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Prevalence of Intracranial and Extracranial Arterial Stenosis in Ischemic Stroke Patients in Badr University Hospital

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Abstract

Stroke is the primary cause of serious neurologic disability in adults and one of the main causes of mortality in the majority of nations. According to the World Health Organization, ischemic stroke accounts for between 70 and 80 percent of all strokes and is the most prevalent form. Strokes have a global impact on 15 million individuals each year, resulting in the death of 5 million and the persistent disability of an additional 5 million. This has a significant impact on families and communities. New research on stroke risk factors has not yet resolved the question of whether specific risk factors directly influence different levels of cerebral arteries in stroke patients. A massive ischemic stroke in the anterior circulation may occur when a major intracranial artery or one of its branches becomes blocked. Exclusion criteria included a follow-up length of one year or less for patients with end-stage renal illness. Both low and high Cr/Cys-C values were found at the cohort median. Kaplan-Meier analysis was used to estimate RFS and OS for patients with high vs low Cr/Cys-C levels, and Cox proportional hazards models were used to assess associations with the outcomes of interest. In our search for connections between Cr/Cys-C and skeletal muscle mass, we employed logistic regression and correlation analysis. Nearly 90% of infarcts and two-thirds of all initial strokes are caused by the occlusion of the middle cerebral artery (MCA) or one of its tributaries. Despite the fact that intracranial vascular damage is more prevalent in Chinese and African American stroke patients than in Caucasian stroke patients. This study's aimed to evaluate the current prevalence of intracranial and extracranial artery stenosis in patients who present with acute ischemic stroke and transient ischemic attacks (TIAs) at Badr University Hospital.Keywords: Intracranial, Extracranial, Arterial stenosis, Ischemic stroke.

Introduction

Ischemia stroke and hemorrhagic stroke, which encompasses intracerebral and subarachnoid hemorrhages, are the two main types of stroke that cause disability and death globally. Ischaemic stroke, which is characterized as a damage to the brain, spinal cord, or retina, accounts for approximately 71% of all worldwide strokes. The classification of ischaemic stroke is now based on tissue findings, rather than on clinical evaluations, thanks to

developments in brain imaging. Many temporary occurrences that lead to complete clinical recovery are now categorized as strokes because MRI may detect persistent tissue damage. Transient ischemic attacks (TIAs) are characterized by a brief interruption of blood flow that goes away before inflicting long-term damage. The pathophysiology, underlying cause research, and secondary prevention techniques are all the same as for ischemic stroke [1].

An area of the brain known as the ischaemic penumbra is hypoperfused, dormant, and electrically non-functional; groundbreaking studies found that this is largely responsible for the initial clinical deficit in stroke patients. The rate at which this area progressively becomes irreparably damaged tissue (the ischaemic core) varies greatly from person to person. Nevertheless, this penumbral brain is salvageable and can regain normal function with quick reperfusion. Since the first successful trial of stroke thrombolysis, The results for patients with ischemic stroke have been transformed by reperfusion therapy, which are based on this ground-breaking discovery [2].

The current gold standard for treating patients suffering from ischaemic stroke involves specialized stroke units staffed by a multidisciplinary team of doctors, nurses, and allied health professionals who work together in accordance with established stroke protocols. These protocols often include the use of intravenous thrombolysis and endovascular thrombectomy. The administration of intravenous thrombolysis reduces impairment if it occurs within 4.5 hours of the stroke. However, in some patients with positive brain perfusion imaging, it only works for nine hours following the wake-up onset of stroke, when symptoms that did not exist before sleep start to manifest upon waking [3, 4].

In a large group of stroke patients with large vessel occlusion, endovascular thrombectomy (mechanical clot retrieval via catheter angiography) lessens disability when done within 6 hours of the last known healthy state of the patient and, in patients chosen using brain perfusion imaging, up to 24 hours after stroke onset. Nevertheless, health system engineering to expedite treatment is still a major obstacle to fully realizing the advantages of time-critical treatments like intravenous thrombolysis and endovascular thrombectomy [5].

Topics covered in this primer include ischemic stroke and transient ischemic attack (TIA) epidemiology, pathophysiology, and diagnosis. There is an extensive discussion of the acute reperfusion treatments. Another topic covered is secondary prevention of ischaemic stroke. While this approach has many similarities with cardiovascular risk management in other domains, it also has some key differences, and the prevention plan needs to be customized based on the stroke mechanism [6].

Epidemiology

With 5.5 million fatalities annually, stroke (including ischaemic and hemorrhagic strokes) is the second biggest killer on a global scale, affecting 13.7 million people. Stroke affects about one quarter of all adults at some point, and over 80 million people have survived one. Efforts to reduce secondary risks are directed towards this high-risk group of stroke survivors [7].

Ischemic stroke has changed in frequency and prevalence over the years. In 2016, there were 9.5 million ischemic strokes worldwide. In 2017, ischemic stroke was the most

common cause of death. Between 1990 and 2013, ischemic stroke's incidence, death, and disability-adjusted life years declined globally. However, the incidence of ischemic stroke rose globally between 1990 and 2005, fell between 2005 and 2013, and then increased somewhat (albeit not considerably) between 1990 and 2013. The shifting prevalence may be due to improvements in secondary prevention, decreased stroke mortality, and improved stroke detection [8].

- **Epidemiology of stroke in Egypt**

The yearly incidence of stroke in Egypt is between 150,000 and 210,000 cases, and the overall prevalence rate is high at 963 per 100,000 inhabitants. Stroke ranks third in Egypt, after cardiovascular disease and gastrointestinal diseases, and accounts for 6.4% of all fatalities, according to official national statistics. Diseases of the circulatory system, including stroke, are the leading causes of death in the country. Stroke mortality has decreased in many nations, but in Egypt it has remained mostly stable over the last decade [9].

Risk factors

Factors related to age, sex, and heredity that increase the likelihood of an ischaemic stroke cannot be changed. The impact of age on the risk of ischemic stroke is influenced by the level of development of a nation, as evidenced by the fact that developed countries have experienced higher increases in incidence and prevalence after the age of 49 and 39, respectively. Between 1990 and 2013, the number of people aged 20 to 64 who had an ischemic stroke nearly doubled worldwide, and the number of disability-adjusted life years linked to this condition increased by 37.3% [10].

Males experienced 133 per 100,000 person-years of ischemic stroke compared to 99 per 100,000 person-years for females, according to the 2013 Global Burden of Disease Study. Cerebrovascular disease with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebrovascular disease with subcortical infarcts and leukoencephalopathy (CARASIL) are two inherited illnesses that can cause ischemic stroke. However, most cases can occur randomly. Ischemic stroke has an estimated 37.9% heritability according to genome-wide complex trait analysis [11].

It is possible to alter a number of risk factors for ischemic stroke. Regardless of age, gender, or location, INTERSTROKE identified eleven variables that were consistently associated with an increased risk of ischemic stroke (91.5% of the total population-attributable risk). Some of the things to be worried about are a family history of hypertension, an abnormally large waist-to-hip ratio, diabetes mellitus, smoking, issues with mental health, heart diseases (including atrial fibrillation and previous myocardial infarction), and excessive alcohol use. A blood pressure reading of at least 160/90 mmHg was also taken into account [12].

