

**PREVALENCE OF CAROTID ARTERY STENOSIS
AND IT'S RISK FACTORS IN PATIENTS WITH
ISCHAEMIC STROKE AS SEEN IN KENYATTA
NATIONAL HOSPITAL //**

**A DISSERTATION SUBMITTED IN PART FULFILMENT OF THE
REQUIREMENTS FOR THE AWARD OF MASTER OF MEDICINE IN
INTERNAL MEDICINE OF
THE UNIVERSITY OF NAIROBI**

BY

DR MWASHA K. MWAZO

MBChB (Nairobi)

2007

University of NAIROBI Library



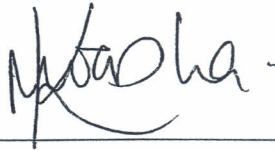
0442594 8

**UNIVERSITY OF NAIROBI
MEDICAL LIBRARY**

DECLARATION.

I certify that this dissertation is my original work and has not been presented for a degree award at any other university.

Signed _____



DR. MWASHA K. MWAZO.

Supervisors:

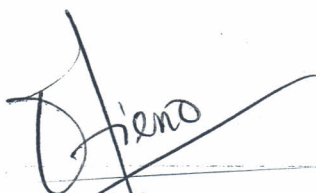
Signed



Prof. E. O. Amayo

Consultant Neurologist, Associate Professor,
Department of Medicine, University of Nairobi.

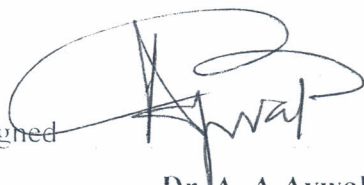
Signed



Dr. C. F. Otieno

Consultant Physician, Senior Lecturer,
Department of Medicine, University of Nairobi.

Signed



Dr. A. A. Aywak

Consultant Radiologist. Lecturer and Chairman.
Department of Radiology and Nuclear Medicine, UON

DEDICATION

This research is dedicated to all the people who continue to suffer from stroke, which through risk factor identification and modification can be prevented. It is my hope that many patients with risk factors for stroke will benefit from this attempt to do a risk factor profiling. This will initiate awareness among persons involved in the care of patients with cerebrovascular risk factors.

ACKNOWLEDGEMENTS

I thank my God who gave me new strength and enthusiasm every challenging day.

I thank my supervisors Prof. E.O. Amayo, Dr. A.A. Aywak, Dr. C.F. Otieno who have spent many hours sharpening my skills. I have learnt so much from their attention to detail and excellence.

I thank Dr. Albert Huho for his tireless assistance with data analysis, as well as my research assistants Kwoba and Mbugua.

I thank Dr Onyambu and Dr Mwangi who assisted tirelessly in doing the carotid dopplers.

The spirit of my belated Mum Maria-Loice Biubwa who never lived to enjoy the fruits of her labour.

Most of all my dear wife Margaret, my sons Michael and Mark, daughters Mitchelle and Mariah who have walked with me every step of the way and sacrificed so much to see me through the programme.

TABLES OF CONTENTS

	Page Number
1. Title	1
2. Declaration	2
3. Supervisors	3
4. Dedication	4
5. Acknowledgement	4
6. List of tables and figures	6
7. List of abbreviations	7
8. Abstracts	10
9. Introduction and Literature review	11
10. Objectives	19
11. Materials and Methods	20
12. Results	25
13. Discussion	35
14. Limitations	40
15. Conclusions	40
16. Recommendations	40
17. References	41
18. Appendixes	50

LIST OF TABLES AND CHARTS:

Tables:

1. Summary of patients demographic and baseline characteristics	26
2. Clinical Characteristics and drug history of study population	29
3. Risk factors distribution between patients with large vessel versus small vessel disease	31
4. Spectral Doppler velocities and plaque estimate correlated with degree of ICA Stenosis Diameter	50

Figures:

1. Illustration of the Imaging sites in the command Internal carotid arteries.....	23
2. Flow of patients in the study	25
3. Age and sex distribution of 126 patients with Ischaemic stroke.....	27
4. Distribution of Patients by gender and occupation.....	28
5. Territorial distribution of infarcts.....	30
6. Distribution of carotid artery Stenosis among patients with Ischaemic stroke.....	32
7. Overall prevalence of risk factors among Ischaemic stroke patients	33

GLOSSARY

APO A	-	Apolipoprotein A
APO B	-	Apolipoprotein B
BMI	-	Basic metabolic index
CRP	-	C - reactive protein
CHD	-	Coronary Heart Disease
CVD	-	Cardiovascular Disease
DBP	-	Diastolic Blood Pressure
FPG	-	Fasting Plasma Glucose
HDL	-	High Density Lipoprotein
IFG	-	Impaired Fasting Glucose
KNH	-	Kenyatta National Hospital
LDL	-	Low Density Lipoprotein
MI	-	<i>Myocardial Infarction</i>
NCEP/ATPIII	-	National Cholesterol Education Program/ Adult Treatment Panel III
SBP	-	Systolic Blood Pressure
WHO	-	World Health Organization
CVA	-	Cerebrovascular Accident
VLDL	-	Very Low Density Lipoproteins
STOP- 2	-	Swedish Trial in Old Patients with Hypertension 2
Type 2 DM	-	Type 2 Diabets Mellitus
WC	-	Waist Circumference
TIA	-	Transient Ischaemic Attack
MS	-	Mitral Valve Stenosis
HIV	-	Human Immunodeficiency Virus
ICA	-	Internal Carotid Artery
CCA	-	Common Carotid Artery
PSV	-	Peak Systolic Velocity
GCS	-	Glasgow Coma Scale
HPS	-	Heart Protection Study

MONICA	-	Monitoring Trends and Determinants in Cardiovascular Disease
EUROSTROKE	-	European Stroke Trial
OCSP	-	Oxfordshire Community Stroke Project
TACI	-	Total Anterior Circulation Infarct
PACI	-	Partial Anterior Circulation Infarct
LACI	-	Lacunar Infarct
POCI	-	Posterior Circulation Infarct
UKPDS	-	United Kingdom Prospective Diabetic Study
NIHSS	-	National Institute of Health Stroke Score
ICH	-	Intra Cerebral Haemorrhage
SAH	-	Subarachnoid Haemorrhage
SHEP	-	Systolic Hypertension in the Elderly Programme
FHS	-	Framingham heart study
NASCET	-	North American Symptomatic Carotid Endarterectomy trial
ECST	-	European Carotid Surgery Trial
CAIMT	-	Carotid Artery Intimal Media Thickness
RES	-	Rotterdam Elderly Subjects Study
ARIC	-	Atherosclerosis Risk in Communities Study
IST	-	International Stroke Trial
NINDS	-	National Institute of Neurological Disorders and Stroke
MACE	-	Mayo Asymptomatic Carotid Endarterectomy Trial
ACAS	-	Asymptomatic Carotid Atherosclerosis Study
CHS	-	Cardiovascular Health Study
TASS	-	Ticlopidine Aspirin Stroke Study
CAPRIE	-	Clopidogrel versus Aspirin for the Prevention of Recurrent Ischaemic Events trial.
ASAP	-	Artovastatin versus Simvastatin on Atherosclerosis Progression trial
HTI	-	Hemorrhagic Transformation of an Infarct
ASCOT	-	Angloscandinavian Cardiac Outcomes Trial

LIFE	-	Losartan Intervention for End point reduction in hypertension study
PROGRESS	-	Perindopril Protection against Recurrent Stroke Study.
HOPE	-	Heart Outcomes Prevention Evaluation
ALLHAT	-	Anti-hypertensives and Lipid Lowering treatment to prevent heart attack trial
4S	-	The Scandinavian Simvastatin Survival Study
LIPID	-	Long Term Intervention with Pravastatin in Ischaemic Disease
NORDIL	-	The Nordic Diltiazem Study
RCT'S	-	Randomised controlled trials
IMT	-	Intimal Media Thickness
ICA	-	Internal Carotid artery
SRU	-	Society of Radiologists in Ultrasound
CDUS	-	Carotid Doppler ultrasound
DSA	-	Digital Subtraction Angiography
CTA	-	Computerised Tomographic Angiography
MRA	-	Magnetic Resonance Angiography
CAS	-	Carotid Artery Stenosis
AHA	-	American Heart Association
ASA	-	American Stroke Association
DCCT	-	Diabetes control and complications trial
EDIC TRIAL	-	Epidemiology of Diabetes Interventions and complications trial
NOMASS	-	Northern Manhattan Stroke Study
BCID	-	Berlin Cerebral Ischaemia Data Bank
TNT	-	Treating To New Targets Trial
SPARCL TRIAL	-	Stroke Prevention by aggressive Reduction in cholesterol levels

ABSTRACT

Background: Stroke is the third most common cause of death worldwide and a leading cause of severe disability. Carotid artery stenosis is an important cause of ischaemic stroke and therefore closely related to cardiovascular morbidity and mortality. The carotid Doppler ultrasound is a non invasive method that facilitates the assessment of carotid artery stenosis. It remains unclear whether carotid artery stenosis is as prevalent among Africans with ischaemic stroke as it is in white populations and also whether the risk factors responsible for the development of carotid artery stenosis in whites apply to blacks.

Objective: To determine the prevalence of Carotid artery stenosis and its risk factors among ischaemic stroke patients as seen in KNH a tertiary referral health facility in Nairobi Kenya.

Design: A cross sectional prospective study.

Setting: Medical wards and the neurology clinic of KNH.

Subjects: Adult patients above the age of 45 years presenting with ischaemic stroke at KNH

Results: One hundred and twenty six patients fulfilled the inclusion criteria. Significant carotid artery stenosis of 70% or more was present in two (1.6%) of the patients. Thirty one (24.6%) of the patients had normal carotids while mild (< 50%) and moderate (51-69%) stenosis were observed in 88 (69.8%) and 5 (4%) of the patients respectively. Risk factors for ischaemic stroke were present in the following proportions: Dyslipidaemia 76%, Hypertension 74.6%, Diabetes mellitus 30.2%, smoking 28.6%, obesity 26.2%, excessive Alcohol consumption 17.5%, and impaired fasting glucose in 16.9%. All the patients had one or more risk factors.

Conclusion

Significant Carotid artery stenosis has a low prevalence of (1.6%) among patients with ischaemic stroke presenting in KNH. With limited resources in our set up, routine screening for extracranial carotid artery disease may not provide extra information to determine stroke aetiology. More resources should be directed towards controlling hypertension, dyslipidaemia, diabetes mellitus and smoking cessation campaigns.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Risk Factors for Ischaemic Stroke.

Stroke is the third leading cause of death and among the leading causes of disability in the United States, Europe and many developing countries [1]. Extracranial carotid artery stenosis is one of the leading causes of ischaemic stroke and therefore closely related to cerebrovascular morbidity and mortality [2-4]. Significant atherosclerotic narrowing of the internal carotid artery ipsilateral to the infarct is found in 20% to 30% of those investigated [5-7] compared with 5% to 10% of the general population [8,9]. Non modifiable risk factors for ischaemic stroke include old age, black race and male gender while hypertension, transient ischaemic attacks, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption, physical inactivity, obesity are modifiable [10].

