. Seizures appear to double the risk of developing dementia after stroke. Prof. Trinka suggested that seizures should be viewed as sensitive markers of underlying neuropathology that convincingly indicate progression to dementia after stroke.

It is important to distinguish between status epilepticus (SE) and a seizure as the status epilepticus is not just the longer lasting seizure (Fig. 2).

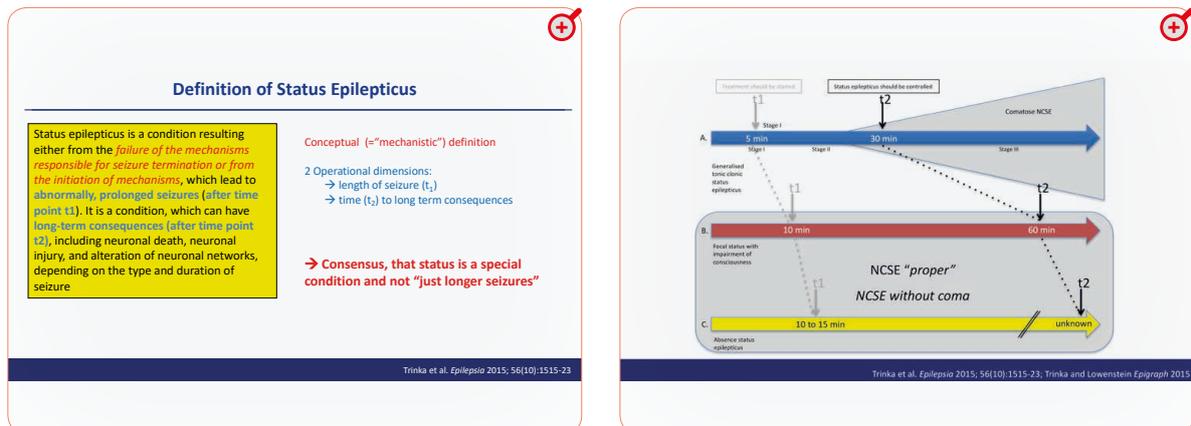


Fig. 2 The definition of status epilepticus

Vascular Dementia and multi-modal treatment concepts



Leonardo Pantoni

„Luigi Sacco“ Department of Biomedical and Clinical Sciences,
University of Milan, Milano, Italy

ABSTRACT:

Vascular dementia (VaD) is the second most common form of dementia after Alzheimer disease (AD). In addition, cerebrovascular diseases contribute to exacerbate and worsen AD and other neurodegenerative dementias course by adding further brain changes. The spectrum of VaD has been expanded by the recognition of pre-dementia stages that might benefit from interventions even more than advanced VaD. These stages are called mild vascular cognitive impairment and together with VaD form the category of vascular cognitive impairment (VCI). Many therapeutic trials have been performed and published over the years in patients affected by VCI but so far no drug has been licensed because most trials have been negative or not completely convincing. The possible reasons for this are many. In addition to the real lack of efficacy of some drugs, it is possible that previous trials have suffered from a number of limitations such as, for example, the inclusion of patients with heterogeneous forms of VaD/VCI that have restricted the possibility of finding

beneficial effects. Also the use of inappropriate end-points may have add inconsistency; this is the case of outcome measures derived from the AD field in which the cognitive profile is partially different. Despite this, some trials performed in VaD patients have indeed found some positive effects of drugs in ameliorating or slowing cognitive decline. Acetylcholinesterase inhibitors and memantine, all licensed for AD, have shown some effects also in VaD patients, although to a lower extent in respects of degenerative dementias. Over the last few years, new compounds have been tested in VCI (e.g., DL-3-n-butylphthalide, NeuroAiD, actovegin, Cerebrolysin) and have returned hope to the field. Also, new approaches like the combined use of different drugs are today under study. Finally, a multi-modal approach, reached by the combined use of drugs, diet, exercise, and cognitive training could be implemented in VCI. Although no data exist to support this multimodal approach, testing this strategy appears warranted.

The symptomatic treatments of cognitive deficits post-stroke was the main theme of Prof. Pantoni's lecture. The main question remains the same since a few decades: is it possible to treat vascular dementia? Most trials to date were negative. A few trials showed positive results, but drugs were not licensed. Clearly, the trials suffered from inadequate therapeutic targets and inclusion of heterogeneous patient samples. Also, the initial hope in cholinesterase inhibitors faded with passing time. This could be partially explained by the fact that placebo arms in Alzheimer's disease and vascular dementia patients show different progression of the cognitive decline. In vascular dementia trials the difference between the placebo arm and the treatment arm is much less pronounced and this effect must be taken into account. Additionally, we need dedicated neuropsychological tests for vascular dementia

rather than rely on the tests developed for other types of dementia, mainly Alzheimer's disease. We also need a drug with a well-defined rationale in a specific disease condition (which previously was lacking), a well-defined population of patients included in a well-designed trial (with outcome measures closely related to the underlying disease). Finally, we also need a well defined pathology to target with the appropriate investigated drug. Prof. Pantoni indicated that subcortical vascular dementia appears to be the entity which is relatively well defined and homogenous in its neuropathological characteristics. He gave an example of Nimodipine Scandinavian trial which showed negative results in its target population of multi-infarct dementia but positive results in the subpopulation of patients with subcortical vascular dementia (**Fig. 1**).



Fig. 1 The efficacy of a drug can heavily depend on the specific subtype of vascular dementia

The future of clinical development in vascular dementia should focus on new treatments, new drugs, and new approaches. Small vessel disease appears to be the right, relatively homogenous target. The use of surrogate markers as possible end-points in small vessel disease will also be helpful. Different target populations should be carefully selected including VaD patients, VCI patients, MCI with SV as well as post-stroke population.

Prof. Pantoni went on to present data on new treatments. DL-3-n-butylphthalide (NBP) a synthetic compound containing L- and D-isomers of butylphthalide from seeds of *Apium graveolens* (celery) was investigated in animal models where it shows several relevant mechanisms: protection against ischemic cerebral injury, inhibition of platelet aggregation, alleviation of oxidative damage and mitochondria dysfunction, improvement of microcirculation, reduction of neurologic deficit after stroke in spontaneously hypertensive rats, and increase in the brain acetylcholine level. When investigated in 281 patients with subcortical ischemic small vessel disease, it showed improvement of cognition and caregiver impression of change. Cerebrolysin was shown to improve outcomes in patients with VaD in several trials summarized in Cochrane systematic review. It induced improvement in the treated group measured with MMSE, ADAS-cog+ and also in general cognitive function reported as responder rates (Fig. 2).