With a population-attributable risk of 45.2%, self-reported hypertension, defined as a blood pressure reading more than 160/90 mmHg, was the most dangerous of these traits. Chronic renal illness, periodontal disease, chronic inflammation, and sleep apnea are other possible risk factors. Furthermore, some research has shown links between exposure to air pollution and temporary increases in the risk of stroke [10].

Pathophysiology of ischemic stroke

The initial phase of the pathogenesis of ischemic stroke is the insufficient blood supply to a particular region of brain tissue. The center core of tissue in this afflicted area, referred to as the area of infarction, moves toward irreparable destruction in a matter of minutes. On the other hand, the penumbra, or surrounding tissue, may recover and avoid immediate cell death if early reperfusion is reached [13].

Adenosine triphosphate (ATP) generation and consumption are out of balance in areas with decreased blood flow, which leads to decreased energy reserves. The result is a cascade of alterations associated with ischemia, including electrical disruptions and ionic imbalances. These alterations produce an upsurge in nitric oxide (NO) and reactive oxygen species (ROS) generation. Cell membranes are eventually destroyed, cell lysis occurs, and cell death is the outcome of the pathophysiological cascade through processes like necrosis or apoptosis *[14]*.

Microglia are quickly activated in the area of ischemia and go to the penumbra region after an ischemic stroke. Within 48 to 72 hours following the onset of stroke, their activity reaches its peak and can last for up to a few weeks **[15]**. Proinflammatory cytokines such intraleukin-1β, tumor necrosis factor-α, NO, and ROS are increased by activated microglia. But they also secrete anti-inflammatory cytokines and neurotrophic factors such basic fibroblast growth factor, neurotrophic factor obtained from brain cells, and neurotrophic factor produced by glial cell types. Neurons and ancillary structures die as a result of the complex ischemia cascade that follows an ischemic stroke [16].

Arterial causes of stroke

- **Atherosclerosis**

A cerebral vascular embolus is a frequent cause of ischemic stroke **(Figure 1)** this resulted from the hardening and narrowing of an atherosclerotic plaque in the brain's blood vessels, the aortic arch, or the neck. Thrombi can form in atherosclerosis patients when the fibrous cap of the plaques becomes irritated and ulcerated, exposing the lipid core to the bloodstream. These thrombi can embolize distally in the major vessels associated with stroke or obstruct the atherosclerotic vessel [17].

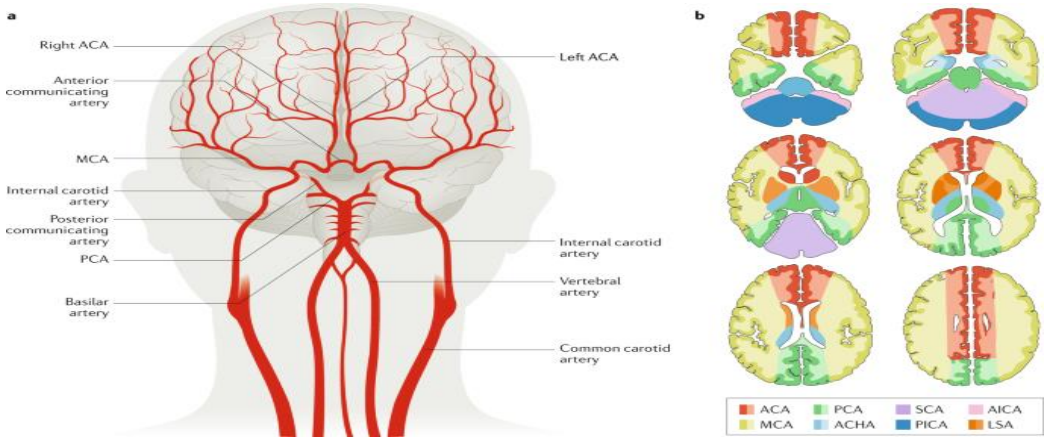

Figure 1: Cerebral vasculature. The major arteries of the brain (part a) and their vascular territories (part b). Although simplified here for illustrative purposes, an

ischaemic stroke in one of these vessels could cause tissue damage in the regions highlighted. ACA, anterior cerebral artery; ACHA, anterior choroidal artery; AICA, anterior inferior cerebellar artery; LSA, lenticulostriate artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery [17]

Ischemic stroke in humans is most commonly caused by atherosclerotic plaques in the internal carotid artery, just after it splits off from the common carotid artery. This is believed to be related to the arterial wall's reduced shear stress there. This vulnerability to the development of cholesterol plaque is believed to be mediated by diminished nitric oxide release and intimal thickening, both of which are linked to low shear stress. While cerebral atherosclerosis is more common in Asia, it can occasionally be seen in patients in Western nations, typically in those who smoke heavily and have diabetes mellitus [18].

In fact, it is estimated that cerebral atherosclerosis accounts for between 30 and 50 percent of ischemic strokes in Asian patients, compared to 5 to 10 percent in white patients. This condition makes standard thrombectomy difficult because it is linked to higher rates of reocclusion following thrombectomy and necessitates more stenting, which carries a higher risk of complications, especially bleeding from the use of antiplatelet drugs to keep the stent open [19].

- **Small vessel disease**

As the name suggests, small vessel disease mostly affects the smaller arteries and arterioles in the brain. Intracerebral haemorrhage, microbleeds in the brain, lacunar stroke, leukoaraiosis, and white matter abnormalities (T2-hyperintensities on MRI or hypodensities on CT) are all symptoms that can indicate a problem with a tiny artery. The circle of Willis's much larger arteries is the source of the small-calibre perforating arteries that supply the deep subcortical and brainstem regions. High pressure is applied to the tiny blood arteries, perhaps increasing the risk of lipohyalinosis, or constriction of the tiny blood vessels in the brain. tiny subcortical infarcts can be caused by more than just lipohyalinosis, and the classic lacunar syndromes aren't very good at identifying strokes caused by tiny vessel disease. Another significant cause of lacunar clinical syndromes is atherosclerosis of the parent artery, which results in obstruction of the perforating vascular origin. Small vessel disease can occasionally be the consequence of monogenic conditions, such as CADASIL, which typically manifests as a migraine, followed by lacunar infarcts and dementia [20].

- **Arterial dissection**

Strokes in younger individuals often occur as a result of a break in the inner arterial wall, which can be caused by intramural thrombus. The vertebral and extracranial carotid artery dissections are the most common cause of ischemic strokes because they can either block the artery at the site of the dissection or cause emboli to develop. Dissection is frequently fairly small, even though it can result from varied degrees of cervical trauma; for some people, dissection can be caused by strong coughing or sneezing. Moreover, dissections frequently occur on their own. Apart from fibromuscular dysplasia and Ehlers-Danlos syndrome, a few collagen and connective tissue disorders can increase the risk of arterial

dissections. However, these conditions are rarely detectable with the tests that are currently available, and there are currently only a few genetic factors that have been linked to dissection risk. Therefore, it is not common practice to test for an underlying connective tissue condition [21].

- **Cerebral vasculitis**

Cerebral artery vasculitis is uncommon, however it can show as systemic vasculitis or as primary central nervous system (CNS) angiitis. Ischemic stroke (and occasionally intracerebral hemorrhage) can result from artery wall inflammation in these situations, which can also cause luminal constriction and thromboembolism [22].