1.2 Risk Factors for Carotid Artery Stenosis

Atherosclerosis is a systemic disease with manifestations in multiple vascular beds. In each regional circulation, clinical events result from progression of the atherosclerotic lesion. Cerebral infarction may result from the reduction in cerebral perfusion pressure that occurs distal to a tight carotid stenosis or occlusion, [11-14]. Plaque instability, rupture, local thrombus formation and distal embolization are also likely to be important [15, 16]. Risk factors associated with carotid artery stenosis include:

1.2.1 Hypertension

According to WHO, 600 million people worldwide are hypertensive, out of which; 30 million people are in Africa. It is the single most important treatable risk factor for stroke and approximately 60% of strokes in men and women of all ages are attributable to Hypertension. It promotes the formation of atherosclerotic lesions at the bifurcation of common carotid artery.

Prospective population based observational studies have shown a continuous, positive relationship between blood pressure and the risk of stroke or other major vascular events. Risk of stroke increases with increasing BP in patients with symptomatic carotid artery disease.

The best evidence for a causal role of increasing BP in cardiovascular disease is an improvement in outcome with antihypertensive therapy as shown in the SHEP [17] and ALLHAT[18] trials.

ALLHAT, a mega study that included high-risk hypertensive patients, had useful lessons for patients in developing countries. This is because it had a significant black population and also patients with carotid artery stenosis. It successfully used the pharmacological agents; thiazides, lisinopril, and calcium channel blockers that may be relatively easy to access by patients in the developing world. It included 33,357 patients with mild to moderate hypertension and at least one risk factor for cardiovascular disease. The study found no clinically important differences between the three drug classes in reducing the risk of coronary heart disease. The ACEI was less effective than the diuretic at protecting against stroke and heart failure especially in blacks.

Limited data exists to address the value of antihypertensive therapy in patients with carotid stenosis. Concerns have been raised about the safety of blood pressure lowering with severe carotid disease.

One study addressed this issue by looking at the relationship between blood pressure and the risk of stroke in medically treated patients in 2 major randomised controlled trials (RCTS) of Carotid endarterectomy and one major RCT of aspirin. The risk of stroke increased with increasing BP in patients with symptomatic carotid artery disease and, to a similar degree, in patients with unilateral carotid occlusion. In contrast, among patients with bilateral >70% carotid stenosis, the risk was inverted and patients with lower SBP had more events. The study recommended that if it is elected to attain usual BP goals (140/90mmhg) in hypertensive patients with severe bilateral carotid stenosis, the blood pressure should be lowered gradually [19].

Guidelines issued in 2006 by the AHA/ASA [20] recommend antihypertensive treatment for all patients with ischaemic stroke and TIA. Target blood pressure in this setting is not well defined and should be individualized. A goal of <140/90 mmhg seems reasonable for most patients. However the applicability of these goals to the very elderly >80 years has been challenged as aggressive treatment may be associated with high mortality.

1.2.2 Diabetes

Globally the prevalence of diabetes is rising relentlessly and now affects 5.9% of people aged 20-79 years. Almost 80% of people with the disease live in developing world. Patients with diabetes mellitus have about twice the risk of ischemic stroke when compared with the general population. Dyslipidemia, endothelial dysfunction, and platelet and coagulation abnormalities are among the risk factors that may promote the development of carotid atherosclerosis in diabetics. Impaired glucose tolerance itself appears to be a risk factor for carotid atherosclerosis, as illustrated by studies in non-diabetics showing that elevated serum hemoglobin A1c is associated with an increased risk of carotid plaque development [21, 22].

Tight glycemic control, which is important in the prevention of micro-vascular complications of type 2 diabetes mellitus, has not been shown to be effective for preventing stroke or other macro vascular disease. The EDIC arm of DCCT trial despite its small sample size has demonstrated a marked reduction in the risk of macro vascular complications among patients with type 1 diabetes mellitus [23].

1.2.3 Tobacco use

Meta- analysis of 22 observational studies have shown that, smoking increases the risk of stroke by approximately 50% and it is estimated that smoking is responsible for 12% of all strokes.

Henning Mast [24] et al did a study to investigate the association of cigarette smoking with high-grade carotid stenosis in Hispanic, Black and white patients with cerebral ischemia in 2 independent samples. Their data was collected from North Manhattan Stroke Study (NOMASS) and the Berlin cerebral ischemia databank (BCID) .High grade carotid stenoses were found in 14% of the NOMASS and in 21% of the Berlin patients. In Berlin the entire sample was white whereas in New York only 19% of the cohorts were white. *In both samples smoking was independently associated with severe carotid stenosis. Patients smoking 20 pack years or more showed a significant association.*

1.2.4 Obesity

Obesity is associated with other cardiovascular risk factors and it is not surprising that it is also associated with an increased risk of stroke. However, abdominal obesity in men and weight gain in women both appear to be independent risk factors for stroke.

1.2.5 High serum cholesterol.

Hyperlipidemia is a major risk factor for coronary heart disease. However, the relationship between the serum cholesterol concentration and stroke incidence appears to be more complex, in that cholesterol is an established risk factor for atherosclerosis, but appears to be only a weak risk factor for ischemic stroke [25, 26].

Both low levels of high-density lipoprotein (HDL) cholesterol and a high total-to-HDL-cholesterol ratio are risk factors for the development of carotid atherosclerosis [27, 28, and 29]. This association is already apparent in patients with asymptomatic carotid disease [30]. This appears to be a graded effect; data from the Framingham Heart Study found an odds ratio for carotid stenosis of 1.10 for every 10 mg/dL (0.26 mmol/L) elevation in serum cholesterol [31]. In addition, a prospective population-based longitudinal study found that HDL levels were inversely associated with carotid plaque growth, suggesting that HDL may stabilize plaques [32]. Best evidence for role of dyslipidaemia in cardiovascular disease is an improvement in outcome with statin therapy as shown in the TNT (Treating to New Targets trial) [33] and SPARCL (stroke prevention by Aggressive Reduction in Cholesterol levels) trials [34].

In the **TNT trial**, 10,001 patients with stable coronary heart disease (CHD) and a baseline LDL-C between 3.4 mmol/L and 6.5 mmol/L were randomly assigned to treatment with Atorvastatin at a low (10 mg daily) or a high (80 mg daily) dose. About 5 percent of patients in each treatment group had a history of ischemic stroke. At a median follow-up of 4.9 years, the following outcomes were reported comparing high-dose with low-dose atorvastatin:

- (i) A significantly lower mean serum LDL-C concentration (2.0 versus 2.6 mmol/L).

(ii) Significant reduction in the rate of fatal or nonfatal stroke (hazard ratio [HR] 0.75, 95% CI 0.59-0.96)

(iii) Significant reductions in the primary outcome measure, the composite rate of major cardiovascular events, defined as death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke (8.7 versus 10.9 percent, HR 0.78, 95% CI 0.69-0.89).

(iv) No reduction in overall mortality (HR 1.01, 95% CI 0.85-1.19). The reason for the lack of benefit on mortality was unclear.

The first direct evidence that high dose statin therapy is of benefit for secondary prevention of stroke in patients with a prior stroke or TIA without coronary heart disease and with normal cholesterol levels came from the **SPARCL** trial. In this trial, primary end points of recurrent fatal and non-fatal stroke were reduced by 16% ($p=0.03$) as compared to the placebo group. The secondary end points were risk of coronary, carotid and peripheral revascularisation procedures, which were lower in the atorvastatin group with a significant p value of 0.001.

1.2.6 Alcohol

Alcohol affects the risk of stroke in contradictory directions depending upon level of consumption, type of stroke, and possibly ethnicity. Light drinking (one to two drinks per day) appears to reduce risk, while heavy drinking increases risk.

National guidelines from the American Heart Association and American Stroke Association (AHA/ASA) issued in 2006 recommend that patients with ischemic stroke or transient ischemic attack (TIA) who are heavy drinkers should eliminate or reduce their alcohol consumption.

The Nurses Health study [35] found a protective effect of mild alcohol consumption (up to 1.2 drinks per day) for ischaemic stroke. A Japanese study did not show a protective effect of alcohol. In Northern Manhattan, a J-shaped relationship between alcohol and

ischaemic stroke existed. A protective effect on stroke was seen with light to moderate alcohol use, four or fewer drinks per day.

1.3 Carotid Artery Stenosis as a Risk Factor for Ischaemic Stroke

Although it is likely that some strokes associated with carotid artery stenosis result from non-compensated hypo-perfusion the majority of such strokes appear to occur as a result of embolization from atherosclerotic carotid plaque or from acute occlusion of the carotid artery and cephalic propagation of thrombus.

At the Western General Hospital in Edinburgh, Mead et al studied 259 inpatients and outpatients with a recent lacunar ischaemic stroke and no other prior stroke. He used carotid Doppler ultrasonography and transcranial Doppler to identify Internal Carotid artery and Middle Cerebral Artery disease. The overall prevalence of severe ipsilateral stenosis was 5% and the prevalence of severe, contralateral stenosis was 4% [36].

A retrospective study of 200 consecutive patients with first ever Ischaemic stroke admitted to Jordan University was carried out over a 2-year period. The most common stroke subtype was lacunar infarction (51.5%); but frequency of cardio embolic stroke was low, 8%. Hypertension, Diabetes Mellitus, and smoking were the most common risk factors for atherosclerotic non-cardioembolic stroke. Chronic atrial fibrillation was the most common risk factor for cardio-embolic stroke. No patient had severe extra cranial carotid or vertebral artery stenosis (>50% narrowing) by ultrasonography [37].

Among the Chinese, a study was conducted to find out the aetiology of Ischaemic stroke among young patients aged between 18 and 45 years between January 1997 and October 2001. A total of 264 consecutive stroke patients were admitted to the Department of neurology university of Taiwan. The four most common risk factors were hyperlipidaemia(53.1%),smoking(49.8%) hypertension(45.8%), and family history of stroke (29.3%).Using ultrasonography, significant carotid artery stenosis of >50% was present in 7.5% of the subjects[38].

A retrospective study to find out the race, presenting signs, symptoms, and use of carotid imaging and appropriateness of carotid endarterectomy was carried out among 803 patients aged over 45 years by Eugene et al in the Veteran affairs trial. These patients were hospitalised between 1991 and 1994 at four veteran affairs medical centres with a diagnosis of TIA or Ischaemic stroke. Blacks were found to be more likely than whites to present with stroke and less likely to present with TIA. In terms of arterial stenosis in the portion of the internal carotid artery distal to that considered potential for carotid endarterectomy, 7% of blacks and 6% of whites had high grade stenosis >70%[39].

1.4 African Studies on Carotid Artery Stenosis

In a review of CVA patients in KNH by Bahemuka through 1975-1979, his subjects gave no history of TIA. He did carotid angiography in 73 selected patients out of which 51% had normal angiography. Extra-cranial arterial abnormalities were uncommon and over 70% of all occlusions or stenosis involved the intracranial vessels, the middle cerebral artery or its branches. Internal carotid artery occlusion or stenosis was seen in 6% of all the patients [40].

