PREVALENCE, ASSOCIATED RISK FACTORS AND PROGRESSION OF ASYMPTOMATIC PERIPHERAL ARTERIAL DISEASE AT KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED AS PART FULFILLMENT OF THE REQUIREMENTS FOR AWARD OF THE DEGREE OF MASTER OF MEDICINE (MMED) IN THORACIC AND CARDIOVASCULAR SURGERY OF THE UNIVERSITY OF NAIROBI.

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DECLARATION

Candidate's declaration

I hereby declare that this study is my original work and has not been presented for dissertation or examination at any other university.

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DEPARTMENTAL APPROVAL

This dissertation has been submitted for examination with the approval of the Department of Surgery, University of Nairobi.

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DEDICATIONS

I dedicate this dissertation to my family for their endless love and encouragement.

To my mother, Pravina who is my rock and an inspiration to me throughout my life, a very special thanks for moulding me in to whom I am today.

To my father, Praful who has actively supported me to realise my true potential, thank you for teaching me, believing in me and encouraging me to fulfil my dreams beyond the dictates of society.

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OPERATIONAL DEFINITIONS

Atherosclerosis: progressive thickening and hardening of the walls of medium sized and large arteries as a result of fat deposits.

Critical limb ischemia: marked decrease in limb perfusion that causes a potential threat to limb viability.

Diabetes mellitus: deficiency or resistance of pancreatic hormone insulin which results in a failure to metabolize glucose.

Dyslipidemia: abnormality in or abnormal amounts of lipids and lipoproteins in the blood.

Hypertension: repeatedly elevated blood pressure; greater than 140mmHg (systolic) and 90mmHg (diastolic).

Intermittent claudication: pain experienced in the calf on walking and which is relieved by rest.

Peripheral arterial disease: narrowing or obstruction of arteries outside the heart due to atherosclerosis and resulting in reduced blood flow distally.

ABBREVIATIONS

ABI: Ankle Brachial Index

CVD: Cardiovascular Disease

DM: Diabetes Mellitus

KNH: Kenyatta National Hospital

PAD: Peripheral arterial disease

LIST OF TABLES AND FIGURES

ABSTRACT

Background: The prevalence of peripheral arterial disease worldwide has been estimated at between 4.5% and 29%. Peripheral arterial disease can be asymptomatic or symptomatic. It is an independent risk factor for cardiovascular morbidity and mortality and the risk burden is similar whether it is in the asymptomatic or symptomatic form. Over two-thirds of patients with peripheral arterial disease are asymptomatic and thus not identified, resulting in inadequate identification and treatment of their risk factors. Clinical experience with amputations at Kenyatta National Hospital suggests that peripheral arterial disease is common, but the actual prevalence and natural disease progression of the asymptomatic form of disease has not been determined.

Objective: To determine the prevalence of asymptomatic peripheral arterial disease and progression over a one year period in patients with cardiovascular risk factors.

Study design: one year, non-interventional longitudinal study

Setting: Medical and surgical outpatient clinics and wards at Kenyatta National Hospital.

Patients and methods: Seventy five consenting patients with asymptomatic peripheral arterial disease determined by ankle brachial index $\leq$0.9 and the presence of cardiovascular risk factors were recruited by convenience sampling. Demographic and risk profile was recorded and extent of disease ascertained at baseline based on ankle brachial index. The patients were then followed up for 1 year and disease progression evaluated based on changes in the ankle brachial index as well as development of claudication symptoms.

Results: Of the 217 people screened, 78 (36%) had asymptomatic PAD affecting 113 legs. A total of 62 (83%) patients returned for the 1-year follow-up visit. On repeat ABI measurement, 8 of the 36 normal legs developed asymptomatic PAD, and 44 (46%) of the 96 legs with asymptomatic PAD at baseline had progression of disease.There was a significant change (-0.03) in mean ABI of the worse leg over the 1 year of follow-up (p=0.001) and 13 (21%) patients developed intermittent claudication at one year.

Conclusion: This study showed a high prevalence of asymptomatic PAD in our population. It also showed that a significant number of patients (52%) with at least one associated cardiovascular risk factor and asymptomatic PAD at baseline, have progression of disease over 1 year, with or without development of intermittent claudication and that those developing claudication have a significant deterioration in the ABI. Progression of asymptomatic PAD was also significantly associated with having 2 or more cardiovascular risk factors (p = 0.031).

INTRODUCTION

Peripheral arterial disease (PAD) is part of a systemic illness caused by atherosclerosis which results in arterial narrowing, causing a mismatch between oxygen supply and demand.
Clinical manifestations of PAD are associated with pain and decreased functional capacity, limb wounds and amputation. Presence of PAD is a marker for atherosclerosis in other parts of the vascular system with possible concomitant atherosclerotic disease of the arteries in the brain and heart.

Peripheral arterial disease may be asymptomatic or present with symptoms ranging from intermittent claudication to critical limb ischaemia.
Over two-thirds of the patients with PAD are asymptomatic and not diagnosed as having a systemic cardiovascular disease, resulting in inadequate treatment of their risk factors.[1]

The cardiovascular disease burden associated with PAD is the same, whether it is the asymptomatic or symptomatic form.[2, 3.] This therefore justifies the need to identify asymptomatic patients in order to intervene early and reduce the risk of cardiovascular-related mortality [4, 5, 6.]

Despite the importance of early detection, the diagnosis of PAD is usually overlooked in routine history and examination[1.] The few patients who complain of claudication are misclassified as having leg pain due to old age, arthritis, or muscular pain. Thus, lack of awareness about the morbidity and mortality associated with PAD are significant barriers to both PAD diagnosis and secondary prevention. There is, therefore, a need to increase physician awareness and knowledge about PAD and clear guidelines for the detection of PAD are needed. The treatment of PAD and the management of risk factors are both effective, which provides justification for performing ABI measurements to help the early diagnosis of PAD.

LITERATURE REVIEW

Peripheral Arterial Disease Prevalence

27 million people in Europe and North America have peripheral arterial disease. Of these, 10.5 million are symptomatic while 16.5 million are asymptomatic[7.]

Approximately 20 percent of adults older than 55 years in the United States have peripheral arterial disease[8]. A study in the United States conducted in 2000 estimated that about five million Americans suffered from peripheral arterial disease, with the number expected to increase to seven million by 2020[9.]

The National Health and Nutritional Examination Survey found the prevalence of peripheral arterial disease was ranging from 2.5% in the age group 50–59 years to 14.5% in subjects >70 years[9.]

Peripheral arterial disease has been identified in 29% of patients with risk factors for atherosclerosis through ankle-brachial index screening (ABIS) and more than half of these cases had not been diagnosed previously[10.]

In North America, 25% of patients over 60 years of age with hypertension had ABI $\leq$ 0.9 and only 4.5% of these had symptoms of intermittent claudiation.[11]

The prevalence of asymptomatic peripheral arterial disease in the general populations, as opposed to clinic populations, is significantly lower. In an American study of adults aged 60 to 69 years, the prevalence was 2% in the general population and 6.6% in current smokers.[12]

It can therefore be concluded that in the developed countries, for every patient with symptomatic peripheral arterial disease there are another three to four patients with asymptomatic peripheral arterial disease[13.]

Sub-Saharan countries are undergoing an epidemiological transition resulting in an increasing incidence of cardiovascular disease[14.] A study done in 2 countries found prevalence of peripheral arterial disease at 32.4% in Brazzaville, Congo and 15% in Bangui, Republic of Central Africa. The higher prevalence in Congo was attributed to a higher socioeconomic status[14.]

A study done in south west Nigeria in diabetic patients showed the overall prevalence of peripheral arterial disease to be as high as 52.5%. The prevalence of symptomatic peripheral arterial disease was 28.7% whilst that of asymptomatic peripheral arterial disease was 71.3%[15.]

A study done in 2007 in South Africa showed that the prevalence of peripheral arterial vascular disease is as high as 29% in rural black South Africans[16.]

A study done at Kenyatta National Hospital on peripheral arterial disease in chronic kidney disease patients showed a prevalence of 11.9%[17], while another established that rheumatoid arthritis was found to be significantly associated with the likelihood of having peripheral arterial disease[18]. Ankle brachial index measurements showed 25% had obstructed lower limb arteries with 91% having mild peripheral arterial disease, 8.7% had moderate and none had severe peripheral arterial disease [18.]

A study done in 2004 at Kenyatta National Hospital by Awori also found peripheral arterial disease to be the main indication for lower limb amputations (55.3%) of which 37.8% were not diabetic. Majority of these patients were between 31 to 45 years. [19]

Cardiovascular Disease Burden in Peripheral Arterial Disease

Patients with peripheral arterial disease are at an increased risk for cardiovascular events, similar to or greater than in patients with coronary artery disease. In subjects with PAD, one-year rates of cardiovascular death and amputation (2.51% and 1.63%,respectively) have been found to be higher than in patients with coronary artery disease (1.93% and 0.25%, respectively).[2]

A low ABI is an independent risk factor for cardiovascular events. A meta-analysis of 15 studies showed that an ABI $\leq$0.90 was strongly correlated with mortality independent of the Framingham Risk Score[20].

