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Carotid IMT is more associated with stroke than risk calculators

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Background – It is unclear whether a natural marker of atherosclerosis (carotid intima-media thickness: CIMT) or calculated risk score is more associated with stroke. We therefore comparatively examined the relationship between CIMT as well as two cardiovascular risk calculators (Omnibus Risk Score -ORS and Framingham Risk Score-FRS) and the occurrence of stroke among hypertensive African patients. *Methods* – CIMT was measured in 555 consecutive consenting hypertensive adults (377 stroke patients and 178 stroke-free subjects). The 10-year cardiovascular risk was calculated for each participant with the FRS and ORS. The strengths of association between FRS, ORS, CIMT, and stroke occurrence were examined using logistic regression. The discriminative capacity of FRS, ORS, and CIMT for stroke occurrence was assessed with c-statistics. *Results* – Higher average CIMT (OR 11.71; 95% CI 1.65–83.07; $P = 0.01$) was strongly associated with stroke after adjusting for age, sex, blood pressure, serum cholesterol, and blood sugar. Neither the FRS (OR: 1.03; CI: 0.89–1.19, $P = 0.68$) nor the ORS (OR: 1.08; CI: 0.90–1.30; $P = 0.41$) was significantly associated with stroke. CIMT had a higher c-statistic for differentiating stroke patients from hypertensive controls (right: c = 0.63, $P < 0.001$; left: c = 0.67, $P < 0.001$; average: c = 0.66, $P < 0.001$) than some conventional risk factors. Neither FRS ($P = 0.39$) nor ORS ($P = 0.55$) was able to independently differentiate between stroke and hypertensive patients. *Conclusion* – CIMT, but neither FRS nor ORS, is independently associated with stroke among Nigerian African hypertensive patients. CIMT may be a better tool for estimating the overall risk of stroke than FRS or ORS in this population.

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Key words: carotid intima-media thickness; framingham risk score; omnibus risk score; African; stroke; epidemiology; hypertension

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Introduction

The burden of stroke and other cardiovascular diseases (CVD) is rising in low and middle income countries (LMIC) (1), where especially, prevention remains the most cost-effective means of intervention. Several cardiovascular risk factors, targeted for prevention, occur concurrently in many individuals where they interact multiplicatively to promote vascular risk (2). Therefore, the estimation of total cardiovascular risk in individuals is required to monitor the overall effectiveness of the intensity of risk factor(s) control aimed at lowering the likelihood of cardiovascular events (3).

The development of multivariable risk prediction algorithms/equations such as the Framingham's Risk Score (FRS) and the Omnibus risk score (ORS) was based on this synergistic interaction among the risk factors (2, 4, 5). These risk calculators, utilizing multiple parameters derived from prospective cohort studies involving predominantly white people in high income countries (HICs), have been used as clinical tools for CVD risk stratification in individuals (4, 6–9). The FRS is the most widely used (3, 4, 8) while the ORS is one of the most recent (9).

Despite the popularity and the sound methodological backgrounds upon which these algorithms were based, it is not known if their risk

prediction equations can be appropriately extrapolated to other populations (including LMICs in Africa). Indeed, the developers recommended that its validity and transportability should be evaluated in future studies (3). While the ORS has not been widely used, the FRS has been reported to overestimate (or underestimate) risk in populations outside of the US settings where it was primarily developed (10, 11) and among Hispanic and Native Americans within the United States (10, 11). Moreover, it has been reported that more than 40% incident events of CVD remain unexplained by these risk prediction scores (7). Carotid intima-media thickness (CIMT) assessed by carotid ultrasonography is a safe, non-expensive, practicable, and accurate method for detecting early signs of atherosclerosis (7, 12–21). CIMT and its change over time reflect cardiovascular disease risk (7). This association between CIMT, and several cardiovascular risk factors and outcomes has been reported to various degrees in diverse populations (7, 12–21). Thus, CIMT which is a single parameter and quantitative measure of atherosclerosis (7, 12, 13) may represent an intermediate cardiovascular phenotype and a natural aggregate of the major cardiovascular risk factors superior to the risk calculators which do not include some of these risk factors in their equations.

