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Current and future perspective on the treatment of ischemic stroke

Arun Kumar, Aparna Tiwary and Sudhakar Kaushik

Abstract

Stroke is one of the major causes of morbidity and mortality in the world and in recent years. To devastating impact of ischemic stroke on society, the researchers continue to seek strategies to achieve better functional recovery in stroke victims. Great advances have been made in understanding the diverse pathophysiology of neuronal cell death induced by ischemic stroke, clinically effective neuroprotective therapies are limited. The objective of this review article is to summarise facts pertaining to ischemic stroke cover all stages of the ischemic cascades, starting with the primary injury until the tissue regeneration and repair stage. This review summarises possible mechanism of current perspective on the use of recombinant tissue plasminogen activator (tPA), antiplatelets, anticoagulants, antihypertensive, free radical scavengers and stains as a therapeutic target in stroke treatment in reducing stroke risk and improving outcomes. Finally, based on present information, an evidence-based perspective about current and future use of treatment of ischemic stroke is presented.

Keywords: Stroke, ischemia, antiplatelets, stains

Introduction

Stroke is the leading cause of acquired adult disability worldwide and the fourth most common cause of death in developed countries [1]. Each stroke subtype has differing etiologies, outcomes, and management strategies. The past 20 years have seen considerable advances in diagnosis (emergence of widely available neuroimaging) and treatment of acute stroke [2]. According to the World Health Organization (WHO), stroke is different as "rapidly developing clinical signs of focal (at times global) interruption of cerebral function, lasting more than 24 hours or leading to death with no detectable cause other than that of vascular origin [3]. The effects of a stroke depend mainly on the location of the obstruction and the extent of brain tissue affected [4]. The two major types of stroke are ischemic and hemorrhagic, accounting for approximately 85% and 15%, respectively. Ischemic stroke is caused by focal cerebral ischemia due to arterial occlusion or stenosis whereas hemorrhagic stroke occurs when a blood vessel in the brain bursts, spilling blood into the spaces near the brain cells or when a cerebral aneurysm ruptures. Hemorrhagic stroke includes spontaneous intracerebral hemorrhage and subarachnoid hemorrhage due to leakage or rupture of an artery [4]. The third type of stroke called a transient ischemic attack or TIA is a minor stroke that serves a warning sign that a more severe stroke may occur. A TIA (transient ischemic attack), or "mini-stroke", is caused by a short-term clot [5]. Ischemic stroke occurs when a vessel supplying blood to the brain is blocked. Ischemic cerebrovascular disease is mainly caused by thrombosis, embolism [6]. Cerebral thrombosis refers to the formation of a thrombus (blood clot) inside an artery such as an internal carotid artery, proximal and intracranial vertebral arteries which produce lacunes, small infarcts to typical locations include basal ganglia, thalamus, internal capsule, cerebellum that develops at the clogged part of the vessel [7]. Cerebral embolism refers commonly to a blood clot that forms at a different location in the circulatory system, usually the heart and large arteries of the upper chest and neck. An embolic stroke occurs when a clot breaks, loose and is carried by the bloodstream and gets wedged in medium-sized branching arteries [8]. Fatty deposits lining the vessel walls, called atherosclerosis, are the central cause for ischemic stroke [9]. Hemorrhagic strokes build up about 13 percent of stroke cases. It's caused by a weakened vessel that ruptures and bleeds into the surrounding brain. The blood accumulates and compresses the nearby brain tissue [10]. The two major types of hemorrhagic strokes are intracerebral (within the brain) hemorrhage or subarachnoid hemorrhage. There are two main types of hemorrhagic stroke. Intracerebral hemorrhage, bleeding caused inside the brain itself (when an artery in the brain bursts, flooding the adjacent tissue with blood) due to both