- **Reversible cerebral vasoconstriction syndrome**

Through vasospasm and vascular dysregulation, reversible cerebral vasoconstriction syndrome can result in focal subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke. It is characterized by recurrent thunderclap (abrupt onset) headaches. Vasospasm may not be visible on the first arterial imaging, and the exact cause is uncertain. Vasospasm following aneurysmal subarachnoid hemorrhage, which can also result in ischemic stroke, is distinct from this [23].

Systemic effects

Bradycardia, pulmonary exudates, and hypertension are some of the initial responses to a major ischemic stroke, but it's unclear whether these changes are directly brought on by brain damage or are the consequence of other events. By decreasing the effective perfusion of brain regions that were either totally or partially untouched by the initial ischemic shock, cardiac ramifications (myocardial "stunning") of severe brain injury can have an indirect influence, such as pulmonary edema. This could lead to secondary insult and injury. However, systemic effects can result with even minor strokes. These include alterations in gut permeability and microbiota, the release of macrophages from the spleen and bone marrow stem cells, a stress response (an increase in cortisol levels), and a systemic immune response. Some of these adaptive alterations may be advantageous at first, but they can also have unfavorable consequences. Therefore, one possible therapeutic goal is to alter the systemic response to stroke [24].

Mechanisms of recovery

In animal models of stroke, the degree of behavioral function recovery can be astounding, and young individuals who have had a stroke or traumatic brain damage can also have comparable recoveries. Neuroplasticity, or the capacity to use alternative pathways to replace those destroyed as a result of stroke, is largely responsible for this recovery. This flexibility could include synaptogenesis, local sprouting, or just the fortification of transmission at preexisting synapses. Crucially, this adaptability appears to have a price; younger patients frequently recover physically well but struggle to manage concurrent events and experiences exhaustion. According to imaging studies, they must enlist far larger, more dispersed networks in order to operate normally, which comes at the expense of effort and the capacity to employ these networks for other tasks [25].

Although the proportional contributions of neurogenesis and neuroplasticity are unclear, endogenous stem cells aid in neurogenesis in animal models of stroke. In human post-mortem research, endogenous stem cells have been discovered in peri-infarct locations, which may suggest that these cells play a part in stroke. Exogenous stem cells (ESCs) probably don't integrate into signaling pathways directly, but rather mediate the beneficial effects of injury-site trophic and supportive factor production and local environment modification to promote regeneration and repair in animal models [26].

Diagnosis, screening and prevention

- **Diagnosis**

Rapid onset of a localized clinical deficit originating in a particular area of the central nervous system is a hallmark of stroke clinical presentation. Some of the symptoms include hemiparesis, hemianaesthesia, homonymous hemianopia, hemispatial inattention, aphasia, and a numbness or weakness on one side of the body [24].

When diagnosing a stroke, neuroimaging is helpful in differentiating it from many other conditions that can mimic it, including migraines, seizures, vestibular abnormalities, metabolic alterations, and functional deficits. Furthermore, distinguishing between ischemic stroke and intracerebral bleeding is of the utmost importance. However, brain imaging is the key to diagnosis, and there are no clinical means to do this. Around the world, CT is typically used for imaging, although in a small percentage of centers, MRI is the primary imaging modality. Some individuals are unable to get an MRI because of metallic implants or agitation, and quick access to MRI is a typical barrier [27].

Brain imaging is increasingly used not only for diagnosis but also to determine which stroke patients are most likely to benefit from reperfusion treatments. Traditionally, thrombolysis and thrombectomy have been tested a short period of time after the patient's last known period of health. Treatment choices for patients with aphasia who cannot explain the start of their symptoms, those with inattention that prevents them from recognizing their impairment, and those with stroke symptoms on waking or other delayed presentations have been limited by this time-based approach. But thanks to advancements in brain imaging, patients can now be identified with brain tissue that can be saved and those who are most likely to benefit from reperfusion outside of the conventional time windows [28].

- **Non-contrast CT**

Brain without contrast Both intraparenchymal and extra-axial (within the skull but outside the parenchyma) hemorrhages can be detected with about 100% sensitivity using CT. Historically, thrombolysis therapy decisions have been based on CT brain scans that screen out hemorrhage in patients showing clinical signs of a stroke. In some cases, early ischemia changes, such as a lack of grey matter–white matter separation, may enable a favorable stroke diagnosis **(Figure 2),** Hyperdense arteries, indicative of acute thrombus or early ionic oedema in the irreparably injured brain, are the two possible explanations. However, these symptoms might not be life-threatening, and it could be difficult to tell whether white matter and gray matter have lost their distinction in the first few hours after a stroke [29].

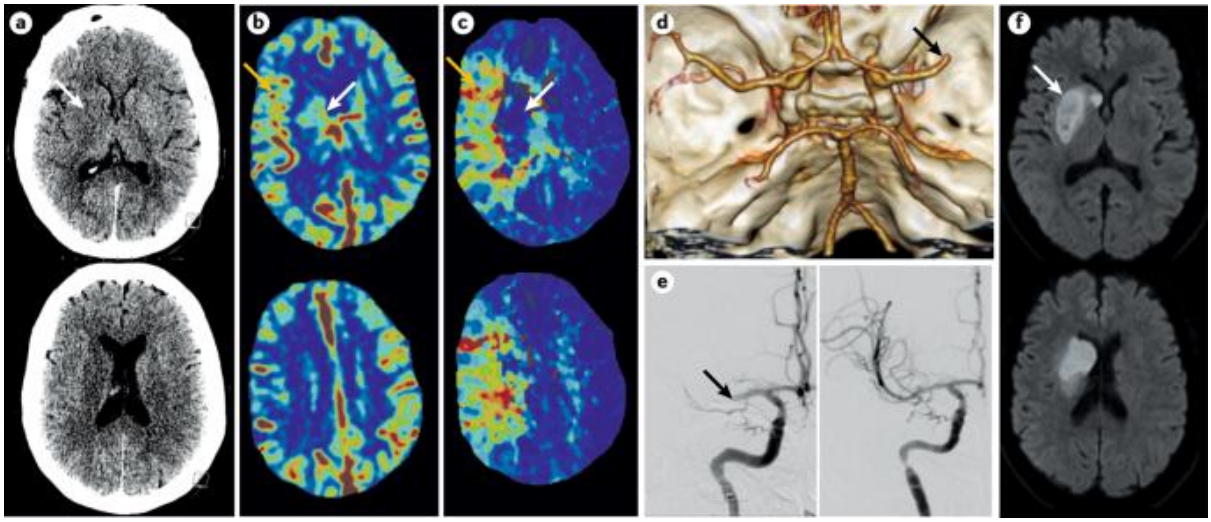

Figure 2: Brain imaging to diagnose ischaemic stroke and identify salvageable brain tissue [17]

Picture taken of a 66-year-old female patient who had been examined 16 hours prior to her current symptoms of left hemiparesis, dysarthria, and lack of attention. The right basal ganglia's loss of grey-white separation (white arrow) on the non-contrast CT scan (panel a) suggests that the right middle cerebral artery was occluded at some point. However, reperfused basal ganglia (white arrows) with enhanced cerebral blood flow (panel b) are visible in CT perfusion processed using RAPID (iSchemaView, Menlo Park, CA, USA) automated software (panels b,c), suggesting post-reperfusion hyperperfusion. The fact that the contrast does not reach the right middle cerebral artery (MCA) area (retrograde via collateral arteries) immediately is shown by the time to maximum (Tmax) (panel c) (yellow arrows). It is quite probable that the ischemic penumbra can be reversed since cerebral blood flow is preserved in the region of delayed Tmax (panel b). The right MCA blockage (black arrows at the distal M1 segment) is confirmed by the digital subtraction catheter angiogram (panel e) and the CT angiography (panel d). Two hours subsequent to the CT perfusion, the patient underwent a successful endovascular thrombectomy with reperfusion. Panel f of the MRI diffusion the next day reveals the preserved cortical areas alongside the anticipated infarct in the basal ganglia (white arrow). After the patient's left side was recovered, they were admitted to a rehabilitation center for inpatient care [17].

