

## Carotid and Vertebral Atherosclerosis in West African Stroke Patients: Findings from the Stroke Investigative Research and Education Network

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### Abstract

**Background:** We evaluated the characteristics of carotid and vertebral atherosclerosis in indigenous West Africans with stroke.

**Methodology:** Of the 3778 stroke patients recruited between 01/2014 and 08/2017, 1070 (28.3%) received carotid and vertebral artery evaluation with B-mode Ultrasound. Carotid and vertebral intima-media thickness (IMT) using multiple site technique were measured bilaterally and plaque frequency was determined. Descriptive and comparative analyses between stroke types and vessels were carried out.

**Results:** There were 809 (75.6%) patients with ischemic stroke. The prevalence of intima-media thickening in the study population was 84.0% (898/1070) [95% CI: 81.7-86.1], being higher in the ischemic stroke (688/809, 85.0%) [95% CI: 82.4-87.3] than in the hemorrhagic stroke group (211/261, 80.8%) [95% CI: 75.6-85.2]. Overall prevalence of plaques which was 26.1% [95% CI: 23.5-28.8], was found also to be higher in ischemic than hemorrhagic

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stroke (29.8% [95% CI: 26.7-33.0] vs. 14.6% [95% CI: 10.8-19.4],  $p < 0.05$ ). The mean IMT (carotids: 2.01±1.33 mm; vertebrals: 0.96±0.54mm,  $p < 0.001$ ) and prevalence of plaques (carotids: 8.8%; vertebrals: 1.7%,  $p < 0.001$ ) were higher in carotid than vertebral arteries. Age, hypertension, level of formal education, history of smoking, average monthly income, and family histories of hypertension and stroke were associated with intima-media thickening in the carotids (all  $p < 0.05$ ) in the ischemic stroke patients while family history of hypertension, diabetes mellitus, and level of formal education were independently associated with intima-media thickening in the carotids (all  $p < 0.05$ ) in the hemorrhagic stroke patients. No CVRF showed an independent association with the presence of plaque in the carotid and vertebral arteries both stroke types.

**Conclusions:** One off our stroke patients in our cohort had atherosclerotic plaques, with ischemic patients being twice as likely to have this burden compared to hemorrhagic patients, and carotid atherosclerosis being five times as frequent as vertebral atherosclerosis.

**Keywords:** Stroke; Carotid; Vertebral; Atherosclerosis; West Africa.

## Introduction

Stroke is associated with high morbidity and mortality, with low-middle-income countries (LMIC) being responsible for about 86% of cases globally.<sup>[1,2]</sup> Although stroke incidence has declined by over 40% in the past four decades in high-income countries (HIC), the incidence has doubled in LMICs over the same period.<sup>[3]</sup> It is also estimated that by 2030, almost eight million stroke events will occur in LMICs if no intervention is made.<sup>[1,2]</sup>

Ultrasound (USS) study of the carotid and vertebral arteries is recommended for stroke patients because detection and characterization of carotid and/or vertebral plaques has direct implications on subsequent stroke management and prognostication.<sup>[4]</sup> Atherosclerosis evidenced by increased intima-media thickness (IMT) and presence of plaques on USS is seen in up to 15-30% of carotid and 20% of the vertebral arterial system of ischemic strokes with variations according to race.<sup>[5-</sup>

<sup>10]</sup> As far as we are aware, the prevalence of carotid atherosclerosis using ultrasound has not been determined among African stroke patients. Moreover, although the pathogenesis of atherosclerosis in both carotid and vertebral arteries is likely similar<sup>[11]</sup>, there is a paucity of data on the pattern of carotid and vertebral atherosclerosis in African patients with stroke.<sup>[12]</sup> The Stroke Investigative Research and Education Network (SIREN) project is so far the largest stroke research study in sub-Saharan Africa (SSA) and provides an opportunity to fill this gap in the literature.

The objective of the study was to investigate the prevalence and pattern of USS-defined carotid and vertebral artery atherosclerosis in West African stroke patients utilizing the SIREN study population.

## Patients and Methods

The Stroke Investigative Research and Education Network (SIREN) is a case-control study whose protocols have been published elsewhere.<sup>[13]</sup> A total of 1070 participants with stroke who had ultrasound studies of their carotid and vertebral arteries between January 2014 and August 2017 were included in this sub-analysis.

The SIREN study participants who had complete data on carotid and vertebral USS were from 15 sites in West Africa. The details of the sites have been described in an earlier publication.<sup>[13]</sup> The SIREN study was approved by the institutional Ethics and Research Committee of the University of Ibadan (UI/EC/18/0706). Ethical approval was also obtained from the institutional ethics review committees of all the participating sites and informed consent was obtained from all subjects.

All participants who had complete data on carotid and vertebral USS were selected for this sub-analysis. Demographic, anthropometric and clinical data were accrued from the SIREN study questionnaire, details of which have been published with the SIREN protocol.<sup>[13]</sup> Serumfasting blood glucose and lipid profile analyses were done using uniform standard operating procedures across all

study sites. The details of blood sample collection and laboratory analyses have been previously published.<sup>[14]</sup>

### Stroke Phenotyping

The diagnosis and phenotyping of stroke were based on clinical examination and neuroimaging (Computerized Tomography or Magnetic Resonance Imaging) as published earlier.<sup>[13]</sup>

### Definition of stroke risk factors

**Hypertension:** Hypertension was defined as sustained elevated blood pressure  $\geq 140/90$  mmHg for more than 72 hours after stroke or pre-morbid history of hypertension or use of anti-hypertensive drugs before stroke/ more than 72 hours after stroke onset.

**Diabetes mellitus:** Diabetes mellitus (DM) was defined as the use of medications for DM or glycated hemoglobin (HbA1c)  $>6.5\%$  or fasting blood glucose (FBG) level  $> 7.0$ mmol/L after the post-acute phase.

**Dyslipidemia:** Dyslipidemia was defined as fasting total cholesterol  $\geq 5.2$ mmol/L or high-density lipoprotein  $\leq 1.03$ mmol/L or triglyceride  $\geq 1.7$ mmol/L or low-density lipoprotein  $\geq 3.4$ mmol/L or use of statins prior to stroke onset.

**Obesity:** Waist-hip-ratio (WHR) was used as a measure of obesity in this sub-analysis. WHR  $> 0.9$  in males or  $> 0.85$  in females was categorized as elevated.

**Alcohol intake:** Alcohol intake was categorized into low quantity intake (1-2 drinks per day for females or 1-3 drinks per day for males) or high quantity intake ( $>2$  drinks per day for females or  $> 3$  drinks per day for males). One drink of alcohol was taken to be equivalent to 80g of alcohol.

Full details of the definition of risk factors have been published earlier.<sup>[13]</sup>

### Carotid and Vertebral arterial Ultrasonographic assessment

All 15 contributing sites had a resident Radiologist

trained to perform the scans and all sites followed a standardized operating protocol for carotid and vertebral artery evaluations to reduce observer variability.<sup>[13, 15-18]</sup> In brief, a high-frequency (5-12 MHz), linear array transducer of the ultrasound machine, using standard techniques, was employed in performing the carotid and vertebral USS studies for all subjects.

