Carotid IMT is more associated with stroke than risk calculators

Mayowa O. Owolabi, MBBS, MSc, Dr.Med, MWACP, FMCP,
aDepartment of Medicine, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria. Nigeria

Onoja M. Akpa, PhD, and
bDepartment of Epidemiology and Medical Statistics, Faculty of Public Health, College of Medicine, University of Ibadan, Nigeria

Atinuke M. Agunloye, MBBS, FMCR, FWACS
cDepartment of Radiology, College of Medicine, University of Ibadan and University College Hospital, Ibadan. Nigeria. Nigeria

Abstract

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.

Corresponding author: Dr. Mayowa O. OWOLABI. MBBS, MSc, DrMed, MWACP, FMCP, Department of Medicine, University College Hospital, Ibadan, 200001 Oyo State, Nigeria and College of Medicine, University of Ibadan. Nigeria, mayowaowolabi@yahoo.com, Tel : +234 8020775595, +234 807 8496 75.

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) were 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 whites 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 United States (US) settings where it was primarily developed (10,11) and among Hispanic and Native Americans within the US (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 have 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 south- western 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 two 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 hours 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 multi-slice 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 inter-observer 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.(29) 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 was 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 versus 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. (28)

Values of the C-statistic of 0.5 indicates 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. (28) 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 $p < 0.05$ (28). All analyses were performed at 5% level of significance using SPSS version 15 (SPSS Chicago Inc.).

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±0.42mm) 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) 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 were strongly associated with stroke (p 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 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 this population are far from optimal. (7,29) 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 to 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 blacks 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 multiethnic 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. (25,26,29) 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 two 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 (0.001mm/year) (,51,52) and the change within two 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.

Acknowledgments

References

1. Owolabi MO, Mensah GA, Kimmel PL, et al. Understanding the rise in cardiovascular diseases in Africa: harmonizing H3Africa genomic epidemiological teams and tools. Cardiovascular Journal of Africa. 2014; 25:134–6. [PubMed: 24878536]

2. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. American Journal of Epidemiology. 2000; 151:478–87. [PubMed: 10707916]

3. D'agostino RB, Vasan RS, Pencina MJ, et al. General Cardiovascular Risk Profile for Use in Primary Care The Framingham Heart Study. Circulation. 2008; 117:743–53. [PubMed: 18212285]

4. Cupples, LA.; D'agostino, RB. Section 34: some risk factors related to the annual incidence of cardiovascular disease and death in pooled repeated biennial measurements. In: Kannel, WB.; Wolf, PA.; Garrison, RJ., et al., editors. Framingham Heart Study: 30 Year Follow-Up. Bethesda, Md: US Department of Health and Human Services; 1987.

5. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. American Journal of Epidemiology. 2002; 156:871–81. [PubMed: 12397006]

6. Van Den, Oord; SC, Sijbrands; EJ, Ten; Kate, GL., et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. 2013; 228:1–11. [PubMed: 23395523]

7. Touboul PJ, Grobbee DE, Den RH. Assessment of subclinical atherosclerosis by carotid intima media thickness: technical issues. European Journal of Preventive Cardiology. 2012; 19:18–24. [PubMed: 22801066]

8. Anderson TJ, Grégoire J, Hegele RA, Couture P, et al. 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. The Canadian Journal of Cardiology. 2013; 29:151–67. [PubMed: 23351925]

9. Goff DC, Lloyd-Jones DM, Bennett G, et al. A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 00:000–000.10.1161/01.cir.0000437741.48606.98

10. Liu J, Hong Y, D'agostino RB SR, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004; 291:2591–9. [PubMed: 15173150]

11. Brindle P, Emberson J, Lampe F, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ. 2003; 327:1267. [PubMed: 14644971]

12. De Freitas P, Piccinato CE, De Paula Martins W, Filho FM. Carotid atherosclerosis evaluated by Doppler ultrasound: association with risk factors and systemic arterial disease. Jornal Vascular Brasiliero. 2008; 7:298–307.

