MMED DISSERTATION

FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI

A dissertation submitted in partial fulfillment of the degree of Master of Medicine in Internal Medicine, University of Nairobi

By

Dr Mary Nigandi Kubo

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STUDENT'S DECLARATION

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

Signed 

Date 27.06.2013

Dr Mary Nigandi Kubo

MBChB (University of Nairobi)

Principal Investigator.

SUPERVISORS' DECLARATION

This dissertation has been submitted for examination with our approval as university supervisors.

1. PROFESSOR J.K. KAYIMA
   Consultant Nephrologist and Associate Professor,
   Department of Clinical Medicine and Therapeutics, University of Nairobi.

   Signed.....
   Date.....25/6/2013.....

2. PROFESSOR E.N. OGOLA
   Consultant Cardiologist and Associate Professor,
   Department of Clinical Medicine and Therapeutics, University of Nairobi.

   Signed.....
   Date.....28/6/13

3. PROFESSOR S.O. MCLIGEYO
   Consultant Nephrologist and Associate Professor,
   Department of Clinical Medicine and Therapeutics, University of Nairobi.

   Signed.....
   Date.....27/6/13

4. DR. A. J. O. WERE
   Consultant Nephrologist and Senior Lecturer,
   Department of Clinical Medicine and Therapeutics, University of Nairobi.

   Signed.....
   Date.....25.6.2013.....

DEDICATION

I dedicate this dissertation to my parents, (Rtd.) Justice Benjamin Kubo and Constance Sophia Kubo, who have always selflessly supported and encouraged my siblings and I. They have patiently nurtured, corrected, cheered on and always encouraged us to strive to be the utmost best that we can be. Words cannot fully express my love and gratitude to you both.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme Inhibitors
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANP	Atrial Natriuretic Peptide
ARBs	Angiotensin Receptor Blockers
BMI	Body Mass Index
BP	Blood Pressure
BPH	Benign Prostatic Hypertrophy
CCBs	Calcium Channel Blockers
CKD	Chronic Kidney Disease
CNIs	Calcineurin Inhibitors
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HTN	Hypertension
JNC7	Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure
KDOQI	Kidney Disease Outcomes Quality Initiative
KNH	Kenyatta National Hospital
KNH RU	Kenyatta National Hospital Renal Unit
KTR	Kidney Transplant Recipient
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
mg	Milligrammes
mg/mmol	Milligrammes per millimole
mg/L	Milligrammes per litre
MI	Myocardial Infarction

ml	Millilitre
µmol/L	Micromole per litre
mmol	Millimole
mTOR	Mammalian Target of Rapamycin
nm	Nanometre
PAI	Plasminogen Activator Inhibitor
PI	Principal Investigator
RAS	Renin Angiotensin System
RTRs	Renal Transplant Recipients
SBP	Systolic Blood Pressure
TGF	Transforming Growth Factor
TRAS	Transplant Renal Artery Stenosis
WHO	World Health Organisation

ABSTRACT

Background

Renal transplantation remains the therapeutic modality of choice for patients with end stage renal disease. Prevalence of hypertension remains high post transplantation, with alarmingly low proportion of patients achieving target blood pressure levels. Pathophysiology of post renal transplant hypertension is multifactorial, with recipient, donor and immunotherapeutic factors implicated. Uncontrolled hypertension results in reduced graft and patient survival. Determining the factors associated with uncontrolled hypertension among renal transplant recipients is thus of utmost importance for improved blood pressure control, which has been shown to positively impact graft and patient survival.

Objective of the Study

The aim of the study was to determine the factors associated with hypertension among renal transplant recipients, their levels of adherence to antihypertensive medications, and to document the changes in antihypertensive medication use post transplantation.

Study design

Cross-sectional descriptive study.

Participants and Study Site

Renal transplant recipients on follow up at the Renal Unit Transplant Clinic at Kenyatta National Hospital (KNH) and nephrology clinics at Kenyatta National Hospital Doctor's Plaza, Nairobi.

Methods

Consecutive kidney transplant recipients were screened for eligibility and enrolled into the study during the months of November 2012 to February 2013. Clinical and sociodemographic data were recorded in a pre-designed questionnaire. Participants also filled in the self-administered 8-item Morisky Medication Adherence Scale. Subsequently samples for determination of serum creatinine and spot urine albumin:creatinine ratio were collected.

Data Analysis

Variables were calculated as proportions with 95% confidence intervals. Continuous data was summarized using means, mode and medians while categorical data was analyzed using proportions. Correlations were tested using the chi-square test for categorical variables, while student's t test was used for comparisons between continuous variables. Statistical significance was defined at a *P* value of less than 0.05.

Results

Between November 2012 and February 2013 a total of 85 renal transplant recipients were studied. There was a male predominance with a male to female ratio of 1.9:1. The mean age was 42.4(±12.2) years. The proportion of patients with uncontrolled hypertension in the post transplant period was 68.2% (95% CI 57.6% - 77.6%). Only a third of all the patients were fully adherent to antihypertensive medications. The mean Morisky adherence score was 6.8. There was a significant reduction in mean number of antihypertensives used from 3.3 (±1.6) drugs per patient in the pre-transplant period to 2.1 (±0.9) drugs per patient in the post transplant period (p <0.001). Mean systolic and diastolic pressures were also significantly lower in the post transplant period (SBP 144.5 mmHg versus 131.8 mmHg; DBP 103.6 mmHg versus 83.5 mmHg in the pre- and post-transplant periods respectively (p <0.001). The most commonly used antihypertensive agents were calcium channel blockers and beta blockers. Male sex and non-adherence were independently associated with uncontrolled hypertension.

Conclusion

Uncontrolled hypertension remains highly prevalent in the post-transplant period. There is a reduction in the mean number of antihypertensive medications used post transplantation. Nonadherence to antihypertensive medications and male sex were predictors of uncontrolled hypertension.

Recommendations

Intensification of blood pressure control among renal transplant recipients, as well as strategies to improve patient adherence to antihypertensive medication should be done. Further studies are necessary to look into patient-perceived reasons for nonadherence to antihypertensive therapy.

1. INTRODUCTION

Hypertension is defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as systolic blood pressure >140 mm Hg, diastolic blood pressure >90mmHg, or the need for antihypertensive therapy[1]. It is associated with increased cardiovascular risk, with higher blood pressure readings linked with greater chances of ischemic heart disease, stroke and kidney disease. Indeed, among individuals between 40-70 years of age, for every 20 mmHg systolic or 10 mmHg diastolic increase in BP, mortality doubles, mainly due to ischemic heart disease and stroke[2].

In chronic kidney disease (CKD), the prevalence of hypertension is high. Data from the USA shows that hypertension occurs in 23.3% of individuals without CKD, and upto 84.1% of stage 4-5 CKD patients[3]. Kenyan data on the same is derived from a study by Rajula *et al*, who found a prevalence of hypertension of 76% overall among CKD patients, with only 16.6% having controlled hypertension[4]. Nadeem *et al,* looking at the prevalence of cardiovascular risk factors among CKD patients, found that 72.3% were hypertensive, out of whom only 19% achieved optimal blood pressure control[5].

The situation among renal transplant recipients (RTRs), a chronic kidney disease state, is not improved. The prevalence of hypertension remains high at 80-90%[6], despite improvement in glomerular filtration rate and fluid status. The pathophysiology of post transplant hypertension has been linked to both recipient and donor factors, including immunosuppressant use, advancing donor age, transplant renal artery stenosis and deteriorating renal function secondary to both acute and chronic rejection. Control of hypertension in renal transplant recipients has been shown to be inadequate, with only 16.5% of local RTRs achieving blood pressure target levels of <130/80mmHg[7]. Okech *et al* in the same population also found low rates of controlled hypertension at 21.2% [8].

What are the consequences of hypertension in the renal transplant recipient? Like in the general, hypertensive population, the consequences are dire. Hypertension has been shown to correlate with increased cardiovascular mortality and morbidity. Presently, the leading cause of death among RTRs is atherosclerotic cardiovascular disease, overtaking mortality from infection and

malignancy combined[9]. In addition, hypertension adversely affects graft survival, with data from the Collaborative Transplant Study demonstrating an inverse relationship between the severity of post transplant hypertension and graft survival[10].

There is thus need for aggressive management of blood pressure and modification of potential factors contributing towards uncontrolled hypertension in the renal transplant recipient population, with dual aims of reducing cardiovascular mortality as well as enhancing graft survival.

2. LITERATURE REVIEW

2.1 DETERMINANTS AND PATHOGENESIS OF POST RENAL TRANSPLANT HYPERTENSION

Renal transplantation is the therapeutic modality of choice for patients with end stage renal disease, with improved quality of life and survival as compared to dialysis.

The blood pressure achieved after transplant is inversely related to postoperative glomerular filtration rate (GFR). Due to improved GFR post transplant, there is significant improvement in blood pressure control, with fewer antihypertensive medications required. However the prevalence of post renal transplant hypertension still remains high, with multiple mechanisms implicated. In contrast to the general population, these mechanisms include both donor and recipient factors, immunosuppression and transplant factors as summarized in table 1 below[11].

Table 1. Factors contributing to hypertension after transplant

1. Recipient Factors
    - Pre-existing hypertension
    - Native kidneys retained in situ
    - Body mass index
2. Donor factors
    - Donor age
    - Familial hypertension
3. Immunotherapy
    - Calcineurin inhibitors (Cyclosporine > Tacrolimus)
    - Corticosteroids
4. Transplant dysfunction
    - Acute rejection
    - Chronic allograft nephropathy
    - Recurrent or de novo glomerular disease
    - Antibody-mediated rejection
5. Transplant Factors
    - Cold ischemia time
    - Warm ischemia time
    - Delayed transplant function
6. Transplant renal artery stenosis
7. Transplant obstruction

a. Recipient factors

- ***Pre-existing Hypertension***

Beji *et al* found that pre-existing hypertension in the recipient was an independent risk factor for post transplant hypertension, with an odds ratio of 8.5 (95% CI: 4.5 to 16.1)[12].

- ***Native kidneys retained in-situ***

The presence of native kidneys may contribute to post transplant hypertension, with Curtis *et al* showing that there was a higher prevalence of hypertension among renal transplant recipients with native kidneys compared to those who had bilateral nephrectomy[13]. A possible explanation is inappropriate renin secretion by the native kidneys. This may lead to drug-resistant hypertension, which may require definitive management such as ablation of host kidneys by percutaneous embolisation[14] or laparoscopic nephrectomy[15].

b. Donor Factors

- ***Age of the donor***

The risk of post-transplant hypertension has been shown to increase by 28% for each 10-year increase in donor age[16]. This risk is further doubled if the donor has atheroma within the renal arteries.

- ***Family history of hypertension***

Patients who receive a kidney from a donor with family history of hypertension were shown to have a higher probability of developing hypertension after transplantation compared to those who receive it from a member of a normotensive family[17]. Conversely, Curtis *et al* showed that essential hypertension can be corrected when the transplanted kidney is from a normotensive donor[18].

c. Immunotherapy

- **Role of Calcineurin Inhibitors (CNI)**

Before the introduction of the calcineurin inhibitor cyclosporine, hypertension occurred in about half of kidney transplant patients[19]. Its prevalence was then noted to rise after cyclosporine was introduced as part of the immunosuppressant regimen. Incidence of hypertension also increased from less than 10% overall to 30-60% among bone marrow patients, and upto 70-90% among cardiac transplant recipients after introduction of cyclosporine[20,21].

Both cyclosporine and tacrolimus have either caused or worsened hypertension in transplant recipients[22]. Cyclosporine in particular has been shown to activate the renin-angiotensin system, leading to increased sodium and water retention, as well as increased systemic vascular resistance[23,24]:

Hypertension is however less common and severe in patients given tacrolimus compared with those on cyclosporine[25]. In case of severe hypertension in cyclosporine-treated transplant patients, switching to tacrolimus resulted in a significant reduction in blood pressure[26]. Hypertension may also be controlled by minimizing the doses of cyclosporine[27].

- **Role of Glucocorticoids**

Glucocortoids have been shown to cause or worsen hypertension through various mechanisms including:

- sodium retention
- decreased production of vasodilators
- increased response to vasoconstrictors
- direct role of the glucocorticoid receptor on vascular smooth muscle[28].

The prevalence of glucocorticoid-associated hypertension is estimated to be about 15%[29], and depends on the dosage used. A maintenance dose of prednisone less than 10 mg/day has been shown to have minimal role in contributing to post-transplant hypertension[30].

d. Transplant dysfunction

Transplant dysfunction may be caused by acute or chronic rejection, cyclosporine toxicity, or recurrent disease. This ultimately is associated with arterial hypertension as a result of reduced GFR[31].

Acute rejection is defined clinically as more than 30% increase in creatinine from baseline, that is not secondary to obstruction nor due to cyclosporine toxicity. Patients with at least one acute rejection episode were found to have higher BP than patients without a history of acute rejection[6].

Chronic allograft nephropathy (defined as kidney transplant dysfunction occurring at least 3 months post transplant in the absence of active acute rejection, calcineurin-inhibitor drug toxicity, or other diseases) is associated with a progressive deterioration in transplant function, proteinuria, and eventually new or worsening hypertension[32].

Poor kidney function may cause salt and water retention, leading to an increase in extracellular volume and cardiac output. Subsequently there is inappropriate activation of the RAS, resulting in increased peripheral vascular resistance and further salt and water retention. This eventually leads to poorly controlled hypertension.

Indeed, Karthikeyan *et al* showed that there were increased requirements of antihypertensive medications from **0.7** in kidney transplant recipients with chronic kidney disease stage 1 to **2.3** in those with stage 5 function[33].

e. Transplant Renal Artery Stenosis (TRAS)

Transplant renal artery stenosis has been shown to account for about 1–7% of cases of post-transplant hypertension[34]. Causes include atheroma in the donor artery and trauma to renal arteries during the transplant procedure.

The diagnosis of TRAS may be suspected in patients with severe or refractory hypertension, presence of a bruit over the transplanted kidney on auscultation, deranged renal function on initiation of RAS inhibitors, or flash pulmonary oedema.

2.2 CONSEQUENCES OF HYPERTENSION IN THE RENAL TRANSPLANT RECIPIENT

a. Cardiovascular complications

Studies in renal transplant recipients have shown that just like in the general population, arterial hypertension is a strong risk factor for ischaemic heart disease[35], congestive heart failure[36], coronary heart disease[37], as well as stroke[38].

Patients with hypertension often have elevated levels of Angiotensin II, which can contribute to atherogenesis by stimulating the growth of smooth muscle cells, increasing inflammation and oxidation of low density lipoproteins. Hypertension also has pro-inflammatory effects on vascular endothelium, with increased formation of free radicals in plasma[39].