### IMT measurement

Avoiding plaques, measurements of IMT were taken at the far walls of the carotid arteries at the following sites bilaterally on a longitudinal scan plane: (i) the common carotid artery (CCA), about 1.5cm proximal to the carotid bulb (CB) (ii) the CB and (iii) the proximal internal carotid artery (ICA). To obtain an optimal image, sound waves were beamed perpendicularly to the arteries to show the two parallel echogenic lines which correspond to the lumen-intima and media-adventitia interfaces. The minimum unit of IMT measurement was set at 0.1 mm. Magnified images were used for measurement to minimize error. The IMT was taken as the distance between the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface). The final IMT was the average of the 3 values at the three sites examined on each side.<sup>[15,16]</sup>

The maximal IMT of the visualized vertebral artery (VA) was also recorded on each side.

### Plaque evaluation

Plaques were identified as localized, elevated lesions in the walls of the carotid or vertebral arteries with a maximum thickness of more than 1 mm, having a point of inflection on the surface of the intima-media complex (IMC). Plaque size is the maximum thickness from the plaque border with the arterial lumen to the border with adventitia. The carotid Plaque score is the cumulative thickness of all plaques in the ICA, CB and CCA on each side.<sup>[12,17]</sup>

Resultant arterial luminal stenoses from plaques were calculated on the short-axis view using the formulae: % Diameter stenosis = normal lumen diameter minus residual lumen diameter/normal



$\text{lumen diameter} \times 100 \% \text{ Area stenosis} = \frac{\text{normal lumen area} - \text{residual lumen area}}{\text{normal lumen area}} \times 100$

Across all the 15 study sites, all measurements were taken 3 times in each segment of the carotid and vertebral arteries and the average was computed to minimize intra-observer variations.

### Data Analysis

Demographic and clinical characteristics were summarized using frequency and percentage. Mean and standard deviation was computed for continuous variables. The Chi-square test was employed to compare differences in the distribution of socio-demographic and clinical characteristics between ischemic and hemorrhagic stroke patients. Fisher's exact test was used as an alternative whenever the expected frequency count violates the assumption required for the Chi-square test. Furthermore, the student's t-test or Mann-Whitney-U test was used for comparison of Intima-media thickness and number of plaques by stroke types and cardiovascular risk factors (CVRF). Linear mixed model and generalized estimating equations were employed to investigate independent factors associated with increased IMT and the presence of plaque respectively. Analyses were done using Stata MP version 14 (StataCorp, College Station, TX). Significant  $p$  was set at  $< 0.05$ .

### Results

**Demographic and clinical characteristics of study participants:** There were 809 (75.6%) patients with ischemic stroke and 261 (24.4%) patients with hemorrhagic stroke. The age range of study subjects was 15 to 102 years with a mean of  $59.3 \pm 14.0$  years. The patients with hemorrhagic stroke were younger ( $p < 0.001$ ), while more patients with ischemic stroke had post-secondary education ( $p = 0.036$ ). More patients with hemorrhagic stroke took alcohol, particularly in high quantities ( $p = 0.049$ ). (Table 1)

Hypertension (95.1%) was the most prevalent cardiovascular risk factor amongst stroke patients, but its prevalence was similar in the 2 stroke types ( $p = 0.121$ ). However, systolic blood pressure, diastolic blood pressure, pulse pressure and mean arterial blood pressure (MAP) were significantly

higher in the patients with hemorrhagic stroke ( $p < 0.001$ ). Diabetes mellitus was commoner in patients with ischemic stroke ( $p < 0.001$ ). (Table 2).

### Prevalence of carotid and vertebral artery intima-media thickening:

Mean IMT values were  $1.99 \pm 1.18$  mm in the CCA,  $2.10 \pm 0.96$  mm in the CB,  $1.80 \pm 1.14$  mm in the ICA and  $0.96 \pm 0.52$  mm in the VA. The prevalence of intimal thickening in the study population was 84.0% (898/1070) [95% CI: 81.7-86.1], being higher in the ischemic stroke (688/809, 85.0%) [95% CI: 82.4-87.3] than in the hemorrhagic stroke group (211/261, 80.8%) [95% CI: 75.6-85.2].

### CVRFs with univariate associations with IMT in the carotid and vertebral arteries:

The CVRFs present in the stroke patients in this study showed associations with IMT mostly in the ischemic group and in the carotid arteries. The associations in the carotid arteries were mostly seen in the CB. Amongst the CVRFs, age and hypertension showed bilateral associations with IMT in all the 3 carotid artery segments (CCA, CB and ICA) which was only seen in the ischemic group. In the VAs, alcohol intake was the only CVRF that showed an association with IMT and this association was unilateral in both stroke types.

**CCA:** Ischemic stroke patients who were above 40 years of age had significantly higher IMT in their CCAs bilaterally compared to those younger than 40 years (Right:  $1.01 \pm 0.67$  vs  $0.80 \pm 0.27$ ;  $p < 0.01$  and Left:  $1.04 \pm 0.77$  vs  $0.76 \pm 0.22$ ;  $p < 0.01$ ), similar to ischemic stroke patients who were hypertensive compared to their non-hypertensive counterparts (Right:  $1.00 \pm 0.66$  vs  $0.76 \pm 0.25$ ;  $p < 0.01$  and Left:  $1.03 \pm 0.76$  vs  $0.79 \pm 0.26$ ;  $p < 0.01$ ) (Tables 3). Hemorrhagic stroke patients who were of the male gender and dyslipidaemic had higher IMT in the left CCA compared to the female gender ( $0.97 \pm 0.32$  vs  $0.94 \pm 0.26$ ;  $p = 0.036$ ) and non-dyslipidaemic ( $0.98 \pm 0.32$  vs  $0.91 \pm 0.29$ ;  $p = 0.044$ ) counterparts respectively.

**CB:** Ischemic stroke patients who were above 40 years of age had significantly higher IMT in their CCAs bilaterally compared to those younger than 40 years (Right:  $1.11 \pm 0.77$  vs  $0.00 \pm 0.00$ ;  $p < 0.01$  and

Left:  $1.07 \pm 0.59$  vs  $0.90 \pm 0.32$ ;  $p < 0.01$ ), similar to ischemic stroke patients who were hypertensive compared to their non-hypertensive counterparts (Right:  $1.10 \pm 0.69$  vs  $0.90 \pm 0.32$ ;  $p < 0.01$  and Left:  $1.07 \pm 0.58$  vs  $0.89 \pm 0.31$ ;  $p = 0.02$ ). Ischemic stroke patients who had a history of high alcohol intake had significantly higher IMT in the right CB compared to those with a history of low or no alcohol intake ( $1.37 \pm 1.09$  vs  $1.29 \pm 1.13$  vs  $1.02 \pm 0.34$  respectively;  $p = < 0.001$ ). The IMT was higher in the left CB of ischemic stroke patients if they were of the male gender ( $1.10 \pm 0.69$  vs  $1.00 \pm 0.34$  respectively;  $p = 0.019$ ) similar to ischemic stroke patients that were diabetic ( $1.11 \pm 0.67$  vs  $1.02 \pm 0.49$  respectively;  $p = 0.041$ ) (Table 4).

**ICA:** Ischemic stroke patients who were above 40 years of age had significantly higher IMT in their CCAs bilaterally compared to those younger than 40 years (Right:  $0.94 \pm 0.72$  vs  $0.71 \pm 0.35$ ;  $p < 0.01$  and Left:  $0.93 \pm 0.73$  vs  $0.72 \pm 0.27$ ;  $p < 0.01$ ), similar to ischemic stroke patients who were hypertensive compared to their non-hypertensive counterparts (Right:  $0.93 \pm 0.71$  vs  $0.71 \pm 0.29$ ;  $p < 0.01$  and Left:  $0.92 \pm 0.72$  vs  $0.73 \pm 0.30$ ;  $p = 0.02$ ) (Table 5).