- **CT angiography and perfusion**

For the purpose of evaluating the cerebral vasculature, iodinated contrast agents can be intravenously delivered using either a static acquisition (CT angiography) or a time-resolved sequence (CT perfusion). The ischemic stroke can be diagnosed and the cause of the stroke, such as atherosclerosis or arterial dissection, can be determined with the use of CT angiography due to its high sensitivity in detecting occlusion and stenosis of the arteries. In order to determine if endovascular thrombectomy is an option, either locally or via a transfer, all patients with ischemic stroke should have standard CT angiography from the aortic arch to the cerebral vertex. Furthermore, the degree of collateral flow can be evaluated using CT angiography, which offers more predictive data regarding the probable degree of tissue damage [30].

Nevertheless, the intended timing of standard single-phase scans at peak arterial enhancement does not allow for an accurate description of delayed-arrival collateral blood flow. Thus, CT angiography might not take collaterals into account to their full extent. Patients who are eligible for thrombectomy based on the quality of their late-arriving collateral blood flow may not be eligible for the procedure even though they have sufficient collateral blood flow to sustain brain viability and would benefit from therapy[31].

The whole passage of the contrast bolus is characterized by CT perfusion, which can be processed to provide maps that show the extent of regional decrease and delay in blood flow within the brain. There are now many automated software methods accessible. As a result, CT perfusion is being used more frequently as a diagnostic and predictive tool. It can also be used to find patients who might benefit from thrombolysis or endovascular thrombectomy outside of the usual time frames [32].

- **MRI**

Several magnetic resonance imaging (MRI) sequences, such as diffusion, perfusion, and T2-based sequences, evaluate various anatomical and functional aspects of brain tissue. Diffusion MRI is the imaging technique that can detect acute ischaemia the most accurately since it can pick up on the random motion of water molecules. Cytotoxic edema regions have impaired diffusion because water distribution changes from extracellular to intracellular compartments. Within minutes of an ischemic stroke occurring, diffusion MRI becomes abnormal, and areas with diffusion limitation seldom regain their completely normal radiological or histological appearance. Ionic and vasogenic edema, which can be identified on contrast-free MRI and CT images, are caused by additional disturbance of the blood-brain barrier in the hours that follow [33].

While susceptibility-weighted imaging is very sensitive for bleeding, time of flight magnetic resonance angiography visualizes the artery lumen using signals from endogenous blood flow (without intravenous contrast). Perfusion Similar to CT perfusion, MRI tracks the cerebral circulation with an intravenous gadolinium contrast bolus and uses image processing to create maps of blood flow and contrast arrival delay. Patients who might benefit from reperfusion therapy outside of conventional time limits have also been identified by the mismatch between tiny diffusion lesions and bigger perfusion lesions on MRI, or by a severe clinical deficiency [34].

We say that carotid stenosis is symptomatic if there has been an ischemia event (stroke, MI, brief monocular blindness, or blockage of the retinal artery) on the ipsilateral side of the carotid area in the past six months [35].

Atherosclerosis is the leading cause of stroke. Since atherosclerotic lesions grow silently over years before becoming symptomatic, finding latent indications of cerebral atherosclerosis disease may be useful in the context of primary stroke prevention and therapy. Extracranial carotid artery stenosis (ECAS) and intracranial carotid artery stenosis (ICAS) are the two general classifications for cerebral atherosclerotic disease. Internal carotid arteries, also known as the common and internal carotid arteries, are the extracranial carotid arteries that are atherosclerotically narrowed. Clinical practice frequently encounters asymptomatic

ECAS. In the general population, its prevalence varies between 0.1 and 7.5%, with elderly men having the highest prevalence [36].

The term "intracranial atherosclerotic disease" (ICAD) refers to atherosclerotic alterations in the intracranial segment of the brain's blood vessels. This illness is a major global health concern since it frequently contributes to ischemic stroke and transient ischemic episodes [37, 38]. According to studies, 20–40 people per 100,000 people globally get cerebral infarctions linked to intracranial atherosclerosis [39].

The burden of ICAD is unequally distributed among all racial and ethnic groups, with Caucasians bearing a smaller burden than Asians, Blacks, Hispanics, and Native Americans, according to population-based studies [40]. Between fifteen and forty-four percent of all ischemic strokes in Asia occur due to ICAD [41]. Caucasians had a five-to sixfold lower prevalence of ICAD-related strokes compared to African Americans and Caribbean Hispanics in the multiethnic Northern Manhattan stroke study group [42].

Pathophysiology of atheromatous plaque formation

The development of cholesterol deposits that create an atheroma in the artery wall is known as atherosclerosis, a cholesterol-mediated illness. A simple model of the pathophysiology of atherosclerosis, inferred from coronary artery disease, starts with intimal cholesterol particle buildup and vascular endothelial dysfunction. After adhering to active endothelium, circulating monocytes penetrate the artery wall, develop into macrophages, attach to accumulating lipoprotein particles, and develop into foam cells. T cells also enter the bloodstream, but to a smaller extent. Smooth cells move from the tunica media into the intima in response to invading leukocytes, promoting the synthesis of collagen matrix and potentially causing pathological intimal thickening [43].

Atheroma is created when lipids, leukocytes, and smooth cells continue to clump together. When combined, these inflammatory factors accelerate the development of plaque and can cause clinical manifestations even when there isn't any noticeable stenosis. Crucially, the degree of fibrous cap formation, the size of lipid-rich necrotic core, and complicating characteristics such thrombi are used to classify atheromatous lesions. The fibrous cap is a unique layer of connective tissue that covers the lipid core and is produced by collagen matrix production mediated by smooth cells. The interstitial collagen may be eroded and the fibrous cap thinned by an infiltrative inflammatory response, making the patient more vulnerable to plaque rupture and the dreaded atherosclerotic complication of acute thrombosis. Other characteristics of plaque vulnerability include intraplaque bleeding and plaque neovascularization [44].

Atherogenesis is generally encouraged by hemodynamic conditions with low wall shear stress and circumferential wall tension. At arterial walls across from flow dividers or arterial branch points where blood flow patterns are distorted, low wall shear stress which is characterized by oscillatory shear stress and flow recirculation occurs. The nonlaminar flow patterns are compensated for by wall tension in artery walls; however, this can wear thin with arterial stiffness from extended stress, particularly in hypertensive people. The cerebral circulation often shows atherosclerotic plaque in two areas: the proximal basilar artery and

the ventral wall of the MCA, which lies opposite the perforator opening. Because of the angle at which the two vertebral arteries converge, certain regions experience altered blood flow **(Figure 3)[45]**.