From the literature review, studies focussing on carotid atherosclerosis in black Africans are lacking, and no study could be found regarding carotid artery stenosis in Kenya, yet this is a potentially modifiable risk factor for Ischaemic stroke. Carotid doppler ultrasound is recommended as a modality for evaluating carotid arteries because of its non-invasive nature, ready availability and low cost. Feussner and Matchar [41] in 1988 reported a sensitivity of approximately 85 % (range 82-100%) and a specificity of approximately 90% (range 81-100%) in a review of 11 studies.

2.0 RATIONALE AND JUSTIFICATION

Stroke is the third most common cause of death worldwide after heart diseases and cancer. According to WHO estimates, 15 million people each year suffer strokes and 5 million are left permanently disabled. In 2002, about 5.5 million deaths occurred due to strokes.

Significant carotid artery stenosis is one of the leading causes of ischaemic stroke. It is a potentially modifiable risk factor that is also associated with morbidity in terms of transient ischaemic attacks and cognitive dysfunction. Its clinical relevance can be expected to increase in view of the growing number of elderly people with advanced atherosclerosis.

Numerous studies have been done in Europe, North America to establish the prevalence of carotid artery stenosis and its risk factors in patients with ischaemic stroke. To the best of our knowledge, there are no studies among Africans, which have investigated carotid artery stenosis, and its risk factors among Ischaemic stroke patients.

Data generated by this study on the prevalence of carotid artery stenosis in our set up will provide physicians involved in stroke management with knowledge on the risk factor profile of our local population and the likelihood of carotid artery stenosis and thus allocate resources rationally when investigating and managing ischaemic stroke patients and in secondary stroke prevention.

3.0 OBJECTIVES

3.1 Broad Objectives

To determine the prevalence of carotid artery stenosis and its major risk factors in patients over 45 years with ischaemic stroke at KNH

3.2 Specific Objectives

1. To Determine the prevalence of carotid artery stenosis among patients diagnosed with ischaemic stroke in KNH
2. To determine the prevalence of the following risk factors: hypertension, diabetes, smoking, dyslipidemia, Alcohol consumption, and obesity among patients with carotid artery stenosis as seen in KNH

4.0 STUDY DESIGN AND METHODOLOGY

4.1 Study Design

This was a hospital based cross-sectional prospective study.

4.2 Study Site and Population

The study was conducted at Kenyatta National Hospital medical wards and neurology clinic and it included adults aged over 45 years presenting with ischaemic stroke.

4.3 Sampling Design

Consecutive sampling of all ischaemic stroke patients.

4.4 Inclusion Criteria

- (1) All adult patients over 45 years of age with a diagnosis of ischaemic stroke evidenced by a CT/MRI scan.
- (2) Informed consent to participate in the study.

4.5 Exclusion Criteria

- (1) Any patient who declined to participate in the study
- (2) Patients with valvular heart diseases.

4.6 Data Collection, Material and Procedures:

Clinical History and Examination

The investigator visited the neurology clinic on Mondays and the medical wards on the post-admission day. Consecutive Patients with stroke were reviewed together with their CT /MRI scans. Those found to have an ischaemic stroke on CT/MRI were interviewed and invited to take part in the study that was approved by the university of Nairobi Department of internal medicine and the Ethics research committee KNH.

After informed consent, a thorough history assessing for absence or presence of stroke risk factors such as hypertension, cardiac diseases, diabetes mellitus, cigarettes smoking, dyslipidaemia, alcohol abuse, obesity, use of oral contraceptives, statins, antiplatelets and a family history of stroke or sudden death in first degree relatives was taken and an investigator-administered questionnaire was filled.

All the participants underwent a basic vascular and neurological examination and were classified into the various clinical stroke subtypes according to the Oxfordshire community stroke project. With a standard mercury sphygmomanometer, the systolic and diastolic blood pressures were taken while the patients were in a seated position, and the mean was determined from two independent measurements, taken five minutes apart. Waist circumferences were measured using a tape measure the standard way. Diabetes mellitus was diagnosed if the patient admitted to be diabetic, or were being treated with insulin or oral hypoglycaemic drugs or if their fasting plasma glucose was ≥ 7.1 mmol. The average number of cigarettes smoked per day and the number of years smoked (pack years) were noted for each smoker. Alcohol consumption was quantified from each subjects estimate of the average amount of alcohol ingested daily or weekly. Patients were then advised to have an overnight fast.

Laboratory Methods:

Venous **6mls** sample of blood was drawn from an accessible antecubital vessel in the morning from each patient after at least 10 hours of fasting. Analysis was done at the University of Nairobi, Department of Biochemistry. **1ml** was analysed for plasma glucose and **5mls** for lipid profile.

Plasma glucose was measured by the glucose oxidase method on the Olympus AU 400 auto-analyser.

Dyslipidaemia was assessed using the cholesterol oxidase and esterase calorimetric method CHOD-PAP. The blood lipid fractions included Total cholesterol (enzymatic colorimetric method), HDL cholesterol (precipitation with phosphotungstic acid-MgCl₂ and enzymatic colorimetric determination of the cholesterol in the supernatant), Triglycerides (enzymatic colorimetric method) and LDL cholesterol level was calculated

from the total cholesterol concentration (TC), the HDL-C and the triglyceride concentration (TG) according to the Friedwald [42] et al equation i.e.

$$\text{LDL-C} = \text{TC} - (\text{HDL} + \text{TG}/2.2 \text{MMOL/L}).$$

Lipid abnormalities were classified as per the National Cholesterol Education Program/ Adult Treatment Panel III.

Assessment of carotid stenosis.

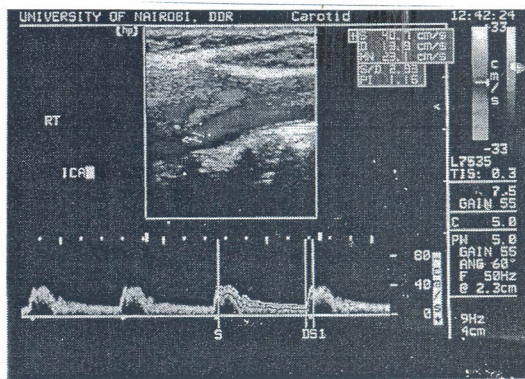
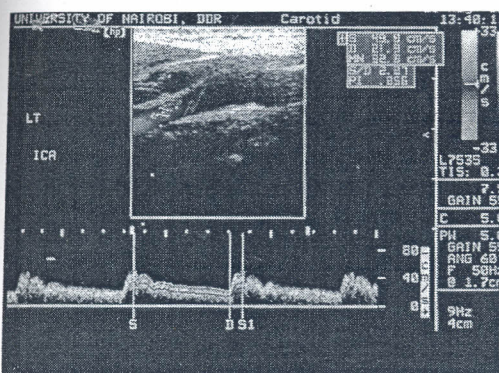
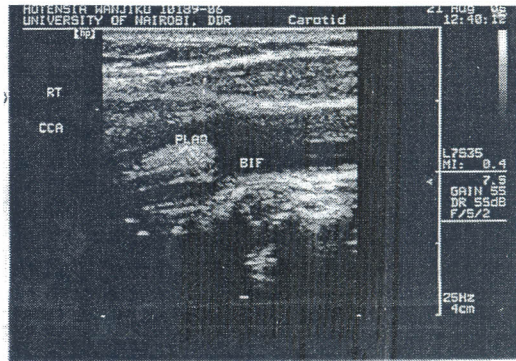
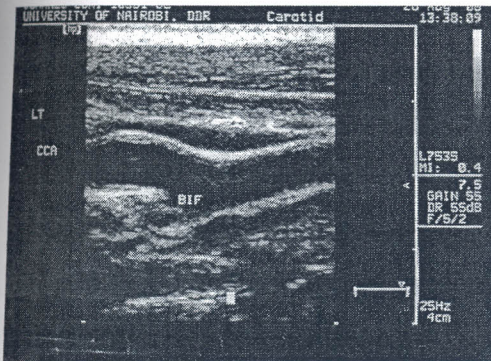
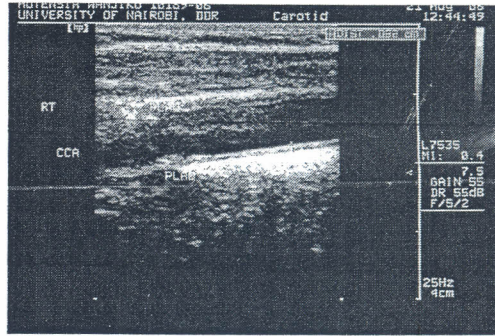
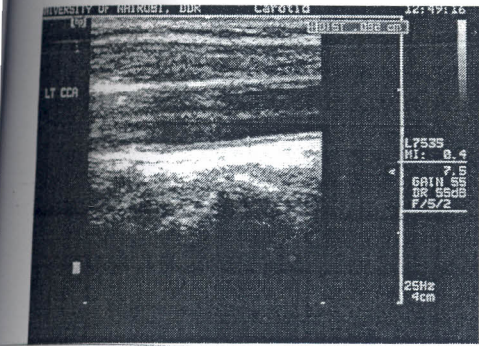
Carotid Doppler ultrasonography was done at the University of Nairobi, department of radiology at KNH by AAA, a specialist radiologist assisted by two other radiologists. The *Logiq 5 expert* machine from General electric was used.

B-mode ultrasound scanning of the carotid arteries was performed. A 10 mHZ transducer was used to provide imaging at 10 mHZ and spectral Doppler at 7mHZ, with the spectral angle of interrogation being maintained at 60°. The subjects lied supine with the neck extended and the chin turned contra lateral to the side being examined. The Scanning protocol involved examination of the carotid arteries first in a transverse plane then longitudinally. The whole length of the extra cranial carotid artery i.e. the common carotid at the lower, mid and distal portions including the bifurcation, and the extra cranial internal carotid artery were assessed as distal as possible. The wall was examined for plaques and degree of stenosis evaluated using peak systolic and diastolic velocities.

The consensus conference of the society of radiologist's 2005 guidelines for grading the severity of carotid artery stenosis was followed in both procedure and reporting [65]. The procedure was repeated for each side of the neck. The side with a severe degree of stenosis was taken to represent the extent of atherosclerosis in a patient .The degree of ICA stenosis was defined as <50 %(mild), 51-69 %(moderate), 70-99 %(significant) and total occlusion. See appendix 1

To ascertain the reliability of our observers in measuring the degree of carotid artery stenosis, we undertook a pilot study on 5 individuals. We examined the inter-examiner and intra-examiner reliability.

Figure 1: Illustration of the imaging sites in the common and internal carotid arteries.



4.7 Study Variables (see Appendix 1)

4.8 Sample Size [43]

The minimum sample size was determined using the formula:

$$n = \frac{z^2 p (1-p)}{d^2}$$

n = minimum sample size

z = standard normal deviate at 95% confidence interval. (=1.96)

p = estimated prevalence of carotid artery stenosis which in this study was 7.5% as found by Tsong Hai Lee et al in a similar study [28].

d = level of precision (set at +/- 5%)

n = 106 was the required minimum sample of Ischaemic stroke patients

5.1 Data Handling and Statistical Analysis

All laboratory and radiological results were in duplicate. One copy was availed to the patients file while the principal investigator handled the second copy. Data was entered into proforma then analysed using the statistical package for social sciences (SPSS inc.version14.0 the Chicago, IL, USA). The following analyses were used: frequency distribution, descriptive statistics, and chi-squared test.

