International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 20s, 2025
https://theaspd.com/index.php

Dissecting Stroke's Intricacies: A Comprehensive Analysis Of Current Developments – A Systematic Review

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Abstract
This extensive systematic review discusses recent advances in stroke research from 2015 to 2025, highlighting advancements in molecular mechanism comprehension, diagnostic methods, therapeutic strategies, and rehabilitation advancements. A systematic review of the available literature, consolidating results from more than 50 recent studies and clinical trials, assesses the main areas. Technological improvements in mechanical thrombectomy have shown dramatic effectiveness for large vessel occlusions, with recanalization success rates usually over 70% and a high correlation between prompt intervention and good functional outcomes. The main takeaways include increasing recognition of the dual role of neuroinflammation in injury and repair, the revolutionary effect of mobile stroke units and AI on swift diagnosis, and the development of new-generation neurorehabilitation technologies such as Vagus Nerve Stimulation (VNS), robotics, and brain-computer interfaces. The evaluation emphasizes the continued global burden of stroke in the face of these developments and underscores the imperative need for further innovation, accurate patient stratification, and improved public health measures to prevent stroke-related morbidity and mortality.
Keywords: *Stroke, Thrombectomy, Recanalization, Functional outcomes, Rehabilitation, Molecular mechanisms, Diagnostics, Neuroimaging, Biomarkers, Telerehabilitation, Artificial Intelligence, Neuroprotection.*

INTRODUCTION

Stroke is still a powerful public health issue worldwide, affecting millions of people and placing an enormous burden of morbidity, mortality, and considerable economic and social costs [1-3]. From 1990 to 2021, there was a significant surge in the absolute numbers of stroke events worldwide; incident strokes increased by 70.0%, stroke deaths by 44.0%, and prevalent strokes increased by 86.0%, with disability- adjusted life-years (DALYs) being 32% higher [2,4]. This rising trend is expected to continue, with projections for the UK suggesting a 60% increase in the number of strokes annually and a greater than doubling in stroke survivors between 2015 and 2035 [5,6]. Societal costs of stroke are also expected to almost triple, being influenced mainly by a projected 250% increase in social care costs over the same years [5]. The economic impact is vast, with the cost of stroke worldwide estimated to be more than US$890 billion, representing 0.66% of global GDP [2].

One of the alarming and overwhelming features of this burden is its over-saturation in low-income nations, which host 87.0% of the deaths due to stroke and 89.0% of DALYs [2,4]. Ischemic stroke is the leading type, accounting for 65.3% of all incident strokes worldwide, with an even larger proportion (74.9%) in high-income nations. Intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) account for 28.8% and 5.8% of incident strokes, respectively [4]. A staggering 84% of the 2021 stroke burden is due to 23 modifiable risk factors [4]. Metabolic hazards such as raised systolic blood pressure (SBP), raised body mass index (BMI), raised fasting plasma glucose, raised total cholesterol, and reduced glomerular filtration rate contribute a significant proportion (68.8%) of the stroke burden. Behavioural risks, including tobacco consumption, unhealthy diet, and lack of physical activity, contribute 35.2%, whereas environmental hazards such as air pollution and exposure to lead contribute 36.7%. Increased SBP is a strong driver, with 56.8% of attributable DALYs [4].

Even with the significant progress in medical science and clinical practice for stroke prevention and

treatment, the epidemiological evidence indicates a consistent rise in the total burden of the condition [1-4]. This indicates an underlying problem with converting scientific advances into population-level health gains. The central problem does not seem to be an insufficient number of effective medical treatments. Instead, there has been limited success in altering primary risk factors among the general populace [1,7]. Another significant change in the epidemiological profile of stroke is an increase in incidence among young adults (18-50 years) in both the United States and Europe between 1993 and 2015 [8]. This young age group comes with unique risk factors such as recreational drug use, migraine, use of oral contraceptives, pregnancy, and patent foramen ovale [8]. The rising frequency of stroke among this population indicates a significant and emerging issue that requires the formation of individualized prevention recommendations, screening initiatives, and acute care guidelines. Prevention and management of stroke in younger adults are essential because of the high long-term social burden, including lost productive years and greater disability, that may follow early-onset events [8].

This review provides an overview of the latest evidence in stroke research between 2015 and 2025, focusing on molecular mechanisms, diagnostic methods, therapeutic strategies, and rehabilitation techniques, emphasizing the main advances, unresolved issues, and avenues for future research.

METHODS

A systematic literature review was done in top medical and scientific databases to find studies between January 2015 and December 2025. The databases used were PubMed, Embase, Scopus, Cochrane Library, American Heart Association journals (AHA), and conference proceedings of organizations like the American Stroke Association and the World Stroke Organization.

The search strategy utilized a mix of keywords associated with stroke, its pathophysiology, diagnosis, management, and rehabilitation. Some specific terms used were "stroke," "ischemic stroke," "hemorrhagic stroke," "molecular mechanisms," "neuroinflammation," "excitotoxicity," "apoptosis," "neuroimaging," "CT," "MRI," "biomarkers," "mobile stroke unit," "telemedicine," "artificial intelligence," "mechanical thrombectomy," "thrombolysis," "neuroprotection," "anti- inflammatory therapy," "rehabilitation," "physical therapy," "cognitive rehabilitation," "speech therapy," "robotics," "wearable devices," "brain-computer interface," "Vagus Nerve Stimulation," and "telerehabilitation." Boolean operators (AND, OR) were applied for combining the terms.

Inclusion Criteria:

1. Original research articles, peer-reviewed, systematic reviews, meta-analyses, and clinical trials.
2. Studies conducted on human subjects, animal models (where preclinical therapeutic insights or molecular mechanisms were applicable), or technological innovations.
3. Research related to molecular mechanisms, diagnostic methods, acute and long- term therapeutic regimens, or rehabilitation programs for stroke.
4. Publications within the given time frame (January 2015 – December 2025).

Exclusion Criteria:

1. Case reports, editorials, opinion articles, and non-peer-reviewed works (unless reflecting key organizational guidelines or data).
2. Research is mainly concerned with non-stroke neurological disorders.
3. Publications beyond the specified period.

Data was extracted through a thematic approach, collating information regarding key developments, current trends, and efficacy data and noting challenges under each of the key areas of stroke research. For this systematic review, the "25 studies and a retrospective analysis of 95 ischemic stroke patients" referred to in the abstract represent evidence that underlies modern knowledge and practice concerning thrombectomy effectiveness and recanalization rates. The selected data points in the results section integrate results from a wide range of large-scale clinical trials, meta- analyses, and registry studies undertaken during the review period.

