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Review Article

Stroke: It is Better to Prepare and Prevent than to Repair and Repent

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Abstract

In the present century, stroke is a debilitating brain disorder with consequential public health implications. Almost half of the survivors from the stroke attack suffer from substantial cognitive deficits and the other half are chronically disabled, leading a crippled life. Stroke is a neurological disorder characterized by occlusion or rupture of blood vessels that supply oxygen and nutrients to the brain, resulting in the sudden death of brain cells. It is challenging to manage the stroke attack therapeutically despite several advances in medical and surgical technology, given the development of a permanent infarct in the brain. Therefore, it becomes crucial to prevent this deadly disease in the first place by identifying susceptible individuals and associated risk factors. The authors have given concrete recommendations for controlling the potential risk factors of stroke that are under our control, like diet, physical activity, obesity, cessation of smoking, etc. The role of factors that are beyond our control, like age, sex, race and genetic constitution, in precipitating the first attack of stroke has also been discussed in this article. Practical interventional approaches to minimize the risk involved in the occurrence of primary stroke attack due to chronic diseases such as diabetes mellitus, atrial fibrillation, hypertension, valvular heart disease, sickle cell disease, migraine, sleep apnea, atherosclerosis, and brain infections have been described. This updated article aims to provide comprehensive and precise guidelines for preventing primary stroke attacks.

Keywords: stroke; guidelines; cardiogenic; atherosclerosis; risk

Introduction

Preamble:

A stroke is a devastating episode causing substantial functional disability. Stroke is a neurological disorder characterized by occlusion or rupture of blood vessels that supply oxygen and nutrients to the brain, resulting in the sudden death of brain cells. It is a challenging task to manage the stroke attack therapeutically despite several advances in medical and surgical domain, given the development of a permanent infarct in the brain. A majority of the patients (older than 65 years of age) who survive the first attack of a stroke depend on their physical activities of daily living on caregivers even after six months of the stroke attack. Almost half of the survivors from the stroke attack are chronically disabled, leading a crippled life, and the other half suffer from substantial cognitive deficits after the first attack, which may last a lifetime. Stroke changes the lives not only of those individuals who experienced the stroke attack but also of their families and other caregivers. A major stroke attack can be viewed as worse than death, given the suffering and physical dependency experienced by the victim. Effective prevention of stroke attack (primary prevention) continues to be the best approach for leading a quality life at an advanced age because >76% of stroke survivors lead a crippled life. Differences in stroke risk among men and women are well recognized, and certain risk factors are specific to women's health (e.g., intake of oral contraceptives and hormone replacement therapy). It would undoubtedly be helpful for the society in particular and healthcare providers in general to identify the stroke susceptible individuals for prevention of the primary stroke attack. Stroke risk assessment tools exist, but the complexities of the interactions of the vulnerabilities interlaced by age, sex, race, lifestyle, and ethnicity are incompletely captured by available global risk assessment tools. Unfortunately, an ideal stroke risk assessment tool that is simple, accurate, and widely acceptable does not exist. Each available device has limitations. Since the burden of stroke is expected to increase significantly in the near future owing to the consumption of junk food, sleep disorders, erratic and stressful lifestyle, there is an urgent need to focus on preventive strategies to avoid further discomfort and crippled life. Fortunately, there are numerous ways and strategies available for preventing stroke attacks. This review article deals with these means and

methods comprehensively, providing helpful guidelines and the relative modifications to be implemented in lifestyle for preventing primary stroke attacks.

Signs and Symptoms of a Stroke Attack: Each minute and second is crucial to save the patient's life and to minimize the damage when faced with a stroke attack. Urgent attention and therapeutic measures would reduce the extent of the brain injury. By understanding the clinical signs and symptoms of a stroke attack, one should take prompt action to rescue a life, perhaps that could be even your own.

We have abbreviated (summarized) the clinical signs and symptoms lucidly (LAST EFFORT), which is self- explanatory.

L.A.S.T. E.F.F.O.R.T

L - Legs become numb

A- Arms become numb, apoplexy

S - Slurred speech

T - Total confusion

E - Epileptic fits

F - Face drooping F - Feet dragging

O - Orientation is lost

R - Raising arms difficulty T - Trouble in seeing

The clinical signs of stroke have been listed below:

The limbs (arms and legs) often become numb on one side of the body. There is a great difficulty in raising arms or moving legs freely. The patient experiences trouble in speaking and difficulty in understanding speech. His speech becomes slurred. The patient suffering from a stroke attack is confused and cannot maintain a body posture. There is a total lack of orientation and a loss of balance. This patient has trouble walking and experiences a lack of coordination and dizziness. Often, epileptic fits coupled with blurred eyesight are observed. There is a severe headache with no identifiable cause and difficulty in expression is observed. Some patients show drooping of the face, weakness in the legs, and start dragging their feet.

Types of Strokes:

Various types of strokes may be classified into four major categories based on the origin of stroke (Fig. 1).

I) Non-Cardiogenic Stroke Cigarette and Drug of abuse –

Tobacco smoking is directly linked to an increased risk of stroke. An average smoker has twice the chance of suffering from a stroke attack than a non-smoker. Cigarette smoking potentiates the effects of other stroke risk factors, including hypertension and consumption of oral contraceptives (OCs). There is a direct relationship between occurrence of stroke attack and alcohol intake. The frequency and severity of stroke attack is linked with the amount of alcohol consumed daily. Illicit drug use is a common predisposing factor for stroke among individuals aged below 35 years. Consumption of the drugs of abuse, such as khat, cocaine, amphetamines, 3, 4-methylenedioxy-N-methylamphetamine, and heroin, are associated with an increased risk of stroke.

Infections -

Ischaemic stroke has been associated with systemic infection and linked to the outcomes of chronic or indolent infections. Stroke incidence rises during winter months because of higher chances of infection. The risk of stroke is the highest during the first three days after the diagnosis of respiratory tract infection or urinary tract infection and gradually decreases in subsequent weeks. Infective endocarditis is strongly linked with the occurrence of stroke attack. Approximately 1 in 5 cases of infective endocarditis are complicated by stroke. Intra cranial hemorrhage and degradation of the arterial wall by bacteria or septic emboli causes numerous mycotic aneurysms at distal portions of the middle and cerebral artery, and their rupture is associated with stroke, resulting in mortality. Inflammation affects the initiation, growth, and stability of atherosclerotic lesions. Furthermore, inflammation has prothrombotic effects. Chronic infections such as periodontitis, chronic bronchitis, and infection with helicobacter pylori, chlamydia pneumonia, or cytomegalovirus might promote atherosclerosis and increase the risk of stroke. There is evidence that the cumulative effect of multiple infections, rather than a single organism, may be associated with the risk of stroke and carotid atherosclerosis. SARS COV-19 infection has also been found to be associated with coagulopathy, which causes venous and arterial thrombosis leading to stroke (Fig. 1).

Chronic Conditions -

Diabetes mellitus is an independent risk factor for stroke. Both types of diabetes are associated with an increased risk of stroke because diabetic patients are more likely to end up with cardiac abnormalities (CVDs) of different patterns. Longer the duration of diabetes mellitus, higher is the risk of non-hemorrhagic stroke. Stroke is a significant complication of sickle cell disease, with the highest stroke rates in early childhood. The risk of ischemic stroke is more remarkable in young women suffering from migraine with aura. Furthermore, there was a significant risk among women aged <45 years using oral contraceptives (OCs) and indulging in smoking for developing ischemic stroke, but not so among men.

