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Original Research Article

Stroke; A Major Cause of Cardiovascular Mortality- A Review

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Abstract

Background*:** The term stroke or cerebro-vascular accident refers to a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or resulting in death with no apparent cause other than of vascular origin. Stroke can be classified into two broad types: Ischemic and Hemorrhagic. There are multiple risk factors for stroke but systemic hypertension (HBP) is the most common yet modifiable risk factor for stroke [9]. Cardioembolic stroke is a heterogenous entity and a variety of cardiac conditions can predispose to cerebral embolism. ***Methodology: Literature search was done using google search, hinari research, PubMed and books from the author's collection. ***Results:*** The GBD study for the years 2002-2030 has estimated that there were 16 million first-ever strokes and 5.7 million deaths in 2005. The prevalence of stroke in subjects with HBP has been reported by various authors worldwide to range from 19.5% in Canada to 29% in USA and 30% in England. Cardiac diseases have been shown to increase risk of stroke. Atrial fibrillation is the most powerful and treatable cardiac precursor of stroke. The cardiovascular risk factors from the current National Cholesterol Education Project Adult Treatment Panel III (NCEP ATP III) include the non- modifiable, modifiable and emerging risk factors.

Keywords: Major Cause Cardiovascular Mortality hinari hinari.

INTRODUCTION

The term stroke or cerebro-vascular accident (CVA) refers to a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or resulting in death with no apparent cause other than of vascular origin [1, 2]. Stroke can be classified into two broad types: Ischemic and Hemorrhagic. It is most commonly caused by disruption in the flow of blood to part of the brain or occlusion of a blood vessel (ischemic-thrombotic), resulting in hypoxia and eventually necrosis but may also result from rupture of a blood vessel (hemorrhagic). About 80% of all acute strokes (AS) are caused by cerebral ischemia (CI), and the remaining 20% are caused by intra-cerebral or subarachnoid hemorrhage (SAH) [3]. Stroke is a major challenge to physicians worldwide with a high incidence, mortality, disability rates and costs [4]. The Global Burden of Disease (GBD) study ranked stroke as the second leading cause of all deaths worldwide.[5]It accounted for 5.5million deaths worldwide which is equivalent to 9.6%of all deaths. Stroke is the leading cause of serious long-term disability worldwide and it tends to affect people in their most reproductive years [1].

There are multiple risk factors for stroke but systemic hypertension (HBP) is the most common yet modifiable risk factor for stroke. Studies among Nigerians and other populations in developed countries have confirmed HBP as the most dominant risk factor for the development of stroke [6-8] which results from large artery infarction, small vessel or lacunar infarction and cardio-embolic infarction [9]. Cardioembolic stroke is a heterogenous entity and a variety of cardiac conditions can predispose to cerebral embolism. These cardiac conditions can be classified into major and minor conditions. Major conditions include; atrial fibrillation (AF), recent myocardial infarction (MI), previous MI, cardiomyopathies, intracardiac thrombus and tumours, marantic vegetations, mitral stenosis, aortic arch atheromatous plaques, endocarditis and mechanical valve prosthesis. Minor conditions include; mitral valve prolapse, mitral annulus calcification, calcified aortic stenosis, atrial septal aneurysms (ASA) and patent foramen ovale (PFO)] [10].

The purpose of this review is to identify the risk factors and potential cardiac sources of stroke.

METHODOLOGY

Literature search was done using google search, hinari research, PubMed and books from the author's collection. The data obtained were from prevalence studies, registry reports, hospital statistics, and government estimates etc. The data sources are mentioned wherever used in the text.

RESULTS AND DISCUSSION

Epidemiology of Stroke

The GBD study for the years 2002-2030 has estimated that there were 16 million first-ever strokes and 5.7 million deaths in 2005 alone. It emphasized that unless additional population wide interventions are undertaken now, the stroke burden will increase to 23 million first-ever strokes and 7.8 million deaths by 2030 [20]. The prevalence of stroke was 62 million globally in 2005 with a projected increase in burden to 77 million in 2030 [20]. Although stroke is widely believed to be a disease of the very old, almost two-thirds of the global burden of stroke occurs in people younger than 70 years and 87% of death from stroke for people of all ages in 2005 occurred in low-income and middle-income countries [21]. African Americans have a 40% greater stroke mortality than Whites and this was shown in the Reason for Geographic and Racial Differences in Stroke (REGARDS) [22] study of which only 28% is explained by traditional risk factors including socioeconomic status [22].