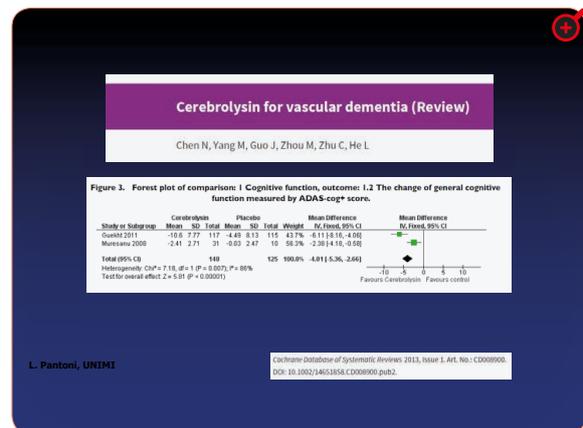
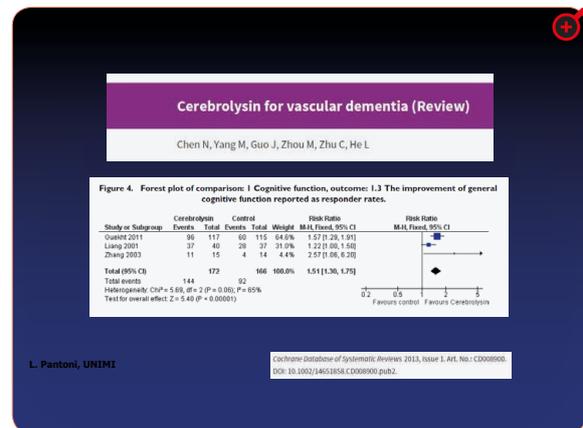
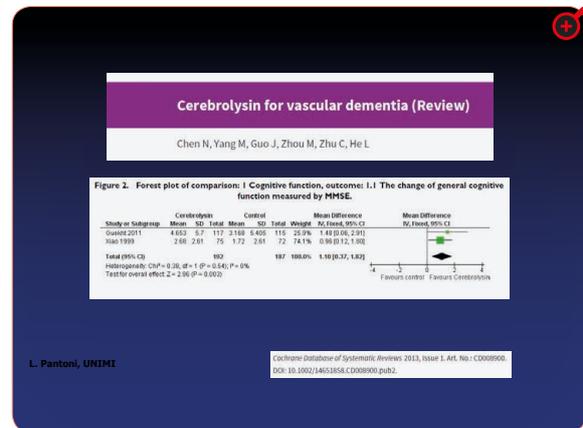


Fig. 2 The Cochrane systematic review of Cerebrolysin in VaD dementia patients

Cerebrolysin is being continuously investigated in animal models, recently in a model of CADASIL. In this study investigating anti-apoptotic properties of the drug in the lymphocytes from CADASIL patients, Cerebrolysin decreased the numbers of apoptotic cells. NeuroAID II and Actovegin were investigated in patients with VCI and also showed some positive results over placebo. Prof. Pantoni investigates currently a novel concept of combination treatment with nimodipine and choline alphoscerate in patients with small vessel disease (ClinicalTrials.gov Identifier: NCT03228498). The results should be available in the middle of 2019.

Apart from pharmacological approaches, there are also attempts to treat patients with cognitive rehabilitation tools. Prof. Pantoni was a principal investigator in one such trial investigating rehabilitation of attention in patients with mild cognitive impairment and brain subcortical vascular changes using the Attention Process Training II. In this 3-year-long randomized, prospective, single-blinded clinical trial the primary outcome was defined as improvement in functionality and quality of life in patients who undergo a rehabilitation program. The trial was negative in its primary outcome measure with some positive effects seen on the secondary outcomes. Physical activity at baseline appear to positively influence the results of pharmacological treatments and this aspect should also be considered in the future trials designs. Prof. Pantoni indicated also that using surrogate imaging markers (like white matter lesion progression) should help in the future investigations of drug candidates in vascular dementia and vascular cognitive impairment. Concluding his lecture, Prof. Pantoni suggested that prevention is possible and likely effective, especially since no drug is licensed for symptomatic treatment of VaD. There are many new treatments under study, also including preparations from herbs and traditional medicine. There appears to be a need for multimodal approaches combining various medications with cognitive rehabilitation. There is also a need for developing appropriate trial designs, including reliable biomarkers.

Post-stroke Depression - problems of diagnosis, methods of treatment



Natan Bornstein

JShaare-Zedek Medical Center, Jerusalem, Israel

ABSTRACT:

Stroke is a major cause of long-term physical, cognitive, emotional and behavioral disability. There is poor recognition of the emotional burden after stroke. Depression is abnormal and considered as “emotional distress”. Post-stroke Depression (PSD) is the most frequent non-cognitive neuropsychiatric complication affecting up to a third of all ischemic stroke patients. PSD is associated with increased mortality, poorer functional recovery and lower quality of life. Despite its great clinical relevance the relationship between stroke, depression and cognitive impairment remains relatively unexplained. The potential mechanisms of PSD are either neuroanatomical, caused by

lesions in the frontal areas, or directly affecting neural circuits involving mood regulation, or as a result of psychological adjustment required by the disease. There is controversy regarding the appropriateness of diagnosing depression in the setting of an acute stroke. Regarding treatment there is insufficient randomized evidence to support the routine use of antidepressants for the prevention of depression or to improve recovery from stroke. The approaches to management should be multidisciplinary including nurses and allied health staff.

One of the most complex sequelae of stroke is post-stroke depression. The importance of PSD increases together with growing epidemiology of stroke and with aging of the world's population. Prof. Bornstein repeated arguments from former lectures about increasing burden of stroke worldwide and pointed to the fact that neuropsychiatric disorders other than dementia contribute to a global burden of disabilities as fourth major cause. Stroke is not just physical condition. It is also cognitive, social and emotional disability and we often forget about this reality in the clinic. In fact, there is a poor recognition of the emotional burden after stroke (Fig. 1).

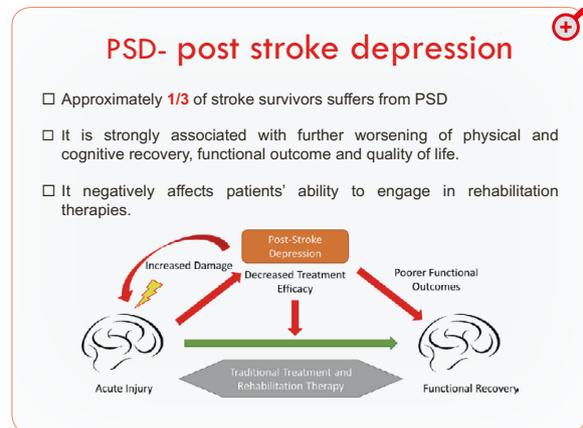
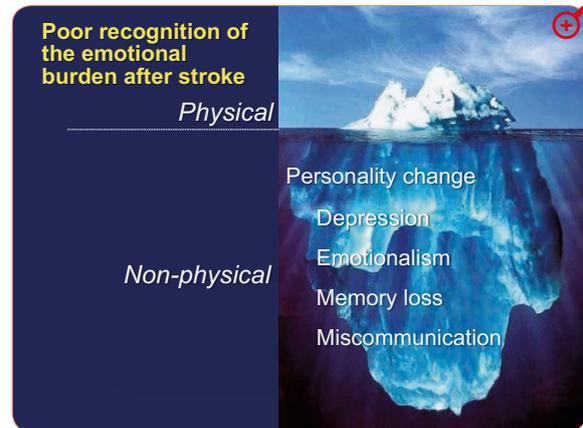