Prevalence rates of risk factors were calculated as percentages with 95% confidence intervals.

The intra and inter-observer reliability in carotid ultrasonography was assessed using the intra and inter class correlation coefficient.

Criteria for statistical significance were defined as a two tailed p value of \leq to 0.05.

5.2 Ethical Approval

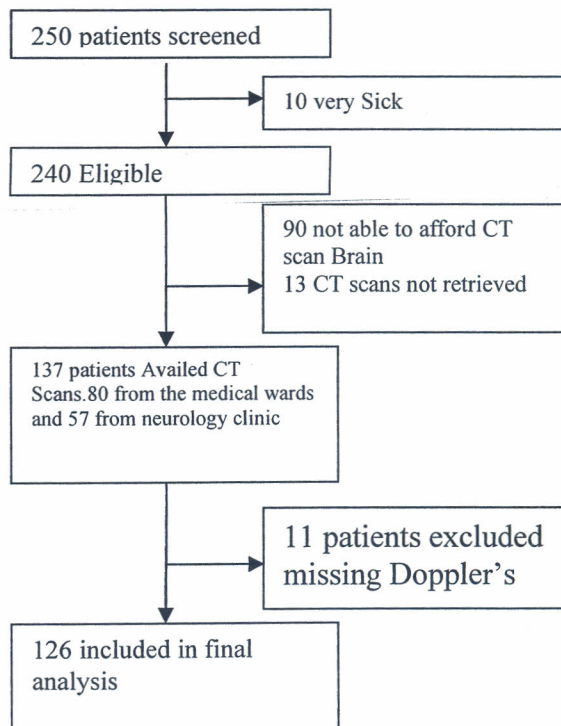
The department of internal medicine, U.O.N and the ethical research committee, KNH approved the study.

6.0 RESULTS

Two hundred and fifty patients with Cerebrovascular accidents were screened and 137 had confirmed ischaemic stroke and underwent a carotid Doppler ultrasound examination. Eleven patients were excluded for various reasons. Six had incomplete carotid Doppler results and five had missing lipid profile results. See figure 2.

The demographic distribution, baseline characteristics and risk factor profile of excluded patients were not substantially different from the 126 patients included in the final analysis.

FIGURE 2: FLOW OF PATIENTS IN THE STUDY



The mean age in the study was 59.54 ± 11.83 years with a range from 45-88 years and a median of 58 years. There were more males 79(62.7%) than females 47(37.3%) giving a male to females ratio of 1.7:1. Majority of the patients 92(73.6%) were married and 39(31%) had retired. On occupation; 35(27.8%) were self employed. Most of the patients

73(59.3%) came from Nairobi. The demographic characteristics of the entire study population are presented in table 1, figure 3 and 4.

Table 1: Summary of Patients Demographics and Baseline Characteristics

sex	male	62.7(79)
	Female	37.3(47)
Age	mean \pm SD	59.54 \pm 11.83
	<i>Range</i>	<i>45-88</i>
	Median	58
Marital Status	Single	5.6% (7)
	Married	73.6% (92)
	Divorced	0.8%(1)
	Widowed	20.0%(25)
Occupation	Self Employed	27.8%(35)
	Employed	18.3%(23)
	Unemployed	23.0%(29)
	Retired	31.0%(39)
Residence	Within Nairobi	59.3%(73)
	Out of Nairobi	40.7%(53)

FIGURE 3:

age sex distribution of 126 patients with ischaemic stroke

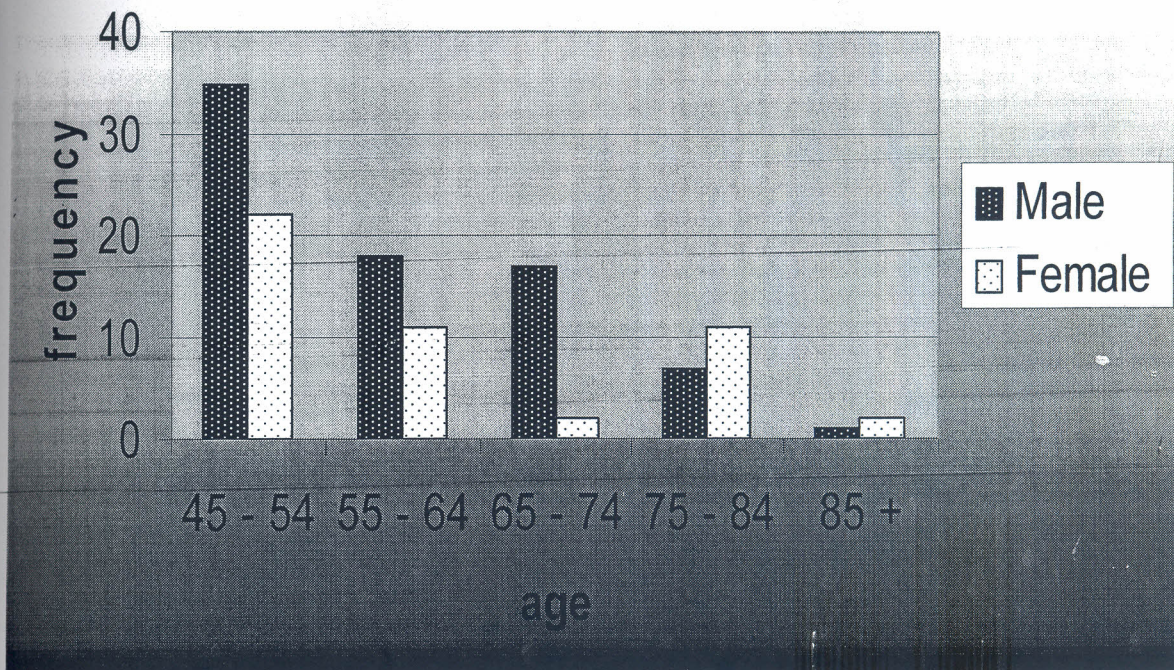
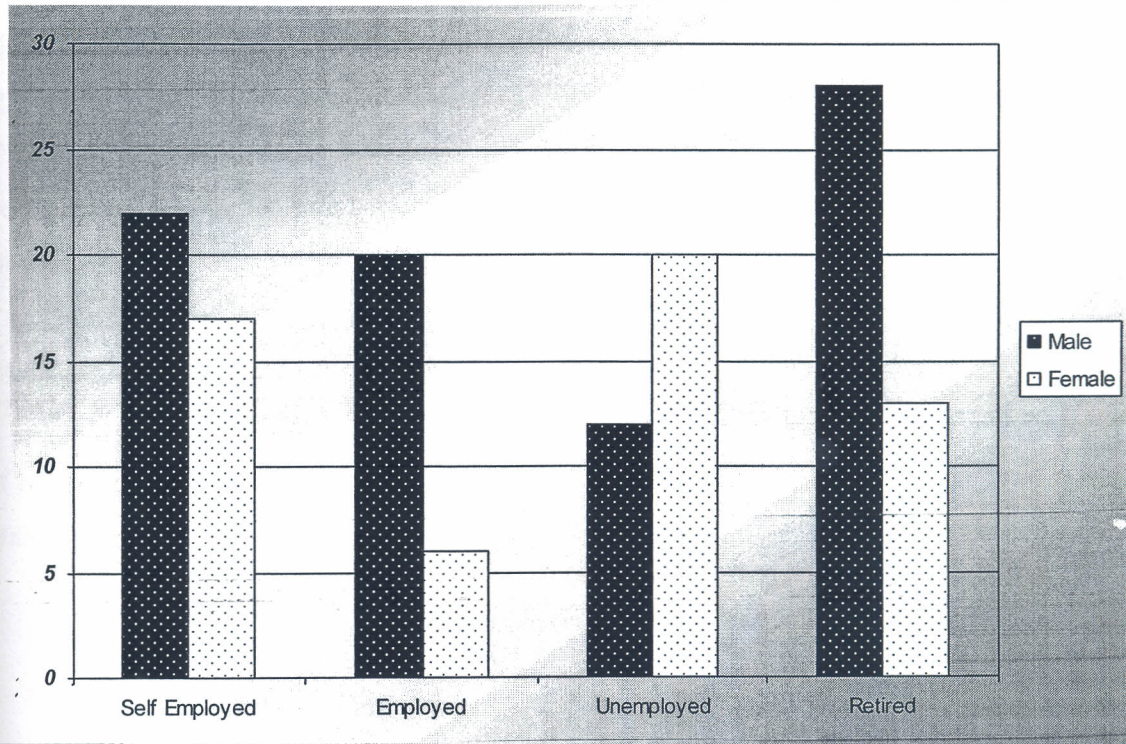


Figure 4: DISTRIBUTION OF PATIENTS BY GENDER AND OCCUPATION.



Patients had the following chronic illnesses: Eighty three (65.9%) had hypertension, of which 66 (79.5%) were on antihypertensive medication, 33 (26.2%) had Diabetes mellitus, of which 28 (84.8%) were on various forms of blood sugar lowering medicines. Twenty one (16.7%) had a previous stroke, out of which eight, were on Aspirin. Sixteen (12.7%) had reported a history suggestive of a TIA none of whom were on antiplatelets. Three patients were on lipid lowering drugs. Fifteen (11.9%) of the women had used oral contraceptive pills.

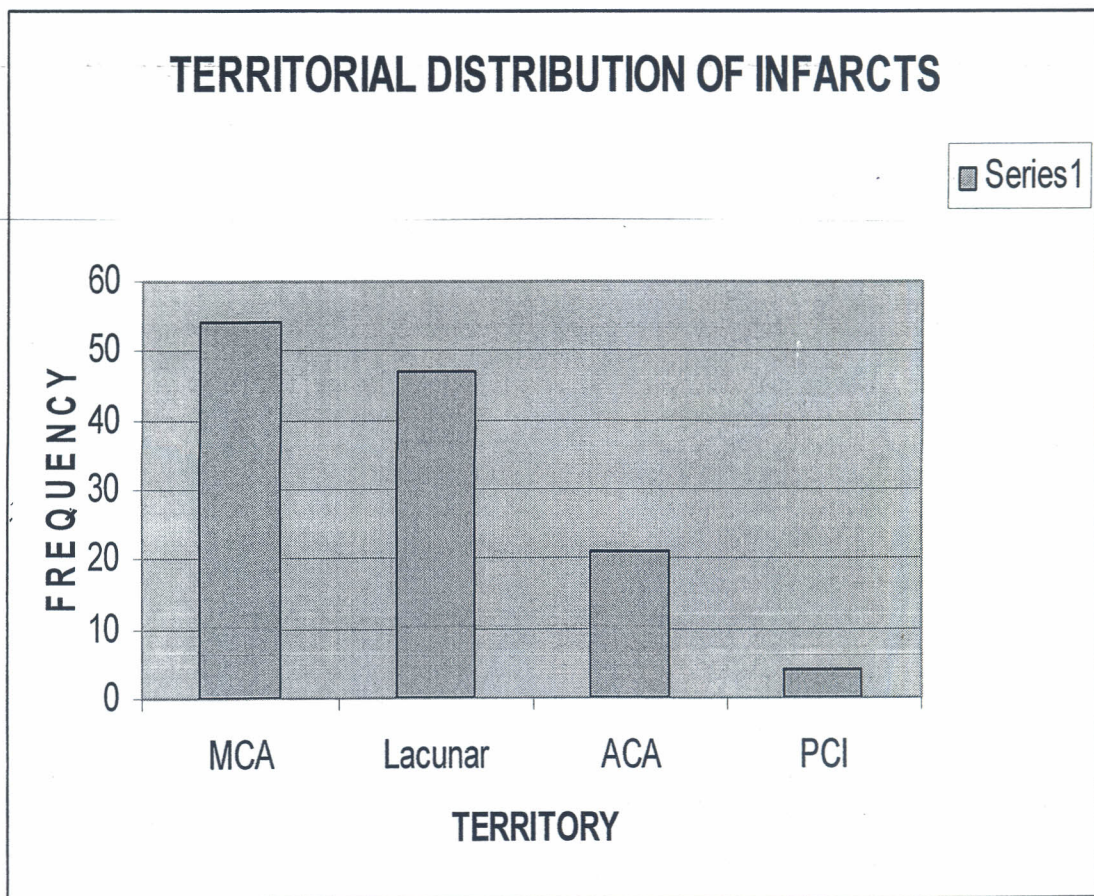
TABLE 2: CLINICAL CHARACTERISTICS AND DRUG HISTORY OS STUDY POPULATION.