The association between HBP and stroke has been well documented [23]. The prevalence of stroke in subjects with HBP has been reported by various authors worldwide to range from 19.5% in Canada to 29% in USA and 30% in England [24]. The national differences in prevalence are most likely related to differences in the interaction between the main determinants of HBP (poor dietary habits, excess sodium intake, physical inactivity, obesity, excess alcohol consumption, age, gender, race and sociodemographic factors) as well as differences in the clinical systems, community programmes, environmental and policy supports for HBP prevention and management [24]. Stroke in subjects with HBP in Nigeria has been well documented. This was shown in a recent study in Abuja that had 272 participants with stroke and found HBP to be the most prevalent risk factor for stroke, being present in 82.7% participants. Obesity (32.6%), DM (23.5%), hyperlipidemia (18.4%), AF (9.2%), and cigarette smoking (7.7%) are the other risk factors found in participants.[25] This study and a meta-analysis of several studies has demonstrated a continuous and graded relationship between BP and stroke risk in many populations, with higher levels of BP conferring greater risks of stroke in hypertensive and normotensive subjects [25].

Cardiac diseases have been shown to increase risk of stroke. Atrial fibrillation is the most powerful and treatable cardiac precursor of stroke. The incidence and prevalence of AF increases with age and with each successive decade of life above the age of 55, incidence of AF doubles [26]. It is estimated that almost half of all cardio embolic strokes occur in the setting of AF. Data from three randomized controlled trials of antithrombotic therapy in AF and epidemiological studies [26] suggest that left atrial enlargement (LAE), mitral annular calcification and perhaps decreased LV systolic function were associated with an excess of stroke during follow-up. Spontaneous echocardiographic contrast and LA thrombus have also been identified as Tran's esophageal echocardiographic predictors of stroke with AF [26]. Cardiac valve abnormalities, in particular mitral stenosis, are important risk factors for stroke. Diabetes mellitus is estimated to increase the relative risk of ischemic stroke 1.8 to nearly 6 fold, independent of other risk factors. In addition, many individuals with DM have HBP and dyslipidemia, both of which are significant risk factors for stroke. Aggressive control of HBP in individuals with DM has been shown to reduce stroke incidence [27].

Pathogenesis of atherosclerosis

Atherosclerosis can involve both large and medium sized arteries diffusely. Many asymptomatic individuals have intimal lesions in their coronary or carotid arteries even in the early decades of life [28]. Post mortem studies done in Nigeria on 279 consecutive asymptomatic patients revealed that 82 (29%) had coronary atherosclerotic lesions. This study also revealed a rise in the amount of fatty streaking among the 11-20 year age group, followed by a fall in the second, third and fourth decades and a rise in the fifth and sixth decades [29].

Atherosclerosis is a multifocal, smouldering, immuno-inflammatory disease of medium-sized and large arteries fuelled by lipids. Endothelial cells, leucocytes and intimal smooth muscle cells are the major players in the development of this disease [30]. There is a progressive inflammatory disorder of the arterial wall that is characterized by focal lipid rich deposits of atheroma that remain clinically silent until they become large enough to impair tissue perfusion, or until ulceration and disruption of the lesion result in thrombotic occlusion or distal embolization of the vessel [31]. The earliest lesion in the development of atherosclerotic plaque is the fatty streak. The chronic inflammatory reaction results from a sequence of events that begins with the trapping of low density lipoprotein (LDL-c) in the subendothelial space of the artery wall. The trapped LDL-c is seeded with oxidative species released by the overlying endothelium and lipid oxidation is initiated within LDL-c particle. Some of the lipids that results lead to the activation of transcription factors that cause the expression of genes