Another major consequence of hypertension is left ventricular hypertrophy, which is a risk factor for congestive heart failure and death[11].

b. Graft dysfunction and survival

Hypertension has been shown to be harmful for the long-term kidney graft outcome. Retrospective studies show that increased levels of systolic blood pressure and diastolic blood pressure after transplantation are significantly associated with an increased risk of graft failure.

Hypertension was found to be an independent risk factor for graft failure, even where serum creatinine concentrations were normal and when patients had never been treated for rejection episodes[40]. Kasiske *et al*, using the United States Renal Data System, found that each increment in systolic blood pressure of 10 mmHg above 140 mmHg was associated with a 12% relative risk for graft failure and an 18% relative risk for patient death, even after adjusting for kidney allograft function and rejection episodes[6].

A study by Mange *et al*[40] looked at the effect of systolic, diastolic and mean arterial pressure on allograft survival. For each 10-mm Hg increment in SBP, DBP, and MAP, there were 15%, 27%, and 30% reductions, respectively, allograft survival rates.

2.3 MANAGEMENT OF POST TRANSPLANT HYPERTENSION

Management of hypertension post renal transplantation has dual aims: to prolong allograft survival and to minimize cardiovascular risk.

Lifestyle modifications like smoking cessation, low salt diet, weight control, regular exercise, and avoidance of heavy alcohol intake should be recommended to transplant patients. However there have been no formal studies to determine their effects among renal transplant recipients.

Pharmacologic management involves not only the use of antihypertensive agents but also optimal adjustment of immunosuppressive medication.

As an example, patients using cyclosporine may have improved BP control after dose reduction or conversion to either tacrolimus or sirolimus[41,42]. Significant improvement in BP control has also been observed when azathioprine is added to the immunosuppressant regimen, so as to reduce the doses of cyclosporine used[43]. Use of low steroid doses also led to reduced blood pressure levels in a study by Buell *et al*[44].

However, despite manipulation of immunosuppressants used, most transplant recipients continue to require one or more antihypertensive agents to achieve adequate blood pressure control. Malyszko *et al*, in a study conducted on 150 renal allograft patients in Poland, found that 60% of them required 3 or more antihypertensive agents, with only 40% demonstrating target blood pressure levels of less than 130/80 mmHg[45]. This is in contrast to the general, hypertensive population, whereby trials such as the ALLHAT Trial showed that an average of two drugs was required to achieve BP control (<140/90mmHg) in two thirds of patients[46].

2.3.1 CLASSES OF ANTIHYPERTENSIVE AGENTS USED

Several antihypertensive agents have been used successfully for management of post transplant hypertension as outlined in Table 2 below[11].

Table 2. Classes of Antihypertensive Medications used after Transplant

CLASS	INTERACTION WITH IMMUNOTHERAPY	BENEFICIAL EFFECTS IN TRANSPLANT RECIPIENTS
Dihydropyridine CCBs	Less pharmacokinetic interactions with CNI compared to nondihyropyridine CCBs	Mitigate CNI-induced HTN & nephrotoxicity
Nondihydropyridine CCBs	Increase plasma levels of cyclosporine, tacrolimus and sirolimus	Decrease requirements for CNI/ mTOR inhibitors Mitigate CNI-induced HTN & nephrotoxicity
ACEi	Caution with concurrent use of CNI due to risk of hyperkalemia	May reduce posttransplant erythrocytosis Mitigate proteinuria
ARB	Caution with concurrent use of CNI due to risk of hyperkalemia	Losartan may decrease uric acid levels
Vasodilators -Hydrallazine -Minoxidil	 None None	 Useful in hospital posttransplant Useful in reversing tacrolimus-induced alopecia
Diuretics	None	Useful in patients with oedema and hyperkalemia
β –blockers	None	Decrease risk of perioperative MI
α – blockers	None	May mitigate BPH

i. Calcium Channel Blockers (CCBs)

CCBs inhibit voltage-gated calcium channels in vascular smooth muscle and cardiac myocytes. This leads to reduced contractility and vasodilatation. They are divided into 2 major classes: dihydropyridine (eg, amlodipine and nifedipine) and nondihydropyridine (eg, diltiazem and verapamil).

Calcineurin inhibitors induce nephrotoxicity and hypertension mainly through vasoconstriction. Thus, CCBs are preferred for the management of hypertension after transplant to mitigate this effect[47]. A large, randomized, comparative study by Midvedt *et al* actually found sustained improvement in kidney transplant function in patients treated with nifedipine compared with lisinopril[48].

The nondihydropyridine CCBs verapamil and diltiazem are potent inhibitors of cytochrome P450 C3A4. Concurrent use with cyclosporine, tacrolimus or sirolimus leads to markedly elevated serum levels of these drugs[49]. This may be a potential advantage in that patients may thus require less doses of the expensive immunosuppressive agents. However these drugs must be used with caution and frequent monitoring.

On the other hand, the dihydropyridine CCBs are less potent CYP450 inhibitors and are thus easier to use in transplant recipients.

ii. ACE inhibitors/ARBs

ACE inhibitors/ARBs are effective in treatment of hypertension as well as slowing progression of chronic kidney disease in the general hypertensive population[50,51]. In kidney transplant recipients, ACEi/ARBs can cause a reduction in GFR[52], masking early signs of acute transplant rejection. They are thus not usually used in the early post- transplant period.

They can also exacerbate hyperkalemia, a common electrolyte abnormality after kidney transplantation due to delayed transplant function. In addition, ACE inhibitors can cause anemia, with a reduction in hematocrit of upto 5-10%[53]. This may be via inhibition of erythropoeisis, an effect that may be worsened by concurrent cyclosporine use[54].

A systematic review of 21 randomized trials showed that ACEi/ ARB use was associated with a significant reduction in GFR (-5.8mL/ min), lower hematocrit (-3.5%), and a decrease in proteinuria (protein excretion, -0.47 g/d)[55]. ACEi and ARBs may thus be indicated in kidney transplant recipients with proteinuria and higher levels of kidney function.

iii. Beta-Blockers

Beta blockers, known to be cardioprotective, are also effective antihypertensives in renal transplant patients. In a retrospective study by Aftab *et al*, beta blocker use was associated with higher 10-year patient survival rates as compared to non-beta blocker therapy (HR 0.61; 95% CI, 0.37- 0.98; p=0.04)[56].

iv. Diuretics

Diuretics are useful in renal transplant patients, especially those who may have fluid overload due to allograft dysfunction. Loop diuretics reduce hyperkalemia, while thiazide diuretics can decrease urinary calcium loss thus mitigating bone disease[57].

v. Other Antihypertensive Agents

Other agents that may be added on as treatment for resistant hypertension include alpha-adrenergic receptor antagonists, centrally acting alpha-2 receptor agonists, and direct vasodilators.

2.4 CHANGES IN ANTIHYPERTENSIVE MEDICATION REQUIREMENTS POST RENAL TRANSPLANTATION

There may be increased, reduced or stable antihypertensive medication requirements post renal transplantation. A study carried out in India showed that upto 52% of post transplant patients required 3 or more antihypertensive drugs, with most (62%) having increased antihypertensive requirements. Only 13% had reduced antihypertensive requirements post renal transplantation, while 25% had stable requirements[58].

In Norway, a study among nephrectomized renal transplant recipients showed that antihypertensive medication requirements reduced from a mean of 2.3 drugs/day in the pre-transplant period to 1.3 drugs/day post renal transplantation[59].

2.5 IMPACT OF HYPERTENSION TREATMENT ON PATIENT AND ALLOGRAFT SURVIVAL

In an analysis of the Collaborative Transplant Study, Opelz *et al* showed that treatment of post renal transplant hypertension to target blood pressure levels was associated with improved long-term graft and patient survival[60]. This study evaluated transplant outcomes in relation to recipient systolic blood pressure for 24,404 renal transplant recipients.

They found that three-year allograft survival rates were better for hypertensive patients who achieved control to less than 140 mmHg compared with patients with sustained hypertension (RR, 0.79; 95% CI 0.73-0.86; $p < 0.001$). Additional examination at 5 years showed that SBP lowering after the third year was associated with improved 10-year allograft survival (RR, 0.83; 95% CI 0.72-0.96; $p=0.01$).

They thus concluded that decreasing SBP, even after several years of post transplant hypertension, is associated with improved allograft and patient survival in kidney transplant recipients**.**

2.6 ADHERENCE TO ANTIHYPERTENSIVE MEDICATION

"Drugs don't work in patients who don't take them."

- C. Everett Koop, MD.

Adherence, as defined by the World Health Organisation (WHO), is "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from the health care provider" [61]. It refers to whether patients take their medications as prescribed, as well as whether they *continue* to take the prescribed medications (persistence).

According to the World Health Organization (WHO), in developed countries, non-adherence to medication among patients with chronic diseases is about 50%, a figure though to be much higher in developing countries[61]. Indeed, non-adherence to treatment is an important and often unrecognized risk factor that contributes to reduced control of blood pressure. High level of adherence to antihypertensive medications is associated with higher odds of blood pressure control compared with those with medium or low levels of adherence[62]. Identifying non-adherent patients is thus of utmost importance in order to effectively increase hypertension control rates. Among hypertensive patients attending medical outpatient clinics at the Kenyatta National Hospital, only 31.8% of patients were adherent to pharmacologic therapy as measured by use of the self-reported Hill-Bone questionnaire[63].

What is the situation regarding adherence among renal transplant recipients? A study in the USA showed that RTRs have preferential adherence to immunosuppressive over nonimmunosuppressive medications (antihypertensives, lipid lowering agents, and antidiabetic agents. Data from this study revealed that 18.4% of RTRs were nonadherent to immunosuppressants, while 44.9% were nonadherent to nonimmunosuppressants ($p=.028$) [64]. It remains to be determined whether nonadherence to medications that treat cardiovascular risk factors contributes to the persistently high cardiovascular mortality in RTRs.

Adherence to medication is assessed through either direct or indirect methods[65]. Direct methods include directly observed therapy, as well as measurement of serum levels of medicine or metabolites. These methods are however not practical for routine use.

Indirect methods include patient questionnaires, pill counts, electronic medication monitors, rate of refill of prescriptions, and patient diaries. The most commonly used indirect methods are patient self-report, pharmacy refills, and pill counts.

Self-report measures are simple to use and economical, but are subject to recall bias and tend to overestimate adherence as most patients tend to give socially acceptable responses. Pill counts are easy to perform and correlate well with electronic medication monitors. They can however be manipulated by pill dumping.

The Morisky Medication Adherence Scale (MMAS) is a validated, four-item self-reported adherence measure shown to be predictive of adherence to cardiovascular medications and blood pressure control[66]. Recently, a new eight-item scale (MMAS-8), with a greater reliability (a=0.83 vs. =0.61), was developed from the MMAS-4. Its objective is to determine adherence to antihypertensive treatment, The MMAS-8 is an 8-item questionnaire with seven dichotomous answers (yes/no) and one question answered on a 5-point Likert scale. A score of 8 equals high adherence, 6 to <8 is medium adherence, and <6 equals low adherence. It was tested in a low-income, predominantly black American population and found to be significantly associated with blood pressure control, and to have higher sensitivity than the MMAS-4 (sensitivity 93%, specificity 53%)[67].

Cross-cultural validation of this tool has been successful, with French, Portuguese and Malaysian versions of the MMAS-8 having been validated for use. In Portugal, the diagnosis of non-adherent behavior through the application of MMAS-8 in patients using antihypertensive medications was predictive of elevated systolic and diastolic BP[68]. The MMAS-8 is also significantly associated with adherence rates as measured by antihypertensive pharmacy refill[69].

The MMAS-8 is simpler to administer compared to the Hill-Bone questionnaire, which has been used previously to determine adherence to therapy among hypertensive patients locally[63]. The Hill Bone compliance to high blood pressure therapy scale consists of 14 items, measuring patient behaviours in 3 domains: reduced salt intake, appointment keeping and medication taking. It has been validated for use among black patients in South Africa[70], but its medication taking subscale has a slightly lower reliability compared to the MMAS-8 (a= 0.68 vs = 0.83)[71] .

2.7 PREDICTORS OF BLOOD PRESSURE CONTROL AMONG RENAL TRANSPLANT RECIPIENTS

Among renal transplant recipients, where target blood pressure levels are more stringent (<130/80mmHg), rates of uncontrolled hypertension remain alarmingly high at between 50-84%[7,45]. Several studies have been done in this population, looking at the predictors of both well controlled as well as poorly controlled hypertension.

Bulatova *et al*, looking at predictors of achieving target blood pressure among Jordanian renal transplant recipients, found that female gender, higher creatinine clearance and lower number of antihypertensive medications were associated with good blood pressure control[72]. In the United Kingdom, predictors of achieving target blood pressure levels were female gender and lower urine albumin:creatinine ratio[73].

On the converse, other studies have looked at factors associated with uncontrolled hypertension. Among 53 renal transplant recipients in Spain, poorly controlled hypertensives as detected by 24 hour ambulatory blood pressure readings were more likely to be older, received grafts from older donors, had worse renal function as measured by serum creatinine or the MDRD 4 formula, and displayed higher levels of proteinuria[74].

In Brazil, a study done among 272 renal transplant recipients showed that cyclosporine and steroid use were independent predictors of higher blood pressure as well as the need for a greater number of antihypertensive drugs [75].

3. STUDY JUSTIFICATION

Hypertension is ubiquitous among the renal transplant population, a population that is unique in that there are risk factors associated with **both** the recipient and the donor. Poorly controlled hypertension in renal transplant recipients is associated with increased cardiovascular morbidity and mortality, as well as decreased graft survival.

Unfortunately, control of hypertension among renal transplant recipients remains suboptimal. A better understanding of the factors associated with uncontrolled hypertension is of utmost importance as some of these factors may be potentially modifiable, leading ultimately to improved graft and patient survival.

No study locally has looked at the patterns of adherence to antihypertensive medications in this population. In addition, this will also be an audit of the impact of renal transplantation on antihypertensive medication requirements.

3.1 THE PROBLEM STATEMENT

The burden of hypertension remains high in our renal transplant recipient population as evidenced by a study carried out by Wagude et al[7], who found a prevalence of 95.6% among local RTRs, with only 16.5% achieving target blood pressure levels below 130/80mmHg. The adverse impact of uncontrolled hypertension on graft survival and patient mortality is well known. This study thus seeks to elucidate the predictors of uncontrolled hypertension in our RTR population.

