EVER PHARMA

ESOC 2023

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Evidence-based therapies for all stroke patients – advances and guideline recommendations

Chair: Ales Tomek, Prague (CZ)

- **Get with the guidelines in post stroke motor recovery**
  Steven Zeiler (US)
- **Effective Cerebroprotection in the stroke reperfusion era – why we need it?**
  Jacek Staszewski, Warsaw (PL)

Evidence-based therapies for all stroke patients – advances and guideline recommendations

For EVER Pharma our satellite symposium titled **'Evidence-based therapies for all stroke patients – advances and guideline recommendation'** at the European Stroke Conference 2023 in Munich was very important. For the first time since ESOC 2019, there was an opportunity to present new evidence, treatment concepts and guideline recommendations at an international conference.

In these years between 2019 and 2023, many new treatment concepts in stroke therapy gained importance, especially thrombectomy. Discussions about pharmacological agents to support recanalization therapies and neurorehabilitation after stroke have also come to the fore.

In this period, Cerebrolysin has evolved from a recognized drug for motor recovery to a widely accepted standard therapy for ALL stroke patients. The reasons for this were convincingly explained by the three speakers.

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Ales Tomek

Neurologist at Motol University
Hospital at Prague, Czech Republic

Introduction

Prof. Ales Tomek from Prague presented the global epidemiological burden of stroke *(figure 1)*, highlighting the loss of DALY's in low- and middle-income countries that contribute to a further increase of the socio-economic burden.

In his lecture, Prof. Tomek emphasized that internationally recognized algorithms have been developed in almost all areas of stroke, leading to improvements in the standard of care.

He pointed out that this is not the case in the field of rehabilitation, where such algorithms have either not yet been developed or implemented or are still too heterogenous.

Dr. Tomek showed existing quality of care measures, but these have not been standardized in neurorehabilitation in the same ways in acute stroke care.

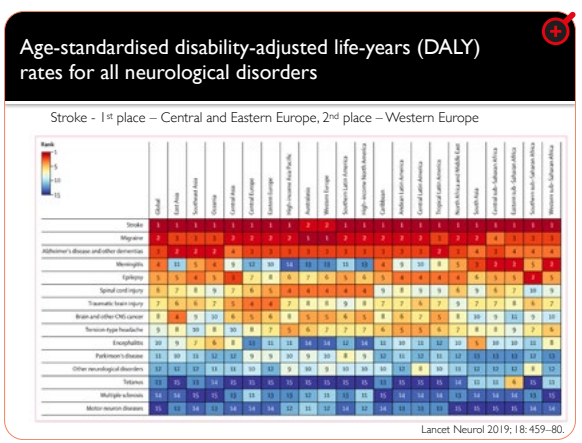
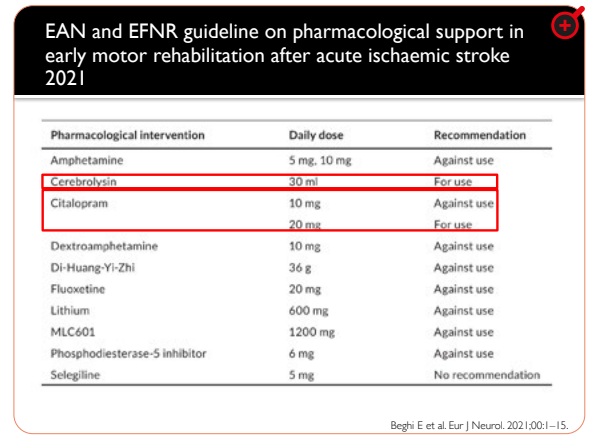


Figure 1

The following requirements are identified by him:

- **Rehabilitation needs to** be organized **more** centrally and equally across different centers
- Rehabilitation needs indicators to monitor the **quality of care** with regular benchmarking
- Stroke rehabilitation needs **detailed and practical guidelines for each type of treatment**, including pharmacological support

Finally, Prof Tomek presented the EAN & EFNR Guideline on Pharmacological Support in Early Motor Rehabilitation of 2021 as an example of the last requirement he mentioned above *(figure 2)*.