Measurement of CIMT is faster and more easily reproducible than carotid plaque assessment making it more attractive as a possible population screening tool (7, 12–14). Moreover, CIMT may be especially useful in the earlier stages of atherosclerosis (e.g., in hypertensive patients) when plaques are still absent (7, 12–24). However, it is not clear whether CIMT or the cardiovascular risk calculator(s) is more strongly associated with stroke among black Africans with hypertension (6, 21). The tool with a stronger relationship to stroke may be more useful for estimating the overall risk of stroke among hypertensive patients.

We therefore examined the relationship between CIMT as well as two cardiovascular risk calculators (ORS and FRS) and the occurrence of stroke among Nigerian African hypertensive patients to find out which of these three parameters (CIMT, ORS, and FRS) has the strongest direct relationship with stroke.

Methods

Participants and setting

A total of 555 consenting adults (age >18 years) of either sex were recruited into the study between 2008 and 2010 (22). Participants consisted of 377 hypertensive stroke patients (ischemic and hemorrhagic) and 178 hypertensive strokes-free controls. The stroke patients were recruited consecutively at presentation in the Department of Medicine of the University College Hospital (UCH), Ibadan, Nigeria, while the hypertensive controls without history of transient ischemic attacks (TIA), stroke, coronary artery disease, heart failure, or kidney disease were enrolled consecutively from the Medical Outpatient Clinic of the same hospital (UCH) during the study period. The UCH is located in Ibadan and the Catchment area included the Ibadan municipal area as well as other rural and urban settings around Ibadan city. The hospital also receives referrals majorly from across southwestern Nigeria.

Ethical approval was obtained from the ethical review committee of the University of Ibadan/University College Hospital, Ibadan. Informed consent was obtained from participants. Assessments were performed within 2 weeks of the ictus for the stroke patients and at entry for the hypertensive controls.

Measurement of conventional CVD Risk Factors and Stroke diagnosis

Participants' demographic characteristics were collected using standard procedures (22). Brachial artery blood pressure (BP) was obtained from all participants at entry with a mercury sphygmomanometer (Accoson, England) using the standard method (21). Stroke was defined as 'a clinical syndrome characterized by a rapidly developing focal or global neurologic deficit, with symptoms lasting more than 24 h or leading to death, with no apparent cause other than a vascular one'. (22) Stroke was diagnosed based on clinical evaluation by a neurologist and neuroimaging including brain computerized tomography (plain and with contrast using multislice Spiral CT machine) or magnetic resonance imaging (including T1, T2, and Fluid attenuated inversion recovery sequences).

A patient without stroke was classified as hypertensive if there was a self-report of previous diagnosis of or ongoing treatment for hypertension, or a record of sustained BP ≥140/90 mmHg on two or more occasions (25, 26). History of cigarette smoking was obtained while the diagnosis of diabetes was noted based on the use of insulin or oral hypoglycemic medications, or a current or previous fasting plasma glucose level of ≥126 mg per deciliter (3, 26). Fasting lipid

profiles were determined in the patients using standardized enzymatic colorimetric methods.

Measurement of carotid intima-media thickness

Carotid intima-media thickness was measured by Ultrasound using the General Electric (GE) Logic P5 Ultrasound machine with a 5–8 MHz multi-frequency linear transducer. The carotid arteries on each side of the neck were examined while patients lay supine with head slightly tilted to the contralateral of the examined side to enhance adequate visualization of the vessels. To eliminate interobserver variation, the same Sonologist (A.M.A.) performed all sonographic examinations and each measurement was taken thrice to minimize variation. Using published guidelines (7, 21), the common carotid arteries (CCA) were examined and the CIMT was measured at its far wall. To obtain an optimal image, the 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 image for the CIMT measurement was manually magnified to minimize error in measurement. The CIMT is 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). For standardization, the CIMT of the CCA was measured in the mid-portion of the vessel in an area devoid of plaques.