whose protein products mediate monocyte binding, monocyte chemotaxis into the subendothelial space and conversion into macrophages. The inverse relation between high density lipoprotein (HDL-c) and atherosclerotic events may in part be due to enzymes associated with HDL-c that destroy the biologically active lipids generated in LDL-c [32]. Atherosclerosis may induce complex changes in the media that lead to arterial remodeling. Some arterial segments may slowly constrict whilst others may gradually enlarge. These changes are important because they may amplify or minimize the degree to which atheroma encroaches into the arterial lumen.[31] One contributing factor to the initiation of the plaque would appear to be hemodynamic forces and especially shear stresses [33]. Atherosclerotic lesions seem to occur at specific sites in patients with predetermined risk factors. These 'pro-atherogenic' places are, broadly speaking, at bifurcation in arteries notably carotid, aortic and femoral, and the risk of developing these lesions is greatly increased in hypertensive patients. Patients with HBP demonstrate abnormalities of vessel wall (endothelial dysfunction or damage), blood constituents (abnormal levels of hemostatic factors, platelet activation and fibrinolysis) and blood flow (rheology and flow reserve) suggesting that HBP does confer a prothrombotic or hypercoagulable state. These components appear to be related to target organ damage, long term prognosis and are altered by treatment [34].

Risk factors for stroke

The cardiovascular risk factors from the current National Cholesterol Education Project Adult Treatment Panel III (NCEP ATP III) include the non-modifiable, modifiable and emerging risk factors [35].

The non- modifiable factors are advancing age (risk of stroke doubles every decade after age 55), gender (men are more affected than women), ethnicity or race (more in Blacks, Hispanics and American Indians), previous history and family history of stroke or first degree relative with premature coronary heart disease which is coronary heart disease (CHD) in male first-degree relative <55 years or in female first-degree relative <65 years, age (men>45 years; women>55 years) and sex (men > women).

Factors modifiable by lifestyle and/or pharmacotherapy include HBP (BP >140/90mmHg or on antihypertensive medication), DM, dyslipidemia (low HDL-c, elevated total cholesterol (TC), LDL-c) and triglycerides), LVH, AF, valvular heart disease, SCD, asymptomatic carotid artery stenosis, lifestyle risk factors such as obesity (body mass index [BMI]≥30 kg/m^2), cigarette smoking, physical inactivity and an atherogenic diet, excessive alcohol consumption, illicit drug use, and psychosocial stress.

Emerging novel risk factors include lipoprotein (a), homocysteine, pro thrombotic factors (fibrinogen and plasminogen activator inhibitor-1), pro inflammatory factors (C reactive protein and fibrinogen), impaired fasting glucose and subclinical atherogenesis.

Risk factor modification

Blood pressure control: The risk of stroke increases progressively with increasing BP, independent of other factors. Both behavioural lifestyle changes and pharmacologic therapy are important parts of the comprehensive strategy recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [36]. Regarding drug choice, first-line agents for the treatment of HBP in stroke include thiazide-like diuretics, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Beta blockers are considered second-line agents, given their inferiority in preventing events despite similar reductions in BP [27].

Lipid lowering therapy: According to the 2011 AHA/ASA guidelines for secondary stroke prevention, patients with atherosclerotic ischemic stroke or TIA without known CHD should have LDL-c treated with the goal of at least a 50% reduction or a target of less than 70 mg/dL [37]. Milionis *et al.* [38] showed a 10-year risk reduction for recurrent stroke when HMG-CoA reductase inhibitors (statins) therapy was added after a first stroke. In The Stroke Prevention by Aggressive Reduction in Cholesterol levels (SPARCL) [39] trial, which looked at patients without a history of CAD and who had a serum LDL-C level of 100-180 mg/dL, found that 80 mg per day of atorvastatin reduced the risk of recurrent stroke by about 16% over 5 years [40].

Anticoagulation: Recommendations of the American College of Chest Physicians (ACCP) in cases of AF [41] are as follows: (1)Warfarin should be used for all high-risk patients and for all patients older than age 75 years regardless of their risk; (2) Low-risk patients (ie, those with only AF) and patients younger than age 65 years should be treated with aspirin; and (3)Patients aged 65-75 years without risk factors may or may not be given warfarin at the discretion of the treating clinician, as their condition may be based on other underlying disorders (eg, valvular disease, prosthetic valve replacement) [41]. Direct thrombin inhibitors and Xa inhibitors, apixaban, dabigatran, and rivaroxaban are alternatives to warfarin for high-risk patients (including those with a history of stroke) who have non-rheumatic valvular AF.