Fig. 1 The emotional burden of stroke and PSD

About 60% of stroke patients exhibit depressive symptoms within 2 years after infarction. 1/3 of all stroke patients have clinically diagnosed depression and it negatively affects patient recovery in all key recovery domains adversely impacting the quality of life after stroke. There are two potential mechanisms of PSD. Neuroanatomical theory assumes that PSD is usually caused by a lesion encroaching upon the left frontal areas or directly affecting neural circuits involved in mood regulation. Psychological theory maintains that PSD is a result of the psychosocial adjustment required or caused by the disease. In the neuroanatomical theory the mechanisms suspected involve the disruption of monoaminergic pathways and the depletion in cortical biogenic amines due to disruption of frontal-subcortical circuits. This leads to interruption of the amine containing axons ascending from the brainstem to the left cerebral cortex, enhanced glutamate-mediated excitotoxicity and neuroinflammatory response. The pro-inflammatory cytokines stimulate the

hypothalamic-pituitary-adrenal axis to release glucocorticoid hormones, which have several detrimental chronic effects on the CNS, including decreased neurogenesis and neuronal survival, and dysfunction of the neurotrophic system, notably in the hippocampus. As the consequences, there is an impairment of adaptive response of brain to ischemia (neuronal plasticity), in which brain derived neurotrophic factor (BDNF) plays a crucial role. Also the vascular factors, such as the white matter lesions could interrupt monoaminergic projections from midbrain and brainstem with similar pro-PSD effects. The involvement of mitochondrial dysfunctions has also been implicated in the overall mechanism underlying development of PSD. In addition, there are several genetic factors identified as associated with PSD. The mechanistic picture is complex, but points to a few common and potentially therapeutically relevant elements (**Fig. 2**).

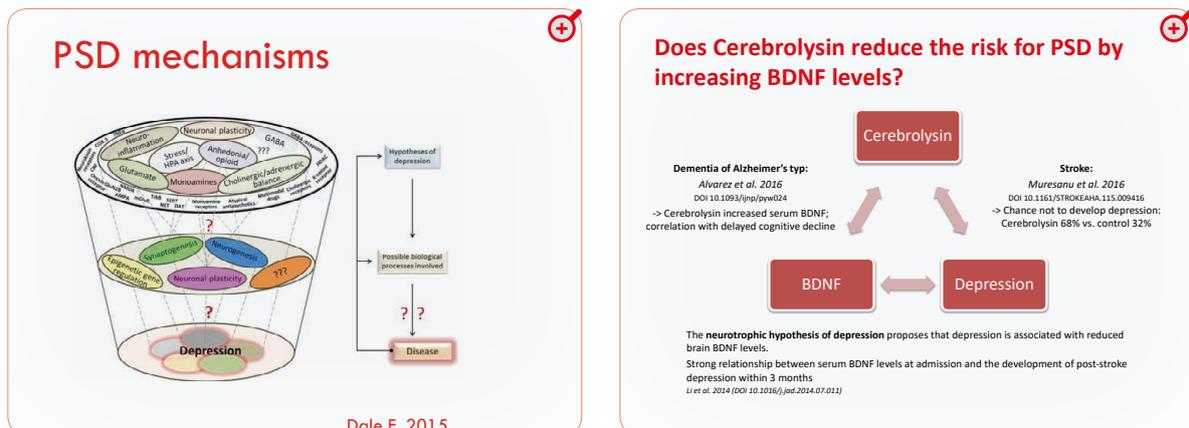
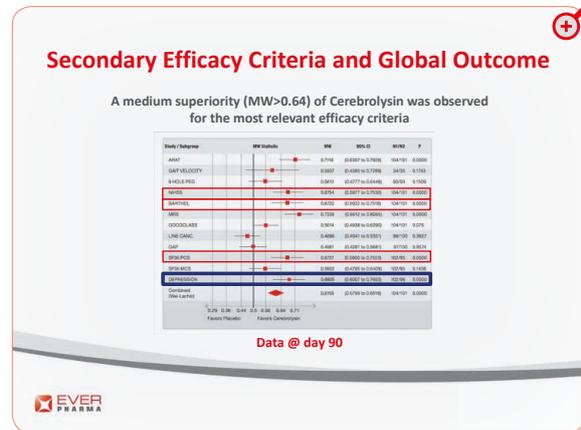


Fig. 2 The complex mechanisms of PSD point to potential treatment targets, including the neurotrophic regulatory pathways targeted by Cerebrolysin

Prof. Bornstein stated that the key to PSD treatment is a preventive treatment. The attempts in this direction were undertaken mainly with SSRIs and the published meta-analysis on 71 such trials showed that there is a significant benefit in preventing depressive symptoms in stroke patients after 3 or 4 weeks of treatment. Therefore, the SSRIs are the first-choice for the pharmacological prevention and therapy of PSD, although the evidence is not robust and there is no definite proof that they are more efficacious than TCAs. In fact, the results should be interpreted with great caution due to the substantial clinical and methodological heterogeneity among trials, most of which were small and presented various sources of bias. Additionally, it must be noted that thrombolysis appears to have been used only in the prospective observational cohort study by Miedema et al., (2010), and this study found that pre-stroke anti-depressant therapy with SSRIs was associated with a trend towards unfavorable outcome at 3 months after stroke (OR = 0.4, 95% 0.14-1.13; P = .08).

Finally, Prof. Bornstein returned to the hypothesis that a neurotrophic treatment might be considered an interesting preventive treatment option from the standpoint of previously described physiopathological mechanisms of PSD involved (Fig. 2). In the recently published CARS (Cerebrolysin And



Cerebrolysin modulates the neurovascular unit



Michael Chopp

Henry Ford Health System, Detroit, USA

ABSTRACT:

The neurovascular unit, the elemental set of cells and the functional unit within the central nervous system consists of endothelial cells, integral to the anatomical blood-brain barrier, neurons and non-neuronal cells such as pericytes, astrocytes, and microglia. The neurovascular unit is compromised and damaged after stroke, neural injury and neurodegenerative diseases. Recovery of neurological function very much depends on the functional recovery and integrity of the neurovascular unit, this interdependent set of cells. Here, we discuss the operational roles of Cerebrolysin in repairing and remodeling the neurovascular unit in response to stroke and neural injury. We show, using both in vivo double blinded preclinical trials for ischemic stroke and traumatic brain injury, and clinically relevant in vitro

models, that Cerebrolysin enhances neurological recovery by promoting vascular/endothelial homeostasis and blood brain barrier integrity and function. Cerebrolysin acts to a large extent on maintaining vascular function and by reducing procoagulant and prothrombotic states within the cerebral circulation after stroke and neural injury. The microvasculature after treatment with Cerebrolysin actively communicates and interacts with parenchymal cells, via the generation of families of therapeutic microRNAs which promote neurite outgrowth, remyelination, and reduce inflammatory responses. Thus, our data suggest that Cerebrolysin by acting on the neurovascular unit has a wide range of therapeutic applications for the treatment of stroke, neural injury and neurodegenerative diseases.