**VA:** Ischemic stroke patients who had a history of high alcohol intake had significantly higher IMT in the left VA compared to those with a history of low or no alcohol intake ( $0.83 \pm 0.32$  vs  $0.61 \pm 0.35$  vs  $0.47 \pm 0.30$  respectively;  $p = 0.0014$ ) (Table 6). Hemorrhagic stroke patients who had a history of low alcohol intake had higher IMT in the right VA compared to those with a history of high or no alcohol intake ( $0.67 \pm 0.42$  vs  $0.63 \pm 0.21$  vs  $0.47 \pm 0.21$  respectively;  $p = 0.016$ ) (Table 6).

#### ***CVRFs with independent associations with abnormal intimal media thickening in the stroke types***

The CVRFs present in the stroke patients in this study showed independent associations with intima-media thickening mostly in the ischemic group. The independent associations were also mostly in the carotid arteries.

**Ischemic stroke:** In the ischemic stroke patients, age and level of education were independently associated with having an abnormal intima-media

thickening of the 3 carotid segments (CCA, CB, ICA), although the association was negative for the level of education. Ischemic stroke patients above 40 years of age were almost five (AOR = 4.59; 95% CI = 2.32 - 9.06), three (AOR = 2.48; 95% CI = 1.41 - 4.36), and two (AOR = 2.39; 95% CI = 1.22 - 4.67) times more likely to have an abnormal intima-media thickening of the CCA, CB and ICA respectively compared to their counterparts less than 40 years in age. Ischemic stroke patients who had secondary education and above were however less likely to have abnormal intima-media thickening of the CCA (AOR = 0.61; 95% CI = 0.38 - 0.96 for secondary education and AOR = 0.55; 95% CI = 0.36 - 0.85 for tertiary education) and CB (AOR = 0.53; 95% CI = 0.31 - 0.89 for secondary education and AOR = 0.52; 95% CI = 0.32 - 0.85 for tertiary education), while only those ischemic patients that attained up to tertiary education were less likely in the ICA (AOR = 0.51; 95% CI = 0.31 - 0.85). While hypertension (AOR = 3.13; 95% CI = 1.38 - 7.09) increased the likelihood of abnormal intima-media thickening of the CCA by three times, a family history of hypertension (AOR = 1.50; 95% CI = 1.01 - 2.23) increased the likelihood of abnormal intima-media thickening of the CB by almost twice. Ischemic stroke patients who ever smoked or took alcohol were about twice more likely to have abnormal intima-media thickening of the CB. Furthermore, ischemic stroke patients with a family history of stroke were twice at risk of intima-media thickening of their CCA (AOR = 1.83; 95% CI = 1.20 - 2.77) and ICA (AOR = 1.89; 95% CI = 1.19 - 2.98). Those who earned above 500 dollars were however less likely to have abnormal intima-media thickening of the CB (Supplementary Table 1).

**Hemorrhagic stroke:** In the hemorrhagic group, family history of hypertension increased the likelihood of abnormal intima-media thickening of the CCA twice (AOR = 1.86; 95% CI = 1.04 - 3.30) and ICA (AOR = 0.38; 95% CI = 0.15 - 0.93). Ischemic stroke patients who were diabetic (AOR = 1.94; 95% CI = 1.00 - 3.77) were also twice more likely to have abnormal intima-media thickening of their CCA. Family history of stroke (AOR = 4.88; 95% CI = 1.84 - 12.93) increased the likelihood of intima-media thickening of the CB by five times. Hemorrhagic stroke patients who attained tertiary



education (AOR = 2.48; 95% CI = 1.41 - 4.36) were less likely to have abnormal intima-media thickening of their CB (Supplementary Table 2).

**Prevalence of carotid and vertebral artery plaques:**

The overall prevalence (95% CI) of plaques in the study population was 26.1% (279/1070) [95% CI: 23.5-28.8]. Presence of plaque was significantly more in ischemic stroke (241/809, 29.8%) [95% CI: 26.7-33.0] compared with hemorrhagic stroke (38/261, 14.6%) [95% CI: 10.8-19.4] patients ( $p < 0.05$ ). Plaques were recorded in all the 3 segments of the carotid arteries while no plaque was recorded in the left VA.

**CVRFs with univariate associations with the frequency of plaque in the carotid and vertebral arteries:**

**CCA:** Ischemic stroke patients who had dyslipidaemia had a higher frequency of plaques compared to those without dyslipidaemia in their CCA bilaterally ( $36 \pm 7.96$  vs  $9 \pm 3.78$ ;  $p = 0.034$  and  $37 \pm 8.28$  vs  $9 \pm 3.86$ ;  $p = 0.03$  on the right and left respectively). Ischemic stroke patients with raised waist-hip-ratio (WHR) had a higher frequency of plaques compared to their counterparts with normal WHR ( $28 \pm 5.1$  vs  $11 \pm 10.4$ ;  $p = 0.035$ ) in the CCA (Table 3).

**CB:** Ischemic stroke patients above 40 years of age had a significantly higher frequency of plaques compared to those younger than 40 years in the CB bilaterally ( $94 \pm 15.36$  vs  $2 \pm 3.45$ ;  $p = 0.013$  and  $81 \pm 13.50$  vs  $0 \pm 0.00$ ;  $p = 0.04$  on the right and left respectively). Stroke patients with raised waist-hip-ratio (WHR) generally had a higher frequency of plaques compared to their counterparts with normal WHR ( $86 \pm 12.1$  vs  $25 \pm 18.7$ ;  $p = 0.039$ ) in the right CB (Table 4). Dyslipidemic stroke patients generally had a higher frequency of plaques relative to those with a normal lipid profile ( $52 \pm 9.35$  vs  $44 \pm 14.24$ ;  $p = 0.028$ ) in the CB. Hemorrhagic stroke patients have a higher frequency of plaques in their left CB compared to the non-hypertensive hemorrhagic stroke patients ( $13 \pm 6.40$  vs  $2 \pm 28.57$ ;  $p = 0.025$ ) (Table 4).

**ICA:** Female stroke patients generally had a higher frequency of plaques relative to their male

counterparts ( $34 \pm 9.26$  vs  $25 \pm 5.48$ ;  $p = 0.032$ ) in the ICA (Table 5). In the left ICA, Ischemic stroke patients with DM had a higher frequency of plaques compared to their counterparts without DM ( $26 \pm 10.57$  vs  $18 \pm 4.59$ ;  $p = 0.004$ ) (Table 5).

**VA:** While no plaque was found in the left VA of the hemorrhagic stroke patients, there was no significant association between the CVRFs and frequency of plaques seen in the left VA of the ischemic group and the right VA of both stroke types (Table 6).

**CVRFs with independent associations with the presence of plaques in the stroke types**

Age and level of education commonly showed associations with the presence of plaques in the CCA (AOR = 4.42; 95% CI = 1.06 – 18.48), CB (AOR = 3.70; 95% CI = 1.58 – 8.67) and ICA (AOR = 5.37; 95% CI = 1.26 – 22.87) of stroke patients generally. Diabetes mellitus showed association with presence of plaques in the CCA (AOR = 1.87; 95% CI = 1.15 – 3.03) and ICA (AOR = 1.67; 95% CI = 1.03 – 2.72). Dyslipidaemia (AOR = 1.90; 95% CI = 1.09 – 3.30) showed association with presence of plaque in the CCA. Stroke patients with any form of education were less likely to have plaques in their CB (AOR = 0.52; 95% CI = 0.30 – 0.91 for primary, AOR = 0.50; 95% CI = 0.30 – 0.84 for secondary and AOR = 0.56; 95% CI = 0.34 – 0.91 for tertiary) and ICA (AOR = 0.49; 95% CI = 0.24 – 0.97 for primary, AOR = 0.30; 95% CI = 0.15 – 0.62 for secondary and AOR = 0.30; 95% CI = 0.15 – 0.58 for tertiary) while those with primary education (AOR = 0.43; 95% CI = 0.20 – 0.96) were less likely in their CCA. The CVRFs did not show any independent association with the presence of plaques in the vertebral arteries of stroke patients.