EAN and EFNR guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke 2021

Pharmacological intervention	Daily dose	Recommendation
Amphetamine	5 mg, 10 mg	Against use
Cerebrolysin	30 ml	For use
Citalopram	10 mg	Against use
	20 mg	For use
Dextroamphetamine	10 mg	Against use
Di-Huang-Yi-Zhi	36 g	Against use
Fluoxetine	20 mg	Against use
Lithium	600 mg	Against use
MLC601	1200 mg	Against use
Phosphodiesterase-5 inhibitor	6 mg	Against use
Selegiline	5 mg	No recommendation

Beghi E et al. Eur J Neurol. 2021;00:1–15.

Figure 2

Steven R. Zeiler

Associate Professor
Director Vascular Neurology Fellowship Johns Hopkins
Vice Chair of Clinical Informatics and Technology, Neurology Johns Hopkins
Johns Hopkins Institute

Get with the guidelines in post stroke motor recovery

ABSTRACT

Stroke remains the leading cause of adult disability and the demand for stroke recovery and rehabilitation services is growing. Most recovery from motor impairment after stroke occurs in the first month and is largely completed by 3 months. In humans, data suggest that this improvement occurs independently of rehabilitative interventions, which predominantly target function through compensatory strategies. As such, substantial advances can and should be made in stroke recovery and rehabilitation to meet the growing demand and improve patient outcomes.

This talk reviewed guidelines for post-stroke standards of rehabilitative care, the deficiencies in these recommendations, and suggest avenues for improvement which include high-intensity, high-complexity movement, enriched environments, and use of pharmacological agents.

LECTURE SUMMARY

Cerebrolysin's mechanism of action in neurorehabilitation has been extensively researched and published by Professor Steven Zeiler, Associate Professor at Johns Hopkins University Hospital in Baltimore, USA.

Professor Zeiler and his colleagues studied Cerebrolysin several years before it became the widely accepted evidence-based treatment that it is today. Professor Zeiler and other international experts in motor recovery played an important role in this recognition and acceptance process.

One of his key findings was the fact that Cerebrolysin induced spontaneous recovery after stroke even in subjects with no prior task-related training *(figure 3)*. Untrained subjects who received Cerebrolysin performed as well as trained subjects and recovered to 100% of pre-stroke levels, which was in contrast to other interventions like SSRIs *(figure 4)*. These findings suggested effectiveness of Cerebrolysin also when used as monotherapy.

Also based on the findings of the E-Compass study where "plasticity in action" was visible by advanced imaging methods, it can be hypothesized that Cerebrolysin is able to repair the cortico-spinal tract *(figure 5)*.