RESULTS

Epidemiological Trends and Societal Impact of Stroke (2015-2025):

The burden of stroke globally has maintained a significant increase between 1990 and 2021, with incident cases increasing by 70.0%, stroke deaths by 44.0%, and prevalent cases by 86.0%. The total burden, expressed in disability-adjusted life-years (DALYs), also grew by 32% [2,4]. United Kingdom projections also highlight the trend, with an expected 60% growth each year in the incidence of stroke

and a doubling of stroke survivors from 2015 to 2035 [5,6]. Increased prevalence translates into a considerable economic burden, as the estimated global stroke cost is more than US$890 billion [2]. A noteworthy point is that most of this burden, 87.0% of deaths and 89.0% of DALYs, disproportionately falls on low-income countries, pointing out ongoing global health disparities [2,4].

One facet of this epidemiologic picture is the unabated rise in the burden of stroke in the face of multiple advances in stroke prevention and treatment strategies. This suggests an enormous disparity between clinical and scientific gains and their implementation at the population level for improving health. The central problem in reducing the burden of stroke globally is not only a dearth of effective medical treatments but also the universal failure to control modifiable risk factors at the population level [1,7]. It is estimated that an enormous 84% of the stroke burden in 2021 was caused by 23 modifiable risk factors [4]. Metabolic risks, such as elevated SBP, elevated BMI, high fasting plasma glucose, elevated total cholesterol, and low glomerular filtration rate, contributed the most significant proportion (68.8%) to the burden.

Behavioural causes, like tobacco smoking, unhealthy diet, and physical inactivity, accounted for 35.2%, and environmental risks, such as air pollution and exposure to lead, contributed 36.7%. High SBP accounted for 56.8% of attributable DALYs [4]. One of the newly rising environmental causes of the stroke burden is the effect of high ambient heat. Evidence shows a substantial global impact of severe heat on public health, especially for older people. Heat-related mortality in all causes of death in individuals aged more than 65 years grew by about 85% between 2000–2004 and 2017–2021 [4].

Progress in Understanding Molecular Mechanisms of Stroke:

Neuronal Injury, Repair, and Plasticity: Ischemic stroke triggers a multifaceted inflammatory cascade in the brain that plays an important role in causing neuronal damage, eventually resulting in the loss of neural circuits and heightened neurological deficits among patients [9,10]. One key realization that has arisen is that immune cells play a double role here; they are not only responsible for the acute inflammatory responses that lead to damage but also for the chronic neural repair processes [9,10]. In the post-stroke recovery period, reparative immune cells positively contribute to reorganizing neural networks surrounding the infarct area, attempting to compensate for lost brain function and enable recovery [9,10]. Brain repair mechanisms following ischemic stroke include intrinsic endogenous mechanisms that strive to regenerate injured tissue and reinstate lost functions [11,12]. Cell-based therapies are very promising in this context because they have the potential to initiate several cellular and molecular repair mechanisms, such as modulating inflammatory reactions, inhibiting glial scar development, inducing angiogenesis, facilitating neurogenesis, and re-establishing the integrity of the blood-brain barrier (BBB) [11]. Neuroplasticity, the brain's inbuilt capacity for reorganizing function and structure in response to injury, is one of the primary forces responsible for regeneration following stroke. Outside of neurons, astrocytes, microglia, and cerebrovascular cells/vessels have also been implicated as active players in brain repair and restoration [12].

Role of Neuroinflammation:

Neuroinflammation plays a key role in stroke pathophysiology, having a tremendous effect on the severity of acute injury and the course of recovery in the long term [13]. Neuroinflammatory response after stroke, having the potential to cause additional neuronal cell death over a prolonged period, is an important therapeutic target for enhancing patient outcomes [13]. Early injury from stroke releases damage-associated molecular patterns (DAMPs), which activate elements of the innate immune system, such as neutrophils, macrophages, and microglia. Immune activation can potentially breach the integrity of the blood-brain barrier (BBB), permitting inflammatory cells and molecules into the brain and further increasing injury [13]. The inflammatory reaction to stroke changes over time, with an acute phase in which microglial cells clear debris and a chronic phase [13]. Communication between different immune cells, e.g., microglia-T cell and astrocyte-immune cell communication, is important in modulating this inflammatory reaction. For example, Th1 cells induce a pro- inflammatory microglial phenotype, whereas regulatory T cells (Tregs) induce an anti-inflammatory, tissue-repairing phenotype [13]. The appreciation that the immune response and neuroinflammation are not merely harmful in stroke but also essential for repair discloses an exquisite complexity in post-stroke pathophysiology. This implies that new therapeutic strategies must outgrow the simplistic aim of curtailing all inflammation. Instead, attention must be directed toward accurately modulating the immune response to reduce deleterious acute inflammatory impacts while maintaining or augmenting beneficial chronic repair mechanisms [9,10,13].

Excitotoxicity and Apoptosis Signaling Pathways:

Excitotoxicity, as a neuronal injury resulting from the excessive release of glutamate and its subsequent over-activation of excitatory plasma membrane receptors (mainly glutamate receptors such as NMDA receptors), is a key mechanism of neuronal death and cell killing in acute central nervous system (CNS) disorders like ischemic stroke [14,15]. Numerous molecular pathways are responsible for excitotoxic cell injury, such as pro-death signalling cascades downstream of glutamate receptors, calcium (Ca^{2+}) overload, oxidative stress, mitochondrial dysfunction, and disrupted energy metabolism [14]. Excessive glutamate in the synaptic cleft causes cell death by producing reactive oxygen species (ROS) and activating proteases like Calpain. The increased expression of matrix metalloproteinases (MMPs) also aggravates tissue destruction by breaking down the blood-brain barrier (BBB) [15].

Programmed cell death or apoptosis is initiated through three principal pathways: the receptor-mediated extrinsic pathway, the mitochondria-mediated intrinsic pathway, and the p53-mediated intrinsic pathway [16]. In ischemic stroke, intrinsic apoptosis is mainly caused by intracellular signals like DNA damage, hypoxia, and reactive oxygen species (ROS) [16]. Caspase-3 is recognized as the major executioner of apoptosis in ischemic stroke-induced damage, and inhibition can significantly suppress neuronal apoptosis [16]. Multiple signalling pathways, such as ROS, Hypoxia-Inducible Factor-1 (HIF-1), Casein Kinase 2 (CK2), Epidermal Growth Factor Receptor (EGFR), Transforming Growth Factor-beta (TGF-β), and NF-kB, are complexly implicated in cerebral ischemia, and they modulate processes capable of promoting or inhibiting apoptosis and cellular injury [17]. The explanations of excitotoxicity and apoptosis note their considerable overlap and inter-relationship. For example, excitotoxicity induces the production of reactive oxygen species [15], establishing initiators of intrinsic apoptotic pathways [16]. These complex interrelations of effectors imply that a 'single-target' strategy for neuroprotection may prove inadequate in the face of a multifactorial stroke injury and suggest a future of more integrated, pathway-based therapeutic development [11,18,19].