intraparenchymal hemorrhage (bleeding in the brain tissue) or intraventricular hemorrhage (bleeding inside the brain's ventricular system) ^[11]. In subarachnoid hemorrhage bleeding that occurs outside of the brain tissue but still inside the skull, and specifically among the arachnoid mater and pia mater (the delicate innermost layer of the three layers of the meninges that enfold the brain) ^[12]. Silent cerebral infarction (SCI), or "silent stroke," is a brain injury likely caused by a blood clot that interrupts blood flow in the brain. It is a risk factor for future strokes and a sign of progressive brain damage ^[13]. Silent strokes normally cause lesions which

are detected via the use of neuroimaging such as MRI. Silent strokes are approximate to occur at five times the rate of symptomatic strokes. The risk of silent stroke increases with age, but may also concern younger adults and children, especially those with acute anemia ^[14]. The drugs used for treating stroke usually work in different ways. Some, in fact, break up existing blood clots. Others help prevent blood clots from forming in blood vessels. Some drugs effort to adjust high blood pressure and cholesterol levels to help prevent blood flow blockages ^[15].

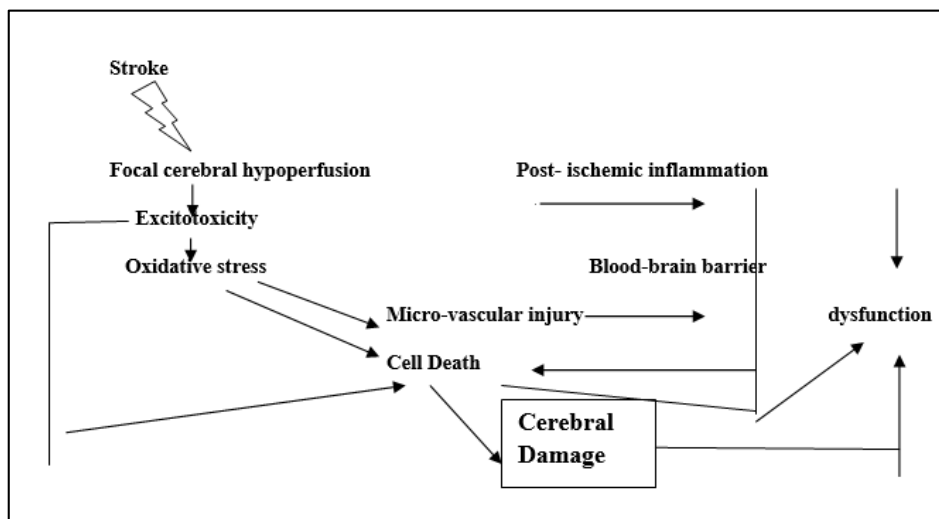


Fig 1: Ischemic cascade important to cerebral damage: Ischemic stroke lead to hypo-perfusion of a brain area that initiates a complex series of events. Excitotoxicity, oxidative stress, microvascular injury, blood-brain barrier dysfunction, and post-ischemic inflammation lead ultimately to cell death of neurons, glia and endothelial cells. The degree and duration of ischemia determine the extent of cerebral damage.

Ischemic Stroke Pathophysiology

The pathophysiology of stroke is composite and involves several processes, including: energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, generation of arachidonic acid products, cytokine-mediated cytotoxicity, complement activation, disruption of the blood-brain barrier (BBB), activation of glial cells, and infiltration of leukocytes. These are interrelated and co-ordinated events, which can lead to ischemic necrosis, which occurs in the severely affected ischemic-core regions. In cerebral ischemia, the core of brain tissue showing the most dramatic blood flow reduction, is mortally injured, and subsequently undergoes necrotic cell death. In this necrotic core is bounded by a zone of less severely affected tissue which is rendered functionally silent by reduced blood flow but remains metabolically active.^[16] Necrosis is morphologically characterized by initial cellular and organelle swelling, subsequent disruption of the nuclear, organelle, and plasma membranes, the disintegration of nuclear structure and cytoplasmic organelles with extrusion of cell contents into the extracellular space ^[17]. The region near the infarct core, known as the ischemic penumbra, comprises as much as half of the total lesion volume during the initial stages of ischemia, and represents the region in which there is opportunity for salvage via post-stroke therapy ^[18]. Less severe ischemia, as occurs in the penumbra region of a focal ischemic infarct, evolves more slowly, and depends on the activation of specific genes and may ultimately result in apoptosis ^[19, 20]. Recent research has revealed that many neurons in the ischemic penumbra, or peri-infarct zone, may undergo apoptosis only after several hours or days, and thus