This technique was selected in preference to the 'multiple carotid sites measurement' because it is easier and quicker to assess thus enabling its widespread utility in everyday clinical and community-based settings (7, 21). Besides, CCA CIMT is more reliable to measure than multiple sites CIMT (27), and it is as good as multiple sites CIMT in improving risk estimation (27).

Estimation of ten-year risk of CVD using the Framingham and Omnibus Risk Calculators

The ten-year risk of CVD was predicted for each participant using the Framingham and the Omnibus risk score calculators. Specifically, the FRS (with and without the calibration factor) was calculated according to the sex-specific Framingham risk equations (3), using the conventional risk factors: age, sex, smoking history, diabetes mellitus, total cholesterol, HDL cholesterol, and systolic blood pressure (28). The Framingham general CVD risk function used in this study had demonstrated very good discrimination and calibration both for predicting CVD and for predicting risk of individual CVD components such as stroke and myocardial infarction (comparable to disease-specific algorithms) (3). The ORS, on the other hand, was calculated according to the sex-specific Omnibus risk equations (9). Based on the 2013 ACC/AHA guideline on the Assessment of Cardiovascular Risk, the following conventional risk factors were used in the ORS estimation: age, sex, smoking history, diabetes mellitus, total cholesterol, HDL cholesterol, treatment for blood pressure, and systolic blood pressure (9).

Statistical analysis

Aggregated data were coded, verified, and checked for outliers, entry errors, and omissions. Associations between categorical variables and cardiovascular phenotype were explored with the chi-squared test, while quantitative variables were compared across the two groups of cardiovascular phenotype using the independent Student's *t*-test. The association of the conventional risk factors, the risk calculators (FRS and ORS), and the CIMT with cardiovascular phenotype was investigated in unadjusted logistic regression. The capability of CIMT and the risk calculators to distinguish between the cardiovascular phenotypes was further investigated using logistic regression adjusting for the conventional vascular risk factors (age, sex, blood pressure, total cholesterol, HDL cholesterol, smoking, and diabetes).

Moreover, for the pair of the cardiovascular phenotypes considered, namely stroke vs hypertensive patients, C-statistics (Area Under Curve: AUC) and their respective 95% confidence intervals were obtained for the conventional cardiovascular risk factors, CIMT, and the risk calculators. We examined the relationship with all stroke (hemorrhagic stroke inclusive) rather than ischemic stroke alone because the relationship with all stroke may be particularly important in a population (e.g., LMIC in Africa) where hemorrhagic stroke is still relatively common due to high prevalence of hypertension (22–24). For receiver operation characteristic (ROC) analysis involving more than one variable, the predicted probability for the logistics model consisting of all variables involved and the cardiovascular phenotype were used as the test and state variables, respectively (29).

Values of the C-statistic of 0.5 indicate that the model is no better than chance at making a prediction of membership in a group while a value of 1.0 indicates that the model perfectly identifies those within a group or otherwise (29). In

general, estimate of C-statistics is considered to be significantly higher than 0.5 (and the model capable of making a prediction of membership in a group) when $P < 0.05$ (29). All analyses were performed at 5% level of significance using SPSS version 15 (SPSS Chicago Inc., USA).

Results

Characteristics of the participants and risk factors

The stroke patients (mean age: 61.10 ± 11.44 years) were significantly ($P < 0.001$) older than the hypertensive controls (53.88 ± 12.12; Table 1). The proportions of male ($P = 0.01$) and diabetic stroke patients ($P = 0.01$) were significantly higher than those of the hypertensive controls ($P < 0.05$) (Table 1). Furthermore, the stroke patients had significantly higher mean total cholesterol levels (190.21 ± 53.32) compared to the hypertensive controls (t = 12.19; $P < 0.01$; Table 1).