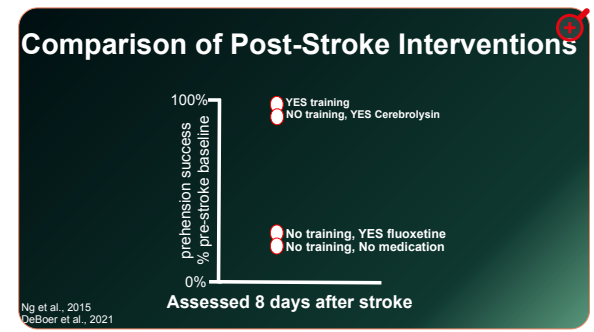


Figure 4

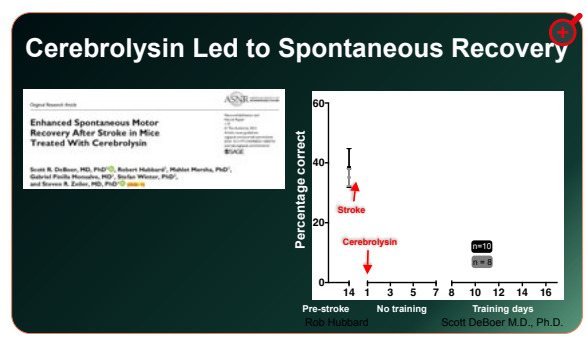


Figure 3

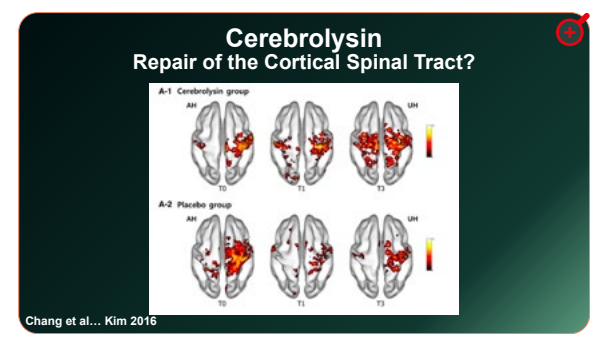


Figure 5

In the final part of his presentation, Professor Zeiler reiterated that three different data sets have led to the guideline recommendations in different countries, highlighting in particular the inclusion in the Canadian EBRSR, which provides information on best practice. In this guideline, Cerebrolysin was included with an 1A recommendation!

Finally, as a co-author of the Lancet Review on "Advances and Challenges in Stroke Rehabilitation", Professor Zeiler highlighted that only Cerebrolysin could show positive results when compared to trials in other areas of neurorehabilitation, such as in physiotherapy or the use of technology such as robotics *(figure 6)*.

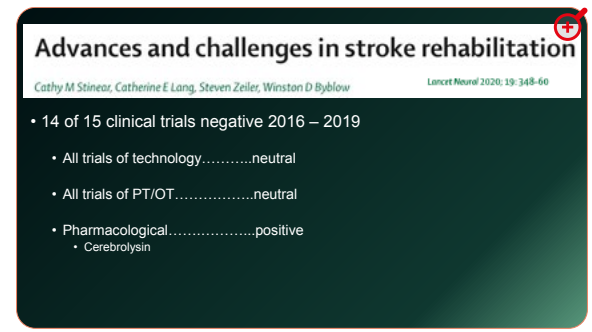


Figure 6

Jacek Staszewski

MD, PhD
Military Institute of Medicine –
National Research Institute

Effective Cerebroprotection in the stroke reperfusion era – why we need it?

ABSTRACT

Recent trials have established a new paradigm for acute ischemic stroke treatment showing that mechanical thrombectomy (MT) significantly reduces the mortality rate and improves clinical outcomes. Despite these advances, it remains strictly time dependent, requiring specialized centers, thus resulting feasible only for a minority of patients. Also the rates of excellent outcome or functional independence following MT performed in both the early and late time window, in clinical trials, or in clinical practice are far from satisfactory compared with the very high rates of successful recanalization and these imply the need to further improve recovery of patients.

Futile recanalization after MT requires studies to determine its predictive factors, patient selection as well as introduce new adjunct therapies to improve clinical efficacy. Attempts to develop effective cerebroprotection before the "reperfusion era" have been unsuccessful, but this approach should now be reconsidered. Recanalization therapy constitutes a novel opportunity for multimodal cytoprotection agents due to a higher chance to reach the ischemic penumbra and protect from the injury and death of neurons after ischemia-reperfusion. Cerebrolysin is a neurotrophic peptidergic preparation with broad cytoprotective properties, recommended by the European Academy of Neurology and European Federation of Neurorehabilitation Societies for both the acute- and poststroke rehabilitation. We hypothesized that adding Cerebrolysin in selected patients based on the clinical and radiological criteria may increase the effectiveness of MT by initiating cytoprotective effects and preventing reperfusion injury.

LECTURE SUMMARY

In the final lecture of the EVER Satellite Symposium, Professor Jacek Staszewski made a very convincing case for **"Effective Cerebroprotection in the Stroke Reperfusion Era – and why we need it"**.

