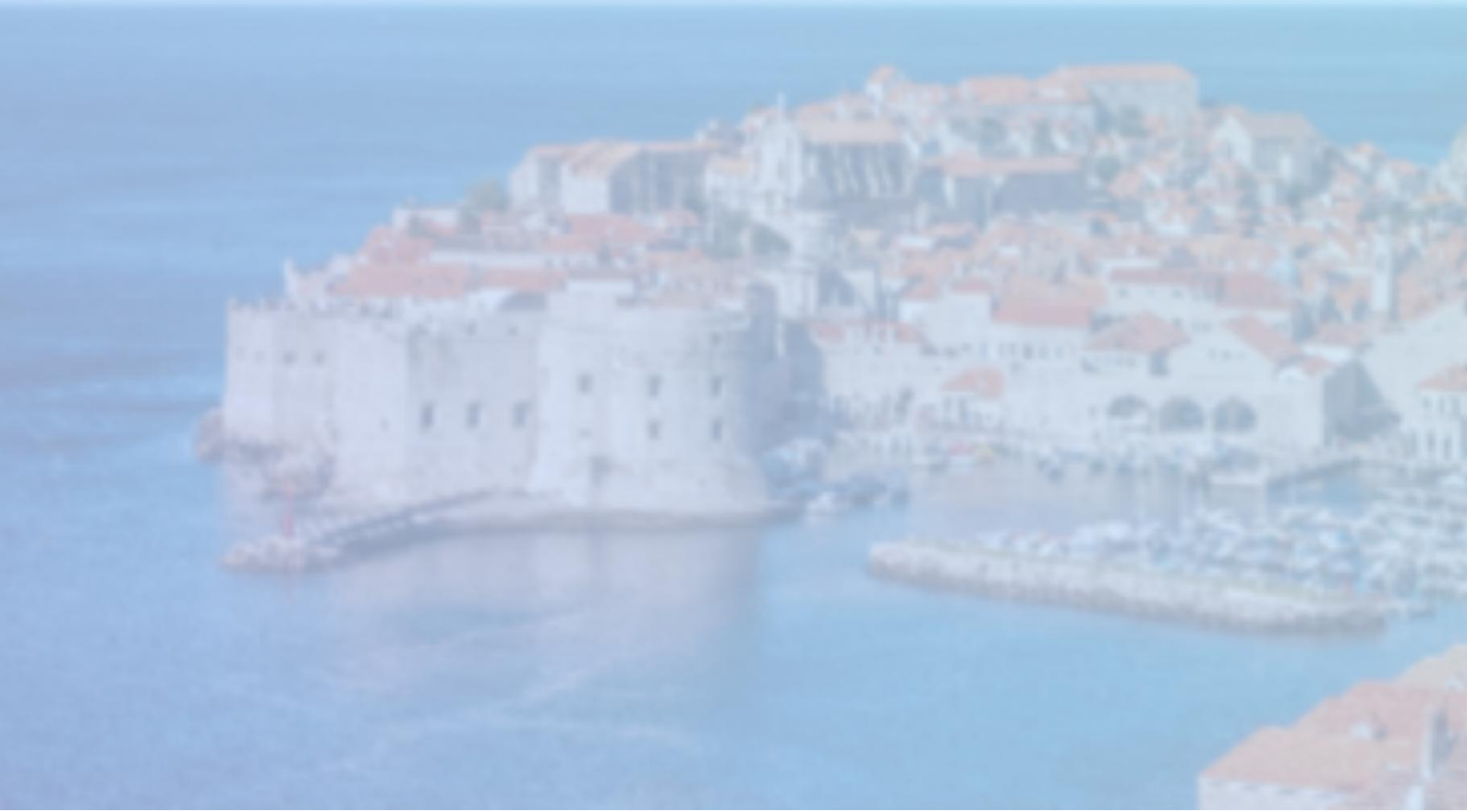
STROKE PROCEEDINGS 2026 01-05/06/2026

36TH SUMMER STROKE SCHOOL

HEALTHY LIFESTYLE AND PREVENTION OF STROKE AND OTHER BRAIN IMPAIRMENTS

DUBROVNIK, CROATIA



STROKE PROCEEDINGS 2026

36th SUMMER STROKE SCHOOL – HEALTHY LIFESTYLE AND PREVENTION OF STROKE AND OTHER BRAIN IMPAIRMENTS

Dubrovnik- Croatia

1st – 5th JUNE 2026.