4. RESEARCH QUESTION

What are the predictors of uncontrolled hypertension among renal transplant recipients at the Kenyatta National Hospital and selected nephrology specialist clinics in Nairobi?

5. STUDY OBJECTIVES

5.1 BROAD OBJECTIVE

To determine selected sociodemographic, clinical and laboratory factors associated with uncontrolled hypertension and the level of adherence to antihypertensive medication among renal transplant recipients attending nephrology clinics in Nairobi.

5.2 SPECIFIC OBJECTIVES

5.2.1 PRIMARY OBJECTIVES

1. To describe the sociodemographic characteristics (age, gender, education level, level of income, health insurance status) of renal transplant recipients with hypertension, and compare them among those with controlled and uncontrolled hypertension.

2. To determine the proportion of hypertensive renal transplant recipients adherent to antihypertensive medication as assessed by the 8-item Morisky Medication Adherence Scale.

3. To determine the association between blood pressure control and level of adherence to antihypertensive therapy.

4. To document the number and types of antihypertensive medications used pre- and post-renal transplantation, and determine the changes in antihypertensive medications used post transplantation.

5.2.2 SECONDARY OBJECTIVE

1. To determine the association between blood pressure control and specific correlates:
    - cyclosporine use and dose
    - steroid use and dose
    - recipient BMI
    - donor age
    - graft function (eGFR, proteinuria)
    - documented history of acute rejection

6. METHODOLOGY

6.1 STUDY DESIGN

This was a cross-sectional descriptive study.

6.2 STUDY SITE

The study was carried out at the Kenyatta National Hospital (KNH) Renal Transplant Clinic, as well as nephrology clinics at the Kenyatta National Hospital Doctor's Plaza. KNH is a national public referral hospital that also serves as the teaching facility for the University of Nairobi Medical School. Data was collected over a period of four months from November 2012 to February 2013. There were 100 renal transplant recipients documented to be on follow up at the clinics during this period.

6.3 STUDY POPULATION

The study population was hypertensive renal transplant recipients attending the selected clinics.

6.3.1 INCLUSION CRITERIA

1. Hypertensive renal transplant recipients.
2. Received renal transplant at least 2 months prior to the study.
3. Age greater than 18 years.
4. Willing to participate in the study and give informed written consent.

6.3.2 EXCLUSION CRITERIA

1. Renal transplant recipients back on dialysis due to non-functional allograft.

6.4 SAMPLE SIZE

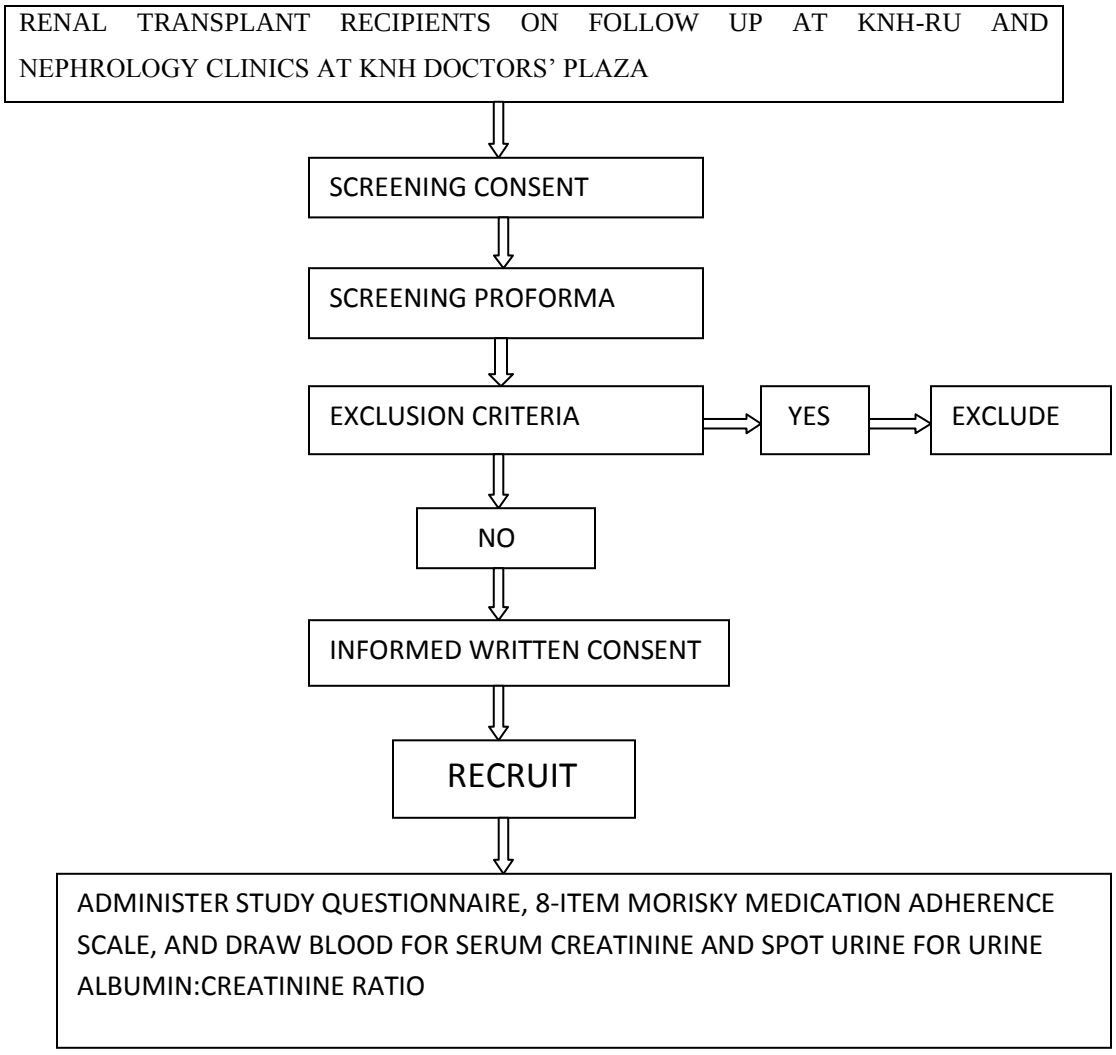
All eligible patients attending the nephrology clinics and fulfilling the inclusion criteria were included.

6.5 SAMPLING METHOD

All eligible patients were consecutively sampled.

6.6 PATIENTS' FLOW CHART

Figure 1: Screening and recruitment flow chart



6.7 DATA COLLECTION

After obtaining screening consent (**Appendix II**), a screening proforma was administered by the PI on consecutive KTRs attending the selected transplant clinics (**Appendix III**). Those meeting the inclusion criteria were then consecutively recruited into the study after signing informed study consent (**Appendix IV**). They were given a unique study number and no identifiers were included in the study tools.

The PI then filled in patients' details in the study data collection tool (**Appendix V**). History taken included: socio-demographic data, duration post transplantation, current antihypertensive and immunosuppressant medications, donor age and history of acute rejection. The KTRs' files were perused to corroborate some aspects of the history specifically: date of transplantation, antihypertensive medications and level of blood pressure control pre-transplantation, and documented history of acute rejection. The KTRs then filled in the self-administered 8-item MMAS questionnaire.

The recruitment and study procedures were done in a room adjacent to the main clinic area, to ensure visual and audio privacy during data collection.

6.8 CLINICAL METHODS

Blood pressure readings were taken with the patient seated quietly for at least 5 minutes in a chair, with feet on the floor, and arm supported at heart level, using a manual sphygmomanometer. The patient should not have smoked, exercised, or taken caffeine within the previous 30 minutes. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) was used to ensure accuracy. Two measurements at least 5 minutes apart were taken and the average of the two readings recorded. SBP was recorded as the point at which the first of two or more Korotkoff sounds was heard (onset of phase 1), while the disappearance of Korotkoff sound (onset of phase 5) was used to define DBP[1].

Height was measured as the standard height to the nearest 0.5cm barefooted, back and scalp against the wall using a standard tape measure. This was then converted to metres. Weight was measured as the weight to the nearest 100gms using a standard bathroom scale. The Body Mass Index (BMI) was then calculated using the WHO criteria as weight (in kilograms) divided by height (in metres) squared.

Assessment of adherence to antihypertensive medication was done using the self-administered 8-item Morisky Medication Adherence Scale (**Appendix V**).

6.9 LABORATORY METHODS

For laboratory measurements, 2 mls of blood were drawn under aseptic technique from the antecubital vein and placed in a sterile plain vacutainer for measurement of serum creatinine. The collected blood specimens were transported from the point of collection to the laboratory for analysis in a cool box. Analysis was carried out at the Kenyatta National Hospital Renal Laboratory using the fully automated Mindray® Clinical Chemistry Analyzer. The specimens were centrifuged and serum separated from blood cells. Analytical work was then carried out immediately. Serum creatinine concentration was determined by measuring absorbance of the *Janovski* complex formed when creatinine reacts with picrate ions. The principle of the method used has been detailed further in **Appendix VI**.

For analysis of spot urine albumin-creatinine ratio, 5 mls of spot urine samples were taken, and measurement done at the University of Nairobi's Department of Clinical Chemistry laboratory using the Clinitek® Micoralbumin Analyzer. The collected urine specimens were transported to the laboratory in a cool box and analysis carried out immediately. Clinitek® microalbumin reagent strips were dipped into the urine sample and the albumin-creatinine ratio determined. Analysis of urine albumin was based on dye binding using a high affinity sulfonephthalein dye, while creatinine determination was based on the peroxidase-like activity of a copper-creatinine complex. Further details on the principle of the test are found in **Appendix VI**.

Blood and urine samples were stored in a refrigerator at -20ºC in case a re-run was required. At the end of the study all samples were subsequently destroyed. All laboratory tests were carried out by qualified medical laboratory technologists.

6.9.1 QUALITY CONTROL MEASURES

The recommended procedure for specimen collection was adhered to at all times, including proper phlebotomy site cleaning and the use of appropriate vacutainers. Proper labelling of the specimens and storage were also ensured to minimise pre-analytical sources of errors. The Mindray® Clinical Chemistry Analyzer and Clinitek Microalbumin Analyzer were calibrated according to manufacturer's recommendations. The KNH Renal Unit and University of Nairobi Department of Clinical Chemistry laboratories run daily internal quality control on all tests before sample analysis to validate the results obtained. External quality assessment was provided by Huqas Company, a local proficiency testing provider. Finally, every tenth sample was sent to another reputable laboratory (Lancet Kenya Laboratory) for counterchecking. Lancet Kenya Laboratory also carries out daily internal quality control on all tests to ensure valid results. 95% confidence intervals were included.

The recommended procedure for clinical measurements including blood pressure, weight and height was also adhered to at all times, with proper calibration of all machines used. The 8 item Morisky Medication Adherence Scale that was used to assess adherence to antihypertensive medication is a reproducible questionnaire validated for use in different cultural settings.

7. DEFINITION OF STUDY VARIABLES

A. Dependent Variable

Hypertension- Was defined as either the use of antihypertensive therapy *or* systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg in patients not on antihypertensive therapy. Hypertension was then classified as controlled or uncontrolled based on target blood pressure <130/80 mm Hg as per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[76].

In the pre-transplant period level of blood pressure control was derived from an average of the documented blood pressure readings at the last two clinic visits prior to transplantation.

B. Independent Variables

Adherence to Antihypertensive Medication- Was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8) and classified as:

- High adherence: Score of 8
- Medium adherence: Score of 6 to <8
- Low adherence: Score <6

Medium and low levels of adherence were then considered nonadherent[68].

Estimated Golmerular Filtration Rate (eGFR)- Was calculated using the Modification of Diet in Renal Disease MDRD) Formula as shown below:

$$\text{eGFR} = 32788 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212\ if\ Black] \times [0.742\ if\ Female]$$

(Serum creatinine in µmol/L)

Proteinuria- Proteinuria was classified based on the spot urine albumin-creatinine ratio. The urine albumin-creatinine ratio was obtained by dividing the urinary albumin concentration by the urine creatinine concentration, and defined as:

- **Microalbuminuria** – Spot urine albumin-creatinine ratio 30 – 300mg/g
- **Albuminuria** – Spot urine albumin-creatinine ratio >300mg/g

Body Mass Index- Calculated as mass in kilograms/ height in m^2.

Acute Rejection Episode- Was clinically defined as documented evidence of more than 30% increase in baseline creatinine with no obstruction and not associated with cyclosporine toxicity, and received intravenous methylprednisolone.

Antihypertensive medication use- Was defined as the number of different *classes* of antihypertensive medications used for management of blood pressure.
In the pre-transplant period this was defined as the total number of antihypertensive medications used for management of blood pressure as documented at the last clinic visit prior to transplantation.

8. DATA MANAGEMENT

8.1 Data Acquisition

The data acquisition instrument was the study questionnaire, which included the 8-item Morisky Medication Adherence Scale (**Appendix V**). At the end of data collection, questionnaires were coded, entered and managed in Microsoft Access database.

8.2 Data Privacy

Standards to protect personal were ensured. Data collection instruments had no subject identifiers, with only a unique serial number entered in the study questionnaire and specimen labels. At the completion of the study upon communication of relevant results, collected data was destroyed, or wiped out in the case of electronic records.

8.3 Data Storage

The filled data forms were verified for completeness by the principal investigator. The data forms were then kept in a secure lockable cabinet only accessible by the PI and the statistician. The data was entered electronically using the Statistical Package for Social Sciences (SPSS) version 17.0, (SPSS Inc.,Chicago, IL,USA). Upon completion of entry, the hard copy forms were used to clean and verify correctness of the entered data and then stored safely in a lockable cabinet. The electronic file was backed up in three compact discs and stored offsite.

8.4 Statistical Analysis

Continuous variables such as age, BMI, eGFR were summarized into means and standard deviations (SD) or medians and inter-quartile ranges (IQR) while categorical variables like gender, marital status, type of immunosuppressant were presented as proportions.

Level of adherence to antihypertensive medications was categorised as high, medium and low, and presented as proportions of all the patients studied. Quality of blood pressure control was summarized as controlled and uncontrolled, and associated with level of adherence to antihypertensive medication using chi-square test.

Antihypertensive medication use was analyzed and presented as mean number of drugs used per patient. Changes in antihypertensive medication use post transplantation was determined by comparing the mean number of drugs before and after transplantation using paired t test.

Association between uncontrolled hypertension and cyclosporine use, graft function and history of acute rejection was determined using the chi-square test of association, or Fischer's exact test for small numbers, while student's t test was used to compare the means of continuous variables such as donor age and recipient BMI.