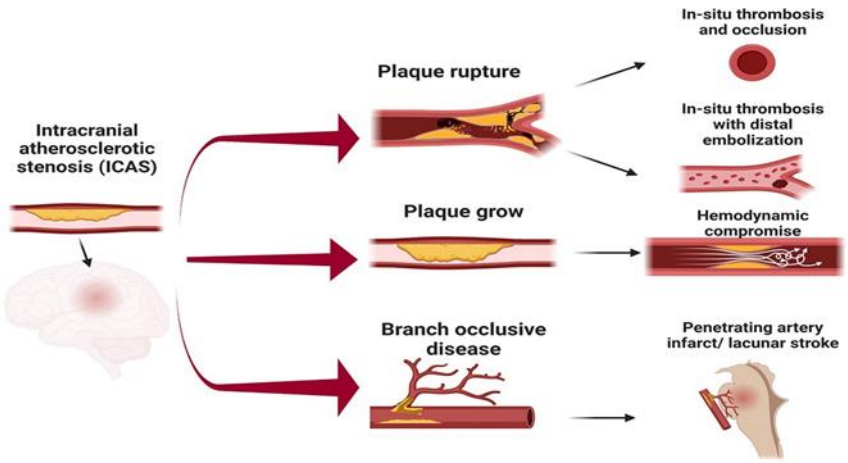

Figure 3: Pathophysiology of ICAD [38]

Mechanism of stroke

Intracranial atherosclerotic disease can cause ischemic stroke through multiple mechanisms:

Artery-to-artery embolism with infarcts distal to the stenotic vessel due to vulnerable plaque rupture was the most common mechanism of stroke in intracranial arterial stenosis (59.7%) **(Figure 40)** [46].

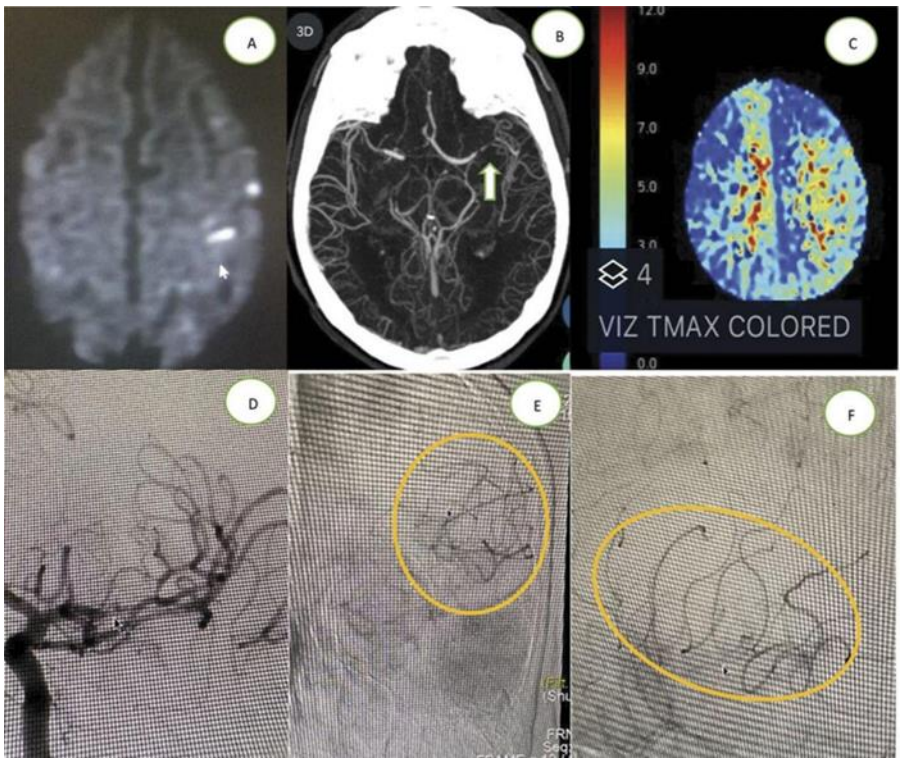

Figure 4: Artery-to-artery embolism with cortical infarction [46]

Local branch occlusion involving ≥1 perforators (14.9%) **(Figure 5)** [46].

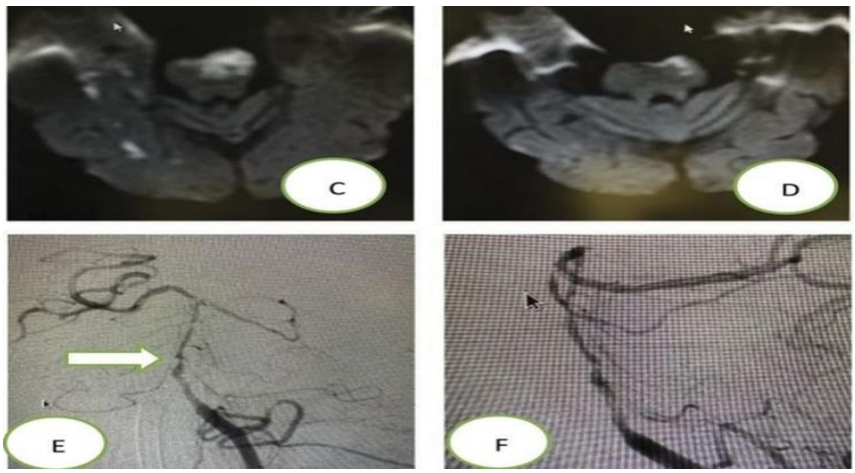

Figure 5: Local branch occlusion with multiple brainstem infarcts [46]

In situ thrombo-occlusion (13.7%) **(Figure 6)** [46].

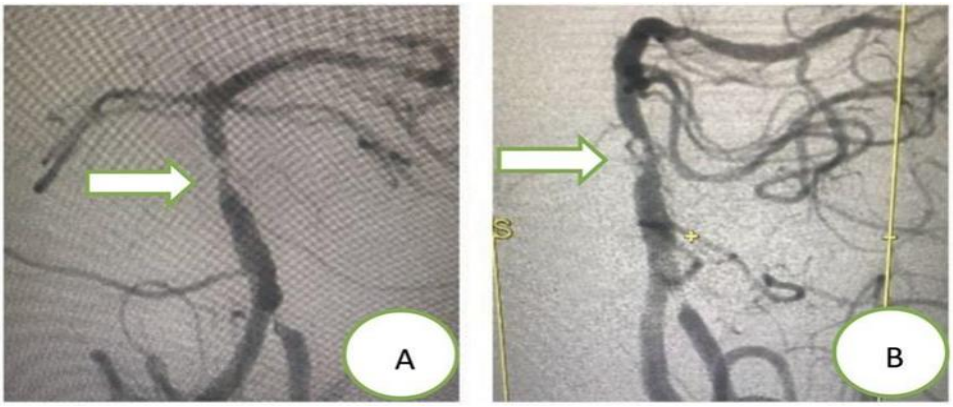

Figure 6: In situ thrombus formation on underling basilar artery [46]

Hemodynamic impairment from high grade stenosis with linear border-zone infarcts (0.9%) **(Figure 7)** [46].