No of patients	126
Hypertension	94(74.6%)
Known	83
Newly diagnosed	11
On treatment	66 (79.5 %)
Diabetes mellitus	38(30.2%)
Known	33
Newly diagnosed	5
On treatment	28 (84.8%)
Current smoking	36(28.6%)
Past history of stroke	21(16.7%)
Use of Aspirin	8
TIA	16(12.7%)
Hyperlipidaemia	95(76%)
Known	3
Newly diagnosed	92
On treatment	3

A modified Glasgow coma scale (see Appendix 1 question 29) was used to assess the level of consciousness. 104(90.5%) of the patients were in light coma while 12(9.5%) were in deep coma.

The following were the CT scan finding: Seventy percent of the patients had left sided infarcts by CT scan. Majority of the cases had large vessel infarcts (62.8%) distributed as follows, 21 (16.6%) were in the anterior cerebral artery territory, 54(42.9%) were in the middle cerebral artery territory, this amounts to 59.5% of the infarcts being in the carotid territory. Four (3.2%) were posterior cerebral infarcts and 47(37.3%) were lacunar infarctions.

FIGURE 5: TERRITORIAL DISTRIBUTION OF INFARCTS



Analysis of risk factors in patients with small versus large vessel disease did not reveal any statistical significant differences as shown in table 3.

TABLE 3:

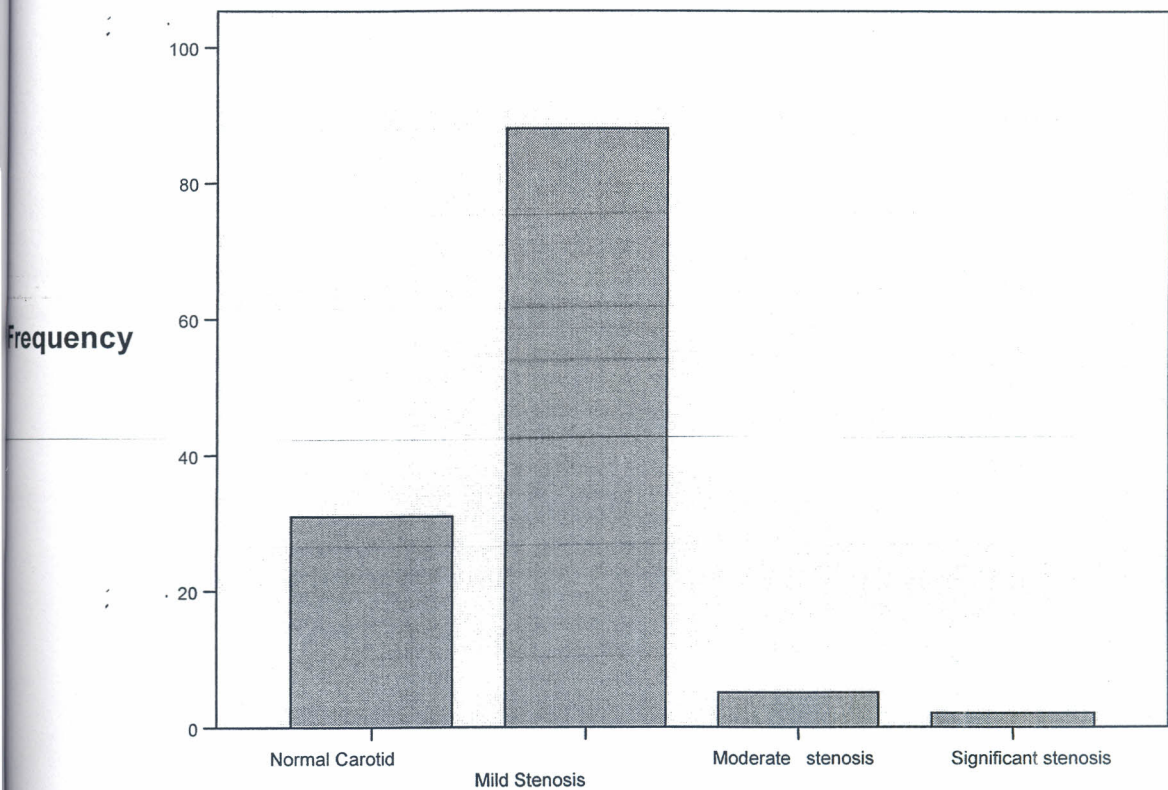
RISK FACTORS DISTRIBUTION BETWEEN PATIENTS WITH LARGE VESSEL VERSUS SMALL DISEASE

Risk factors	Prevalence		P value
	Large vessels	Small vessel	
Dyslipidaemia	66.2	33.8	0.085
Hypertension	57.8	42.2	0.322
Diabetes mellitus	69	31	0.277
Current smoking	50	50	0.173

A carotid bruit was heard in 18(14.4%) of the patients out of which only 2 had significant carotid artery stenosis. Thirty three (26.2%) of the patients had abdominal obesity.

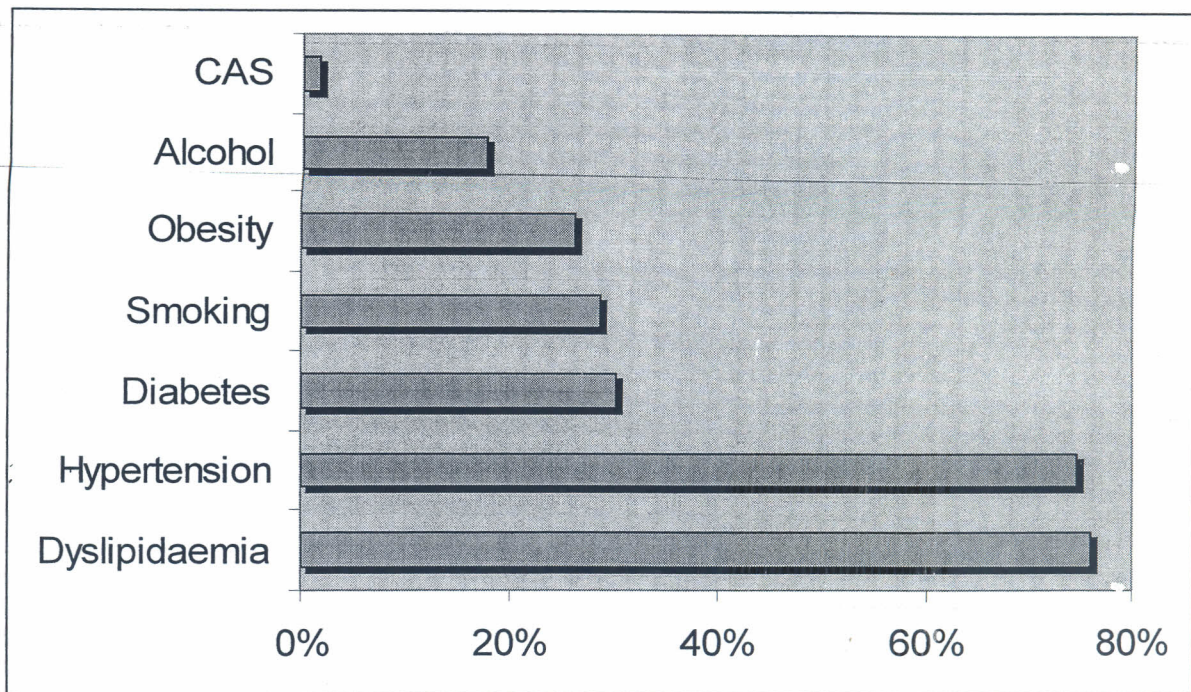
The overall prevalence of significant (70% or more) carotid artery stenosis was 1.6% (95%CI 0.6-3.79). The grading was as follows: Majority (88)64.2% had < 50% stenosis, 31(22.6%) of the patients had normal carotid arteries and (5) 3.6% of the patients had moderate; 51-69% stenosis.

FIGURE 6: DISTRIBUTION OF CAROTID ARTERY STENOSIS AMONG PATIENTS WITH ISCHAEMIC STROKE.



The most frequent risk factors for ischaemic stroke were: dyslipidaemia 76 % (95% CI 68.5-83.5), hypertension 74.6 % (95% CI 67.0-82.2%), diabetes 30.2 % (95%CI 22-38.0), cigarette smoking 28.6% (95% CI 24.6-32.6), obesity 26.2% (95% CI 18.4-33.6), and heavy alcohol consumption, 17.5%. In view of the few patients (2) with significant carotid artery stenosis, the prevalence of traditional risk factors in these few patients could not be calculated.

FIGURE 7: OVERALL PREVALENCE OF RISK FACTORS AMONG ISCHAEMIC STROKE PATIENTS



CAS=CAROTID ARTERY STENOSIS

Review of the risk factor profile of the two patients with significant carotid artery stenosis revealed they had dyslipidaemia with high total cholesterol levels of more > 6.21 mmol/l, very high LDL Cholesterol of > 4.91 mmol/ l, high triglycerides levels of > 5.64 mmol/l with favorable HDL levels. In view of the few numbers, univariate analysis was not done.

10.0 DISCUSSION.

The morbidity and mortality associated with stroke with no definitive treatment options emphasizes the need for risk factor identification and modification. Cerebral infarction in the territory of the carotid arteries accounts for most strokes in western countries [44, 45]. Significant atherosclerotic narrowing of the internal carotid artery ipsilateral to the infarct is found in 20 % to 30 % of those investigated [5-7]. The prevalence and determinants of carotid artery stenosis have been determined in well conducted studies done in the west. This study sought to document the prevalence and determinants of carotid artery stenosis among patients presenting with ischaemic stroke in KNH.

One hundred and thirty seven Ischaemic stroke patients aged above 45 years were recruited into the study from KNH medical wards and neurology clinic. The Inclusion age of 45 years was chosen by design with the intention of getting a population with manifestations of atherosclerosis.