For Prof. Chopp, the vascular component of stroke and other cerebrovascular conditions is key to understanding the ability of the brain to recover after the injury, but also should determine our rationale in the therapeutic approaches. He dedicated his lecture to presenting results of the pre-clinical studies performed by his laboratory which evaluate the mechanisms of action of Cerebrolysin in stroke and other brain injuries. Prof. Chopp's group performed several high quality studies in animal models of stroke and TBI which demonstrated significant therapeutic benefits of Cerebrolysin. What underlies these therapeutic benefits? asked Prof. Chopp. In order to understand that, one has to look into pathophysiological events that occur after the brain injury. In stroke, the thrombotic clot transforms over time leading to damage in the blood vessels. This interaction is dynamic and evolves in time. Importantly, downstream of the clot there occur the profound pathophysiological effects impacting the structure and function of the microvasculature. These include pro-coagulating state, inflammation, secondary thrombosis, and hypo-perfusion, which persists also after successful thrombectomy (as seen on imaging data). The fibrin deposition in the microvasculature appears to be another prominent negative process post-stroke as well as in vascular dementia and TBI. It has been linked with upregulation of pro-inflammatory cytokines and plasminogen activator inhibitor (PAI-1) which block endogenous thrombolysis (**Fig. 1**).

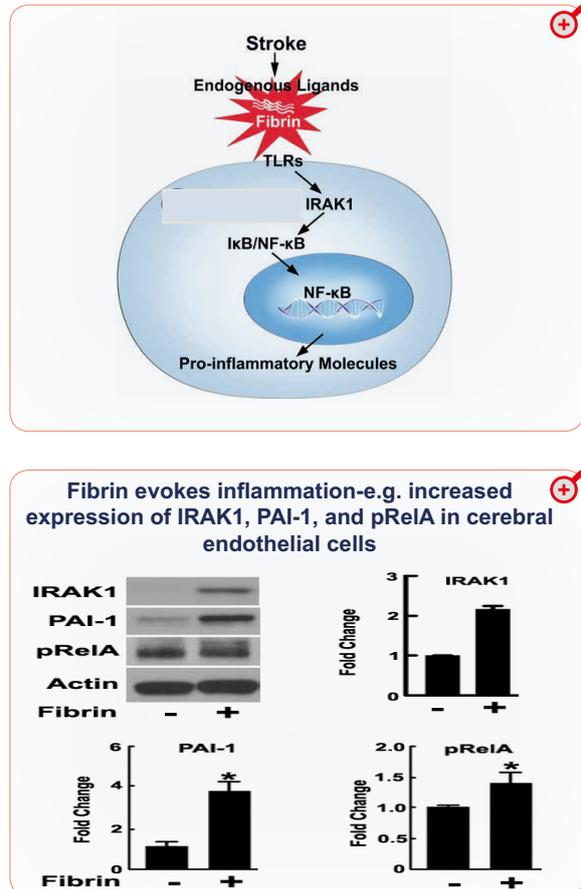


Fig. 1 Fibrin deposition in microvasculature leads to pathological events post-brain injury

In effect, the fibrin deposition makes it more difficult to achieve tissue reperfusion after stroke. Prof. Chopp went on to show the new data describing how Cerebrolysin counteracts this pathological

events. In the in vitro model of blood brain barrier, based on human endothelial cells, Cerebrolysin reduced fibrin induced vascular permeability and production of pro-inflammatory cytokines (Fig. 2).

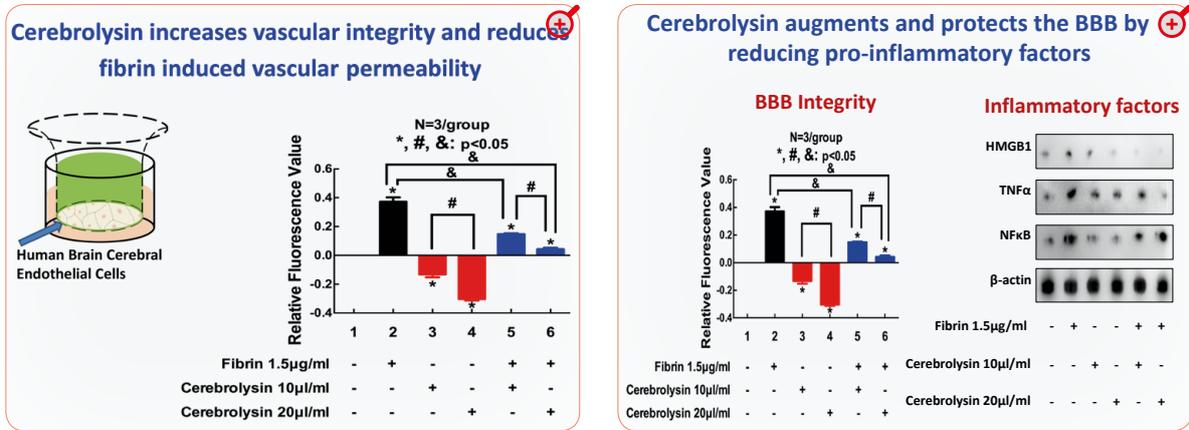


Fig. 2 Cerebrolysin reduces fibrin induced vascular permeability and production of pro-inflammatory cytokines by the endothelial cells

Another prominent mechanism through which Cerebrolysin exerts its effects in the brain injury models is linked to stimulation of micro RNAs (miRs). These are little pieces of non-coding RNA that regulate simultaneously hundreds of genes. The sophistication and complexity of miR-based regulation differentiates humans from other animal species. Prof. Chopp's team have published the

extensive data on Cerebrolysin inducing certain families of miRs (miR 17-92) after brain injuries, through the mechanism involving sonic hedgehog (Shh) morphogen. This cluster of miRs regulate inflammation, axonal growth (underlying brain plasticity processes), and has profound effect on psychiatric diseases and depression.

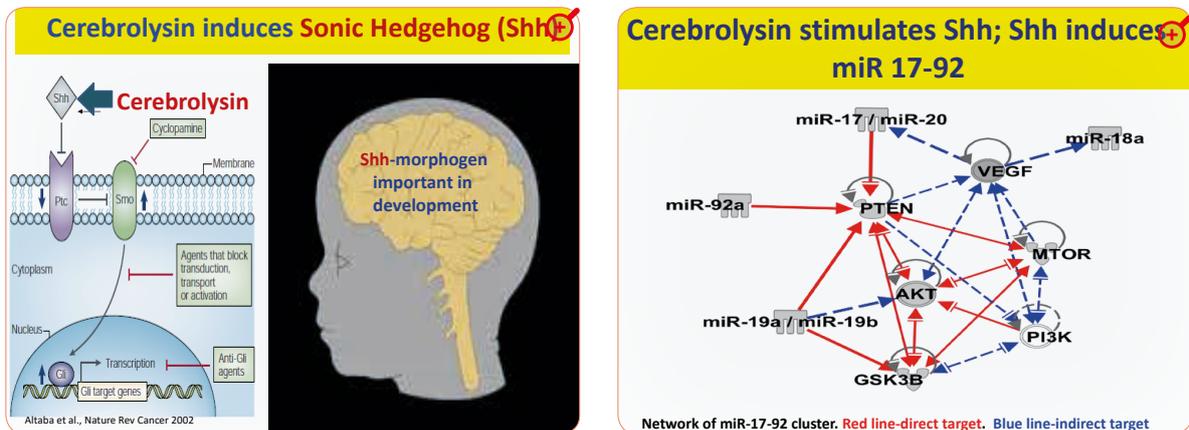


Fig. 3 Cerebrolysin acts through signaling pathway involving sonic hedgehog (Shh) and micro-RNAs (miR 17-92) and counteracting physiopathological effects of stroke and stimulating axonal outgrowth

In summary, Cerebrolysin helps in maintaining the integrity of blood brain barrier, reduces the pro-inflammatory processes, and also concurrently induces clusters of miRs which is conduc-

tive to enhancing the brain plasticity processes needed for recovery from the brain injuries of various etiology.

