COMPARATIVE COST EFFECTIVENESS OF METFORMIN MONOTHERAPY AND METFORMIN/DIPEPTIDYLPEPTIDASE4 INHIBITOR COMBINATION THERAPY IN DRUG NAÏVE TYPE 2 DIABETES PATIENTS AT KENYATTA NATIONAL HOSPITAL

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A thesis submitted in partial fulfillment of requirements for the award of the degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance.

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2016

STUDENTS DECLARATION

I declare that this thesis is my original work and has not been presented for the award of a degree in any other university.

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DEDICATION

I dedicate this work to the mother of my children Brenda for the perseverance and patience as I spent long hours with the lap top.

ACKNOWLEDGEMENTS.

Foremost, all glory and honor be to the almighty God for the provision and protection. Secondly, I thank my supervisors; Dr.F.A. Okalebo, Dr P.C. Mutai, and Dr M. N.Mulaku for the guidance and support. I also thank the employees of the renal unit of Kenyatta National Hospital and Miss Safia, the administrator of the drugs and registration department of the Pharmacy and Poisons Board. Lastly, I thank my classmates at the School of Pharmacy.

TABLE OF CONTENTS

Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

ADA/EASD Diabetes	American Diabetes Association/European Association for the study of
AMP	Adenine Monophosphate
AMPK	Adenine Monophosphate Kinase
CI	Confidence Interval
CNS	Central Nervous System
DCCT	Diabetes Control and Complications Trial
DPP 4	Dipeptidyl Peptidasae 4 inhibitors
ESRF	End Stage Renal Failure
FDC	Fixed Dose Combination
GIP	Glucose Dependent Insulinotropic polypeptide
GLP-1	Glucagon like Peptidase- 1
$HbA_{1/C}$	A minor component of haemoglobin to which glucose is bound
HOMA β	Homeostatic model assessment β Unit.
HRQoL	Health Related Quality of Life
IDF	International Diabetes Federation
IUD	International United States Dollar
KNH	Kenyatta National Hospital
KSh	Kenyan shillings

L E	Life Expectancy
LPGW	Lowest Paid Government Worker
NIDDM	Non-Insulin Dependent Diabetes Mellitus
OADS	Oral Antidiabetic Drugs
QALY	Quality Adjusted Life Years
SDFs	Single Dosage Forms
$T_{1/2}$	Half Life
T2DM	Type Two Diabetes Mellitus
UKPDS	United Kingdom Progressive Diabetes Study
USA	United States of America
USD	United States Dollar
WHO/HAI	World Health Organization/ Health Action International

OPERATIONAL DEFINITIONS

Cost effectiveness analysis. An economic study design in which the consequences of different interventions are measured using a single outcome usually in natural units. Alternative interventions are then compared in terms of cost per unit effectiveness.

Life expectancy. The probable number of years remaining in the life of an individual or a cohort of people determined statistically and that is affected by such factors as the location, physical condition, nutrition and occupation of the individual.

Incremental cost effectiveness ratio. The quotient of the differences in the cost of two interventions and the difference in effect/consequence of the same interventions.

Quality adjusted life years. It is the product of life expectancy and the quality of the remaining life years which can be measured in terms of the health related quality of life.

Markov model. A sequence of random variables that is memory less and time invariant (homogenous)

Technical efficiency. The effectiveness (measured in terms of cost of inputs) of an intervention in minimizing the occurrence of an undesired outcome.

Cost Effectiveness Ratio: The quotient of the cost of an intervention and its effectiveness.

ABSTRACT

Introduction

The combination of metformin and Dipeptidyl Peptidase 4 inhibitors has superior health outcomes as compared to metformin alone. However, the cost may be prohibitive and the combination is being considered as a replacement of metformin alone as first line therapy for management of Type 2 diabetes. The comparative cost effectiveness of either treatment is unknown.

Objectives

To compare the cost effectiveness of changing the first line therapy in the treatment of Type 2 diabetes mellitus from metformin monotherapy to dual therapy of metformin and Dipeptidyl Peptidase 4 inhibitors in drug naïve patients.

Methodology

The study was divided into three parts. The first part was a local and international price survey on the prices of metformin and Dipeptidyl Peptidase 4 inhibitors. The second part, a key informant interview with staff at Kenyatta National Hospital to identify the key resource input required in the management of diabetic nephropathy and lastly a Markov chain model is developed to obtain the long term cost and effectiveness of treating type 2 diabetes patients on either metformin monotherapy or metformin/Dipeptidyl Peptidase 4 inhibitor dual therapies.

The design was a predictive model based cost effectiveness study. The comparator interventions were metformin monotherapy and metformin/Dipeptidyl Peptidase 4 inhibitor dual therapy. Costing was done from the perspective of the provider and only health care costs were considered. The time horizon was 25 years. A macro-ingredient approach was considered for costing. Effectiveness data was obtained from literature and the measures of effectiveness was the life expectancy and time to development of diabetic nephropathy. A sensitivity analysis was used to determine how variation in the costs of the different therapies affected the overall cost effectiveness ratio.

Results

The factors affecting the price of metformin andDipeptidyl Peptidase inhibitors were found to be the pack size of the drug (P<0.05) and the country of importation of the drug (P<0.05). The median local price of the daily defined dose of metformin was KShKSh22.8 (International United States Dollar (IUD) 0.48). The median price ratio of the international median price and the local median price of metformin 500mg tablets and 850mg was 1.3 and 8.4 respectively. The median local price of a daily defined dose of Dipeptidyl Peptidase 4 inhibitors was KShKSh 58 (IUD1.22) while that of Fixed Dose Combination of metformin and Dipeptidyl Peptidase 4 inhibitors was KShKSh122 (IUD 2.58).

The annual cost of dialysis treatment, with the perspective of the health provider, at Kenyatta National Hospital was found to be KShKSh 1,871,640 (IUD 39,678). The annual cost of treating microalbuminuria and macroalbuminuria was KShKSh 174,360 (IUD 3696) and KShKSh 251,160 (IUD 5324) respectively.

The crude life expectancy of drug naïve diabetic patients taking metformin was 21 years. Those taking Fixed Dose Combination of metformin/Dipeptidyl Peptidase 4 inhibitors had a crude life expectancy of 23 years.

The incremental cost effectiveness ratio of Fixed Dose Combination of metformin/Dipeptidyl Peptidase 4 inhibitors compared with metformin monotherapy in drug naïve diabetes patients was found to be 336,698 (IUD 7138) per person per year.

CONCLUSION

It is more cost effective to treat drug naïve type 2 diabetes patients with dual therapy of metformin and Dipeptidyl Peptidase inhibitors as compared to metformin monotherapy.

1.0 CHAPTER ONE

1.1 BACKGROUND

Type 2 Diabetes mellitus (T2DM) accounts for 90% of the diabetic cases in the world (1). According to the Diabetes Atlas, it is projected that by 2035, the population of diabetics in Africa will grow by 109% (1). Africa will have the highest incidence rates in the world. This situation is a consequence of demographic changes, increasing urbanization and associated changes in risk factor levels such as leading a sedentary life, obesity and smoking tobacco(1).A majority of diabetic patients in the developing world die when they are below the age of 60 years (2). In the developed world, diabetic patients suffer complications much later in life and they die when they are much older. Access to medication and information is the major reason for their low mortality rates and slow development of complications (1).

Metformin lowers the level of glycated haemoglobin (HbA_{1C}) but it fails after 5 years of treatment. An additional hypoglycaemic drug must be added (3). Dipeptidyl peptidase 4 (DPP 4) inhibitors, a novel class of hypoglycaemic drugs approved for use by The Federal Drug Agency (FDA) of United States of America (USA), has a unique mechanism of action and minimal adverse effects. These drugs have also demonstrated beta cell preservation capability in preclinical studies (4).

The therapeutic goal of administering hypoglycaemics in patients with T2DM is to reduce the glycated haemoglobin levels ($\%HbA_{1c}$) and to preserve pancreatic beta cell function. This would delay development of complications (5). Studies have demonstrated the direct correlation of beta cell function and $\%HbA_{1c}$ (6). Dual therapy at diagnosis with metformin and a DPP 4 inhibitor achieves this objective in a safe and more convenient way (7).

In the private clinics in Kenya, metformin and DPP 4 inhibitors are being used for drug naïve patients suffering from T2DM. Most public funded facilities offer metformin monotherapy. This study investigated the cost effectiveness of changing the guidelines to administration of Metformin/DPP 4 inhibitors as first line therapy in the management of T2DM. It also assessed the comparative incremental cost effectiveness ratio (ICER) of the two interventions.

1.2 PROBLEM STATEMENT

In Africa, 76.4% of people who died due to diabetes in 2013 were under the age of 60 years (1) with cardio-vascular complications causing 60% to 80% of the deaths (1). Africa had the lowest prevalence of the disease but the highest incidence rates. This was bound to increase because an estimated 70% of the population was to reside in urban areas by 2030 (2). It has been found that urbanization is a major risk factor in development of T2DM (2)

In the developed world, the mortality rates and development of complications in diabetic patients has been reduced or delayed due to increased accessibility to medication and information. The American Diabetic Association/European Association for the Study of Diabetes ADA/EASD guidelines insist on individualized therapy which is a euphemism for how much a patient is willing to pay (5, 8).

While dual therapy of DPP 4 inhibitors and metformin had superior glycaemic control, tolerable adverse effects and beta cell protective functions, their cost may have been too high as compared to their effectiveness. New technologies which demonstrate superior efficacies have not been adopted fast and this has put the patient at a higher risk of developing complications (2). If the therapies were to be adopted, there would be budgetary implications. This study evaluated the cost effectiveness of adding a DPP4 inhibitor to metformin in the treatment of drug naïve T2DM patients from the health provider's perspective. It determined whether the new intervention was more cost effective as compared to metformin monotherapy especially in consideration of the benefits accrued from delayed occurrence of complications and preservation of beta cell function.