they are potentially recoverable for some time after the onset of stroke. In contrast to necrosis, apoptosis appears to be a relatively orderly process of energy-dependent programmed cell death to dispose of redundant cells. Cells undergoing apoptosis are dismantled from within in an organized way that minimizes damage and disruption to neighboring cells ^[21]. There are two general pathways for activation of apoptosis: the intrinsic and extrinsic pathways.

Glutamate excitotoxicity

A significant portion of ischemia-induced neuronal damage is mediated by excessive accumulation of excitatory amino acids, leading to toxic increases in intracellular calcium ^[22]. Although this is an intrinsic defensive response to defend against ischemia by activating a reaction to severe cell stress, paradoxically, this enhance in intracellular calcium activates multiple signaling pathways, which ultimately leads to cell death. Shortly after reduction or termination of cerebral blood flow, energy-dependent cellular pumps fail due to a fall in glucose-dependent ATP generation, resulting in the flow of numerous ionic species into the cell. This results in cellular swelling throughout osmosis and cellular depolarization. Calcium ions (Ca^{2+}) penetrate the cell through voltage-dependent and ligand-gated ion channels, resulting in activation of a number of proteases, kinases, lipases, and endonucleases, triggering of the intrinsic apoptotic pathway and thus ending in cell death ^[23, 24]. Glutamate, which is the major excitatory neurotransmitter in the brain, accumulates in the extracellular space following ischemia and activates its receptors.^[25] Glutamate receptor activation induces alterations in the concentration of intracellular ions, most notably

Ca^{2+} and sodium ions (Na^+). Elevations of intracellular Na^+ can be detrimental to neuronal survival at earlier time points after ischemia [26]. However, experimental studies groups suggest that glutamate toxicity is primarily dependent on Ca^{2+} influx [27, 28]. Collectively, these results suggest that cellular self-harm processes exist within the brain itself, but also, that stroke-induced central nervous system (CNS) damage may be reduced by medicinal strategies to relieve the tendency of the brain to injure itself, under conditions of stroke. The inflammatory paradox of cellular self-injury is amplified by the special sensitivity of CNS neurons to sudden deprivation of oxygen and glucose; the catastrophic temporal and anatomical nature of stroke conspires with these realities to produce consequences that are difficult to treat with medicines, and thus far, this has been a challenge beyond the capacities of modern medicine.

Oxidative stress

Growing evidence suggests that oxidative stress and apoptosis are closely correlated phenomena in the pathophysiology of ischemic stroke. Neurons are in general exposed to a baseline level of oxidative stress from both exogenous and endogenous sources, as are all cells in the body. Free radicals are highly reactive molecules with one or more unpaired electrons. Free radicals can react with DNA, proteins, and lipids, causing varying degrees of damage and dysfunction [29, 30]. Various experimental and clinical observations have shown increased free radical formation during all forms of stroke injury [31]. Free radicals, involved in stroke-induced brain injury, include superoxide anion radical, hydroxyl radical and nitric oxide (NO). The damaging effects of free radicals are normally prevented or reduced by antioxidant enzymes and free radical scavengers [32]. The primary source of oxygen-derived free radicals (often referred to as 'reactive oxygen species') during ischemic-stroke injury is the mitochondria, which produce superoxide anion radicals during the electron transport process [33]. Another potentially significant source of superoxide in post-ischemic neurons, is the metabolism of arachidonic acid through which the cyclooxygenase and lipoxygenase pathways [34, 35]. Oxygen free radicals can be generated by activated microglia and infiltrating marginal leukocytes through the NADPH oxidase system following reperfusion of ischemic tissue [36]. This oxidation causes further tissue damage and an important trigger molecule for apoptosis after ischemic stroke.