The Edinburgh Artery Study[21] found that, a third of the patients with asymptomatic peripheral arterial disease had complete occlusion of a major artery supplying the lower limb. The study also showed that measurement of ABI can predict cardiovascular events. It proved that a decrease in ABI of 0.10 was associated with a 10% increase in risk for a major vascular event. [21]

Mortality rates in patients with peripheral arterial disease average 2% per year and the rates of myocardial infarction, stroke and vascular death are 5% to 7% per year [22, 23]. The 5-, 10- and 15-year morbidity and mortality rates from all causes are approximately 30%, 50% and 70%, respectively. Coronary artery disease is the most common cause of death (40%–60%), with cerebral artery disease accounting for 10% to 20% of deaths. Other vascular events, like ruptured aortic aneurysm, cause 10% of deaths. Thus, only 20% to 30% of patients with peripheral arterial disease die of non-cardiovascular causes.

A large international registry found that 5.4% of patients with peripheral arterial disease had a major cardiovascular event (myocardial infarction, or stroke) by one year, and 21% experienced these endpoints or hospitalization for an atherosclerotic event [24].

Eleven-year follow-up in the Cardiovascular Health Study found, after controlling for other risk factors, an almost two-fold increased risk for mortality in participants with ankle brachial index 0.71 to 0.8 (Hazard ratio1.80) and 0.81 to 0.9 (Hazard ratio 1.73) compared to those with ankle brachial index 1.1 to 1.2 [25].

In a meta-analysis of nine studies evaluating ankle brachial index and subsequent cardiovascular outcomes for patients with mild PAD with ankle brachial indicesof 0.8 to 0.9 compared to those with normal ankle brachial index, risk of developing coronary heart disease, stroke, and cardiovascular death was 2.5, 2.5, and 5.6 percent, respectively [26]. More than half of these patients were asymptomatic and identified through screening.

Thus, the current American College of Cardiology / American Heart Association (ACC/AHA) guidelines on peripheral arterial disease, identify these patients as a high-risk group who require intensive risk factor modification [27]. Also, due to the evidence that measurement of the ankle brachial index predicts cardiovascular morbidity and mortality, current Task Force guidelines also support the measurement of ankle brachial index in patients at risk of peripheral arterial disease[28].

Risk Factors for Peripheral Arterial Disease

In addition to age, major risk factors for peripheral arterial disease are similar to those for other cardiovascular diseases: smoking, hyperlipidemia, hypertension, diabetes mellitus, and diagnosis of atherosclerosis in other sites[9, 10, 29.]

'The 2011 Guidelines from the Trans-Atlantic Inter-Society Consensus (TASC)[4], define increased risk for peripheral arterial disease as the presence of:

- Age <50 years with diabetes and one additional risk factor (smoking, dyslipidemia, hypertension, or Homocysteinemia)
- Age 50 to 69 years with history of smoking or diabetes
- Age ≥ 65years
- Abnormal lower extremity pulses
- Leg symptoms with exertion or ischemic rest pain
- Known coronary, carotid, or renal atherosclerosis'

AGE: Prevalence increases with age from 3% in those less than 60 years of age to 20% in patients older than 75 years[30.]

GENDER: the Framingham heart study found the male gender to be a significant risk factor for the development of peripheral arterial disease though this has not been shown in other studies[31].

HYPERTENSION: The Framingham study and German epidemiological trial have shown hypertension to be a major risk factor for development of peripheral arterial disease[29, 32.]

SMOKING: The amount and duration of smoking directly correlates with the development and progression of peripheral arterial disease. Cessation of smoking results in improvement as early as 10 month from cessation[33.]

DIABETES MELLITUS: The cardiovascular health study showed a 3.8 fold increase in prevalence of peripheral arterial disease in diabetic patients older than 65 years[34.] In the Rotterdam study diabetes was present in 11.9% and 16% of male and female patients with asymptomatic peripheral arterial disease[35.]

ETHNICITY: Black ethnicity increases the risk of peripheral arterial disease by over two-fold independent of other risk factors such as diabetes, hypertension or obesity [36].

Diagnosis of Peripheral Arterial Disease

The initial diagnosis of peripheral arterial disease is from history and physical examination. A history of intermittent claudication or absent pulses on examination raises the suspicion of peripheral arterial disease [13.]

It has been found that claudication and an abnormal femoral pulse are specific (95% – 99%) but not sensitive (20%) for PAD diagnosis and may miss patients in the asymptomatic stage of disease. Palpable pedal pulses have a negative predictive value of over 90% that may rule out PAD in many cases but the absence of a dorsalis pedis pulse is less specific (73.1%) and has a very low positive predictive value (17.7%) for PAD.[13]

Thus, objective testing is needed in all patients suspected of having peripheral arterial disease. The primary non-invasive screening test is the ankle brachial index.

Although ankle brachial index measurements are easy to perform, this technique is poorly utilised in general practices [37].

Ankle brachial index screening is accurate and reliable in the diagnosis of peripheral arterial disease, comparable to angiography and Doppler ultrasound[38, 39, 40.]

Ankle brachial index measurements can accurately differentiate between normal and angiographically-diseased limbs with a sensitivity of 97% and a specificity of 100%.

The ankle brachial index detects peripheral arterial disease at all stages[41.] It can be used to stratify severity of the disease and hence assist in guiding treatment. Based on ABI measurements, PAD can be classified into:

0.91- 1.3: normal

0.71 – 0.90: mild PAD

0.41- 0.70: moderate PAD

$\leq$0.40: severe PAD

Progression of Peripheral Arterial Disease

The natural history of patients with peripheral arterial disease is not well understood. Studies show that approximately 75% of patients who have claudication remain stable, without progressive leg deterioration, throughout their lifetime[4]. However; one study indicated that functional decline was more common than originally thought[42.]

The pathophysiology leading to development of claudication and decline in functional status is due to progression of the underlying lower extremity atherosclerosis[1.] Few patients go from being asymptomatic to sudden acute arterial occlusion; rather, most have an insidious development of claudication. Functional decline is related to baseline ankle brachial index and limb symptoms. A lower ankle brachial index is associated with a more rapid decline [42.]

About 5 to 10% of individuals with asymptomatic peripheral arterial disease develop symptoms over five years [43]. Critical leg ischemia occurs infrequently in 1 to 2% of patients but is more likely to affect patients with diabetes [8].

Lower extremity arterial ultrasound mapping combined with ankle brachial index can assess the location and hemodynamic severity of peripheral arterial disease[44,]
Evidence suggests that progression of peripheral arterial disease is the same whether or not the patient is symptomatic and the risk of deterioration, with progression to critical limb ischaemia, is not dependent on the presence or absence of symptoms of intermittent claudication[13.]

It is thus important to detect this group of patients early when risk factor control can change outcomes. There is evidence that smoking cessation and monitored walking programmes can slow disease progression and improve peripheral arterial disease symptoms and functional impairment[. 8, 45]
A clinical trial of 882 men with peripheral arterial disease detected by screening found that, compared to "usual care," a "stop smoking and keep walking" programme resulted in about a 50% increase in the number of men who improved their maximum walking performance at 12 month follow-up [46].
One cross-sectional study found that statin therapy was associated with better ambulatory function in patients with peripheral arterial disease, independent of cholesterol levels [47].

STUDY RATIONALE AND JUSTIFICATION

Since epidemiological data for PAD may be affected by a several factors, including genetics, ethnicity, diet and environment, it is therefore also plausible that the prevalence and natural history of peripheral arterial disease in African countries may differ from that of European countries. Also, the management of PAD has to be planned in the context of its natural history, modifiable risk factors as well as those that predict deterioration of limb circulation.

Locally, we manage a lot of patients with peripheral arterial disease who present late with obvious gangrene and for whom amputation is the only mode of treatment. Rarely are these patients diagnosed early in the disease when preventive measures and other treatment modalities can be offered to them and amputations can be avoided.

Up to now there is no local data on asymptomatic peripheral arterial disease. This is needed in order to adequately manage this disease in our setup. Therefore, the results of this study will help identify the disease burden and pattern of progression in our population.

It will also provide a means of defining a patient population with increased risk factors for cardiovascular disease who are not already receiving maximal preventive therapy and for whom identification of further risk would lead to change in management so that therapeutic interventions known to decrease their cardiovascular risk may be offered.

The results may also provide sufficient evidence to allow for a screening protocol using ankle brachial index in order to identify early peripheral arterial disease and intervene to prevent progression and complications directly related to peripheral arterial disease.

BROAD OBJECTIVE

To determine the prevalence of asymptomatic peripheral arterial disease and to determine disease progression over a one year period in patients with associated cardiovascular risk at Kenyatta National Hospital.

SPECIFIC OBJECTIVES

(1) To assess the prevalence of asymptomatic peripheral arterial disease in patients at risk at Kenyatta National Hospital.

(2) To characterize the extent of asymptomatic peripheral arterial disease, at baseline, using ankle brachial index and to evaluate progression over one year based on changes in the ankle brachial index and development of intermittent claudication.

(3) To correlate progression of asymptomatic peripheral arterial disease with associated risk factors of age, gender, diabetes, hypertension, smoking and dyslipidaemia.

MATERIALS AND METHODS

Study Design
Non-interventional, longitudinal study.

Study Site
Medical and surgical outpatient clinics and wards at the Kenyatta National Hospital; a national and referral hospital situated in the city of Nairobi. This hospital covers the local population of the city and neighbouring towns and acts as a referral centre for the entire country.