There is a dearth of research on the cost effectiveness of incretomimetics. A literature search revealed that, thus far, no study had been done in sub-Saharan Africa.

1.3 CONCEPTUAL FRAMEWORK

The theoretical framework of this economic evaluation was driven by the principle of technical efficiency. It requires that the healthcare provider selects the most cost effective intervention. This was measured using the incremental cost effectiveness ratio. Figure 1 is a representation of the theoretical framework of this study. It demonstrates how the study was carried out starting

with a price survey to determine the market prices of metformin and DPP 4 inhibitors followed by a key informant interview to determine the cost of treating complications accruing from T2DM. Finally a Markov model was done to determine the effectiveness of both interventions.

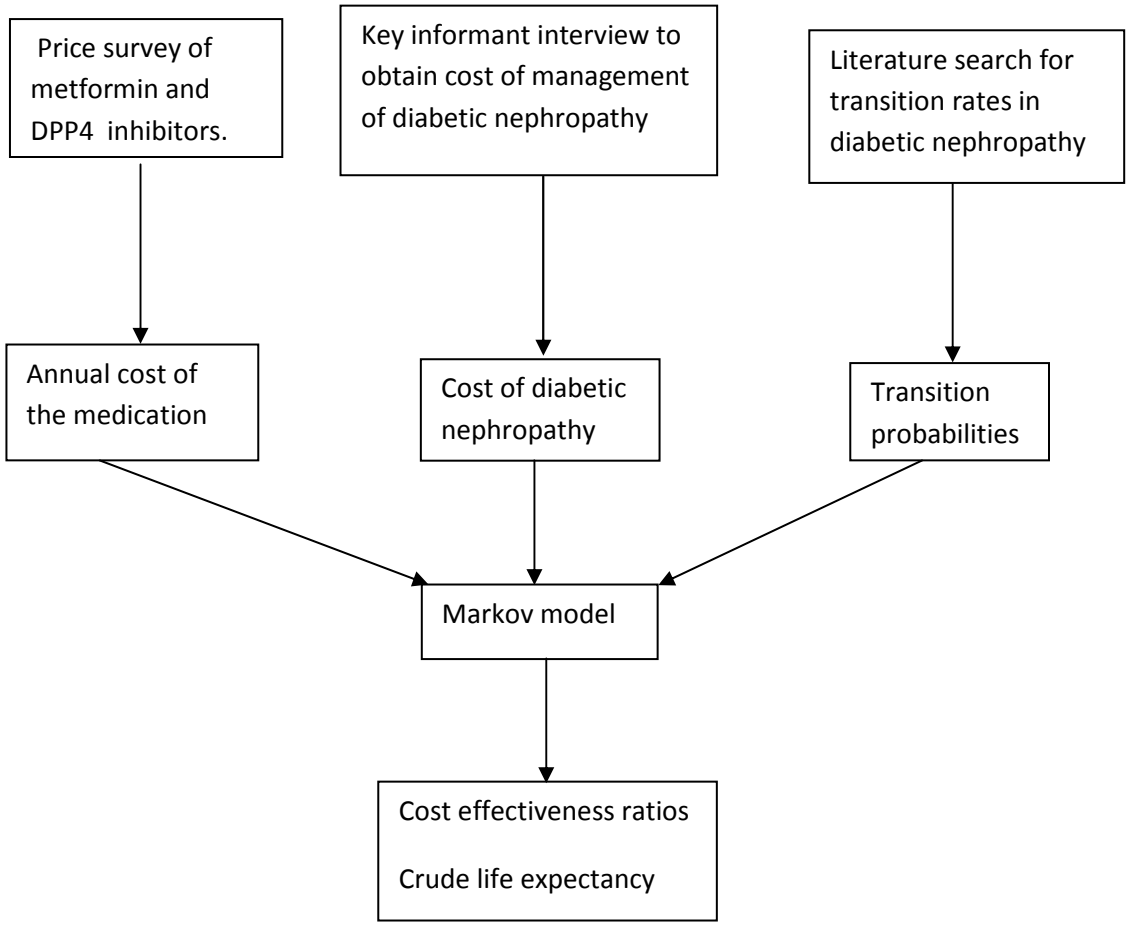


Figure 1: The conceptual framework of the cost effectiveness study.

1.4 RESEARCH QUESTIONS

1. What are the local and international prices of fixed dose combinations of metformin and DPP 4 inhibitors and of metformin monotherapy?

2. What are the 25 year cumulative costs to the healthcare system of initiating a patient on metformin monotherapy as opposed to fixed dose combination of metformin and DPP 4 inhibitors?
3. Is initiation with metformin and DPP 4 inhibitors more effective than metformin alone in delaying development of diabetic nephropathy and improving the life expectancy?
4. Does metformin/DPP 4 inhibitors fixed dose combination have a lower incremental cost effectiveness ratio compared to metformin alone?

1.5 OBJECTIVES

1.5.1 Main Objective

The main objective of this study is to compare the cost effectiveness of changing the first line therapy in treatment of T2DM from metformin monotherapy to dual therapy of metformin and DPP 4 inhibitors in drug naïve T2DM patients in a public facility.

1.5.2 Specific Objectives

The specific objectives were:

1. To obtain the local and international prices of metformin and FDC metformin/DPP 4 inhibitors.
2. To estimate the cost of treating diabetic nephropathy at the renal unit of Kenyatta National Hospital.
3. To compare the effects of initiating metformin/DPP 4 inhibitors and metformin alone in patients with diabetes with regard to life expectancy and development of diabetic nephropathy.
4. To compute the Cost Effectiveness Ratio and the Incremental Cost Effectiveness Ratio of metformin/DPP 4 inhibitors and metformin monotherapy.

1.6 STUDY SIGNIFICANCE.

The incremental cost effectiveness ratios that were illustrated in the study would enable policy makers to make an informed choice on the appropriate treatment of T2DM.

The cost of dialysis quantified in this study may be used by county governments in the implementation of their dialysis programs in the county hospitals as a tool in planning for the financing of their renal units.

Researchers may use the transition rates arrived at to design Markov processes so as to compare the interventions used for treatment of diabetes illustrated in this study with other interventions.

2.0 CHAPTER TWO

LITERATURE REVIEW

Diabetes Mellitus is a metabolic disorder characterized by chronic hyperglycemia and abnormal fat, protein and carbohydrate metabolism (9). Patients with Diabetes mellitus present with polyuria, polyphagia and polydipsia. They may also have central nervous system symptoms such as delirium and confusion. The long term complications of Diabetes Mellitus include micro vascular complications affecting the eyes, kidneys, reproductive system and the nervous system. The macro vascular complications include effects on the myocardium, peripheral vasculature and the cerebral vasculature. The types of diabetes mellitus are: insulin dependent (Type 1), non-insulin dependent (Type 2), gestational and other specific forms.

2.1 EPIDEMIOLOGY OF DIABETES MELLITUS

The number of people living with Diabetes Mellitus in the year 2013 was 382 million globally (1). The proportion of this people that were undiagnosed was 46% (1). It is projected that 592 million people will be living with the disease by 2035 which would be a 55% increase (1). The increasing numbers of patients with T2DM can be attributed to an ageing population, increased cases of obesity, inactivity and longevity of patients due to improved management especially in developed countries (10). Globally, T2DM accounts for 80% to 90% of the patients with diabetes mellitus.

Africa has the lowest diabetic population as compared to other regions as mapped by the International Diabetic Federation (IDF) (11). However, it is projected that by 2035, the numbers would increase by 109.1% (11). In Sub-Saharan Africa the proportion of undiagnosed cases is as high as 90% (2).

The prevalence of diabetes mellitus in Kenya was 3.5% in the year 2013 (1). The number of diabetic cases was estimated to be 749,250 in the same year. Mortality associated with diabetes was 20,350. The projected prevalence by 2035 will be 4.5% (1).

2.2 COMPLICATIONS OF DIABETES

Half of the patients with diabetes die of cardiovascular complications: angina, myocardial infarction, stroke, peripheral artery disease and congestive heart failure. The risk is further compounded by smoking, abnormal blood lipids and high blood pressure (11).

Diabetic nephropathy accounts for 50% of patients receiving renal transplants in developed countries (10). Diabetic mellitus retinopathy accounts for 5% of the causes of blindness worldwide. Patients with diabetes are 25 times more likely to be amputated as compared to patients without diabetes. The range of complications in diabetes mellitus is represented in Figure 2.