**Ischemic stroke:** No CVRF showed association with the presence of plaques in the carotid and vertebral arteries in the ischemic stroke group.

**Hemorrhagic stroke:** Similarly, no CVRF showed association with the presence of plaques in the carotid and vertebral arteries in the hemorrhagic stroke group.

**Table 1:** Socio-demographic characteristics of study participants

Variable	Ischemic stroke	Hemorrhagic stroke	All stroke	Test statistics	p value
Age: Mean (SD)	60.9 (13.8)	54.4 (13.7)	59.2 (14.0)	6.662	<b>&lt;0.001</b>
Gender: n (%)					
Male	452 (56.1)	158 (60.5)	612 (57.2)	1.573	0.210
Female	355 (43.9)	103 (39.5)	485 (42.8)		
Type of domicile: n (%)					
Rural/semi-urban	275 (34.2)	105 (40.7)	380 (35.8)	3.634	0.057
Urban	530 (65.8)	153 (59.3)	683 (64.2)		
Marital status: n (%)					
Not currently married	207 (25.6)	57 (21.8)	264 (24.7)	1.492	0.222
Currently married	602 (74.4)	204 (78.2)	806 (75.3)		
Formal education: n (%)					
None	127 (15.8)	38 (14.8)	165 (15.6)	8.521	<b>0.036</b>
Primary	146 (18.2)	47 (18.3)	193 (18.2)		
Secondary	211 (26.3)	90 (35.0)	301 (28.4)		
Higher	319 (39.7)	82 (31.9)	401 (37.8)		
Average total monthly income ≤ \$500h (%)	706 (87.3)	228 (87.4)	934 (87.3)	0.001	0.970
Family history of hypertension: n (%)	598 (73.9)	176 (67.4)	774 (72.3)	0.274	0.600
Family history of diabetes mellitus: n (%)	153 (15.2)	33 (12.6)	156 (14.6)	1.039	0.308
Family history of stroke: n (%)	147 (18.2)	40 (15.3)	187 (17.5)	1.107	0.293
History of alcohol: n (%)	254 (31.4)	90 (34.5)	344 (32.2)	0.862	0.353
Never use	545 (77.6)	169 (74.5)	714(76.9)		
Ever use & Low quantity	140 (19.4)	45 (19.8)	185(19.9)		
Ever use & high quantity	17 (2.4)	13 (5.7)	30(3.2)	6.031	<b>0.049</b>
History of smoking: n (%)	75 (9.3)	16 (6.1)	91 (8.5)	2.501	0.114
Family history of heart disease: n (%)	28 (3.5)	9 (3.5)	37 (3.5)	0.0001	0.992

Significant  $p < 0.05$  (in bold)

**Table 2:** Basic clinical characteristics of study participants

Variable	Ischemic stroke	Hemorrhagic stroke	All stroke	Test statistic	p value
Handedness (Right): n (%)	732 (92.8)	228 (90.1)	960 (92.1)	2.078	0.361
Hypertension: n (%)	765 (94.6)	253 (96.9)	1018 (95.1)	2.405	0.121
Diabetes Mellitus: n (%)	316 (39.1)	56 (21.5)	372 (34.8)	26.967	<b>&lt;0.001</b>
Dyslipidemia: n (%)	542 (67.3)	168 (64.4)	710 (66.6)	0.777	0.378
Height (m): mean (SD)	165.4 (8.1)	164.6 (8.1)	165.2 (8.1)	1.351	0.178
Weight (Kg): mean (SD)	72.5 (14.1)	72.9 (13.9)	72.6 (14.1)	0.434	0.665
Waist-Hip-Ratio: mean (SD)	0.94 (0.07)	0.95 (0.08)	0.95 (0.08)	0.782	0.435
SBP (mmHg): mean (SD)	153.3 (29.6)	169.1 (33.2)	157.3 (31.3)	6.738	<b>&lt;0.001</b>
DBP (mmHg): mean (SD)	92.2 (16.2)	103.1 (19.2)	95.0 (17.7)	8.118	<b>&lt;0.001</b>
Heart rate (bpm): mean (SD)	88.0 (17.5)	86.8 (18.3)	87.7 (86.4)	0.825	0.409
Pulse pressure (mmHg): mean (SD)	61.1 (20.6)	66.0 (20.3)	62.3 (20.6)	3.32	<b>0.001</b>
MAP (mmHg): mean (SD)	91.8 (22.7)	100.4 (23.7)	94.0 (23.2)	5.023	<b>&lt;0.001</b>
HDL (mmol/L):Median (Q1, Q3)	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	0.951	0.343
LDL (mmol/L):Median (Q1, Q3)	3.0 (2.2, 3.9)	3.1 (2.4, 4.0)	3.1 (2.3, 3.9)	0.849	0.397
TC (mmol/L):Median (Q1, Q3)	4.8 (3.9, 5.7)	4.9 (4.1, 6.0)	4.8 (4.0, 5.8)	1.354	0.177
TG (mmol/L):Median (Q1, Q3)	1.2 (0.9, 1.6)	1.0 (0.8, 1.4)	1.1 (0.8, 1.6)	1.609	0.109
Platelet (μL <sup>-1</sup> ): Median (Q1, Q3)	207 (168, 262)	201 (148, 254)	206 (160, 261)	0.911	0.364
INR: Median (Q1, Q3)	1.2 (1.1, 1.7)	1.2 (1.1, 1.3)	1.2 (1.1, 1.6)	1.399	0.167
Creatinine (μmol/L): Median (Q1, Q3)	88.4 (70.7, 114.9)	91.0 (70.7, 132.6)	88.7 (70.7, 118.0)	1.022	0.982
Uric acid (μmol/L):Median (Q1, Q3)	320.0 (260.0, 420.0)	340 (250.0, 420.0)	326.0 (259.5, 420.0)	0.997	0.320

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, bpm: beats per minute, MAP: Mean Arterial Pressure, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TC: Total Cholesterol, TG: Triglyceride, INR: International Normalized Ratio; Significant  $p < 0.001$  (in bold);  $Q_1$  and  $Q_3$  are first and third quartile respectively