Haemorrhage -

There are two types of haemorrhagic stroke including intracerebral haemorrhage and subarachnoid haemorrhage. Intracerebral haemorrhage is the most common type of non-traumatic intracranial haemorrhage; it accounts for 80% of haemorrhagic stroke and 10-15% of all strokes. Subarachnoid haemorrhage is mainly due to saccular aneurysms though it is also associated with arteriovenous malformation, intracranial neoplasm, and side effects of some medications such as anti-coagulants.

II) Cryptogenic Stroke

When the stroke attack occurs without any identifiable cause it is termed as cryptogenic stroke. In the other words, the etyology of the stroke attack is unknown in this type of stroke.

III) Cardiogenic Stroke Atherosclerosis:

Atherosclerosis is the build-up of fatty substances in the arteries, which can lead to heart disease and stroke. About fifty percent of all strokes are caused by atherosclerosis, the same process of narrowing and hardening of the arteries that causes heart attacks. Atherosclerosis can affect the arteries in any region of the body, but it increases the risk of an ischemic stroke when it develops in the brain arteries.

Atrial Fibrillation (AF):

The relationship between AF and stroke is very complex. Atrial fibrillation (AF) describes the rapid and irregular beating of the atria (the heart's upper chambers). These fast contractions of the heart are weaker than usual. This results in slowing of the blood flow in the atrium. The blood flow becomes sluggish, and as a result, there is stagnation of blood flow, leading to the formation of blood clots. If a lump leaves the heart and travels to the brain, it can cause a stroke by blocking blood flow through the brain's arteries. Furthermore, patients with AF often have aortic arch atheroma, which are associated with an increased risk of stroke.

Hypertension:

Hypertension is one of the predominant risk factors for stroke attack. High blood pressure damages arteries throughout the body, creating conditions where they can easily burst or clog. Weakened or blocked arteries in the brain put individuals at a much higher risk for stroke. Hypertension is a significant risk factor for both cerebral infarction and ICH. The relationship between high blood pressure (BP) and stroke risk is intimate, progressive, graded, consistent, independent, predictive, and etiologically significant.

Patent Foramen Ovale (PFO):

A patent foramen ovale (PFO) is a small opening between the right and left atria of the heart. PFO is normal in most infants (fetuses), and the opening (hole) naturally closes shortly after the birth. However, in some cases, it does not close. A patent foramen ovale (PFO) can increase the risk of stroke because it allows blood clots to travel from the right atrium to the left atrium and into the brain, blocking the blood flow.

Myocardial Infarction:

Acute myocardial infarction (MI) is a long-established risk factor for ischemic stroke. The association seems causal because thrombi are often seen in overlying areas of ventricular dyskinesias.

Systolic Heart Failure:

Heart failure affects ≈26 million people worldwide. Regional stasis, a hyper-coagulable state, and undiagnosed AF seem to predispose heart failure patients to cardiac thrombus and, ultimately, stroke.

IV) Mixed Origin (Ischemic Stroke):

Ischemic stroke can be classified as having mixed origin, since it can result from cardiac as well as extra cardiac origin. Approximately 85% of the strokes are ischaemic, predominantly as the result of cerebral small vessel disease (CSVD), cardio-embolism, and/or atherosclerosis. Intracranial atherosclerosis with in- situ thrombosis is also an important mechanism of stroke, particularly in Asian and Black ethnic groups. Small vessel disease causes small subcortical infarcts (i.e., lacunar stroke) and deep intracerebral haemorrhage. Cervical artery dissection is one of the common causes of stroke in younger patients (e.g. less than 60 years), and arterial inflammation can also cause stroke. Inflammatory arteriopathy after infection is a major cause of paediatric stroke and can also occur after herpes zoster in adults. When a cerebral artery is occluded and blood flow decreases below a critical level, neuronal electrical function ceases and a clinical deficit develops. If cerebral blood flow is severely reduced, then irreversible tissue injury will ensue rapidly. Ischaemic stroke is caused by interruption of the blood supply to a part of the brain resulting in sudden loss of function, while haemorrhagic stroke is attributed to rupture of a blood vessel or an abnormal vascular structure.

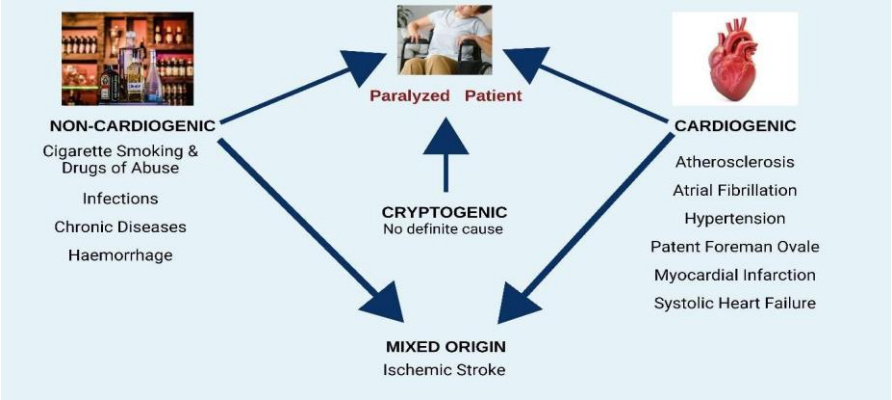

Figure. 1: Types of Strokes (based etymology)

Classification of Risk Factors Responsible for causing Stroke Attack
Risk Factors Beyond Our Control

Age: Age is the most vital determinant of a stroke attack. The risk of stroke doubles every decade above 55 years of age. The advancing age contributes adversely to cardiovascular diseases, which in turn enhances the risk of ischemic stroke and intracerebral hemorrhage (ICH). The incidence of ICH increases with age from 45 years to 85 years [1]. The Framingham Heart Study estimated the lifetime risk [2] of stroke to be less than 16 % for middle-aged adults. Younger individuals, too, face stroke attacks occasionally and suffer from lifetime disability (Fig. 2).

Gender: Women are at a higher risk of stroke than men, irrespective of the age. The findings from eight European countries revealed that the combined risk of fatal and non-fatal stroke increased by 9% per year in men and 10% per year in women [3]. Intake of oral contraceptives by adult women and adoption of hormone replacement therapy by menopausal women have been found to evoke adverse effects on women health.

Low Birth Weight: Low birth weight has been associated in several populations with a higher risk of stroke attacks in later life. Stroke mortality rates among adults in England and Wales are higher among people with lower birth weights. The mothers of these low-birth-weight babies were typically poor, malnourished, and had poor health overall [4]. The prevalence of stroke attack was more than double in those babies with low birth weights <2500g, compared with those weighing 4000 g. However, whether there is a direct link between low birth weight and stroke attack remains to be clarified.

Race and Ethnicity: Epidemiological studies support racial and ethnic differences in the risk of stroke [5]. US research shows that Hispanic and black populations are at a higher risk of stroke than white populations. The incidence of hemorrhagic stroke is significantly higher in blacks than in age-matched white persons [6]. Blacks [7] and some Hispanic/Latino Americans [8]have a higher incidence of all stroke types and mortality rates than whites. This is particularly true for young and middle-aged blacks, who have a substantially higher risk of subarachnoid hemorrhage (SAH) and ICH than whites of the same age [9]. In the Atherosclerosis Risk in Communities (ARIC) study, blacks showed a 38% higher occurrence of all types of strokes than whites [10]. American Indians have a higher incidence rate for stroke than non-Hispanic whites [11]. Whether these racial differences are genetic, environmental, or an interaction, between the two remains unclear. Possible reasons for the higher incidence and mortality rates of stroke in blacks include a higher prevalence of pre-hypertension, hypertension, obesity, and diabetes

mellitus [12]. Several studies have suggested that racial/ethnic differences may be the consequence of social determinants [13], geography [14], language, access to and use of healthcare facilities [5] and nativity [15].