Study Duration
The study was performed over a one year period from 1st December 2014 to 30th November 2015 with an annual follow up in between. Study end point was one year from recruitment into the study for every patient.

Study Population
Study subjects attending the diabetic, cardiac, renal and cardiothoracic clinics as well as medical and surgical wards

Sample Population
Participants found to have an abnormal ankle brachial index of less than or equal to 0.90 in addition to one or more cardiovascular risk factors.

Sampling
Convenience sampling stratified by age and sex was undertaken until the required sample size was achieved.

Inclusion and Exclusion Criteria
The inclusion criteria were adult patients with asymptomatic peripheral arterial disease defined as an abnormal ankle brachial index of less than or equal to 0.90 and no intermittent claudication on the Edinburgh questionnaire.

Other inclusion criteria included at least one of the following cardiovascular risk factors: cigarette smoking, hypertension, diagnosed diabetes, diagnosed dyslipidaemia or family history of early coronary heart disease.

Exclusion criteria were patients with immeasurable ankle brachial index (calcified arteries giving ankle brachial readings of >1.39, those who already had symptoms of peripheral

arterial disease as seen on the Edinburgh questionnaire, overt vascular disease, those unavailable for a 1 year follow up or those who declined consent.

Sample Size Determination

Sample size formula for one proportion:

$$N \geq \left(\frac{Z}{w}\right)^2 \times p(1-p)$$

Where:

N = the total sample size needed

Z = the confidence interval (the 95% confidence interval for the true proportion of asymptomatic participants in the population eventually developing signs of peripheral arterial disease).

p = proportion of asymptomatic participants in the population who eventually develop signs of peripheral arterial disease after a certain period of time e.g. one year. This study will assume an incidence of development of symptoms of 5% after one year (this is based on a study by Stoffers et al[3] which showed that 5 to 10% of individuals with asymptomatic peripheral arterial disease develop symptoms over the next five years).

w = the width of the 95% confidence interval. This study assumed a confidence interval no wider than 5% (0.05) on either side of the true proportion of the population of patients with asymptomatic peripheral arterial disease who subsequently develop symptoms (i.e. if the true proportion is 10% then the confidence interval should not be more extreme than 5% - 15%).

Thus:

$$N \geq \left(\frac{1.96}{0.05}\right)^2 \times 0.05(1-0.05)$$

$$N \geq (1536.64) \times 0.05(0.95)$$

$$N \geq (1536.64) \times (0.0475)$$

$$N \geq 72.99$$

Due to the one year duration of follow up, a loss to follow up rate of 5% was assumed. This was based on previous studies. This was added to the calculated sample size in order to account for this and the new sample size thus calculated as:

$N \geq 72.99/ (1-0.05)$

$N \geq 72.99 / 0.95$

$N \geq 76.8$

Hence, the final sample size was 77 patients.

SAMPLING METHODOLOGY

Patients seen at the cardiac, renal, diabetic clinics as well as medical and surgical wards were triaged with the assistance of the nurses and house officers. Those with risk factors such as hypertension, diabetes, dyslipidaemia and smoking formed the study population and were selected for further assessment.

The nurses and house officers managing the patients were requested to direct patients with hypertension, dyslipidaemia, diabetes and chronic smokers to the principal investigator once they were through with their clinic consultation. The principle investigator then performed the ankle brachial index and assessed the presence of intermittent claudication based on the Edinburgh questionnaire.

Those who had ankle brachial index of less than or equal to 0.90 upon measurement and without any intermittent claudication or overt vascular symptoms then formed the cases and were invited to participate in the study. Informed consent was then taken. Patients continued to be recruited into the study until the sample size was achieved.

Demographic and clinical data was collected and recorded on standardized questionnaires:

Personal History of cardiovascular disease (myocardial infarction, angina, or stroke) was considered when diagnosed by a physician.

History of diagnosed dyslipidaemia and diabetes was noted. Family history of heart disease was taken.

Blood pressure was measured with the subject seated with a calibrated sphygmomanometer and an adult sized cuff. Two measurements were taken, at least 20 minutes apart, and the lower value recorded.

Participants were considered hypertensive if previously diagnosed by a physician or presented with systolic blood pressure ≥140 or diastolic blood pressure ≥90mmHg.

A history of cigarette consumption was taken. Patients were classified as smokers (current or quit< 5 years), former smokers (quit ≥ 5 years) orhad never smoked.

Ankle–brachial index measurement

The ankle brachial index was measured only by the primary researcher to avoid operator dependent bias: Brachial and ankle (right dorsalis pedis and left dorsalis pedis) systolic pressures were measured with adult sized cuffs with attached sphygmomanometers. Return of flow was determined using a continuous wave Doppler (PD1cv 8MHz vascular pocket Doppler.)

Each ankle pressure divided by the highest brachial pressure was used to calculate each ankle brachial index.

The primary outcome variable was the percentage of subjects with peripheral arterial disease, defined as an ankle brachial index of ≤0.90. Ankle brachial indexes in the 0.91–1.39 range were considered normal; ankle brachial index >1.39 were excluded from evaluation since the possible influence of arterial wall stiffness made it impossible to rule out arterial obstruction.

Functional questionnaire

Claudication was assessed using patients' answers to the Edinburgh questionnaire. Peripheral arterial disease was considered asymptomatic when ankle brachial index was less than or equal to 0.9 and the Edinburgh questionnaire showed no intermittent claudication.

DATA COLLECTION AND DATA ANALYSIS

Data was transferred from questionnaires to a MS Excel spread sheet for cleaning. Data was then exported to IBM SPSS (Statistical Package for Social Sciences) version 22 for statistical analysis.

Frequency tables and summary statistics were made for demographic and clinical characteristics of evaluable subjects with asymptomatic peripheral arterial disease. Continuous variables were presented as means and standard deviations. Student's *t*-test was used for differences in continuous variables and Chi square tests for categorical variables.

Prevalence was calculated as number of patients with asymptomatic peripheral arterial disease at baseline divided by the total number of patients screened and expressed as a percentage.

Ankle brachial index and leg symptoms were compared at baseline and after 1 year. Association between degree of change in ankle brachial index and change in claudication was analysed.

To examine the relationship between various cardiovascular risk factors on the progression of asymptomatic peripheral arterial disease, the Odds ratio (OR) and 95% confidence interval of frequency of risk factors in subjects with ankle brachial index ≤ 0.90 was calculated. Subject data was investigated among the following variables: demographics (age, sex), cardiovascular risk factors (smoking habits, family history of heart disease, hypertension, diabetes and diagnosed dyslipidaemia). A value of $p < 0.05$ was considered statistically significant.

To explore the risk factor burden, the cumulative number of cardiovascular risk factors in each subject was analysed and subjects were evaluated for the presence of > 1 risk factor in order to assess the association between risk of progression of peripheral arterial disease and the number of cardiovascular risk factors. Data was expressed as Odds ratio (± 95% CI).

ETHICAL CONSIDERATIONS

Consent and approval was obtained from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee.

An introductory letter was included with the questionnaire to describe the purpose of the study, the research team, voluntary nature of participation and confidentiality of the data. All patients taking part in the study were given an informed consent form to sign.

All data for the study was collected on data forms designed specifically for the study. Personal details like mobile/telephone numbers were collected to ensure that contact was maintained with the patients over the full 12 months of follow-up.

Patients found to have asymptomatic disease were referred to the attention of the clinic concerned.

Study data was entered into a password-protected database, which was accessible only to the researchers.

Data was used only for the purpose of the study, and was not passed to anyone else.

Results of the study are presented with the data from the groups aggregated together; no individual patient will be identified in any way in reports of the study.

Upon completion of the study, all data, questionnaires and material will be destroyed after publication of the dissertation.

Results will form the basis for initiating change/to screen for and manage asymptomatic peripheral arterial disease early and adequately. These results will be disseminated to the medical fraternity at a conference or some other suitable forum.

RESULTS

A total of 217 patients were screened over 12 month duration between November 2013 and October 2014 of which 75 patients met the study inclusion criteria.

During the one year follow up period, 11 patients died from the various associated cardiovascular comorbidities and 2 patients were lost to follow up.