NO is generated from L-arginine through one of several NO synthase (NOS) isoforms. The neuronal form (nNOS), which requires calcium/calmodulin for activation, is expressed by subpopulations of neurons throughout the brain [37]. Inducible NOS (iNOS) is expressed by inflammatory cells such as microglia and monocytes. These two isoforms are, for the most part, damaging to the brain under ischemic conditions. A third isoform found in endothelial cells (eNOS), has vasodilatory effects and is likely to play a beneficial role by improving local blood flow [38]. NMDA receptor activation has been exposed to stimulate nitric oxide (NO) production by NOS, and to possibly play a role in excitotoxic-mediated injury in ischemic stroke [39]. NO diffuses freely across membranes and can react with superoxide at its point of generation to produce peroxynitrite (ONOO^-), another highly reactive oxygen species [40]. Both oxygen-derived free radicals and reactive nitrogen species are involved in activating several pathways involved in cell death following stroke, such as apoptosis and inflammation [41-43]. A reduction of oxygen

supply also leads to the accumulation of lactate via anaerobic glycolysis and so to acidosis [44-47].

Lipid peroxidation

Besides the assembly of different species of oxygen radicals, acidosis furthermore interferes with intracellular protein synthesis. Lipid peroxidation appears to play a major role in the pathogenesis of stroke. The mechanism, whereby membrane lipid peroxidation induces neuronal apoptosis, involves generation of an aldehyde called 4-hydroxynonenal (4-HNE), which covalently modifies membrane transporters such as the Na^+/K^+ ATPase, glucose transporters and glutamate transporters, thereby impairing their function [48]. Whilst potentially damaging via their direct actions, Ca^{2+} and free radicals can also activate neuroprotective transcription factors, including nuclear factor- κB (NF- κB), hypoxia-inducible factor 1 and interferon regulatory factor 1 [49]. Some of these transcription factors induce the expression of inflammatory cytokines (for example, IL-1, IL-6 and TNF- α) and chemokines (for example, IL-8 and MCP-1), endothelial cell adhesion molecules (for example, selectins, ICAM-1 and VCAM-1), and other proinflammatory genes (for example, interferon-inducible protein-10) [50].

Inflammation

There are several local cell populations within brain tissue that are able to hide away pro-inflammatory mediators after an ischemic insult. These include endothelial cells, astrocytes, microglia and neurons. Activation of transcription factors marks an increased protein levels for cytokines and increased expression of endothelial cell adhesion molecules (CAMs) in post-stroke brain tissue [51-54]. A most important role in brain inflammation following stroke is attributed to microglia, particularly in the penumbral region of damage [55]. Activated microglia produce numerous proinflammatory cytokines, as well as toxic metabolites and enzymes [56]. In addition to microglial cells, astrocytes also have an important part in stroke-induced brain inflammation. These cells can produce both proinflammatory cytokines and neuroprotective factors, such as erythropoietin, TGF β 1, and metallothionein-2 [57]. The diverse nature of microglial and astrocyte products (both destructive and protective factors), the overall role of glia may differ at different moment points following stroke insult, with protective or regenerative activities occurring days to weeks after the onset of ischemia [58]. These factors add layers of complexity, in both adducing their pathophysiological roles in stroke, and in the goal of developing new therapeutics for stroke therapy.