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Dubrovnik - Croatia

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Vida Demarin: HYPERTENSION AND THE RISK OF COGNITIVE DECLINE
International Institute for Brain Health, Zagreb, Croatia

Hypertension, particularly during midlife, is a major, manageable risk factor for cognitive decline, vascular dementia, and Alzheimer's disease. It was proved by the results of many studies, which were analyzed and published as part of the Lancet Commission on Prevention of Dementia Report. High blood pressure damages cerebral vasculature, causing microvessel dysfunction, brain atrophy, and white matter injury. Controlling blood pressure, especially in midlife, significantly slows cognitive decline. Key Connections Between Hypertension and Cognition are as follows. midlife vulnerability: hypertension developed in middle age (40s–60s) has a stronger association with future cognitive decline and dementia than hypertension developed in late life. Then, impacted cognitive domains- high blood pressure specifically impacts executive function (planning, organizing), mental processing speed, and memory. Vascular and Alzheimer's risk: hypertension is linked to vascular cognitive impairment (VCI), small vessel disease, and Alzheimer's disease pathology. Brain damage mechanisms should also be mentioned, such as elevated blood pressure increasing arterial stiffness, oxidative stress, inflammation, and blood-brain barrier disruption, which can lead to microhemorrhages and structural brain damage. When it comes to prevention and management, the most important thing is effective blood pressure control. Managing blood pressure through medication is linked to a reduced risk of dementia. Lifestyle interventions like regular exercise, a healthy diet, smoking cessation, and stress management are critical for reducing hypertension-related cognitive risks.

Keywords: Hypertension; Cognitive Decline; Dementia

Vida Demarin: BRAIN AND NEUROPLASTICITY IN REHABILITATION
International Institute for Brain Health, Zagreb, Croatia

Neuroplasticity is an important, integral biological adaptive mechanism of the nervous system that constantly modifies its structural organization and function. It requires neurochemical, synaptic, and structural changes. Plastic changes do not alter the original functional representation, but probably include unmasking of secondary routes, reorganization (remapping), and compensation and adaptation to brain lesions. Due to neuroplasticity, brain functions could be improved and even restored in different conditions, such as after stroke or traumatic brain injury, as well as in certain neurodegenerative disorders, like multiple sclerosis, Parkinson's disease, etc. Stroke frequently causes long-term and even lifelong disability in stroke survivors. Over the past several decades, a vast majority of stroke research targets neuroprotection in the acute phase, while little work has been done to enhance stroke recovery at the later stage. Lifelong brain plasticity offers the long-lasting possibility to repair a stroke-damaged brain. Stroke impairs the structural and functional integrity of entire brain networks; restorative approaches with multiple components have great potential to maximize stroke recovery by rebuilding and normalizing these disrupted networks and brain functioning. The restorative window for stroke recovery is much longer than previously thought. The optimal time for brain repair appears to be at a later stage of stroke rather than the earlier stage. It is expected that these new insights will advance our understanding of stroke recovery and assist in developing the next generation of restorative approaches, enhancing and harnessing neuroplasticity through multiple actions: enhancing the mirror neuron system for chronic stroke recovery and using different pharmaceutical interventions to activate growth factors and neurotrophins to rewire the neurovascular network. Through neuroplasticity, the brain can form new connections, activate new pathways, and unmask secondary routes. Music is a strong stimulus for neuroplasticity, thus potentially enhancing recovery after stroke. fMRI studies have shown reorganization of the motor and auditory cortices in professional musicians, and other studies have shown changes in serum neurotransmitter and hormone levels in correlation with music. Results from numerous studies have shown that listening to music can improve cognition, motor skills, and mood, thereby enhancing recovery after brain injury. In the field of visual art, a brain lesion can lead to visuospatial neglect, loss of detail, and significant impairment of artistic work, while activation of neuroplasticity can restore skill and function. All kinds of arts (music, painting, dancing...) stimulate the brain. They should be a part of the treatment processes.

Keywords: Neuroplasticity; Neurorehabilitation; Neurologoical Disorders

Nikola Barić: SLOWING DOWN THE AGING PROCESS BY FPS-ZM1 RAGE RECEPTOR BLOCKERS AND LRP1 GENE THERAPY

Private Family Medicine Practice Labin, Croatia

Introduction: A number of researchers of Alzheimer's disease (AD) consider it a neurodegenerative disorder related to the accumulation of amyloid β-peptide (Aβ) in brain structures. Both the amyloid and vascular hypotheses about the causes of AD, agree that the breakdown of the blood-brain barrier (BBB) leads to the accumulation of a series of vasculotoxic and neurotoxic macromolecules in the brain, accompanied by reduced cerebral blood flow (CBF) and hypoxia, thereby inducing functional and structural neuronal alterations even prior to the amyloid deposition. In these events, the receptor for advanced glycation end products (RAGE), which mediates Aβ-induced perturbations in cerebral vessels, neurons, and microglia, plays a key role.

Aim: The aim of this study is to contribute to the current understanding of the attempts aimed at slowing the aging process of humans.

Materials and methods: Through the analysis of a number of scientific papers addressing the attempts to slow the rate of human aging, the author has found interesting data regarding the two methods: 1) slowing the rate of aging in experimental animals (mice and rats) by blocking the RAGE receptor using the specific compound FPS-ZM1, and 2) activating LRP1 through LRP1 gene therapy. Although both methods remain in their experimental phase, they show a promising potential and may represent important future therapeutic approaches.

Results: A detailed analysis of available literature clearly indicates that the scientific approach underlying both methods is correct.

Conclusion: FPS-ZM1 RAGE blockade, as well as LRP1 gene therapy, represent increasingly promising and interesting methods in the attempts to slow the aging process. Both methods are still applied only in the experimental phase, indicating that their safety and efficacy in humans have not yet been established. At present, both methods have been applied only in experimental laboratory animals, mice and rats. Further research is required before the potential application in humans can be considered.