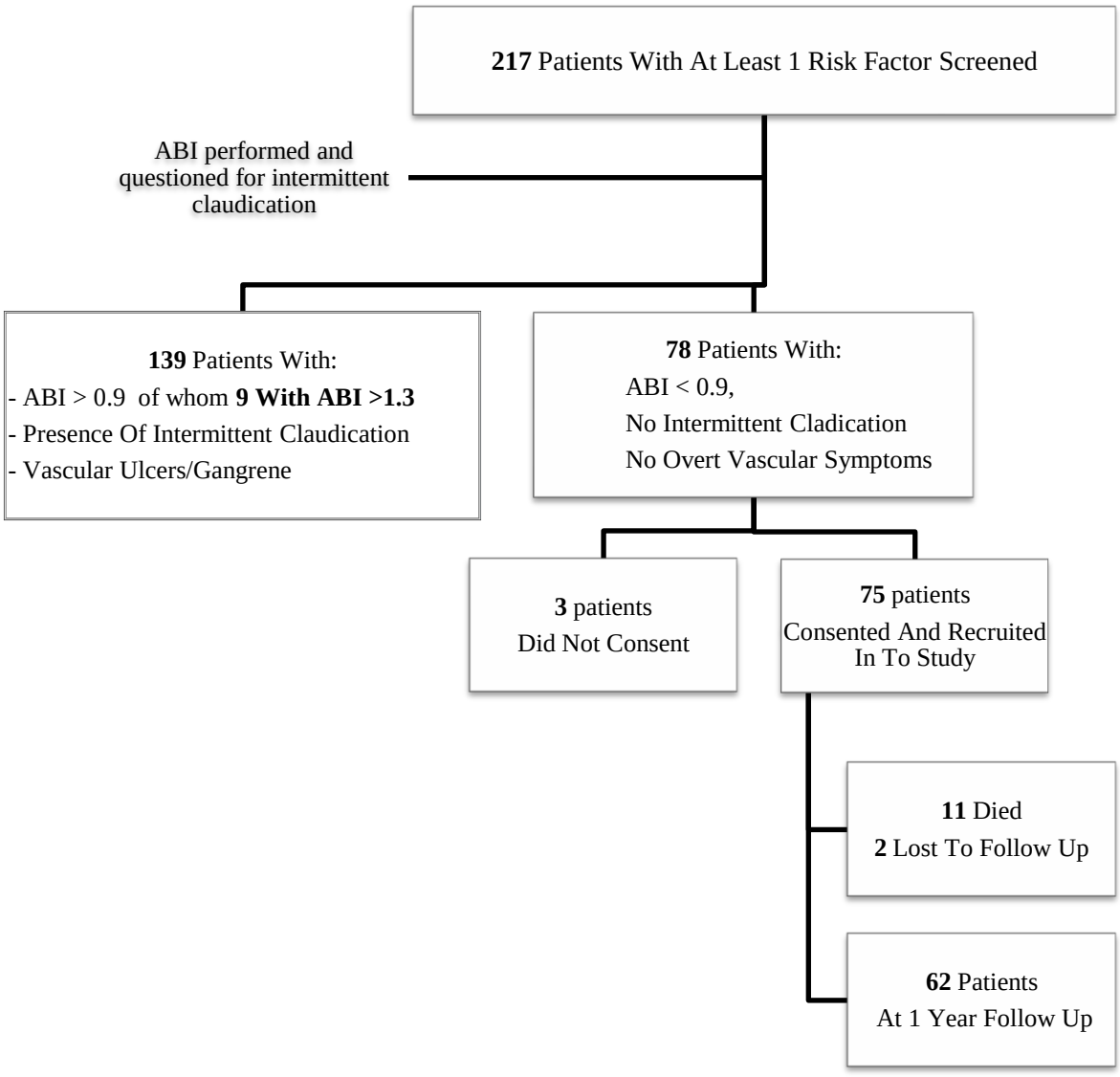

Figure 1: flow chart of screening and enrollment of study subjects

Demographic Characteristics of Study Patients

Table1: Summary of demographic characteristics and cardiovascular co-morbidities based on gender

Parameter	Female	Male	Total (%)
n	41 (55%)	34 (45%)	75
Age:			
Mean	55.6	61.4	58.2
SD	14.5	11.1	13.3
Range	65 (21-86)	43 (38-81)	65 (21-86)
Age groups:			
Below 50 Years	11 (27%)	4 (12%)	15 (20%)
51 -65 Years	21 (51%)	19 (66%)	40 (53%)
Above 65 years	9 (22%)	11 (32%)	20 (27%)
Family History of CVD	4 (10%)	2 (6%)	6 (8%)
Smoking history	2 (5%)	23 (68%)	25 (33%)
History of DM	18 (44%)	14 (41%)	32 (43%)
History of dyslipidaemia	12 (29%)	18 (53%)	30 (40%)
Hypertension	38 (93%)	29 (85%)	67 (89%)

The mean age of study subjects was 58 years (SD=13.3). Males were older than females with a mean age of 61.35years while females had a mean age of 55.59 years.

The patients were grouped into 3 age groups as shown in table 1. A majority of the patients were between 51 and 65 years, accounting for 49.3% of the patients.

There was only one patient below 30 years and 3 patients above 80 years of age. Females predominated the below 50 years age group while males predominated the above 65 years age group. The sex distribution was slightly higher for the females amounting to 55% and 45% for the males

Prevalence of Asymptomatic Peripheral Arterial Disease

ABI measurements were undertaken for all patients and 78 (36%, n = 217) patients had an ABI of ≤0.9 in a total of 113 legs with no symptoms of intermittent claudication at baseline. Three of the 78 patients were subsequently excluded from the study as they declined consent.

Nine of the 139 patients with an ABI >0.9 had an ABI of > 1.3 and hence were excluded. Six of these were diabetic.

Among the 75 patients with asymptomatic PAD, 38 (51%) had abnormal ABIs on both legs, while 11(15%) and 26(35%) patients had involvement of only the right or left legs, respectively.

Severity of Asymptomatic Peripheral Arterial Disease at Baseline

Study patients were classified into 3 severity categories on basis of the ABI measurement as shown in table 2, table 3 and figure 2 below.

Majority of the patients: 89% (67/75) presented at baseline with mild form of disease. None of the patients had severe disease or critical limb ischaemia.

Eight (11%) patients had moderate PAD. Two of the patients who had moderate disease had involvement of both lower limbs and 6 out of the 8 patients with moderate disease had died at 1 year of follow up.

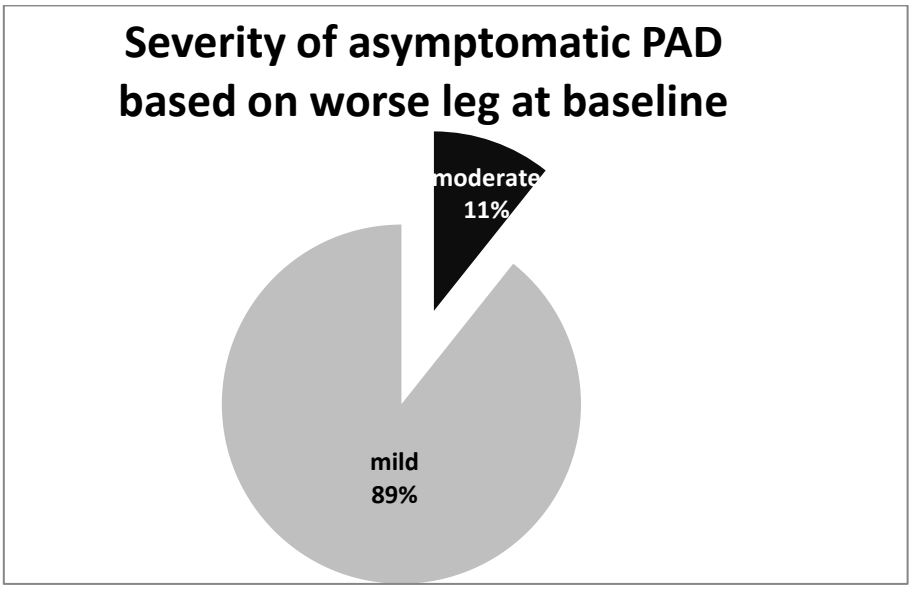

Figure 2: severity of asymptomatic PAD at baseline based on worse leg at KNH

The left lower limb had a higher incidence (57%; 64 of 113 legs) of having asymptomatic PAD as compared to the right lower limb. The baseline mean ABI was also lower for the left leg (0.85) as compared to the right (0.86) though this was not statistically significant (p = 0.17)

Table 2: Severity of asymptomatic peripheral arterial disease at baseline based on ABI for each limb at KNH

ABI Severity Classification	Left Leg (n = 64)	Right Leg (n = 49)	Total Limbs (n = 113)
ABI Mean (SD) Median Range	 0.85(0.07) 0.88 0.27 (0.63-0.9)	 0.86(0.06) 0.9 0.3(0.60-0.90)	
Severe (< 0.4)	0 (0%)	0 (0%)	0
Moderate (0.41- 0.70)	7 (10.9%)	3 (6.1%)	10
Mild (0.71-0.90)	57 (89.1%)	46 (93.9%)	103
Total	64	49	113

Table 3: Classification of study participants by sex and ABI severity at baseline

ABI Category	Female	Male	Total
Moderate	3	5	8
Mild	38	29	67
Total	41	34	75

Out of the 8 patients in the moderate category, 5 (62.5%) were male patients while 93% of the females were in the mild category at baseline.

Frequency of Associated Cardiovascular Comorbidities

All patients screened were patients at risk with at least one associated risk factor for cardiovascular disease. Figure 3 summarizes the frequency of cardiovascular risk factors for the patients selected at baseline.

Hypertension was the most common comorbidity at 89.3% followed by diabetes mellitus, dyslipidemia and smoking at 42.7%, 40% and 33% respectively.

A majority of the male subjects reported history of smoking (68%) and dyslipidemia (53%) as compared to the female patients who reported 5% and 29% respectively. More of the female subjects had a history of diabetes mellitus (44%) and hypertension (93%) as compared to the males who had 85% and 41% respectively.