Blood Brain Barrier (BBB) dysfunction

The brain endothelium is quite distinctive compared with other organs, as evidenced by the blood-brain barrier (BBB). However, it responds to stroke injury with better permeability and diminished barrier function, along with degradation of the basal lamina of the vessel wall, as occurs as in other organs after ischemic injury [59]. Also, there is significant evidence that acute ischemic stroke enhances the interactions of brain endothelium with extravascular CNS cells (astrocytes, microglia, neurons with intravascular cells (platelets, leukocytes), and that these interactions contribute to the injury process [60]. The remaining result of all these responses to stroke is that the cerebral vasculature assumes the following phenotypes: 1) poor capillary perfusion of brain tissue, 2) pro-adhesive for circulating cells, 3) pro-inflammatory, 4) pro-

thrombogenic, and 5) diminished endothelial barrier function. These changes in common physiological functions cumulate with each of these inflammatory responses tilting in the same detrimental direction, such that the end-result is harmful to the host CNS cells and tissues. Indeed, this is the essential problem facing rapid and effective treatment of stroke.

Current and future use of treatment of stroke

1. Acute thrombolytics: Thrombolytic drugs dissolve blood clot by activating plasminogen, which forms plasmin. Plasmin is a proteolytic enzyme that breaks cross-links between fibrin molecules and restricts the damage caused by the blockage in the blood vessel. Because of this action, it is also known as “plasminogen activator” and “fibrinolytic drugs” [61]. The main aim of thrombolysis in acute ischemic stroke is recanalization of an occluded intracranial artery. Recanalization is a significant predictor of stroke outcome as a timely restoration of regional cerebral perfusion helps salvage threatened ischemic tissue [62]. At present, Intravenous tissue plasminogen activator (IV-TPA) i.e. streptokinase, alteplase, reteplase remains the only FDA approved therapeutic agent for the treatment of ischemic stroke. [63] Intravenous administration of alteplase is the only US Food and Drug Administration (FDA)-approved medical therapy for the treatment of patients with acute ischemic stroke. Its use is associated with improved outcomes for a broad group of patients. Recent trials have shown the therapeutic window may be extended out to 4.5 hours in selected patients. [64] Earlier treatment is more likely to result in a favorable outcome [65]. Alteplase and other plasminogen activators such as streptokinase and urokinase promote thrombolysis by hydrolyzing the arginine-valine peptide bond in plasminogen to form the active proteolytic enzyme plasmin [67]. Alteplase initiates local fibrinolysis when administered intravenously. The FDA approved the use of intravenous alteplase in 1996 based on the results of the NINDS (National Institute of Neurological Disorders and Stroke) Stroke Study. In this study, which consisted of two trials, 624 patients were treated with alteplase (0.9 mg/kg) or placebo within 3 hours of onset of symptoms of AIS [68]. Clinical trials of streptokinase were halted prematurely because of unacceptably high rates of hemorrhage, and this agent should not be used to treat acute ischemic strokes in clinical practice [68]. Tenecteplase was compared to alteplase in a recent initial trial for acute ischemic stroke [69]. This study enrolled a total of 75 patients into three groups: alteplase IV 0.9 mg/kg, tenecteplase IV 0.1 mg/kg, and tenecteplase IV 0.25 mg/kg. Patients were enrolled within 6 hours of symptoms based on CT-based penumbral imaging selection (with potentially reversible penumbra estimated to be at least 20% or larger than the presumed irreversible infarct core). Tenecteplase was associated with better outcomes than alteplase without an increase in bleeding or other serious adverse events in this open-label study. A large Phase IIb/Phase III trial (but without imaging selection) was stopped prematurely at 112 subjects due to poor recruitment, and showed no benefit [70]. Further studies are needed to verify any benefit of tenecteplase over alteplase. The intravenously administered desmoteplase is also under study [71].