Genetic Factors: A parental or family history of stroke increases the chance of an individual developing a stroke attack. Obtaining a family history can help identify susceptible persons at risk for a stroke attack. Secondly, a rare single gene mutation can contribute to pathophysiology in which stroke is the primary clinical manifestation, such as cerebral autosomal dominant arteriopathies. Further, stroke can be one of the many after-effects of multiple syndromes caused by genetic mutation, such as sickle cell anaemia. Referral for genetic counseling may be considered for patients with rare genetic causes of stroke. Furthermore, some common genetic variants, such as genetic polymorphism are associated with increased stroke risk. Genome-wide association studies have identified a wide range of genes associated with stroke. Some of these genes include Apo lipoprotein E (APOE), methylenetetrahydrofolate reductase (MTHFR), Endothelial Nitric Oxide Synthase (ENOS), Factor V Leiden (F5), Cytochrome P450 4F2 (CYP4F2), beta- Fibrinogen and Phosphodiesterase 4D (PDE4D) [16]. A genomic study on stroke showed high heritability (around 40%) for large blood vessel disease and low heritability (16.7%) for minor vessel disorders. Recent evidence suggests that studying heritability will improve understanding of stroke sub-types, improve patient management, and enable earlier and more efficient prognosis. The Framingham study showed that a documented parental history of stroke before 65 years of age was associated with a 3-fold increase in the risk of stroke in children [17]. The odds of both monozygotic twins having strokes is 1.65-fold higher than for dizygotic twins. Younger stroke patients are more likely to have a first-degree relative with stroke [18]. Women having a parental history of stroke are more likely than men to suffer from stroke attacks [19]. Personalizing medicine through genetic testing can improve the safety of primary prevention of stroke attacks. Several monogenic disorders are associated with stroke. Although rare, their effect on the individual patient is substantial because individuals carrying a mutation are likely to develop a stroke attack. Except for sickle cell disease, no treatment explicitly based on genetic factors has been shown to reduce the incidence of stroke. Fabry disease is a rare inherited disorder that can lead to ischemic stroke. It is caused by lysosomal α-galactosidase -A deficiency, which causes a progressive accumulation of globotriaosylceramide and related glycosphingolipids [20], affecting primarily small vessels in the brain and other organs. Enzyme replacement therapy appears to improve cerebral vessel function. Genetic factors could arguably be classified as potentially modifiable, but because specific gene therapy is not presently available for most conditions, genetic factors have been classified as non-modifiable. Non-invasive screening for unruptured intracranial aneurysms may be considered in patients with cervical fibromuscular dysplasia, and also in patients suffering with autosomal-dominant polycystic kidney disease, and ≥ one relative with autosomal-dominant polycystic kidney disease [21].

Risk Factors Under Our Control

Physical Inactivity: Physical inactivity is associated with numerous adverse health effects, including increased cardiovascular morbidity and mortality risk. Lack of exercise/physical activity increases an individual's chances of a stroke attack. Exercise exerts multiple benefits on one's physique, including preventing stroke attacks, heart attacks, and reducing insulin resistance. Exercise alone, however, will not lower body weight substantially without caloric restriction in obese patients [22]. Insufficient physical activity is also linked to other health issues like high blood pressure, obesity, and diabetes, all related to high stroke incidence [23]. The benefits begin from various physical activities, such as leisure-time physical activity, occupational activity and walking as an exercise. Overall, the relationship between physical activity and stroke is not influenced by age or sex [24]. Moderate-to-high-intensity physical activity was protective against the risk of ischemic stroke in men as well as women. Increased physical activity has also been associated with a lower prevalence of brain infarcts [25]. Vigorous physical exercise, regardless of sex, is associated with a decreased incidence of stroke [26].

Mechanism of Protection: The protective effect of physical activity may be partly mediated through its role in reducing diastolic as well as systolic blood pressure (BP) and controlling other risk factors for cardiovascular diseases (CVD), including diabetes mellitus, dyslipidemia and excess body weight. Physical activity also reduces plasma fibrinogen and platelet activity. It elevates plasma tissue plasminogen activator activity and HDL cholesterol concentrations. Physical activity may also exert positive health effects by increasing circulating anti-inflammatory cytokines, such as interleukin-1 receptor antagonists, interleukin-10, etc., and strengthening immunity. There is ample evidence suggesting that regular physical activity prevents stroke. Adults should engage in ≥150 min/week of moderate-intensity (e.g., fast walking) or, 75 min/week of vigorous-intensity aerobic physical activity (e.g., running) or an equivalent combination of moderate and vigorous-intensity aerobic activity. These guidelines also note that some physical activity is better than none and that adults who participate in any physical activity gain some health benefits. Cardiovascular risk is significantly reduced by performing moderate to vigorous aerobic physical exercise for at least 40 minutes daily 3 to 4 days a week to lower BP and improve lipid profile. A sedentary lifestyle is associated with several adverse health effects, including an increased risk of stroke. Incorporation of physical activity into the daily schedule, alcohol abstinence, and tiny waist circumference reduces the incidences of heart and stroke attacks in multi-ethnic communities. The risk of stroke is reduced substantially when physical activity becomes an integral part of the daily schedule of events.

Cigarette Smoking: Tobacco smoking is directly linked to an increased risk of stroke. An average smoker has twice the chance of suffering from a stroke attack than a non-smoker [27]. Smoking contributes to 15% of stroke-related mortality. Research suggests that an individual who stops smoking reduces the relative risk of stroke, while prolonged second-hand smoking confers a 30% elevation in the risk of stroke [23]. Cigarette smoking has been identified as a fatal risk factor for ischemic stroke attack. Smoking is associated with a 2 to 4-fold increased risk for subarachnoid haemorrhage (SAH). The annual number of stroke deaths attributed to smoking increased remarkably among men and women worldwide [28]. Cigarette smoking may potentiate the effects of other stroke risk factors, including hypertension and consumption of oral contraceptives (OCs). A synergistic toxic effect exists between using OCs and smoking on the risk of cerebral infarction. Exposure to environmental tobacco smoke (passive or second-hand smoke) is an established risk factor for heart disease. Community-wide or state-wide bans on smoking in public places help reduce the risk of stroke and MI [21]. Smoking contributes to increased stroke risk through both short-term impacts on the risk of thrombus generation in atherosclerotic arteries and long-term effects related to increased atherosclerosis [29]. Smoking as little as a single cigarette increases heart rate, mean BP, and cardiac burden, besides decreasing arterial distensibility. In addition to the harmful effects of smoking, both active and passive exposure to cigarette smoke is associated with the development of atherosclerotic plaque. Apart from placing individuals at enhanced risk for both thrombotic and embolic stroke, cigarette smoking triples the risk of cryptogenic stroke among individuals with a low atherosclerotic burden and no evidence of a cardiac source of emboli. The most effective preventive measures are quitting

(never) smoking and minimizing exposure to environmental tobacco smoke. Smoking cessation is associated with a rapid reduction in the risk of stroke and other cardiovascular events [30]. Cigarette smoking increases the risk of ischemic stroke and SAH, but the data on ICH are inconclusive. Counseling, in combination with drug therapy using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking (Fig. 2).