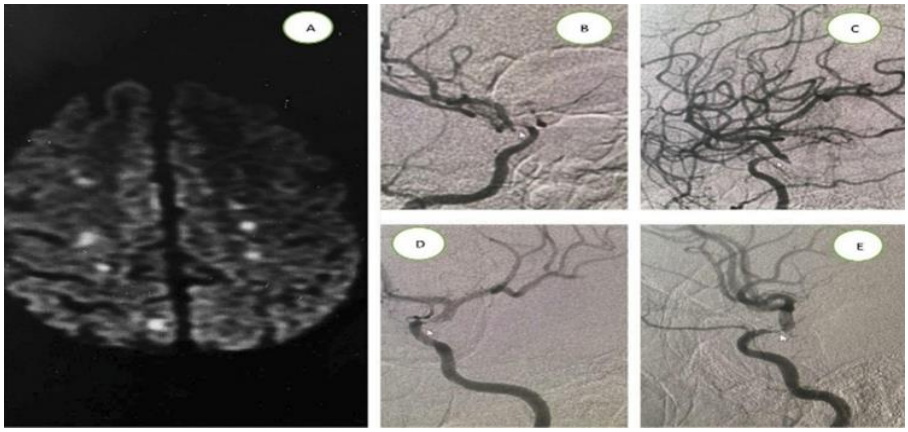

Figure 7: Hemodynamic impairment with bilateral linear border-zone infarcts [46]

Mixed mechanisms (10.8%) **(Figure 8)** [46].

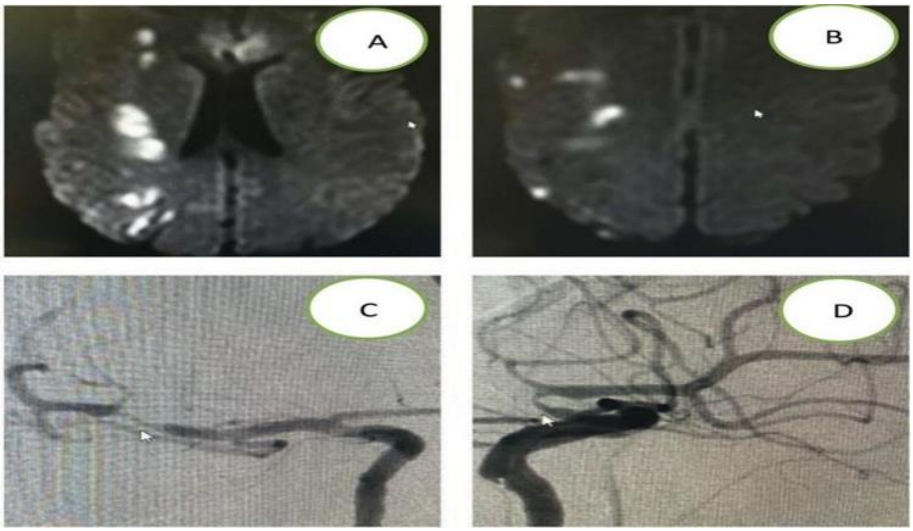

Figure 8: Mixed mechanisms of strokes with internal and external border-zone and cortical infarcts [46]

The majority of earlier research on the risk factors for symptomatic ICAS or ECAS was conducted in hospitals. The incidence and function of traditional risk factors for both asymptomatic ECAS and ICAS may differ in China due to the stark contrast between rural and urban lifestyles and the country's geographic disparity [47].

Intracerebral atherosclerosis is regarded as one of the most prevalent causes of AIS globally, and stroke is a diverse illness. Even in Asian nations, where it makes up around half of cases, its incidence and prevalence differ by geographic location and ethnicity. ICAS may be underestimated in comparison to extracranial lesions since it has historically received little research attention in Western nations. In a prior study, 438 stroke patients (35% Black, 46% Hispanic, and 19% White) had 8% cerebral atherosclerosis. While cerebral lesions were more common in Black and Hispanic individuals, the rate of extracranial atherosclerosis was comparable across ethnic groups. Ethnic groupings did not significantly differ from one another in this investigation. Nonetheless, White people made up 69.1% of our ICA patients [48].

The low control of traditional risk factors for cerebrovascular disorders in the sample is another factor contributing to the high incidence of cerebral atherosclerosis. With a prevalence rate of 76.9%, systemic arterial hypertension was the most common risk factor among patients. This was followed by diabetes (40.6%), dyslipidemia (39.2%), and a history of stroke or TIA (44.1%). According to a study on stroke victims, people with MCA stenosis were more likely to have diabetes, hypertension, and high cholesterol. High blood pressure and ICAS have also been linked in a number of other studies [49].

Low HDL levels have been linked in numerous prior investigations to the onset of cerebral atherosclerosis. According to a CICAS study analysis, there is a significant negative connection between low HDL levels and the onset of ICAS [50].

Management of cerebrovascular atherosclerotic disease to reduce stroke risk

Carotid revascularization, which comprises carotid endarterectomy (CEA) and carotid artery stenting (CAS), is a significant medical technique for preventing strokes connected to the carotid. Patients with atherosclerotic carotid stenosis benefit from the multispecialty decision-making and therapy provided by a neuro-vascular team. This group consists of medical, surgical, and endovascular specialists that specialize in treating carotid artery stenosis.The most effective treatment techniques are defined by patient traits and the available local expertise [51].

- **Lifestyle modification**

The risk of a carotid-related stroke can be decreased by changing one's lifestyle, just like with other cardiovascular conditions. Advocating for healthy lifestyle changes like giving up smoking, cutting back on food intake, increasing physical activity, and decreasing body fat percentage is advised [52].

- **Medical management**

Triple medical therapy medication to reduce low-density lipoprotein cholesterol, medication to manage blood pressure, and medication to prevent blood clots—reduces the risk of stroke in patients with asymptomatic or symptomatic carotid stenosis [53].

- **Antiplatelet medications**

For "stable" CarAD (asymptomatic stenosis and long-term secondary prevention after intervention), a single anti-platelet medication is necessary; this should be low-dose clopidogrel or aspirin [53].

Recurrent neurologic episodes are most likely to occur in patients with symptomatic carotid stenosis who experience a transient ischemic attack (TIA) or a mild stroke, especially in the initial days following the start of symptoms. Compared to single anti-platelet treatment while awaiting CEA, starting dual anti-platelet treatment (DAPT; 75 mg of aspirin and 75 mg of clopidogrel) after ruling out intra-cerebral or parenchymal hemorrhage resulted in a five-fold decrease in recurrent events without increasing significant peri-operative bleeding complications [54].

- **Blood pressure control**

To maintain proper systemic perfusion, hypotension and hypovolemia should be corrected. When flow-limiting stenosis or large vessel occlusions have weak collateral blood flow, or when symptoms are fluctuating or seem to be blood pressure dependent, blood pressure lowering during the acute phase may worsen stroke symptoms and prolong infarcts in certain patients due to a failure of autoregulation [55].