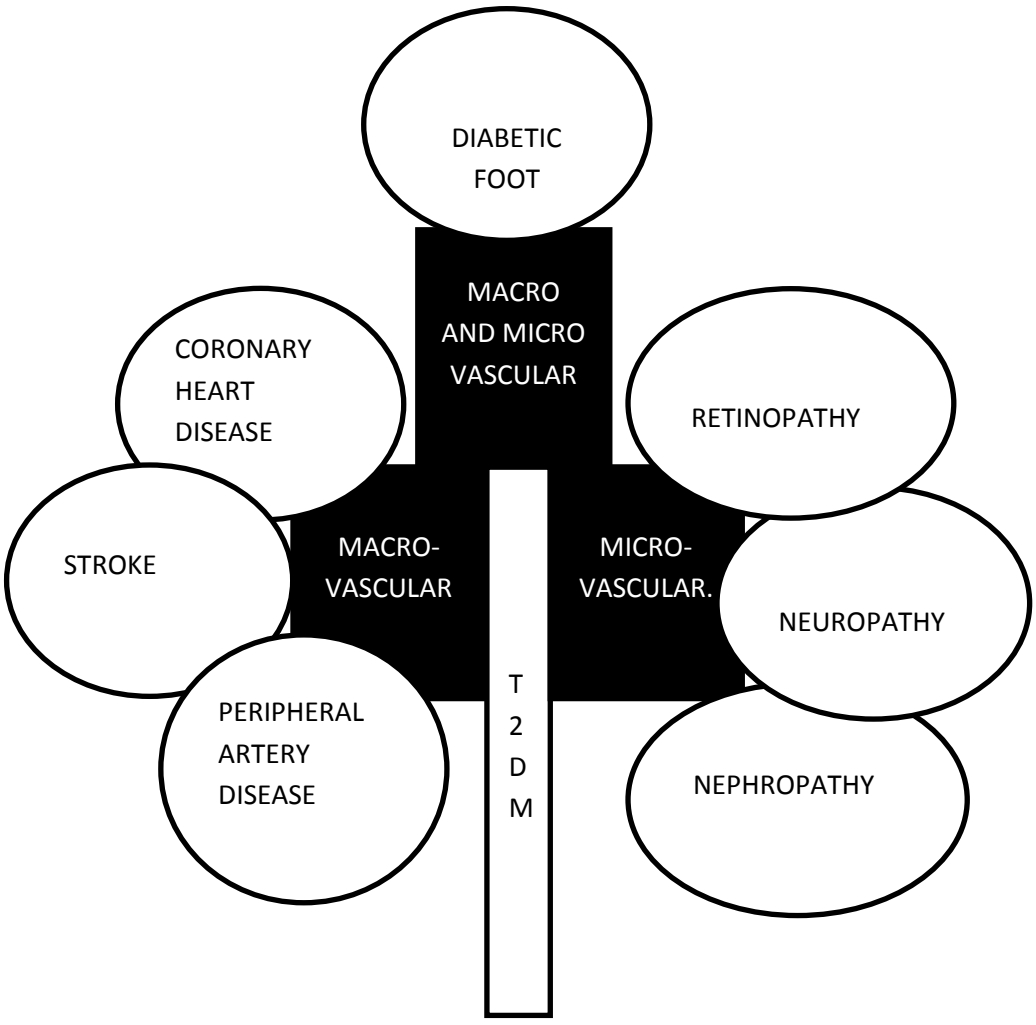


Figure 2: Complications of diabetes mellitus

2.3 Benefits of tight glycemic control

The Steno 2 study demonstrated that tight glycemic control delays development of complications (15). There was a 61% relative risk reduction in the development of nephropathy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study discouraged intensive glucose lowering in patients with high risk of cardiovascular complications due to increased mortality in the treatment group. However, a more recent meta-analysis of the effect of intensive glycemic control on mortality did not reaffirm the conclusions of the ACCORD study (17).

2.4 Economic impact of diabetes mellitus

Diabetes imposes a large economic burden on individuals, families, society and the national health systems. The annual expenditure on treatment of diabetes and its complications is projected to increase to USD 627 billion by 2035 (1). This is equivalent to 678 International Dollars (ID). An average of USD 1437, equivalent to ID 1522, per person with diabetes was spent globally in the year 2013 (1). A proportion of 20% of the total expenditure was incurred in low to middle income countries yet 80% of diabetic patients reside in these countries (1).

In Africa, USD 4 billion was spent in the treatment of diabetes and its complications. This accounted for less than 0.6% of the total global expenditure. Most of the payments were out of pocket because many insurance companies exclude diabetes in their policies (19).

In Kenya, the health expenditure for diabetes in 2010 was USD 22,334,000 (1). This was 5% of the total health expenditure in 2010. The mean health expenditure per person with diabetes was USD 43 as compared to Somalia which was USD 13 short of matching Kenya's average in 2010. The expenditure on diabetic patients in Kenya is nearly similar to that of Somalia in spite of the war in the latter country. There is a disparity between expenditure on non- communicable diseases and the infectious diseases in Kenya.

The medical and socioeconomic burden of diabetes is caused by the resultant complications (18). Globally, diabetes caused 8.4% of all-cause mortality in adults aged between 20 and 79 years. The number of deaths worldwide caused by diabetes was 5.1 million (14).

Globally, approximately 548 billion United State Dollars (USD) which constituted 11% of the total budget on healthcare in adults; was spent on diabetes. In Africa, spending on diabetes accounted for less than 1% of the global health expenditure on the disease. The number of people who died from the disease in 2013 was 522,600 which were 8.6% of deaths from all causes in adults (1).

Diabetes particularly affects those who are socially and economically disadvantaged. The estimates show that 76% of the global health expenditure in 2013 was for people between the ages of 50 and 79 years. In Kenya, most of the people in this age group are in the rural areas with no formal employment (19). This poses a great challenge in the management of the disease. Eventually, the disease is managed very poorly resulting in the early onset of complications and premature death.

The management of complications resulting from T2DM is very expensive. Macro-vascular complications occur much earlier and they form a major cost component in managing the disease. The cost of treating T2DM increases with the rate of progression to complications and the level of glycemic control. The cost increases substantially with relatively small increases in the level of $\%HbA_{1/c}$.

A prevalence study on the risk factors associated with diabetic nephropathy in Kenyatta National Hospital found that 60.1% of the patients in the renal unit had poor glycemic control in spite of 61.1% of them being on insulin therapy (20).Factors such as compliance and poor maintenance of the cold chain for insulin may be responsible for this undesirable outcome.

A cost effectiveness study on intensive glucose control concluded that patients with T2DM incur lower costs of managing complications and have a longer time to development of complications when intensive glucose control is attained but the cost of doing this is high (21).

2.5 METFORMIN

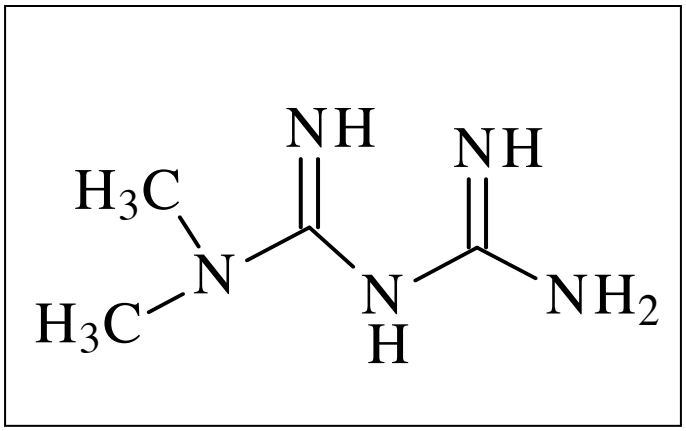


Figure 3: Structure of metformin

Metformin is the only biguanide that has been approved for use in the treatment of hyperglycaemia (3). Patients on this drug have lower rates of cardiovascular disease and mortality compared to patients on sulphonylureas (25). Metformin delays progression to diabetes in persons with impaired glucose tolerance. It has also been used in treatment of infertility in women with polycystic ovarian syndrome. It improves ovulation and menstruation cyclicity and reduces circulating androgens and hirsuitism (25).

The most common adverse effects associated with metformin are gastrointestinal. About 10% to 25% of patients initiated on metformin complain of nausea, indigestion, abdominal cramps or bloating (25). Use of metformin is also associated with 20 to 30% lower blood levels of vitamin B_{12} but no neurological consequences have been reported. The incidence of lactic acidosis with motorman is between 0.003% and 0.006%. This is not a significant difference when compared to other hypoglycemic drugs. Metformin should be discontinued if it is anticipated that renal function could be precipitously impaired such as before radiological procedures that use contrast dyes, in severe pulmonary disease, decompensated heart failure, severe liver disease and fulminant diarrhea leading to dehydration. Most studies have demonstrated that metformin monotherapy results in a 10% to 30% reduction in basal hepatic gluconeogenesis and a 15% to 40% increase in insulin stimulated whole body glucose uptake (3). Metformin therapy resulted in a reduction of 0.6% to 2% of $\%HbA_{1c.}$ This decline is abolished within five years of monotherapy.

In the United Kingdom Prospective Diabetes Study (UKPDS) there was a 32% reduction in risk of any diabetes related complication and a 42% reduction in diabetes related deaths with the use of metformin (26). In preclinical studies, metformin has been found to increase plasma glucagon like Peptide 1 (GLP 1) levels in a dose dependent manner even in the presence of DPP 4 inhibitors (27). This demonstrates that the effects of dual therapy of DPP inhibitors and metformin is additive.

2.6 The role of Glucagon like Peptide 1 agonists in diabetes

Glucagon like Peptide 1 and Glucose Dependent Insulinotrophic Peptide (GIP) are the best known incretins. GLP 1 is effective in stimulating insulin release and lowering blood glucose in T2DM patients (28). At supraphysiologic quantities, GLP 1 stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, reduces food intake and normalizes fasting and postprandial insulin secretion. Its insulinotropic effect is glucose dependent. GLP 1 is rapidly inactivated by DPP 4 with plasma half-life ($T_{1/2}$) of 1 to 2 minutes (28).

Two therapeutic applications of GLP1 actions have been adopted: development of an injectable, DPP 4 resistant, peptide agonist of the GLP 1 receptor and development of DPP 4 inhibitors (29).Exenetide (BYETTA) $^{(R)}$ and liraglutide (VICTOZA) $^{(R)}$ are GLP 1 agonist marketed as pens. Sitagliptin (JANUVIA) $^{(R)}$ saxagliptin (ONGLYZA) $^{(R)}$, vidagliptin (GALVUS) $^{(R)}$ and alogliptin (NESINA) $^{(R)}$ are DPP 4 inhibitors in the global market.