Diabetes Mellitus: Multiple studies on glycemic control in type 2 DM have shown no effect or inconclusive results in reducing stroke risk, however, aggressive control of HBP in diabetics has been found to reduce stroke incidence [42]. Angiotensin converting

enzyme inhibitors and ARBs are useful individuals with DM [43]. Several studies have shown that statins are beneficial in reducing stroke risk in diabetic individuals, especially those with other risk factors such as retinopathy, albuminuria, current smoking, or HBP [39, 44]. Therefore, treatment with statins is recommended and monotherapy with fibrates has also shown some benefit in reducing stroke risk in diabetics and may also be considered [45].

Smoking cessation: Counseling, nicotine replacement (nicotine patch, bupropion, or varenicline) and oral smoking-cessation medications should be offered to all individuals who smoke. Cessation of smoking has been shown to reduce the risk of both stroke and cardiovascular events to levels approaching those of individuals who have never smoked [46].

Obesity and body fat distribution: A meta-analysis of BMI and stroke risk reported that each 5 kg/m^2 increase in BMI was associated with a 40% increased risk of stroke mortality in individuals with BMI greater than 25 kg/m^2 [47] Studies comparing the predictive value of BMI and abdominal body fat has also found that abdominal body fat is a stronger predictor of stroke risk [48, 49]. Multivariate analyses controlling for risk factors such as HBP, DM and dyslipidemia show a consistent, though weaker, relationship between BMI and stroke risk, suggesting that the effects of adiposity are mediated in part through these other risk factors. Thus, weight reduction is recommended to reduce BP and risk of stroke in overweight and obese persons [27].

SYSTEMIC HYPERTENSION

Systemic hypertension is defined as sustained BP levels above or equal to systolic BP 140mmHg and/or diastolic BP 90mmHg in an adult [50]. Clinically, HBP is that level of BP associated with significant cardiovascular risk and institution of therapy reduces BP related morbidity and mortality. Current clinical criteria are based on the average of two or more seated BP recordings during each of two or more outpatient visits [51]. Lawes *et al*. concluded that HBP is, overall, the major contributor to the risk for CVD which are the leading cause of death worldwide in the economically developed countries, but also in the developing world, as about 80% of the attributable burden of HBP occurs in low income and middle income economies [52]. They also noted that when the total global impact of known risk factors on the overall burden of disease is calculated, 54% of stroke and 47% of ischemic heart disease (IHD) are attributable to HBP [52]. Home BP and 24 hours ambulatory BP monitoring are generally lower than clinic BP and provide a more comprehensive assessment of the vascular burden of HBP as well as being more reliable in predicting target organ damage [53]. However the international guidelines still recommend clinic or office measurements as a standard diagnostic tool [36].

The Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of HBP (JNC VII), states that the prevalence estimates worldwide for HBP may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to complications of HBP [36]. The global burden of HBP is thought to be rising because of escalating obesity, increase in salt and fat intake from consumption of processed foods, participation in jobs with minimal physical activity and increasing age of the population in developed and developing countries [53]. Systemic hypertension is the commonest CVD in sub-Saharan Africa [54]. The estimate of the overall prevalence of HBP in the adult population for sub-Saharan Africa in 2008 was 16.2%, with the urban areas having a higher burden than the rural areas [55]. The national survey in Nigeria comprised urban and rural populations and gave crude national prevalence rates of 11.1% for men and 11.2% for women (based on BP threshold of 160/90mmHg) [56]. However with the current definition of HBP based on the JNC VII guidelines, many more Nigerians can be said to be hypertensive [57].

In a community survey of a semi urban area in western Nigeria of adults aged 20 years and above, the prevalence of HBP was 36.6%, with a male to female ratio of 1.7:1, with an increasing prevalence across the age gradient from young to old adults [58]. In another community based survey in Eastern Nigeria, the prevalence was as high as 42.2%, with the majority of them being unaware of the disease [59]. In Port Harcourt metropolis, a community based study [60] showed a rather high HBP prevalence of 40.8% of which only 13.0% were aware of being hypertensive. The reason for the high prevalence in this study may be due to the fact that the subjects were mostly urban dwellers and sedentary white collar workers in government offices. This study also reported an increasing prevalence of HBP with rising age. Blood pressure control is not achieved in a significant proportion of hypertensive patients as data from the US revealed that in advanced countries only 29% of hypertensive subjects had good BP control defined as BP< 140/90mmHg [61]. A Nigerian study [62] revealed that BP control was achieved in 21.2% of patients with HBP. The authors reported that the most important factor to predict BP control was the monthly income, irrespective of the level of education of the subjects.