Alcohol Consumption: The relationship between stroke risk and alcohol intake follows a curvilinear pattern, with the risk related to the amount of alcohol consumed daily. Low to moderate consumption of alcohol (a maximum of 2 standard drinks for men and 1 for women daily) reduces stroke risk, whereas high intake increases it [23]. A standard drink is 12 fl oz of regular beer, five fl oz of table wine, or a 1.5 fl oz shot of 80-proof spirits. The National Institute on Alcohol Abuse and Alcoholism (NIAAA, USA) defines heavy drinking for a man as >4 drinks on any single day or >14 drinks per week, whereas, heavy drinking for a woman as > three drinks on any single day and >7 drinks per week. For individuals who choose to drink alcohol, consuming ≤2 drinks per day for men and ≤1 drink per day for non-pregnant women might be reasonable [32]. Heavy alcohol consumption can lead to multiple medical complications, including stroke. Most studies suggest a J-shaped association between alcohol consumption and the risk of total and ischemic stroke, with a protective effect in light (<151 g/wk) or moderate (151 to 300 g/wk) drinkers and an elevated risk with heavy (>300 g/wk) alcohol consumption. However, this needs a re-thought since average consumption does not fully capture individual differences in drinking patterns [31]. On the other hand, it advised to refrain from consuming alcohol even in small amounts, in Asian countries or tropical nations, where temperature never falls below five degrees Celsius, to prevent stroke attack. In contrast, a linear association exists between alcohol consumption and the risk of ICH. In a prospective cohort study of 540 patients with spontaneous ICH, heavy alcohol intake was associated with ICH at a young age (median age, 60 versus 74 years in non-abusers). Reduction or elimination of alcohol consumption in heavy drinkers is recommended for reducing the risk of stroke attack.

Mechanism: Light-to-moderate alcohol consumption is associated with higher levels of HDL cholesterol, reduced platelet aggregation, lower fibrinogen concentrations, increased insulin sensitivity, enhanced glucose metabolism, and reduced risk of ischemic stroke. On the other hand, heavy alcohol consumption increases stroke risk. Heavy alcohol consumption can result in hypertension, hypercoagulability, decreased cerebral blood flow and an increased risk of AF. Studies show an increased risk for stroke in hypertensive patients who consume alcohol [21].

Substance Abuse: Drug addiction is often a chronic, relapsing condition associated with societal and health-related hazards. Illicit drug use is a common predisposing factor for stroke among individuals aged below 35 years. US research showed that the proportion of illegal drug users among stroke patients aged 15–44 years was six times higher than among age-matched patients admitted with other severe conditions [23]. Consumption of the drugs of abuse, such as khat, cocaine, amphetamines, 3, 4-methylenedioxy-N- methylamphetamine (also known as MDMA or ecstasy), and heroin, are associated with an increased risk of stroke. Khat chewing was associated with an increased risk of stroke and death. Cathinone, the primary ingredient of the khat plant, has sympathomimetic and central nervous system–stimulating effects. The literature also includes case series of strokes associated with cannabis use; however, the mechanism remains unclear. In a prospective study of 48 young patients with ischemic stroke, 21% had multifocal intracranial stenosis associated with cannabis use. Amphetamine abuse was associated with fatal ICH but not with ischemic stroke, whereas cocaine abuse was associated with both ICH and ischemic stroke [21]. Long-term treatment strategies include medication, psychological counseling, and community-based programs to manage drug addiction and dependency effectively. Referral to an appropriate therapeutic program is advised for patients dependent on drugs of abuse, including cocaine, heroin, khat, and amphetamines [33].

Diet and Nutrition: Reckless diet (junk food) is a cause of hypertension, hyperlipidemia, obesity, and diabetes, which in turn raises the risk of stroke. Specific dietary components are well known to heighten the risk of stroke; for example, excessive salt intake is linked to high blood pressure and stroke. Nutrition plays a critical role in initiating or preventing stroke attacks. Vitamin B-12 deficiency is common among most individuals and is usually missed. It has severe neurological consequences, including an increased risk of stroke. Conversely, a diet rich in fruits and vegetables (notably, the Mediterranean diet) has decreased the risk of stroke. There is sufficient evidence to link individual dietary components with the pathogenesis of hypertension, the cardinal modifiable risk factor for ischemic stroke [21]. Specifically, dietary risk factors related to elevate BP include excessive salt intake, low potassium intake, excessive weight, high alcohol consumption, and malnutrition. A robust inverse relationship between servings of fruits and vegetables and subsequent stroke attacks has been observed in several studies [22]. A randomized, controlled trial of the Mediterranean diet in individuals at high cardiovascular risk showed that those on an energy-unrestricted Mediterranean diet supplemented by nuts (walnuts, hazelnuts, and almonds) or extra virgin olive oil had a lower risk of stroke [23]. High sodium intake was associated with an increased risk of stroke, whereas high potassium intake was associated with a reduced risk of stroke. The effects of sodium and potassium on stroke risk are likely mediated through direct effects on BP and outcomes independent of BP. Diets comprising low sodium, low-fat dairy products, reduced saturated fat, and rich in fruits and vegetables, such as the Mediterranean and DASH (Dietary approaches to stop hypertension)-style diets, reduce stroke risk by lowering blood pressure.

Obesity and Body Fat Distribution: One is said to be overweight or obese when abnormal or excessive fat accumulates around the waist or abdomen. An individual's body mass index (BMI), defined as weight in kilograms divided by the square of the height in meters, differentiates overweight persons (BMI, 25 to 29 kg/m2) from obese individuals (BMI >30 kg/m2) and morbid obesity (BMI >40 kg/m2). This description of BMI accounts best for both genders and age groups between 05-65 years [21]. The fundamental cause of obesity and overweight is an energy imbalance between calories ingested and burnt. Increasing public awareness about obesity and government initiatives have placed this health issue at the forefront. Obesity is an established risk factor for high stroke incidence and mortality. Obesity is a primary cause of many conditions like hyperlipidemia, hypertension, heart disease, and diabetes mellitus, which in turn enhances the risk of stroke attack [22]. The prevalence of obesity in the United States has tripled for children and doubled for adults since 1980. Men presenting with a waist circumference of >102 cm (40 in) and women with a waist circumference >88 cm (35 in) are categorized as having abdominal obesity. Abdominal body fat has proved to be a stronger predictor of stroke risk than BMI in men and women. Mounting evidence shows a direct relationship between stroke and obesity independent of age, lifestyle, or other cardiovascular risk factors. Obesity is associated with socioeconomic inequality in low and middle-income countries. There is no clear-cut evidence that weight loss in isolation reduces the risk of stroke. It remains to be determined whether the disparities among studies stem from choosing BMI, waist-to-hip ratio, or waist circumference as the measure of obesity. Among overweight

(BMI=25 to 29 kg/m2) and obese (BMI >30 kg/m2) individuals, weight reduction is recommended for lowering BP and, consequently, the risk of stroke [23].

Risk Factors Owing to Chronic Diseases Cardiac Abnormalities:

Cardiac abnormalities, such as dyslipidemia, atrial fibrillation (AF), hypertension, PFO, myocardial infarction (MI), valvular heart disease, cardiac tumours, and atherosclerosis, are all associated with an increased risk for stroke. Therapies to prevent stroke in many cardiac-related abnormalities should be based on well-reasoned consensus. Cardiac embolism accounts for an alarmingly high proportion of ischemic strokes and is likely to multiply several folds in coming years. Embolic stroke may often stem from atrial fibrillation, which can be diagnosed. Emerging evidence indicates that a thrombogenic atrial substrate can lead to atrial thrombo-embolism even without atrial fibrillation [21].