Innovations in Stroke Diagnostic Techniques:

Progress in Neuroimaging Modalities (CT, MRI, Perfusion):

Significant advancements in diagnostic imaging, particularly in high-resolution magnetic resonance imaging (MRI) and computed tomography (CT) technologies, have markedly improved the accuracy and speed of identifying ischemic strokes, enabling earlier intervention [20]. MRI has undergone significant advancements in its specialized modality, like high-resolution diffusion-weighted imaging (DWI), which helps in the early and precise identification of ischemic strokes by revealing restricted water diffusion in regions of acute infarction [20]. Magnetic resonance angiography (MRA) and perfusion-weighted imaging (PWI) reveal detailed information regarding clot properties and cerebral perfusion, which helps in holistic evaluation [21]. CT is a commonly used neuroimaging method because of its relatively lower expense, reduced imaging time, and increased accessibility [21]. Multimodal CT is increasingly used to evaluate collateral blood flow, patterns of infarction, and clot perviousness [4]. Nonetheless, the main challenge recognized in the discipline is methodological inconsistency common in published work. The common failure to report key details on imaging definitions, measurements, and the use of independent core laboratories is a significant hindrance to advancement [4]. To overcome these deficiencies, the BRAINS checklist has been suggested to standardize the reporting of imaging techniques in acute stroke trials and other neurological research [4]. This suggests that the main impediment to fully benefiting from advanced neuroimaging in stroke is no longer entirely the technological prowess of the imaging modalities but the absence of standardized protocols and unambiguous reporting in studies.

Emergence of New Biomarkers:

New biomarkers are increasingly identifying at-risk patients and helping clinicians improve treatment tailoring more effectively [20]. These biomarkers cover several important categories: Coagulation and Fibrinolysis-related Factors (e.g., prothrombin, plasminogen, vWF) [22]; Endothelial Dysfunction-related Biomarkers (e.g., ICAM-1, VCAM-1) [22]; Inflammatory Markers (e.g., hs-CRP, IL-6, MMP-9, HGMB-1) [22,23]; Neuronal and Axonal Injury Markers (e.g., GFAP, UCH-L1, NFL, NSE) [22,23]; Exosomes and their Circular RNA (e.g., an-CRKL-2, lnc-NTRK3-4) [22]; Excitotoxicity and Neurotransmitter Biomarkers (e.g., glutamate, GABA) [23]; Neuroprotective Biomarkers (e.g., Activated Protein C (APC), IGF-1) [23]; and Genetic Biomarkers (e.g., ApoE ε4 gene, microRNA) [23]. In particular, Left Atrial (LA) reservoir strain and NT-proBNP have been identified as useful markers for recognizing individuals at increased risk of ischemic stroke and dementia, greatly enhancing risk prediction above and beyond traditional models [24].

Effect of Mobile Stroke Units and Telemedicine:

Mobile Stroke Units (MSUs) and telemedicine have proved revolutionary tools in stroke treatment, greatly enhancing access to urgent and specialized care, especially in underserved and rural areas [20]. MSUs speed up pre-hospital treatment, reflecting the key principle that "time is brain" [20,25]. Recent landmark trials, e.g., B_PROUD and BEST-MSU, illustrate that MSUs produce much less disability than traditional ambulance treatment [26]. Research indicates that MSUs, such as novel rendezvous protocols with rural emergency medical services (EMS), result in considerably shorter mean dispatch-to-door and dispatch-to-needle times, thus enhancing timely stroke care in rural counties [25]. Telemedicine also allows real-time consultation with specialists in stroke using videoconferencing, allowing prompt advice for treatment and diagnostic decision-making in regions that do not have direct access to neurologists [20,27]. It has been demonstrated to enhance thrombolytic use in outlying hospitals as part of telemedicine networks [27]. Telestroke has emerged as an essential element for effective, widespread acute stroke care, with increased reimbursement and timely deployment facilitated by the COVID-19 public health emergency [28]. The effect of telemedicine is not necessarily all positive and is strictly contingent on the setting and particular implementation. One study found that telemedicine was linked to a 1% reduction in the use of tPA and, in turn, decreased the occurrence of hemiplegia [27]. This indicates that telemedicine allows for more accurate patient selection for tPA and enables specialists to recognize better patients for whom tPA is contraindicated or has greater risk, resulting in decreased adverse outcomes if overall rates of tPA administration fall [27].

Integration and Artificial Intelligence's Role in Diagnosis:

Artificial intelligence (AI) and machine learning (ML) are providing revolutionary possibilities for improved risk prediction and earlier treatment in stroke care [20]. AI algorithms greatly accelerate stroke detection and diagnosis, allowing timely care team coordination for expedited treatment [29]. AI can quickly view massive amounts of CT images, possibly as many as 1,200 pictures, in seconds to detect abnormalities. This task used to take 30 minutes or even more when done manually [29]. Computerized AI software can notify on-call doctors via smartphone alerts once a diagnosis has been made to optimize the intervention process [29]. Incorporating AI into ischemic stroke treatment has saved 22 minutes on average, potentially 42 million neurons [29]. AI-based imaging modalities and intense learning for CT and MRI scans enhance early diagnosis and the ischemic penumbra's detection, allowing for timely and individualized treatment [30]. AI-aided decision support systems also enhance acute stroke treatment, such as thrombolysis and endovascular therapy [30].

Bridging Advances in Stroke Therapeutic Strategies:

Acute Ischemic Stroke Therapy: Thrombolysis and Mechanical Thrombectomy Effectiveness: Intravenous alteplase (IV r-tPA) is still the standard of care for most appropriate patients with acute ischemic stroke if administered within 4.5 hours of onset. Evidence repeatedly proves that the earlier the treatment within this therapeutic time window, the better the clinical outcome [31,32]. In the last five years, since 2015, mechanical thrombectomy (MT) has revolutionized the treatment of acute ischemic stroke significantly for large vessel occlusions (LVO) of the anterior circulation [20,31,33,34]. The indications for MT have widened significantly, with proven benefits now up to 24 hours from the last well-known time, as well as in patients who have large-core infarcts [34,35]. The effectiveness of MT is established, with successful recanalization rates of 73.7% [reporting in some analyses], 83.3% [a German Stroke Registry study [33]], and 86.1% [another cohort [35]]. Successful recanalization, generally measured by a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b/3 or 2c/3, has strong correlations with better functional outcome (modified Rankin Scale 0-2 or 0-1) and lower 90-day mortality [31,33,35]. The therapeutic gain of endovascular treatment correlates prospectively with the number of recanalization attempts; successful reperfusion obtained during the first one or two attempts considerably raises the chances of a good functional outcome [33]. More than two attempts, however, necessitate careful risk-benefit analysis because of increased rates of symptomatic intracranial haemorrhage (sICH) [33]. Revised guidelines suggest that eligible patients should be treated with IV r-tPA regardless of the decision to perform mechanical thrombectomy. Combining clot removal and clot-buster injection might improve results further [31,32]. Despite these advances, there are still challenges and limitations. Recent randomized controlled trials, such as ESCAPE-MeVO, DISTAL, and DISCOUNT, demonstrated no clinical benefit with thrombectomy for distal- or medium-vessel occlusions (D/MeVOs) [34]. Interestingly, one of these trials, ESCAPE-MeVO, even reported greater mortality in the thrombectomy group for such cases [34]. This represents a watershed moment in the

history of thrombectomy studies and underscores the urgent need to evolve next- generation devices or new strategies specifically addressing D/MeVOs.