2. Antiplatelet drugs : Early antiplatelet treatment is suggested to treat generally patients with acute ischemic stroke because only some patients can be treated with thrombolysis due to the bound of severe indications, such as a

time window [72]. Two clinical trial studies, The Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST) showed a significant benefit of aspirin as to the reduction of morbidity and mortality rates. Therapy should be initiated with aspirin 160-325mg daily within 48 hours of symptom onset provided contraindications such as allergy and gastrointestinal bleeding are absent, and the patient has or will not be treated with recombinant tissue-type plasminogen activator [73]. Initiation of aspirin within 48 hours after ischemic stroke leads to a significant reduction in recurrence within 2 weeks [74]. The addition of dipyridamole appears to be slightly more effective [75] and clopidogrel appears to be equally effective on stroke prevention when compared to aspirin plus dipyridamole [76]. Clopidogrel has been shown to be slightly more efficacious than aspirin for the composite outcome of ischemic stroke [77]. The long-term treatment with aspirin plus clopidogrel (dual antiplatelet therapy [DAPT]) in patients with the severe coronary syndrome were never simulated in stroke patients. The efficacy has shown in DAPT but due to additional bleeding complication than aspirin monotherapy. [78] and long-term DAPT after lacunar strokes is associated with increased mortality [79]. A Chinese study has shown that a 90-day regimen of DAPT after TIA or minor stroke reduces risk of recurrence [80]. A reduction of major ischemic events (with most of the prevented measures being ischemic strokes) with DAPT has been replicated in Western populations. However, patients on DAPT also showed a higher risk of major hemorrhage (namely extracranial) at 90 days than those who received aspirin alone [81]. However, DAPT was useful (compared to aspirin monotherapy) in reducing the composite endpoint of ischemic stroke, MI, or death from ischemic vascular causes, as well as the composite endpoint of ischemic and hemorrhagic stroke. Particularly, the secondary study of the results discovered that prevention of ischemic outcomes with DAPT was significant throughout the first 7 to 30 days of treatment, whereas the risk of the main hemorrhage became greater only during the period from 8 to 90 days. For every 1,000 patients treated with DAPT, a total of 15 ischemic events would be prevented and five major hemorrhages would occur. In patients with ischemic stroke or TIA with potentially symptomatic atherosclerotic stenosis of ipsilateral intracranial or extracranial arteries, ticagrelor plus aspirin reduced stroke recurrence compared to aspirin alone. A complex vascular endpoint (i.e., stroke, MI, or vascular death) occurred within 90 days for 6.7% of patients treated with ticagrelor, which was significantly less than the 9.6% in the aspirin arm of the trial [82]. Another antiplatelet drug, cilostazol, [83] was found to be non-inferior to aspirin in a recent clinical trial for the prevention of cardiovascular events (the composite of stroke, MI, or vascular death) in Asian patients who had ischemic stroke with a history of or imaging findings of intracerebral hemorrhage or two or more microbleeds; however, it did not reduce hemorrhagic events [84]. In an open-label part of the similar trial, the addition of probucol to aspirin or cilostazol seemed to reduce the incidence of cardiovascular events.

3. Anticoagulants: Routine anticoagulation with unfractionated or low-molecular-weight heparin is not recommended in acute ischemic stroke, particularly for patients with moderate to extensive cerebral infarction due to increased risk of severe intracranial hemorrhagic complications [85]. The use of fixed-dose subcutaneous unfractionated heparin is not recommended for decreasing the