Estimates of the risks of uncontrolled hypertension were presented as Odds ratios. The independent factors associated with uncontrolled hypertension were determined using logistic regression analysis. All the statistical tests were performed at 5% level of significance (95% confidence interval). Results were finally presented in form of tables, graphs and charts.

9. ETHICAL CONSIDERATIONS

The study was undertaken after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi and the KNH/ UON Ethics and Research Committee. Patients eligible to participate in the study were included only after providing informed written consent following the process as outlined below:

i. The patients were informed about the purpose of the research. Study procedures and all tests to be done were explained clearly.
ii. The patients were assured that participation was voluntary, confidentiality would be maintained, and no medical attention would be denied should they decline to participate.
iii. The patients were informed of the medical benefits as well as explanation of any potential physical and psychological harm to their satisfaction prior to being included in the study.
iv. The patients were assured of full and free access to their results and that therapeutic interventions would be recommended should the need arise in the course of the study. All costs would be borne by the principal investigator.
v. Only specimens needed for the study (ie. 2mls of venous blood and 5mls of spot urine) were obtained from the patient.

10. STUDY PLAN

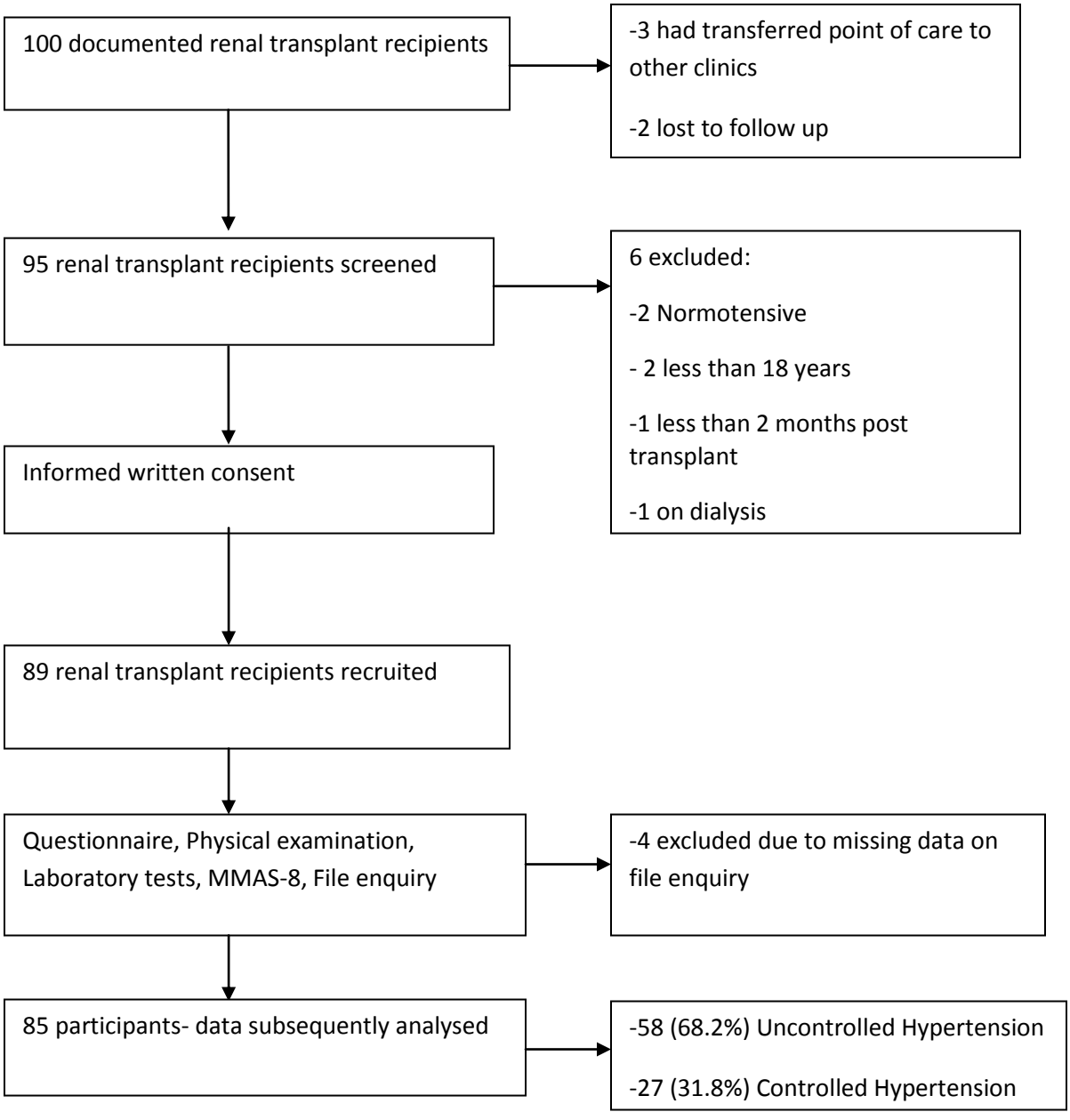
Table 3. Study plan

Proposal write up	January – July 2012
Proposal presentation	August 2012
Ethics approval	September- October 2012
Data collection	November- February 2012
Data analysis	March 2013
Results presentation	April 2013

11. RESULTS

Out of 100 documented renal transplant recipients attending the nephrology clinics, 85 were found to be eligible and recruited into the study. Data for all 85 study participants was subsequently analysed. The study flow chart is as shown below.

Figure 2. Study Flow Chart



11.1 SOCIODEMOGRAPHIC CHARACTERISTICS OF RENAL TRANSPLANT RECIPIENTS WITH HYPERTENSION

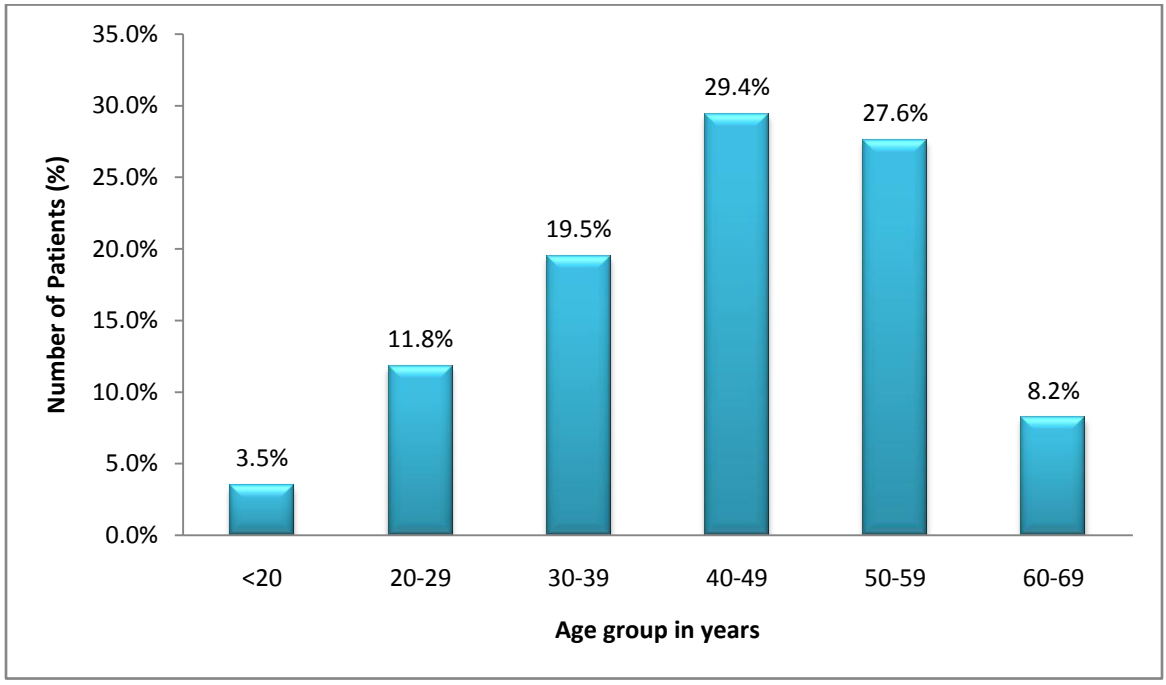
Table 4: Sociodemographic Characteristics of renal transplant recipients with Hypertension

Variables	Frequency (%)
Age in years (Recipient)	
Mean (SD)	**42.4** (12.2)
Min – Max	18 – 68
Sex (Recipient)	
Male	56 (**65.9)**
Female	29 (34.1)
Marital status	
Single	18 (21.1)
Married	65 (**76.5**)
Divorced/Separated	1 (1.2)
Widowed	1 (1.2)
Education	
Primary	2 (2.4)
Secondary	36 (42.3)
College/university	47 (**55.3**)
Occupation	
Unemployed	14 (16.5)
Employed	37 (**43.5**)
Self-employed	24 (28.2)
Retired	10 (11.8)
Age in years (Donor)	
Mean (SD)	**33.2** (8.5)
Min – max	21 – 54
Sex donor	
Male	46 (**54.1**)
Female	39 (45.9)
Health Insurance	
Yes	85 (**100**)
Income (Kshs/month)	
<5000	5 (5.9)
5000-19999	29 (**34.1**)
20000-49999	25 (29.4)
50000-99999	19 (22.4)
100000-149999	4 (4.7)
>150,000	3 (3.5)

The average age of the renal transplant recipients in our study was 42.4 (±12.2) years, with the donors being younger at a mean age of 33.2 (±8.5) years. Most recipients were male (65.9%), with a male to female ratio of 1.9:1. The male predominance was also noted among the donors, 54.1% of whom were male.

Majority of the renal transplant recipients were married (76.5%) and more than half (55.3%) had attained tertiary level of education. About 71% were in gainful employment, with 40% earning less than Kshs 20,000 per month and only 8.2% earning more than Kshs 100,000 per month. Universal health insurance coverage by the National Health Insurance Fund was noted.

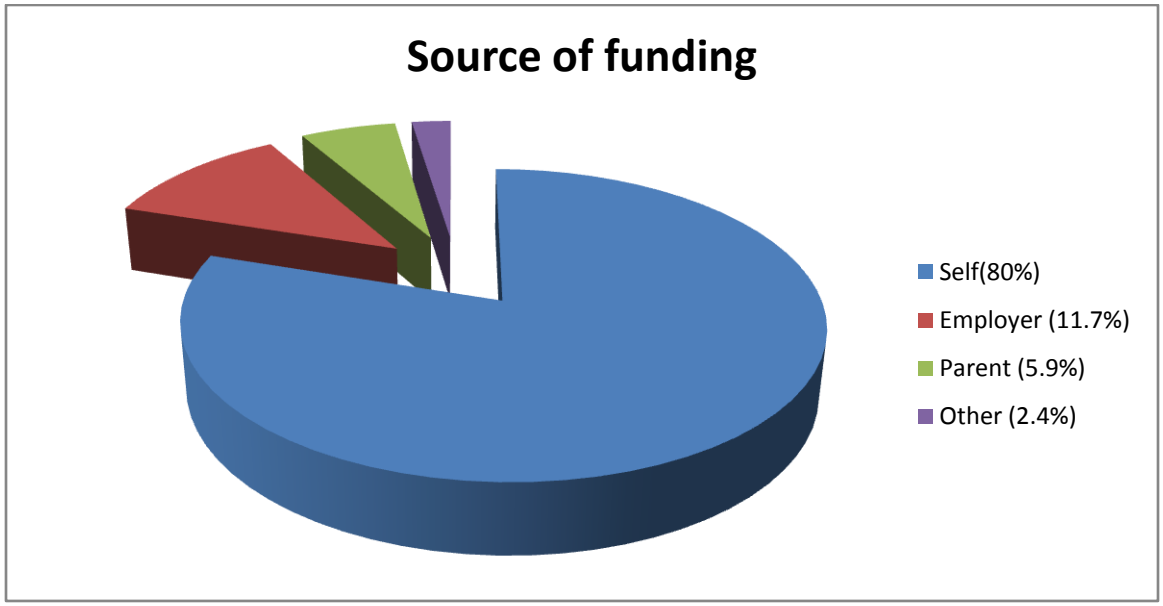
Figure 3. Age distribution of Renal Transplant Recipients



Majority of the study participants (57%) were between 40 and 59 years of age. The youngest participant was 18 years, with the oldest at 68 years of age.

SOURCE OF FUNDING FOR ANTIHYPERTENSIVE MEDICATIONS

Figure 4. Source of funding for antihypertensive medications



80% of the study participants had to rely on their own out-of-pocket expenditure to fund their antihypertensive medications.

Majority of the patients (49.4%) found their medications relatively affordable, and 25.9% found them easy to afford. However, about a quarter of the patients (24.7%) found them difficult to afford.

SOCIODEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH UNCONTROLLED VERSUS CONTROLLED HYPERTENSION

Table 5. Sociodemographic characteristics of Uncontrolled versus Controlled hypertensives

Variable	Hypertension		OR (95% CI)	P value
	Uncontrolled (n=58)	Controlled (n=27)		
Age of recipient (SD)	43.2 (11.5)	40.6 (13.6)	-	0.347
Sex of recipient				
Male	44 (75.9%)	12 (44.4%)	**3.9** (1.5-10.3)	**0.004**
Female	14 (24.1%)	15 (55.6%)	1.0	
Level of education				
Primary	2 (3.4%)	0 (0.0%)	-	1.000
Secondary	22 (37.9%)	14 (51.9%)	0.6 (0.2-1.5)	0.279
College/university	34 (58.7%)	13 (48.1%)	1.0	
Income (Kshs/month)				
<5000	5 (8.6%)	0 (0.0%)	-	0.107
5000-19999	23 (39.7%)	6 (22.2%)	7.7 (0.6-99.5)	0.147
20000-49999	16 (27.6%)	9 (33.3%)	3.6 (0.3-44.9)	0.543
50000-99999	12 (20.7%)	7 (25.9%)	3.4 (0.3-45.0)	0.544
100000-149999	1 (1.7%)	3 (11.1%)	0.7 (0.0-18.1)	1.000
>150,000	1 (1.7%)	2 (7.5%)	1.0	

Study participants with uncontrolled hypertension were slightly older at 43.2 (±11.5) years compared to those with controlled hypertension at 40.6 (±13.6) years. However this difference was not statistically significant (p 0.347).

Male sex was associated with poorly controlled hypertension (p 0.004).

There were no statistically significant differences between the two groups in terms of level of education and income.