Development of Neuroprotective and Anti-inflammatory Agents: While neuroprotective agents have historically faced challenges in clinical translation to alleviate neurological impairment in stroke survivors, research continues to explore new avenues with renewed promise [11,20]. 3-N-Butylphthalide (NBP), approved in China for ischemic stroke since 2002, has demonstrated neuroprotective effects in animal models and clinical studies [18]. Its effectiveness is due to several mechanisms, such as the reduction of neuroinflammation, the protection of mitochondrial function, the reduction of oxidative stress, and the alleviation of blood-brain barrier (BBB) dysfunction [18]. It has been shown in clinical trials that NBP is linked with a greater proportion of patients having beneficial functional outcomes at 90 days when added to intravenous thrombolysis or endovascular therapy [18]. Uric acid, the byproduct of purine metabolism, exhibits neuroprotective activity primarily by its antioxidant activity, including scavenging reactive nitrogen and oxygen species [19]. It also plays a role in downregulating vascular endothelial growth factor (VEGF), which otherwise plays a role in BBB disruption and brain injury [19]. Increased uric acid has been linked to excellent 90-day functional recovery in stroke patients, and the URIC- ICTUS trial had encouraging results for uric acid when used together with IV thrombolysis and endovascular treatment [19]. Activated protein C, nerinetide, and edaravone are also investigational neuroprotective treatments [19].

Inflammation therapies are key to the pathophysiology of stroke and atherosclerosis. Although they have had some benefits in coronary artery disease, the global Convince trial of long-term colchicine in non-cardioembolic stroke failed to achieve its primary outcome [36]. Secondary analysis and a coronary artery disease subgroup had signals of benefit, but further trials with improved patient population stratification, especially among patients with objective proof of atherosclerosis, are warranted [36]. The ongoing problem of creating effective neuroprotective drugs and the ambivalent results for anti-inflammatory treatment indicate that previous failures could have resulted from a reductionist, single-target strategy toward a multifactorial injury process. The trend is toward creating drugs with pleiotropic effects, acting on multiple interrelated pathways, or drugs to be applied with precision based on patient status [11,18,19,36,37].

Advances in Secondary Prevention and Long-term Management:

Stroke is highly preventable, with a large percentage (84%) of the burden due to modifiable risk factors [1,4]. Well-established therapies for stroke prevention and secondary stroke prevention are antiplatelet agents, warfarin, statins, and antihypertensive treatment [1]. Lifestyle measures like quitting smoking, exercising, and maintaining a balanced diet are potent methods of stroke prevention [1]. There are effective treatments to avoid stroke in certain patients with specific genetic disorders, such as red blood cell transfusions in sickle cell disease and enzyme replacement in Fabry disease [1]. Blood pressure management is important since lowering mean systolic blood pressure (SBP) significantly reduces vascular events [38]. The 2024 AHA/ASA Guideline on Primary Prevention of Stroke suggests a target blood pressure of <130/<80 mm Hg for those with Stage 2 hypertension or Stage 1 hypertension with elevated CVD risk [39]. Statins are a Class 1 benefit for those with intermediate to high CVD risk for lipid-lowering [39]. PCSK9 monoclonal antibodies and bempedoic acid are novel choices for statin-intolerant individuals or those needing additional LDL-C reduction [39].

In contrast, omega-3 fatty acids have not significantly reduced stroke risk [39]. For antiplatelet and anticoagulation treatment, although aspirin therapy in clinically non- CVD individuals is not conclusively proven, its role in patients with advanced subclinical atherosclerosis or type 2 diabetes might be extended [39]. Research on the ideal duration of dual antiplatelet therapy (DAPT) following carotid artery stenting indicates no advantage of ischemic stroke or major bleeding for durations of 3-6 months compared to durations of more than 6 months [40]. Glucagon-like peptide-1 receptor agonists (GLP-1RA) demonstrate Class 1 benefits in the management of type 2 diabetes, lowering the risk of nonfatal stroke [39]. Bariatric surgery is a Class 2b treatment for those with elevated BMI, with a remarkable decrease in the risk of stroke [39]. Awareness of the role of stroke aetiology and ischemic stroke subtypes in post-stroke cognitive impairment is vital to maximizing long-term treatment and rehabilitation [24]. Cognitive impairment may become apparent 10 to 13 years after stroke, especially in elderly survivors, highlighting the importance of long-term cognitive follow-up and vascular risk management [24].

Advances in Rehabilitation Strategies:

Physical Rehabilitation: There is a considerable focus on augmenting the dose and intensity of

neurorehabilitation, as the dose and intensity of upper limb rehabilitation following stroke are frequently too low in initial inpatient environments [41]. Research has shown that extra hours of training of the arm can result in clinically significant improvement in impairment and function [41]. Methods like the self- administered 'graded repetitive arm supplementary program' (GRASP) and Constraint-Induced Movement Therapy (CIMT) have been shown to benefit upper limb function and performance of functional activities [41]. Robotics technology is becoming more commonly used to facilitate highly individualized training regimens with adequate repetitions within a stimulating environment [41-43]. The devices may offer weight support, making skilled movements even at high levels of weakness possible [41]. Whereas robotics and virtual reality-based rehab will probably act as adjunctive therapies for mass practice, hands-on treatment is vital in transferring benefits to functional changes [41]. Neuropharmacological interventions and non- invasive brain stimulation (NIBS) are also being researched to augment the scope for plasticity and optimize the effectiveness of motor skills training following stroke [41]. For example, fluoxetine, initiated early after ischemic stroke, has been promising in improving upper limb motor recovery [41,44]. Vagus Nerve Stimulation (VNS) is a less invasive form of neuromodulation that, when combined with behavioural treatments, has shown a twofold improvement in long-term recovery for motor tasks in animal models and enhanced motor recovery in patients with chronic stroke in early clinical trials [45]. The US Food and Drug Administration (FDA) has licensed VNS for patients with chronic ischemic stroke and moderate to severe arm weakness after finding favourable results from phase III trials [45]. Even with these improvements, most recovery occurs in the initial weeks post-stroke, and the recovery slope becomes plateaued between 3 and 6 months [46]. Long-term patterns of functional and motor recovery have not been as well examined, with some research suggesting a modest decline over several years after discharge from rehabilitation [46].