Professor Staszewski showed the audience the current evidence of how EVT (endovascular treatment) is changing stroke outcomes by focusing on improving the processes to rapidly recanalize patients within 3-6 hours. However, even when this is achieved, a large percentage of patients remain impaired, making the case for effective add-on therapies in combination with EVT, particularly in more severe strokes with an Aspects score < 6 *(figure 7)*.

He continued to make the case for the use of cerebroprotective agents by showing the association between asymptomatic intracerebral hemorrhage (aICH) and 90-day outcome as measured by mRS, NIHSS and Barthel-Index, as well as higher mortality rates *(figure 8)*.

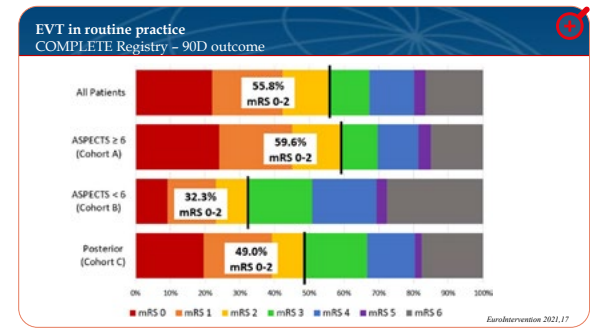


Figure 7

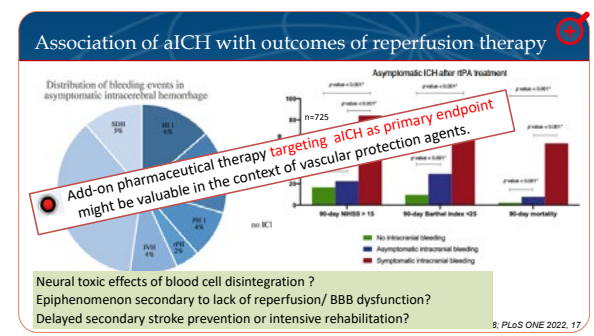


Figure 8

In the second part, Professor Staszewski's focused on why EVT is an excellent model for studying cerebroprotection *(figure 9)* and why this multimodal treatment approach may improve long-term outcome.

All the above arguments set the stage for the introduction of Professor Staszewski's ongoing clinical trial *(figure 10 and 11)*.

Full details of the study are also available in a published methodology paper (https://www.frontiersin.org/articles/10.3389/fneur.2022.910697/full), prominently featured in Frontiers in Neurology.