RECIPIENT CLINICAL HISTORY

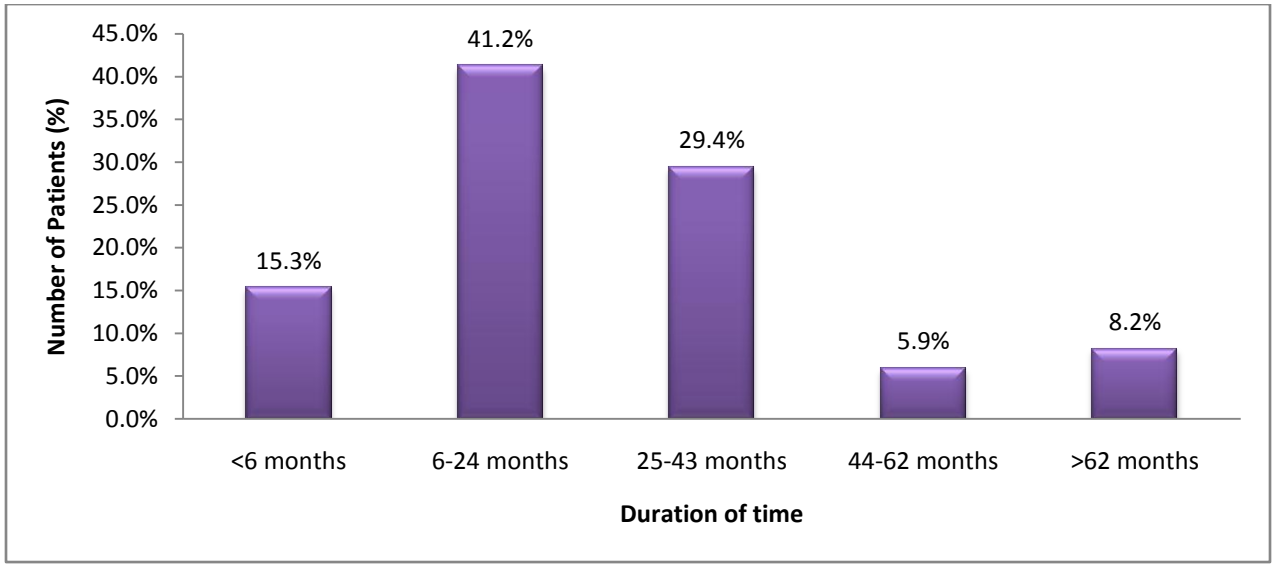
Table 6: Recipient clinical history

Category	Variable	Frequency (%)
Pre-transplant	**Presence of pre-transplant hypertension** Yes No	 80 (94.1) 5 (5.9)
Post-transplant	**Duration post- transplant (Months)** Median (IQR) Mean (SD) Range	 22.0 (12.5 - 32.5) 30.2 (36.4) 3 – 233
	Transplant type Living donor related Living donor unrelated	 79 (92.9) 6 (7.1)

Most of the renal transplant recipients had hypertension pre-transplant (94.1%). Majority had received their kidneys from living related donors (92.9%).

The median duration post transplant was 22 months, with the longest duration being over 19 years (233 months). Majority of the patients (41.2%) were between 6 to 24 months post transplant as shown in figure 5 below.

Figure 5. Duration of time post transplant

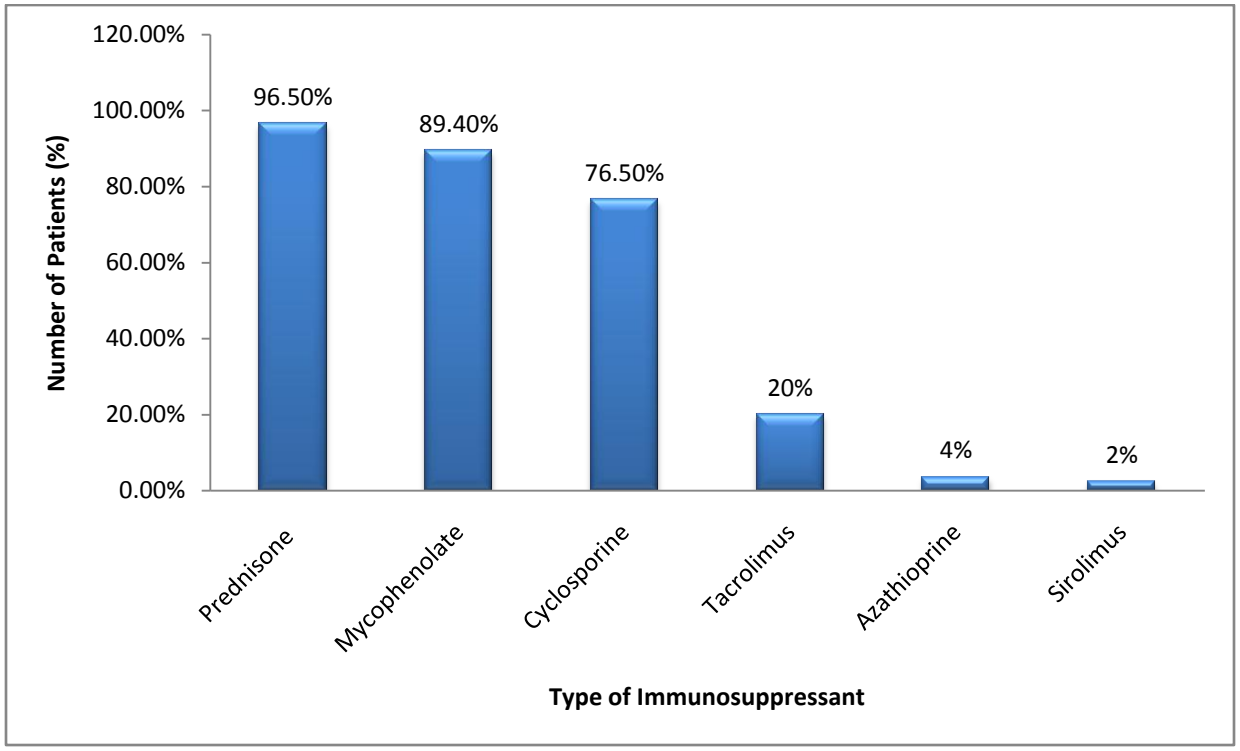


IMMUNOSUPPRESSANTS USED

The most commonly used immunosuppressant was Prednisone (96.5%) followed by Mycophenolate (89.4%) and Cyclosporine (76.5%). The alternative calcineurin inhibitor Tacrolimus was used in a fifth of the patients, with only 2% using the mTor inhibitor Sirolimus.

These immunosupressants are used in combination, with the most common being Cyclosporine, Mycophenolate plus Prednisone.

Figure 6. Immunosuppressants



OTHER BASELINE CHARACTERISTICS

Table 7: Other Baseline Characteristics

Variable	Frequency (%)
Serum creatinine (µmol/L) Mean (SD) Min – max	 118.2 (37.2) 69 – 321
GFR (ml/min/1.73m^2) Mean (SD) Min – max	 74.2 (18.4) 16 – 115
Median Urine albumin : creatinine ratio in mg/g (IQR) <30 (Normal) 30-300 (Microalbuminuria) >300 (Macroalbuminuria)	60 (20-100) 40 (47.1) 36 (**42.4**) 9 (10.5)
History of acute rejection post –transplant Yes No	 14 (**6.5**) 71 (83.6)
Number of episodes of rejections 1 2	 12 (85.7) 2 (14.3)
Mean BMI in kg/m^2 (SD)	24.8 (4.4)

Mean serum creatinine was 118.2 (±37.2) µmol/l, with a range of 69 to 321µmol/l. Mean GFR was 74.2 (±18.4) ml/min/1.73m^2 as calculated by the MDRD4 formula.

With regard to urine albumin:creatinine ratio, 42.4% had microalbuminuria, and 10.6% had overt macroalbuminuria.

Mean BMI was within normal at 24.8 (±4.4) kg/m^2. Fourteen patients (6.5%) had documented acute rejection episodes, 85.7% of whom had had one episode.

11.2 HYPERTENSION

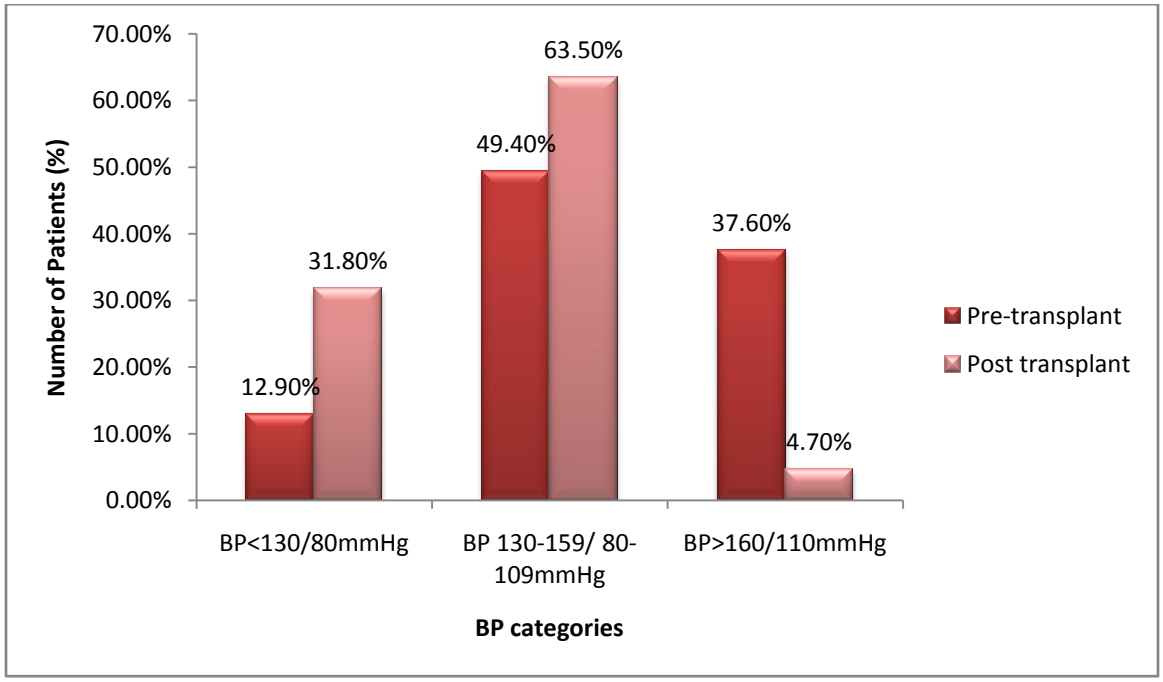
Table 8: Blood pressure levels and control

Variable	Pre-transplant	Post – transplant	p-value
Blood pressure, mean (SD)			
Systolic	144.5 (18.2)	131.8 (16.6)	**<0.001**
Diastolic	103.6 (37.7)	83.5 (12.9)	**<0.001**
Hypertension control, n (%)			
Uncontrolled	74 (87.1%)	58 (68.2)	**0.006**
Controlled	11 (12.9%)	27 (31.8**)**	

In the pre-transplant period, uncontrolled hypertension was noted in 87.1% of the patients (95% CI, 78.9- 94.1), while in the post-transplant period 68.2% (95% CI, 57.6- 77.6) had uncontrolled hypertension.

Compared to the pre-transplant period, significantly lower mean systolic and diastolic blood pressure levels were noted post-transplantation (mean SBP 144.5mmHg vs 131.8mmHg; mean DBP 103.6mmHg vs 83.5mmHg in the pre- and posttransplant periods respectively, p<0.001).

Figure 7: Blood pressure categories pre- and post transplant



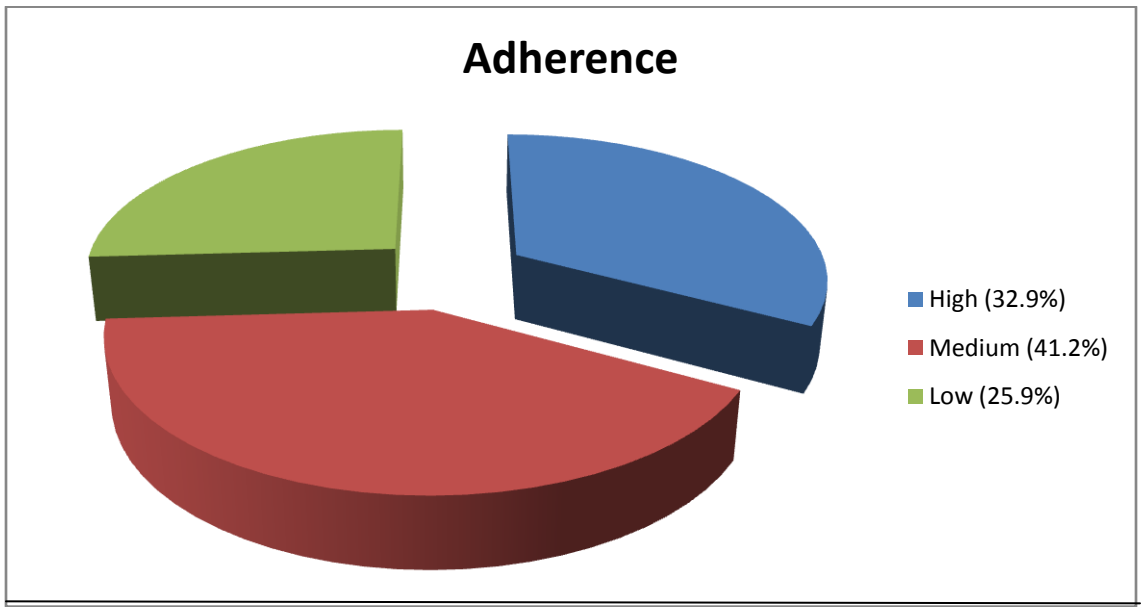
It was noted that in the pre-transplant period more than a third of the patients (37.6%) had blood pressure levels greater than 160/110mmHg. This was however reduced to 4.7% in the post transplant period.

11.3 ADHERENCE

32.9% had high adherence to antihypertensive medication as assessed by the MMAS-8. 41.2% had medium and 25.9% had low level of adherence. Both those with medium and low levels of adherence were considered nonadherent.

Mean Morisky score was 6.8, representing a medium adherence level.

Figure 8. Adherence levels as assessed by the MMAS-8



When the individual components of the MMAS-8 were assessed (Table 9 below), it was noted that 27.1% of the participants felt that sticking to their blood pressure treatment plan was a burden, while another 23.5% sometimes forgot to take their blood pressure medications.