Hemorrhagic stroke was present in 37.1% while 62.9% had ischemic stroke by neuroimaging. There was no significant difference ($P = 0.89$) in mean FRS (without calibration factor) between stroke patients (8.09 ± 7.61) and hypertensive controls (8.33 ± 5.92). Similarly, there was no significant difference ($P = 0.53$) in the mean ORS between stroke patients (9.65 ± 7.44) and hypertensive controls (8.55 ± 6.22). Conversely, bilaterally, the mean CIMT among stroke patients (right: 0.94 ± 0.39 mm, left: 1.00 ± 0.42 mm) were significantly ($P < 0.001$) higher than for hypertensive controls (right: 0.78 ± 0.18, left: 0.78 ± 0.21).

Relationship of conventional vascular risk factors, CIMT, and risk scores with stroke

Among hypertensive patients, stroke was significantly associated with most of the conventional risk factors included in this study (Table 2). In particular, older (OR: 1.05; 95% CI: 1.04–1.07) and male patients (OR: 1.62; 95% CI: 1.13–2.32) were more likely to develop stroke. Furthermore, patients with higher right CIMT (OR 8.01; 95% CI: 2.96–21.72; $P < 0.001$) or higher left CIMT (OR: 13.98; 95% CI: 4.98–39.26; $P < 0.001$) were more likely to develop stroke. However, neither the Framingham risk score (without calibration factor, OR: 1.00; 95% CI: 0.94–1.06, $P = 0.89$)

Table 1 Association of cardiovascular risk factors and risk scores with stroke

Risk factors and risk scores	Stroke Patients Mean ± SD or proportion $n = 377$	Hypertensive control Mean ± SD or proportion $n = 178$	X^2 value	P
Sex (male)%	204 (54.1)	75 (42.1)	6.94	0.01
Diabetes %	78 (20.7)	21 (11.8)	6.06	0.01
Smoking %	29 (7.7)	12 (6.7)	0.20	0.66
Alcohol %	77 (20.4)	14 (7.9)	9.90	0.002
Ischemic heart disease%	26 (6.9)	0 (0.0)	n/a	n/a
Heart failure%	2 (0.5)	1 (0.6)	1.50	0.22

Risk factors and risk scores	Stroke Patients Mean ± SD or proportion $n = 377$	Hypertensive control Mean ± SD or proportion $n = 178$	t value	P
Age (years)	61.10 ± 11.44	53.88 ± 12.12	6.80	<0.001
Total cholesterol (mg/dl)	190.21 ± 53.32	124.18 ± 38.45	12.19	<0.001
HDL cholesterol (mg/dl)	44.24 ± 18.51	36.48 ± 11.73	2.12	0.04
LDL cholesterol (mg/dl)	121.87 ± 43.56	88.91 ± 30.86	2.44	0.02
Triglyceride	113.85 ± 47.51	113.27 ± 91.07	0.04	0.97
Fasting Plasma Glucose (mg/dl)	150.24 ± 74.61	102.73 ± 23.76	7.10	<0.001
Body mass index (kg/m^2)	26.58 ± 5.90	24.53 ± 3.90	2.32	0.02
Waist circumference (cm)	89.81 ± 13.32	85.52 ± 15.22	1.98	0.05
Systolic blood pressure (mmHg)	148.28 ± 25.63	153.19 ± 26.39	−1.96	0.05
Diastolic Blood pressure	92.12 ± 17.78	94.19 ± 15.19	0.85	0.40
FRS*	1.79 ± 1.87	8.33 ± 5.92	−10.11	<0.001
FRS†	8.09 ± 7.61	8.33 ± 5.92	−0.14	0.89
ORS	9.65 ± 7.44	8.55 ± 6.22	0.63	0.53
Right CIMT (mm)	0.94 ± 0.39	0.78 ± 0.18	4.58	<0.001
Left CIMT (mm)	1.00 ± 0.42	0.78 ± 0.21	5.76	<0.001
Average CIMT (mm)	0.97 ± 0.36	0.78 ± 0.17	5.84	<0.001

SD, Standard deviation; CIMT, Carotid intima-media thickness; ORS, Omnibus risk score.
*FRS—Results for Framingham risk score with calibration factor showing higher risk of stroke for the controls rather than stroke patients (distorted).
†FRS Results for Framingham risk score without calibration factor.