Keywords: FPS-ZM1 RAGE blockade; LRP1 gene therapy; Epigenetics.

Nikola Barić, Yoshikazu Yonei: A NEW HYPOTHESIS ABOUT THE AGING PROCESS OF MAN

Private Family Medicine Practice, Labin, Croatia
Aging Medical Research Center and Glycative Stress Research Center, Faculty of Life and Medical Sciences, Doshisha University, Kyoto, Japan

Introduction: The process of aging, essentially a natural, complex, purposeful, multi-profile, and inevitable process in the life cycle of living beings, therefore also of humans, is, according to current knowledge, most likely based on a program encoded in the genome. As research indicates, this process consists of two closely interconnected components: normal or physiological aging and accelerated or pathological aging associated with diseases. Life essentially represents a conglomerate of more or less complex physiological and biochemical processes that continuously occur within living beings, and whose disruption or cessation ultimately results in the termination of life and death.
Aim: To contribute to the current knowledge about attempts aimed at slowing the aging process in humans.
Materials and methods: Through a detailed analysis of a number of relevant scientific papers by eminent researchers in the field of physiological and pathological aging of living beings, the authors have found an interesting phenomenon suggesting that two great transmembrane and multiligand receptors, the low-density lipoprotein receptor-related protein 1 (LRP1), and the receptor for advanced glycation end products (RAGE), may have a crucial role in the aging proces of living beings, therefore also of humans.
Results: These analyses increasingly indicate the crucial importance of the process of regeneration of gene transcription associated with the aforementioned receptors. These transcriptions, which are under the strong control of Sp1 and Sp3 proteins (transcription factors), and their genome-encoded programs, appear to influence the maximum possible lifespan of individuals within a species.
Conclusion: Due to differences in the methylation status of their promoters, LRP1 undergoes faster and stronger methylation, whereas RAGE is methylated more slowly and weakly. This discrepancy seems to represent a crucial factor in determining the progression of aging.

Keywords: Aging process; Epigenetics; Methylation and demethylation

Bojana Žvan: TENECTEPLASE VS. ALTEPLASE IN ACUTE ISCHEMIC STROKE: "ARE WE READY FOR A PARADIGM SHIFT?"

MEDICOR d.o.o., Ljubljana, Slovenia

Intravenous thrombolysis (IVT) remains the cornerstone of early treatment for acute ischemic stroke (AIS). For more than two decades, alteplase has been the only widely established fibrinolytic agent with proven clinical efficacy. Despite its demonstrated benefit, its use is limited by the complexity of administration, time sensitivity, and organizational challenges, particularly within modern stroke care systems that incorporate mechanical reperfusion therapy (endovascular thrombectomy - EVT) and interhospital transfers.

The aim of this summary is to review the currently available evidence regarding the efficacy and safety of tenecteplase (TNC) in the treatment of AIS, to highlight its advantages and limitations compared with alteplase, and to discuss the unresolved issues that will ultimately determine its role in future therapeutic strategies.

Over the past decade, TNC, a genetically modified tissue plasminogen activator with a longer half-life and greater fibrin specificity, has gradually emerged as a promising alternative to alteplase. Pivotal randomized clinical trials have demonstrated that TNC at a dose of 0.25 mg/kg is non-inferior to alteplase with respect to functional outcome at 90 days and has a comparable safety profile. Moreover, in patients with large-vessel occlusion (LVO), TNC has been shown to be more effective at achieving early reperfusion and spontaneous recanalization prior to mechanical thrombectomy.

The practical advantages of TNC, particularly single-bolus intravenous administration and simplified logistics, have significantly contributed to its rapid clinical implementation in many advanced stroke centers. These features are especially relevant in contemporary hub-and-spoke systems, where time efficiency and uninterrupted patient transfer to EVT centers are of critical importance.

Despite the growing body of evidence and the increasing use of TNC, several important questions remain unresolved. It is not yet clear whether TNC will completely replace alteplase in the future or whether its use will remain selective, depending on specific clinical subgroups, time windows, or organizational settings. Although data supporting the use of TNC in the extended time window among perfusion-imaging–selected patients are promising, they have not yet been fully incorporated into all clinical guidelines. Additional uncertainty arises from regulatory and economic considerations, as well as from limited data in specific patient populations.

Key words: Acute ischemic stroke, Alteplase, Intravenous thrombolysis, Mechanical thrombectomy, Tenecteplase.

Senta Frol: ANTICOAGULATION WORKSHOP: HOW TO MANAGE ISCHEMIC AND HEMORRHAGIC STROKE ON DIRECT ORAL ANTICOAGULANTS

University Medical Center Ljubljana, Slovenia

The widespread use of direct oral anticoagulants has transformed stroke prevention in patients with atrial fibrillation and other thromboembolic conditions. However, management of acute ischemic and hemorrhagic stroke in anticoagulated patients remains clinically challenging and requires rapid, evidence-based decision-making. Uncertainty regarding anticoagulant activity, eligibility for reperfusion therapies, reversal strategies, and optimal timing of anticoagulation resumption continues to complicate acute stroke care.