The best answered questions were those asking whether the patients had taken their blood pressure medication the previous day (94.1% had) and whether they stopped taking their medications when they felt their blood pressure was under control (91.8% denied this)**.**

Table 9: Adherence to antihypertensive medications- MMAS 8

Variables	**Frequency (%)**
Do you sometimes forget to take your high blood pressure pills?	
Yes	20 (**23.5**)
No	65 (76.5)
Any days in the past 2 weeks when you did not take antihypertensives?	
Yes	15 (17.6)
No	70 (82.4)
Ever cut back or stopped taking your medications?	
Yes	11 (12.9)
No	74 (87.1)
Forgetting medications when traveling or leaving home	
Yes	6 (7.1)
No	79 (92.9)
Did you take your blood pressure medicine yesterday?	
Yes	80 (**94.1**)
No	5 (5.9)
Do you stop medicines when you feel blood pressure is under control?	
Yes	7 (8.2)
No	78 (**91.8**)
Feeling hassled about sticking to blood pressure treatment plan	
Yes	23 (**27.1**)
No	62 (72.9)
Having difficulty remembering to take all medications	
Never	41 (48.2)
Almost never	26 (30.6)
Sometimes	18 (21.2)
Mean morisky score (SD)	**6.8** (1.2)

ASSOCIATION BETWEEN ADHERENCE AND BLOOD PRESSURE CONTROL

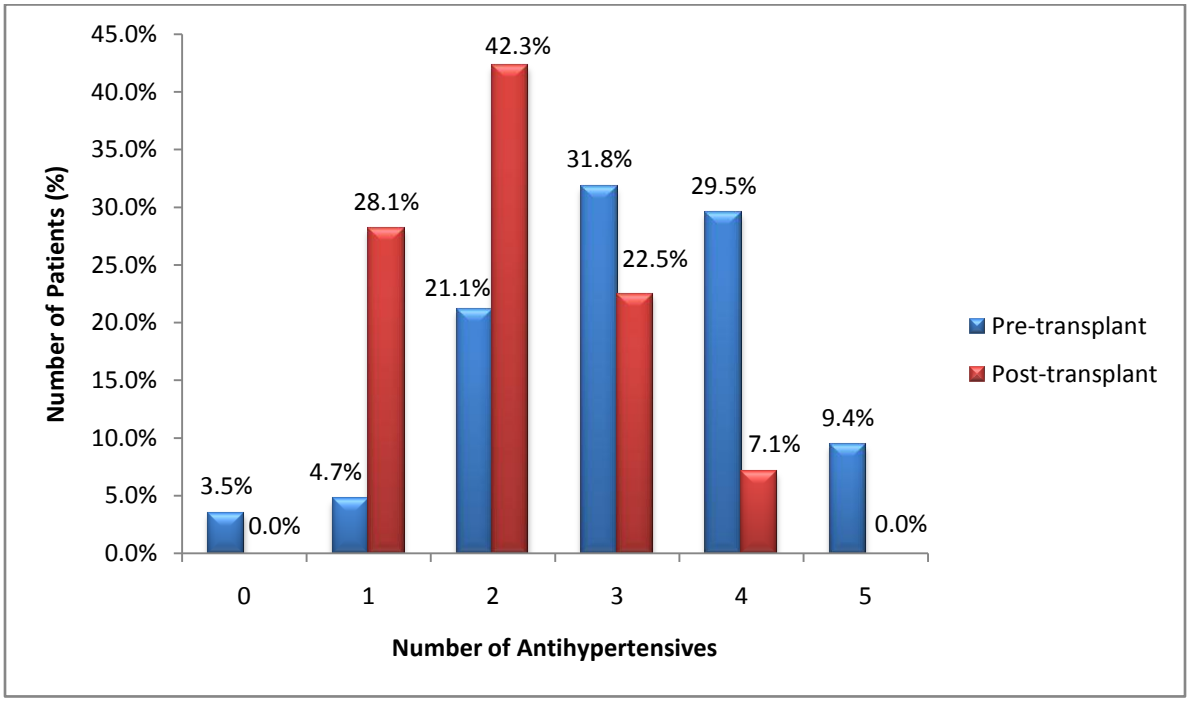
Table 10: Blood pressure control and Adherence

Variable	Hypertension		OR (95% CI)	P value
	Uncontrolled (n=58)	Controlled (n=27)		
Adherence				
High	8 (13.8%)	20 (74.1%)	1.0	
Medium	28 (48.3%)	7 (25.9%)	10.0 (3.1-32.1)	**<0.001**
Low	22 (37.9%)	0 (0.0%)	-	**<0.001**

Study participants with high levels of adherence were more likely to have controlled blood pressure levels (74.1% of patients with controlled blood pressure had high adherence levels). Those who were nonadherent (medium and low levels of adherence) were more likely to have uncontrolled hypertension compared to those who were fully adherent ($p<0.001$). Of note is that no patient with low adherence level had controlled blood pressure.

11.4 ANTIHYPERTENSIVE MEDICATIONS

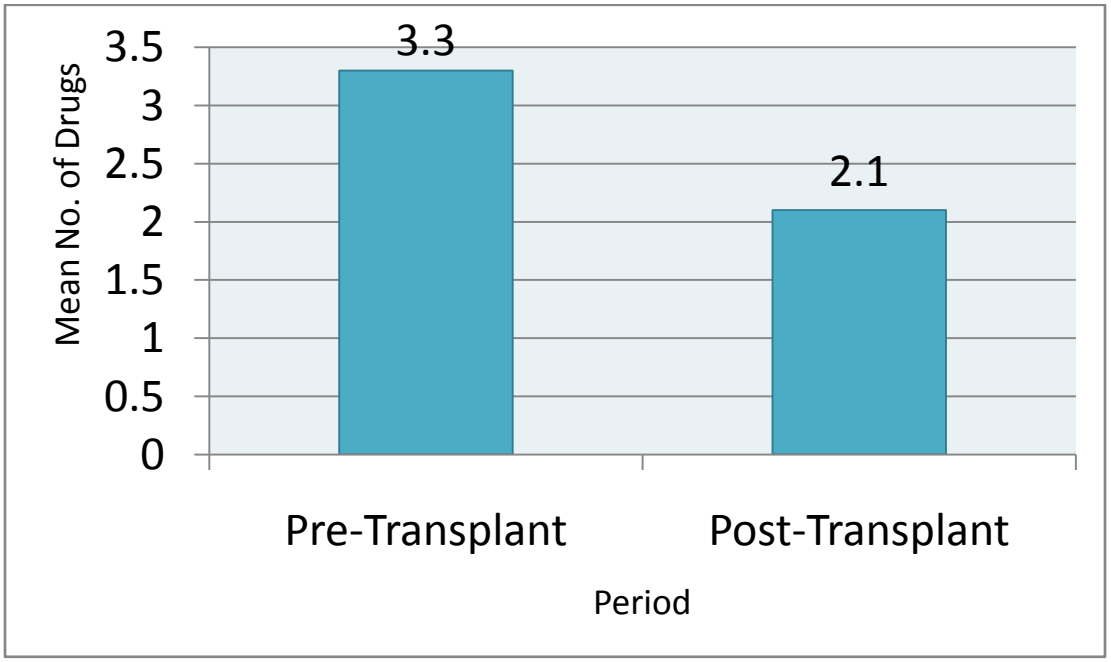
Figure 9. Number of antihypertensives used in the pre- and post transplant periods



In the pre-transplant period most patients (70.7%) were on 3 or more classes of antihypertensive medications. In the post transplant period the converse was noted, with most patients (70.4%) on 2 or less antihypertensive medications.

There was a significant reduction in the mean number of antihypertensive agents used after transplantation, with an average of 3.3 (±1.6) drugs in the pre-transplant period compared with 2.1 (±0.9) drugs in the post-transplant period ($p < 0.001$). This is shown in figure 10 below.

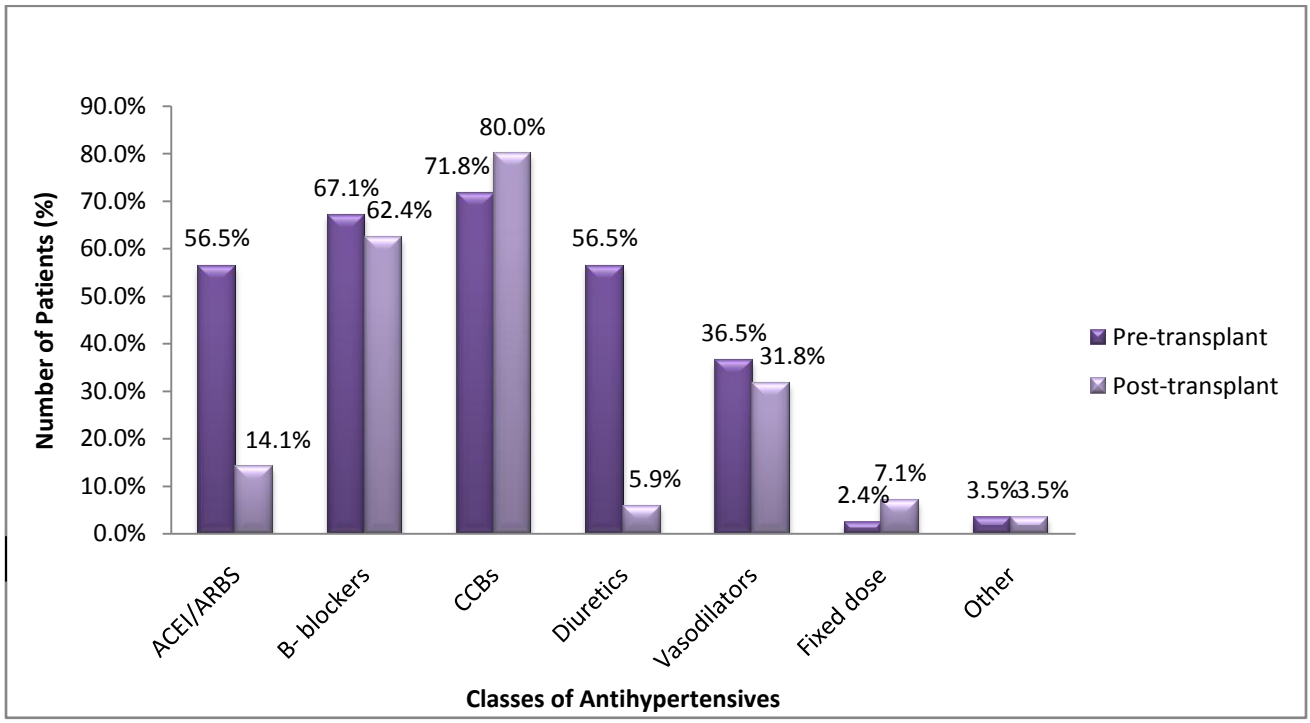
Figure 10. Mean number of Antihypertensives used in the Pre- and Post transplant periods



Suboptimal dosing of one or more antihypertensive agents was noted in 89.4% of patients in the pre-transplant period and 78.8% in the post-transplant period.

TYPES OF ANTIHYPERTENSIVE AGENTS USED

Figure 11: Types of antihypertensive drugs used pre- and post-transplant



With regard to the types of antihypertensive agents used, it was noted that there was a marked reduction in ACE-inhibitor use from 56.5% pre-transplant to 14.1% in the post transplant period, as well as diuretic use (56.5% to 5.9%).

Use of CCBs increased slightly in the post transplant period from 71.8% to 80%, as did use of fixed dose combinations (2.4% to 7.1%). Beta-blocker and vasodilator use remained almost similar pre- and post transplantation.

The most commonly used classes of antihypertensives were CCBs and beta-blockers.

LIFESTYLE MODIFICATION MEASURES

More than half the study participants (54.1%) were on a low salt diet. However only about a third of the patients (30.6%) were on a regular exercise program. One patient (1.2%) was a current smoker.

Table 11: Lifestyle Modification Measures

Variables	**Frequency (%)**
Diet	
Normal	39 (45.9)
Low-salt diet	46 (**54.1)**
Exercise	
None	19 (22.4)
Once in a while	40 (47.1)
At least in 30minutes 3times/week	26 (30.5)
Smoking	
Never	68 (80.0)
Current	1 (1.2)
Past	16 (18.8)

11.5 ASSOCIATION BETWEEN UNCONTROLLED HYPERTENSION AND OTHER CLINICAL AND LABORATORY CORRELATES

Table 12: Factors associated with uncontrolled hypertension

Variable	Hypertension		OR (95% CI)	P value
	Uncontrolled (n=58)	Controlled (n=27)		
Recipient BMI in kg/m^2 (SD)	24.5 (3.9)	25.2 (5.4)	-	0.502
Age of donor in years (SD)	33.6 (8.7)	32.4 (8.0)	-	0.529
GFR in ml/min/1.73m^2 (SD)	73.6 (19.9)	75.4 (14.9)	-	0.669
Proteinuria in mg/g (IQR)	75.0 (30.0-150.0)	30.0 (20.0-80.0)	-	**0.029**
Rejection history Yes No	 10 (17.2%) 48 (82.8%)	 4 (14.8%) 23 (85.2%)	 1.2 (0.3-4.2) 1.0	 1.000
Cyclosporine Yes No	 47 (81.0%) 11 (19.0%)	 18 (66.7%) 9 (33.3%)	 2.1 (0.8-6.5) 1.0	 0.146
Cyclosporine dose in mg/kg (SD)	2.9 (1.6)	2.7 (1.7)	-	0.687
Prednisone Yes No	 55 (94.8%) 3 (5.2%)	 27 (100.0%) 0 (0.0%)	 -	0.548
Prednisone dose in mg/kg (SD)	0.14 (0.14)	0.15 (0.11)	-	0.677

Uncontrolled hypertension was associated with higher levels of proteinuria (75mg/g versus 30mg/g in those with controlled hypertension), p 0.029.

There were no statistically significant differences between those with uncontrolled versus controlled hypertension in terms of recipient BMI, donor age, GFR, documented history of rejection or immunosuppressant used.

MULTIVARIATE ANALYSIS

Table 13. Logistic Regression Analysis

Variable	OR (95% CI)	P value
Sex of recipient		
Male	3.8 (1.1-13.4)	**0.040**
Female	1.0	
Proteinuria	1.0 (1.0-1.01)	0.442
Adherence		
High	1.0	
Medium/Low	16.6 (4.9-56.3)	**<0.001**

Factors that were found to be associated with uncontrolled hypertension on bivariate analysis were then subjected to multivariate analysis using logistic regression.

Male sex and nonadherence to antihypertensive medication (medium/low adherence) were found to be independently associated with uncontrolled hypertension.