Table 2 Unadjusted logistic regression and C-statistics for the association of CVD Risk factors and risk scores with stroke

Risk factors and risk scores	Odds ratio (95% CI)	*P*	C-statistics (95% CI)	*P*
Age	1.05 (1.04–1.07)	<0.001	0.67 (0.62–0.72)	<0.001
Sex (male)	1.62 (1.13–2.32)	0.01	0.56 (0.51–0.61)	0.02
Total cholesterol	1.03 (1.03–1.04)	<0.001	0.86 (0.81–0.90)	<0.001
HDL cholesterol	1.04 (1.01–1.07)	0.02	0.63 (0.52–0.75)	0.02
Systolic Blood pressure	0.99 (0.99–1.00)	0.05	0.56 (0.51–0.62)	0.03
Diastolic Blood pressure	0.99 (0.98–1.00)	0.40	0.63 (0.52–0.75)	0.02
Smoking	1.17 (0.58–2.36)	0.66	0.51 (0.45–0.56)	0.84
Alcohol	2.77 (1.45–5.32)	0.002	0.63 (0.53–0.68)	0.01
Diabetes	1.91 (1.13–3.21)	0.02	0.54 (0.49–0.60)	0.10
FRS*	1.00 (0.94–1.06)	0.89	0.56 (0.44–0.67)	0.39
ORS	1.02 (0.95–1.10)	0.53	0.54 (0.41–0.67)	0.55
Right CIMT	8.01 (2.96–21.72)	<0.001	0.63 (0.56–0.69)	<0.001
Left CIMT	13.98 (4.98–39.26)	<0.001	0.67 (0.61–0.73)	<0.001
Average CIMT	20.04 (6.24–64.23)	<0.001	0.66 (0.60–0.73)	<0.001
Conventional Risk Factors (CRF)			0.83 (0.68–0.97)	0.003
CRF with Right CIMT			0.84 (0.65–1.00)	0.005
CRF with Left CIMT			0.85 (0.69–1.00)	0.004
CFR with Average CIMT			0.87 (0.80–0.94)	<0.001

CIMT, Carotid intima-media thickness; ORS, Omnibus risk score; CRF, Conventional Risk Factors (age, sex, alcohol, cholesterol, diabetes, smoking, systolic blood pressure, diastolic blood pressure).
*FRS—Framingham risk score FRS without calibration factor.

nor the Omnibus risk score (OR: 1.02; 95% CI: 0.95–1.10; $P = 0.53$) was significantly associated with stroke (Table 2). The FRS with calibration factor gave distorted results with lower scores in stroke patients.

In adjusted logistic regression analyses (Table 3), average CIMT was significantly associated with stroke. Specifically, patients with high average CIMT (OR 11.71; 95% CI 1.65–83.07, R^2 35%) were almost twelve times more likely to develop stroke. In contrast, the adjusted analyses involving either the FRS (without the calibration factor) or the ORS did not show any significant association between stroke and the risk scores (Table 3). Also, in adjusted logistic regression analyses (Table 4), both right and left CIMT were significantly associated with stroke irrespective of the individual conventional risk factor in the model. For example, adjusting for age, high right (OR 4.17; 95% CI 1.52–11.44), or left CIMT (OR:8.39; 95% CI:2.95–23.85) were strongly associated with stroke. Similarly, high right or left CIMT was strongly associated with stroke ($P \leq 0.003$) after adjusting for total cholesterol, blood pressure, sex, smoking, or diabetes mellitus (Table 4). In contrast, all adjusted analyses involving either the FRS (without calibration factor) or the ORS did not show any significant