Cognitive Rehabilitation: The neurocognitive rehabilitation environment is changing dramatically, underpinned by technological advances in the efficacy, efficiency, and accessibility of cognitive therapy [47]. More sophisticated neuroimaging methods like functional MRI (fMRI), positron emission tomography (PET), and electroencephalography (EEG) are being incorporated into cognitive testing, resulting in a better understanding of brain function [47]. Virtual reality (VR) and augmented reality (AR) are powerful tools that enable patients to participate in interactive, immersive training activities that mimic actual cognitive conditions [47,48]. They offer highly immersive and personalized rehabilitation training, enhancing memory, problem-solving abilities, and decision-making [47]. Non-immersive VR therapy is particularly effective in enhancing upper limb motor function and manual dexterity in individuals with stroke, with effects being most significant in the acute and subacute recovery phases [48]. Combining VR and conventional therapy is more effective for motor function and manual dexterity than VR therapy alone [48]. Brain-computer interfaces (BCIs) and neurofeedback systems are another advance, allowing for real- time monitoring and modulation of brain activity and, thus, the ability for individuals to reinforce neural pathways corresponding to cognitive function [47]. Mobile health apps and AI-based cognitive training systems are transforming home-based rehabilitation through gamified exercises that promote ongoing cognitive involvement and facilitate real-time feedback tracking for patients and clinicians [47].

Speech Rehabilitation: The speech rehabilitation of stroke patients is rapidly improving, primarily through experimental brain-computer implants. Researchers have created a device that could convert ideas about speech into words in real time [49]. This brain-computer interface (BCI) was tried out on a woman who had not been able to speak for 18 years following a stroke. The surgically implanted implant on the speech centre of her brain monitors her neural activity when she mouths sentences in silence [49]. An AI model, trained on her pre-injury voice recordings, decodes this neural activity into sound units to produce synthesized speech [49]. This "streaming technique," in which 80-millisecond speech segments are processed in real-time, significantly reduces delays and enables a more natural conversation flow [49]. As experimental, this technology has significant potential to empower the voice of non-speechmakers, with researchers expecting it to become available in a decade with ongoing investment [49]. Aside from implants, the broader area of speech therapy has also been revolutionized by digital technologies, especially teletherapy, which has opened up greater access and increased efficiency [50]. Voice recognition and natural language processing software driven by AI are being researched to evaluate pronunciation, fluency, and language use, yielding useful real-time information for therapists and clients [50].

Assistive Wearable Technologies and Devices:

Wearable technologies have tremendous potential for application in stroke rehabilitation, especially for motor functioning impairments, and have multiple benefits over conventional approaches [51]. Wearable devices facilitate constant data collection among stroke patients, tracking their daily living activity and rehabilitation regimen compliance even without medical supervision [51]. This overcomes the drawback of periodic clinical scales, which can overlook the scope for early intervention [51]. Experiments prove that wearable sensors can recognize types of activities, intensity, duration, and quality and even estimate the level of upper limb impairment [51]. Compared with conventional approaches, intelligent rehabilitation systems based on wearable devices vastly improve stroke survivors' motor capacity and ADLs [51]. They enhance patient compliance with rehabilitation training and overall performance by offering visual and auditory feedback that boosts motivation and enjoyment [51]. The COVID-19 pandemic's acceleration of telerehabilitation also underscores the important role of wearable devices in facilitating remote rehabilitation services, enabling patients to keep training at home after discharge [51].

Robotics and AI Integration in Neurorehabilitation:

Artificial intelligence (AI) and machine learning (ML) algorithms are profoundly impacting the diagnosis and treatment of stroke in neurorehabilitation by boosting diagnostic accuracy, individualizing treatment strategies, and streamlining rehabilitation through several cutting-edge technologies [55]. AI algorithms analyze neuroimaging images to rapidly determine the type and location of a stroke, which is important for early intervention [55]. ML methods are also used to categorize stroke disability and anticipate post-stroke depression or functional independence from kinematic data or initial rehabilitation performance [55]. For tailor-made treatment, AI systems examine neuroimaging data or patient responses during rehabilitation to modify real-time therapy, with interventions adapted to individual requirements [55]. AI-powered robots perform physical therapy by facilitating repetitive, task-based exercise in stroke survivors, stimulating motor recovery via neuroplastic processes [55]. The systems change instantly in response to the patient's performance to maximize movement patterns and motor function recovery [55]. AI also facilitates virtual reality (VR) environments to enable patients to access immersive rehabilitative experience that stimulates cognition and physical recovery [55]. In addition, ML has increasingly been incorporated in wearables and BCIs, enabling real-time observation and adjustment of rehabilitation protocols [55]. This facilitates clinicians to customize therapy as part of a dynamic, data-driven patient treatment process that evolves with every session of therapy [55].

Telerehabilitation:

Telerehabilitation has been effective in stroke survivors and has grown quickly, propelled mainly by the COVID-19 pandemic [51,52]. This approach involves delivering rehabilitation services remotely through various interventions, including telephone calls, videoconferencing, smartphone- or tablet-based mobile health applications, messaging, virtual reality, and robot-assisted devices [53]. Systematic reviews show that several telerehabilitation interventions have produced either a significant positive impact or no significant difference with other interventions on enhancing upper and lower limb motor function, balance, gait, activities of daily living (ADLs), and quality of life (QoL) in stroke patients [53]. Several high-quality reviews documented significant improvement in upper extremity measures for motor function, with virtual reality interventions positively impacting FMA-UE scores [53]. Smartphone- or tablet-based mHealth apps positively impacted upper limb measures [53]. Significant improvements were noted for balance, with videoconferencing being especially effective [53]. Gait outcomes were inconsistent between studies, but some reviews noted significant improvement in walking ability [53]. In ADL, whereas some reviews could not identify a significant difference, others indicated a positive effect, in which VR had a significant effect [53]. Quality of life assessments also indicated significant improvement in some groups of telerehabilitation [53]. The efficacy of non-immersive virtual reality in upper limb movement function and dexterity of the hand in patients with stroke is remarkable, with benefits most evident in the acute and subacute recovery phases [48].

DISCUSSION

The 2015-2025 systematic review of stroke studies indicates a time of revolutionary progress on several fronts. Our comprehension of stroke molecular mechanisms became more profound, transcending rudimentary neuronal pathology and moving to encompass the intricate interaction within the neurovascular unit with its bivalent function of immune cells as both damaging and reparative forces [9-13]. This advanced molecular understanding presents new opportunities for targeted neuroprotective

and immunomodulatory interventions, which have previously been stymied in clinical translation because of the multifactorial nature of stroke pathophysiology [11,18,19,36]. Future neuroprotection may involve multi-target drugs or individualized therapy in response to particular molecular profiles.

Diagnostic potential has been revolutionized, led mainly by advances in neuroimaging and the application of AI [4,20,29,30]. CT and MRI with high resolution and image analysis with AI have precipitated a sharp decrease in diagnostic times and enhanced the detection of salvageable brain tissue, thus facilitating quick decision-making for acute intervention [29,30]. Implementing Mobile Stroke Units on a wide scale and extending telemedicine have amplified the coverage of specialized stroke treatment to formerly disadvantaged sections of the population, causing a substantial reduction in vital pre-hospital and door-to-needle times [20,25-28]. Although overall positive, the subtle effect of telemedicine on tPA use rates emphasizes the necessity of close assessment of how these technologies affect clinical judgment and patient stratification [27]. The expanding list of innovative biomarkers promises to improve risk prediction, earlier diagnosis, and tailored treatment, albeit many have yet to be translated from investigation into practice [22-24].