12. DISCUSSION

Adequate blood pressure control among renal transplant recipients has been shown to be beneficial, associated with better graft outcomes and reduced mortality[60]. This study sought to find out the factors associated with inadequate blood pressure control among local renal transplant recipients, some of which may be modifiable, leading eventually to improved patient outcomes.

The mean age of our study participants was 42.4 (±12.2) years, a relatively young population. This is comparable to that found by Wagude *et al* in a study on local renal transplant recipients, where the mean age was 44.2 (±12.4) years[7]. Our patients were however noted to be about a decade younger compared to studies carried out in the West, with Mason et al finding a mean age of 50.2 years in a study in the UK[73.] It has been shown by Barsoum *et al* that renal disease tends to occur at an earlier age in tropical countries[77].

There was a male predominance noted among study participants, with a male to female ratio of 1.9:1, similar to other local studies. Wagude *et al*[7] found a ratio of 2.1:1 while Okech *et al*[8] had a ratio of 2.3:1 among renal transplant recipients at KNH. Among Jordanian renal transplant recipients Bulatova *et al* found a slightly lower male to female ratio of 1.4:1[72]. The male predominance reflects the distribution of patients with chronic kidney disease attending nephrology clinics, with Nadeem *et al* finding a male to female ratio of 2.5:1[5], and Muthui *et al* a ratio of 1.4:1[78] among CKD patients locally. Therefore, as more males are diagnosed with chronic kidney disease, more will eventually require renal transplantation. Another possible explanation could be that since renal transplantation is a costly undertaking, males who are economically advantaged are better able to access the service compared to their female counterparts.

In terms of financial ability, this was noted to be a mostly low to middle income population, with majority of the patients (69.4%) earning less than Ksh 50,000 per month. These income levels are quite low when compared with the hefty monthly medical costs incurred for purchase of immunosuppressants, antihypertensives and other medications. Level of income has actually been shown to correlate with blood pressure control. In a study carried out among African-Americans, Kotchen *et al* showed that lower socioeconomic strata was associated with poor

blood pressure control, as a result of inaccessible medical care. Patients from low socioeconomic strata had less visits to physicians and were also less likely to be screened for hypertension[79].

Despite universal health insurance coverage of the study population by the National Health Insurance Fund (NHIF), 80% of the patients had to rely on out-of-pocket expenditure to fund their antihypertensive medication expenses. This is due to the fact that the NHIF currently does not cover outpatient health costs. Of concern is that a notable number (24.7%) found their antihypertensive medications difficult to afford. This may have an impact on patient access to medications, adherence and ultimately their blood pressure control. Indeed, studies in minority populations have underscored the contribution of inadequate health insurance cover to poor blood pressure control[80].

The mean duration post renal transplantation was 30.2 (±36.4) months, reflecting the growth in the KNH renal transplantation program (Interlife program) over the past three years. This is in contrast to studies done in countries that have had a long-standing renal transplantation program. Mean duration post transplantation in a study done in the UK[73] was 76 months while one done in Jordan was 38 months[72].

Blood pressure control in our renal transplant population still remains a challenge, with 68.2% of renal transplant recipients in our study having uncontrolled hypertension. High rates of uncontrolled hypertension among local RTRs were also demonstrated by Wagude *et al* [7](84.4%) and Okech *et al*[8] (78.8%). In comparison, studies in the West showed much lower rates of uncontrolled hypertension, with figures of 50% in the UK[73] and 58% in Jordan[72]. This difference could be attributed to the fact that their populations had access to free medications. In addition, their mean duration post transplantation was much longer than ours. Studies have demonstrated that blood pressure control tends to improve as time post transplantation increases[6]. This is because of stabilization of graft function as well as tapering off of immunosuppressant doses, especially cyclosporine and steroids that have been implicated in causation of hypertension.

As compared to the post-transplant period, there were higher rates of uncontrolled hypertension in the pre-transplant period, with 87.1% of the patients not achieving target blood pressure goals. This was comparable to that found by Rajula et al, where 84.4% of patients with chronic kidney

disease at KNH did not meet target blood pressure levels of <130/80mmHg[4]. It has been shown that higher blood pressure levels are seen with decreased or worsening renal function[81].

Reasons for better rates of blood pressure control in the post transplant period include the fact that blood pressure post renal transplantation is inversely related to the glomerular filtration rate. Many patients thus note a reduction in blood pressure levels with the improvement in renal function achieved post transplantation, as well as the reduced fluid overload status. Indeed, mean systolic and diastolic pressures were noted to decrease significantly from 144.5 (±18.2) mmHg to 131.8 (±16.6) mmHg and 103.6 (±37.7) mmHg to 83.5 (±12.9) mmHg in the pre- and post transplant periods respectively.

In terms of antihypertensive medication use, it was noted that there was a significant reduction in mean number of antihypertensives used from 3.3 (±1.6) in the pre-transplant period to 2.1 (±0.9) in the post transplant period. This was also noted in a study carried out by Midvedt *et al* in Norway, where antihypertensive medication use reduced from 2.3(±0.3) to 1.3(±0.9) among renal transplant recipients who also underwent bilateral nephrectomy[59]. Similar reduction in antihypertensive use was noted in both the patients who had nephrectomy and those who did not. Reduced antihypertensive medication use is attributed to the lower blood pressure levels seen with improved GFR post renal transplantation.

The most commonly used class of antihypertensive agents were calcium channel blockers in both the pre- and post transplant period, followed by beta blockers. Bulatova *et al* in Jordan also had similar findings, with 58% of their patients on CCBs followed by beta blockers at 33%[72]. Calcium channel blockers are preferred agents especially in the early post transplant period because they have been shown to mitigate the vasoconstrictive effects of cyclosporine. A large randomized comparative study also showed that nifedipine was associated with improved kidney function at one year post transplant when compared to the ACE inhibitor, lisinopril[48] .

There was a marked reduction in ACE inhibitor/ Angiotensin receptor blocker use from 56% in the pre- transplant period to 14% in the post transplant period. This reflects the fact that ACEi/ARBs are usually avoided in the immediate post transplant period because they may cause a reduction in glomerular filtration rate that may mimic or mask rejection episodes. They may

also precipitate renal failure in patients with transplant renal artery stenosis. Bulatova *et al* also noted that only 19% of their renal transplant recipients were on ACE inhibitors[72]. In addition, we also observed a decline in diuretic use post transplantation (56.5% to 5.9%), probably as a result of the reduced fluid overload status achieved with improved renal function post transplantation.

As regards lifestyle modification measures, more than half (54.1%) of our study population were on a low salt diet, whereas only a third (30.6%) regularly engaged in exercise. Only 1.2% were current smokers. Non pharmacological blood pressure control measures should be recommended to renal transplant recipients, although these measures have not been formally tested in this population[11].

Adherence

Only a third of our study population was found to be fully adherent to their antihypertensive medications as assessed by the MMAS-8. Similar to a study by Oliviera *et al* in Portugal, those with medium and low levels of adherence were considered nonadherent[68]. Our adherence levels were lower than that shown among African-American renal transplant recipients, whereby Terebelo *et al*[64] found that 55% were adherent to their nonimmunosuppressant medication, including antihypertensives, antidiabetics and lipid lowering agents. There were however differences between the two studies in terms of assessment tools used as well as definition of nonadherence. In the US study a structured, closed ended interview was used to determine adherence, and nonadherence in their study was defined as missing any dose of medication over the preceding one month. In addition, their study population had free access to medications, whereas 80% of our population had to rely on out-of-pocket expenditure to finance their medication. It has been shown in various studies that prohibitive cost of drugs is one of the greatest hindrances to adherence[82,83].

Our adherence level was however comparable to that found by Achieng' *et al* in a study done among patients with hypertension attending medical outpatient clinics at the Kenyatta National Hospital[63]. 31.8% of her study population were adherent as assessed by the Hill-Bone questionnaire. Delving further into the patient-percieved reasons for nonadherence, her study

found that barriers to adherence included high cost of drugs, side effects of the antihypertensives as well as use of alternative therapies like herbal medications and prayer. Our study however did not look into the patient-perceived reasons for nonadherence. Some of these factors like cost may also be a barrier in our renal transplant recipient population, as well as the high pill burden faced by these patients. Barriers to adherence picked up from the MMAS-8 tool in our study included forgetting to take antihypertensive medications in 24% of patients, while another 27% felt that sticking to their blood pressure treatment plan was a burden. These represent possible areas of intervention to improve adherence rates among our renal transplant recipient population.

Factors associated with uncontrolled hypertension

Male sex was independently associated with uncontrolled hypertension in our study. In an analysis of data from the third National Health and Nutrition Survey, Hyman *et al* found male sex to be independently associated with uncontrolled blood pressure among 16,095 adults in the US[84]. Reckelhoff, in a paper looking at sex steroids, cardiovascular disease and hypertension, postulated that this sex difference could be due to various factors. These include increased plasma renin activity in males or androgen stimulation of sodium reabsorption and vasoconstrictor molecules such as endothelin[85]. In the UK, female sex was associated with target blood pressure control among renal transplant recipients[73].

Non adherence to antihypertensive medications was also independently associated with poor blood pressure control among our study participants. Oliviera et al in Portugal also demonstrated that nonadherence as measured by the same tool, the MMAS-8, was predictive of elevated systolic and diastolic pressures among patients with hypertension[68]. To our knowledge, there has been no other study looking at the association between adherence and blood pressure control specifically among renal transplant recipients, and we have no reason to believe that this population should be different from the general hypertensive population in this regard.

In terms of renal function and blood pressure control, our study showed that patients with uncontrolled hypertension had higher levels of proteinuria compared to those with controlled hypertension (mean urine albumin: creatinine ratio 75 vs 30 mg/g, p 0.029). This difference was however statistically significant only on bivariate analysis, probably because our study was

underpowered to determine the association conclusively. Lower level of proteinuria was an independent predictor of achieving target blood pressure among renal transplant recipients in the UK[73]. Proteinuria in the post transplant period may be a marker of chronic allograft nephropathy, which is associated clinically with gradual deterioration of transplant function and frequently, new or worsening hypertension[86].

Immunosuppressants, especially cyclosporine and steroids have been linked with hypertension. In our population, we found no statistically significant difference between those with controlled versus uncontrolled hypertension in terms of prednisone use and dose. This could be due to the fact that the population was more or less homogenous, with 95.6% of patients on prednisone. Among the patients on cyclosporine, it was noted that more of them had uncontrolled hypertension than controlled hypertension (81% vs 66.7%). Mean cyclosporine dose was also higher in those with uncontrolled hypertension compared with controlled hypertension (2.9 vs 2.7mg/kg). However these differences did not reach statistical significance in our study population. This should be further investigated as the renal transplant recipient population grows. Further studies looking at the differences in blood pressure control between those on cyclosporine versus tacrolimus would also be prudent, as previous studies have shown that tacrolimus may have less effects on blood pressure levels[25].

Finally, suboptimal dosing of antihypertensive medications may also have contributed to poor blood pressure control. We noted that upto 78% of our renal transplant recipients were on less than maximal doses of one or more antihypertensive agents, despite not achieving target blood pressure levels. This may be a consequence of therapeutic inertia, widely described in literature as reluctance by clinicians to initiate or intensify therapy when warranted[87]. Among renal transplant recipients, clinical inertia was reported as a barrier to achieving target blood pressure by Kiberd *et al* in Canada, where they noted that only 36% of patients in their kidney transplant clinic were prescribed a change in therapy despite a systolic blood pressure $\geq$130mmHg[88]. There was however improvement noted when strategies to reduce therapeutic inertia were introduced in their clinic, including use of an automated, accurate blood pressure monitoring device, the BpTRU machine[88]. Such strategies may also be of help in our setup.

13. CONCLUSION

Uncontrolled hypertension remains highly prevalent at 68.2% in the post renal transplant period, although there was an improvement in blood pressure control when compared to the pre-transplant period.

It was also noted that there was a reduction in mean number of antihypertensive medications used in the post transplant period compared to the pre-transplant period.

Levels of adherence to antihypertensive therapy were quite low, where only a third of the patients were fully adherent to blood pressure lowering medications. However, it is worth noting that not all patients who were completely adherent to their antihypertensive medications had optimal blood pressure control.

Factors independently associated with uncontrolled hypertension in this population were male sex and nonadherence to antihypertensive medications. The latter is amenable to intervention for improvement.

14. STUDY LIMITATIONS

1. Measurement of blood pressure levels at one point in time may not be a true reflection of blood pressure control levels.

2. Part of data was from file records hence had to rely on nonstandardized blood pressure measurement pre-transplantation. Some of the file records were also incomplete.

15. RECOMMENDATIONS

1. Intensification of blood pressure control among renal transplant recipients.

2. Improve rates of adherence to antihypertensive medications among renal transplant recipients. Possible areas of intervention include:

    a) Use of reminders for those patients who forget to take their antihypertensive medications.
    b) Patient counseling to understand the importance of sticking to their blood pressure treatment plan for those who feel that this is a burden.

3. Follow up studies to look into the patient-perceived reasons for nonadherence to antihypertensive medications.

4. Follow up analytical studies as the renal transplant population grows, to look further into the associations alluded to in this cross-sectional study.

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17. APPENDICES

17.1 APPENDIX I: STUDY EXPLANATION FORM

STUDY TITLE: FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI

My name is Dr Mary Nigandi Kubo, a postgraduate student in Medicine at the University of Nairobi. I am carrying out a study looking at the factors associated with uncontrolled high blood pressure among renal transplant recipients, with an eventual aim of improving control of high blood pressure and ultimately graft and patient outcomes in renal transplant recipients. The study is also part of the curriculum requirements for successful completion of the Masters in Internal Medicine (MMed) program. This study is being carried out only after ethical approval by the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee. The ethical approval has been given for a period of one (1) year.

The study will involve answering some questions regarding your medical history, physical examination to determine blood pressure and body mass index (BMI), and two laboratory investigations (kidney function test from a blood sample and quantification of protein from a urine sample). There will be no financial cost to you as I shall fully pay for these laboratory tests. You will further be required to fill in a self-reported questionnaire consisting of 8 questions to determine the level of adherence to antihypertensive medications.

Benefits

The study will help the health-care provider identify any gaps in the management of hypertension in the renal transplant recipient population, some of which can be modified to ultimately result in better control of your blood pressure.

In case any abnormality in the blood or urine test carried out is identified, your healthcare provider shall be immediately notified for further remedial action. You shall also be informed of all your laboratory results and whether you need to seek medical advice for any abnormal test results.

Risks

Since the study involves taking a blood sample, there may be mild pain at the venepuncture site.

