EVER PHARMA

Official symposium of the
"16th World Stroke Congress"
October 23 – 26 I Abu Dhabi, UAE

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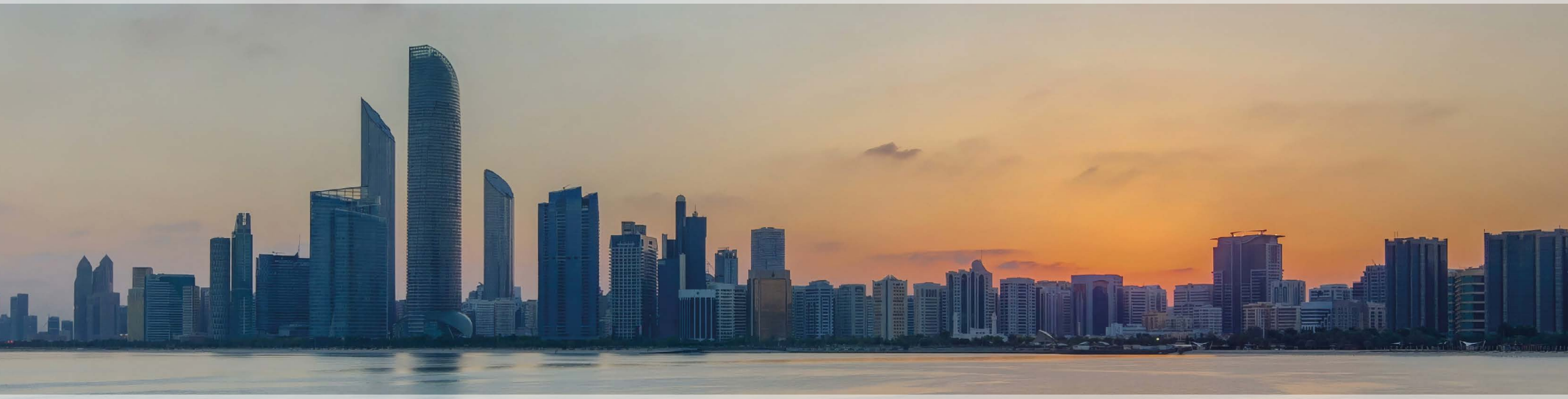

Cerebroprotection in AIS – New evidence from two different trials

Chair: Steven Zeiler (USA)

- **Add-on therapy following MT in patients with embolic stroke**
  Ahmed ElBassiouny (Egypt)
- **C-REGS2 – First results of a large high-quality comparative effectiveness study**
  Michael Brainin (Austria)

Cerebroprotection in AIS – New evidence from two different trials

The World Stroke Congress (WSC), held in October 2024 in Abu Dhabi, united leading experts, clinicians and researchers from around the globe to discuss the latest developments in stroke treatment, rehabilitation and recovery.

The official symposium of EVER pharma featured two pivotal lectures on stroke treatment. Dr. Ahmed ElBassiouny presented the role of add-on therapies following mechanical thrombectomy (MT) in patients with embolic stroke, emphasizing strategies to enhance recovery outcomes. Dr. Michael Brainin presented the preliminary results of the C-REGS2 study, a large-scale comparative effectiveness trial designed to evaluate the most effective post-stroke treatments approaches.

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Steven Zeiler

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Associate Professor
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Introduction

Dr. Zeiler highlighted the crucial topic of post-reperfusion recovery in stroke patients, with a particular emphasis on cerebroprotection. He addressed the challenges faced by millions of stroke survivors in the chronic stage of recovery, when rehabilitation efforts often plateau *(figure 1)*. Many of these individuals live with moderate to severe disabilities, which significantly affect their daily lives. Dr. Zeiler discussed the importance of early intervention in post-stroke recovery, emphasizing cerebroprotective therapies and rehabilitation strategies.

He underscored the importance of mechanism-driven, human-specific trials and cautioned against overreliance on animal models due to differences between mouse and human brains. He highlighted the need for treatments aligned with specific recovery mechanisms, such as the dual role of glutamate, which, despite its toxicity, is crucial for recovery immediately after a stroke. Precise timing in administering therapies, he noted, is critical to maximizing recovery outcomes and avoiding potential setbacks.