Pathogenesis of Systemic Hypertension

Systemic hypertension may be categorized as either primary or secondary. Primary hypertension is diagnosed in the absence of an identifiable secondary cause. Approximately 80-95% of adults with HBP have primary hypertension, whereas secondary hypertension accounts for about 5-20% of the cases [51]. The pressure required to move blood through the circulatory bed is provided by the pumping action of the heart (cardiac output) and the tone of the arteries (peripheral

resistance). Each of these primary determinants of the BP is, in turn, determined by the interaction of an exceedingly complex series of factors [63]. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 nanometers) and arterioles [51].

The pathogenesis of primary hypertension is multifactorial, involving an interaction of genetic and environmental factors [64] and although specific genetic variants have been identified in rare Monogenic forms of HBP [65], these variants are not applicable to the vast majority (>98%) of patients with primary hypertension [51]. A multitude of mechanisms interact to varying degrees in driving the hemodynamics of primary hypertension [66], some of which include (1) Abnormal renal sodium handling due to altered renal physiology; (2)Long term high sodium intake; (3) Sympathetic nervous system hyperactivity; (4) Renin Angiotensin Aldosterone activity; and (5)Vascular remodeling, arterial stiffness and endothelial dysfunction. The kidney is the culprit and victim in HBP, producing a vicious cycle of progressive renal dysfunction and HBP [53]. Regulation of body fluid volume and sodium excretion rate by the kidneys is a dominant mechanism for the long term control of BP (pressure natriuresis phenomenom). The earliest physiologic lesion of primary hypertension is diffuse, predominantly efferent but also afferent, vasoconstriction of all nephrons. This renal vasoconstriction is reversible and could lead to reduced pressure and flow in the post glomerular circulation, which may predispose to increased tubule sodium reabsorption [67]. Increased sympathetic nervous system activity increases BP and contributes to the development and maintenance of HBP through stimulation of the heart, peripheral vasculature and kidneys, causing increased cardiac output, increased vascular resistance and fluid retention [68]. Activation of the renin angiotensin aldosterone system (RAAS) is one of the most important mechanisms contributing to renal sodium retention, endothelial cell dysfunction, vascular inflammation, remodeling and eventual HBP [69].

Systemic hypertension and stroke

Systemic hypertension is associated with both CI and CH. Ischemic stroke associated with HBP is divided into three major subtypes [9]: (1)large artery infarction which typically results from embolization of atherosclerotic debris originating from the common or internal carotid arteries or from a cardiac source and it commonly affect the MCA territory [9]; (2)small vessel or lacunar infarction which is caused by atherothrombotic or lipohyalinotic occlusion of the penetrating branches of the MCA, lenticulostriate arteries,or the penetrating branches of the Circle of Willis, vertebral artery or basilar artery; and (3) cardioembolic infarction where sources of cardiogenic emboli include valvular thrombi, mural thrombi or atrial myxoma with embolization in the MCA, PCA or one of their branches and less commonly the ACA [9]. Cardioembolic stroke may be isolated, multiple and in a single hemisphere, or scattered and bilateral which indicates multiple vascular distributions, multiple bilateral infarcts can be the result of embolic showers or recurrent emboli [9]. Hypertensive intraparenchymal hemorrhage (hypertensive hemorrhage or hypertensive intracerebral hemorrhage) usually results from spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (especially the putamen), thalamus, cerebellum and pons [13]. Subarachnoid hemorrhage results from rupture of saccular berry aneurysm, vasospasm and narrowing of the arteries at the base of the brain cause symptomatic ischemia and infarction [70]. The relationship between BP and risk for first stroke or a recurrent stroke appear to be log linear throughout normal range of BP, with a 10mmHg rise in mean arterial pressure (MAP) conferring about 20-30 percent increase in stroke risk.[71] This has important implications from a public health perspective because of the high prevalence of HBP and its susceptibility to effective treatment [72]. Treating HBP is an important therapeutic target in the prevention or recurrence of stroke [73, 74]. Yet more than 50% of the hypertensive population worldwide are unaware of their condition despite the availability of therapy [75] and even in developed countries many patients with HBP remain undetected or untreated [76].