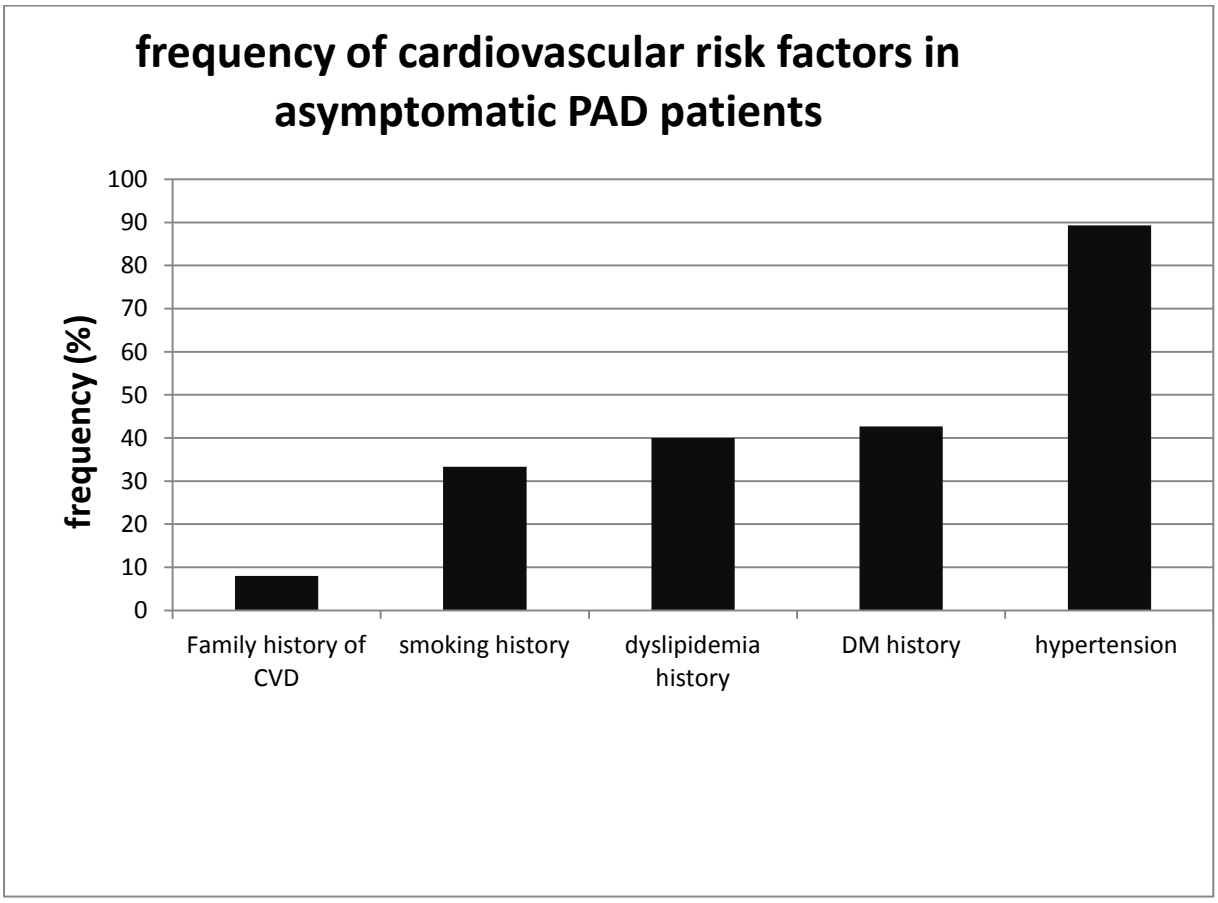

Figure 3: Distribution of cardiovascular risk factors in patients with asymptomatic PAD at KNH

The risk factor burden (total number of CV risk factors in addition to age) in the study population is shown in Table 4. Of the study population at baseline, 73.3 % had 2 or more known risk factors for cardiovascular disease while 26.7% had only 1 risk factor.

Table 4: percentage frequency of risk factor burden in patients with asymptomatic PAD at KNH

No. of Risk Factors	Participants n = 75 (%)
1	20 (26.7%)
2	20 (26.7%)
3	22 (29.3%)
4	12 (16%)
5	1 (1.3%)

Mortality

During the follow-up period, 11 patients (15%) died, of whom 7 (64%) were males. Distribution of the baseline variables (age, sex, ankle-brachial index, possible risk factors, and cardiovascular comorbidity) among those who died showed that those who died were mainly older men with a mean age of 63 years.

All 11 (100%) patients who died had involvement of both lower limbs, 7 (64%) had moderate PAD with at least one limb with an ABI < 0.7.

Seven patients (64%) had a more unfavourable risk factor profile with more than 2 associated risk factors. The main causes of death were due to the associated cardiovascular comorbidities.

Progression of Asymptomatic PAD at 1 Year

In study completers (62 patients), asymptomatic PAD at baseline was present in 88 (71%) of the 124 legs.

A total of 32 (52%) patients had progression of disease at one year with deterioration in the ABI, 22 patients had no change in ABI and had no disease progression and 8 patients showed a degree of improvement in the ABI at follow up.

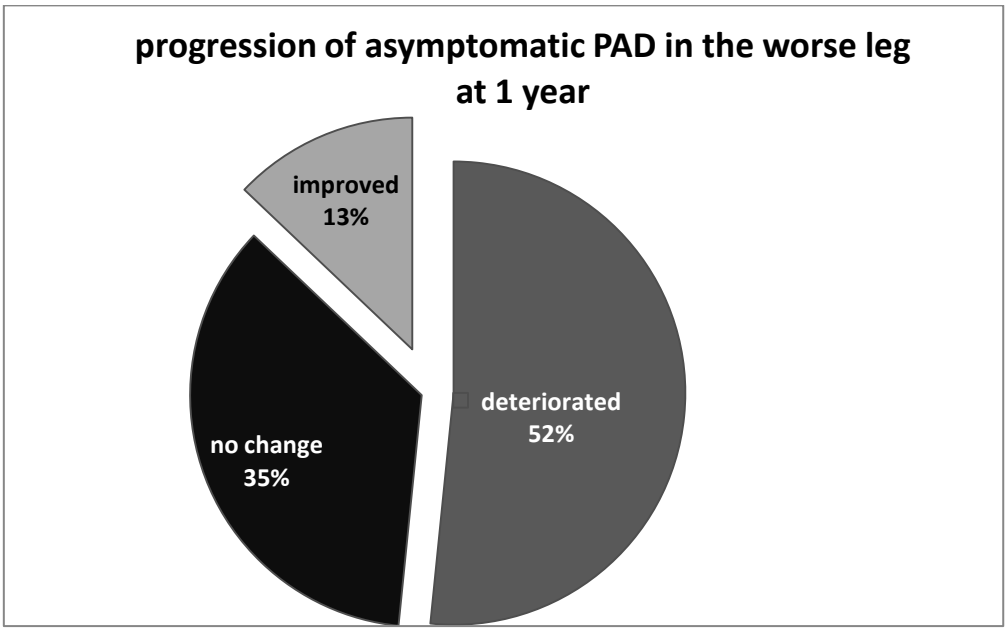

Figure 4: Progression of Asymptomatic PAD at 1 Year of Follow up Based on ABI for Worse Leg

At 1 year, 8 of the 36 normal legs at baseline developed asymptomatic PAD, and 36 of the 88 legs with asymptomatic PAD at baseline, had worsening of PAD. A total of 44 (46%) legs had progression of disease while 13 (14%) legs showed some improvement in the ABI.

Table 5: Progression of asymptomatic PAD at 1 year of follow up based on ABI for left and right legs

ABI at 1 year	Right leg n (%)	Left leg n (%)	Total limbs
No Change	24 (45.1%	15 (21.6%)	39
Improved	8 (15.7%)	5(13.5%)	13
Deteriorated	20 (38.5%)	24 (54.5%)	44
Total	52	44	96

More of the left legs had worsening of disease as well as development of new symptoms as compared to the right legs.

Figure 5 shows that there was a shift toward lower mean ABI levels over time when the population distribution of ABI at baseline and 1 year was examined with more of the population having mean ABIs of < 0.8 at 1 year and some even progressing to severe disease with ABIs of <0.6.

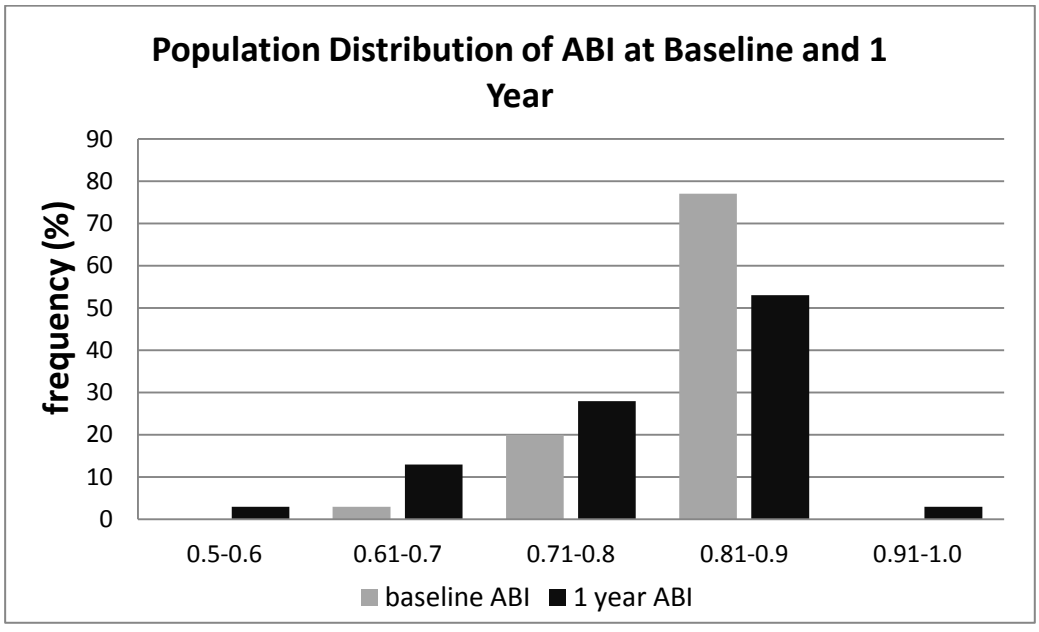

Figure 5: Population distribution of ABI at baseline and one year in patients with asymptomatic PAD at KNH

Table 6 shows the change in mean ABI level at baseline and 1 year of follow up when the analysis was restricted to the 62 study completers. The lower ABI (indicating the worse leg at baseline) showed a significant change over the 1 year of follow-up (p=0.001).