Dyslipidemia: Hyperlipidemia/dyslipidemia significantly contributes to coronary heart disease, but its relationship to stroke is complicated. Therefore, evaluation of lipid profile enables estimation of the risk of stroke. It is observed that low levels of HDL (<0.90 mmol/L), high levels of triglyceride (>2.30 mmol/L), and hypertension were associated with a two-fold increase in the risk of stroke-related deaths [23]. High total cholesterol levels in the blood are found to be a risk factor for ischemic stroke. Overall, epidemiological studies suggest dissimilar effects of cholesterol levels on different types of strokes. Low levels of total cholesterol increase the risk of ICH [34]; on the contrary, high levels of total cholesterol increase the risk of ischemic stroke. Therefore, a complete lipid profile must be considered for determining the overall effects of lipids as a risk factor for stroke attack. Several studies indicate the absence of an association between HDL and ischemic/ haemorrhagic stroke in contrast to the clear inverse association between HDL cholesterol and coronary heart disease. It is observed that elevated non-fasting triglyceride levels increase the risk of ischemic stroke in both, men and women. A higher risk for ischemic stroke among men and women was observed with the highest triglyceride levels (≥443 mg/dL) when compared to the lowest (<89 mg/dL) non-fasting triglyceride levels. High values for total cholesterol, low HDL levels, elevated insulin resistance, and unusually high non-fasting triglyceride levels were all responsible for adverse cardiovascular events and ischemic stroke [35]. Treatment with statins (3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors) reduces the risk of stroke in patients at high risk for atherosclerosis. The risk of all strokes was estimated to decrease by 15.6% for each 10% reduction in LDL cholesterol. The beneficial effect of statins on ischemic stroke is most likely related to their capacity to reduce progression or induce atherosclerosis regression [21]. The efficacy of statin therapy depends on the drug and the dose. For example, lovastatin at 20 mg/day is considered low-power therapy, and lovastatin at 40 mg/day is considered moderately powerful therapy. Atorvastatin at 10 mg/day is regarded as a relatively powerful therapy, and atorvastatin at 80 mg/day is considered highly powerful. Niacin increases HDL cholesterol and decreases plasma levels of lipoprotein (a) [Lp(a)]. Niacin may be considered for patients with low HDL cholesterol levels or elevated Lp(a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be used with niacin because it increases the risk of myopathy. The Coronary Drug Project found that treatment with niacin reduced mortality in men with prior MI. Fibric acid derivatives such as gemfibrozil, fenofibrate, and bezafibrate lower triglyceride levels and increase HDL cholesterol levels, thereby reducing the risk of all strokes, primarily ischemic [36]. Fibric acid derivatives may be considered for patients with hyper-triglyceridemia, but their efficacy in preventing ischemic stroke is not established [37]. Besides lifestyle change, treatment with an HMG coenzyme-A reductase inhibitor (statin) is recommended to prevent ischemic stroke in patients with dyslipidemia.

Atrial Fibrillation (AF): The relationship between AF and stroke is very complex. Atrial fibrillation (AF) describes the rapid and irregular beating of the atria (the heart's upper chambers). These fast contractions of the heart are weaker than usual. This results in slowing of the blood flow in the atrium. The blood flow becomes sluggish, and as a result, there is stagnation of blood flow, leading to the formation of blood clots. If a lump leaves the heart and travels to the brain, it can cause a stroke by blocking blood flow through the brain's arteries. Furthermore, patients with AF often have aortic arch atheroma, which are associated with an increased risk of stroke [38]. Atrial Fibrillation (AF), even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke resulting from embolism of stasis-induced thrombi forming in the left atrial appendage (LAA). AF is also an independent predictor of increased mortality. Paroxysmal AF increases stroke risk similar to sustained AF. Fortunately, there exists an essential advantage for primary stroke prevention in patients with AF because dysrhythmia can be precisely diagnosed before stroke in many patients. However, a substantial minority of AF-related stroke occurs in patients without a prior diagnosis. Once the diagnosis of AF is established, the next step is to estimate an individual's risks for cardioembolic stroke and hemorrhagic complications of anti-thrombotic therapy. AF is a prevalent, potent, and treatable risk factor for embolic stroke [21]. Surgical excision is recommended for the treatment of atrial myxomas. However, identifying which treatment offers optimal benefits and risks for a particular patient remains challenging.

i) Selecting proper treatment to reduce stroke risk in AF patients involves looking at the benefits of Vitamin K Antagonists versus Anti-Platelet Drugs: The mainstay of preventive therapy for cardioembolic stroke is to prevent clot formation in the first place. Anti-coagulants are indicated in patients with mitral stenosis, left atrial thrombus, enlarged left atria, and a prior embolic event. Warfarin therapy significantly decreases the occurrence of ischemic stroke attacks as compared to aspirin. Warfarin therapy, although it increases the risk of intracranial hemorrhage, substantially raises the clinically relevant threshold condition necessary for ischemic or hemorrhagic stroke attacks.

ii) Non–Vitamin K Antagonists: Non–vitamin K antagonist oral anti-coagulants (NOACs) work as either direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban). These drugs perform similarly to warfarin in reducing the incidence of ischemic stroke attack while significantly reducing the risk of hemorrhagic stroke and mortality in patients suffering from AF. Apixaban remarkably reduced the occurrence of ischemic stroke without precipitating hemorrhagic stroke, unlike aspirin, in AF patients. These newer anti-coagulants offer the advantages of a fixed dose, circumventing the need for frequent therapeutic drug monitoring compared to warfarin. Initially, these agents were not preferred because there was no antidote to reverse the minor bleeding episodes. Fortunately, a bleeding reversal agent (idarucizumab) has been approved for dabigatran. Furthermore, a reversal agent for the factor Xa inhibitors (andexanet) is in the pipeline for approval. Although NOACs cost more than vitamin K antagonists, such as warfarin, the net costs of laboratory monitoring and the downstream costs of strokes and hemorrhages suggest that these newer agents are reasonably cost-effective for primary and secondary stroke prevention. For patients with non-valvular as well as valvular AF, the selection of anti-thrombotic agent should be individualized based on patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient acceptance, potential for drug interactions, and other clinical characteristics. Active screening for AF in the primary care

setting in patients above 65 years of age by pulse assessment followed by ECG is helpful. For patients with non-valvular AF, smooth blood flow, and an almost no risk for hemorrhagic complication, anti-thrombotic/anti-coagulant therapy or aspirin therapy may be unnecessary.

Hypertension:

Hypertension is one of the predominant risk factors for stroke attack. High blood pressure damages arteries throughout the body, creating conditions where they can easily burst or clog. Weakened or blocked arteries in the brain put individuals at a much higher risk for stroke. Therefore, managing high blood pressure is critical to reducing stroke risk. The Seventh Joint National Committee defined hypertension as systolic blood pressure (SBP)>140 mm Hg and diastolic blood pressure (DBP) >90 mm Hg [39]. Hypertension is a significant risk factor for both cerebral infarction and ICH. The relationship between high blood pressure (BP) and stroke risk is intimate, progressive, graded, consistent, independent, predictive, and etiologically significant. BP, particularly SBP, rises with increasing age [39]. Patients who have hypertension should be treated with anti-hypertensive drugs to a target BP of <140/90 mm Hg. Individuals who are normotensive at 55 years of age have a 90% life-time risk for developing hypertension. More than two-thirds of people ≥65 years of age are hypertensive [40]. The chance of stroke increases progressively with increasing BP. Non-drug therapy or lifestyle approaches are recommended to reduce BP in non-hypertensive individuals with an elevated BP (i.e., pre-hypertension: 120 to 139 mm Hg SBP or 80 to 89 mm Hg DBP). Pharmacological treatment of pre-hypertension appears to reduce the risk of stroke [41]. Annual screening for high BP and health-promoting lifestyle modification is recommended for patients with pre- hypertension. The Seventh Joint National Committee recommends behavioral lifestyle changes as part of a comprehensive treatment strategy for hypertension. Controlling isolated systolic hypertension (SBP) ≥160 mm Hg and DBP >90 mm Hg in the elderly is also crucial [39]. We need to focus on age as a guide for therapeutic targets. We recommend lowering BP pharmacologically to <150/90 mm Hg for patients >60 years and targeting a BP of <140/85mm Hg for younger patients [41]. The International Society on Hypertension in Blacks recommended managing blood pressure of susceptible individuals in the absence of target-organ damage. The desired target BP should be <135/85 mm Hg in the presence of target-organ damage [42]. Hypertension remains the most important, well-documented, modifiable stroke risk factor. Treatment of hypertension is among the most effective strategies for preventing ischemic and hemorrhagic stroke. The benefit of regulating blood pressure in preventing stroke attack is confirmed across all age groups, including individuals above 80 years of age. Successful reduction of BP is more critical in reducing stroke risk than choosing a specific medicine. Regular BP monitoring and appropriate drug therapy, and non-drug therapy for the management of patients with hypertension is essential to prevent the stroke attacks. Possession of blood pressure apparatus at home for regular monitoring of BP is advised for better BP control.

Myocardial Infarction: Acute myocardial infarction (MI) is a long-established risk factor for ischemic stroke. The association seems causal because thrombi are often seen in overlying areas of ventricular dyskinesias. Vitamin K antagonist therapy is advised for patients suffering from myocardial infarction indicated by ST-segment elevation (STEMI) and asymptomatic left ventricular mural thrombi [21].

Valvular Heart Disease: The prevalence of moderate-to-severe valvular heart disease is ≈2.5% in the general population and 12% in those aged above 75 years. The risk of stroke seems similar regardless of the use of traditional surgical aortic valve replacement or trans-catheter aortic valve replacement. Bioprosthetic valves seem to confer a lower risk of stroke than mechanical valves, especially over the long term. It is reasonable to give warfarin and low-dose aspirin during the first three months after aortic or mitral valve replacement with a bioprosthesis. Although stroke risk has decreased over time, thromboembolic complications remain a significant cause of morbidity and mortality [21].

Aortic Arch Atheroma: Approximately 45% of individuals aged above 45 years harbour atherosclerotic plaques in their aorta, which has been associated with stroke. Large, ulcerated, non-calcified, or mobile atheroma, which occur in ≈8% of the population, have been typically linked with stroke. In clinical practice, aortic atheromas may be an under-recognized cause of stroke [21].

Atherosclerosis: Atherosclerosis is the build-up of fatty substances in the arteries, which can lead to heart disease and stroke. About fifty percent of all strokes are caused by atherosclerosis, the same process of narrowing and hardening of the arteries that causes heart attacks. Atherosclerosis can affect the arteries in any region of the body, but it increases the risk of an ischemic stroke when it develops in the brain arteries. Fibroelastosis is a rare heart disorder that affects children, causing the muscular lining of the heart chambers to thicken. It is characterized by an increase in elastic fibres, and non-elastic collagen. Surgical intervention is recommended for symptomatic fibroelastosis and asymptomatic fibroelastosis. It is more prevalent among blacks, hispanics, and asians, than whites [43].

Systolic Heart Failure: Heart failure affects ≈26 million people worldwide. Regional stasis, a hyper- coagulable state, and undiagnosed AF seem to predispose heart failure patients to cardiac thrombus and, ultimately, stroke [21]. Anti-coagulants or anti-platelet agents are reasonable for patients with heart failure who do not have AF or a previous thromboembolic event.

Metabolic Syndrome (Met S):

MetS is different from metabolic disorders, which are rare genetic conditions. A metabolic disorder is a condition that disrupts body's process of converting food into energy. This disorder can happen when: a) there is a genetic abnormality, b) the organs like pancreas or liver don't work properly, and/or c) when abnormal chemical reactions in the body alter the normal metabolic processes. Metabolic disorders can cause the bodies to produce too many or too few hormones involved for metabolism. MetS defined as a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), atherosclerosis, and diabetes mellitus. Abdominal obesity or insulin resistance (IR) has recently taken as the core manifestation of the syndrome. Its main components are dyslipidemia, arterial blood pressure (BP) elevation and dysregulated glucose homeostasis. Recently, other abnormalities, such as chronic pro- inflammatory and prothrombotic states, non-alcoholic fatty liver disease, and sleep apnea, have been added to the entity of the syndrome, making its definition even more complex. Met S is diagnosed to exist if any three of the following criteria are met -

- Elevated waist circumference (as per country-specific definitions).
- Triglycerides 150 mg/dl or greater.
- HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women.
- BPs 145/95 mm Hg or greater.
- Fasting glucose 110 mg/dl or greater.

Cardiac abnormalities inclusive of CHD, atherosclerosis, dyslipidemia, and hypertension, as major risk factors of stroke have been described above.

Diabetes Mellitus: Diabetes has two forms: Type I (i.e., insulin-dependent) and Type II (i.e., insulin- independent). Type II diabetes is much more common, accounting for most (about 90%) cases. Both types of diabetes are associated with an increased risk of stroke because diabetic patients are more likely to end up with cardiac abnormalities (CVDs) of different patterns. Diabetes mellitus is an independent risk factor for stroke. Diabetes mellitus more than doubles the risk for stroke, and ≈20% of patients with diabetes mellitus will die of stroke. Longer the duration of diabetes mellitus, higher is the risk of non-hemorrhagic stroke. It is observed that ischemic stroke patients with diabetes mellitus were younger, and were more likely to suffer from hypertension, MI, and high cholesterol. Age-specific incidence rates showed that diabetes mellitus increased ischemic stroke incidence for all ages but that risk was most prominent before 55 years of age in blacks and before 65 years of age in whites [5]. Those subjects with elevated fasting glucose had an increased stroke risk, but those with a fasting blood glucose level <126 mg/dL were not at increased risk. People with diabetes mellitus are more susceptible to atherosclerosis, hypertension, and dyslipidemia. A glycated haemoglobin goal of <7.0% has been recommended by the American Diabetes Association to prevent long-term microangiopathic complications in patients with type 2 diabetes mellitus. The decrease in glycated haemoglobin was associated with reduced risk of CVD [44].

Diabetes Mellitus and Hypertension together: More aggressive lowering of BP in patients suffering from both, diabetes mellitus and hypertension, reduces stroke incidence. Overall, aggressive BP control significantly reduced stroke risk in patients suffering from diabetes mellitus. The risk of stroke decreased by 13% for each 5-mm Hg reduction in SBP and 12% for each 2-mm Hg reduction in DBP. A comprehensive program that includes tight control of hypertension with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARB) reduces the risk of stroke in people with diabetes mellitus. Glycemic control reduces microvascular complications, but there remains no evidence that improved glycemic control reduces the incidence of stroke attack. A target of <140/90 mm Hg is recommended in patients with type 1 or type 2 diabetes mellitus.