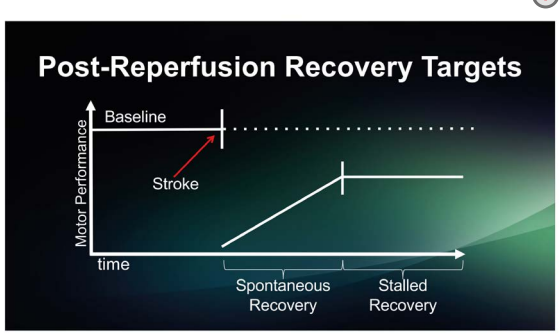

Figure 1

Dr. Zeiler emphasized the importance of expanding the focus beyond neuroprotection to encompass the broader concept of cerebroprotection. He explained that neurons are only one part of the brain's complex ecosystem, and addressing multiple toxicity pathways simultaneously can improve recovery outcomes.

As an example of a promising therapeutic approach, Zeiler discussed Cerebrolysin, a neuropeptide preparation designed to mimic growth factors and neurotrophins. *(figure 2)* He highlighted evidence from both animal and human studies showing its efficacy in supporting brain function, protecting neurons, and potentially preserving the blood-brain barrier. Ongoing clinical research is exploring Cerebrolysin's role in protecting the blood-brain barrier using advanced imaging techniques.

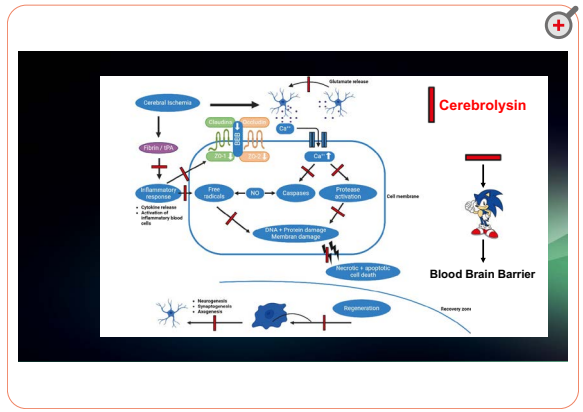

Figure 2

Ahmed ElBassiouny

Prof.
Ain Shams University,
Abbassia – Waili, Cairo, Egypt

Add-on therapy following MT in patients with embolic stroke

ABSTRACT

Introduction: Endovascular recanalization therapy has shown substantial clinical efficacy in the treatment of acute ischemic stroke (AIS). For patients who do not benefit from this therapy, there is an urgent need for alternative cerebroprotective approaches to achieve a positive prognosis. This study was the first to evaluate the role of Cerebrolysin after mechanical thrombectomy (MT).

Methods: 150 patients with cardioembolic AIS and a National Institutes of Health Stroke Scale ≥10, who underwent successful MT ± rtPA were included in this study. Of these, 75 patients received 30 ml of Cerebrolysin for 14 days and were compared with 75 patients who did not receive Cerebrolysin. The primary outcome parameters were the functional outcome as measured by the mRS and the NIHSS. Secondary outcomes included rates of hemorrhagic transformation, mortality, and adverse events.

Results: Patients in the Cerebrolysin group improved in both, the NIHSS scores at 2 weeks ($p<0.001$), 1 month ($p<0.01$), and 3 months ($p<0.02$) and in the mRS at 2 weeks ($p<0.001$), 1 month ($p<0.001$), and 3 months ($p<0.001$). Hemorrhagic transformation was significantly lower in the Cerebrolysin group compared to the control group (21.3% vs 44%, $p=0.003$).

Conclusion: This study showed a significant benefit of Cerebrolysin administered after mechanical thrombectomy in terms of functional outcome, hemorrhagic transformation and mortality, with no safety concerns.

SUMMARY OF THE PRESENTATION

Prof. Ahmed ElBassiouny addressed the significant burden of stroke in Egypt, where approximately 250,000 new cases occur annually, with large vessel occlusions comprising 30% of these cases. He emphasized the critical need for timely intervention, highlighting the importance of mechanical thrombectomy and thrombolysis in improving patient outcomes, particularly in the critical early hours following symptom onset.