13. Sharma P, Lohani B, Chataut SP. Ultrasonographic evaluation of carotid intima media thickness in hypertensive and normotensive individuals. Nepal Medical College Journal. 2009; 11:133–5. [PubMed: 19968157]

14. Mathiesen EB, Johnsen SH, Wilsgaard T, et al. Carotid Plaque Area and Intima-Media Thickness in Prediction of First-Ever Ischemic Stroke: A 10-Year Follow-Up of 6584 Men and Women: The Tromso Study. Stroke. 2011; 42:972–8. [PubMed: 21311059]

15. Jensen-Urstad K, Jensen-Urstad M, Johansson J. Carotid artery diameter correlates with risk factors for cardiovascular disease in a population of 55-year-old subjects. Stroke. 1999; 30:1572–6. [PubMed: 10436103]

16. Fukuhara T, Hida K, Manabe Y, et al. Reduced flow velocity in the internal carotid artery independently of cardiac hemodynamics in patients with cerebral ischemia. Journal of Clinical Ultrasound. 2007; 35:314–21. [PubMed: 17427213]

17. Bes AA, Guell AA, Braak LL, Farah MM, Barrere MM. Influence of age on several parameters of the Doppler signal at the carotid level. Rev Electroencephalogr Neurophysiol Clin. 1980; 10:190–6. [PubMed: 7209082]

18. Chuang S, Bai C, Chen J, et al. Common carotid end-diastolic velocity and intima-media thickness jointly predict ischemic stroke in Taiwan. Stroke. 2011; 42:1338–44. [PubMed: 21415400]

19. Nakatou T, Nakata K, Nakamura A, Itoshima T. Carotid haemodynamic parameters as risk factors for cerebral infarction in type 2 diabetic patients. Diabetic Medicine. 2004; 21:223–39. [PubMed: 15008831]

20. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007; 115:459–67. [PubMed: 17242284]

21. Peters SA, Den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012; 98:177–84. [PubMed: 22095617]

22. O'donnell MJ, Xavier D, LIU L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010; 376:112–23. [PubMed: 20561675]

23. Owolabi MO, Ugoya S, Platz T. Racial disparity in stroke risk factors: the Berlin-Ibadan experience - a retrospective study. Acta Neurologica Scandinavica. 2009; 119:81–7. Epub July 13. 10.1111/j.1600-0404.2008.01077.x [PubMed: 18638038]

24. Owolabi MO. Taming the burgeoning stroke epidemic in Africa: stroke quadrangle to the rescue. West Indian Medical Journal. 2011; 60:412–21. [PubMed: 22097671]

25. Polak JF, Pencina MJ, O'leary DH, D'agostino RB. Multi-Ethnic Study of Atherosclerosis Common Carotid Artery Intima-Media Thickness Progression as a Predictor of Stroke in Multi-Ethnic Study of Atherosclerosis. Stroke. 2011; 42:3017–21. [PubMed: 21885840]

26. Polak JF, Pencina MJ, Pencina KM, O'donnell CJ, Wolf PA, D'agostino RB. Carotid-Wall Intima–Media Thickness and Cardiovascular Events. New England Journal of Medicine. 2011; 365:213–21. [PubMed: 21774709]

27. Nambi V, Chambless L, HE M, et al. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. European Heart Journal. 2012; 33:183–90. [PubMed: 21666250]

28. Hosmer, DW.; Lemeshow, S. Applied logistic regression. New York, NY: John Wiley & sons; 2000.

29. Schlendorf KH, Nasir K, Blumenthal RS. Limitations of the Framingham risk score are now much clearer. Preventive Medicine. 2009; 48:115–6. [PubMed: 19124038]

30. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation. 2008; 118:2243–55. [PubMed: 18997194]

31. Brautbar A, Ballantyne CM, Lawson K, et al. Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid modifying therapy in the Atherosclerosis Risk in Communities study. Circulation and Cardiovascular Genetics. 2009; 2:279–85.

32. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Archives of Internal Medicine. 2008; 168:1333–9. [PubMed: 18574091]

33. Espeland MA, O'leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for CVD events in trials of HMG-CoA reductase inhibitors. Current Control Trials Cardiovascular Medicine. 2005; 6:3.

34. Bots ML. Carotid intima-media thickness as a surrogate marker for CVD in intervention studies. Current Medical Research Opinion. 2006; 22:2181–90. [PubMed: 17076979]

35. Salim H. The association of carotid intima-media thickness (cIMT) and stroke: A cross sectional study. Perspectives in Medicine. 2012; 1:164–6.

36. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). European Heart Journal. 2010; 31:2041–8. [PubMed: 20530503]

37. El-Hafez, HA.; Elrakhawy, MM.; El-Baiomy, AA.; El-Eshmawy, MM. Carotid Intima Media Thickness Is Independently Associated with Male Gender, Middle Age, and IGF-1 in Metabolically Healthy Obese Individuals. ISRN Obesity. 2014. Article ID 545804. http://dx.doi.org/10.1155/2014/545804

38. Okeahialam BN, Alonge BA, Pam SD, Puepet FH. Carotid Intima Media Thickness as a Measure of Cardiovascular Disease Burden in Nigerian Africans with Hypertension and Diabetes Mellitus. International Journal of Vascular Medicine. 2011 Article ID 327171. 10.1155/2011/327171

39. Owolabi MO, Agunloye AM, Umeh EO, Akpa OM. Can carotid intima media thickness serve as an indicator of cardiovascular risk among black Africans? European Journal of Preventive Cardiology. 201410.1177/2047487314547656

40. Rodgers H, Aitken PD, French JM, Curless RH, Bates D, James OFW. Alcohol and Stroke: A case-control study of drinking habits past and present. Stroke. 1993; 24:1473–7. [PubMed: 8378949]

41. You RX, Mcneil JJ, O'malley HM, Davis SM, Thrift AG, Donnan GA. Risk factors for stroke due to cerebral infarction in young adults. Stroke. 1997; 28:1913–8.10.1161/01.str.28.10.1913 [PubMed: 9341695]

42. Camargo CA. Moderate Alcohol Consumption and Stroke The Epidemiologic Evidence. Stroke. 1989; 20:1611–26. [PubMed: 2688194]

43. Patra J, Taylor B, Irving H, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. BMC Public Health. 2010; 10:258.10.1186/1471-2458-10-258 [PubMed: 20482788]

44. Amer MS, Khater MS, Omar OH, Mabrouk RA, Mostafa SA. Association between Framingham risk score and subclinical atherosclerosis among elderly with both type 2 diabetes mellitus and healthy subjects. American Journal of Cardiovascular Diseases. 2014; 4:14–9.

45. Lorenz MW, Von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006; 37:87–92. [PubMed: 16339465]

46. Moon JH, Lim S, Han JW, et al. Carotid intima-media thickness is associated with the progression of cognitive impairment in older adults. Stroke. 2015; 46:00–00.10.1161/STROKEAHA.114.008170

47. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. Journal Internal Medicine. 2005; 257:430–7.

48. Simon A, Megnien J, Chironi G. The Value of Carotid Intima-Media Thickness for Predicting Cardiovascular Risk. Arteriosclerosis Thrombus Vascular Biology. 2010; 30:182–5.

49. Bots ML, Groenewegen KA, Anderson TJ, et al. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. Hypertension. 2014; 63:1173–81. [PubMed: 24614213]

50. Gardin JM, Bartz TM, Polak JF, O'leary DH, Wong ND. What do carotid intima-media thickness and plaque add to the prediction of stroke and cardiovascular disease risk in older adults? The cardiovascular health study. J Am Soc Echocardiogr. 2014; 27:998–1005. [PubMed: 25172401]

51. Mackinnon AD, Jerrard-Dunne P, Sitzer M, Buehler A, Von Kegler S, Markus HS. Rates and determinants of site-specific progression of carotid artery intima-media thickness: the carotid atherosclerosis progression study. Stroke. 2004; 35:2150–4. [PubMed: 15243147]

52. Nguyen QM, Toprak A, XU JH, Srinivasan SR, Chen W, Berenson GS. Progression of segment-specific carotid artery intima-media thickness in young adults (from the Bogalusa Heart Study). American Journal of Cardiology. 2011; 107:114–9. [PubMed: 21146698]

Table 1

Association of cardiovascular risk factors and risk scores with stroke

Risk Factors and Risk scores	Stroke Patients	Hypertensive control	X^2 value	p
	Mean±SD or proportion n=377	Mean±SD or proportion n=178		
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
			t value	
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/m2)	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

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

ORS- Omnibus risk score

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% C I)	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

FRS*- Framingham risk score FRS without calibration factor

ORS- Omnibus risk score

CRF- Conventional Risk Factors (age, sex, alcohol, cholesterol, diabetes, smoking, systolic blood pressure, diastolic blood pressure)

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	R²
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

FRS*- Results for FRS without calibration factor

ORS- Omnibus risk score

**
- Distorted results

#
- Estimate not reliable due to distorted results

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