The major adverse effects associated with GLP 1 agonists are gastrointestinal (11). Since they delay gastric emptying, drugs that require rapid absorption at the gastrointestinal tract (GIT) have an altered pharmacokinetic profile if administered with GLP 1 agonists. The drugs have also been associated with pancreatitis including fatal and not fatal hemorrhagic or necrotizing pancreatitis (29).

DPP 4 is expressed as an ectoenzyme on the endothelial cells surface of T lymphocytes and in circulating form (32). It inactivates both GLP1 and GIP. Sitagliptin and alogliptin are competitive inhibitors of DPP 4. Vidagliptin and saxagliptin bind the enzyme covalently. At appropriate doses they lower the activity of DPP 4 by more than 95% for 12 hours which doubles the concentration of GLP 1 and GIP leading to increased insulin secretion, reduced glucagon

levels and improvement in both postprandial and fasting glucose levels. Their effect on DPP 4 inhibitors are additive when combined with metformin, a thiazolidinedione or a glitazone. Increased incidences of upper respiratory tract infections in patients taking DPP 4 inhibitors have been reported. This has led to speculation on the possibility of immune suppression caused by the drugs, but in some studies, the difference with incidences in patients taking placebo is insignificant. (29)

2.7 Metformin and DPP 4 inhibitors

Reasner et al compared the efficacy and safety of sitagliptin/metformin FDC with that of metformin monotherapy in patients with T2DM. The reduction in $\%HbA_{1c}$from baseline at the eighteenth week of therapy in the FDC group was: - 2.4 (95% CI-2.5, -2.2) and 1.8 (95% CI -1.9, -1.6) in the group on metformin monotherapy. The decrease from baseline in fasting glucose was -3.8mmol/1 with the combination therapy and -3.0mmol/1 with metformin monotherapy. There was improved beta cell function as measured by the Homeostatic Model Assessment (HOMA) β unit. The body weight loss and the lipid profiles were comparable in both groups. There was a higher incidence of GIT effects in the metformin monotherapy group.

Combination therapy of metformin and DPP 4 inhibitors can easily be administered since it is an oral agent (33). As compared to metformin/sulphonylurea combination, which is the recommended regimen in drug naïve patients in Kenya, DPP 4 inhibitors are weight neutral and have a low risk of causing hypoglycaemia. Thiazolidinediones cause fluid retention, weight gain, may cause cardiac failure and they increase the risk of bone fractures in post-menopausal women. The American Diabetes Association and the European Association for the study of Diabetes (ADA/EASD) released a consensus statement recommending a stringent target of 6.5% $HbA_{1c}$for patients with short disease duration, long life expectancy and no significant cardiovascular disease (8, 5). These characteristics are likely to be present in drug naïve patients. To attain the recommended $\%HbA_{1c,}$ dual therapy at initiation is very viable (33). It is recommended when a patient is unlikely to achieve target $\%HbA_{1c}$ andwhen $\%HbA_{1c}$ is high. Since most diabetic patients in Kenya will be diagnosed upon admission in hospital (14), Initiation of the dual therapy will drastically reduce $\%HbA_{1c}$ as recommended.

3.0CHAPTER THREE

METHODOLOGY

The study was divided into three sections: A local and international price survey, a key informant interview and a model based cost effectiveness study (Markov model).

The findings of the first two studies were used to model the long term cost of managing diabetic nephropathy using a Markov model.

3.1 Local and international price survey of metformin and DPP4 inhibitors.

3.1.1 Study design

A cross sectional study design was used in this study. A survey was done on the acquisition price of metformin/DPP 4 inhibitors FDCs and Metformin. For each medicine, data on the prices of the originator brand and the lowest priced generic version of the drug was collected.

3.1.2 Study population and study site

The study population was the distributors of metformin and DPP 4 inhibitors in Nairobi county. The survey was conducted in the month of July 2015. Nairobi county was chosen as a study site because it is the capital city of Kenya and the median prices of the drugs were a reflection of the prices of the drug in the entire country.

3.1.3 Inclusion and exclusion criteria

The distributers were contacted if they met the following criteria: If they were registered distributors and if they distributed any brand of FDC of Metformin/DPP 4 inhibitors or any Metformin brand. The exclusion criteria were that of distributors who refused to participate in the survey and those whose brands were not in the Kenyan retail shops.

3.1.4 Sample size determination

A census was undertaken for the price survey of FDC dipeptidyl peptidase inhibitors and metformin. This approach was used because the anecdotal evidence indicated that there were very few distributors of the FDC metformin/DPP 4 Inhibitors in Kenya.

3.1.5 Participant recruitment

A list of all DPP 4 inhibitor, metformin and the FDC distributors was obtained from the Pharmacy and Poisons Board. Distributors who consented to participating in the interview and had their brands in the retail shops were requested were recruited for the study.

3.1.6 Data collection

Data was collected by visiting the distribution companies and filling the forms attached in Appendix 05. The distributors were also requested to avail their price lists.

3.1.7 Variables

The dependent variable was the unit trade price of acquiring the drugs. The independent variables were: country from which the drug was imported; whether the drug was an originator brand or a generic brand; pack size of the drug and type of formulation that is if it was a sustained release formulation or not.

3.1.8 Data analysis

Data were analyzed using STATA 2011 version and Microsoft Excel 2007. The data were entered into Microsoft Excel 2007 and transferred to STATA 2011 for further analysis. The factors affecting the price of the drug were determined at a level of significance of 95%. The p-value therefore did not exceed 0.05. A regression analysis was conducted and a parsimonious model arrived at.

3.2 Key informant interview to obtain cost of dialysis

The second part of the study was a key informant interview. The objective of the interview was to identify and quantify the resource inputs for dialysis at KNH.

3.2.1 Study design

A qualitative cross sectional study design was used.

3.2.2 Study site

The study site was the Renal Unit at Kenyatta National Hospital. KNH is the largest hospital in East Africa and at the time of the study it was the only public facility offering dialysis services in Nairobi County.

3.2.3 Study population and sample size determination

The study populations were the employees at the renal unit of Kenyatta National Hospital.

The interviewees were the administrative personnel involved in the procurement of resources used in the renal unit, clinicians who provided care to patients diagnosed with diabetic nephropathy and nursing officers who were in charge of the renal department.

A sample size of 4 was adequate for this key informant interview. Data collection continued until saturation was achieved.

3.2.4 Inclusion criteria for the key informant interview

The inclusion criteria were any healthcare worker in an administrative position involved in procurement and planning; the healthcare worker must have been in the renal department for at least 6 months and the health care worker had to consent to the interview.

The exclusion criteria were health workers who did not give their consent; those who were not working at the renal department at the time of study and administrators who were not providing direct clinical services.

3.2.5 Sampling method and participant recruitment

Purposive sampling was used whereby participants who met the inclusion criteria were sought and approached through the use of a phone and followed up by a visit. In the first visit the researcher introduced himself and gave the potential interviewee a detailed explanation on the

purpose of the study. The participants were then requested to give their consent without coercion. The participant was requested to select an appropriate time and venue for the interview.

3.2.6 Data collection for the key informant interview

The interview was conducted the principal investigator. He took written notes while conducting the interview. The participants were asked if they were comfortable if the interview was recorded using a digital recorder. The interview was guided by the appended interview guide in appendix 3. The guide was designed to identify the resource inputs used in dialysis from the perspective of the health provider.

3.2.7 Data management and quality assurance

A pilot study was conducted to evaluate the data collection forms. Amendments to the forms were made from lessons accruing from the study. Comparisons were made of the data in the voice recorder and those in the written notes and any errors were corrected.

At the end of each interview the audio tapes were transcribed within 24 hours and the audio record destroyed to ensure that the interviewee remained anonymous. The interview was transcribed into a word document. The documents were always backed up using a flash disk.

Data cleaning and validation were done by correcting transcription errors. Backup of data were always done using a flash disk. All information obtained remained confidential.

3.2.8 Data analysis

The cost component of treating diabetic nephropathy was extracted from the interviews. The total annual cost of dialysis was determined relying on the Key Informant Interview as well as the current available literature. Grounded theory was used to analyze the data.

The data obtained was analyzed using Microsoft Excel version 2007.

3.2.9 Ethical considerations

Ethical approval was obtained from Kenyatta National Hospital and the University of Nairobi Ethical review committee (KNH/UoN-ERC). (P140/03/2015)

The respondents of the key informant interview were given detailed explanation of the study and were only interviewed after they consented by signing the information consent forms attached in Appendix 4.

3.3 Modeling of costs and effectiveness of metformin and metformin/DPP 4 inhibitors.

The aim of this study was to compare the cost and effectiveness of metformin monotherapy and metformin/DPP 4 inhibitor dual therapies in drug naïve type 2 diabetes mellitus patients in a public facility. In this case the renal unit of Kenyatta National Hospital was the facility used. This study used a Markov model stochastic process. This process has health states that have transition probabilities from one health state to the other and that are mutually exclusive.

3.3.1 Description of Markov model

A Markov model is a probabilistic process in which the future behavior of the system depends only on the current state and not on any other of the previous states. In this study the health states of the patients suffering from diabetic nephropathy were mutually exclusive, time homogenous states with transition probabilities from one state to the other. There were five transition states which were:

The first state is where the patient has no microalbuminuria, no macroalbuminuria, no persistently elevated plasma creatinine and no need for renal replacement. No renal complication. This state is denoted as N_o.

The second state is where the concentration of albumin in urine is more or equal to 50mg/L but less than 300mg/L and the plasma creatinine concentration is less than 175μmol/L. This state is denoted as N_1.

The third state is where the patient has a concentration of urine albumin that is more or equal to 300mg/L and plasma creatinine concentration of less than 175μmol/L.this state will be denoted as N_2.