On average, right leg ABI was higher than left leg ABI at baseline, mean of 0.88 versus 0.86,with the right leg showing a greater decrease (-0.02) over 1 year than the left leg (-0.01). Using t- test for paired samples, the right leg showed a significantly greater ABI reduction than the left leg (p = 0.005).

Table 6: Change in ABI from baseline to one year of follow up in patients with asymptomatic PAD at KNH

ABI	baseline Mean (SD)	1 year Mean (SD)	ABI Change	*p*
Worse Leg n=62	0.86 (0.11)	0.83 (0.14)	- 0.03	**0.001**
Left Leg n=52	0.86 (0.11)	0.85 (0.14)	-0.01	0.325
Right Leg n=44	0.88 (0)	0.86 (0.01)	-0.02	**0.005**

Development of Intermittent Claudication at 1 Year

During follow-up, 6 patients developed symptoms of claudication at 6 months while 13 patients (21%) became symptomatic with intermittent claudication at 1 year. Seven (54%) of the 13 patients were females while 6 (46%) were males. The mean age of patients who developed intermittent claudication was 53.5 years (32-86 years).

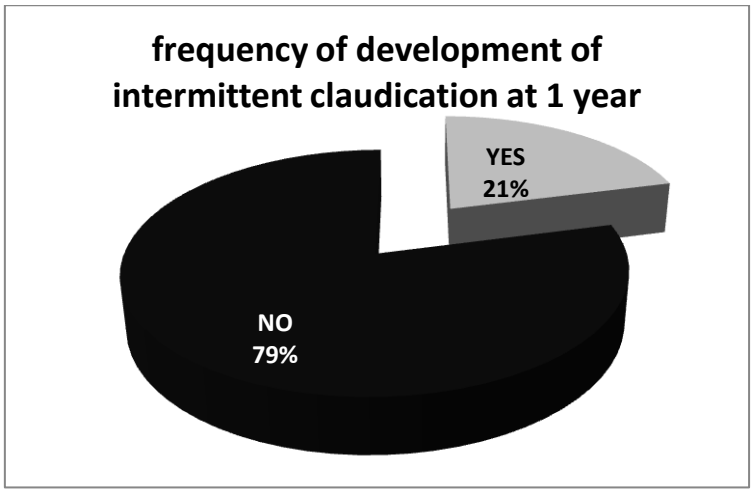

Figure 6: Distribution of patients who developed intermittent claudication at 1 year of follow up

In Table 7, change in ABI is compared in patients who had no intermittent claudication (n = 49), relative to the 13 patients who developed claudication during follow-up. The mean ABI in patients with intermittent claudication was lower than the mean ABI of the asymptomatic group (0.79 vs. 0.87).

The mean ABI level of the claudicants fell on average by 0.09 over 1 year to 0.71; whereas there was no significant change in those who remained free of symptoms.

Table 7: Change in ABI in patients with intermittent claudication as compared to the asymptomatic group

	Mean ABI (SD) Baseline	**Mean ABI (SD) 1 year**	**Change: baseline to 1 y**	***p***
Intermittent claudication (n =13)	0.79(0.03)	0.71(0.06)	- 0.08	**< 0.001**
No intermittent claudication (n =49)	0.87 (0.05)	0.86 (0.07)	-0.01	0.29

As seen in table 8, of the 32 patients who progressed with deterioration in ABI, 19 (59%) patients had significant worsening of ABI ($p<0.001$) but without development of intermittent claudication.

Table 8: change in ABI in patients who progressed with intermittent claudication as compared to patients who progressed without intermittent claudication

	Mean ABI (SD) Baseline	**Mean ABI (SD) 1 year**	**Change: baseline to 1 y**	***p***
Intermittent claudication (n =13)	0.79(0.03)	0.71(0.06)	- 0.08	<0.001
Asymptomatic PAD (n = 19)	0.87(0.04)	0.83(0.06)	-0.04	**<0.001**

Risk Factor Profile for Progression of Asymptomatic PAD

None of the risk factors of hypertension, DM, smoking, dyslipidemia or family history of CVD were independently significantly associated with progression; $p > 0.05$ on Spearman's correlation analysis.

Table 9:Frequency of risk factors in patients who progressed or did not progress at 1 year of follow up

	Progression	No Progression
1 risk factor	7 (22%)	16 (53%)
$\geq$ 2 risk factors	25 (78%)	14 (47%)
Total	32	30

At 1 year of follow up, patients who had progression of asymptomatic PAD were compared to those who had no progression of disease or who improved as seen in table 9.

There was an increased risk of progression of asymptomatic PAD in patients presenting with multiple risk factors.

Of the 32 patients who had progression of disease based on worsening of ABI, 25 (78%) had more than 1 risk factor. Of these, 14 had 3 risk factors while 10 had 2 risk factors.

Patients with 2 or more risk factors had an almost 2-fold increase in the progression of asymptomatic PAD as compared to those with 1 additional risk factor; (x^2,$p = 0.031$); Odds ratio 1.8 (95% Confidence Interval:1.06 - 2.96).

In the 13 patients who developed intermittent claudication, 9 (69.2%) patients had more than 1 associated risk factor. Seven(53.8%) of these had 3 associated risk factors.

For the seven patients who had progression of disease with only one associated risk factor, 71% were hypertensive and 29% were smokers.

DISCUSSION

The cardiovascular disease burden associated with presence of peripheral arterial disease is the same, whether it is the asymptomatic or symptomatic form[2, 3.] Despite this, limited information is available on the asymptomatic form of peripheral arterial disease in our population and hence the purpose of this study was to further describe this.

Demographic Distribution and Prevalence of Asymptomatic PAD

The population prevalence of peripheral arterial disease ranges from 4.5% to 32% worldwide depending on PAD definition, sex, age, ethnicity as well as presence of associated risk factors.[21, 35, 48, and 49.]

This study showed that asymptomatic PAD is highly prevalent (36%) in patients with at least one associated cardiovascular risk factor in our population. This was at the upper end of what is reported internationally. This is supported by the fact that non-white ethnicity is a risk factor for PAD. Studies have shown that black ethnicity increases the risk of PAD by two-fold independent of other risk factors such as diabetes, hypertension or obesity[36.]

The PARTNERS study screened subjects with risk factors for vascular disease; asymptomatic PAD was detected in 29% of the total population[1]. The Greece subgroup of the PANDORA study, which was a cross-sectional study conducted in 6 European countries on patients with moderate cardiovascular risk but no overt vascular disease or diabetes, showed a prevalence of 28% of asymptomatic PAD[50.] The slightly lower prevalence could be attributed to the fact that patients with diabetes were excluded from this study.

Ashish Paul et al in 2007[14] showed that the prevalence of peripheral arterial vascular disease is as high as 29%, in rural black South Africans.
At Kenyatta national hospital, Maritim et al in 2007[17] detected a prevalence of 11.9% in chronic kidney disease patients, while Oyoo et al in 2011[18] established a prevalence of 25.5% in patients with rheumatoid arthritis. These studies combined both symptomatic and asymptomatic forms of PAD and not all patients had cardiovascular risk factors.

Even in the general population asymptomatic PAD is more prevalent than symptomatic PAD[13] and our study was specific for asymptomatic peripheral arterial disease in patients at cardiovascular risk. This possibly explains the higher prevalence in our study.

The high prevalence in our study confirms our anecdotal experience of performing a large number of amputations for gangrenous limbs. Awori et al in 2004 also established that the main indication of amputations in our setup was peripheral arterial disease.[19]

There is a wide variation in the demographic profile amongst different population studies. Most studies have found prevalence of PAD, symptomatic or asymptomatic to be slightly greater in men than women, especially in the younger age groups. Other studies have, however, shown a more equal distribution of PAD and even a higher predominance in women[28.]

The mean age of subjects in this study was 58 years (range 21-86 years). Most of the patients were between 51 and 65 years, accounting for 49.3% of the patients. Females predominated the 'below 50 years age group' while males predominated the 'above 65 years age group' and overall the female patients were slightly more (55%) than their male counterparts.

The Greek sub group of the PANDORA study found the mean age to be 62.1 ± 9.1 years and 61.2% of the subjects were male[50.] A study by Birgitta et al in the Swedish population found that asymptomatic PAD was more frequent among women (P =.03) than men in all age groups[48.]