His study, which exclusively selected cardioembolic stroke patients, aimed to assess the efficacy and safety of the cerebroprotective agent Cerebrolysin, administered within eight hours following thrombectomy. A total of 150 patients participated, with 75 in the control group receiving standard treatment and 75 in the intervention group receiving Cerebrolysin as add-on therapy. The primary outcome was a favorable functional recovery, measured by the modified Rankin Scale (mRS) at day 90. Results showed that 64% of patients in the treatment group achieved favorable outcomes (mRS 0-2) at day 90, compared to 34.7% in the control group. *(figure 3)*

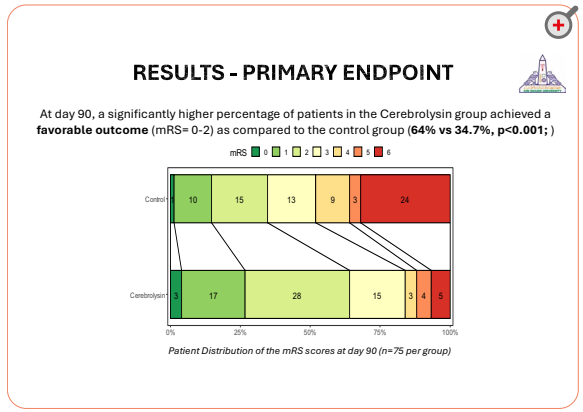

Figure 3

Furthermore, only 2.7% of patients in the Cerebrolysin group experienced symptomatic hemorrhagic transformation, compared to 41.3% in the control group. Hemorrhagic transformation was observed in 20% of patients in the Cerebrolysin group, and 57.3% of patients in the control group. *(figure 4)* The significant difference between the Cerebrolysin group and the control group may have occurred due to the late arrival of patients. Prof. ElBassiouny also discussed the critical role of maintaining the integrity of the blood-brain barrier during reperfusion. The use of Cerebrolysin helped to reduce blood-brain barrier permeability by decreasing inflammatory markers and stabilizing tight junctions, which in turn lowered the risk of reperfusion injury.

As a consequence mortality at day 30 was 5% in the Cerebrolysin group versus 21% in the control group, with most deaths occurring within the first month. *(figure 5)*

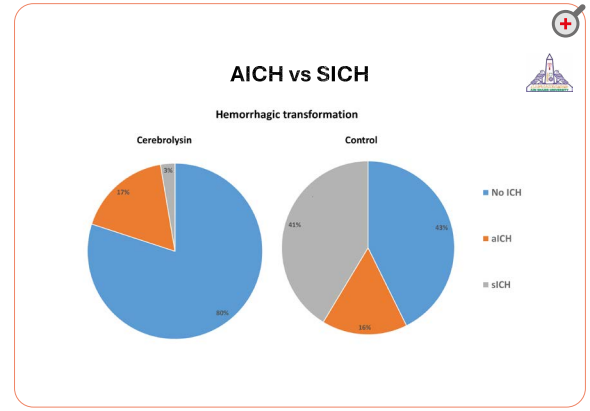

Figure 4

aICH - asymptomatic intracerebral hemorrhage,
sICH – symptomatic intracerebral hemorrhage

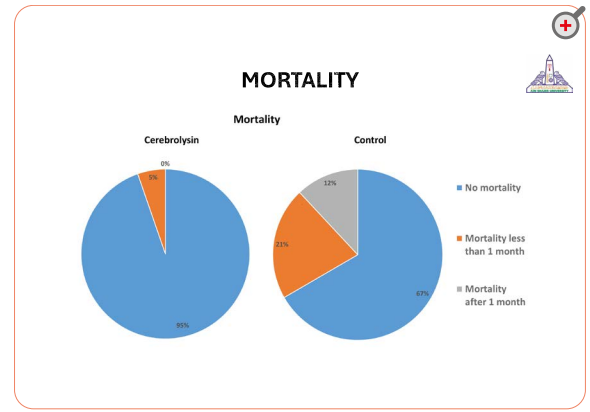

Figure 5

Michael Brainin

Univ.-Prof. Dr. Dr. h.c. mult.
Department for Clinical Neurosciences and Preventive Medicine,
Danube University Krems, Krems, Austria

C-REGS2 – First results of a large high-quality comparative effectiveness study

ABSTRACT

Background and Aims: C-REGS2 investigated the effectiveness of Cerebrolysin in patients with moderate to severe neurological deficits following an acute ischemic stroke in a real-world setting.