Anticorrelated processes in neurobiology - consequences for neurorehabilitation strategies



Dafin Muresanu

Chairman Department of Neurosciences, University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

ABSTRACT:

Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes. Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care. It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke. The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination

with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke. The study showed a statistically significant group difference in the upper limb motor function (ARAT) at day 90 – primary end point. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach. Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.

Prof. Muresanu began by stating that in the last decade, we have seen an increase in efforts to establish evidence based parameters for the practice of CNS neuroprotection and neurorecovery, as well as to find the best way to assess external validity of these data. This effort has been placed in a broader context involving the role of theory and basic research in advancing rehabilitation science, particularly in relation to specifying the active components and mechanisms of drugs and interventions. There is still a significant gap between these directions. Particularly, our approach to rehabilitation must increasingly rely on interdisciplinary teams and personalized approach to a patient. The concept of anti-correlated processes in neurobiology helps in better understanding which pathophysiological processes should be targeted and also how we should target them. After an acute brain lesion there is always an endogenous continuous brain

defense response consisting of two main anti-correlated sequences: an immediate one, aiming to reduce brain damage and impairment (target for neuroprotection), and a later one, aiming to repair the brain damage and, in consequence, disability (target for neurorepair and neurorecovery). This two sides of post-lesional regulation cannot be active at the same time, said Prof. Muresanu. The brain functions seen at cellular, circuitries and dynamic networks level are all embedded in this pattern of anti-correlated process. Every level in turn comprises several sub-levels, each of them is characterized by a multitude of anti-correlated processes. The concept of endogenous neuromodulation, refers to the brain's capacity to balance anti-correlated processes at these key regulatory levels.

Treatment of stroke has to be seen as a time-dependent process (**Fig. 1**).

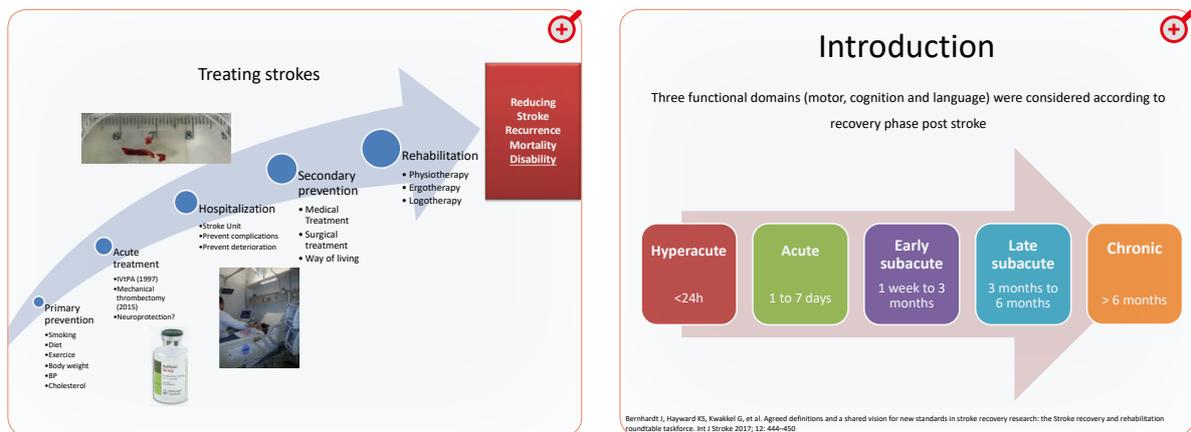


Fig. 1 The progress in stroke management overlaps with our capacity to address its subsequent phases

Timing and intensity of acute rehabilitation are important issues in post-stroke functional outcomes, but remain controversial. Early mobilization after stroke is recommended in many clinical practice guidelines worldwide, but we know that we need more reliable biomarkers in order to be able to precisely administer our pharmacological and rehabilitation therapies. In motor rehabilitation, DTI appears to be such a marker of choice. In cognitive and language domains, we are still in need of properly established biomarkers.

Our up-to-date knowledge resulting from published literature indicated that the recovery of the upper limb deficits became a core objective of rehabilitation after stroke. Upper limb impairment has devastating consequences on quality of life, not only impeding the returning to previous activities, but also interfering with the ADLs like eating, dressing and washing. We also understood that the recovery of upper limb is much more difficult than of the lower limb, irrespective of the outcomes scales used. The ARAT score was used to develop the methodology

(PREP algorithm) helpful in predicting recovery of the upper limb and appears to be a precise tool of choice for clinical investigations in the rehabilitation after stroke.

With respect to pharmacological strategies for stroke, we have seen many monomodal drugs tested in clinical neuroprotective trials as well as a few tested in the context of rehabilitation. As the first group failed to deliver expected results (mainly due to violation of the anti-correlation principles by a study design), the second, like SRRIs, provided some evidence that pharmacological support of rehabilitation is possible. However, the best success should be expected from drugs with multimodal properties, mimicking and matching the anti-correlated mechanisms of the brain itself, said Prof. Muresanu.

He went on to introduce the audience to the results of the recently published CARS trial in which Cerebrolysin was used in combination with upper limb rehabilitation and the sensitive ARAT score was employed for the outcome assessment (**Fig. 2**).

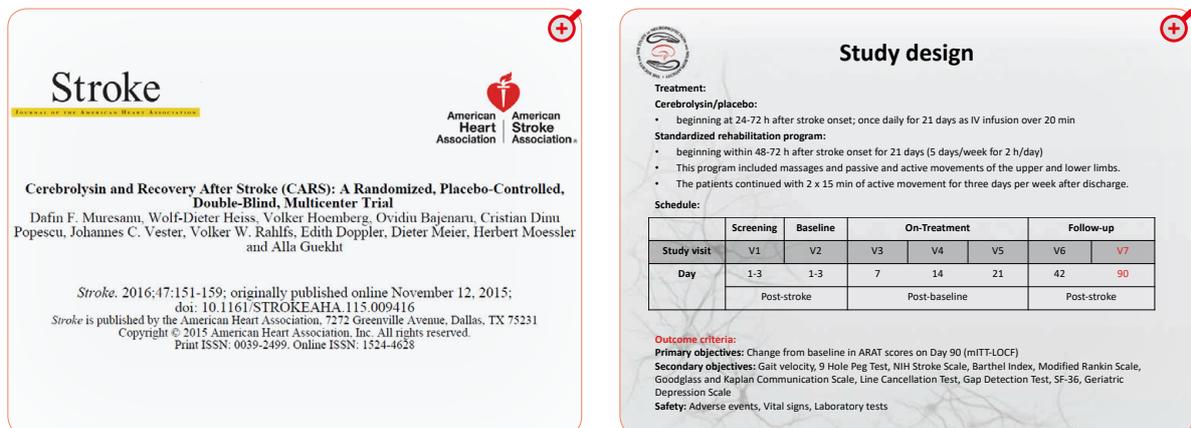


Fig. 2 The CARS trial design was derived from the former experience with Cerebrolysin in acute stroke

The primary outcome measure (change from baseline in ARAT scores on Day 90) as well as several secondary outcome measures (including mRS, NIHSS) were positive (Fig. 3).