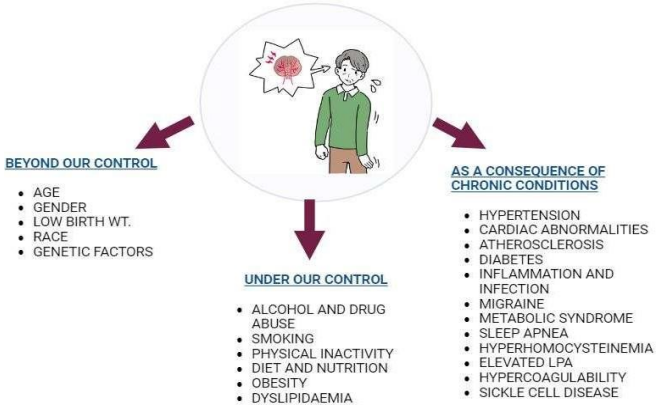

Figure. 2: Classification of Risk Factors Responsible for causing Stroke Attack

Inflammation and Infection: Ischaemic stroke has been associated with systemic infection and linked to the outcomes of chronic or indolent infections [45]. Additionally, stroke incidence rises during cold months because infections are prone to the seasonal fluctuation. The risk of stroke was highest during the first three days after the diagnosis of respiratory tract infection or urinary tract infection and gradually decreased in subsequent weeks. Infection is generally defined as recent when occurring within the preceding 1–4 weeks; however, the specific organism or pathogen causing this infection is often not identified [46, 47]. The magnitude of the association between infective endocarditis and stroke is found out to be dramatically higher than involvement of other risk factors. Approximately 1 in 5 cases of infective endocarditis are complicated by stroke. Intra cranial hemorrhage and degradation of the arterial wall by bacteria or septic emboli causer numerous mycotic aneurysms at distal portions of the middle and cerebral artery, and their rupture is associated with stroke, resulting in mortality. Inflammation affects the initiation, growth, and stability of atherosclerotic lesions. Furthermore, inflammation has prothrombotic effects. Several serum markers of inflammation, including fibrinogen, amyloid A, lipoprotein-associated phospholipase A2, and interleukin-6, have been proposed as risk markers of stroke. Several studies suggested a relationship between hs-CRP and lipoprotein-associated phospholipase A2 and stroke risk. Recent evidence indicates that elevated plasma levels of YKL-40, a product of lipid-laden macrophages, are associated with an increased risk of ischemic stroke independently of hs-CRP levels [48]. Another way to evaluate the role of inflammation as a risk factor for stroke is to examine the incidence of vascular disease in people with systemic chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). At least 50% of premature deaths in patients with RA have been attributed to CVDs. Excess risk was especially apparent in 35- to 55-year-old women with RA [49]. Chronic infections such as periodontitis, chronic bronchitis, and infection with helicobacter pylori, chlamydia pneumonia, or cytomegalovirus might promote atherosclerosis and increase the risk of stroke. There is evidence that the cumulative effect of multiple infections, rather than a single organism infection, may be associated with the risk of stroke and carotid atherosclerosis [46]. A final issue in the role of infection and inflammation in stroke relates to acute infectious diseases (such as influenza). Possible mechanisms include the induction of procoagulant acute-phase reactants (such as fibrinogen) or destabilization of atherosclerotic plaques [21]. An increase in cardiovascular deaths has long been observed in association with influenza. A retrospective study found that treatment with an antiviral agent within two days of an influenza diagnosis was associated with a 28% reduction in the risk of stroke or transient ischemic attack (TIA) over six months.

COVID-19: COVID-19 is a SARS caused by a novel coronavirus named SARS-CoV-2. In recent studies from three hospitals in Wuhan, China, up to 36% of COVID-19 patients manifested neurological symptoms. SARS-CoV-19 infection has also been found to be associated with coagulopathy, which causes venous and arterial thrombosis leading to stroke. However, treatment with antibiotics for chronic infections as a means to prevent

stroke is not recommended. Annual influenza vaccination can help lower the risk of stroke in susceptible patients

Migraine: The risk of ischemic stroke is more remarkable in young women suffering from migraine with aura. Furthermore, there was a significant risk among women aged <45 years using oral contraceptives (OCs) and indulging in smoking for developing ischemic stroke but not so among men. Nevertheless, preventive measures for avoiding a stroke attack in women patients suffering with migraine are yet to be identified. The stroke risk of migraine in men seems to be less established. Women with migraine headaches should strictly abstain from smoking. Alternatives to OCs, especially those containing estrogen, might be considered in women with active migraine headaches with aura.

Sleep Apnea: Approximately 4% of adults in the United States have sleep apnea. The diagnosis of sleep apnea is based on the apnea-hypopnea index (AHI), which describes the number of abnormal respiratory events (cessations or reductions in airflow) observed during sleep. Sleep apnea is considered to exist if the AHI is ≥ five events per hour, and an increasing AHI indicates increasing severity [21]. Several longitudinal studies have identified sleep apnea as an independent risk factor for stroke. There was a 3-fold increase in the risk of stroke for subjects with an AHI ≥20 events per hour. The unadjusted stroke risk associated with sleep apnea was higher in men than women. Although alternative therapeutic strategies exist, the mainstay of sleep apnea treatment is continuous positive airway pressure (CPAP), which improves various clinical outcomes (e.g., daytime sleepiness). As the severity of sleep apnea increases, the stroke risk also increases proportionately [50]. Treatment of sleep apnea to reduce the risk of stroke is recommended, although its effectiveness for primary stroke prevention is yet not established.

Elevated Lipoprotein (a): Lp (a) is a LDL (low-density lipoprotein) particle in which apolipoprotein B- 100 is covalently linked to the glycoprotein apoprotein (a). This lipoprotein particle's structure and chemical properties are similar to LDL's. Lp (a) contributes to atherogenesis in experimental models and is associated with an increased risk for coronary artery disease [51]. Apoprotein (a) also has structural homology to plasminogen but does not possess its enzymatic activity. Thus, it may inhibit fibrinolysis, binding to the catalytic complex of plasminogen, tissue plasminogen activator, and fibrin, thereby contributing to thrombosis [52]. Epidemiological studies have found that Lp (a) is associated with an increased risk of ischemic stroke. Niacin decreases Lp (a) levels. Elevated Lp (a) is associated with a higher risk of stroke, albeit niacin lowers Lp (a) levels, but its supplementation does not reduce the risk of stroke [21]. Using niacin, which lowers Lp (a), might help in preventing ischemic stroke attack in patients with high Lp(a).

Hypercoagulability: The acquired and hereditary hyper-coagulable states (thrombophilia) are associated with venous thrombosis, but its relationship to arterial cerebral infarction is not well established. Retrospective and prospective studies suggested a strong link between anti-cardiolipin antibodies (aCL) and first ischemic stroke attack. Inherited and acquired hypercoagulable states are associated with venous thrombosis, but their association with arterial cerebral infarction is uncertain. Young women with ischemic stroke attack have a higher concentration of anti – phospho lipid (aPL) [21].

Sickle Cell Disease: Sickle cell disease (SCD), an autosomal-recessive disorder where the abnormal gene product is an altered haemoglobin β-chain, typically manifests very early in life. Signs and symptoms associated with SCD result from chronic anaemia or acute vaso-occlusive crises, most commonly manifesting as painful episodes. Complications of SCD include acute chest syndrome, pulmonary hypertension, bacterial infections, and organ infarctions, especially stroke. Other effects include cognitive deficits related to MRI-demonstrated strokes and otherwise asymptomatic white matter hyperintensities [53]. Stroke is a significant complication of SCD, with the highest stroke rates in early childhood. The prevalence of stroke by 20 years of age is at least 11%, with a substantial number of strokes being silent strokes on brain MRI. Stroke prevention is most important for patients with homozygous SCD because most SCD-associated strokes occur in these patients. Improvements in prediction may come from incorporating additional predictors such as anterior cerebral artery velocity, blood biomarkers, variations in several genes, and nocturnal oxygen saturation. Transcranial Doppler (TCD) ultrasounds are non-invasive scans that measure blood flow to the brain. They are used to help diagnose and monitor cerebro-vascular changes in children. TCD are particularly important for children suffering with SCD. TCD screening for children with SCD is indicated starting at two years of age and continuing annually up to 16 years of age. Transfusion therapy (target reduction of haemoglobin S, <30%) effectively reduces stroke risk in those children at elevated risk. It might be reasonable to consider hydroxyurea or bone marrow transplantation in children at high risk for stroke who are unable or unwilling to be treated with periodic red cell transfusion [21].