LEFT VENTRICULAR HYPERTROPHY

The prevalence of LVH among hypertensive patients varies depending on the population, mode of assessment and cut off values used. Among the Caucasians, Martinez *et al*. [77] reported that the prevalence of echocardiographic LVH was 32%, this was substantially higher than that detected by ECG (9%). This study was done on newly diagnosed hypertensive patients who may suggest that target organ damage occurs early in HBP. Zabalgoitia [78] reported a higher prevalence of LVH in patients with HBP of 62% and this could be due to the longer duration of HBP in this study. Coca *et al*. [79] also reported a high prevalence (59.2%) of LVH. All of these studies used LVM indexed to body surface area and cut off values of 134g/m^2 for men and 110g/m^2 for women. In a British multi-ethnic study, Black hypertensive subjects had greater left ventricular septal and posterior wall thickness compared to white or Indo-Asian subjects, despite similar BP and BMI and the prevalence of LVH (defined as a left ventricular mass index (LVMI) >134 g/m^2 in men and >110 g/m^2 in women) was highest amongst Black subjects [80]. In a Nigerian study to determine the prevalence of echocardiographic LVH in a treated hypertensive population, Salako *et al*. [81] reported that LVH was found in 20.8% of the

uncontrolled hypertensive group and 24.1% of the controlled hypertensive group when LVM was indexed to body surface area (also defined as a LVM >134 g/m^2 in men and >110 g/m^2 in women). These similar LVMI suggest that hypertensive subjects with apparent BP control may still be at risk of events. Studies have shown that echocardiographic LVM is said to correlate better with twenty-four hours BP recordings than casual clinic BP [82-84] Adeseye *et al*. [85] reported the prevalence of LVH among hypertensive subjects to be 12.2%, with increasing duration of HBP correlating with increased LVM and LVMI. These hypertensive patients were on antihypertensive medications which may include ACE inhibitors and ARBs which are known to attenuate cardiac modeling and this may explain the low prevalence in this study.

Pathogenesis of LVH

Left ventricular hypertrophy is mediated not only by the mechanical stress of pressure overload, but also by various neurohormonal substances that independently exert trophic effects on myocytes and non-myocytes in the heart. Trophic factors such as angiotensin II, aldosterone, norepinephrine and insulin directly promote myocyte hypertrophy and matrix deposition independent of their effects on systemic arterial pressure. These trophins stimulate the production of a series of cytokines and growth factors including transforming growth factor beta, fibroblast growth factor, and insulin growth factor that directly stimulate cardiac protein synthesis and hypertrophy. While elevated systemic arterial pressure plays a role in the pathogenesis of LVH, the extent of cardiac growth and response to increased pressure loading is not uniform among patients suggesting genetic mechanisms in cardiac hypertrophy [86]. The mechanisms by which cardiac hypertrophy may promote cardiovascular morbidity and mortality are incompletely understood. Left ventricular hypertrophy increases myocardial oxygen consumption and there is evidence that coronary blood flow reserve is impaired in hypertrophied ventricles. This supply-demand mismatch may predispose the patient to angina pectoris, MI, and sudden death. The coronary blood supply may be impaired by atherosclerosis in persons with LVH, because factors associated with myocardial hypertrophy are atherogenic [87, 88].

Prognostic implications of LVH

The presence of LVH in patients with HBP can be regarded as a paradox. Left ventricular hypertrophy attenuates the damaging effect of pressure overload on the ventricular wall and augments pump function, yet its presence is associated with a substantial increase in cardiovascular risk [86]. Vakili *et al*. [89] in a review article spanning over four decades, provided a detailed and comprehensive examination of the prognostic implications of LVH. They demonstrated a strong and consistent relationship between the presence of either ECG or echocardiographic LVH at baseline and subsequent cardiovascular morbidity and all-cause mortality. These findings persisted in the various population and ethnic groups studied. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study [90] offers the strongest evidence that treating LVH is beneficial. This study examined the prognostic implications of treating LVH detected by echocardiography. In this prospective cohort sub study, patients who had a lower LVMI during treatment with antihypertensive drugs had lower rates of cardiovascular morbidity and all-cause mortality, independent of the BP achieved or the drug treatment used. The results suggest that there may be a role not only for treating LVH, but also for monitoring for a reduction in the LVMI as a goal of therapy [90]. Angiotensin-converting enzyme inhibitors or ARBs, followed by calcium channel antagonists most rapidly facilitate the regression of LVH. A 2003 meta-analysis of antihypertensive medications in the treatment of LVH (controlling for the degree of BP lowering) showed that ARBs were the most efficacious class of agents for reducing the LVM. Specifically, ARBs decreased the mass by 13%, followed by calcium-channel blockers at 11%, ACE inhibitors at 10%, diuretics at 8%, and beta-blockers at 6% [91].