Most studies have selected patients above 55 years of age. This has been one of their inclusion criteria as PAD has been shown to be associated with an increase in age. Our study sought to screen all adult patients without an age limit and this possibly represents a truer picture of asymptomatic PAD being more prevalent in those between 50-65 years while those above 65 years possibly having more symptomatic and severe forms of the disease.

Women dominated in our study as they did in the National Health and Nutrition Examination Survey [51] and the study by Birgitta[48]. 'Higher ABI in women, postmenopausal hormonal effects and smaller vessels could be possible explanations for this difference'[52, 53, 54.] A gender bias in health seeking behavior may also explain this predominance as well as the fact that in our study women had a higher frequency of having associated hypertension and diabetes which are major risk factors for PAD.

Severity of Asymptomatic PAD

In this study majority of the patients (89%) presented at baseline with mild form of disease (ABI 0.71-0.90) and 11% with moderate disease (ABI 0.41-0.70). None of the patients had severe disease (ABI < 0.4). This is not surprising as we were looking at the asymptomatic form of PAD.

In a study by Sikkink[55], the 5 year cumulative survival rates were 63% for severe disease, 71% for moderate disease and 91% for mild disease. In our study, 6 of the 8 patients with moderate PAD had died by one year of follow up and this correlates with the evidence from other studies that a worsening of the ABI predicts a higher risk of cardiovascular events and mortality[21, 22, 23]

Nine (4%) patients had an ABI > 1.3 suggestive of incompressible vessels due to medial arterial calcification. This was mainly seen in the diabetic patients. These patients had to be excluded from the study as they had spuriously elevated ABIs and may have caused a misclassification bias.

Risk Profile

This study revealed a high frequency of most cardiovascular risk factors. Hypertension was the most common comorbidity at 89.3% followed by diabetes mellitus, dyslipidemia and smoking at 42.7%, 40% and 33% respectively.

The Limburg PAD Study as well as the PANDORA study showed that smoking, hypertension and diabetes are the most important risk factors for PAD. Our results are in agreement with these studies which showed evidence of an association between smoking, age, hypertension and diabetes with PAD[50, 56.]

Sub-Saharan Africa is currently experiencing a raised incidence of non-communicable diseases, especially cardiovascular disease and a local study by Joshi et al[57] showed a high prevalence of hypertension with 23% of the population classified as hypertensive. The prevalence was higher in women in the older age categories and there was a significant association with diabetes. This high incidence of CVD risk factors, mainly hypertension in women in our population may be a cause of the high prevalence of PAD in our study[57.]

Progression of Asymptomatic PAD

This study showed a significant progression of asymptomatic PAD in patients at risk with 52% of patients having a worsening of the ABI at 1 year and 21% of these developing symptoms of intermittent claudication. This is not surprising, since asymptomatic and symptomatic PAD are not different diseases but a continuum of the same disease appearing at different times.

Unlike other studies which show an increased incidence in men, in our study there was a slightly higher proportion of female patients who developed intermittent claudication at a mean age of 53 years.

The high rate of developing intermittent claudication in our study was similar to a publication from the Edinburgh Artery Study; a large-scale cohort study of 695 subjects aged 55–74 years, which reported claudication developing in 179 cases (25%)[21.]

Mohler et al also showed that there is a population of subjects without claudication symptoms who have reduced ABI in whom a significant number of legs (21%) developed claudication over 1 year[44.]

The difference in mean age and sex of patients developing intermittent claudication in our study may be as a result of the inclusion of a younger age group in our study as well as the higher prevalence of females with a lower ABI at baseline.

Of note was the fact that there was a significant deterioration in mean ABI at one year in the patients who developed claudication while the ABI at 1 year had hardly changed in the asymptomatic group of patients. This is in concordance with a study by McDermott et al who showed that functional decline over two years is related to baseline ankle brachial index whereby a lower ankle brachial index was associated with a more rapid decline[42.]

We also found that a significant number of patients had progression of disease without development of intermittent claudication. Misclassification of symptomatic PAD could have occurred in patients who adapted their lifestyle to avoid symptoms or patients who had asedentary lifestyle preventing symptom onset thus being classified as asymptomatic. This was unlikely to have caused a major bias in our study as most of our patients were mobile, patients seen in outpatient clinics. These results are also in keeping with the evidence from the TASC inter society consensus for the management of peripheral arterial disease[13], which

suggests that progression of peripheral arterial disease is identical whether or not the subject is symptomatic. There is nothing to suggest that the risk of local deterioration, with progression to critical limb ischaemia, is dependent on the presence or absence of symptoms of intermittent claudication.

Also, slight improvements in ABI occurred at one year in 8 patients with asymptomatic PAD at baseline, although this was not statistically significant. This may be due to the development of collateral circulation in the affected limbs; Medical care and advice on need for exercise given to the patients at baseline may also be a potential source of confounding for this.

Surprisingly, our study showed that the ABI was lower in the left leg than the right at baseline suggesting a unilateral predisposition to disease. Even more surprising was the finding that progression of disease in the leg with a higher ABI at baseline occurred more rapidly that in the leg with more severe disease and this was statistically significant.

'Asymmetry in ABI of the lower limbs has been shown in both studies of healthy individuals,[58] and patients with intermittent claudication or low ABI.[59.] This could point towards a unilateral predisposition to atherosclerosis because it has been shown that there is very little variation in measurement between the legs.[60.] However, the order in which pressures are taken may influence the measurements. Central pressure tends to fall as length of rest in the supine position increases. Hence, a higher pressure would be recorded in the first leg in which pressure is measured (usually the right leg as in the present study) and a lower pressure would then tend to occur in the left leg as the central aortic pressure continued to fall[61.],

Very few studies have investigated the role of cardiovascular risk factors on the progression of PAD. Jurenne et al showed that older age, hypertension, and diabetes probably play a role in the progression of asymptomatic PAD to symptomatic PAD [56] while Victor et al showed that risk factors contribute differently to the progression of Large vessel-PAD and Small vessel-PAD with Cigarette smoking, lipids, and inflammation contributing to Large vessel-PAD progression, whereas diabetes was the only significant predictor of Small vessel-PAD progression[62.]

This study showed that the probability of progression of PAD increased with the number of risk factors. There was a significant risk of worsening of disease in patients presenting with 2 or more cardiovascular risk factors as compared to patients with only one risk factor.

There seemed to be some association of having hypertension and smoking with the development of intermittent claudication but no statistical significance was reached, possibly because of small numbers.

STUDY LIMITATIONS

1. Given the 1 year duration of the study there were patients who died or were lost to follow-up (17%). These patients had to be excluded from the total number at 1 year.This may have constituted a possible source of bias with a certain loss of power.

2. Upon diagnosing patients with asymptomatic peripheral arterial disease, they were referred to a physician for management. Any interventions given to modify risk factors may have then affected the disease progression and outcome.

3. Misclassification of symptomatic PAD could have occurred in the study population. Symptomatic patients who adapted their lifestyle to avoid leg pain or patients who had a sedentary lifestyle preventing symptom onset may have been classified as asymptomatic.
In our data, very few of the asymptomatic patients reported being bed ridden. Thus, the occurrence of misclassification bias in our study was not likely to be substantial.

4. Spuriously elevated ankle-brachial indices due to calcified vessels, especially in diabetic patients, may have also formed a source of misclassification bias. In our data, 9 patients had an ABI $\geq$1.30 and had to be excluded from the study resulting in a loss of power.

5. The ability to predict an independent association of each risk factor with progression of PAD was limited due to the small number of patients.

6. The generalizability of results to the whole population may be limited. However, the study was carried out in the country's national referral hospital where a majority of the population is treated. Thus, by sampling study patients from the clinics and wards in this national hospital, a study populationwas derived that should be relatively similar to the general population.

CONCLUSIONS

1. The prevalence of asymptomatic PAD is high in our population of patients who have at least one associated cardiovascular risk factors. There is an almost equal distribution of PAD amongst men and women with a higher incidence in those above 50 years.

2. In patients with asymptomatic PAD the lower ABI obtained from the two legs showed significant progression over 1 year of follow-up. Deterioration occurred more rapidly in the limb with the higher ABI at baseline, possibly indicating a systemic tendency to atherosclerosis.

3. Once asymptomatic disease is present, the incidence of developing intermittent claudication is significantly elevated and patients who developed intermittent claudication tended to experience a greater decline in the ABI of both legs compared with symptom-free patients.

4. Progression of asymptomatic PAD with significant deterioration in ABI occurred even without development of intermittent claudication.

5. There is an almost two fold risk of progression of asymptomatic PAD in patients with 2 or more cardiovascular risk factors.

Due to the high prevalence and significant progression of asymptomatic PAD in our population, early detection of PAD is justifiable in patients at risk. Measuring ABI with a Doppler device is an easy and reproducible tool which should be recommended for use not only to the vascular specialist, but also to the general practitioners.

These findings suggest that measurement of ABI is not necessary for patients if they have only one risk factor, with the exception of hypertensives and smokers. It could be suggested, therefore, that patients with multiple risk factors for PAD be screened during routine visits.
In asymptomatic patients who are thus identified, smoking, hypertensionand diabetes would be the most relevant risk factors to tackle.