This interactive workshop will provide a practical overview of the management of ischemic and hemorrhagic stroke in patients receiving direct oral anticoagulants. The session will review the pharmacology and mechanisms of action of currently available direct oral anticoagulants and discuss their implications for acute stroke treatment. Particular emphasis will be placed on the assessment of anticoagulant status in emergency settings, including interpretation of coagulation assays, evaluation of last-dose timing, renal function, and clinical risk stratification.

Participants will explore current recommendations regarding intravenous thrombolysis and mechanical thrombectomy in anticoagulated patients, with discussion of available evidence, safety considerations, and unresolved controversies. The workshop will also address management of anticoagulant-associated intracerebral hemorrhage, including reversal strategies, blood pressure control, neurocritical care principles, and neurosurgical considerations. Specific reversal agents and emerging therapeutic approaches will be reviewed in the context of current international guidelines.

Case-based discussions will form the core of the workshop and will focus on real-world clinical scenarios frequently encountered in stroke units and emergency departments. Topics will include wake-up stroke, uncertain anticoagulant exposure, recurrent ischemic stroke despite anticoagulation, balancing hemorrhagic and thromboembolic risk, and determining the optimal timing for restarting anticoagulant therapy after ischemic or hemorrhagic stroke.

The workshop is intended for neurologists, stroke physicians, emergency physicians, neuroradiologists, trainees, and allied healthcare professionals involved in acute stroke care. By integrating contemporary evidence with practical clinical experience, the session aims to improve confidence in clinical decision-making and promote standardized, safe, and patient-centered management strategies for anticoagulated stroke patients.

Keywords: Direct oral anticoagulants; Ischemic stroke; Intracerebral hemorrhage

Marjan Zaletel: PERIPHERAL INTERVENTIONAL APPROACHES IN MIGRAINE: FROM PATHOPHYSIOLOGY TO CLINICAL APPLICATION

Pain Clinic, Department of Vascular Neurology, University Clinical Center of Ljubljana, Ljubljana, Slovenia

Chronic migraine is a highly disabling neurological condition associated with significant individual and societal burden. Despite advances in preventive pharmacotherapy, a substantial proportion of patients continue to experience frequent attacks, incomplete therapeutic response, or treatment intolerance. Increasing evidence suggests that migraine chronification is driven by persistent peripheral nociceptive input and the development of central sensitization within the trigeminovascular system and the trigeminocervical complex. These mechanisms contribute to amplified pain transmission, allodynia, and reduced responsiveness to standard therapies.

Peripheral interventional approaches have emerged as a mechanism-based strategy targeting upstream drivers of migraine. By modulating nociceptive input from cranial and cervical structures, these interventions may reduce activation of the trigeminocervical complex and subsequently attenuate central sensitization. Among these techniques, the greater occipital nerve block has the most robust evidence, demonstrating consistent reductions in headache frequency and intensity, particularly in chronic migraine and medication-overuse headache. The convergence of cervical and trigeminal afferents within the trigeminocervical complex provides a strong anatomical and functional rationale for its effectiveness.

Myofascial trigger points represent another important source of peripheral nociceptive input. These hyperirritable muscle nodules are highly prevalent in migraine patients and may contribute to both peripheral and central sensitization. Targeted therapies, including manual techniques, dry needling, and trigger point injections, have shown beneficial effects in reducing headache frequency, pain intensity, and associated cervical dysfunction. These findings support the concept of a bidirectional interaction between cervical musculoskeletal structures and central pain processing.

Botulinum toxin type A is an established preventive treatment for chronic migraine, acting through inhibition of neurotransmitter release, including calcitonin gene-related peptide, and modulation of trigeminovascular activity. Clinical trials have demonstrated significant reductions in headache days, acute medication use, and improved quality of life, with sustained benefit over repeated treatment cycles. In addition, acupuncture represents a complementary approach with growing evidence for migraine prevention. Its effects are mediated through both segmental and supraspinal mechanisms, including activation of endogenous pain inhibitory pathways, modulation of autonomic function, and reduction of central sensitization.

Clinical experience and case-based observations indicate that combining pharmacological and interventional strategies can lead to substantial improvements in patient outcomes, including reduction in headache frequency, decreased medication overuse, and improved functional capacity. Importantly, these interventions are not intended to replace pharmacotherapy but to complement it within a multimodal, individualized treatment framework.

In conclusion, peripheral interventional therapies offer a clinically relevant and neurobiologically plausible approach to migraine management. By addressing key mechanisms of peripheral and central sensitization, they provide valuable therapeutic options, particularly in refractory cases or in patients with contraindications to pharmacological treatment. Their integration into a multidisciplinary, guideline-informed algorithm represents an important step toward more effective and personalized migraine care.

Keywords: Migraine; Peripheral nerve blocks; Trigeminocervical complex; Central sensitization; Acupuncture

Marjan Zaletel, Gorazd Požlep: THE MIGRAINE INTERVENTION WORKSHOP: FROM ANATOMY TO APPLICATION

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Migraine is a complex neurological disorder in which peripheral nociceptive input and central sensitization play a key role in the development of chronic and treatment-resistant forms. Despite significant advances in pharmacological prevention, many patients continue to experience high disease burden, incomplete therapeutic response, and functional impairment. This highlights the need for mechanism-based, multimodal treatment approaches that extend beyond medication alone.