**Table 3:** IMT and plaque frequency in the Common Carotid Artery

	Maximum IMT (mm): Mean(SD)						Plaque frequency: n(%)					
	Right			Left			Right			Left		
	Ischemic stroke	Hemorrhagic stroke	All stroke	Ischemic stroke	Hemorrhagic stroke	All stroke	Ischemic stroke	Hemorrhagic stroke	All Stroke	Ischemic stroke	Hemorrhagic stroke	All Stroke
<b>Age</b>												
≤40 years	0.80(0.27)		0.85(0.28)	0.76(0.22)	0.92(0.27)	0.83(0.25)	1(1.67)	0(0.00)	1(1.05)	2(3.39)	0(0.00)	2(2.13)
>40 years	1.01(0.67)	0.95(0.25)	1.00(0.60)	1.04(0.77)	0.96(0.30)	1.02(0.69)	44(6.97)	4(2.25)	48(5.93)	44(7.07)	10(5.59)	54(6.74)
<i>p</i> -value	<b>&lt;0.001</b>	0.515	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.279	<b>&lt;0.001</b>	0.111	0.371	0.052	0.281	0.373	0.111
<b>Gender</b>												
Male	1.02(0.68)	0.94(0.26)	1.00(0.60)	1.03(0.68)	0.97(0.32)	1.02(0.61)	23(5.91)	3(2.33)	26(5.02)	22(5.73)	7(5.43)	29(5.65)
Female	0.96(0.61)	0.95(0.27)	0.96(0.55)	1.00(0.82)	0.94(0.26)	0.98(0.73)	22(7.21)	1(1.18)	23(5.90)	24(8.00)	3(3.49)	27(6.99)
<i>p</i> -value	0.201	0.813	0.251	0.541	<b>0.036</b>	0.422	0.49	0.544	0.562	0.239	0.509	0.41
<b>Waist-Hip Ratio</b>												
Not raised	1.07(0.84)	0.95(0.26)	1.04(0.75)	1.08(0.77)	1.00(0.31)	1.06(0.69)	11(10.4)	0(0.00)	11(8.2)	7(6.7)	0(0.0)	7(5.3)
Raised	0.99(0.63)	0.95(0.26)	0.98(0.56)	1.01(0.76)	0.94(0.27)	0.99(0.68)	28(5.1)	03(1.7)	31(4.3)	31(5.7)	8(4.6)	39(5.5)
<i>p</i> -value	0.297	0.914	0.289	0.357	0.282	0.249	<b>0.035</b>	0.631	0.055	0.691	0.604	0.931
<b>Hypertension</b>												
Yes	1.00(0.66)	0.95(0.26)	0.99(0.59)	1.03(0.76)	0.96(0.29)	1.01(0.68)	45(6.89)	4(1.93)	49(5.70)	45(6.99)	10(4.81)	55(6.46)
No	0.76(0.25)	0.78(0.34)	0.77(0.27)	0.79(0.26)	0.82(0.36)	0.80(0.27)	0(0.00)	0(0.00)	0(0.00)	1(2.50)	0(0.0)	1(2.13)
<i>p</i> -value	<b>&lt;0.001</b>	0.195	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.296	<b>&lt;0.001</b>	0.082	0.71	0.089	0.272	0.552	0.232
<b>Diabetes mellitus</b>												
Yes	0.99(0.61)	0.99(0.25)	0.99(0.57)	1.03(0.76)	1.04(0.38)	1.03(0.72)	23(8.61)	1(2.50)	24(7.82)	20(7.69)	3(7.14)	23(7.62)
No	1.00(0.68)	0.93(0.26)	0.98(0.59)	1.01(0.73)	0.93(0.27)	0.99(0.63)	22(5.15)	3(1.72)	25(4.16)	26(6.13)	7(4.05)	33(5.53)
<i>p</i> -value	0.869	0.103	0.735	0.68	0.057	0.309	0.072	0.744	0.021	0.429	0.393	0.221
<b>Dyslipidemia</b>												
Yes	0.99(0.57)	0.93(0.26)	0.97(0.51)	1.00(0.66)	0.98(0.32)	1(0.59)	36(7.96)	4(2.92)	40(6.79)	37(8.28)	8(5.84)	45(7.71)
No	1.01(0.80)	0.97(0.26)	1.00(0.70)	1.05(0.90)	0.91(0.29)	1.02(0.78)	9(3.78)	0(0.00)	9(2.86)	9(3.86)	2(2.56)	11(3.54)
<i>p</i> -value	0.634	0.298	0.515	0.428	<b>0.044</b>	0.714	<b>0.034</b>	0.299	<b>0.013</b>	<b>0.03</b>	0.273	<b>0.014</b>
<b>Smoking</b>												
Yes	0.97(0.32)	1.03(0.18)	0.98(0.30)	1.05(0.41)	0.96(0.26)	1.03(0.38)	2(3.03)	0(0.00)	2(2.53)	2(3.13)	1(8.33)	3(3.95)
No	1.00(0.68)	0.94(0.27)	0.99(0.61)	1.02(0.78)	0.96(0.30)	1.00(0.69)	43(7.05)	4(2.03)	47(5.82)	43(7.14)	9(4.55)	52(6.50)
<i>p</i> -value	0.543	0.103	0.922	0.54	0.975	0.49	0.213	0.604	0.222	0.223	0.55	0.381
<b>Alcohol</b>												
Never use	0.98(0.61)	0.95(0.28)	0.97(0.55)	0.99(0.74)	0.96(0.32)	0.98(0.67)	36(7.8)	4(2.9)	40(6.7)	37(8.1)	8(5.8)	45(7.6)
Ever low	1.06(0.82)	0.97(0.18)	1.04(0.72)	1.11(0.84)	0.98(0.26)	1.08(0.74)	5(4.0)	0(0.0)	5(3.0)	6(4.8)	2(5.3)	8(4.9)
Ever high	0.93(0.33)	0.98(0.38)	0.95(0.34)	1.00(0.24)	0.96(0.33)	0.98(0.28)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
<i>p</i> -value	0.407	0.862	0.389	0.277	0.927	0.259	0.332	0.645	0.1347	0.420	1.000	0.341