risk of death or stroke-related morbidity or for preventing early stroke recurrence because of the concomitant increase in the occurrence of hemorrhage. Dose-adjusted, unfractionated heparin is not suggested for reducing morbidity, mortality, or in the early hour's recurrent stroke in patients with acute stroke (i.e., in the first 48 hours) because the evidence indicates it is not effective and may be associated with increased bleeding complications. Apart from the positive results with aggressive antiplatelet therapy (either DAPT or ticagrelor), a breakthrough in 2017 was the publication of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. For the initial time, a combination of an anticoagulant (2.5 mg of rivaroxaban twice a day) and aspirin was proven superior both to aspirin alone and to 5 mg of rivaroxaban twice a day in stable atherosclerotic disease.^[86] This study included patients with different terms of atherosclerosis: coronary, peripheral, and carotid artery disease that was also symptomatic (after intervention) or asymptomatic (>50% stenosis). A combined outcome of ischemic and hemorrhagic events was significantly in favor of patients in the combined treatment group. What is even more stimulating is the fact that efficacy outcomes were mainly driven by a 50% relative risk decline in ischemic stroke risk ($P < 0.001$). It should be a significant reduction in mortality and was noted with a twice-daily 2.5-mg dose of rivaroxaban, as seen in a previous trial on acute coronary syndrome in which a twice-daily 2.5-mg dose of rivaroxaban on top of DAPT was superior to DAPT alone or DAPT plus a twice-daily 5-mg dose of rivaroxaban.^[99] Nevertheless, extra bleeding was noted in the combined treatment group, even if fatal and intracranial bleeding were not significantly different. Hence, rivaroxaban plus aspirin should be used with care in patients who are at risk of bleeding, such as older patients and those with a history of gastrointestinal bleeding, taking into consideration the higher risk for gastrointestinal bleeding in AF-anticoagulation doses of rivaroxaban^[87].

4. Free radical scavengers: Free radicals have been implicated in stroke pathophysiology as pivotal contributors to brain cell injury. The increased amount of free radicals in ischemic stroke condition damages all cellular components, including DNA, lipids, and proteins, leading to injuries of neurons, glial cells, nerve fibers, and blood vessels.^[88] Tirilazadmesylate (U-74006F), an inhibitor of lipid peroxidation was studied extensively in pre-clinical models in the mid-1990s and was shown to reduce infarct size in rats following transient focal ischaemia. Edaravone, a free radical scavenger, has been clinically available in Japan since 2001 and has been reported to advance clinical outcomes in patients exhibiting ischemic strokes^[89]. Experimental studies have revealed that the possible mechanisms of Edaravone decreasing oxidative stress, protecting neurovascular units, and reducing the activation of microglia after ischemic stress. Tirilazad was demonstrated to reduce lesion size by an average of 29% and improve the neurological score by 48%. Ebselen, an inhibitor of glutathione peroxidase-like activity, may be a promising neuroprotective agent and improve the outcome of acute ischemic stroke^[90]. Mitoquinone (mitoQ) a derivative of ubiquinone, reduced to ubiquinol and has been found to be an effective antioxidant protecting mitochondria from oxidative damage and apoptosis caused by H₂O₂. The use of antioxidant vitamin (Vit.C and E) supplements are another choice^[91].

5. Antihypertensive drugs: Elevated systolic pressure, with or without an accompanying elevation in diastolic pressure, has been shown to increase stroke risk. BP reduction was associated with a 32% risk reduction in stroke incidence^[105]. In the case of arterial hypertension, the target for systolic blood pressure is under 140mmHg, except for older patients (>160-150 mmHg)^[92]. Hypertension is the main risk cause for both ischemic and hemorrhagic stroke. Whereas hypertension is strongly linked to small vessel cerebrovascular disease such as lipohyalinosis-related lacunar infarction, it is also a major cause of atherosclerotic stroke^[93]. Throughout the range of BP, including normal values, a higher BP is associated with a greater risk of stroke^[94]. Mean BP levels of 133/76 mm Hg, compared with 140/81 mm Hg, were associated with a reduction in risk of stroke by 22% in a meta-analysis of prevention studies^[95]. The outcome is even more superior (at 27%) while only secondary prevention studies are considered: both SBP and diastolic BP drop are linearly related to the lower the danger of frequent stroke, and destructive BP control to a target of <130 mm Hg seems to be useful for secondary stroke prevention^[96]. Recent guidelines have confirmed the significance of strict BP control and eliminated the term "pre-hypertension" by lowering normal BP levels to <120/80 mm Hg^[97]. BP ranging from 130/80 to 140/90 mm Hg is considered stage 1 hypertension and should be treated in all symptomatic ASCVD individuals and asymptomatic individuals with 10-year ASCVD risk over 10%; an exception is simply prepared for secondary stroke prevention, for which the cutoff for antihypertensive treatment initiation of 140/90 mm Hg is maintained, but the BP goal for those treated remains at 130/80 mm Hg. The elevated cutoff planned for secondary stroke prevention is based on multiple observations that very low BP may harm stroke patients. A lower SBP target (<130 mm Hg) is recommended only after lacunar stroke; however, even in this context, the benefit seems to be derived from a reduced risk for hemorrhagic but not ischemic stroke.^[98] SBP of >140 mm Hg in symptomatic patients with intracranial stenosis is associated with an increased risk of stroke;^[99] however, low diastolic BP may be deleterious, especially when accompanied by increased pulse pressure of >60 mm Hg^[100]. In a post hoc examination of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, low BP in patients after non-cardioembolic stroke was related with worse outcomes; however, it could not be discerned whether low BP was causal or simply an indicator of poor health status^[101].