This workshop presents an integrated, clinically oriented framework that links migraine anatomy and pathophysiology with practical interventional strategies. Particular emphasis is placed on the trigeminovascular system and the trigeminocervical complex as central integration sites where peripheral and central mechanisms interact. Persistent nociceptive input from cranial and cervical structures contributes to neuronal hyperexcitability, reduced activation thresholds, and amplification of pain transmission, ultimately leading to migraine chronification.

Building on this mechanistic understanding, the workshop explores peripheral interventional techniques aimed at modulating nociceptive input and reducing central sensitization. Greater occipital nerve block represents a key intervention with consistent clinical evidence for reducing headache frequency and intensity, particularly in chronic migraine and medication-overuse headache. Myofascial trigger point therapies are also highlighted as an important component, given their high prevalence in migraine patients and their role in maintaining peripheral sensitization, especially in the presence of cervical dysfunction. Additional modalities, including botulinum toxin type A and acupuncture, are discussed within a unified neurophysiological framework, emphasizing their effects on neuropeptide release, autonomic regulation, and endogenous pain modulation.

A distinctive feature of this workshop is its strong focus on clinical translation. Case-based discussions demonstrate how combining pharmacological and interventional approaches can lead to substantial improvements in headache frequency, intensity, and functional outcomes. For example, patients with chronic migraine and medication overuse may achieve significant reduction in headache days and disability when interventional therapies are integrated with preventive treatment strategies.

The workshop concludes with a structured, evidence-informed approach to patient selection and treatment integration, highlighting the importance of individualized care. Interventional techniques are presented not as replacements for pharmacotherapy, but as valuable adjuncts within a multidisciplinary treatment algorithm, particularly in refractory cases, during transitional phases, or when pharmacological options are limited.

In summary, this workshop bridges the gap between neuroanatomy, pathophysiology, and hands-on clinical practice, providing participants with both theoretical understanding and practical skills for the modern management of migraine.

Keywords: Migraine; peripheral nerve block; Trigeminocervical complex; Central sensitization; Interventional therapy

Ilir Alimehmeti: STROKE PSYCHOSOCIAL RISK FACTORS

Faculty of Medicine, University of Medicine, Tirana

Stroke remains one of the leading causes of mortality and long-term disability worldwide, with increasing evidence demonstrating the significant role of psychosocial risk factors in stroke onset, progression, and recovery. Recent studies have identified chronic stress, depression, anxiety, social isolation, loneliness, low socioeconomic status, occupational strain, and sleep disturbances as important contributors to cerebrovascular disease. A large international case-control study involving 26,812 participants reported that psychosocial stress was significantly associated with increased odds of acute stroke, emphasizing stress as a modifiable risk factor. Furthermore, a 2024 meta-analysis found that social isolation, limited social support, and loneliness were independently associated with higher stroke incidence and post-stroke mortality. Research from Harvard University also demonstrated that chronically lonely older adults had up to a 56% greater risk of stroke compared with non-lonely individuals. Psychosocial factors influence stroke risk through behavioral and biological pathways, including hypertension, inflammation, unhealthy lifestyle behaviors, impaired treatment adherence, and dysregulation of neuroendocrine responses. Post-stroke depression remains one of the most common neuropsychiatric complications, negatively affecting rehabilitation outcomes, cognition, social participation, and quality of life. Recent evidence also highlights the interaction between stress, poor sleep quality, and depression among stroke survivors, suggesting a multidimensional psychosocial burden after cerebrovascular events. This review summarizes current evidence regarding psychosocial determinants of stroke and discusses the mechanisms linking psychological and social factors to cerebrovascular health. Integrating psychosocial assessment, mental health screening, and social support interventions into stroke prevention and rehabilitation programs may improve clinical outcomes and reduce the global burden of stroke.