Voluntary nature of the study/ Confidentiality

Participants shall only be recruited into the study after full explanation and signing of the written informed consent. Should you choose not to participate in the study, you will continue to receive your healthcare as usual, with absolutely no discrimination against you. You are also free to withdraw your consent and participation in the study at any time.

All data collected shall be kept confidential, and any information that would make it possible to identify you or any other participant will never be included in any sort of report. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you.

Contact Information

In case of any queries regarding the study during or after the study duration please feel free to contact the following:

1. DR. MARY NIGANDI KUBO, UNIVERSITY OF NAIROBI, DEPARTMENT OF CLINICAL MEDICINE AND THERAPUTICS, Mobile: 0721- 541 439 ***OR***

2. CHAIRPERSON, KNH/UON ETHICAL REVIEW COMMITTEE,
   TEL: 020-2726300 EXT. 44102/ 0722829500/ 0733606400
   P.O. Box 20723, Nairobi.
   Email: uonknh_erc@uonbi.ac.ke

17.2 APPENDIX II: SCREENING CONSENT FORM

STUDY TITLE: FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI

Statement of Consent

I have read the above information concerning the study on factors associated with uncontrolled hypertension among renal transplant recipients. This study has been given ethical approval for a period of one (1) year. I have asked any questions I had regarding the study and they have been answered to my satisfaction. I consent to undergo screening to determine whether I shall be eligible to participate in the study.

Name of Participant_____

Signature of Participant _____ Date:_____

Name of witness:_____ Signature of witness:_____

INVESTIGATOR'S STATEMENT:

I, the Principal Investigator, have fully educated the research participant on the purpose and implication of this study, and that he/she must first undergo screening to determine their eligibility to participate in the study.

Signed: ..... Date: _____

CONTACT INFORMATION

In case of any queries regarding the study during or after the study duration please feel free to contact:

1. DR. MARY NIGANDI KUBO, UNIVERSITY OF NAIROBI, DEPARTMENT OF CLINICAL MEDICINE AND THERAPUTICS, Mobile: 0721- 541 439 ***OR***

2. CHAIRPERSON, KNH/UON ETHICAL REVIEW COMMITTEE,
   TEL: 020-2726300 EXT. 44102/ 0722829500/ 0733606400
   P.O. Box 20723, Nairobi. Email: uonknh_erc@uonbi.ac.

17.3 APPENDIX III: SCREENING PROFORMA

Name: _____ Hospital No.:_____

Study Date: _____

1. **CONSENT GIVEN:**

YES ☐ **NO** ☐ **IF YES PROCEED TO 2.**

2. **AGE OVER 18 YEARS:**

YES ☐ **NO** ☐ **IF YES PROCEED TO 3.**

3. **MORE THAN 2 MONTHS POST RENAL TRANSPLANT:**

YES ☐ **NO** ☐ **IF NO EXCLUDE, IF YES PROCEED TO 4.**

4. **HYPERTENSIVE:**

YES ☐ **NO** ☐ **IF NO EXCLUDE.**

5. **ON DIALYSIS:**

YES ☐ **NO** ☐ **IF YES EXCLUDE.**

FOR OFFICIAL USE ONLY

RECRUITED ?

YES ☐ **NO** ☐

Interviewers Name:_____

Signature:..... Date:_____

17.4 APPENDIX IV: STUDY CONSENT FORM

STUDY TITLE: FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI

Statement of Consent

I have read the above information concerning the study on factors associated with uncontrolled hypertension among renal transplant recipients. This study has been given ethical approval for a period of one (1) year. I understand that the cost of any tests done shall be fully borne by the Principal Investigator, and that there will be no monetary gain from participating in this study. I have asked any questions I had regarding the study and they have been answered to my satisfaction. I consent to participate in this study.

Name of Participant_____

Signature of Participant _____ Date:_____

Name of witness:_____

Signature of witness:_____

INVESTIGATOR'S STATEMENT:

I, the Principal Investigator, have fully educated the research participant on the purpose and implication of this study.

Signed: ..... Date: _____

CONTACT INFORMATION

In case of any queries regarding the study during or after the study duration please feel free to contact:

1. DR. MARY NIGANDI KUBO, UNIVERSITY OF NAIROBI, DEPARTMENT OF CLINICAL MEDICINE AND THERAPUTICS, Mobile: 0721- 541 439 ***OR***

2. CHAIRPERSON, KNH/UON ETHICAL REVIEW COMMITTEE,
   TEL: 020-2726300 EXT. 44102/ 0722829500/ 0733606400
   P.O. Box 20723, Nairobi. Email: uonknh_erc@uonbi.ac.ke

KUHUSU IDHINI

Jina langu ni Daktari Mary Nigandi Kubo. Mimi ni mwanafunzi katika chuo kikuu cha Nairobi. Ninatarajia kufanya utafiti kuhusu shida ya shinikizo la damu (presha ya damu kuwa juu) katika wagonjwa waliopewa figo mpya**.** Shinikizo la damu likiendelea kuwa juu bila kutibiwa vilivyo, huleta madhara kwa figo na hata moyo.

Sababu ya kufanya utafiti huu

Utafiti huu utasaidia kujua jinsi tunavyoweza kuhakikisha kwamba shinikizo la damu linatibiwa vilivyo ili kukinga figo na moyo kutokana na madhara ya presha kuwa juu.

Manufaa ya kuhusika

Utaweza kufanyiwa uchunguzi wa damu kujua jinsi figo inavyoendelea, pamoja na kuchunguzwa mkojo. Kukipatakana shida yoyote daktari wako ataweza kuambiwa ili upate matibabu.

Madhara ya kuhusika

Huenda ukasikia uchungu kidogo kutokana na sindano wakati wa kutolewa damu. Uchungu huu ni sawa na ule unaosikika wakati unapotolewa damu kwa vipimo vingine**.**

Idhini kwa kuhusika

Kuhusika kwako katika utafiti huu ni kwa hiari yako. Unaweza kujiondoa kwa utafiti kwa wakati wowote kabla au baada ya utafiti kuanza. Matibabu yanayostahili yatapewa kwa watu wote na wale watakaokataa kuhusika hawatabaguliwa kwa njia yoyote.

Mawasiliano

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana nami katika nambari ya simu 0721-541 439, ama Mwenyekiti wa kamati ya kimaadili katika nambari ya simu 0722829500/ 0733606400. Asante.

FOMU YA IDHINI

Mimi, _____ nimesoma na nimeelewa maelezo niliyopewa kuhusu utafiti huu. Maswali yangu yote yamejibiwa kwa ukamilifu na watafiti. Nimetoa ruhusa kwangu kuhusika katika utafiti huu.

SAHIHI: _____ (Mhusika)

TAREHE: _____

UMRI: _____

SHAHIDI _____ (Jina kamili)

_____ (Sahihi)

MTAFITI MKUU

Nimemweleza mhusika kuhusu utafiti huu kwa ukamilifu.

SAHIHI_____

TAREHE _____

17.5 APPENDIX V: DATA COLLECTION QUESTIONNAIRE

I. BIODATA- RECIPIENT

1. Study number
   [ ]

2. Current age
   [ ]

3. Sex

Male	Female

4. Marital status

Single	Married	Divorced/Separated	Widowed

5. Residence (Urban)_____ Rural(Province)_____

6. Level of education

None	Primary	Secondary	College/University

7. Occupation

Unemployed	Employed	Self-employed	Retired

8. Smoking history
   - Never_____
   - Past?_____
   - Current?_____ If yes, number of pack years_____

9. Do you have health insurance? Yes_____
   No_____

10. Who buys your blood pressure medications?

Self	Insurance/ Employer	Parent	Child	Other (specify)

11. How affordable are your blood pressure medications?

Easily affordable	Relatively affordable	Difficult to afford	Beyond my financial means

12. What is your total combined family income per month, before taxes, from all sources, wages, benefits, help from relatives, alimony, and so on? (If you do not know exact income please estimate).

< Ksh 5,000		Ksh 50,000-99,999	
Ksh 5,000- 19,999		Ksh 100,000- 149,999	
Ksh 20,000-49,999		>Ksh 150,000	

II. DONOR PROFILE

1. Age at renal graft donation_____
2. Sex: Male_____ Female_____

III. RECIPIENT CLINICAL HISTORY

A. PRE-TRANSPLANT

1. Documented cause of End stage renal disease_____
2. Total duration on renal replacement therapy before transplantation_____
3. Presence of pre-transplant hypertension? Yes_____ No_____
4. Antihypertensive medications used pre-transplant:

CLASS	NAME	DOSE
1. ACE-I/ ARBS		
2. B-BLOCKER		
3. DIURETICS a. LOOP b. THIAZIDE c. K+ SPARING		
4. CCBs a. Dihydropyridine b. Non-dihydropyridine		
5. VASODILATORS a. Centrally acting (Methyldopa, Clonidine)		

b. Direct acting (Hydralazine)		
6. FIXED DOSE COMBINATION		
7. OTHER		

TOTAL NUMBER OF ANTIHYPERTENSIVES (CLASSES) PRE-TRANSPLANT:_____

Optimal dosing? Yes_____ No_____

5. Documented well controlled blood pressure pre-transplant?

   Blood pressure readings at last 2 clinic visits (1) _____ mmHg
   (2) _____ mmHg
   Average of last 2 clinic blood pressure readings _____ mmHg

B. POST TRANSPLANT

1. Duration post transplant _____(months)

2. Number of transplants done to date_____

3. Type of transplant

Cadaveric	Living donor related	Living donor unrelated

4. Average of two blood pressure readings taken during current clinic visit:
   1st reading: Systolic_____ mmHg
   :Diastolic_____ mmHg

   2nd reading: Systolic _____ mmHg
   Diastolic _____ mmHg

   Average: Systolic _____ mmHg
   Diastolic _____mmHg

5. Antihypertensive medication requirements post transplant:

CLASS	NAME	DOSE
1. ACE-I/ ARBS		
2. B-BLOCKER		
3. DIURETICS a. LOOP b. THIAZIDE c. K+ SPARING		
4. CCBs a. Dihydropyridine b. Non-dihydropyridine		
5. VASODILATORS a. Centrally acting b. Direct acting		
6. FIXED DOSE COMBINATION		
7. OTHER		

TOTAL NUMBER OF ANTIHYPERTENSIVES (CLASSES) POST-TRANSPLANT: _____

Optimal dosing? Yes_____ No_____

6. Current immunosuppressant medications and dose used post transplant

IMMUNOSUPRESSANT	DOSE	DOSE/KG
1. CYCLOSPORINE		
2. TACROLIMUS		
3. SIROLIMUS		
4. MYCOPHENOLATE MOFETIL/ SODIUM		
5. PREDNISONE		

7. Serum creatinine _____ µmol/L

8. Estimated GFR _____ ml/ minute per 1.73m^2

9. Urine albumin:creatinine ratio_____ mg/g

10. History of acute rejection post transplant

Yes	No

If yes, number of episodes of acute rejection _____

11. BMI _____ kg/m^2 (Weight _____ kg, Height _____ cm = _____m)

IV. NON-PHARMACOLOGIC BLOOD PRESSURE CONTROL INTERVENTIONS

1. Diet: Normal_____
   Low-salt diet_____

2. Exercise: None_____
   Once in a while_____
   At least 30 minutes 3 times a week_____

V. ADHERENCE TO ANTIHYPERTENSIVE MEDICATIONS

8-item Morisky Medication Adherence Scale (MMAS-8)

Question	Response Options
1. Do you sometimes forget to take your high blood pressure pills?	Yes / No
2. Over the past two weeks, were there any days when you did not take your high blood pressure medicine?	Yes / No
3. Have you ever cut back or stopped taking your blood pressure medication without telling your doctor because you felt worse when you took it?	Yes / No
4. When you travel or leave home, do you sometimes forget to bring along your blood pressure medications?	Yes / No
5. Did you take your high blood pressure medicine yesterday?*	Yes / No
6. When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?	Yes / No
7. Do you ever feel hassled about sticking to your blood pressure treatment plan?	Yes / No
8. How often do you have difficulty remembering to take all your blood pressure medications?*	Never / Almost never / Sometimes / Quite often / Always

TOTAL SCORE_____

- Scoring: Question 1-4, 6-7: Yes=0, No=1
- Question 5: Yes=1, No=0
- Question 8: Never=1, Almost never=0.75, Sometimes=0.5, Quite often=0.25, Always=0.

17.6 APPENDIX VI: LABORATORY METHODS

Serum creatinine estimation (Mindray® Clinical Chemistry Analyzer)

Principle of the method:

Creatinine reacts directly with picrate ion under alkaline conditions to form a red-orange compound, called a *Janovski* complex, with an absorbance peak at 520 nm whose color intensity is directly proportional to the creatinine concentration in the sample. The analytical procedure will be fully automated.

Procedure:

1. 10µl of sample will be mixed with 1500µl of working reagent and mixed well
2. The mixture will be incubated for 5 min at 37^{o} C
3. Absorbance will be read at 520 nm
4. Serum creatinine concentration will be expressed in µmol/L

Urine albumin-creatinine ratio (Clinitek® Microalbumin Analyzer)

Principle of the method:

Albumin: This test is based on dye binding using a high affinity sulfonephthalein dye. At a constant pH, the development of any blue colour is due to the presence of albumin.

Creatinine: This test is based on the peroxidase-like activity of a copper creatinine complex that catalyzes the reaction of diisopropyl-benzene dihydroperoxide and 3,3',5,5'-tetramethylbenzidine.

Albumin is then recorded as concentration in mg/L, and creatinine in g/L. Albumin-creatinine ratio is then finally given in mg/g.

17.7 APPENDIX VII: ETHICAL APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonkeh erc@uonbi.ac.ke
Website: www.uonbi.ac.ke
Link:www.uonbi.ac.ke/activities/KNHUoN

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/312

12th November 2012

Dr. Mary Nigandi Kubo
Dept.of Clinical Medicine & Therapeutics
School of Medicine
University of Nairobi

KENYATTA NATIONAL HOSPITAL
APPROVED
12 NOV 20
ETHICS & RESEARCH COMMITTEE

Dear Dr. Kubo

RESEARCH PROPOSAL: "FACTORS ASSOCIATED WITH UNCONTROLLED HYPERTENSION AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI" (P496/08/2012)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above revised proposal. The approval periods are 12th November 2012 to 11th November 2013.

This aporoval 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**

Yours sincerely

"Protect to discover"

PROF. A.N. GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Dean, School of Medicine, UoN
The Chairman, Dept. of Clinical Med. & Therapeutics, UoN
The HOD, Records, KNH
Supervisors: Prof. J.K. Kayima, Prof. E.N. Ogola, Prof. S.O. Mcligeyo, Dr. A.J.O. Were