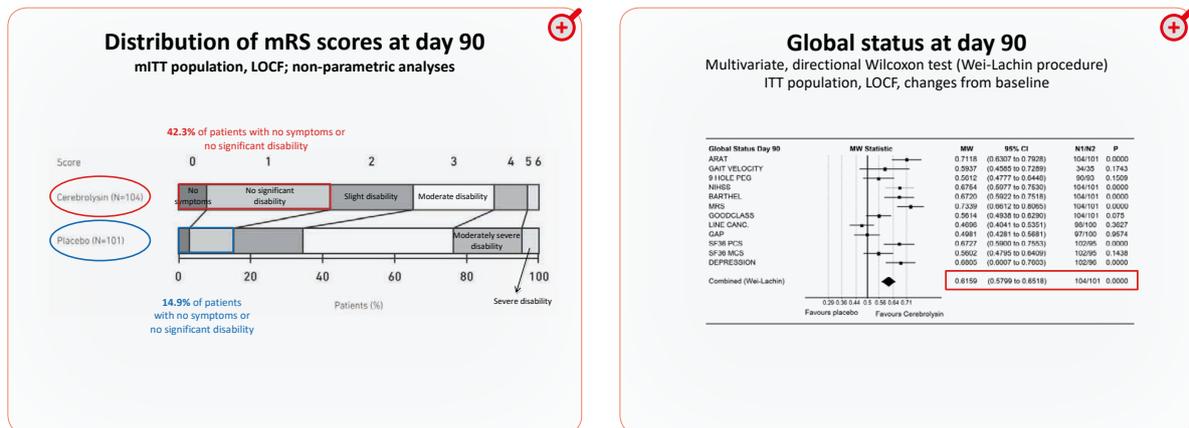
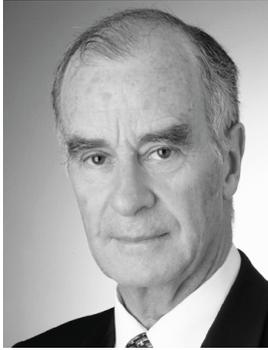


Fig. 3 The results of the CARS trial showed additive effect of Cerebrolysin on motor rehabilitation after stroke

These results confirmed the validity of the approach of multimodal support of the motor rehabilitation in stroke patients and correspond to well established pre-clinical evidence elucidating the neurotrophic mode of action of Cerebrolysin. The study confirmed also the excellent safety profile of this agent reported in earlier RCTs. The same design was used for studying rehabilitation of patients with different baseline severity (mild stroke patients). The meta-analysis of both trials confirmed the primary findings of the CARS trial.

Prof. Muresanu ended his talk mentioning ECOM-PAS study, in which Cerebrolysin was used from day 8 after stroke in the motor rehabilitation. DTI and fMRI imaging techniques were employed to elucidate the mechanistic effects of Cerebrolysin on stroke recovery. Interestingly, this study showed that Cerebrolysin promotes true recovery of lost motor functions by counteracting the early compensation mechanisms.

After many trials: A meta-analysis finally proves efficacy of Cerebrolysin in ischemic stroke



Wolf-Dieter Heiss

Max Planck Institute of Metabolism Research, Cologne, Germany

ABSTRACT:

Treatment of ischemic stroke remains insufficient and is only successful during the first hours after the attack if reperfusion of the ischemic territory can be achieved. Thrombolysis resulting from the intravenous administration of recombinant tissue plasminogen activator (rt-PA) within 4.5 h significantly reduces the incidence of death or dependency at 3 to 6 months, but the benefit of its administration ceases between 4.5 and 6h after the ictus. Attempts to recanalize occluded vessels by intra-arterial rt-PA or mechanical thrombectomy enhance reperfusion and have recently been shown to improve clinical outcome in carefully selected patients. However, the number of patients who may benefit from these reperfusion therapies is small and probably totals less than 20% of all stroke victims, even for those treated at specialized centers. Therefore, many therapeutic strategies have been developed targeting the pathophysiological cascade that starts with ischemia and ultimately leads to irreversible tissue damage. Despite beneficial results obtained in experimental ischemia neuroprotective drugs have not shown efficacy in clinical trials. This failure to translate results from experimental studies to clinical application might be due in part to the

use of inappropriate animal models and also to the design of human trials, which usually does not consider the limited time windows of targeted steps in the pathophysiological cascade or the complexity of the biochemical and molecular mechanisms leading to ischemic brain damage. As a consequence, treatments directed at correcting one biochemical or molecular step in the pathophysiological cascade of ischemic cell damage have not been successful in stroke, warranting the testing of a multi-targeted therapy that includes compounds with effects on several of the associated pathophysiologic events. One of these multimodal compounds is Cerebrolysin, a neuropeptide preparation of porcine origin produced by a standardized manufacturing process and consisting of low molecular-weight neuropeptides (<10 kDa) and free amino acids. In experimental models this compound has been shown to have neuroprotective properties and to be effective against excitotoxicity, and additionally, it has been demonstrated to exhibit neurotrophic activity, promote neuronal sprouting, improve cellular survival and stimulate neurogenesis. Cerebrolysin has shown success in experimental middle cerebral artery occlusion

models, resulting in a reduction in the infarction volume and improvement of functional recovery. Cerebrolysin has been tested in several clinical trials during the acute phase after ischemic stroke with positive findings and significant results especially in more severe strokes and at earlier time points. However, observed effects have not reached statistical significance in the primary outcome parameters on day 90, and small sample sizes have limited the precision of these studies. In the largest randomized, double-blind, placebo-controlled trial a subgroup analysis in patients with more severe stroke has indicated a clear trend in favor of Cerebrolysin for improved outcome and reduced mortality. The treatments in these previous clinical trials were initiated during the acute phase after stroke and were mainly limited to 10 days. The neuroprotective effects of Cerebrolysin have been primarily assessed, and its neurotrophic and neuroplastic effects on recovery, as indicated in animal experiments, have initially been neglected. Studies in early rehabilitation patients after stroke have been completed recently investigating also the efficacy of a longer duration of Cerebrolysin application on motor function recovery. These studies found a large superiority of Cerebrolysin over placebo on motor function recovery on day 90 and in the global outcome.

The primary objective of a recent meta-analysis (Bornstein et al 2018) was to assess whether these findings can be confirmed by a broader ensemble of randomized placebo-controlled

clinical trials. This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30 50 ml Cerebrolysin once daily for 10-21 days, with treatment initiation within 72 hours after onset of ischemic stroke. For five studies original analysis data were available for the meta-analysis (individual patient data analysis), for four studies aggregate data were used. The combination by meta-analytic procedures was pre-planned and the methods of synthesis were pre-defined under blinded conditions. The nonparametric Mann-Whitney (MW) effect size for NIHSS on day 30 (or 21), combining the results of nine RCTs by means of the robust Wei-Lachin Pooling Procedure [MERT], indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, $P < 0.0001$, $N = 1879$). The combined number-needed-to-treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full scale ordinal analysis of mRS at day 90 in the moderate to severe patients resulted in MW 0.61 with statistical significance in favor of Cerebrolysin (95% CI 0.52 to 0.69, $P = 0.0118$, $N = 314$). Safety aspects were comparable to placebo. This meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke. Ref.: Bornstein NM et al: *Neurol Sci* 2018;39:629-640

Prof. Heiss began his lecture by outlining the concepts of ischemic stroke, penumbra and reperfusion, indicating that reperfusion (both thrombolysis and thrombectomy) while being an effective acute treatment approach, unfortunately cannot be applied successfully in majority of stroke patients. Therefore, we need some easier to deploy therapies. In the recent decades more than 1000 experimental treatments have been tested as candidates for neuroprotective therapies which could be used in majority of stroke patients. More than 50 of them reached the clinical stage development, but none has shown efficacy in trials with patients suffering from focal ischemic stroke. New avenues in neuroprotection have been proposed including: treatment as early as possible, using imaging to select appropriate candidates, combine neuroprotectant with rtPA, investigate severe strokes with hypothermia and decompression, promote recovery mechanisms (neurotrophic factors, stem cells) and use of multimodal drugs with early neuroprotective and prolonged neurorestorative effects. Cerebrolysin fulfills the last category of multimodal drugs and hence was investigated in stroke in the past (**Fig. 1**).