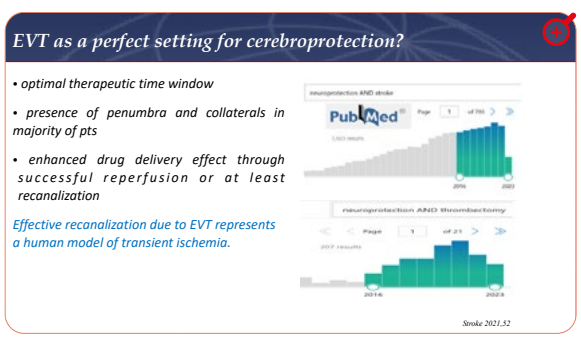


Figure 9

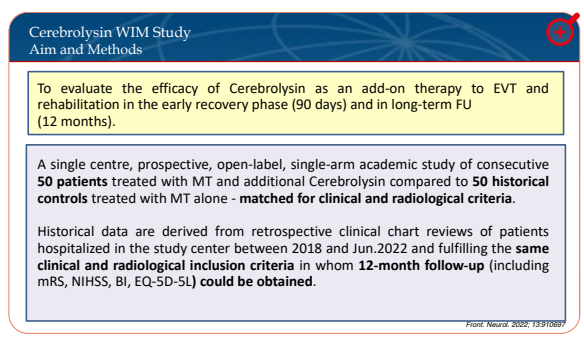


Figure 10

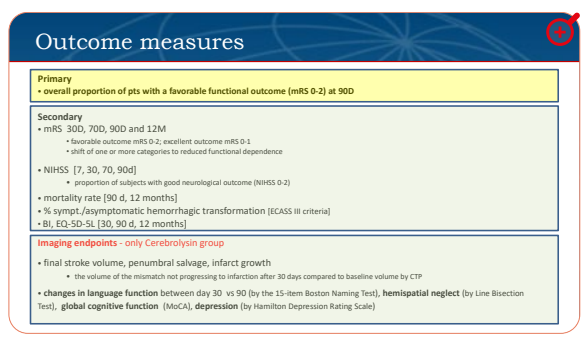


Figure 11

He was able to share the results of the interim analysis of the study, the full cohort has not yet been analyzed. The data show a very encouraging result at the primary endpoint *(figure 12)* but also, and for the first time, excellent 12-month data *(figure 13)*. As in previously published studies, a significant reduction in hemorrhagic transformation was achieved *(figure 14)*.

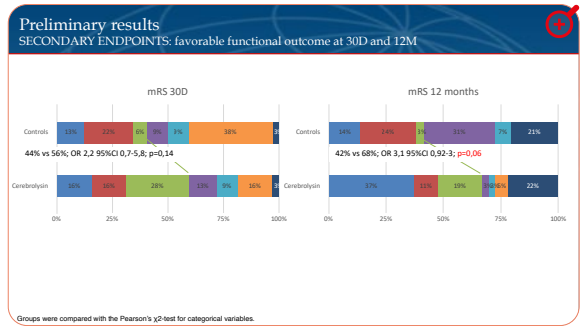


Figure 13

Professor Staszewski summarized his presentation with very optimistic take-home messages – he made a very strong case for the need for add-on therapies after EVT and also offered a potential solution *(figure 15)*.

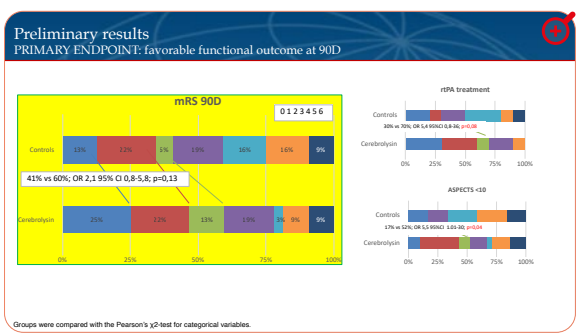


Figure 12

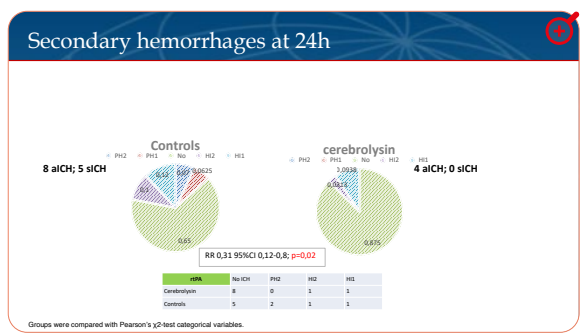


Figure 14

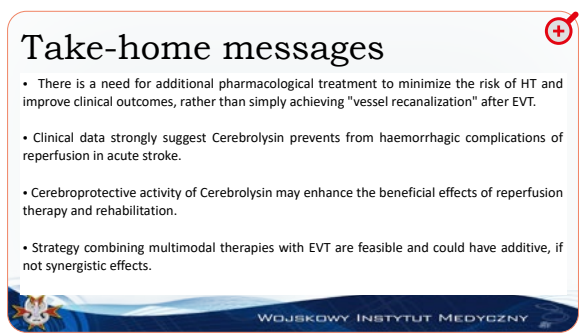


Figure 15

Summary

Cerebrolysin has not only achieved the status of evidence-based medicine in post-stroke motor rehabilitation, it is also **a potent therapeutic option for all stroke patients** in acute stroke medicine to improve treatment safety and long-term outcome.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). 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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