**Table 4: IMT and plaque frequency in the Carotid Bulb**

	Maximum IMT (mm): Mean(SD)						Plaque frequency: n(%)					
	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke
<b>Age</b>												
≤40 years	1.11(0.71)	1.10(0.75)	0.99(0.53)	0.90(0.32)	1.00(0.34)	0.94(0.88)	2(3.45)	4(10.81)	6(6.32)	0(0.00)	1(2.94)	1(1.12)
>40 years	1.06(0.68)	1.03(0.56)	1.09(0.68)	1.07(0.59)	1.02(0.38)	1.06(0.54)	94(15.36)	15(8.33)	109(13.76)	81(13.50)	14(8.00)	95(12.26)
<i>p</i> -value	<b>&lt;0.001</b>	0.562	0.077	<b>&lt;0.001</b>	0.793	<b>0.002</b>	<b>0.013</b>	0.627	<b>0.041</b>	<b>0.004</b>	0.296	<b>0.002</b>
<b>Gender</b>												
Male	1.12(0.80)	0.97(0.30)	1.08(0.71)	1.10(0.69)	1.02(0.36)	1.08(0.63)	44(11.64)	11(8.46)	55(10.83)	41(11.05)	7(5.51)	48(9.64)
Female	1.06(0.68)	1.14(0.86)	1.07(0.59)	1.00(0.34)	1.01(0.39)	1.01(0.35)	52(17.63)	8(9.09)	60(15.67)	40(13.94)	8(9.64)	48(12.97)
<i>p</i> -value	0.176	0.068	0.865	<b>0.019</b>	0.872	<b>0.026</b>	0.028	0.872	0.033	0.264	0.256	0.121
<b>Waist-Hip Ratio</b>												
Not raised	1.21(1.22)	0.99(0.27)	1.16(1.08)	1.07(0.69)	1.08(0.35)	1.07(0.63)	21(20.4)	4(12.9)	25(18.7)	14(13.6)	2(6.9)	16(12.1)
Raised	1.07(0.56)	1.05(0.65)	1.06(0.57)	1.05(0.56)	0.99(0.38)	1.03(0.52)	71(13.3)	15(8.5)	86(12.1)	65(12.4)	13(7.6)	78(11.2)
<i>p</i> -value	0.223	0.342	0.089	0.710	0.196	0.463	0.061	0.430	<b>0.039</b>	0.740	1.00	0.766
<b>Hypertension</b>												
Yes	1.10(0.69)	1.05(0.60)	1.09(0.67)	1.07(0.58)	1.02(0.36)	1.05(0.54)	93(14.69)		112(13.27)	79(12.78)	13(6.40)	92(11.21)
No	0.90(0.32)	0.79(0.37)	0.89(0.33)	0.89(0.31)	1.05(0.61)	0.92(0.37)	3(7.50)		3(6.38)	2(5.00)	2(28.57)	4(8.51)
<i>p</i> -value	<b>0.001</b>	0.094	<b>&lt;0.001</b>	<b>0.002</b>	0.864	<b>0.017</b>	0.207		0.17	0.147	<b>0.025</b>	0.567
<b>Diabetes mellitus</b>												
Yes	1.13(0.74)	1.194(0.98)	1.14(0.77)	1.11(0.67)	1.06(0.34)	1.11(0.64)	38(14.62)	6(13.64)	44(14.47)	34(13.71)	3(7.50)	45(10.61)
No	1.07(0.64)	1.00(0.45)	1.05(0.59)	1.02(0.49)	1.01(0.38)	1.02(0.46)	58(14.04)	71(7.47)	71(12.10)	47(11.46)	12(7.06)	36(15.58)
<i>p</i> -value	0.246	0.179	0.059	<b>0.041</b>	0.388	<b>0.022</b>	0.836	0.195	0.315	0.395	0.922	0.065
<b>Dyslipidemia</b>												
Yes	1.10(0.73)	1.02(0.58)	1.08(0.70)	1.06(0.56)	1.03(0.41)	1.05(0.53)	64(14.75)	11(7.97)	75(13.11)	45(10.61)	7(5.30)	52(9.35)
No	1.08(0.57)	1.08(0.63)	1.08(0.59)	1.07(0.59)	1.00(0.31)	1.05(0.53)	32(13.62)	8(10.00)	40(12.70)	36(15.58)	8(10.26)	44(14.24)
<i>p</i> -value	0.688	0.432	0.998	0.819	0.592	0.996	0.691	0.609	0.861	0.065	0.178	<b>0.028</b>
<b>Smoking</b>												
Yes	1.14(0.43)	1.11(0.45)	1.14(0.43)	1.09(0.42)	1.14(0.45)	1.10(0.42)	12(18.46)	2(15.38)	14(17.95)	11(17.74)	0(0.00)	11(14.67)
No	1.09(0.71)	1.04(0.61)	1.07(0.69)	1.05(0.59)	1.01(0.37)	1.04(0.54)	82(13.87)	16(8.00)	98(12.39)	67(11.55)	14(7.29)	81(10.49)
<i>p</i> -value	0.338	0.551	0.227	0.559	0.267	0.276	0.316	0.354	0.162	0.156	0.313	0.267
<b>Alcohol</b>												
Never use	1.02(0.34)	0.98(0.49)	1.01(0.38)	1.02(0.45)	1.00(0.39)	1.02(0.45)	62(13.9)	10(7.3)	72(12.4)	54(12.4)	10(7.6)	64(11.3)
Ever low	1.29(1.13)	1.14(0.70)	1.25(1.04)	1.13(0.73)	1.01(0.26)	1.09(0.64)	21(16.9)	8(19.5)	29(17.6)	16(13.1)	4(10.0)	20(12.4)
Ever high	1.37(1.09)	1.28(1.34)	1.33(1.19)	1.19(0.49)	1.11(0.49)	1.15(0.49)	2(16.7)	1(10.0)	3(13.6)	1(9.1)	0(0.0)	1(5.3)
<i>p</i> -value	<b>&lt;0.001</b>	0.105	<b>&lt;0.001</b>	0.067	0.613	0.071	0.610	0.075	0.226	0.955	0.866	0.773

**Table 5: IMT and plaque frequency in the Internal Carotid Artery**

	Maximum IMT (mm): Mean(SD)						Plaque frequency: n(%)					
	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke
<b>Age</b>												
≤40 years	0.71(0.35)	0.90(0.36)	0.79(0.36)	0.72(0.27)	0.84(0.32)	0.77(0.30)	0(0.00)	2(6.06)	2(2.17)	1(1.75)	1(3.45)	2(2.33)
>40 years	0.94(0.72)	0.90(0.55)	0.93(0.88)	0.93(0.73)	0.87(0.34)	0.91(0.66)	56(9.51)	3(1.71)	59(7.72)	43(7.44)	4(2.42)	47(6.33)
<i>p</i> -value	<b>&lt;0.001</b>	0.991	<b>0.001</b>	<b>&lt;0.001</b>	0.666	<b>&lt;0.001</b>	<b>0.006</b>	0.135	0.051	0.107	0.103	0.136
<b>Gender</b>												
Male	0.93(0.78)	0.86(0.34)	0.91(0.69)	0.90(0.67)	0.88(0.35)	0.90(0.60)	26(7.08)	1(0.79)	27(5.48)	21(5.72)	2(1.71)	23(4.75)
Female	0.90(0.57)	0.95(0.70)	0.91(0.60)	0.91(0.75)	0.84(0.32)	0.89(0.67)	30(10.56)	4(4.82)	34(9.26)	23(8.49)	3(3.85)	26(7.45)
<i>p</i> -value	0.483	0.225	0.965	0.861	0.36	0.946	0.116	0.082	<b>0.032</b>	0.173	0.355	0.103
<b>Waist-Hip Ratio</b>												
Not raised	0.95(0.82)	0.86(0.27)	0.93(0.72)	0.91(0.87)	0.89(0.30)	0.90(0.76)	9(9.2)	0(0.0)	9(7.1)	9(9.2)	0(0.0)	9(7.4)
Raised	0.90(0.68)	0.91(0.56)	0.90(0.65)	0.89(0.59)	0.85(0.35)	0.88(0.54)	44(8.5)	5(2.9)	49(7.1)	32(6.3)	5(3.1)	37(5.5)
<i>p</i> -value	0.549	0.420	0.692	0.840	0.479	0.722	0.815	1.000	0.983	0.290	1.00	0.411
<b>Hypertension</b>												
Yes	0.93(0.71)	0.90(0.52)	0.92(0.66)	0.92(0.72)	0.87(0.34)	0.90(0.64)	55(9.00)	60(7.38)	23(9.16)	43(7.19)		48(6.09)
No	0.71(0.29)	0.80(0.46)	0.73(0.32)	0.73(0.30)	0.70(0.36)	0.72(0.31)	1(20.50)	1(2.13)	33(8.25)	1(2.50)		1(2.22)
<i>p</i> -value	<b>&lt;0.001</b>	0.556	<b>&lt;0.001</b>	<b>0.002</b>	0.277	<b>0.001</b>	0.155	0.173	0.686	0.257		0.283
<b>Diabetes mellitus</b>												
Yes	0.96(0.86)	1.04(0.91)	0.97(0.86)	0.98(0.89)	0.89(0.30)	0.96(0.82)	0(0.00)	23(7.96)	37(8.92)	26(10.57)	0(0.00)	26(9.19)
No	0.89(0.57)	0.86(0.35)	0.88(0.51)	0.86(0.55)	0.85(0.35)	0.86(0.49)	5(2.92)	38(6.65)	19(8.19)	18(4.59)	5(3.16)	23(4.18)
<i>p</i> -value	0.216	0.175	0.073	0.067	0.445	<b>0.045</b>	0.587	0.482	0.753	<b>0.004</b>	0.586	<b>0.004</b>
<b>Dyslipidemia</b>												
Yes	0.93(0.69)	0.86(0.32)	0.91(0.62)	0.92(0.72)	0.88(0.36)	0.91(0.65)		3(2.27)	40(7.31)	28(6.85)	4(3.33)	32(6.05)
No	0.90(0.71)	0.96(0.74)	0.92(0.72)	0.89(0.68)	0.84(0.29)	0.87(0.59)		2(2.60)	21(6.80)	16(7.11)	1(1.33)	17(5.67)
<i>p</i> -value	0.69	0.207	0.81	0.588	0.375	0.429		0.882	0.778	0.9	0.39	0.822
<b>Smoking</b>												
Yes	0.88(0.53)	1.11(0.58)	0.93(0.55)	0.82(0.34)	0.94(0.28)	0.85(0.33)	5(8.20)	1(7.14)	6(8.00)	2(3.39)		2(2.82)
No	0.92(0.72)	0.89(0.51)	0.91(0.67)	0.92(0.74)	0.85(0.34)	0.90(0.65)	50(8.73)	3(1.58)	53(6.95)	42(7.47)		47(6.34)
<i>p</i> -value	0.606	0.164	0.798	0.099	0.31	0.254	0.889	0.249	0.734	0.245		0.233
<b>Alcohol</b>												
Never use	0.89(0.59)	0.88(0.58)	0.89(0.59)	0.89(0.67)	0.84(0.36)	0.88(0.60)	36(8.4)	3(2.3)	39(7.0)	36(8.5)	5(4.0)	41(7.5)
Ever low	0.98(0.68)	0.94(0.38)	0.97(0.61)	0.98(0.63)	0.89(0.24)	0.96(0.55)	10(8.2)	1(2.5)	11(6.8)	7(5.9)	0(0.0)	7(4.6)
Ever high	0.88(0.41)	0.91(0.36)	0.89(0.38)	1.09(0.54)	0.78(0.31)	0.95(0.47)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
<i>p</i> -value	0.381	0.781	0.307	0.255	0.527	0.306	0.943	1.000	0.766	0.587	0.669	0.315