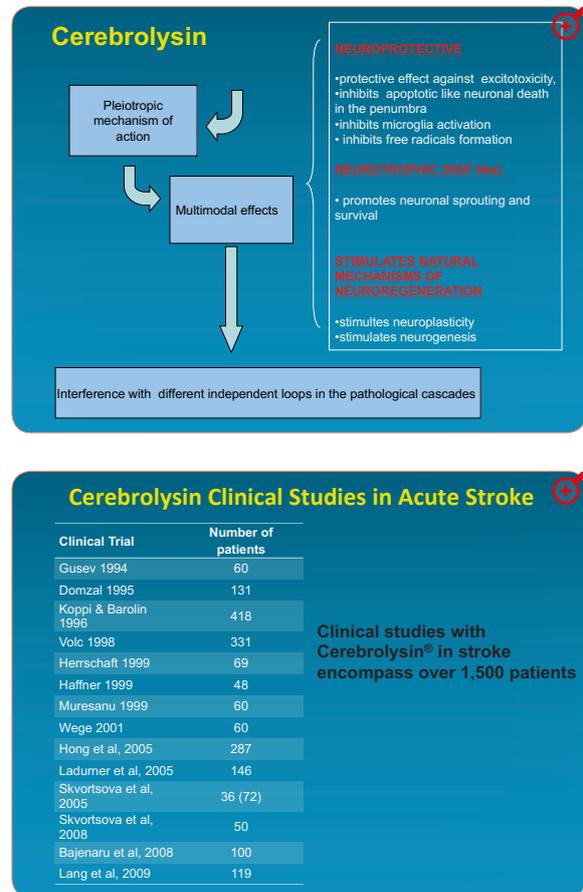


Fig. 1 The multimodal treatment of stroke with Cerebrolysin

None of the past trials with Cerebrolysin showed unequivocally positive results and Prof. Heiss mentioned as example the CASTA study in which he was personally involved. This study indicated that the effect of Cerebrolysin is seen mainly in moderate to severely affected stroke patients. This was also a conclusion important for establishing the future clinical trials. The CARS trial showed that the combination of Cerebrolysin with motor rehabilitation is working and that the findings from the CASTA hold true also in the rehabilitation trial. The CARS results confirmed that in patients with severe motor involvement (FMA<50) at 7 days after stroke onset, Cerebrolysin treatment for 3 weeks in subacute phase of stroke, in addition to the rehabilitation therapy, showed better improvement of motor function at 3 months after stroke onset than placebo group, with statistical significance ($p < 0.05$). Again, in patients with moderate to severe stroke severity (NIHSS ≥ 6) at 7 days after stroke onset, Cerebrolysin treatment for 3 weeks in subacute phase of stroke in addition with the rehabilitation therapy showed better improvement of motor function at 3 months after stroke onset than placebo group with statistical significance ($p < 0.05$). The results from this study showed that Cerebrolysin can be administered safely to provide beneficial effect on motor recovery in subacute stroke patients with moderate to severe stroke and severe motor involvement.

The pyramid of clinical evidence is useful for evaluating the efficacy of the drugs which were extensively studied in the past and continue to deliver convincing results. It indicates that the highest level of clinical evidence can be obtained through meta-analysis of RCTs. This was the reason why Cerebrolysin investigators decided to perform such an analysis, with the aim to evaluate the efficacy and safety of Cerebrolysin in patients with ischemic stroke. The focus was on early neurological conditions, as measured with NIHSS, and on functional status, using mRS (Fig. 2).

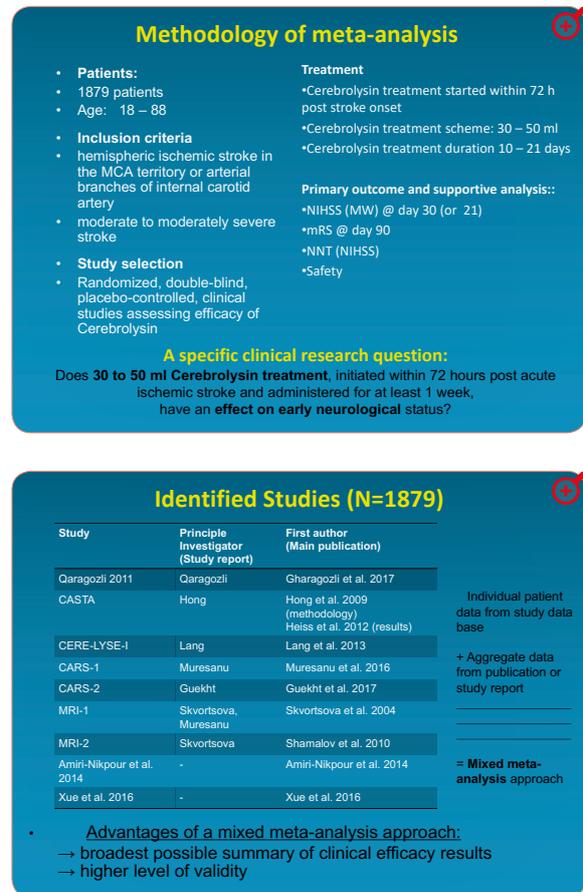


Fig. 2 The meta-analysis of Cerebrolysin in the ischemic stroke

The specific research question posed for this meta-analysis was: Does 30 to 50 ml Cerebrolysin treatment, initiated within 72 hours post acute ischemic stroke and administered for at least 1 week, have an effect on early neurological status? While the individual studies' results failed to deliver unequivocal results, the meta-analysis provided evidence of efficacy in NIHSS (Fig. 3).

Importantly, the meta-analysis showed that the patients receiving Cerebrolysin have a 60% higher chance for a better outcome. Interestingly, similarly to results from CASTA, in predominantly mild stroke patients there was a trend for improvement, but not statistical significance. However, in patients with moderate to severe status at baseline as well as in patients with NIHSS>12 at baseline, the observed treatment effect was significant. This result confirmed basic validity of CASTA design and the research conclusions drawn from its results. The safety and tolerability of Cerebrolysin was confirmed as excellent, with a trend toward decreasing the rate of mortality in the Cerebrolysin treated patients.