In this cross-sectional study the mean age of the population was 59.41 ± 11.83 with a range from 45 to 88 years. Local stroke studies with a different methodology have shown lower mean ages. Kwasa [46] in 1986 and Bahemuka [40] in 1985 found mean ages of 52 and 54 years respectively. The high mean age found in this study is due to the selection bias and therefore cannot be generalized to represent the mean age of stroke patients seen in KNH.

Bahou et al [37] in Jordan found a mean age of 61.2 years, and this compares well with that found in this study. This mean age is also younger than that found in the North American and European studies like the NASCET [48], ECST [49] and the UK-TIA trials [47]. They found mean ages of 68, 67 and 66 years respectively. This could be due to the increased life expectancy and better health care in Europe and North America.

There were more males (62.7%) than females, similar to the findings of Bahemuka[40] (66%) in 1985. This gender disparity has also been observed in Korea (75.2%) [68], India (76.3%) [69], Europe and North America (71.8 % to 73.4%) [47-49]. This is in keeping with the fact that male gender is a non modifiable risk factor for Ischaemic stroke with the risk being 24 % to 30 % greater in men [10].

This study has demonstrated a low prevalence (1.6%) of significant extracranial carotid artery stenosis. Majority of the patients had mild stenosis (64.2%) and 3.6% had moderate stenosis. Similar patterns of low prevalence of significant extracranial carotid artery stenosis have been reported in the Middle East by Bahou et al [37] and Qari [53], who found no significant stenosis among his patients using Doppler U/S. The prevalence in this study is lower than that found by Bahemuka (6%) [40] In 1985. A higher prevalence of significant CAS has been found in studies conducted in North America and Europe. The NASCET [48] and ECST [49] studies found prevalence's of 28% and 18% respectively.

The findings from this study are similar to those of Bahou [37] probably from the fact that the risk factor profile of his patients was almost similar to that observed in this study. The overall risk factors in this study were dyslipidaemia (77 %), hypertension (74.6%), diabetes mellitus (31 %) and smoking (28 %) compared to hypertension (76.0%), Diabetes mellitus (44.0%), Smoking (35 .0 %) and hyperlipidaemia (33.0 %) in the study by Bahou[37]. In both studies, carotid stenosis was evaluated using Doppler ultrasound.

The higher prevalence observed in Bahemuka's study could be an over estimate due to the fact that he used angiography for diagnosis of CAS which tends to overestimate the degree of stenosis [70].

Racial differences between the patients in this study and those in European and North America studies can also account for the findings in this study. Atherosclerosis of the larger extracranial arteries is more prevalent among caucasians whereas occlusive disease of the intracranial arteries is more often seen in patients of black and oriental origin [54, 51, and 71]. The patients seen in this study were all Blacks and probably with less genetic predisposition to atherosclerosis.

The younger mean age (59.41) seen in this study compared to (66-68) years seen in the NASCET, ECST and UK TIA trials is another possible explanation to the low findings.

Carotid Doppler ultrasound was the method used to assess the degree of stenosis. The procedure is operator dependent and to minimise bias, three sufficiently experienced radiologists did the scanning. The Inter and Intra observer reliability were found to be 89.4 % and 82% respectively. Previous studies have suggested a good level of agreement among experienced radiologists for detecting significant carotid artery stenosis [52].

Bahemuka [40] in 1985 concluded that Atherosclerosis was not the major pathological factor for cerebrovascular accidents at least in those cases that are seen in KNH; a finding supported by this study.

Large vessel atherosclerotic strokes were predominant (62.8%) and mostly distributed in the carotid territory (95%) as opposed to the vertebrobasilar region (5%). With the high prevalence of hypertension and diabetes mellitus seen in this study, one would have expected a higher prevalence of small vessel disease. The difference in prevalence's of hypertension and diabetes mellitus among patients with large versus small vessel disease was not statistically significant as shown in table 3 page 31.

Carotid Bruits were heard in 18 (24%) of the patients. Strikingly, only 2 of these patients had hemodynamically significant extracranial carotid atherosclerosis (>70% narrowing) on carotid Doppler. However, the presence of carotid bruit has only 50 % sensitivity for carotid disease and does not help to assess the degree of stenosis [72].

With the high prevalence of large vessel disease and traditional risk factors we expected a larger number of patients to have atherosclerotic narrowing of the extracranial carotids. Majority (64.2%) of the patients in this study had mild stenosis evidenced by plaques. It is possible that the results of this study reflect the low prevalence of significant extracranial carotid artery stenosis among Ischemic stroke patients seen in KNH and blacks in general as supported by literature [54-56].

Other possible reasons to explain the low prevalence of significant carotid artery stenosis seen in this study include the lower mean age of the patients, black race and the method used to assess carotid artery stenosis. Routine screening for significant carotid stenosis among patients with Ischemic stroke seen in KNH may not be cost effective in view of

the fact that it costs an average of 6000 Kenya shillings, equivalent to 75 US Dollars. It may probably be worthwhile to reserve this money for purchase of Aspirin for secondary stroke prevention.

Dyslipidaemia was the only risk factor found in the two patients with significant extracranial carotid stenosis. These patients had a high total Cholesterol (> 6.21 mmol/l), very high LDL levels of >4.91 mmol, high triglyceride levels of > 2.26 mmol/l with favourable HDL levels of > 1.55 mmol/l. Comparison with the patients without stenosis was not done in view of the few numbers..

LDL and triglyceride cholesterol have been found by Hodis et al [73] to correlate with progression of carotid atherosclerosis while high HDL has been found by Wilson et al to be protective for carotid stenosis [74].

This implies that the burden of stroke and carotid artery stenosis among Ischaemic stroke patients is largely due to modifiable risk factors. Risk factor identification and modification is the most important tool in stroke prevention.

11.0 LIMITATIONS OF THE STUDY.

This study has inherent limitations which include:

1. This was a small study. Risk factors associated with carotid artery stenosis could not be analyzed.
2. There was a selection bias with very sick patients and those who could not afford CT scan being excluded.

12.0 CONCLUSION.

1. This study has shown a younger age of stroke prevalence compared with developed countries.
2. There is a low prevalence of significant carotid artery stenosis among Ischaemic stroke patients seen on KNH.
3. There is a high prevalence of traditional modifiable risk factors among Ischaemic stroke patients seen on KNH

13.0 RECOMMENDATIONS.

1. Routine Carotid Doppler ultrasound among Ischaemic stroke patients may not be cost effective.
2. A case control study is recommended to be able to correlate carotid artery stenosis and its risk factors.
3. A future study including patients with large vessel disease and excluding lacunar infarcts is recommended.

14 REFERENCES

1. Bonita R, Stewart A, Beaglehole R. International trends in stroke mortality: 1970-1985. *Stroke*, 1990, **21**:989-992
2. Sacco RL, Ellenberg JH, Mohr JP, *et al*: Infarcts of undetermined cause: The NINDS Stroke Data Bank. *Ann Neurol* 1989; **25**:382-390.
3. Autret A, Pourcelot L, Saudeau D, *et al*. Stroke risk in patients with carotid stenosis
Lancet 1987; **1**: 888-890.
4. Chambers BR, Norris JW: Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1986; **315**:860-865.
5. Harrison MJG, Marshall J. Angiographic appearance of carotid bifurcation in patients with completed stroke, transient ischaemic attacks, and cerebral tumour. *BMJ*.1976; **1**:205-207.
6. Thiele BL, Young JV, Chikos PM, *et al*. Correlation of arteriographic findings and symptoms in cerebrovascular disease. *Neurology*.1980; **30**:1041-1046.
7. Harrison MJG, Marshall J. Prognostic significance of severity of carotid atheroma in early manifestations of cerebrovascular disease. *Stroke*.1982; **13**:567-569.
8. Ricci S, Flamini FO, Celani MG *et al*. Prevalence of internal carotid artery stenosis in subjects older than 49 years: a population study. *Cerebrovasc Dis*.1991; **1**:16-19.
9. Jose MO, Touboul PJ, Mas JL *et al*. Prevalence of asymptomatic internal carotid artery stenosis. *Neuroepidemiology*.1987; **6**:150-152.

10. Sacco RL. Stroke risk factors: An overview. In: Norris JW, Hachinski V, eds. Stroke prevention. Oxford: *Oxford university press*, 2001; 2:17-42.
11. Baron JC, Bousser MG, Rey A *et al*. Reversal of focal 'misery-perfusion syndrome' by extra-intracranial arterial bypass in hemodynamic cerebral ischaemia: A case study with positron emission tomography. *Stroke*. 1981; 12:454-459.
12. Levine RL, Dobkin JA, Rozental JM, *et al*. Blood flow reactivity to hypercapnia in strictly unilateral carotid disease: preliminary results. *J Neurosurg Psychiatry*. 1991; 54:204-209.
13. Powers WJ. Cerebral haemodynamics in ischemic cerebrovascular disease. *Ann Neurol*. 1991; 29:231-240.
14. Grubb RL, Derdeyn CP, Fritsch SM *et al*. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA*. 1998; 280:1055-1060.
15. Fuster V, Badimon L, Badimon JJ *et al*. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med*. 1992; 326:242-250.
16. Safian RD, Gelbfish AS, Emy RE *et al*. Coronary atherectomy: Clinical angiographic and histological findings and observations regarding potential mechanisms. *Circulation*. 1990; 82:69-79.
17. SHEP cooperative research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results *JAMA* 1991; 265 (24): 3255 -32 64.
18. The ALLHAT Officers and Coordinators for ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patient randomised to

- angiotensin converting enzyme inhibitor or calcium channel blocker vs. diuretic: the antihypertensive and lipid-lowering treatment to prevent health attack trial (ALLHAT). *JAMA* 2002; **288**(23): 2981-2997.
19. International Society of Hypertension (ISH): Statement on blood pressure lowering and stroke prevention. *J. Hypertension*.2003; **21**:651-663.
 20. Sacco RL, Adams R, Albers G, *et al.* Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Stroke* 2006; **37**:577-617.
 21. Jorgensen L, Jenssen T, Joakimsen O, *et al.* Glycated hemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in nondiabetic individuals: The Tromso study. *Circulation* 2004; **110**:466- 470.
 22. Vitelli LL, Shahar E, Heiss G, *et al.* Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals. The Atherosclerosis Risk in Communities Study. *Diabetes Care* 1997; **20**:1454-1458.
 23. David M, Nathan M.D, Patricia A. Cleary., *et al.* The writing committee 2005 DCCT/EDIC follow up. Tight glycaemic control and macrovascular complications.*NEJM* 2005; **353**:2643-2653.
 24. Piechowski-Jozwiak B, Bogousslavsky, J. Cholesterol as a risk factor for stroke: the fugitive? *Stroke* 2004; **35**:1523-1524.
 25. Henning Mast, John LP, Thompson *et al.* the association of cigarette smoking with high grade carotid stenosis. *Stroke* 1998; **29**: 908 – 912.