**Table 6: IMT and plaque frequency in the vertebral artery**

	Maximum IMT (mm): Mean(SD)						Plaque frequency: n(%)					
	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke	Ischemic stroke	Right Hemorrhagic stroke	All stroke	Ischemic stroke	Left Hemorrhagic stroke	All stroke
<b>Age</b>												
≤40 years	0.46(0.46)	0.46(0.28)	0.46(0.42)	0.43(0.25)	0.44(0.30)	0.43(0.26)						
> 40 years	0.50(0.31)	0.51(0.27)	0.51(0.30)	0.50(0.31)	0.47(0.24)	0.50(0.30)						
p-value	0.527	0.489	0.406	0.073	0.702	0.077						
<b>Gender</b>												
Male	0.52(0.34)	0.51(0.32)	0.52(0.34)	0.50(0.31)	0.45(0.24)	0.49(0.30)	4(1.38)		5(1.38)			
Female	0.47(0.32)	0.50(0.22)	0.48(0.29)	0.48(0.30)	0.49(0.26)	0.48(0.29)	2(0.90)		2(0.72)			
p-value	0.22	0.844	0.234	0.463	0.431	0.678	0.615		0.432			
<b>Waist-Hip Ratio</b>												
Not raised	0.49(0.44)	0.53(0.21)	0.49(0.42)	0.45(0.27)	0.46(0.24)	0.45(0.27)	2(2.5)	0(0.0)	2(2.3)	1(1.4)		1(1.2)
Raised	0.50(0.31)	0.51(0.28)	0.50(0.31)	0.50(0.32)	0.47(0.25)	0.49(0.30)	2(0.5)	1(0.9)	3(0.6)	4(1.0)		4(0.8)
p-value	0.813	0.777	0.851	0.212	0.841	0.230	0.122	1.000	0.151	0.573		0.535
<b>Hypertension</b>												
Yes	0.51(0.34)	0.50(0.28)	0.51(0.32)	0.50(0.31)	0.46(0.25)	0.49(0.30)						
No	0.41(0.23)	0.60(0.16)	0.44(0.23)	0.41(0.21)	0.63(0.17)	0.44(0.22)						
p-value	0.069	0.336	0.148	0.058	0.145	0.235						
<b>Diabetes mellitus</b>												
Yes	0.52(0.36)	0.59(0.27)	0.53(0.35)	0.51(0.33)	0.49(0.29)	0.51(0.33)	4(2.06)	1(3.70)	5(2.26)			
No	0.48(0.31)	0.49(0.27)	0.48(0.30)	0.48(0.29)	0.46(0.23)	0.48(0.28)	2(0.63)	0(0.00)	2(0.48)			
p-value	0.32	0.134	0.163	0.333	0.669	0.246	0.145	0.211	0.039			
<b>Dyslipidemia</b>												
Yes	0.49(0.33)	0.48(0.19)	0.49(0.31)	0.50(0.33)	0.45(0.24)	0.49(0.31)	3(0.96)	0(0.00)	3(0.78)			
No	0.51(0.34)	0.54(0.35)	0.52(0.34)	0.49(0.28)	0.48(0.26)	0.49(0.28)	3(1.55)	1(1.79)	4(1.60)			
p-value	0.653	0.271	0.382	0.762	0.517	0.937	0.552	0.437	0.333			
<b>Smoking</b>												
Yes	0.544(0.28)	1.04(0.56)	0.61(0.36)	0.61(0.51)	0.64(0.21)	0.62(0.49)						
No	0.50(0.34)	0.48(0.22)	0.49(0.32)	0.48(0.28)	0.46(0.25)	0.48(0.27)						
p-value	0.368	0.09	0.063	0.153	0.124	0.084						
<b>Alcohol</b>												
Never use	0.48(0.35)	0.47(0.21)	0.48(0.33)	0.47(0.30)	0.45(0.25)	0.46(0.29)	5(1.5)	1(1.2)	6(1.4)			
Ever low	0.58(0.27)	0.67(0.42)	0.60(0.31)	0.61(0.35)	0.58(0.21)	0.61(0.32)	1(1.1)	0(0.0)	1(0.9)			
Ever high	0.77(0.29)	0.63(0.21)	0.70(0.24)	0.83(0.32)	0.50(0.10)	0.67(0.28)	0(0.0)	0(0.0)	0(0.0)			
p-value	0.071	<b>0.016</b>	<b>0.006</b>	<b>0.0014</b>	0.125	<b>0.0005</b>	1.000	1.000	1.000			

**Discussion**

We investigated the prevalence and pattern of atherosclerosis in the carotid and vertebral arteries among West African stroke patients as well as CVRFs associated with them. We present findings in the sub-Saharan African region where the prevalence of carotid and vertebral atherosclerosis using ultrasound has not been determined before now; our study being the first study to evaluate the pattern of association of traditional CVRFs with carotid and vertebral atherosclerosis in both stroke types.