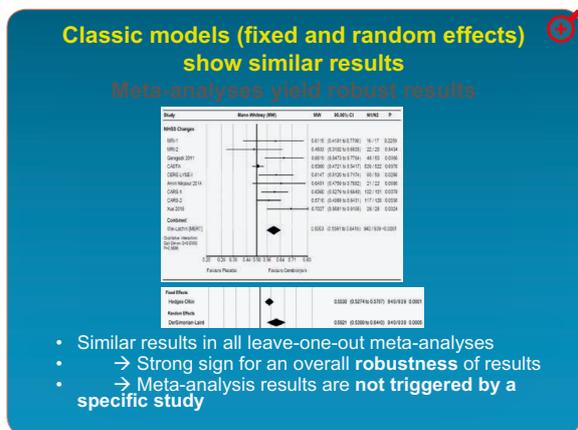
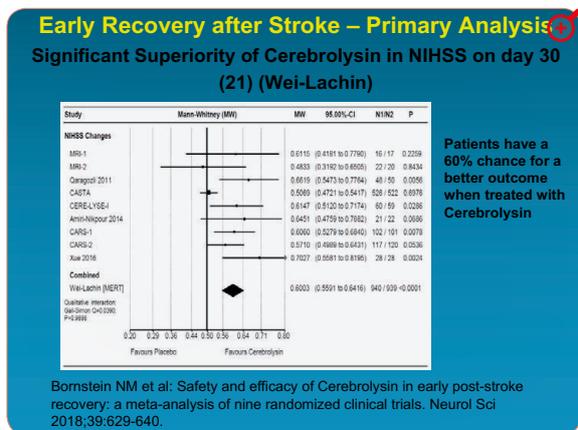


Fig. 3 Early recovery after stroke - results of meta-analysis of Cerebrolysin in the ischemic stroke

Summarizing his lecture, Prof. Heiss indicated that the meta-analysis showed superiority of Cerebrolysin at day 30 indicating the early pro-recovery action. The combined number needed to treat (NNT) for clinically relevant changes in early recovery was 7.7. Statistically significant long-term benefits were shown with strongest effects observed by patients with higher baseline severity. The safety of Cerebrolysin was comparable to placebo with a tendency to reduction of death rate.

VASCage – research center on Vascular Ageing



Stefan Kiechl

Department of Neurology, Medical University Innsbruck,
Innsbruck, Austria

ABSTRACT:

Life expectancy is continuously increasing worldwide and will exceed 90 years in a few countries until 2030. Unfortunately, health span - defined as the period of living without disability - is not increasing at the same pace. Vascular ageing is a key to healthy ageing and to extension of health span. VASCage represents a large FFG-funded international Research Centre on Vascular Ageing with its headquarters in Innsbruck. This presentation will summarize the key R&D output of VASCage over the past four years and give an outlook into the planned and currently submitted follow-up project. Within the program proposed for 2019-2023, stroke will have a top

priority and several individual projects will focus on recovery after stroke. One innovative initiative attempts to extend the time window for successful recovery and rehabilitation by a combined pharmacological and transcranial direct-current stimulation approach. Other projects address disease prevention; improved diagnosis and therapy as well as a better understanding of the mechanism underlying vascular ageing. As an overall aim, VASCage intends to improve vascular health in the ageing community and to develop strategies to better cope with the consequences of vascular ageing.

VASCage is a collaboration of universities and research centers with the industry partners and is focused on clinically relevant projects with Bruneck and other cohort studies included or planned. Scientific assets and achievements (conduction of the 6th phase of the renowned Bruneck Study and its extension), recruitment of one of the largest cohorts of 15/16-year-old students (EVA, n>2000), build-up of an infrastructure for “big data” management, collection of valuable specimens like stool, gain in analytical know-how and expertise in nutritional epidemiology, and the initiation of a huge international consortium of atherosclerosis studies in Innsbruck (Proof-ATHERO) are among major activities of the program. It is estimated that this collaboration will yield about 100 publications in this initial 4 years period. Some of them were already published in the most prestigious medical journals, like Lancet and NEJM. The ongoing rigorous programs for health prevention in apprentices and students (EVA), dissemination of the impactful output of VASCage beyond the academic audience (PR activities and direct dialogue with the public in Minimed and Pint of Science) are among the priorities.

Regarding the recent scientific projects, Prof. Kiechl mentioned the work on new biomarkers, including micro-RNA which should help in predicting metabolic risks in healthy individuals (**Fig. 3**).

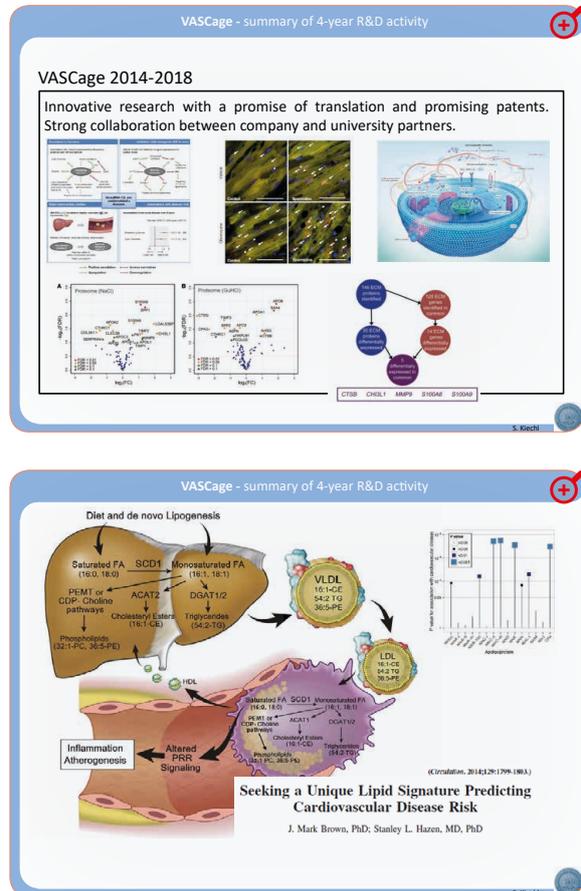


Fig. 3 The examples of innovative research projects of VASCage

VASCage provided first strong epidemiological evidence that spermidine contained in various concentrations in human diet can prolong life not only of laboratory animals, but also of humans. In further phases of VASCage, stroke and stroke rehabilitation will be included as priority projects. These include among many others: development of new blood-thinning therapy for the secondary prevention of stroke; automated imaging analysis; test allowing to establish the origin of the thrombus in order to inform anti-coagulation decisions; establishing an Austria-wide clinical trial platform which will be open to all Austrian stroke researchers; studying the CHIP mutations which are accumulating somatic mutations linking cardiovascular events with cancer development; establishment of the sensor shirt which would be dedicated to continuous monitoring of key bodily functions in stroke units and beyond; targeting the less known complications of stroke, like osteopathy and fracture risk.

Prof. Kiechl added that in the stroke rehabilitation and recovery, EVER Pharma intends to contribute to very ambitious project of VASCage program together with innovative startup companies (Fig. 4). This project intends to increase the therapeutic window for stroke rehabilitation for up to 2 months or longer after stroke by combining tDCS with Cerebrolysin treatment.



Fig. 4 The joint VASCage and EVER Pharma project in stroke rehabilitation

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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EVER Neuro Pharma GmbH
Oberburgau 3
4866 Unterach
Austria
www.everpharma.com