End Stage Renal Failure is the fourth state. The plasma creatinine concentration at this state is more than 175μmol/L. it is denoted as N_3.

Finally the fifth state is death from any cause. This state is an absorbing state, a state in a Markov chain is called an absorbing state if once the state is entered it is impossible to leave. The power of the transition matrix approaches a limiting matrix. This state has been denoted as D_4.

This study assumed that if all other factors affecting progression of diabetic nephropathy are held constant, the $\%HbA_{1c}$ of the patient will be directly proportional to the rate of progression of diabetic nephropathy.

The transition probabilities used in this study were adopted from the UKPDS 64 study (9) due to lack of studies that record the Kenyan transition rates. These rates were derived from annual transition rates with 95% confidence intervals as illustrated in Table 3.1. The cycle length for this study was therefore one year. The UKPDS 64 study was a longitudinal study conducted from 1977 to 1997. During this time, the drug of choice for the treatment of diabetes mellitus in drug naive patients was metformin. The transition rates were therefore a representation of the expected rates in patients taking metformin monotherapy.

Table 3.1: A matrix of transition rates from one of diabetic nephropathy patients taking metformin monotherapy.

State	**N_0 (%)**	**N_1 (%)**	**N_2 (%)**	**N_3 (%)**	**D (%)**	**Totals (%)**
N_0 (%)	96.4(96.2-96.6)	2.0(1.9-2.2)	0.1(0.2-0.2)	0.1(0.0-0.1)	1.4(1.3-1.5)	100
N_1 (%)	0.6(-1.4-1.5)	93.3(93.3-94.4)	2.8(2.5-3.2)	0.3(0.1-0.4)	3.0(2.6-3.4)	100
N_2 (%)	0	0	93.1(91.8-94.4)	2.3(1.5-3.0)	4.6(3.6-5.7)	100
N_3 (%)	0	0	4(2.2-5.6)	80.8(75.6-86)	19.2(14.0-24.4)	100
D (%)	0	0	0	0	100	100
Totals (%)	100	100	100	100	128.2	

3.3.2 Study design

The study design was a predictive based cost effectiveness study. A Markov chain was used as the model. This study design was used because it synthesizes the available evidence and

forecasts the costs and effectiveness of the two comparator groups. The transition probabilities that were used were obtained from the landmark UKPDS study.

3.3.3 Time horizon

This study was modelled in a time horizon of 25 years. This horizon was selected because the progression of diabetic nephropathy from diagnosis to death was estimated to be 35 years (9). The African population progressed faster to end stage renal failure (10).

3.3.4 Comparator groups

The study focused on a theoretical cohort of 10000 drug naïve diabetic patients in Kenya. The two comparator groups were: patients on metformin and patients on metformin/DPP 4 inhibitors.

3.3.5 Costing methodology

A macro-ingredient approach of costing was used to determine the cost of managing diabetic nephropathy at the various transitional states. The resources to be used were first identified and then the quantities required were determined and finally the value of the resources used collated**.**

3.3.6 Measures of effectiveness

The measures of effectiveness used in this study were the life expectancy and 25 year survival rate.

3.3.7 Data analysis

The future costs and utilities were not discounted since both arms of the intervention would have been discounted at the same rate therefore the effect of discounting would be neutered.

3.3.7.1 Generation of cycle profile.

Using the matrix in table 3.1, the cohort of patients was redistributed over a period of 25 years. The cohort was of 10,000 patients suffering from type 2 diabetes mellitus.

The cycle profile of transition probabilities for a 25 year time frame are attached in the appendices 5 and 6. These distribution was calculated using the formula stated:

$A_{(n+1)} = A_n \times T^n$……..**Equation 1**

Where:

A is the number of people in the n^{th} cycle.

T is the transition matrix.

n is the duration of the Markov cycle.

3.3.7.2 Calculation of life expectancy.

Life expectancy= $\frac{\text{Length cycle } \mathbf{X} \text{ patients alive}}{\text{Cohort size}}$ **uation 2**

The formulae below were used to calculate the ICER:

ICER=. $\frac{C_{M/DPP4I} - C_M}{Q_{M/DPP4I} - Q_M}$ ……...……**Equation 3**

Where:

$C_{M/DPP\ 4I}$was the total expenditure incurred in acquisition of metformin and DPP 4 inhibitors.

C_M was the total expenditure incurred in acquisition of metformin.

$Q_{M/DPP\ 4I}$ was the life expectancy of a patient on metformin and DPP 4 inhibitors.

Q_M was the life expectancy of a patient on metformin.

3.3.8 Presentation of data

Data were presented using an output table and graphical survival curves which represented the two interventions.

4.0 CHAPTER FOUR
RESULTS

This chapter is divided into three sections. The first is a price survey of metformin and DPP 4 inhibitors. The second are the findings of key informant interviews that sought to determine the costs incurred by patients with acute and chronic kidney failure undergoing dialysis as a result of long term diabetes mellitus. The last section presents the findings of a cost utility analysis that compared the cost effectiveness of metformin monotherapy versus metformin/ Dipeptidyl Peptidase 4 inhibitors and finally the results of aMarkov model that has been used to estimate the long term cost of treating diabetes mellitus are highlighted.

4.1 SURVEY OF THE PRICES OF METFORMIN AND DIPEPTIDYL-PEPTIDASE 4 INHIBITORS IN THE KENYAN MARKET

The Drug and Registration Department of the Pharmacy and Poisons Board provided a list of 46 registered distributors of metformin and DPP 4 inhibitors. Twenty of these distributors met the eligibility criteria for inclusion. The excluded distributors did not have their brands in the market at the time of the study. Fourteen of the distributors responded and filled the form in appendix 4. The remaining six did not respond to requests to participate in the study.

4.1.1 Prices of Metformin

The local prices of metformin obtained from the survey are illustrated in Table 4.1. The international prices of Metformin were obtained from the International Price Indicator Guide of 2014 (Management Sciences for Health, 2014) (42). The MSH guide pools together information from recent price lists of large nonprofit generic medicine suppliers. It therefore reflects the prices the government could be expected to pay for the medicines. The comparison of the prices shows that the international prices are lower than the local prices. This is reflected by the median price ratio (table 4.1). The prices of one gram of metformin are not provided in the international price indicator guide. The quoted prices are the international buyer prices which include the cost of shipment. The difference in the international prices may partly be due to the fluctuation of the exchange rate of the dollar which stands at Kenya shillings (KSh) 102 in the year 2015but the value of the USD was 85 shillings per dollar when the 2014 indicator guide was published. A comparison of the prices of different strengths of metformin is represented in the form of a box

and whisker graph (Figure 4.1). It demonstrates that the prices of metformin increases with increasing strength.

Table 4.1 Local and International prices of metformin.

Strength.	Local price Median(IQR) per tablet	International reference price per tablet	Highest:lowest (local prices)	Highest:lowest (international prices)	Median price ratio (MPR)*
500mg(Kush) (USD)	3[2,6.5]	2.3[0.9,3] 0.02[0.03,0.01]	5.33	3.21	1.304
850mg(Kush) (USD	7.5[3,12]	0.89[0.53,3.57] 0.01[0.006-0.04]	6.667	6.662	8.42
1000mg(KSh)	14[14,15.5				

*MRP is the ratio of the local median price to the international median price.