Our patients with hemorrhagic stroke were younger compared with patients with ischemic stroke, consistent with previous reports.<sup>[19]</sup> The CVRFs explored in this study included age, gender, level of formal education, hypertension, DM, dyslipidemia, history of alcohol intake, history of smoking, WHR, as well as family histories of hypertension, stroke, diabetes mellitus and heart disease. The prevalence of these CVRFs was comparable between the 2

stroke types ( $p > 0.05$ ) except for DM ( $p < 0.001$ ) which was evidently commoner in the ischemic stroke group. Hypertension was the most prevalent risk factor as reported in the larger SIREN study<sup>[14]</sup> which demonstrated that hypertension was associated with both stroke types and is the leading risk factor for stroke among West Africans.

Intima-media thickness is a structural abnormality of atherosclerosis and plaques are generally seen in the later stages of atherosclerosis. Uniform thickening of the intima-media is measured for the IMT while the focal elevation of the intima-media with a maximum thickness of more than 1.0 mm is measured for plaque.<sup>[11]</sup> In stroke, the implication of intima-media thickening and plaques is in the pathophysiology of ischemic stroke which is related to luminal narrowing and plaque embolization from the extracranial vessels that result in reduction or occlusion of blood flow to the brain and ultimately brain ischemia.<sup>[20, 21]</sup> Intima-media thickening was



found in both stroke types, being more prevalent in the ischemic group (85%) than hemorrhagic group (80.8%) as well as in both carotid and vertebral arteries in this study; although the associations with CVRFs were significantly more in the ischemic stroke group and were seen almost exclusively in the carotid arteries. Plaques were also found in both stroke types as well as in the carotid and vertebral arterial systems in the index study. The plaques were more prevalent in the carotid arteries (8.76%) than in the VAs (1.69%). This may be related to the higher incidence of stroke in the anterior circulation which originates from the carotid system.<sup>[4-9]</sup> There was also an increased plaque burden in ischemic stroke (29.8%) compared to the hemorrhagic stroke (14.6%) population. These findings suggest that carotid ultrasound for IMT and plaque is more relevant in ischemic stroke than in hemorrhagic stroke.

Even though plaques were more common in the ischemic stroke patients in this study, the presence of carotid and vertebral plaques in both stroke types may be related to the similar CVRFs shared by the stroke types. This is supported by the findings of a study that these CVRFs are also associated with carotid plaques even in non-stroke African subjects.<sup>[22]</sup> The clinical implication of the plaques in the hemorrhagic stroke group is likely a marker of cardiovascular risk burden rather than as a risk for the incident stroke.

In the index study, the CVRFs had more contributions to carotid atherosclerosis (all studied CVRFs had one form of significant univariate and independent association or the other with IMT in the carotids) compared with vertebral atherosclerosis (only alcohol intake had univariate association and no CVRF has an independent association with IMT in the vertebrae). Age and hypertension which have been shown to be the two most common risk factors for stroke<sup>[22]</sup> were independently associated with increased IMT in the ischemic stroke patients (all the 3 segments of the carotid arteries for age and CCA for hypertension) but not in the hemorrhagic stroke patients. A Norwegian study in young ischemic stroke patients found age to be associated with IMT in all the 3 carotid segments<sup>[23]</sup> similar to this study despite differences in the genetic makeup

of the participants of both studies. That study also found hypertension to be associated with CCA IMT only, similar to our study that found hypertension to have an independent association with CCA IMT only even though hypertension showed univariate association with IMT in all the 3 carotid segments. With regards to primary prevention, the clinical implication is that IMT of all segments of the carotid arteries can be routinely followed up as subjects get older, and in those with hypertension. For secondary prevention, blood pressure control may reduce atherosclerosis and stroke risk in our population. History of smoking, DM, family history of hypertension, and family history of stroke showed varied independent associations with increased IMT in different segments of the carotid artery in both stroke types. The varying associations of these CVRFs with IMT in different segments of the carotid artery may be a result of the difference in their pathophysiological pathway leading to intima-media thickening and plaque formation. Compared to age which was independently associated with atherosclerosis in all the segments of the carotid artery, hypertension, history of smoking, DM, family history of hypertension, and family history of stroke were independently associated with atherosclerosis in only one segment of the carotid artery, implying that age is likely to cause more burden of atherosclerotic disease than these other CVRFs. The sidedness of some of the associations seen in this study may have been influenced by the non-symmetrical distribution of carotid atherosclerotic plaque size and composition in the carotid arteries. However, we did not explore this in the present analysis.

It is worth mentioning that although the history of alcohol showed an association which was dependent on other CVRFs with IMT in the vertebral arteries in both stroke types, the quantity of alcohol intake associated with IMT differed between the stroke types. While a low quantity of alcohol intake was associated with hemorrhagic stroke, a high quantity of alcohol intake was associated with ischemic stroke. Having demonstrated that a low quantity of alcohol is protective against coronary artery calcification and a high quantity of alcohol is a risk for CCA IMT in South Asians<sup>[24]</sup>, further studies are recommended in

Africans to unravel the role of alcohol in the pathophysiological pathway leading to the intima-media thickening seen in our stroke population.

In this study, having a form of formal education was an independent protective factor for intima-media thickening in all the carotid segments in ischemic stroke patients and CB in the hemorrhagic stroke patients. An average monthly income above 500 dollars was also seen as a protective factor for intima-media thickening in the CB in ischemic stroke patients. These findings suggest that having a formal education and economic empowerment may reduce the risk of carotid atherosclerosis and stroke in our population.

There was no CVRF that had an independent association with the presence of plaque in both stroke types in the carotid and vertebral vessels even though age and hypertension had univariate bilateral associations with the prevalence of plaques in all the 3 segments of the carotid artery while dyslipidemia showed univariate bilateral association with prevalence of plaques in the CCA in the ischemic stroke patients. On the other hand, hypertension showed a univariate unilateral association with the prevalence of plaques in the left CB in the hemorrhagic patients. Our findings suggest that extracranial plaques may not pose significant risks for stroke in our population. Although our study did not evaluate intracranial plaques, our findings may indirectly support the findings of a previous study that found intracranial atherosclerotic strokes more prevalent in non-white populations including blacks and Hispanics.<sup>[25]</sup> Evaluation of the intracranial vessels for plaques in the stroke cohort of the SIREN study may provide additional evidence to support this. This will be addressed in a future analysis.

This study has several strengths, including the presentation of comparisons between the 2 stroke types in our unique dataset within the largest stroke investigative network in the sub-region region and the inclusion of vertebral artery data. However, our study also has some limitations. The fact that our analysis was based on only the SIREN patients who had Doppler USS may have resulted in selection bias. The cross-sectional design of this study, as well

as its non-comparison with controls, may limit the evidence emerging from the study, however, the robustness of our data and the exploratory analyses provide new insights on the contribution of carotid arteriosclerosis to stroke in African patients who represent a unique group with distinct genetic and environmental factors. Evaluation of plaque characteristics like size echotexture, echogenicity and surface, as well as assessment of Doppler velocimetry indices in future studies will provide additional evidence about carotid and vertebral atherosclerosis in our African stroke patients.

### Conclusion

The carotid arteries carry a greater burden of intima-media thickening and plaque than the vertebral arteries and the plaque burden is higher in ischemic stroke compared to hemorrhagic stroke patients of West African descent. Age and hypertension are the two CVRFs that could be associated with any segment of the carotid bed in terms of intima-media thickening while other known traditional CVRFs showed varied associations with different segments of the carotid arteries.

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### Authors' Contributions

ADO, GO, and MO conceived the idea and designed the study. JA performed the analysis. ADO wrote the first draft. MO, GO and BO served in the role of overseeing the execution of the manuscript and provided critical intellectual input. All authors edited the manuscript and approved the final version.



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