Keywords: Stroke; Psychological Factors; Social Factors

Serla Grabova: ROLE OF ELECTROENCEPHALOGRAPHY (EEG) IN MIGRAINE

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Migraine is a common and disabling neurological disorder characterized by recurrent headache attacks and a range of sensory, cognitive, and autonomic symptoms. Electroencephalography (EEG) has gained increasing attention as a noninvasive tool for investigating the neurophysiological mechanisms underlying migraine and identifying functional brain abnormalities associated with the disease. Recent research suggests that migraine patients exhibit altered cortical excitability, abnormal sensory processing, and disrupted brain connectivity during both ictal and interictal phases. EEG abnormalities reported in migraine include increased theta and delta activity, altered alpha rhythm modulation, photic hypersensitivity, and abnormal evoked potentials, particularly in patients with migraine with aura. Over the past five years, advances in quantitative EEG and machine learning have improved the understanding of migraine-related electrophysiological changes. A 2021 ultra-high-density EEG study demonstrated abnormal cortical coherence patterns in migraine patients, supporting the concept of altered functional connectivity in migraine brains. A 2022 longitudinal EEG study monitoring migraine patients over 30 consecutive days found that somatosensory and brainstem excitability increased significantly within 24 hours before migraine attacks, suggesting that EEG changes may help identify the pre-ictal phase of migraine. Furthermore, a 2023 study using transcranial magnetic stimulation combined with EEG showed altered cortical responsivity in patients with migraine with aura compared with healthy controls, reinforcing the hypothesis of cortical hyperexcitability in migraine pathophysiology. More recently, a 2024 study applying machine learning to somatosensory evoked EEG responses identified altered brainstem-cortex interactions in migraine patients, highlighting the potential of EEG-based biomarkers for diagnosis and disease monitoring. Another 2024 clinical neurophysiology study involving 144 migraine patients reported focal subdelta and delta slowing on wide-band EEG recordings, with findings correlating with migraine phase and clinical severity. Although routine EEG is not recommended for the diagnosis of uncomplicated migraine, it remains valuable in selected clinical situations, particularly when epilepsy, atypical aura, or other neurological disorders are suspected. Current evidence suggests that EEG may also contribute to predicting migraine attacks, differentiating migraine subtypes, and evaluating treatment response. This review highlights recent advances in the role of EEG in migraine patients and discusses its potential applications in improving diagnostic accuracy, understanding migraine pathophysiology, and developing personalized therapeutic strategies.

Keywords: Migraine; Electroencephalography; Pathophysiology

Irena Đorčeva: DISSECTIONS OF CERVICAL ARTERIES AND THEIR TREATMENT

University Clinic for Neurology, Department of Urgent Neurology, Skopje, North Macedonia

Background: Cervical artery dissections are a leading cause of ischaemic stroke in younger adults, typically affecting patients around 45 years of age. The underlying mechanisms are not fully understood and likely result from a complex interplay between genetic predisposition, environmental triggers, trauma, infection, connective tissue abnormalities, and common vascular risk factors such as migraine and hypertension. While functional outcomes are generally favorable, many patients face considerable psychological consequences, particularly post-traumatic stress disorder.

Objectives: This review summarises current evidence on acute treatment strategies for cervical artery dissections, focusing on intravenous thrombolysis, endovascular approaches, and antithrombotic therapy, with additional attention to mental health. A representative clinical case of cervical artery dissection will also be presented.

Methods: A narrative synthesis of recent observational studies, registries, randomized controlled trials, and meta-analyses was performed. Emphasis was placed on clinically relevant outcomes, safety profiles, timing, and treatment duration, with particular attention to antithrombotic strategy and patient-centered considerations.

Results: Recent evidence from registry studies (STOP-CAD 2024; US nationwide cohort 2025) indicates that intravenous thrombolysis may be linked to improved functional recovery in selected patients, despite a symptomatic intracranial hemorrhage rate of approximately 4%. Endovascular therapy achieves higher recanalization rates and may improve outcomes, although effectiveness is influenced by initial stroke severity. Findings from the CONCORDIA collaboration support endovascular therapy in patients with large-vessel occlusion and NIHSS scores ≥6, while highlighting an increased risk of hemorrhagic complications in those with lower scores. Evidence regarding antithrombotic therapy remains mixed; data from CADISS and TREAT-CAD suggest anticoagulation may reduce the risk of ischaemic stroke but carries a higher risk of major bleeding. Importantly, most recurrent ischaemic events occur within the first month, emphasizing a critical early therapeutic window. Beyond neurological recovery, post-traumatic stress disorder affects up to 44% of patients, underlining the significant psychosocial burden.

Conclusions: Optimal management of cervical artery dissection remains uncertain, particularly with regard to antithrombotic strategy and duration of therapy. Current evidence supports an individualized approach that balances the prevention of ischaemic events against the risk of hemorrhage. Further randomized studies are required to clarify treatment pathways. Research should also incorporate vascular risk factor assessment and mental health evaluation, particularly for younger patients. Inclusion of patient-reported outcomes and active patient involvement in future studies will be crucial for optimizing long-term, patient-centered care. A representative case will be presented to illustrate clinical management.

Keywords: Cervical artery dissection; Ischaemic stroke; Thrombolysis; Endovascular therapy; Antithrombotic therapy

Snježana Cenić Stojaković, Marko Obranović: POMEGRANATE SEED OIL (*PUNICA GRANATUM* L.) AS A FUNCTIONAL LIPID SUPPLEMENT: BIOACTIVE PROFILE, NEUROIMMUNE MECHANISMS, AND RELEVANCE TO CEREBROVASCULAR RISK — A PNEI PERSPECTIVE