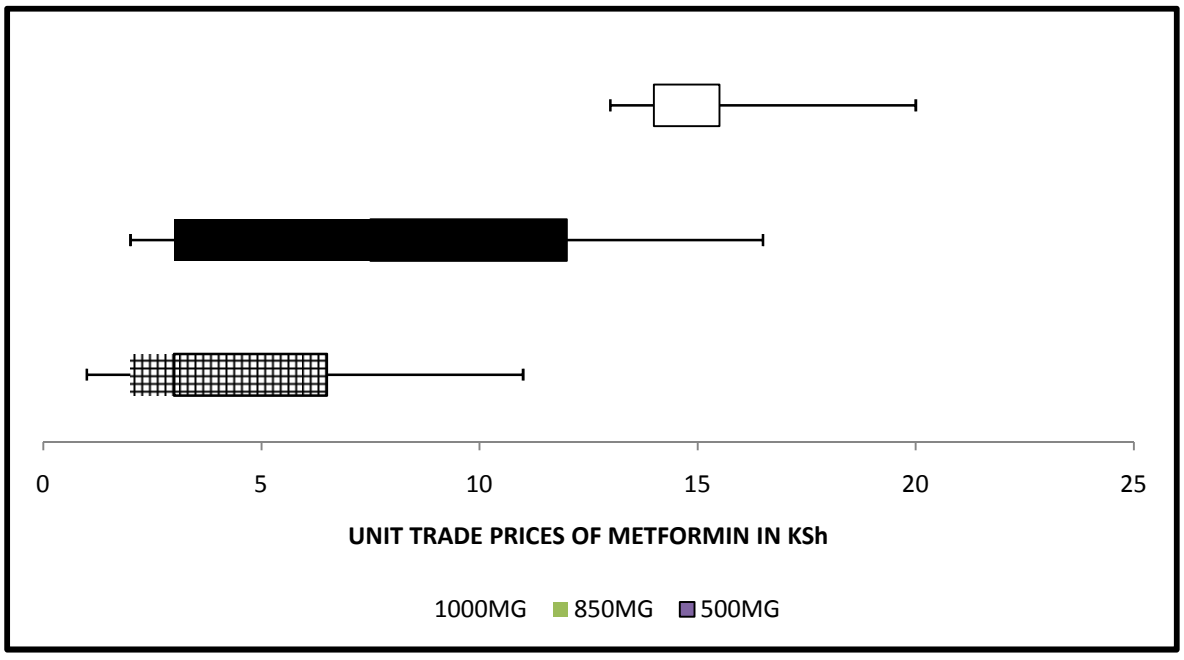
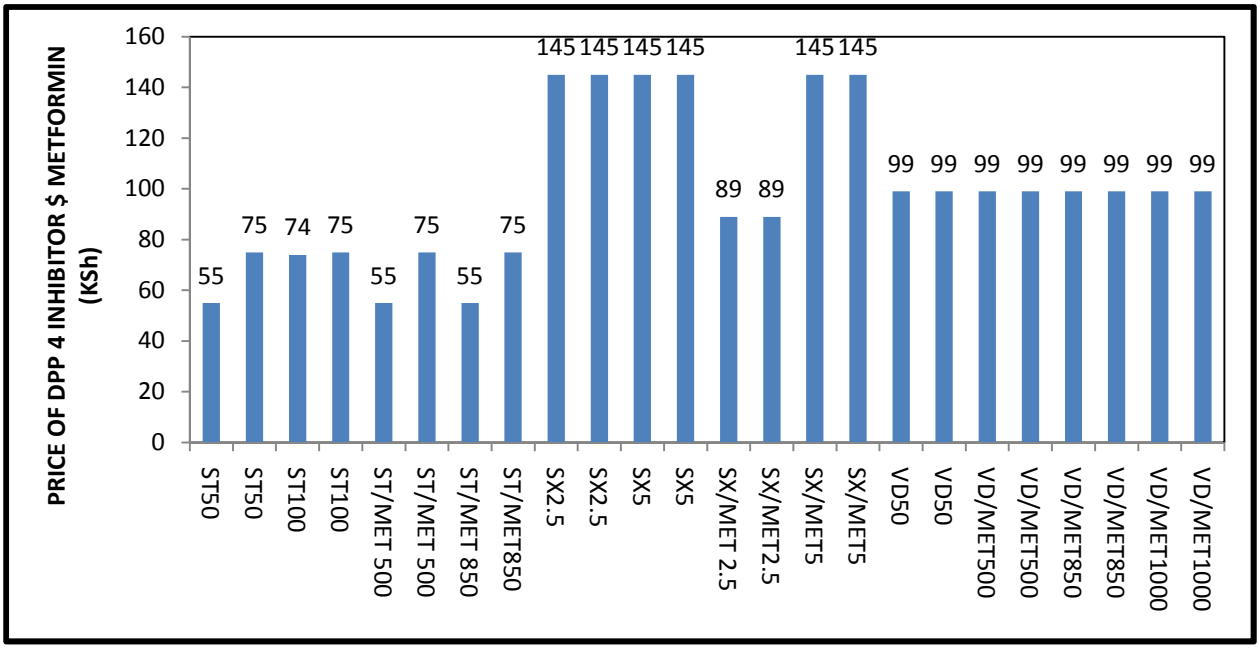


Figure 4: A box and whisker graph of local prices of metformin.

4.1.2 Prices of Dipeptidyl Peptidase Inhibitors

There are two major importers of Dipeptidyl peptidase 4 inhibitors in Kenya. The other distributors purchase the drug from these major distributors at a discounted rate as compared to the retailers. The prices have been illustrated using bar graphs. Figure 4.2 is a bar graph of all the 24 prices obtained during the survey. The prices of these products did not vary with the strength of the products. Three brands of single dose formulations were found in the market each of these brands had two different dosages. The fixed dose combinations had different metformin strengths but the same DPP 4 inhibitor strengths for two brands while one brand had different strengths of the DPP 4 inhibitor but same strength of metformin.



ST:Sitagliptin.ST/MET:Sitagliptin/Metformin.SX:Saxagliptin.
SX/MET:Saxagliptin/Metformin. VD:Vidagliptin.VD/MET:Vidagliptin/Metformin.

Figure 5: A bar graph of the unit cost of DPP 4 inhibitors and Fixed Dose Combinations of metformin and Dipeptidyl Peptidase 4 inhibitors.

The graph in Figure 4.2 highlights the difference of the DPP 4 inhibitor drug prices. The prices of the drugs do not vary with the strength of the drug or the distributing company. The sitagliptin based products were cheaper followed by the vidagliptin products while the saxagliptin based products were the most expensive. There is no international reference price for Dipeptidyl

peptidase 4 inhibitors in the international price indicator guide by MSH (Management Science for Health), WHO (World Health Organization) and HAI (Health Action International).

Table 4.2 illustrated the local prices of DPP4 inhibitors single dose formulations and fixed dose combinations of DPP 4 inhibitors and metformin.

Table 4.2 Prices of Dipeptidyl Peptidase 4 Inhibitors and their combinations.

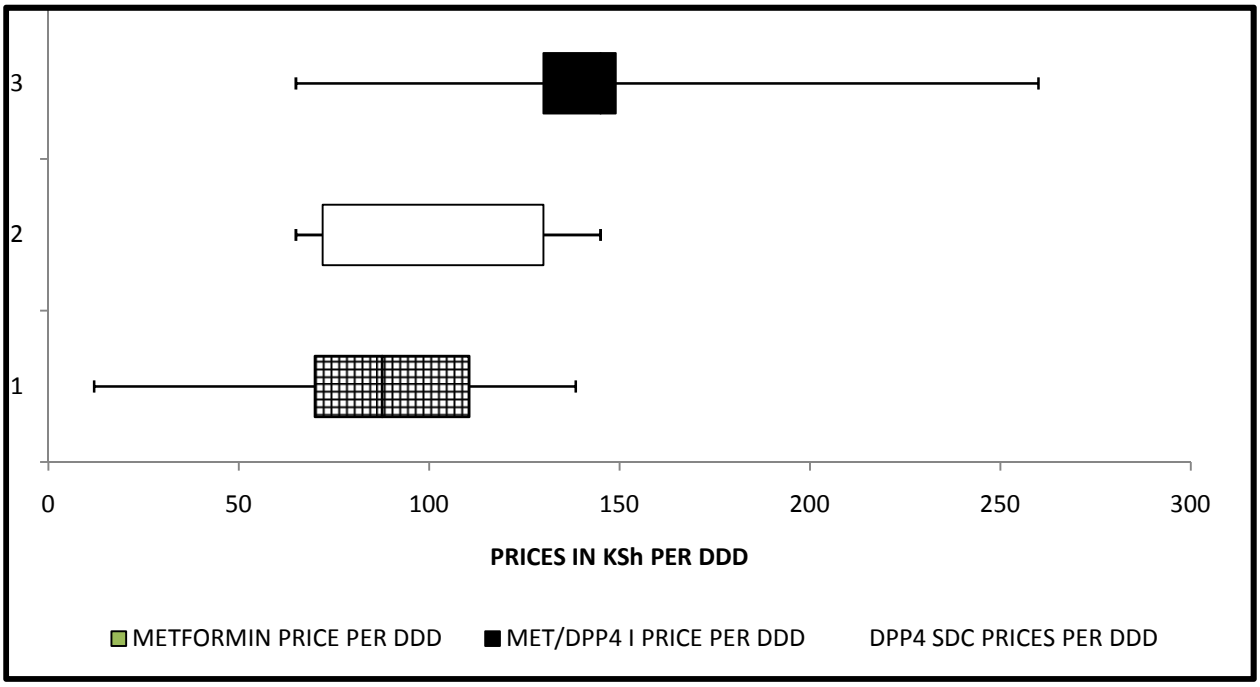
Name of the drug	Strength	Price in KSh [mean] n=2
Sitagliptin	50mg	65
	100mg	75
Vidagliptin	50mg	65
Saxagliptin	2.5mg	65
Saxagliptin	5mg	145
Sitagliptin/metformin	50/500	65
	50/1000	74.5
Vidagliptin/metformin	50/1000	99
	50/850	99
	50/1000	99
Saxagliptin/metformin	2.5/1000	145
	5/1000	145

The prices of the drugs do not vary with the strength of the drug. There is no price difference among the two distributors whose prices are illustrated in Figure 4.2.

4.1.3 Daily cost of DPP 4 inhibitors and metformin.

The daily cost of the drugs to patients was calculated using the Defined Daily Dose (DDD). Figure 4.3 is a box and whisker graph of the prices of the drugs per Defined Daily Dose.

There is an increase in the cost per DDD as the formulation changes from single dose formulation of metformin and DPP 4 inhibitor single dose formulation to fixed dose combination formulations of metformin and DPP 4 inhibitors.



Defined Daily Dose (DDD) is the average maintenance dose of the main indication of the drug for adults(43).

Figure 6: A box and whisker plot of the prices of DPP 4 inhibitors and metformin per Daily Defined Dose.

4.1.4 Factors affecting the prices of metformin and DPP 4 inhibitors.

Known factors that determine the prices for medication were evaluated for their impact on the prices of metformin and DPP 4 inhibitors. We did a comparison across different strengths, pack sizes, country of importation and type of brand (whether the drug is an originator brand or a generic brand.) This comparison is presented in the table 4.3.