Stroke and left ventricular hypertrophy

Left ventricular hypertrophy is a strong predictor of cardiac death and studies have shown that echocardiographic LVH was present in 96 of 126 patients with stroke (76.2%) with a LVMI of 181.6 +/- 47.5 [92] which shows that LVH is common enough in stroke patients to potentially make a major contribution to their high rate of cardiac disability [93]. Left ventricular hypertrophy is associated with a two-fold increased risk of stroke and the risk was particularly profound for fatal stroke [94]. The presence of LVH confers an increased risk for subsequent major cerebrovascular event. This evidence suggests that major cerebrovascular injury can be preceeded by asymptomatic cerebrovascular damage, which parallels the onset of cardiac hypertrophy [95]. The development of atherosclerotic lesions and myocardial remodeling share common pathological mechanisms, so structural cardiac alteration indicating remodeling could be associated with the presence of atherosclerotic plaque of the aorta in patients with cerebrovascular events. Echocardiographic LAE is commonly found in hypertensive patients with features of LVH on electrocardiography. These changes are due to alterations in systolic and diastolic LV function and are a risk factor for AF and stroke [96]. Early detection and treatment of LVH could offer a window of opportunity to reduce cardiac disability in stroke patients, as regression of LVH is associated with improved prognosis, irrespective of BP changes [97, 98].

Atrial fibrillation and stroke

Non-rheumatic valvular AF is the most common cardiac disease associated with cerebral

embolism. Almost half of cardiogenic emboli in the United States occur in patients with non-rheumatic valvular AF [99]. The risk of stroke in patients with non-rheumatic valvular AF is five to seven times greater than that in controls without AF. Atrial fibrillation is a common arrhythmia that is found in 1% of persons older than 60 years to more than 5% of patients older than 69 years [99]. In the United States, approximately 5.1million people are estimated to have AF [100] while the estimate is 4.5 million people in Europe [101]. The number of people with AF is expected to more than double by 2050 [101]. Patients with AF have an average annual risk of stroke of 5% [102]. Atrial fibrillation related strokes are more likely to be severe, disabling and fatal than non-AF related strokes [103]. Many AF related strokes can be prevented with appropriate antithrombotic therapy [104]. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage, with subsequent embolization [99]. The risk of stroke can be estimated by calculating the CHADS2 score (Congestive heart failure**,** HBP, Age >75years, Diabetes, previous Stroke or TIA) [105]. Left atrial enlargement is an additional risk factor for formation of atrial thrombi.

There are two electrophysiologic mechanisms for AF: one or more automatic, triggered, or microreentrant foci, so called drivers, which fire at rapid rates and cause fibrillation-like activity; and multiple reentrant circuits meandering throughout the atrial, annihilating and reforming wavelets that perpetuate the fibrillation. In many studies, the LA contains the site of dominant frequency discharge, with a left-to-right gradient and both mechanisms may be present simultaneously [99]. Risk factors that predict stroke in patients with non-rheumatic valvular AF include a history of previous stroke or TIA, DM, history of HBP and increasing age. Patients with any of these risk factors have an annual stroke risk of at least 4 percent if untreated [12]. Antithrombotic therapy with warfarin is recommended for any patient with AF who has risk factors for stroke. A target international normalized ratio (INR) of 2.0 to 3.0 is required for stroke prevention if the individual is a good candidate for oral anticoagulation. Patients with contraindications to anticoagulation and unreliable individuals should be considered for aspirin treatment [121]. A study by Watila *et al*. [106] reported AF as the risk factor for 1.5% of all stroke admissions, while Ikeh *et al*. [107] found that the commonest observed risk factor in 21.7% of all stroke admissions was AF. Kolo *et al*. [92] reported AF as risk factor in 4% of patients with stroke. In Port Harcourt, a study conducted by Onwuchekwa et al showed AF to be the risk factor in 0.6% of all stroke admissions [108].