Table 3 Adjusted logistic regression for the CVD Risk factors showing the odds ratio for having stroke

Risk factors and Risk scores	Adjusted Odds of having stroke AOR (95% CI) (with calibration factor)	*P*	R^2
AOR for CIMT			
Sex (male)	0.74 (0.34–1.60)	0.45	0.35
Age	1.02 (0.98–1.06)	0.43	
Diabetes	0.92 (0.29–2.90)	0.89	
Total Cholesterol	1.03 (1.02–1.04)	<0.001	
Systolic Blood Pressure	0.99 (0.97–1.00)	0.12	
Average CIMT	11.71 (1.65–83.07)	0.01	
AOR for FRS			
Sex (male)	*	*	‡
Age	1.46 (0.80–2.64)	0.22	
Diabetes	*	*	
Total Cholesterol	1.09 (0.98–1.210)	0.10	
Systolic Blood pressure	1.35 (0.86–2.14)	0.20	
FRS	*	*	
AOR for FRS†			
Sex (male)	0.37 (0.08–1.84)	0.23	0.05
Age	0.97 (0.91–1.02)	0.25	
Diabetes	1.29 (0.31–5.46)	0.73	
Total Cholesterol	1.01 (1.00–1.02)	0.12	
Systolic Blood pressure	1.01 (0.98–1.04)	0.51	
FRS†	1.03 (0.89–1.19)	0.68	
AOR for ORS			
Sex (male)	0.79 (0.17–3.66)	0.76	0.06
Age	0.95 (0.88–1.02)	0.17	
Diabetes	2.02 (0.33–12.57)	0.45	
Total Cholesterol	1.01 (1.00–1.02)	0.08	
Systolic Blood pressure	1.00 (0.97–1.04)	0.84	
ORS	1.08 (0.90–1.30)	0.41	

AOR, Adjusted odds ratio; CIMT, Carotid intima-media thickness; FRS, Framingham risk score; ORS, Omnibus risk score.
*Distorted results.
†FRS—Results for FRS without calibration factor.
‡Estimate not reliable due to distorted results.

association between stroke and the risk scores (Table 5).

Furthermore, apart from age, total cholesterol, and HDL cholesterol, CIMT had a higher c-statistic for differentiating stroke patients from hypertensive controls (right: c = 0.63, $P < 0.001$; left: c = 0.67, $P < 0.001$; average: c = 0.66, $P < 0.001$), than any of the conventional vascular risk factors (Table 2). Conversely, neither the FRS (without calibration factor, $P = 0.39$) nor ORS ($P = 0.55$) had significant c-statistic for differentiating stroke patients from hypertensive controls (Table 2).

The adjusted odds ratio as well as the c-statistic relating stroke and CIMT were higher on the left side than the right.

Discussion

Although risk calculators are used for assessing overall risk of cardiovascular events in clinical practice, we observed that the predicted risks in

Table 4 Logistic regression for CIMT showing the odds ratio for developing stroke adjusted for individual CVD Risk factors

Risk factors and risk scores	Right CIMT adjusted for individual risk factors		Left CIMT adjusted for individual risk factors	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age	1.04 (1.02–1.06)	0.001	1.04 (1.01–1.06)	0.003
CIMT	4.17 (1.52–11.44)	0.01	8.39 (2.95–23.85)	<0.001
Total cholesterol	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
CIMT	6.46 (1.92–21.76)	0.003	15.65 (3.42–71.67)	<0.001
Blood pressure	0.99 (0.98–0.10)	0.04	0.99 (0.98–0.10)	0.02
CIMT	9.18 (3.04–27.71)	<0.001	14.89 (4.87–45.47)	<0.001
Sex (male)	1.40 (0.86–2.26)	0.17	1.30 (0.79–2.13)	0.30
CIMT	7.32 (2.71–19.76)	<0.001	13.00 (4.62–36.60)	<0.001
Smoking	0.58 (0.21–1.64)	0.30	0.70 (0.25–1.95)	0.50
CIMT	7.65 (2.81–20.86)	<0.001	12.95 (4.56–36.80)	<0.001
Diabetes	1.66 (0.87–3.17)	0.12	1.42 (0.73–2.77)	0.30
CIMT	8.00 (2.88–22.26)	<0.001	12.67 (4.43–36.23)	<0.001