26. Thrift, AG. Cholesterol is associated with stroke, but is not a risk factor. *Stroke* 2004; **35**:1524- 1525.
27. Donnan GA, Davis SM. Stroke and cholesterol: Weakness of risk versus strength of therapy. *Stroke* 2004; **35(6)**:1526-1526.
28. Hedblad B, Wikstrand J, Janzon L, *et al.* Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness. Main results from the β -blocker cholesterol-lowering asymptomatic plaque study (BCAPS). *Circulation* 2001; **103**:1721-1726
29. Ford CS, Crouse JR III, Howard G., *et al.* The role of plasma lipids in carotid bifurcation atherosclerosis. *Ann Neurol* 1985; **17**:301-305.
30. Van Merode, Hick P, Hoeks APG, Reneman RS. Serum HDL/total cholesterol ratio and blood pressure in asymptomatic atherosclerotic lesions of the cervical carotid arteries in men. *Stroke* 1985; **16**:34- 38
31. Wilson PW, Hoeg JM, D'Agostino RB, *et al.* Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N. Engl J. Med* 1997; **337**:516- 522.
32. Johnsen SH, Mathiesen EB, Fosse E, *et al.* Elevated high-density lipoprotein cholesterol levels are protective against plaque progression: A follow-up study of 1952 persons with carotid atherosclerosis. The Tromso study. *Circulation* 2005; **112**:498- 504.

33. Waters DD, Guyton JR, Herrington DM *et al.* Treating to New Targets(TNT) study: Does lowering low density lipoprotein cholesterol levels below currently recommended levels yield incremental benefits? *AM J cardiol* 2004;**93**:154-158.
34. SPARCL investigators. High dose atorvastatin after stroke or TIA. *NEJM* 2006; **355**:549-559.
35. Nurses health study. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *NEJM* 1988 Aug 4; **319**(5):267-273.
36. Mead G E, Lewis S C, Wardlaw J M *et al.* Severe ipsilateral carotid stenosis and middle cerebral artery disease in lacunar ischaemic *Stroke. J. Neurol* 2002, March; 249 (3): 266 – 271.
37. Bahou Y, Hamid A. Ischaemic Stroke in Jordan. A 2-year Hospital based study of subtypes and risk factors. *East Mediterr Health J.* 2004; **10**(1 – 2): 138 – 146.
38. Tsong-Hai Lee, Wen-Chuin Hsu, Chi-Jen Chen *et al.* Etiologic Study of Young Ischaemic Stroke patients in Taiwan. *Stroke*, Aug 2002; **33**:1950-1959.
39. Eugene Z Oddone, Ronnie D Horner, Richard Sloane *et al.* Race, presenting signs and symptoms, use of carotid artery imaging and appropriateness of carotid endarterectomy. *Stroke* 1999; **30**: 135-140 Veteran Affairs.
40. Bahemuka M. Cerebrovascular accidents (strokes) in 207 Kenyans; general peculiarities and prognosis of stroke in urban medical centre. *East Afr. Med. J.* 1985; **62**: 315-322
41. Feussner JR, Matchar DB .When and how to study carotid arteries. *Ann intern med* 1988;**109**:805-818.

42. Fried Wald W.T. Calculation of LDL cholesterol. *Clinical chem.*, 1972; **18**: 499-500.
43. Calculation of sample size, *WHO*, 2000. www.who.int.com.
44. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;**337**:1521–1526.
45. Anderson C, Taylor BV, Hankey GJ, Stewart-Wynne EG, Jamrozik KD. Validation of a clinical classification for subtypes of acute cerebral infarction. *J Neurol Neurosurg Psychiatry*. 1994;**57**:1173–1179
46. Kwasa T.O, Lore W. Stroke at Kenyatta National Hospital. *East African Med J*. 1990; **67**: 482-486.
47. UK-TIA study group. The United Kingdom Transient Ischaemic attack Aspirin Trial: Final results. *J Neurol Neurosurg Psychiatry*. 1991;**54**:1044-1054.
48. NASCET collaborators. Beneficial effects of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N. Engl. J. Med*. 1991; **325**: 445- 453.
49. European Carotid Surgery Trialist's Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998; **351**:1379-1387.
50. Al Rajesh S, Awada A. Stroke in Saudi Arabia. *Cerebrovascular diseases*, 2002, **13**(1):3-8
51. Chamorro A, Sacco RL, Mohr JP, *et al*. Clinical-computed tomographic correlations of lacunar infarction in the Stroke Data Bank. *Stroke* 1991; **22**:175.

52. Blakely D, Oddone E Z, Hasselbald V et al. Non invasive carotid artery testing:A meta-analytic review. *Ann Intern Med* 1995;**122**:360-367.
53. Qari F. Profile of stroke in Saudi Arabia. *Neurosciences*, 2002, 6(1):38-41.
54. Caplan LR, Gorelic PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. *Stroke* 1988; **17**:648-655.
55. Feldman E, Daneault N, Kwan E, et al. Chinese-whites differences in the distribution of occlusive cerebrovascular disease. *Neurology* 1990; **40**:1541-1545.
56. Mori K, Hasegawa T, Araki G, et al. A clinical evaluation of transient focal cerebral ischemia with some comments on its concept. *Jpn circ J* 1965;**29**:847-854.
57. Tejada J, Diez-Tejedor E, Hernandez-Echebarria L, Balboa, O. Does a relationship exist between carotid stenosis and lacunar infarction? *Stroke* 2003; **34**:1404.
58. Ay H, Oliveira-Filho J, Buonanno FS, et al. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. *Stroke* 1999; **30**:2644.
59. Wessels T, Rottger C, Jauss M, et al. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. *Stroke* 2005; **36**:757.
60. Bots ML, Launer LJ, Lindemans J, et al. Homocysteine and short-term risk of myocardial infarction and stroke in the elderly: the Rotterdam Study. *Arch Intern Med* 1999; **159**:1120-1124

61. Eikelboom JW, Hankey GJ, Anand SS, et al. Association between high homocysteine and ischemic stroke due to large- and small-artery disease but not other etiologic subtypes of ischemic stroke. *Stroke* 2000; **31**:1069.
62. Lodder J, Bamford JM, Sandercock PA, et al. Are hypertension or cardiac embolism likely causes of lacunar infarction? *Stroke* 1990; **21**:375.
63. Whisnant JP. Ischemic stroke subtypes: A population-based study of incidence and risk factors. *Stroke* 1999; **30**:2513.
64. NCEP Report update. *Circulation* 2004; **110**:227-239.
65. Diana Gaitini and Michalle Saudack. Diagnosing carotid stenosis by Doppler sonography: state of the Art. *J ultrasound* 2005; **24**: 1127-1136.
66. World health organisation definition of stroke. www.who.int/chp/steps/stroke/en/
67. Albers G W. Transient ischaemic attack. Proposal for new definition. *NEJM* 2002; **347**:1713
68. Kwon SU, Kim JS, Lee JH et al. Ischaemic Stroke in Korean young Adults. *Acta Neurol Scand* 2000; **101**: 19-24.
69. Nayak SD, Nair M, Radhakrishnan K, Sarma PS. Ischaemic Strokes in young adults: Clinical features risk factors and outcome. *Nat med J India*. 1997; **10** 107-112
70. Neder Koorn PJ, Vander Graaf Y, Hunink Mg et al. Duplex ultra sound and magnetic resonance angiography compared with digital subtraction angiography on carotid artery stenosis: A systematic review. *Stroke* 2003; **34**: 1324-1332

71. Leung SY, Yuen ST, Lauder IJ *et al.* Pattern of cerebral atherosclerosis on Hong Kong Chinese: Severity in intracranial and extracranial vessels . *Stroke*. 1993; **24**: 779-786
72. Hankey GJ, Warlow CP. Symptomatic Carotid Ischaemic events .Safest and most cost effective way of selecting patients for angiography, before carotid endarterectomy. *BMJ* 1990; **300** : 1485-1491
73. Hodis HN, Mack WJ, Labree L, et al LDL and carotid stenosis. 1996. *Ann Intern Med*. **124 (6)** 548-550.
74. Wilson PNF, Hoeg Jm, D'Agostino RB *et al.* HDL and carotid stenosis. 1997. *N Engl J Med*. **337 (8)** 516-518

14.0 APPENDICES.

APPENDIX I: DIAGNOSTIC CRITERIA.

DEPENDENT VARIABLE.

CAROTID ARTERY STENOSIS.

The consensus conference of the society of radiologists 2003 recommendations[65] were followed in the performance of the procedure and reporting.

Significant carotid artery stenosis was evidenced by ICA Peak systolic velocity ≥ 230 cm/s, a plaque estimate of $\geq 50\%$, ICA/CCA Peak systolic ratio of ≥ 4 and ICA end diastolic velocity of >100 cm/s. The side with the greatest degree of stenosis was taken to represent the magnitude of stenosis in a patient.

TABLE 4: Spectral Doppler Velocities and Plaque Estimate Correlated With Degree of ICA Stenosis Diameter

Stenosis, %	ICA PSV, cm/s	Plaque Estimate, %	ICA/CCA PSV Ratio	ICA EDV, cm/s
Normal	<125	NA	<2	<40
<50	<125	<50	<2	<40
50–69	125–230	>50	2–4	40–100
70-99%	>230	>50	>4	>100
Near occlusion	High/low/undetectable	Visible	Variable	Variable
Total occlusion	NA	Visible, no detectable lumen	NA	NA

The *logiq 5 expert* machine from General electric and the linear probe 7 MHZ available at the University of Nairobi Dept of Diagnostic radiology was used.

INDEPENDENT VARIABLES

a) AGE AND GENDER

Age >55 years for both men and women and male gender were defined as risk factors for carotid artery stenosis.

b) HYPERTENSION:

1. Those currently on antihypertensive medication
2. Those with a SBP >140 mmHg and DBP >90 mmHg. For diabetics and chronic kidney disease patients, the cut off was SBP \geq 130 mmHg and DBP \geq 80 mmHg. This will be measured using a mercury sphygmomanometer.
3. Those previously diagnosed to be hypertensive not meeting criteria 1 and 2 above. The severity of Hypertension was assessed using the JNC VII Criteria.

BP CLASSIFICATION SYSTOLIC BP MMHG DIASTOLIC MMHG

Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage II hypertension	>160	>100

If the diastolic and systolic blood pressures fall into different categories then the higher of the two will determine the grade of hypertension

c) DIABETES MELLITUS.

- (i) Self report of diabetes
- (ii) Use of hypoglycaemic medication or insulin
- (iii) Fasting blood sugar of \geq 7.0 mmol/l
- (iv) Impaired fasting glucose was defined as FPG ranging from 5.6 mmol/l to 6.9 mmol/l.

d) Cigarette smoking

1. Current smokers - those who had smoked at least 100 cigarettes in their lifetime and were still smoking.
2. Former smokers were those who had smoked at least 100 cigarettes in their lifetime but had quit smoking more than one year earlier.
3. Non-smokers were those who had smoked less than 100 cigarettes or who had never smoked in their lifetime.

e) Dyslipidaemia

Study participants were classified as per National cholesterol education program/Adult treatment panel III (NCEP/ATP III)

- | | | |
|-------|-------------------|--|
| (i) | Total cholesterol | < 5.17 mmol/l - Desirable
5.17 - 6.18 mmol/l - Borderline high
>6.21 mmol/l - high |
| (ii) | LDL cholesterol | < 2.58 mmol/l - optimal
2.58 - 3.33 mmol/l - Near optimal
3.36 - 4.11 mmol/l - Borderline High
4.13 - 4.88 mmol/l - High
>4.91 - very high |
| (iii) | HDL Cholesterol | <1.03 mmol/l – risk indicator
<1.29 mmol/l – standard risk level
>1.55 mmol/l - favourable |
| (iv) | Triglycerides | <1.69 mmol/l - Normal
1.69 - 2.25 mmol/l - Border line High.
2.26 - 5.64 mmol/l - High
>5.65 mmol/l - very high. |

Patients were classified as having dyslipidaemia if their cholesterol levels were above the cut-offs specified above or below the risk indicator level for HDL.