Methods: Employing a high-quality comparative effectiveness research (HQCER) design, the study recorded treatment modalities and concomitant medications according to local standards. Outcomes were assessed on day 21 and day 90 post-stroke. The methodology included rigorous pre-specification of analytical procedures and risk-based centralized monitoring. To minimize enrollment bias, patient groups were standardized using nonparametric multilevel stratification and a ‚restricted cohort' design, following GRACE Principles. Specific subgroups of interest, including age, dosage, baseline NIHSS, and „high-enrolling countries", were pre-specified to evaluate potential subgroup effects and generalizability. A pre-specified bundle of leave-one-out analyses was used to identify any bias.

Results: The study is notable for its robust data integrity, with an overall dropout rate of only 5.7% and a valid N of 90.9% for evaluation the primary endpoint of mRS on day 90 with multilevel case-mix standardization. Violation of intention to include (ITI) criteria is reported with only 3.2%. These figures underscore the high quality and reliability of the collected data, ensuring the validity of the findings.

Conclusion: Real-world studies like C-REGS2, based on HQCER, supplement classical designs by including larger patient numbers and providing valuable insights into treatment safety, effectiveness, and tolerability in day-to-day practice contributing to better-informed clinical decisions in acute stroke treatment and stroke rehabilitation.

SUMMARY OF THE PRESENTATION

Prof. Michael Brainin presented the preliminary findings from an extensive multinational comparative effectiveness trial investigating the impact of Cerebrolysin on moderate ischemic stroke patients. This real-world, observational study evaluates the efficacy and safety of the cerebroprotective agent Cerebrolysin, administered across diverse clinical settings. It includes both treated and untreated patients, with stroke outcomes measured using the NIH Stroke Scale (NIHSS), the modified Rankin Scale (mRS), and the Montreal Cognitive Assessment (MoCA) for cognitive function.

Following the GRACE principles for real-world effectiveness research, the study enrolled 1,865 patients with moderate ischemic stroke (NIHSS scores of 8–15), ensuring controls for confounding factors such as age, diabetes, and pre-existing small vessel disease. *(figure 6)* Outcomes were evaluated at various intervals up to three months post-stroke, employing fixed and random effects models to assess Cerebrolysin's effectiveness in practical care conditions. The non-randomized study design supports an objective assessment of treatment impact in diverse patient populations. The study utilized a high-quality observational approach incorporating pre-specified procedures and risk-based centralized statistical monitoring to ensure robust data collection and analysis. To minimize bias, the methodology included multilevel stratification and a restricted cohort design, strengthening the validity and reliability of the findings.

Present data revealed that patients receiving Cerebrolysin achieved significant improvements indicating functional and cognitive gains over the untreated cohort. These findings are based on preliminary data, with final results to follow upon completion of the study.

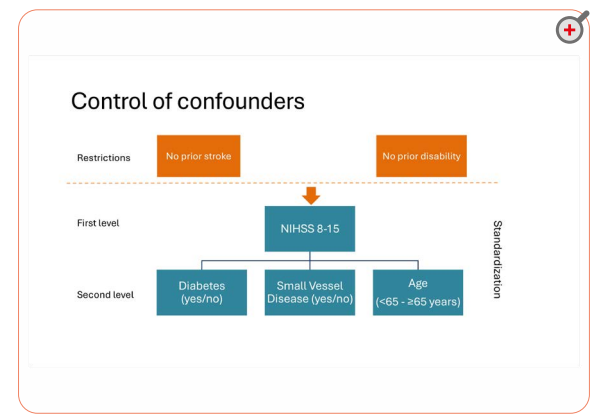

Figure 6

Summary

Cerebrolysin studies show the following results in ischemic stroke patients:

- Improvement of functional recovery
- Cognitive enhancement
- Reduction of hemorrhagic transformation after recanalization therapy
- Decreased mortality after mechanical thrombectomy

Ongoing research will further clarify the role of Cerebrolysin, offering hope for improved post-stroke care worldwide.

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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