Table 4.3 Summary statistics of the factors affecting the prices of DPP 4 inhibitors and metformin

Drug		Variable	Median[IQR] n[c]	P-value
Metformin HCl	Strength of drug	500 mg 850 mg 1000 mg	3[2-7],15 9.5[4-16],6 14 [12.517],4	<0.05
	Country of origin	Local Indian European	1[3] 3[2-3],14 16[15-22],9	<0.05
	Pack size of drug	30 60 90 100	20[15-24],6 8[5-15],6 1[7] 3[2-3]11	<0.05
Dipeptidyl peptidase 4 inhibitors [a]	Type of drug	Sitagliptin Saxagliptin Vidagliptin	74.5[64.5-75]4 4[145] 2[99]	<0.05
	Pack size of drug	14 30 56	74.5[64.5-75]4 4[145] 2[99]	<0.05
Metformin/DPP 4 Inhibitors.[b]	Type of drug.	Sitagliptin/metformin Saxagliptin/metformin Vidagliptin/metformin	[75]2 [145]2 [99]6	<0.05

[a]SDF single dose formulations.[b]FDC fixed dose formulations[c]n Number of distributors

From this analysis, as the strength of metformin increased, the prices also increased. The analysis also showed that the prices of the drugs imported from Europe were higher than the prices of drugs manufactured locally and those imported from India. The larger packsizes of the drugs are also cheaper than the small pack sizes and the cost of the FDCs is more than that of the SDFs. A regression analysis was done. The analysis was conducted on the metformin prices since the prices of the DPP 4 inhibitors had very few variables. The results of the regression analysis are illustrated in Table4.4.

Table 4.4 Bivariable and multivariable analysis of factors affecting prices of drugs

Bivariable Analysis				**Multivariable Analysis**	
variable	Crude β coefficient value (95%CI)			Adjusted β coefficient (95%CI)	P-value
Pack sizes	4.855	(2.40,7.30)	0.000	-0.078 (-0.117,-0.039)	0.00
Strength	-0.0125	(-0.18,-0.07)	0.000	-1.026 (-0.817,-2.839)	0.259
Country	4.855	(5.38,10.71)	0.000	6.096 (3.83, 8.35)	0.000

Unit trade price=24.16 + 6.096 **Country** - 0.078**Pack size**

The model above can be used to explain the variation in metformin prices in this survey. The country from which the drugs are imported has the largest β coefficient which is also statistically significant. This variable is similar to the originator and generic variable since most generics are obtained from India and the originator brands are from Europe. The strength of the drug has a statistically insignificant β coefficient which may be attributed to the fact the strength of a drug is not a major price determinant.The packsize has an inverse relationship with the unit trade price of the drug implying that drugs with a large pack size are cheaper than those packed in small quantities.

4.2 COST OF DIALYSIS - KEY INFORMANT INTERVIEW.

Four respondents, at the renal unit of Kenyatta National Hospital, were interviewed. The purpose was to obtain the cost of pharmaceutical and non-pharmaceutical resources used in managing patients on dialysis. Information was also obtained on the indirect costs to patients and the cost of managing complications that arise during dialysis.

4.2.1 Management of acute and chronic dialysis patients.

The respondents indicated that a sub-clavian catheter was inserted if patients had acute renal failure and chronic renal failure patients had a permanent catheter. They underwent two, four hour sessions of dialysis depending on their kidney function test results. The costs incurred by the acute and chronic renal failure patients on dialysis were found to be different. The patients on acute renal failure dialysis paidKSh20900 (234.1 IUD) for the first session and KSh10000 (112

IUD) for the remaining weekly sessions. The chronic renal failure patient paidKSh28000 for the for the dialysis procedure. A breakdown of the components of the cost incurred by the two categories of patients is presented on Table 4.5.This costs were confirmed to be true from a charge sheet obtained from the procurement department of Kenyatta National Hospital.

Table 4.5 Cost incurred by chronic and acute dialysis patients.

Patient Category	Cost component	Cost(KSh2014)	[a]IUD(2014)
Chronic dialysis.	Permanent catheter.	18000	379.8
	Insertion procedure.	5000	105.5
	Dialyzer	1700	35.9
	Bicarbonate cartridge	1000	11.2
	Diluent of bicarbonate.	550	6.2
	Bloodline	750	8.4
Total		28000	313.6
Acute dialysis.	Subclavian catheter	10900	122.1
	Insertion procedure	5000	56
	Dialyzer	1700	19.4
	Bicarbonate cartridge	1000	11.2
	Diluent of bicarbonate.	550	6.2
	Bloodline	750	8.4
Total		20900	234.1

[a]IUD-International United States Dollar

The subsequent dialysis sessions that the patients went through was charged at KSh5000 per session.This cost was taken to be equivalent to the non-pharmaceutical cost incurred by the hospital per dialysis patient. The monthly cost was KSh58,000 (IUD650) for chronic dialysis patients and KSh50,900 (IUD570.1) for acute dialysis patients.

4.2.2 Cost of management of complications of dialysis

From this study complications of hemodialysis were classified into complications associated with: hemolysis equipment, cardiovascular system, neurological system, anticoagulant therapy, electrolyte abnormalities, and others complications like nausea, vomiting and itching. Table 4.6 lists the complications, their remedies and the cost of management. An estimate of the cost of complications was obtained based on the product of the respondents' estimation of the number of incidences of occurrence of the complication per week and the cost of treatment per patient. For rare complications a factor of 0.1 was used as the number of incidences of occurrence of the complications per week. This was based on the key informants' assertion that she could not

recall an occurrence of the complication in the past six months even though she has encountered one. This costs were further ascertained from a price list obtained from the pharmacy department.

Table 4.6 Cost of treating complications during dialysis

Complication category	**Complication**	**Incidence per week**	**Remedy (treatment)**	**Cost per week. (KSh)**	**Overall cost per week (KSh)**
Complications associated with dialysis equipment.	Air embolism	Rare (0.1)	Hyperbaric oxygen (100%)	350	9000
	Type A and B hypersensitivity reactions	1	Adrenaline Methyl prednisolone Chlorpherniramine	50	2600
Cardiovascular complications.	Anaemia	924	Erythropoietin Intravenous iron	4550	18200
	Hypertension	400	Rennin Angiotensin blockers. B blockers		
	Arrhythmias	Rare(0.1)	Defibrillators		
Neurological complications.	Disequilibrium syndrome	Rare	Urea Sodium	500	500
Complications of anticoagulant therapy.	Heparin associated thrombocytopenia Bleeding diathesis	Rare Rare	Lepirudin Danaparoid Protamine sulphate	1250	1250
Electrolyte abnormalities	Hyperkalemia	200	Potassium binding resins	500	500
	Hypokalemia Hypocalcaemia Hypercalcaemia Hyponatremia Hypernatremia	3 1 2 2 1	Thorough monitoring of electrolyte balances.		
Musculoskeletal system	Muscle cramps	200	Calcium gluconate	250	250
Totals					21800

The hospital did not incur the cost of managing some of the complications. Patients were advised to source for their own medicines. For instance intravenous iron and erythropoietin was not provided to the patient. The cost of treating complications was taken to be equivalent to the pharmaceutical cost incurred by the hospital per week in the management of the patient. The monthly cost of managing complications per patient was therefore found to be KSh87,200 (IUD 203.8).

4.2.3 Overhead costs incurred by the provider.

The overhead costs incurred by the renal unit per month are in the Table 4.7. The consumption of water was approximated to be 180 liters per day. At KSh 21 per liter, the cost of water was KSh 16200. Electricity was KSh 6000 per day. The miscellaneous bills were charged at 30% of the total overhead cost. The cost of the space used was a modest estimation of the amount of rent the interviewee would be willing to pay for the building housing the renal unit. This costs were confirmed from previous bills obtained from the nursing department of Kenyatta national hospital.

Table 4.7 overhead costs incurred per month

Overhead cost	**Amount per month.(KSh)**	**Amount in IUD**
Electricity bill	180000	2016
Water bill	113400	1270
Stationery	30000	336
Cost of space	50000	560
Miscellaneous	112020	1354.6
Total	485,420	5436.7

This cost was also divided by the number of patients seen per month so as to obtain the overhead cost incurred per patient per month which was found to be KSh270.

4.2.4Personnel costs incurred by health care providers.

The renal unit had members of staff who were permanently deployed and those who were deployed elsewhere but offered their services when called to the unit. Table 4.8 presents the cost incurred by the hospital on permanently deployed employees at the renal unit and Table 4.9 is for the employees who were temporarily deployed.

Table 4.8 Personnel cost for permanently deployed staff at the renal unit.

Cadre	Number	Gross monthlySalaries(KSh)	Total annual salaries	Annual salaries in IUD
Consultant nephrologist	2	700,470	8,405,640	94,143.2
Physicians	1	240,005	2,880,060	32,256.7
Clinical officer	1	138,116	1,657,392	18,562.8
Nurses	51	7,023,426	84,281,112	943,948.5
Biomedical staff	6	588,966	7,067,592	79,157
Laboratory technicians	7	266,443	3,197,316	35,809.9
Counselors	1	121,184	1,454,208	16,287.1
Nutritionists	1	64,698	776,376	8,695.4
Social workers	1	171855	2,062,260	23,097.3
Health information office	1	44,473	533,676	5977.2
Support staff	1	88,578	1,062,936	11,904.8
Totals	74	9,408,214	112,898,568	1,264,464

Table 4.9 Personnel cost for staff at the renal unit employed on casual and temporary basis.

Cadre	Number	Calls per week	Salary per month	Cost per month	Cost per month in IUD
Surgeons	3	4	250000	75000	840
Urologists	3	10	250000	500000	5600
Pharmacists	1	3	150000	4500	50.4
Radiologist	1	5	150000	12000	134.4
Totals				591500	6624.8

The cost of part time personnel was calculated by the number of times an employee worked in a week. Each call was assumed to be worth thirty minutes of the employees work time. The working hours per week were taken to be forty hours. These costs were confirmed from the pay roll of the accounting department.

4.2.5 Cost of laboratory investigations.

The costs of laboratory investigations are highlighted in the Table 4.10.

Table 4.10 table of cost of laboratory investigations.

Investigation	Cost Per Patient (KSh)	Cost in IUD
Full Haemogram	430	4.8
Haemoglobin	100	1.1
Concentration	900	10.1
Chest Xrays	400	4.5
Electrocardiogram(Ecg)	2500	28
Totals	4330	48.8

The cost per patient per month of the laboratory investigations was found to be KSh 4,330.(IUD48.8)

4.2.5.1Cost of machines.