RECOMMENDATIONS

1. There is a need to increase public awareness of PAD and its risk factors and the awareness of preventive measures/lifestyle modifications that could be undertaken to prevent worsening of disease.

2. Train primary care physicians on use of Doppler devices for measuring ABI and increase their awareness of the importance of ABI measurement for the detection of asymptomatic PAD and the need for early vascular referrals.

3. Possible incorporation of ABI measurement in screening programs for cardiovascular risk assessment.

4. Further longitudinal studies are required to investigate the relevance of changes of ABI over longer study duration and to compare this method of assessment of atherosclerosis with imaging techniques for disease progression.

5.Cost-effectiveness of ABI screening is unknown thus the need of more studies are needed to determine whether adding the ABI measurement in a screening strategy would be cost-effective and feasible in the general population.

6. Conduct a study to determine the effect that risk factor modification has on disease progression.

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APPENDICES

APPENDIX 1: DATA COLLECTION SHEET

1. Date of recruitment into the study

2. Study number 3. Hospital number

4. Sex M F 5. Age 6. Mobile no.

7. Personal history of cardiovascular disease Y N

8. Family history of coronary Heart Disease Y N

9. Smoking: Current quit > 5 years never smoked

10. History of Diabetes Y N

11. History of dyslipidemia Y N

12. Hypertension: Previously diagnosed/on treatment

Systolic blood pressure ≥140 mmHg

Diastolic blood pressure ≥90mmHg

	Baseline	6 months	At 1 year
13. Ankle brachial index			
14. Claudication			

APPENDIX 2: Edinburgh questionnaire

1. Do you get any pain or discomfort in your legs when you walk? (Yes)

2. Does this pain ever occur when you are standing still or sitting? (No)

3. Do you get this pain if you walk uphill or hurry? (Yes)

4. Do you get this pain if you walk at an ordinary pace on level ground?
(No=mild, Yes=moderate/severe)

5. What happens to the pain if you stand still? (It goes away)

6. Does the pain disappear within 10 min or less when you stand still (Yes)

7. Where do you get the pain or discomfort? (leg diagram is presented to
patient)

Based on the conditions fulfilled by the response, patients are classified as follows:

1) Definite claudication
- All responses to questions as noted above
- Calf area marked on the diagram of the leg (question 7)

2) Atypical claudication
- All responses to questions as noted above
- Thigh or buttock marked on the diagram of the leg, in the absence of calf pain (question 7)

3) No claudication. Any other combination of responses

APPENDIX 3: Study Consent form

PREVALENCE, ASSOCIATED RISK FACTORS AND PROGRESSION OF ASYMPTOMATIC PERIPHERAL ARTERIAL DISEASE AT KENYATTA NATIONAL HOSPITAL

I am Dr. Nikita Mehta, a post-graduate student in the department of surgery at the University of Nairobi. I am carrying out a study on presence of blockage in vessels of the leg and progression of this blockage even before it causes pain in the legs.

Purpose of the study:

Peripheral arterial disease commonly occurs in patients with cardiovascular risks and is due to formation of fat blockages in the arteries which compromise blood flow to the legs. This result in leg pain, wounds, gangrene and patients are also at increased risk of stroke and heart attack. Sometimes patients may suffer from all these without any warning signs or pain in the legs.The purpose of this study is to determine the presence and progression of this disease in our population when it is still silent. This will be determined by filling in a questionnaire and doing a blood pressure measurement on your arms and legs.

This study has been authorized by the KNH/UON-ERC for one year and will be renewed thereafter.The information will guide doctors to identify patients who need treatment.

Risk and benefits

There is no harm or risk to you for participating in this study. No additional tests outside the usual ones for treatment will be done and there will be no extra cost to you for participating.

There will be a one year period of follow up once you enter the study. For this I will require to have your telephone number so that I can reach you. If you are found to have the condition at any time during the study, I will refer you to the physician to treat you.

Voluntary participation

Participation in this study is out of your own free will. You will not be denied medical care in case you refuse to participate in the study. You may stop participating at any time.

I will be grateful if you will consider taking part in this study.

Confidentiality

All information will be treated with confidentiality. Your identity will not be exposed and all information collected on you will be used only for the purpose of the study and will be destroyed at end of the study.

I, the undersigned have been explained to, understand and voluntarily accept to participate in the study.

Signature/Thumb print: ---------- Date: ----------

(Patient/guardian)

Researcher: ---------- Date: ----------

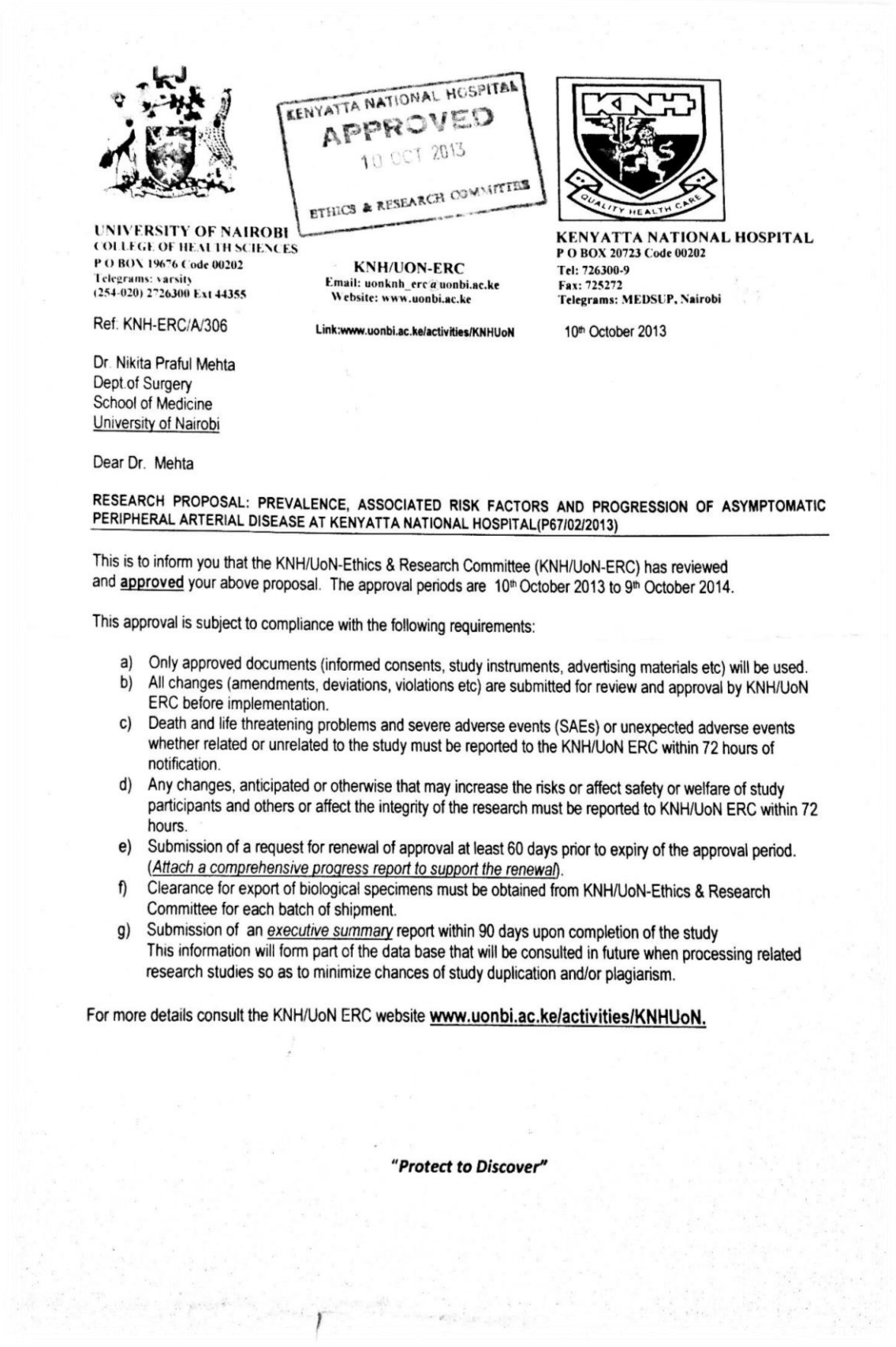
For any enquiries or further clarification, please contact the following people:

1. DR NIKITA MEHTA – PRINCIPAL RESEARCHER Tel. 0722393427

For any queries relating to complaints or authenticity of study;

2. Chairperson, KNH/UON ERC Tel. 02042439

APPENDIX 4: ETHICAL APPROVAL LETTER



KENYATTA NATIONAL HOSPITAL
APPROVED
10 OCT 2013
ETHICS & RESEARCH COMMITTEE

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Ref: KNH-ERC/A/306

10th October 2013

Dr. Nikita Praful Mehta
Dept of Surgery
School of Medicine
University of Nairobi

Dear Dr. Mehta

RESEARCH PROPOSAL: PREVALENCE, ASSOCIATED RISK FACTORS AND PROGRESSION OF ASYMPTOMATIC PERIPHERAL ARTERIAL DISEASE AT KENYATTA NATIONAL HOSPITAL(P67/02/2013)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 10th October 2013 to 9th October 2014.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

"Protect to Discover"

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. Prof. A.N.Guantai, Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Dean, School of Medicine, UoN
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