CIMT- Carotid intima-media thickness.

Table 5 Logistic regression for the risk scores showing the odds ratio for developing stroke adjusted for individual CVD Risk factors

Risk factors and risk scores	Framingham Risk Score *(without calibration factor)* adjusted for individual risk factors		Omnibus Risk Score adjusted for individual risk factors	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age	0.97 (0.92–1.01)	0.14	0.95 (0.90–1.00)	0.04
RC	1.01 (0.94–1.08)	0.79	1.08 (0.98–1.18)	0.13
Total cholesterol	1.01 (1.00–1.02)	0.04	1.01 (1.00–1.02)	0.06
RC	0.97 (0.91–1.04)	0.37	1.03 (0.96–1.10)	0.44
Blood pressure	1.02 (0.99–1.04)	0.19	1.01 (0.99–1.04)	0.27
RC	0.98 (0.92–1.05)	0.62	1.00 (0.93–1.08)	0.93
Sex (male)	2.18 (0.65–7.31)	0.21	1.58 (0.55–4.50)	0.40
RC	1.03 (0.95–1.12)	0.50	1.01 (0.94–1.09)	0.82
Smoking	**	**	**	**
RC	1.00 (0.94–1.06)	0.89	1.02 (0.95–1.09)	0.68
Diabetes	0.94 (0.26–3.50)	0.93	0.72 (0.20–2.68)	0.63
RC	1.00 (0.93–1.07)	0.93	1.03 (0.95–1.12)	0.44

CIMT, Carotid intima-media thickness. RC, Risk calculator.
**Distorted results.

this population are far from optimal (7, 28). These algorithms are mostly limited by variable thresholds for different populations and presence of residual risk (7). Some of this residual risk may be accounted for by putative factors including genetic markers, and CIMT not included as variables in the risk equations (30–32).

Whereas CIMT has been accepted as a marker of cardiovascular risk in many clinical and epidemiological studies (25, 26, 33–39) and has the advantages of an imaging tool, as patients and physicians may relate better to visible structures rather than abstract concepts of risk calculators (38), information about its capacity as an independent determinant of cardiovascular events in comparison with the risk calculators among black Africans is lacking.

We found mean CIMT measurement to be significantly higher for stroke patients than hypertensive controls while the FRS and ORS were not significantly associated with stroke in the study participants. It would be expected that the risk score algorithms should predict higher risk of CVD for stroke patients (as against hypertensive control) if the algorithm appropriately captures the complete dynamics of CVD risk in the population of interest. The inability of FRS and ORS to do this may suggest that their use among black Africans for clinical decisions should be with caution (39). Most risk scores were developed using populations with characteristics that are clinically, environmentally, and genetically different from most population of black people living in Africa.

Alcohol consumption seems a very strong risk factor for stroke in the current study with unadjusted odds ratio exceeding all other classical risk factors. Some studies have also reported even stronger association between stroke and alcohol consumption with unadjusted odds ratio of up to 15.3 (40, 41). This strong relationship (40, 41) may be due to the unadjusted effect of several other vascular risk factors which modulate the complex relationship between alcohol and stroke (42, 43). Nevertheless, the non-inclusion of alcohol in the FRS and ORS might contribute to their weaker relationship to stroke occurrence in this study.