6. Statins - Lipid management remains a vital component of primary stroke prevention. The benefits of statins in stroke prevention in patients with coronary heart disease have been supported by several meta-analyses.^[102] The Cholesterol and Recurrent Events (CARE) study found patients with average cholesterol levels treated with pravastatin after a myocardial infarction had a lower risk of stroke than patients receiving a placebo. A large randomized prospective study involving over 20,000 patients followed for 5 years showed a benefit of simvastatin versus placebo in reducing mortality, stroke and myocardial infarction in high-risk vascular patients regardless of cholesterol levels. People with cholesterol levels above 200 mg/dl and cardiovascular risk factors should have a complete lipid analysis (total cholesterol, LDL, HDL, and triglycerides) and most likely would benefit from cholesterol-lowering regimens, including statins^[103]. The exact mechanism of how

statins provide stroke protection is uncertain. Although some of the stroke reduction may be due to lipoprotein alterations, other mechanisms unrelated to their lipid-lowering properties, are improved endothelial function, plaque stabilization, and antithrombotic, anti-inflammatory, and neuroprotective properties. To date, the largest trials suggest a beneficial effect of statins for stroke prevention in high-risk elderly subjects aged 82 years or younger^[118]. Treatment with statins reduces the risk of recurrent stroke among patients with coronary artery disease or those at risk for atherosclerotic disease^[104]. Treatment with atorvastatin 80 mg/day reduced recurrent stroke in patients with evidence of atherosclerosis and LDL-C level >100 mg/dl, with a target to reduce the LDL-C by half or to an LDL-C level of <70 mg/dl^[105-107]. Administration of statins after 48 hours of the occurrence of stroke is safe^[108]. Pravastatin significantly reduce the rate of stroke and other vascular endpoints in patients with a history of ischemic heart disease, irrespective of initial cholesterol concentrations, and possibly independent of cholesterol lowering. Simvastatin 40mg/day was shown to reduce the risk of stroke in patients with vascular diseases. Patients who are previously on statins at the time of stroke onset should continue taking them^[109-111].

Conclusion

Basic and clinical research has resulted in important advances in the medical and surgical prevention of ischemic stroke. However, therapies to reduce the neuronal damage that results from cerebral ischemia are still lacking. Nevertheless, useful therapies should emerge soon from ongoing clinical trials. In the past several years, attempts to develop new pharmacological treatment modalities for acute ischemic stroke have been met with somewhat limited success. Significant efforts have been placed on identifying new treatment targets, yet translation from animal models to human models. Researchers continue to seek new ways to deliver pharmacotherapy as early as possible and an ever-growing understanding of the pathophysiology underlying acute ischemic stroke provides encouragement for new avenues of study and methods to deliver patient care.

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