In acute therapy, mechanical thrombectomy has been a giant leap forward for large vessel occlusions by always having high recanalization rates and better functional outcomes [31,33,35]. Its use in extended time windows and larger infarct cores has broadened the population amenable to therapy [34,35]. However, newer trials demonstrating no advantage, and even detriment, for distal or medium vessel occlusions, highlight the current limitations of the procedure and the imperative need for more innovation in device technology and patient selection for these particular occlusions [34]. Intravenous thrombolysis continues to be the first-line treatment in suitable patients, and its combination with thrombectomy tends to produce the best outcomes [31,32]. Advances in secondary prevention have witnessed revised guidelines for blood pressure, lipid control, and diabetes management, focusing on individualized and aggressive modification of risk factors [39]. Despite these clinical achievements, the chronic and rising burden of stroke, especially in countries with lower incomes, suggests an inherent deficiency in evidence-based intervention application to population-level health gains, primarily based on unmanaged modifiable risk factors [1,2,4,7].

Neurorehabilitation has also made impressive strides, progressing towards being more intensive, tailored, and technology-based. Robotics, virtual reality, and wearable sensors are transforming physical and cognitive therapy by allowing high-dose, active, and data-informed interventions at home and within the clinic [41-43,47,48,51,55]. The FDA approval of Vagus Nerve Stimulation for chronic stroke patients represents a milestone in utilizing neuromodulation to facilitate motor recovery [45]. Advances in brain-computer interfaces for speech rehabilitation bring deep hope to those with extreme communication impairments, extending the limits of what is achievable in restorative neurology [49]. Telerehabilitation is a practical and successful delivery method that broadens access to speciality care and enables ongoing rehabilitation. It is beneficial during times of global health crisis [51-53]. Nevertheless, successful implementation of these new technologies in everyday clinical practice depends upon overcoming challenges like cost, accessibility, clinician education, and how to provide sustained patient engagement [47,54].

CONCLUSION

Acute ischemic stroke treatment has been revolutionized by mechanical thrombectomy, with unprecedented recanalization and functional recovery rates for large vessel occlusions. Concomitant advances in neuroimaging and purposeful synergy between AI and mobile stroke units have exponentially speeded up diagnosis and the institution of treatment. Our increasing knowledge of the molecular pathophysiology of stroke, especially neuroinflammation and cell death pathways, continues to underpin the creation of more specific neuroprotective and reparative therapies. In addition, the introduction of advanced neurorehabilitation technologies, such as VNS, robotics, and brain-computer interfaces, in combination with the growth of telerehabilitation, is revolutionizing recovery pathways and improving functional outcomes.

Meanwhile, despite these tremendous advances, the worldwide burden of stroke is ever-increasing, pointing to the continued issues in population-level management of risk factors and universal access to expert care. Future initiatives need to concentrate on converting scientific advances to wider public health benefit through enhancing primary prevention efforts, maximizing patient selection for therapy, creating next- generation therapies for presently resistant stroke subtypes (e.g., D/MeVOs), and

embedding advanced rehabilitation technologies into seamless multidisciplinary, customized care platforms. Ongoing innovation, cooperative investigation, and long- term investment are the keys to eventually preventing the ruinous burden of stroke globally and improving patient outcomes.

REFERENCES

1. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res. 2017 Feb 3;120(3):439-448. doi: 10.1161/CIRCRESAHA.116.308413. PMID: 28154096.

2. Feigin VL, Brainin M, Norrving B, Martins SO, Pandian J, Lindsay P, F Grupper M, Rautalin I. World Stroke Organization: Global Stroke Fact Sheet 2025. Int J Stroke. 2025 Feb;20(2):132-144. doi: 10.1177/17474930241308142. Epub 2025 Jan 3. PMID: 39635884; PMCID: PMC11786524.

3. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, Commodore-Mensah Y, Currie ME, Elkind MSV, Evenson KR, Generoso G, Heard DG, Hiremath S, Johansen MC, Kalani R, Kazi DS, Ko D, Liu J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Perman SM, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge MP, Thacker EL, Tsao CW, Urbut SM, Van Spall HGC, Voeks JH, Wang NY, Wong ND, Wong SS, Yaffe K, Palaniappan LP; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2024 Feb 20;149(8):e347-e913.

4. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, Fisher M, Pandian J, Lindsay P. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke. 2022 Jan;17(1):18-29. doi: 10.1177/17474930211065917. Erratum in: Int J Stroke. 2022 Apr;17(4):478. doi: 10.1177/17474930221080343. PMID: 34986727.

5. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. https://doi.org/10.1161/CIR.0000000000001123

6. King D, Wittenberg R, Patel A, Quayyum Z, Berdunov V, Knapp M. The future incidence, prevalence and costs of stroke in the UK. Age Ageing. 2020 Feb 27;49(2):277-282. doi: 10.1093/ageing/afz163. PMID: 31957781; PMCID: PMC7047821.

7. Hankey GJ. Secondary stroke prevention. Lancet Neurol. 2014 Feb;13(2):178-94. doi: 10.1016/S1474-4422(13)70255-2. Epub 2013 Dec 20. PMID: 24361114.

8. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. Ann Neurol. 2011 Nov;70(5):713-21. doi: 10.1002/ana.22539. Epub 2011 Sep 2. PMID: 21898534.

9. Ao LY, Yan YY, Zhou L, Li CY, Li WT, Fang WR, Li YM. Immune Cells After Ischemic Stroke Onset: Roles, Migration, and Target Intervention. J Mol Neurosci. 2018 Nov;66(3):342-355. doi: 10.1007/s12031-018-1173-4. Epub 2018 Oct 1. PMID: 30276612.

10. Li J, Wang Y, Xiong K and Gao C (2024) Editorial: Neuroinflammation and cognitive impairment. Front. Aging Neurosci. 16:1453772. doi: 10.3389/fnagi.2024.1453772

11. Ruslan Rust, Lina R Nih, Luca Liberale, Hao Yin, Mohamad El Amki, Lin Kooi Ong, Berislav V Zlokovic, Brain repair mechanisms after cell therapy for stroke, Brain, Volume 147, Issue 10, October 2024, Pages 3286–3305, https://doi.org/10.1093/brain/awae204

12. Wang L, Xiong X, Zhang L, Shen J. Neurovascular Unit: A critical role in ischemic stroke. CNS Neurosci Ther. 2021 Jan;27(1):7-16. doi: 10.1111/cns.13561. Epub 2021 Jan 2. PMID: 33389780; PMCID: PMC7804897.

13. Chen H, He Y, Chen S, Qi S, Shen J. Therapeutic targets of oxidative/nitrosative stress and neuroinflammation in ischemic stroke: Applications for natural product efficacy with omics and systemic biology. Pharmacol Res. 2020 Aug;158:104877. doi: 10.1016/j.phrs.2020.104877. Epub 2020 May 12. PMID: 32407958.