When blood pressure exceeds 220/120 mm Hg, acute antihypertensive medication is usually recommended. Patients with AIS who have blood pressure above 220/120 mm Hg should think about reducing their blood pressure by 15% within 24 hours after the onset of AIS. Lowering blood pressure by 15% is deemed safe for patients with AIS who also have a

concomitant condition where hypertension poses a risk, such as acute coronary event, acute heart failure, preeclampsia, or eclampsia [56].

- **Lipid lowering medications**

All patients with severe CarAD are encouraged to undergo intensive statin therapy in order to reach an LDL-C level below 55 mg/dL. Possible substitute or additional medications include ezetimibe or a proprotein convertase subtilisin/kexin type 9 inhibitor [57]. There are a number of positive clinical and molecular outcomes linked to intensively decreasing LDL-C in individuals with CarAD [54].

Statins have anti-thrombotic effects in addition to decreasing LDL-C because they directly interfere with the clotting mechanism and platelet activation. This impact may become significant in clinical settings, especially when statin dosages are high [58].

- **Carotid endarterectomy**

First performed in 1953, carotid endarterectomy (CEA) is one of the most thoroughly evaluated surgical procedures ever. It is surgery to treat carotid artery disease. In carotid artery disease, these arteries become narrowed. This reduces blood flow to the brain and could cause a stroke [59]. The procedure is done while the patient is awake under local anesthesia or while you are asleep under general anesthesia [60].

- **Indications**

Carotid endarterectomy (CEA) is the gold standard for treating asymptomatic stenosis levels of 70–99% and symptomatic low-risk surgical patients with stenosis levels of 50–99%. Reduce the risk of a second stroke by waiting until the patient's neurological status is stable, which should be achieved between 48 hours and 14 days following the start of symptoms. The procedure should be carried out as soon as this stability is achieved, provided that the estimated risk of perioperative morbidity and death is less than 6%. To lower the periprocedural stroke rate, it seems sense to choose CEA over CAS in patients ≥70 years old who have had a stroke or TIA and are considering carotid revascularization [61].

- **Carotid angioplasty and stenting**

Forty years after CEA, a less invasive treatment for CarAD was introduced: carotid angioplasty and stenting (CAS). It provides an endovascular substitute for CEA and is recommended as a good choice for patients who are considered high-risk for open CEA because of comorbidities or technical issues with the procedure [62].

In conclusion, ischemic stroke is significantly linked to intracranial and extracranial artery stenosis, which is quite common. For the evaluation of ICAS and ECAS for secondary prevention of ischemic stroke, MRA and Doppler investigations are strongly advised.

References

1. Fan J, Li X, Yu X, Liu Z, Jiang Y, Fang Y, et al. Global burden, risk factor analysis, and prediction study of ischemic stroke, 1990–2030. Neurology. 2023;101:137-50.
2. Potla N, Ganti L. Tenecteplase vs. alteplase for acute ischemic stroke: a systematic review. Int J Emerg Med. 2022;15:1-40.

3. Banerjee P, Koumans H, Weech MD, Wilson M, Rivera-Morales M, Ganti L. AHORA: a Spanish language tool to identify acute stroke symptoms. Stroke Vasc Neurol. 2022;7:176-8.
4. Stead T, Ganti L, McCauley E, Koumans H, Wilson M, Weech MD, et al. What Do Spanish Speakers Think of the Andar, Hablar, Ojos, Rostro, Ambos Brazos o Piernas (AHORA) Stroke Tool? Cureus. 2021;13:207-20.
5. Pohl M, Hesszenberger D, Kapus K, Meszaros J, Feher A, Varadi I, et al. Ischemic stroke mimics: A comprehensive review. J Clin Neurosci. 2021;93:174-82.
6. Ahmed Z, Chaudhary F, Agrawal DK. Epidemiology, Pathophysiology, and Current Treatment Strategies in Stroke. Cardiol Cardiovasc Med. 2024;8:389-404.
7. Ferrari F, Moretti A, Villa RF. Hyperglycemia in acute ischemic stroke: physiopathological and therapeutic complexity. Neural Regen Res. 2022;17:292-9.
8. McCrimmon RJ. Consequences of recurrent hypoglycaemia on brain function in diabetes. Diabetologia. 2021;64:971-7.
9. Aref H, Zakaria M, Shokri H, Roushdy T, El Basiouny A, El Nahas N. Changing the Landscape of Stroke in Egypt. Cerebrovasc Dis Extra. 2021;11:155-9.
10. Osuegbu OI, Adeniji FO, Owhonda GC, Kanee RB, Alblihed M, Batiha GE-S, et al. Non-Modifiable Risk Factors (Age and Sex), Stroke Types, and Outcomes in Rivers State, Nigeria: A Retrospective Hospital-Based Study. 2021. p. 10-50.
11. McGlennen KM, Jannotta GE, Livesay SL. Nursing Management of Temperature in a Patient with Stroke. Crit Care Nurs Clin North Am. 2023;35:39-52.
12. Ganti L. Management of acute ischemic stroke in the emergency department: optimizing the brain. Internl J Emergy Med. 2025;18:7-50.
13. Alshahrani M, Almalki LZ, Hasoosah NA, Alahmari AH, Alqahtani AM, Alqahtani AA, et al. Prevalence and assessment of risk factors of chronic kidney disease in the ASIR region of Saudi Arabia. Ann Med Surg (Lond). 2024;86:3909-16.
14. Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. Intern J Stroke. 2012;7:378-85.
15. Lalancette-Hébert M, Gowing G, Simard A, Weng YC, Kriz J. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. J Neurosci. 2007;27:2596-605.
16. Battista D, Ferrari CC, Gage FH, Pitossi FJ. Neurogenic niche modulation by activated microglia: transforming growth factor beta increases neurogenesis in the adult dentate gyrus. Eur J Neurosci. 2006;23:83-93.
17. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. Na Rev Dis Primers. 2019;5:70-80.
18. Kim JS, Kim YJ, Ahn SH, Kim BJ. Location of cerebral atherosclerosis: Why is there a difference between East and West? Int J Stroke. 2018;13:35-46.
19. Jia B, Feng L, Liebeskind DS, Huo X, Gao F, Ma N, et al. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. J Neurointerv Surg. 2018;10:746-50.
20. Markus HS, de Leeuw FE. Cerebral small vessel disease: Recent advances and future directions. Int J Stroke. 2023;18:4-14.