1) Obesity

This was assessed using the waist circumference. Recommended for women is < 88cm and for men <102cm will be obese.

2) Alcohol

1. Less than recommended i.e. less than 2 units per day
2. Recommended i.e. 2 to 4 units per day
3. More than recommended i.e. more than 4 units.

A bottle of ordinary beer measuring 340ml, 115ml of non-fortified wine, 1 tot of spirit, 340ml of busaa/muratina and 1 tot of changa'a are equivalent to a unit of alcohol.

Excessive alcohol consumption, more than 4 units per day, may predispose to stroke.

OTHER VARIABLES:

a) STROKE

Rapidly developing clinical signs of focal and at times global disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin [66].

b) TRANSIENT ISCHAEMIC ATTACK.

A brief episode of neurologic dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction[67].

13.2 APPENDIX II

STUDY PROFORMA

Name _____ Study No _____
Date _____ IP No. _____
DOB (Month Year) _____ Age in years _____
Time to presentation to hospital (specify duration) (_____) Days/weeks/months/
(tick the appropriate)

DEMOGRAPHICS (Please enter the appropriate number in the brackets provided)

1. Gender 1= Male 2= Female (_____)
2. Marital status 1=Single 2= Married 3= Divorced 4= Widowed
5 = Separated (_____)
3. Usual residence _____
4. Usual occupation
1=Self employed 2= employed 3= unemployed
4= retired 5=training/student (_____)

CHRONIC ILLNESS (known)

5. Diabetes 1= Yes 2= No (_____)
Duration: _____ years.
6. Hypertension 1= Yes 2= No (_____)
Duration _____ years
7. Dyslipidaemia 1= Yes 2 = No (_____)

PAST MEDICAL HISTORY

8. Have you ever had any of the following? (Tick response)
1 = had a stroke before (_____)
2 = Transient Ischaemic attacks (neurological deficit lasting <24 hours) (_____)
3 = Amaurosis fugax (mono ocular blindness lasting <24 hours (_____)

FAMILY HISTORY

9. Do any of your relatives suffer from diabetes?

1 = Yes 2 = No ()

If yes please specify by ticking the appropriate bracket

Father () Mother () Sibling () Children

()

10. Do any of your relatives suffer from hypertension?

1 = Yes 2 = No ()

If yes please specify by ticking the appropriate bracket

Father () Mother () Sibling () Children ()

11. Have any of your relatives suffered a stroke?

1 = Yes 2 = No ()

If yes please specify by ticking the appropriate bracket

Father () Mother () Sibling () Children

()

12. Has any of your relatives suffered a heart attack or sudden death

1 = Yes 2 = No ()

If yes please specify by ticking the appropriate bracket

Father () Mother () Sibling () Children

()

SMOKING HABITS

13. Do you smoke cigarettes

1 = Yes, regularly 2 = No ()

14. On average how many cigarettes do you smoke per day?

_____ Cigarettes per day

15. Did you ever smoke cigarettes regularly in the past?

1 = Yes, regularly 2 = No ()

(a) When did you stop smoking cigarettes regularly? Year _____

If in the last 12 months

1 = Less than 1 month ago (____)

2 = 1- 6 months ago (____)

3 = 6-12 months ago (____)

6. For how many years have you been smoking cigarettes? _____ Years.

ALCOHOL INTAKE

7. Do you drink alcohol

1 = Yes 2 = No (____)

Specify type by ticking the appropriate type. Bottled Beer/Busaa/
changaa/Muratina /others specify _____

8. On average how many bottles do you drink in a day?

1. = <2 2. =2-4 3. =more than 4 (____)

CURRENT MEDICATIONS

Are you currently on any of the following medications?

19. Drugs to lower blood glucose (oral/insulin)

1 = Yes 2 = No (____) If yes specify

Drug _____ Dose _____ Duration _____

20. Blood pressure lowering drugs

1 = Yes 2 = No (____) If yes specify

Drug _____ Dose _____ Duration _____

21. Blood lipid-lowering drugs

1 = Yes 2 = No (____) If yes specify

Drug _____ Dose _____ Duration _____

22. Anti platelet/Anti coagulation drugs (Aspirin/ clopidogrel / Warfarin)

1 = Yes 2 = No (____) If yes specify

Drug _____ Dose _____ Duration _____

23. Oral contraceptive pills for females

1 = Yes 2 = No () If yes specify

Drug _____ Dose _____ Duration _____

PHYSICAL EXAMINATION

24. 1ST BP reading _____ MMHG 2nd BP reading _____ MMHG

Average of 2 BP readings _____ MMHG

25. Weight (Kg.) _____

26. Height in meters squared (m²)

27. Pulse rate _____

28. Pulse rhythm _____ 1 = Regular 2 = Irregular

29. Coma scale.

1. Responds to light pain, has spontaneous movements, can obey simple commands.

2. Responds to painful stimuli by making avoidance movements, he can move spontaneously.

3. No response to painful stimuli, has decerebrate posturing, papillary reactions may be present.

4. Flaccid paralysis, no deep tendon reflexes, no spontaneous respiration.

Please tick the appropriate

1-2 = Light coma ()

3-4 = Deep coma. ()

30. Waist circumference (inches) _____

31. Eyes ARCUS Senilis 1 = Yes 2 = No ()

 Xanthelasma 1 = Yes 2 = No ()

32. Anterior Neck Carotid bruit 1 = Yes 2 = No ()

THE OXFORDSHIRE COMMUNITY STROKE PROJECT [58] (please tick the appropriate)

33. Has features of Total anterior circulation infarction

- i. Presence of hemiparesis or hemisensory loss
- ii. Dysphasia or new higher cortical dysfunction.
- iii. Homonymous hemianopia.

Tick if patient has the three features ()

34. Has features of Partial anterior circulation infarction.

- i. Presence of two of the features in number 34 above. OR
- ii. Isolated dysphasia.

Tick if patient has either i OR ii of the above. ()

35. Has features of Lacunar infarction.

- i. Pure motor hemiparesis

Weakness involving the face, arm and the leg on one side of the body in the absence of cortical signs or sensory deficit.

- ii. Pure sensory stroke.
Numbness of the face, arm and leg on one side of the body in the absence of motor deficit or cortical signs.

- iii. Ataxic hemiparesis.
Ipsilateral weakness and limb ataxia that is out of proportion to the motor deficit.
Presence /absence of dysathria, nystagmus and gait deviation to the affected side in the absence of cortical signs.

- iv. Sensorimotor stroke.

Weakness and numbness of the face, arm and leg on one side of the body in the absence of cortical signs.

Tick if a patient has one of the findings above (_____)

Patient has features of Posterior Cerebral Infarction.

Features of brainstem infarction.

Has cerebellar signs and /or

Isolated homonymous hemianopia.

Tick if a patient has any or all of the findings (_____)

Uncertain type of stroke by OCSP. Tick if findings not falling under any or in more than one of the above categories. (_____)

3 APPENDIX III

LABORATORY RESULTS

Fasting blood sugar _____ mmol/l

Fasting lipid profile

Total cholesterol _____ mmol/l

HDL cholesterol _____ mmol/l

LDL cholesterol _____ mmol/l

Triglycerides _____ mmol/l

CT/MRI scan brain infarction

1 = Right side 2 = Left side (_____)

Specify position

1. Anterior cerebral artery territory
2. Middle cerebral artery territory
3. Lacunar infarction
4. Posterior cerebral artery territory

Carotid Doppler Ultrasound (where there is stenosis specify either right or left carotid).

1 = Normal

2 = Less than 50% stenosis

3 = 50-69% stenosis

4 = 70 -99% stenosis

5 = total occlusion

(_____)

APPENDIX IV CONSENT EXPLANATION

My name is Dr. Mwazo M.K. a postgraduate student in Internal Medicine, University of Nairobi.

I am conducting a study on patients who have had stroke or sudden paralysis or weakness on one side of their body. The main purpose of this study is to find out the diseases that may have contributed to the occurrence of the stroke. These diseases include narrowing of the blood vessels that transport blood to the brain through the neck, high blood pressure, diabetes, High levels of cholesterol in the Blood, and being overweight. I will also like to know whether you smoke or drink alcohol.

The results of this study will help the Doctors understand diseases of the neck blood vessels; therefore know the relevant investigations to carry out on other people who may have a stroke in the future. The information obtained from you shall remain confidential.

You are free to accept or decline to participate in the study since it is voluntary. If you choose not to participate, your care will not be compromised in any way. If you accept I shall conduct a full medical examination on you. Any other ailment that shall be discovered in the course of the examination shall be reported to your attending Doctors for proper management.

Some blood (one table spoon full) will be drawn from your forearm under hygienic precautions. You will feel some pain at the site of injection. This blood will be to ascertain your blood glucose / sugar and cholesterol levels. I shall then request that you have an ultrasound scan examination of your neck blood vessels performed at the university of Nairobi department of Radiology by Dr A.A.Aywak to check whether there is any narrowing. The Doctor will apply some harmless liquid gel on both sides of the neck to facilitate proper examination after which the gel shall be wiped off. The cost for his investigations and transport outside your scheduled visits shall be met by me the principal investigator.

shall personally explain all the results from these investigations to you and copies shall be available in your file. Appropriate treatment shall be offered after liaison with my supervisors and as per the accepted standard of care in the ward or clinic you are attending.

In case you have questions related to this study you can contact the following:

1. Dr. Mwazo M.K. Principal investigator
2. Prof. E. Amayo Supervisor, Department of Internal medicine, University of Nairobi, KNH
3. Dr. C.F Otieno Supervisor, Department of Internal medicine, University of Nairobi, KNH
4. Dr. A.A. Aywak Supervisor, Department of Diagnostic Radiology, University of Nairobi, KNH

UNIVERSITY OF NAIROBI
MEDICAL LIBRARY

APPENDIX V CONSENT FORM [patient]

I _____ from _____ after reading the consent explanation form and having been explained to by Dr. Mwazo, (The Principal Investigator) do voluntarily agree to take part in this research study on: PREVALENCE OF CAROTID ARTERY STENOSIS AND ITS RISK FACTORS IN ISCHAEMIC STROKE PATIENTS AS SEEN IN KNH.

I am also aware that I can withdraw from this study without quality of management of my medical problem being affected.

Signature / Thumbprint: _____

Witness: _____

Date: _____

CONSENT FROM [relative to the patient]

I _____ relative to _____ (patient) after reading the consent explanation form and having been explained to by Dr. Mwazo, The Principal Investigator) do voluntarily agree on behalf of the patient to take part in this research study on PREVALENCE OF CAROTID ARTERY STENOSIS AND ITS RISK FACTORS IN ISCHAEMIC STROKE PATIENTS AS SEEN IN KNH.

I am also aware that I can withdraw from this study without quality of management of my medical problem being affected

Signature / Thumbprint: _____

Witness: _____

Date: _____