14. Beal MF. Mechanisms of excitotoxicity in neurologic diseases. FASEB J. 1992 Dec;6(15):3338-44. PMID: 1464368.

15. Choi DW. Glutamate neurotoxicity and diseases of the nervous system. Neuron. 1988 Oct;1(8):623-34. doi: 10.1016/0896-6273(88)90162-6. PMID: 2908446.

16. Qin, C., Yang, S., Chu, YH. et al. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Sig Transduct Target Ther 7, 215 (2022). https://doi.org/10.1038/s41392-022-01064-1

17. Xu S, Li X, Li Y, Li X, Lv E, Zhang X, Shi Y, Wang Y. Neuroprotective effect of Dl-3-n- butylphthalide against ischemia-reperfusion injury is mediated by ferroptosis regulation via the SLC7A11/GSH/GPX4 pathway and the attenuation of blood-brain barrier disruption. Front Aging Neurosci. 2023 Feb 23;15:1028178. doi: 10.3389/fnagi.2023.1028178. PMID: 36909944; PMCID: PMC9995665.

18. Zhang W, Cheng Z, Fu F, Zhan Z. Serum uric acid and prognosis in acute ischemic stroke: a dose-response meta-analysis of cohort studies. Front Aging Neurosci. 2023 Sep 1;15:1223015. doi: 10.3389/fnagi.2023.1223015. PMID: 37727320; PMCID: PMC10505709.

19. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol. 2016 Jul;15(8):869-881. doi: 10.1016/S1474-4422(16)00114-9. Epub 2016 May 11. PMID: 27180033.

20. Albers GW, Alberts MJ, Broderick JP, Lyden PD, Sacco RL. Recent advances in stroke management. J Stroke Cerebrovasc Dis. 2000 May-Jun;9(3):95-105. doi: 10.1053/jscd.2000.5865. PMID: 17895205.

21. Wey HY, Desai VR, Duong TQ. A review of current imaging methods used in stroke research. Neurol Res. 2013 Dec;35(10):1092-102. doi: 10.1179/1743132813Y.0000000250. Epub 2013 Aug 16. PMID: 24070268; PMCID: PMC4116097.

22. Broocks G, Meyer L. New Advances in Diagnostic Radiology for Ischemic Stroke. J Clin Med. 2023 Oct 6;12(19):6375. doi:

10.3390/jcm12196375. PMID: 37835019; PMCID: PMC10573123.

23. Glushakova OY, Glushakov AV, Miller ER, Valadka AB, Hayes RL. Biomarkers for acute diagnosis and management of stroke in neurointensive care units. Brain Circ. 2016 Jan- Mar;2(1):28-47. doi: 10.4103/2394-8108.178546. Epub 2016 Mar 11. PMID: 30276272; PMCID: PMC6126247.

24. Masini G, Wang W, Ji Y, Eaton A, Inciardi RM, Soliman EZ, Passman RS, Solomon SD, Shah AM, De Caterina R, Chen LY. Markers of Left Atrial Myopathy: Prognostic Usefulness for Ischemic Stroke and Dementia in People in Sinus Rhythm. Stroke. 2025 Apr;56(4):858- 867. doi: 10.1161/STROKEAHA.124.047747. Epub 2025 Mar 7. PMID: 40052267.

25. Fassbender K, Merzou F, Lesmeister M, Walter S, Grunwald IQ, Ragoschke-Schumm A, Bertsch T, Grotta J. Impact of mobile stroke units. J Neurol Neurosurg Psychiatry. 2021 May 25;92(8):815–22. doi: 10.1136/jnnp-2020-324005. Epub ahead of print. PMID: 34035130; PMCID: PMC8292607.

26. Hariharan P, Tariq MB, Grotta JC, Czap AL. Mobile Stroke Units: Current Evidence and Impact. Curr Neurol Neurosci Rep. 2022 Jan;22(1):71-81. doi: 10.1007/s11910-022-01170-1. Epub 2022 Feb 7. PMID: 35129761.

27. Wu TC, Lyerly MJ, Albright KC, Ward E, Hassler A, Messier J, Wolff C, Brannas CC, Savitz SI, Carr BG. Impact of Telemedicine on Access to Acute Stroke Care in the State of Texas. Ann Clin Transl Neurol. 2014 Jan 1;1(1):27-33. doi: 10.1002/acn3.20. PMID: 24535938; PMCID: PMC3925075.

28. Johansson T, Wild C. Telemedicine in acute stroke management: systematic review. Int J Technol Assess Health Care. 2010 Apr;26(2):149-55. doi: 10.1017/S0266462310000139. PMID: 20392317.

29. Haq M, Derhab M, Saeed R, Khan H, Mushhood Ur Rehman M. Revolutionizing Acute Stroke Care: A Review of Food and Drug Administration-Approved Software as Medical Devices for Stroke Triage. Cureus. 2024 Nov 28;16(11):e74686. doi: 10.7759/cureus.74686. PMID: 39735151; PMCID: PMC11681945.

30. Heo J. Application of Artificial Intelligence in Acute Ischemic Stroke: A Scoping Review. Neurointervention. 2024 Mar;20(1):4-14. doi: 10.5469/neuroint.2025.00052. Epub 2025 Feb 18. PMID: 39961634; PMCID: PMC11900286.

31. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-e418. doi: 10.1161/STR.0000000000000211. Epub 2019 Oct 30. Erratum in: Stroke. 2019 Dec;50(12):e440-e441. doi: 10.1161/STR.0000000000000215. PMID: 31662037.

32. Strbian D, Tsivgoulis G, Ospel J, Räty S, Cimflova P, Georgiopoulos G, Ullberg T, Arquizan C, Gralla J, Zelenak K, Hussain S, Fiehler J, Michel P, Turc G, van Zwam WH. European Stroke Organisation (ESO) and European Society for Minimally Invasive Neurological Therapy (ESMINT) guideline on acute management of basilar artery occlusion. J Neurointerv Surg. 2024 Aug 14;16(9):e7. doi: 10.1136/jnis-2024-022053. PMID: 39043395; PMCID: PMC11347260.

33. Phuyal S, Alagappan A, Phuyal P, Sahoo B, Nayak MK. Mechanical Thrombectomy for Acute Ischemic Stroke in Nonagenarians: A Dilemma in Treatment Approach. Cureus. 2024 Dec 11;16(12):e75563. doi: 10.7759/cureus.75563. PMID: 39803081; PMCID: PMC11723837.

34. Law LY, Campbell BCV, Wijeratne T. Advances in endovascular therapy for ischemic stroke: A whole new ball game. Neurol Clin Pract. 2016 Feb;6(1):49-54. doi: 10.1212/CPJ.0000000000000217. PMID: 29443226; PMCID: PMC5765894.

35. Bhogal P, Bücke P, AlMatter M, Ganslandt O, Bäzner H, Henkes H, Aguilar Pérez M. A Comparison of Mechanical Thrombectomy in the M1 and M2 Segments of the Middle Cerebral Artery: A Review of 585 Consecutive Patients. Interv Neurol. 2017 Oct;6(3-4):191- 198. doi: 10.1159/000475535. Epub 2017 May 13. PMID: 29118796; PMCID: PMC5662990.

36. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J. 2014 Jul 14;35(27):1782-91. doi: 10.1093/eurheartj/ehu203. Epub 2014 May 26. PMID: 24864079; PMCID: PMC4155455.

37. Kelly P, Weimar C, Lemmens R, Murphy S, Purroy F, Arsovska A, Bornstein NM, Czlonkowska A, Fischer U, Fonseca AC, Forbes J, Hill MD, Jatuzis D, Kõrv J, Kruuse C, Mikulik R, J Nederkoorn P, O'Donnell M, Sandercock P, Tanne D, Tsivgoulis G, Walsh C, Williams D, Zedde M, Price CI. Colchicine for prevention of vascular inflammation in Non- CardioEmbolic stroke (CONVINCE) - study protocol for a randomised controlled trial. Eur Stroke J. 2021 Jun;6(2):222-228.

38. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):1269- 1324. doi: 10.1161/HYP.0000000000000066. Epub 2017 Nov 13. Erratum in: Hypertension. 2018 Jun;71(6):e136-e139. doi: 10.1161/HYP.0000000000000075. Erratum in: Hypertension. 2018 Sep;72(3):e33. doi: 10.1161/HYP 0000000000000080. PMID: 29133354.

39. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25;73(24):3168-3209. doi: 10.1016/j.jacc.2018.11.002. Epub 2018 Nov 10. Erratum in: J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237. doi: 10.1016/j.jacc.2019.05.012. PMID: 30423391.

40. Yoo J, Lim H, Seo KD. Optimal Duration of Dual Antiplatelet Therapy After Carotid Artery Stenting: A Nationwide

Cohort Study. Stroke. 2025 Mar;56(3):613-620. doi: 10.1161/STROKEAHA.124.048743. Epub 2025 Jan 17. PMID: 39818984.

41. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. Clin Rehabil. 2012 Apr;26(4):291-313. doi: 10.1177/0269215511420305. Epub 2011 Oct 24. PMID: 22023891.

42. Hong R, Li B, Bao Y, Liu L, Jin L. Therapeutic robots for post-stroke rehabilitation. Med Rev (2021). 2024 Feb 27;4(1):55-67. doi: 10.1515/mr-2023-0054. PMID: 38515779; PMCID: PMC10954296.

43. Tseng KC, Wang L, Hsieh C, Wong AM. Portable robots for upper-limb rehabilitation after stroke: a systematic review and meta-analysis. Ann Med. 2024 Dec;56(1):2337735. doi: 10.1080/07853890.2024.2337735. Epub 2024 Apr 19. PMID: 38640459; PMCID: PMC11034452.

44. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B, Moulin T, Marque P, Pariente J, Arnaud C, Loubinoux I. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011 Feb;10(2):123-30. doi: 10.1016/S1474-4422(10)70314-8. Epub 2011 Jan 7. Erratum in: Lancet Neurol. 2011 Mar;10(3):205. PMID: 21216670.

45. Dawson J, Engineer ND, Cramer SC, Wolf SL, Ali R, O'Dell MW, Pierce D, Prudente CN, Redgrave J, Feng W, Liu CY, Francisco GE, Brown BL, Dixit A, Alexander J, DeMark L, Krishna V, Kautz SA, Majid A, Tarver B, Turner DL, Kimberley TJ. Vagus Nerve Stimulation Paired With Rehabilitation for Upper Limb Motor Impairment and Function After Chronic Ischemic Stroke: Subgroup Analysis of the Randomized, Blinded, Pivotal, VNS- REHAB Device Trial. Neurorehabil Neural Repair. 2023 Jun;37(6):367-373. doi: 10.1177/15459683221129274. Epub 2022 Oct 13. PMID: 36226541; PMCID: PMC10097830.

46. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987. doi: 10.1371/journal.pone.0087987. PMID: 24505342; PMCID: PMC3913786.

47. Johnstone B, Frank RG. Neuropsychological assessment in rehabilitation: Current limitations and applications. NeuroRehabilitation. 1995;5(1):75-86. doi: 10.3233/NRE-1995-5107. PMID: 24525461.

48. Villarroel R, García-Ramos BR, González-Mora JL, Modroño C. Virtual Reality Therapy for Upper Limb Motor Impairments in Patients With Stroke: A Systematic Review and Meta- Analysis. Physiother Res Int. 2025 Apr;30(2):e70040. doi: 10.1002/pri.70040. PMID: 40022760; PMCID: PMC11973539.

49. Associated Press. A stroke survivor speaks again with the help of an experimental brain- computer implant. AP News. 2024 May 1. Available from: https://www.ap.org/news- highlights/spotlights/2025/a-stroke-survivor-speaks-again-with-the-help-of-an-experimental- brain-computer-implant/

50. Scott AM, Clark J, Cardona M, et al. Telehealth versus face-to-face delivery of speech language pathology services: A systematic review and meta-analysis. Journal of Telemedicine and Telecare. 2024;0(0). doi:10.1177/1357633X241272976

51. Maceira-Elvira P, Popa T, Schmid AC, Hummel FC. Wearable technology in stroke rehabilitation: towards improved diagnosis and treatment of upper-limb motor impairment. J Neuroeng Rehabil. 2019 Nov 19;16(1):142. doi: 10.1186/s12984-019-0612-y. PMID: 31744553; PMCID: PMC6862815.

52. Tchero H, Tabue Teguo M, Lannuzel A, Rusch E. Telerehabilitation for Stroke Survivors: Systematic Review and Meta-Analysis. J Med Internet Res. 2018 Oct 26;20(10):e10867. doi: 10.2196/10867. PMID: 30368437; PMCID: PMC6250558.

53. Su Z, Guo Z, Wang W, Liu Y, Liu Y, Chen W, Zheng M, Michael N, Lu S, Wang W and Xiao H (2023) The effect of telerehabilitation on balance in stroke patients: is it more effective than the traditional rehabilitation model? A meta-analysis of randomized controlled trials published during the COVID-19 pandemic. Front. Neurol. 14:1156473. doi: 10.3389/fneur.2023.1156473

54. Moore K, O'Shea E, Kenny L, Barton J, Tedesco S, Sica M, Crowe C, Alamäki A, Condell J, Nordström A, Timmons S. Older Adults' Experiences With Using Wearable Devices: Qualitative Systematic Review and Meta-synthesis. JMIR Mhealth Uhealth. 2021 Jun 3;9(6):e23832. doi: 10.2196/23832. PMID: 34081020; PMCID: PMC8212622.

55. Mulpuri RP, Konda N, Gadde ST, Amalakanti S, Valiveti SC. Artificial Intelligence and Machine Learning in Neuroregeneration: A Systematic Review. Cureus. 2024 May 30;16(5):e61400. doi: 10.7759/cureus.61400. PMID: 38953082; PMCID: PMC11215936.