CARDIAC THROMBUS AND STROKE

Left atrial enlargement with circulatory stasis is a risk factor for formation of atrial thrombi[102] and development of stroke [27]. Atrial fibrillation, atrial flutter, atrial asystole and ASA are associated with LA thrombi while LV thrombi are associated with prothrombotic state [109]. Intracardiac thrombus is a common cause of cardiogenic CI and it is associated with a high recurrence of stroke but thrombus detection with therapeutic intervention can reduce the risk [110]. In Kenya, Jowi *et al*. [111] reported mitral valve stenosis with enlarged atria and intramural thrombi as the risk factor for 4.2% of all stroke admissions. Kolo *et al*. [92] in assessing the role of echocardiography in the management of stroke reported rheumatic heart disease with demonstrable clot in the LA as risk factor in 4.0% of patients with stroke and biventricular thrombi in 1.6% of these patients.

Valvular heart disease and stroke

Cardiac diseases especially rheumatic heart disease associated with AF causing embolic stroke are common determinants of stroke [3]. Valvular thrombi (e.g in mitral stenosis, endocarditis or from use of a prosthetic valve) is a source of cardiogenic embolism [109]. Mitral stenosis with resultant LAE and stasis of blood flow is associated with an increased risk of thrombus formation and systemic embolism [27]. Mitral annular calcification is also a risk factor for stroke. In the Framingham Study, mitral annular calcification was associated with a doubled rate of stroke in follow-up after adjusting for traditional risk factors for stroke. As with mitral stenosis, the presence of AF and mitral annular calcification resulted in an amplification of risk for stroke [26]. Jowi *et al*. [111] reported mitral valve stenosis and mitral valve prolapse as risk factors in 4.2% and 2.1% of all stroke admissions. Ikeh *et al.* [107] reported mitral valvulopathy (stenosis and regurgitation) of rheumatic origin as risk factor for 17.4% of all stroke admissions. In contrast Onwuchekwa *et al*. [112] found that none of all admitted stroke patients had rheumatic heart disease.

Left ventricular systolic dysfunction and stroke

Left ventricular systolic function is assessed using LV ejection fraction (LVEF), fractional shortening (FS), stroke volume, cardiac index, systolic time velocity of the mitral annulus and regional wall motion analysis [113]. Left ventricular ejection fraction is the most well accepted expression of global LV function [113]. Left ventricular dysfunction is associated with cardiovascular mortality. The mechanism underlying the association between LV dysfunction and stroke is not clear [114]. One possibility is that LV dysfunction promotes increased blood stasis in both the LV and LA, increasing the chance of thrombus formation and the risk of embolic stroke. Also, transient arrhythmias especially AF could also be involved in the stroke mechanism [114]. Allison *et al*. [114] reported that decreased LV function is associated with an increased risk of stroke after adjusting for established stroke risk factors. In their study, the association with increased stroke risk was

observed across a wide range of LV dysfunction severity and was as strong for dysfunction of mild degree as for dysfunction of moderate or severe degree. Ezekowitz *et al*. [115] found that LV systolic dysfunction was a powerful, consistent and independent predictor of stroke in patients with AF.

Regional wall motion abnormality which is a possible predictor of intracardiac thrombosis can reliably be detected by TTE [116]. Resting wall motion abnormality is associated with a higher cardiovascular event rate [117]. Yasser *et al*. [118] reported that regional wall motion abnormalities were higher in patients with recurrent stroke compared to those with the first episode of stroke.

CONCLUSION

Potential cardiac sources of embolism should be considered in all patients presenting with stroke because the recurrence of cardioembolic stroke and mortality rates are high. Furthermore the incidence of cardioembolic stroke is expected to increase in the future, mainly due to age related incidence of AF. Therefore TTE and transesophageal echocardiography where available, play a central role for the detection of cardioembolic sources for stroke and provides important information for secondary prevention.

Systemic hypertension and DM were identified as the most important risk factors for stroke. Therefore treatment of SH should be started early to prevent development and progression of LVH, which confers an increased risk for subsequent major cerebrovascular events.

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