Universal Guidelines for the Prevention of Primary Stroke Attack:

Obtaining a family history of the patients having genetic susceptibility for a stroke attack would be helpful in the preventing the attack. Genetic counseling with an expert geneticist may be considered for patients with rare genetic causes of stroke. The risk of stroke is reduced substantially when physical activity becomes an integral part of the daily schedule of events. Healthy adults should perform moderate to vigorous aerobic physical activity for at least 40 minutes per day for 4-6 days in a week to reduce blood pressure and improve lipid profile. Tobacco smoking is directly linked to an increased risk of stroke, therefore the best way to prevent a stroke attack is quitting smoking absolutely. Counseling, in combination with drug therapy using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking. Heavy drinkers should make determined efforts to gradually reduce and then abstain the alcohol intake completely. This process of quitting alcohol totally will not be achieved overnight, but the effort is worthwhile. Alcohol drinking is harmful to the developing baby in pregnant women. An appropriate therapeutic abstinence program is advised for patients dependent on drugs of abuse, including alcohol, cocaine, heroin, khat, and amphetamines. Among overweight and obese individuals, weight reduction is recommended for lowering blood pressure, thereby, diminishing the risk of stroke in turn. Besides lifestyle changes, treatment with HMG coenzyme-A reductase inhibitors (e.g. statins) is recommended to prevent ischemic stroke in patients with dyslipidemia. For patients suffering with non-valvular as well as valvular atrial fibrillation, the selection of anti-thrombotic agent should be individualized based on patient risk factors (particularly risk for intracranial hemorrhage) such as cost, tolerability, and patient acceptance. A general guideline for managing both, hypertension as well diabetes, is to maintain body weight and blood pressure under control with the use of both, appropriate medicines and lifestyle changes. Ideally, the blood pressure to the tune of 140/90 mm Hg should be taken as the upper limit in order to reduce the risk of stroke. Successful reduction of blood pressure is more critical in reducing stroke risk than choosing a specific medicine. Reduced intake of sodium and increased intake of potassium is beneficial in hypertensive patients. A diet that is rich in fruits, dry fruits, and vegetables is helpful for lowering the risk of stroke. Anti-coagulants are indicated in patients with mitral stenosis, left atrial thrombus, enlarged left atria, and a prior embolic event. Warfarin and low-dose aspirin are

indicated in patients with mechanical aortic and mitral valve replacement. Anti-coagulants or anti-platelet agents are reasonable for patients with heart failure who do not have atrial fibrillation or a previous thromboembolic event. Vitamin K antagonist therapy is advised for patients with myocardial infarction diagnosed by ST- segment elevation (STEMI) and asymptomatic left ventricular mural thrombi. Patients with chronic inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus (SLE) should be considered at increased risk of stroke. Annual influenza vaccination can help lower stroke risk in patients susceptible to stroke. Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended. Women with migraine headaches should abstain from smoking. Using niacin, which lowers Lp (a), might be reasonable for preventing ischemic stroke in patients with elevated Lp(a). Nevertheless, the authors advise all the individuals keen to prevent a primary stroke attack, should keep in mind to not treat these guidelines as applicable in hundred per cent of the cases, because of unique health characteristics of each individual.

Lacunae in Literature for the Prevention of the Stroke Attack

Several knowledge gaps complicate the application of the general guidelines in preventing primary attacks of stroke in routine clinical practice. Although the risk factors responsible for the occurrence of stroke attacks have been identified precisely, there are substantial loopholes in the primary prevention of stroke attacks. The existing literature includes observational studies, retrospective, and prospective trials that show the utility of various strategies to prevent vascular abnormalities. Atrial fibrillation is a prevalent, potent, and treatable risk factor for embolic stroke. Knowing which treatment offers optimal benefits and risks for a particular patient is still challenging. However, a few questions arise in experts' minds while dealing with patients suffering from cardiovascular diseases. The first and foremost question is, does every patient suffering from cardiac abnormality carry the risk of getting a stroke attack? If so, what constitutes zero risk, low risk, and high risk in patients relative to the extent of severity of cardiac problems? There remains a considerable controversy about the relative and absolute stroke risks in patients with AF (atrial fibrillation) with few or no concomitant risk factors. Since atrial fibrillation is a grave cause of developing a stroke attack, it becomes essential to define AF (atrial fibrillation) more clearly. Often, AF is a single episode, and the cardiac rhythm begins to return to normalcy without any treatment in a few hours. The second question arises: Which AF (atrial fibrillation) is pathological, needs medical intervention, and may prove dangerous, likely to result in a stroke attack? The third question arises whether or not the patients with severe AF need to be administered anti-coagulant therapy concomitantly with anti- arrhythmic medicines to prevent the stroke attack? However, a crucial scenario that needs to be addressed is what if a patient has a potentially abnormal Atrial Substrate with a normal ECG and no evidence of AF (atrial fibrillation). Stroke risk assessment tools exist, but the complexities of the interactions of the vulnerabilities interlaced by age, sex, race, lifestyle, and ethnicity are incompletely captured by available global risk assessment tools. Unfortunately, an ideal stroke risk assessment tool that is simple, accurate, and widely acceptable does not exist. Each available device has limitations. Despite these lacunae in literature, extensive ongoing research being carried out worldwide is expected to yield promising methods and devices to assess stroke risk precisely.

Concluding Remarks:

Stroke is a major cause of death and permanent disability globally. Stroke continues to be a devastating brain disease of enormous public health relevance with serious economic and social consequences in the present century. Almost half of the survivors from the stroke attack are chronically disabled, leading a crippled life, and the other half with substantial cognitive deficits. It is a challenging task to manage the stroke attack therapeutically despite several advances in medical and surgical domain, given the development of a permanent infarct in the brain. Therefore, it becomes crucial to prevent this deadly disease in the first place by identifying susceptible individuals and associated risk factors. Diabetes mellitus, chain-smoking, sedentary lifestyle, and cardiac abnormalities inclusive of atrial fibrillation, hypertension, and atherosclerosis remain the leading risk factors of stroke in both the developed and developing countries despite the ethnic and racial differences. Since burden of stroke is expected to increase substantially in the near future owing to the consumption of junk food, sleep disorders, erratic and stressful lifestyle, there is an urgent need to focus on preventive strategies to avoid further discomfort and crippled life. It is high time to identify and execute special measures to systematically take care of risk factors in susceptible individuals, thereby preventing the stroke attacks. Easy accessibility to healthcare facilities is necessary, but not sufficient to guarantee the prevention of primary stroke attacks. A focused approach towards preventing the stroke attacks in the first place, and integration of in-patient and out-patient services must be considered. Although the risk factors for the occurrence of stroke have been identified precisely, there are substantial loopholes in the primary prevention of stroke attacks. As health professionals, we must know that advances in preventive measures should not lead to complacency. We must acknowledge that several guidelines may become outdated and irrelevant in a few cases. Stroke-prone individuals can be identified adeptly nowadays and persuaded to adopt appropriate preventive measures, although with not much success. It is easier to convince a patient to take a pill than to expect a radical change in his or her lifestyle.

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