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Background & Purpose: Stroke prevention increasingly requires addressing modifiable upstream risk factors, including chronic low-grade neuroinflammation, oxidative stress, and vascular endothelial dysfunction. Within the psychoneuroendocrinoimmunological (PNEI) framework, these processes are understood as interconnected — linking immune dysregulation, gut microbiota composition, and neuroimmune signaling to cerebrovascular vulnerability. Pomegranate seed oil (PSO), a lipophilic by-product of *Punica granatum* processing, represents a biochemically distinct functional lipid whose primary component, punicic acid (PA; C18:3, 9*cis*,11*trans*,13*cis*) — a conjugated α-linolenic acid (CLnA, ω-5) — accounts for up to 85% of its fatty acid profile. The aim of this lecture is to integrate available evidence on PSO's bioactive profile and mechanistic actions within a PNEI framework relevant to cerebrovascular risk.
Methods: Narrative review of preclinical (in vitro, animal) and available clinical data on PSO and punicic acid, with particular focus on neuroimmune signaling, gut microbiota modulation, and cerebral ischemia models.
Results: PSO and PA demonstrate consistent antioxidant activity via Nrf2/NQO1 pathway activation and reduction of reactive oxygen species, with neuroprotective effects documented in rat cerebral ischemia-reperfusion models (tMCAO) at low doses. Anti-inflammatory actions operate through NF-κB and MAPK inhibition, with reduction of TNF-α, IL-1β, and IL-6 across multiple cell and animal models. In a 12-month pilot human study in mild cognitive impairment, PSO supplementation was associated with reduced serum TNF-α and improved cognitive biomarkers. Relevant to the gut-brain axis, PA modulates gut microbiota composition in vitro and in vivo, promoting *Akkermansia*, *Bifidobacterium*, and *Roseburia/Blautia* with concurrent shifts in short-chain fatty acid profiles including acetate and GABA — metabolites with established roles in neuroimmune regulation. CLnA and CLA isomers, structurally related to PA, suppress NF-κB activation and ROS production in human microglial models, acting via GPR120/FFA4 receptors, with evidence of altered N-acylethanolamine profiles potentially mediating anti-neuroinflammatory effects. Antiplatelet and endothelial-supporting properties further support a vasculoprotective role. Commercial quality variability — including reduced punicic acid content (27–67%) and accelerated oxidative instability — remains a critical limitation for clinical translation.
Conclusions: PSO and its primary bioactive, punicic acid, exert pleiotropic effects relevant to cerebrovascular risk through neuroimmune, antioxidant, and gut microbiota-mediated pathways consistent with a PNEI framework. No human trials directly demonstrating stroke prevention with PSO currently exist. Future research should address standardized supplementation protocols, bioavailability optimization, and controlled trials targeting PNEI-relevant endpoints in cerebrovascular risk populations.

Keywords: Psychoneuroendocrinoimmunology; Pomegranate seed oil; Stroke prevention

Hrvoje Budinčević: HORMONAL THERAPY AND STROKE RISK

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Hormonal factors play an important role in the development of cerebrovascular disease in women. Menopause is associated with a marked decline in endogenous estrogen production, leading to metabolic and vascular changes that contribute to an increased cardiovascular and stroke risk. Although estrogen exerts several potentially beneficial effects on vascular function, lipid metabolism, and endothelial health, these protective effects diminish with aging and the menopausal transition.

Women-specific stroke risk factors include the use of combined oral contraceptives and menopausal hormone therapy (MHT). Combined estrogen–progestin contraceptives are associated with an increased risk of ischemic stroke, particularly in women who smoke, are older than 35 years, or have migraine with aura. In contrast, progestogen-only contraceptives have not been linked to an increased stroke risk.

Current evidence does not support the use of menopausal hormone therapy for primary or secondary stroke prevention. Large clinical trials have demonstrated an increased risk of stroke among postmenopausal women receiving oral estrogen, with or without progestin. However, the effect of hormone therapy appears to depend on the timing of initiation, age at treatment onset, and route of administration. Women who begin hormone therapy before the age of 60 years or within 10 years after menopause may experience cardiovascular benefits with a relatively low absolute stroke risk, whereas initiation later in life is associated with a higher risk of stroke and thromboembolic events. Non-oral routes of administration, particularly transdermal preparations, appear to have a more favorable vascular safety profile than oral formulations.

Previous hormone therapy use does not appear to influence mortality in postmenopausal women who experience an acute stroke. Therefore, decisions regarding hormonal therapy should be individualized, taking into account age, cardiovascular risk factors, timing since menopause, and the route of hormone administration.

Keywords: stroke, hormone therapy, hormone replacement therapy, women, menopause

Hrvoje Budinčević, Juraj Mark Poje: CEREBROVASCULAR ULTRASOUND

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Cerebrovascular ultrasound is a non-invasive, readily available, cost-effective, and repeatable diagnostic method that plays a key role in the evaluation and monitoring of patients with cerebrovascular diseases. It includes extracranial carotid and vertebral artery ultrasonography, transcranial Doppler (TCD), and transcranial color-coded duplex sonography (TCCD). These techniques provide real-time assessment of vascular morphology and cerebral hemodynamics and are widely used in stroke units and intensive care settings.

Carotid ultrasonography is essential for detecting and characterizing atherosclerotic lesions, determining the degree of carotid stenosis or occlusion, and evaluating plaque morphology and stability. Features such as echolucent plaques, ulceration, intraplaque hemorrhage, and progressive lesions are associated with an increased risk of ischemic stroke. Ultrasound is also useful in the diagnosis of non-atherosclerotic vascular disorders, including arterial dissections, fibromuscular dysplasia, Takayasu arteritis, temporal arteritis, and subclavian steal syndrome.