Independent association between CIMT, FRS, ORS, and stroke among hypertensive subjects

Furthermore, in this group of patients, CIMT was associated with stroke independent of conventional cardiovascular risk factors while risk scores estimated from FRS and ORS were not. This reaffirms our earlier suggestion that transporting risk predictors for use in populations other than where it was developed should be with caution. As a further confirmation, a study conducted in northern Africa (44) reported that FRS failed to reflect atherosclerotic state in apparently healthy participants when compared to CIMT (44). A review of eight epidemiologic studies showed that the CIMT had independent predictive capacity for cardiovascular events (20, 25, 26, 37–39, 44, 45). Furthermore, CIMT was the only vascular risk factor that was independently associated with cognitive decline in older adults in another study (46). More so, in a multi-ethnic study of Atherosclerosis with over 5000

participants comprising white, Chinese, Hispanic, and black participants (25, 26), CIMT measurement was associated with stroke in a cohort free of prevalent cardiovascular diseases (25, 26).

Reclassification capacity of CIMT, FRS, and ORS compared to cardiovascular risk factors

Apart from age, total cholesterol, and HDL cholesterol; CIMT had higher capacity than the conventional cardiovascular risk factors for differentiating stroke from hypertension phenotype while neither the FRS nor the ORS showed significant capacity for differentiating stroke from hypertension phenotype. With these additional results, the consistent capability of the CIMT over the risk prediction calculators suggests that our finding is far from mere chance among this population (Nigerian Africans).

The results so far indicate that some conventional risk factors do better than average CIMT in determining which patients develop stroke and the addition of CIMT to these conventional risk factors improved the c-statistic (but not significantly in view of the overlap of the confidence intervals). Although the additional value of CIMT appeared to be small but significant in those with intermediate risk in a meta-analysis of many studies from North America and Europe (non-Africans) (47), other authors have reported stronger value of the CIMT when compared with risk prediction equations in classifying patients' CVD risk status (48). For instance, 23% of participants classified to have low risk by the FRS had evidence of subclinical atherosclerosis identified by CIMT and were at increased long-term risk for vascular events in a multi-ethnic population (49). Similarly, in another study, 38% of asymptomatic younger participants classified by the FRS to have ≤5% (low) risk of CVD had abnormal CIMT which was associated with increased risk for cardiovascular events (25, 26, 28). Moreover, a study in older adults also showed that addition of CIMT modestly improves 10-year risk prediction for stroke and CVD beyond the capability of a FRS-type risk factor model (50). The addition of plaque category information to CIMT provided no incremental benefit (50).

Strengths, limitations, and future directions

This is the first study to compare CIMT with FRS and ORS among hypertensive African patients, demonstrating the reclassification capacity of the CIMT over the risk calculators. Although CIMT was measured immediately (within 2 weeks) after the stroke, it is expected to reflect measurements taken prior to the stroke in a prospective cohort design (7, 12–21) because CIMT progression is very slow (0.001 mm/year) (51, 52) and the change within 2 weeks after stroke is likely to be insignificant (51, 52). Moreover, some of the variables utilized in the ORS and FRS equations to compute the cardiovascular risk (e.g., smoking history) were retrospectively obtained. Although these features support the longitudinal nature of our study, our findings still need to be confirmed by prospective studies. Ideally, developing a new risk prediction calculator specific to black Africans (in a prospective cohort study) and comparing its predictive capacity with the CIMT, FRS, and the ORS would provide better evidence in a subsequent prospective study.

Conclusion and clinical implications

Carotid intima-media thickness (unlike FRS and ORS) was significantly and independently associated with stroke among hypertensive black Africans. CIMT differentiated stroke from hypertension phenotype while FRS and ORS did not. Therefore, CIMT appears to be a better tool for estimating the overall risk of stroke than FRS or ORS among hypertensive African patients.

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Disclosures

'The Authors declare that there is no conflict of interest'.

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