21. Salehi Omran S. Cervical Artery Dissection. Continuum (Minneap Minn). 2023;29:540-65.
22. Campos AC, Sarmento S, Narciso M, Fonseca T. Primary Central Nervous System Vasculitis: A Rare Cause of Stroke. Cureus. 2023;15:3954-80.
23. Singhal AB. Reversible cerebral vasoconstriction syndrome: A review of pathogenesis, clinical presentation, and treatment. Int J Stroke. 2023;18:1151-60.
24. Murphy SJ, Werring DJ. Stroke: causes and clinical features. Medicine (Abingdon). 2020;48:561-6.
25. Campos B, Choi H, DeMarco AT, Seydell-Greenwald A, Hussain SJ, Joy MT, et al. Rethinking Remapping: Circuit Mechanisms of Recovery after Stroke. J Neurosci. 2023;43:7489-500.
26. Huang H, Qian K, Han X, Li X, Zheng Y, Chen Z, et al. Intraparenchymal Neural Stem/Progenitor Cell Transplantation for Ischemic Stroke Animals: A Meta-Analysis and Systematic Review. Stem Cells Int. 2018;2018:4826407.
27. Rowley H, Vagal A. IDKD Springer Series Stroke and Stroke Mimics: Diagnosis and Treatment. Diseases of the Brain, Head and Neck, Spine 2020–2023: Diagnostic Imaging. Cham (CH): Springer 2020. p. 25-36.
28. Kakkar P, Kakkar T, Patankar T, Saha S. Current approaches and advances in the imaging of stroke. Dis Model Mech. 2021;14:80-90.
29. Srivatsan A, Christensen S, Lansberg MG. A Relative Noncontrast CT Map to Detect Early Ischemic Changes in Acute Stroke. J Neuroimaging. 2019;29:182-6.
30. Panicker S, Wilseck ZM, Lin LY, Gemmete JJ. CT Imaging Computed Tomography/Computed Tomography Angiography/Perfusion in Acute Ischemic Stroke and Vasospasm. Neuroimaging Clin N Am. 2024;34:175-89.
31. Pereira A, Alakbarzade V, Lowe D, Hargroves D. Computed Tomography Perfusion in Acute Stroke Assessment. Cerebrovasc Dis. 2025;54:208-14.
32. Christensen S, Lansberg MG. CT perfusion in acute stroke: Practical guidance for implementation in clinical practice. J Cereb Blood Flow Metab. 2019;39:1664-8.
33. Tedyanto EH, Tini K, Pramana NAK. Magnetic Resonance Imaging in Acute Ischemic Stroke. Cureus. 2022;14:272-624.
34. Bachtiar NA, Murtala B, Muis M, Ilyas MI, Abdul Hamid HB, As'ad S, et al. Non-Contrast MRI Sequences for Ischemic Stroke: A Concise Overview for Clinical Radiologists. Vasc Health Risk Manag. 2024;20:521-31.
35. Ismail A, Ravipati S, Gonzalez-Hernandez D, Mahmood H, Imran A, Munoz EJ, et al. Carotid Artery Stenosis: A Look Into the Diagnostic and Management Strategies, and Related Complications. Cureus. 2023;15:387-94.
36. Suo Y, Jing J, Pan Y, Chen W, Zhou H, Li H, et al. Concurrent intracranial and extracranial artery stenosis and the prognosis of transient ischaemic symptoms or imaging-negative ischaemic stroke. Stroke Vasc Neurol. 2021;6:33-40.
37. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2013;12:1106-14.

38. Chen LH, Spagnolo-Allende A, Yang D, Qiao Y, Gutierrez J. Epidemiology, Pathophysiology, and Imaging of Atherosclerotic Intracranial Disease. Stroke. 2024;55:311-23.
39. Sanchez S, Mossa-Basha M, Anagnostakou V, Liebeskind DS, Samaniego EA. Comprehensive imaging analysis of intracranial atherosclerosis. J Neurointerv Surg. 2025;17:311-20.
40. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. Circulation. 2005;111:1327-31.
41. Mehndiratta MM, Khan M, Mehndiratta P, Wasay M. Stroke in Asia: geographical variations and temporal trends. J Neurol Neurosurg Psychiatry. 2014;85:1308-12.
42. Del Brutto OH, Del Brutto VJ, Mera RM, Pérez P, Recalde BY, Costa AF, et al. Prevalence and Correlates of Intracranial Atherosclerotic Disease Among Community-Dwelling Older Adults of Amerindian Ancestry. The Three Villages Study. J Stroke Cerebrovasc Dis. 2020;29:105-35.
43. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5:56-80.
44. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114:1852-66.
45. Xu WH, Li ML, Gao S, Ni J, Zhou LX, Yao M, et al. Plaque distribution of stenotic middle cerebral artery and its clinical relevance. Stroke. 2011;42:2957-9.
46. Tekle WG, Hassan AE. Intracranial Atherosclerotic Disease: Current Concepts in Medical and Surgical Management. Neurology. 2021;97:145-57.
47. Al-Nidawi F, Mohamed MW, Hussein A, Alataibi N, Althahabi R, Almaawi A, et al. Demographic and risk factors profile of intracranial atherosclerotic stenosis in the Kingdom of Bahrain. Egypt J Neurol Psychiat Neurosurg. 2022;58:118-80.
48. Krasteva MP, Lau KK, Mordasini P, Tsang ACO, Heldner MR. Intracranial Atherosclerotic Stenoses: Pathophysiology, Epidemiology, Risk Factors and Current Therapy Options. Adv Ther. 2020;37:1829-65.
49. de Almeida Rocha LJ, Zotin MCZ, Santos RdSA, Libardi MC, Camilo MR, Barreira CMA, et al. High prevalence of intracranial arterial stenosis among acute ischemic stroke patients in a Brazilian center: a transcranial color-coded duplex sonography study. Arquivos de Neuro-Psiquiatria. 2024;82:5-42.
50. Wu Z, Li X, Wen Q, Tao B, Qiu B, Zhang Q, et al. Serum LDL-C/HDL-C ratio and the risk of carotid plaques: a longitudinal study. BMC Cardiovascular Disorders. 2022;22:501-50.
51. Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg. 2023;65:7-111.
52. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with

representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European heart journal. 2021;42:3227-337.
53. Musialek P, Bonati LH, Bulbulia R, Halliday A, Bock B, Capoccia L, et al. Stroke risk management in carotid atherosclerotic disease: A Clinical Consensus Statement of the ESC Council on Stroke and the ESC Working Group on Aorta and Peripheral Vascular Diseases. Cardiovascular research. 2025;121:13-43.
54. Paraskevas KI, Gloviczki P, Mikhailidis DP, Antignani PL, Dardik A, Eckstein H-H, et al. Optimal periprocedural antithrombotic treatment in carotid interventions: an international, multispecialty, expert review and position statement. Prog Cardiovas Dis. 2022;74:28-37.
55. Nogueira RC, Beishon L, Bor-Seng-Shu E, Panerai RB, Robinson TG. Cerebral autoregulation in ischemic stroke: from pathophysiology to clinical concepts. Brain sciences. 2021;11:511-60.
56. McManus M, Liebeskind DS. Blood pressure in acute ischemic stroke. J clin neurology 2016;12:137-200.
57. Leys D, Casolla B, Cordonnier C. Low-Density Lipoprotein Cholesterol Level After a Stroke—Reducing It by Any Means. JAMA neurology. 2022;79:329-30.
58. Lee M, Cheng C-Y, Wu Y-L, Lee J-D, Hsu C-Y, Ovbiagele B. Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention: a meta-analysis of randomized clinical trials. JAMA neurology. 2022;79:349-58.
59. Rerkasem A, Orrapin S, Howard DP, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. CDSR. 2020:50-60.
60. Uno M, Takai H, Yagi K, Matsubara S. Surgical technique for carotid endarterectomy: current methods and problems. Neurologia medico-chirurgica. 2020;60:419-28.
61. AbuRahma AF, Avgerinos ED, Chang RW, Darling III RC, Duncan AA, Forbes TL, et al. Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. J vas surgery. 2022;75:4-22.
62. Machin M, Salim S, Onida S, Davies AH. The less invasive paradox, why carotid artery stenting is not suitable for the high-risk patient. Annals trans med. 2020;8:1269-300.