Transcranial Doppler enables assessment of intracranial circulation, detection of intracranial stenosis and occlusions, monitoring of thrombolytic therapy, identification of microembolic signals, and evaluation of right-to-left cardiac shunts using the „bubble“ test. These techniques are also valuable in monitoring vasospasm after subarachnoid hemorrhage, assessing cerebral autoregulation, detecting increased intracranial pressure, and confirming brain death.

Additional applications include evaluating intima-media thickness as a marker of subclinical atherosclerosis, perioperative monitoring during carotid interventions, follow-up after carotid endarterectomy and stenting, and assessing cerebral hemodynamics in patients with arteriovenous malformations, Moyamoya disease, and sickle cell disease.

In conclusion, cerebrovascular ultrasound represents an indispensable diagnostic and monitoring tool in modern vascular neurology, providing valuable information on vascular pathology, cerebral blood flow, and stroke risk while supporting timely therapeutic decision-making.

Keywords: Cerebrovascular ultrasound; Carotid ultrasonography; Transcranial Doppler; Stroke; Cerebral hemodynamics; Vascular imaging

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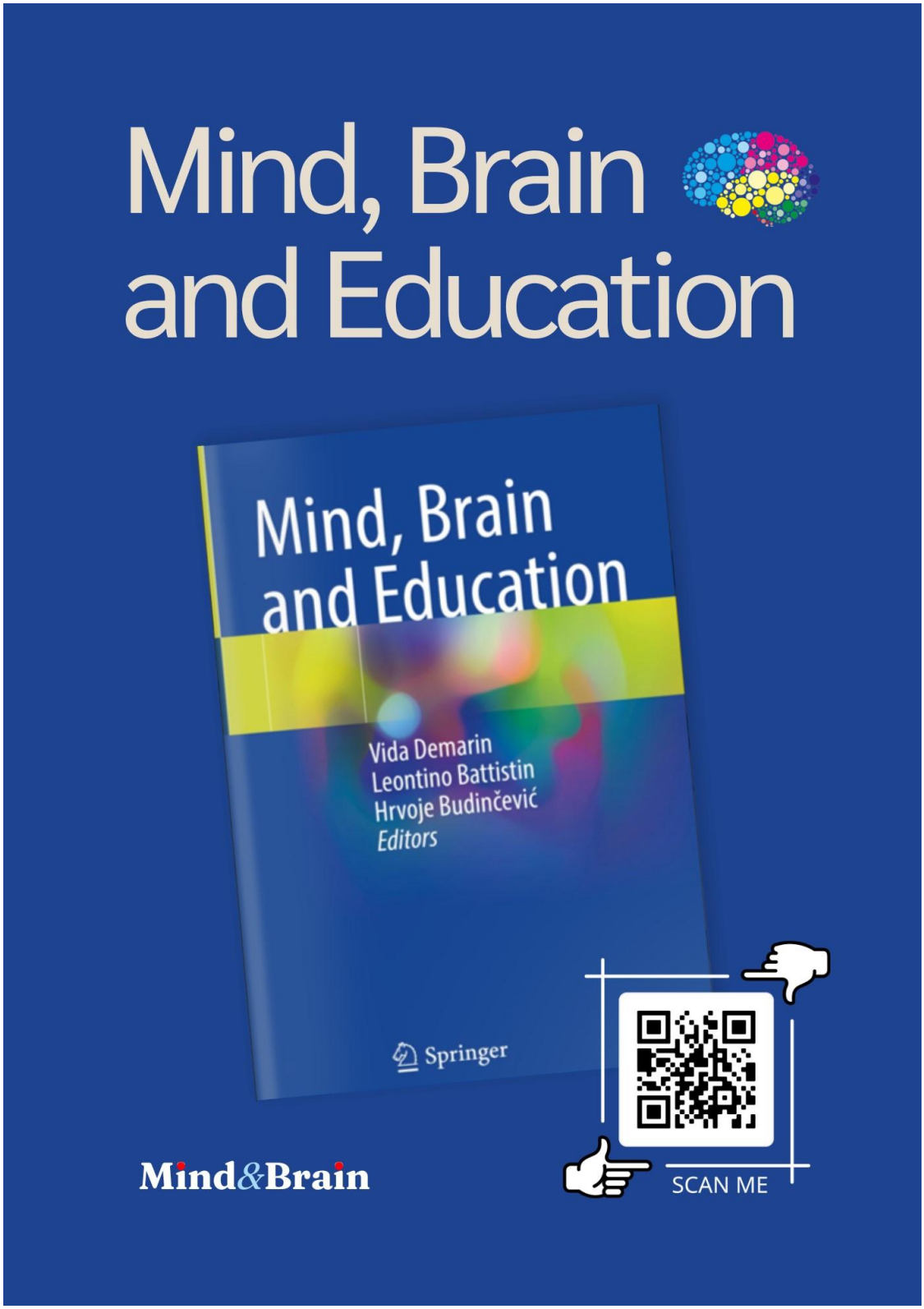

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