It was found that the renal unit had 22 dialysis machines. The cost components of the machines are characterized in Table 4.11

Table 4.11 Cost of machines

Cost component	Value (Kush)	units	Total value	Value after annuitization	Value in IUD
Machines	1,400,000	22	30,800,000	5,866,666	65,706.7
Spare parts	400,000	4	1,600,000	1,600,000	17920
Depreciation	280,000	22	14,000,000	14,000,000	156800
Repair and maintenance	200,000	11	4,400,000	4,400,000	49280
Totals				25,866,666	289,706

Dialysis machine had a life span of 5 years. There were 22 machines at the renal unit. The depreciation rate was therefore calculated using the straight line depreciation method but the salvage value (resale value) was not considered in this study. The spare parts cost was calculated based on the most commonly replaced spare part which was the mother board. The repair and maintenance cost was as per the informants estimation. The cost of dialysis machine was the price of the cheapest machine in the market. The total cost was annuitized so as to obtain the present value of the machines in a single year. The informant averred that the renal unit is not a profit making department:

"I would not advise anyone to operate a dialysis unit as a profit making enterprise. This is a service industry."

The cost of the capital expenditure has been annuitized at a discounting rate of 5%. This cost was divided by the number of patients seen monthly so as to obtain the capital cost per patient per month. The capital cost per patient per month was found to be KSh 1198. (IUD13.41)

4.2.6 Intangible cost incurred by the patient

The intangible costs were also highlighted during the interview. Respondents reported that patients had psychosocial problems at the renal unit; these problems were caused by consequences of diabetic nephropathy like psychosis and erectile dysfunction.

"There are a lot of family psycho social issues, family breakages in terms of reduced libido in men, the family may break and incur extra costs as they try to sort out their issues. The man ends

up mistrusting the wife and it's so costly to the family and the society at large. Some go into hallucinations, paranoia and delirium probably. An extra cost is therefore incurred when psychiatrists have to be consulted. Some traumatize their spouses because they become abusive. This is all psychosocial. This is also costly."

The physical pain and suffering that the patient goes through and the emotional pain that accompanies the loss of status as the family bread winner formed part of the intangible cost of patients undergoing dialysis.

4.2.7 Modes of payment of dialysis

Patients who were covered by the National Health Insurance Fund paid KShKSh5000 for the weekly sessions. The out of pocket payment was the most common mode of payment. The majority of these patients were therefore making catastrophic payments that were driving their households to extreme poverty. After several dialysis sessions they opted to do without the weekly sessions. The annual cost of dialysis at KNH is highlighted in Table 4.12

Table 4.12 Annual cost of dialysis.

Cost	Amount (KSh 2014)	Amount (IUD 2014)
Machines	14,376	161
Non pharmaceuticals	696,000	7795.2
Pharmaceuticals	1,046,400	11719.6
Laboratory	51,960	582
Overhead	3,240	36.3
Personnel	66,672	746.7
Total	1,871,640	20,962

The total cost of dialysis with the health providers perspective was found to be KShKSh 1,871,640. Figure 7 below is a pie chart of the costs incurred.

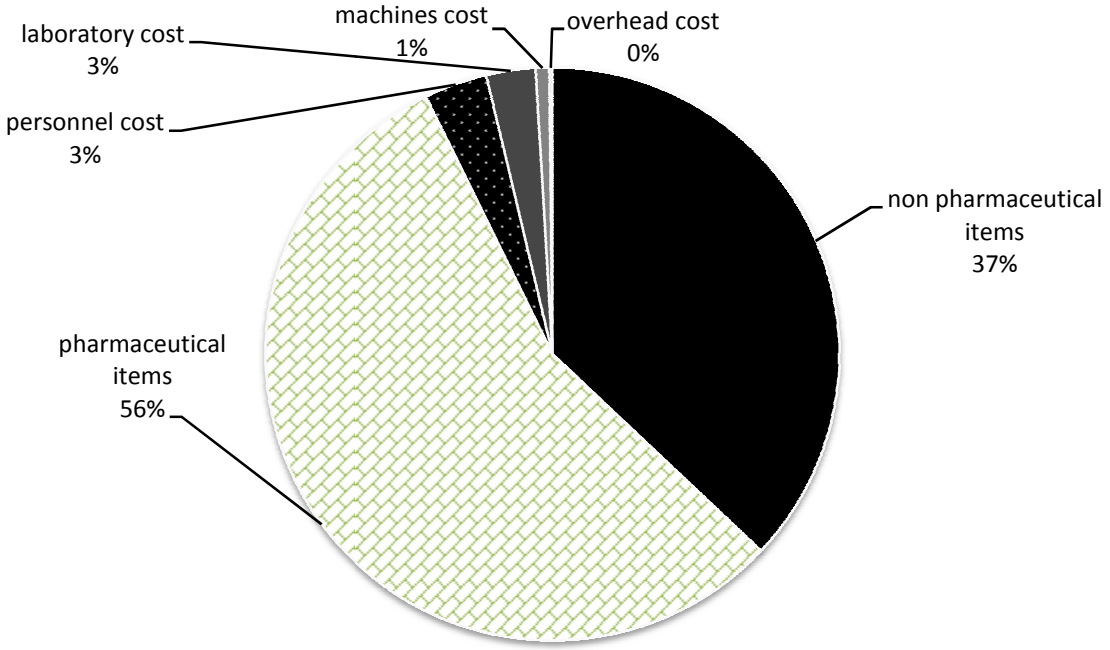


Figure 7: Pie chart of the annual cost of dialysis.

4.2.8 Costing of management of microalbuminuria.

The cost components of the management of microalbuminuria are presented in Table 4.13 below. The table illustrates the cost of evaluation and therapeutic management.(3)

Table 4.13: Cost of managing microalbuminuria in diabetic nephropathy.

Number	Cost component	Drug used	Cost per unit (Kush)	Cost per month (KSh)
1	Doctors fee	n/a	200	400
2	Renal function tests	n/a	4330	4330
3	Antihypertensives	Nifedipine	15	900
4.	Angiotensin Receptor Blocker	Lorsartan	20	600
5.	HMG CoA reductase inhibitor	Artovastatin	30	3000
6.	Smoking cessation	Nicotine patch	1	5000
7	Antiplatelets	Acetyl salicylic acid	5	300

The cost of treating microalbuminuria was KShKSh14,530 (IUD 308)

4.2.9 Costing of management of macroalbuminuria

The cost of treating patients suffering from macroalbuminuria has been illustrated in the Table 4.14. At the stage of macroalbuminuria, metformin is contraindicated. In this study, pioglitazone was used to replace metformin monotherapy.(3)

Table 4.14: Cost of managing macroalbuminuria in diabetic nephropathy.

Number	Cost component	Drug used	Cost/unit (KSh)	Cost/ month (KSh)
1	Doctors fee	n/a	200	800
2	Renal function tests	n/a	4330	4330
3	Antihypertensives	Nifedipine	15	1800
4.	Angiotensin Receptor Blocker	Lorsartan	20	1800
5.	HMG CoA reductase inhibitor	Artovastatin	30	6000
6.	Smoking cessation	Nicotine patch	1	5000
7	Antiplatelets	Acetyl salicylic acid	5	300
8	Hypoglycaemic	Pioglitazone	10	600
9	Diuretics	Hydrochlorthiazide	5	300

The cost of managing macroalbuminuria was KSh 20930.

4.2.10 Cost of death.

The annual cost of death was estimated to be equivalent to the annual salary of the lowest paid government worker in Kenya. The cost of death was KSh13592 per month(4).

4.2.11Cost of treating diabetic nephropathy

The cost of treating the various transition states of diabetic nephropathy are highlighted in Table 4.15.

Table 4.15 cost of treating diabetic nephropathy

Transition state	Metformin cohort costs KShIUD		Metformin/DPP 4 Cohort costs KSh	IUD
No renal disease	8330	176	79388	1683
Microalbuminuria	174360	3696	246548	5226
Macroalbuminuria	251160	5324	251160	5324
End Stage Renal Failure.	1951028	41361	1951028	41361
Death	163104	3457	163104	3457

4.3 THE LONG TERM COST OF TREATING DIABETES MELLITUS IN KENYA

The long term cost of treating diabetes mellitus at Kenyatta National Hospital was obtained through a Markov process with the various transition states highlighted in Table 3.1. Based on assumption in section 3.3.1, a matrix of transition rates of patients on FDC Metformin/DPP 4 inhibitors was calculated: The Reasner et al trial demonstrated that sitagliptin/metformin FDC had a superior reduction in $\%HbA_{1c}$ of 0.6% (11) Studies have also demonstrated that a 1% increase in $\%HbA_{1c}$ would result in a 37% increase in the risk of renal failure (9). The transition rate of patients moving from macroalbuminuria to end stage renal failure was therefore obtained by the product of the transition rate of those taking metformin and 0.402 as presented in the table 4.5.The DCCT study concluded that intensive therapy reduced the risk of microalbuminuria by 34% and that of macroalbuminuria by 54% (50).

In the UKPDS study, each percentage reduction in $\%HbA_{1c}$ was associated with a 7% reduction in all cause deaths in patients with T2DM(5). These figures were used to modify the transition rates and arrive at a matrix having transition probabilities to the various transition states when the patients were put on metformin/DPP 4 inhibitor fixed dose combinations. Table 4.16 is a matrix modified from table 3.1. It illustrates the change in transition rates that is projected if

FDCmetformin/DPP 4 inhibitors are used instead of metformin monotherapy in the treatment of drug naïve diabetes Type 2 patients.

Table 4.16 Matrix of transition probabilities of patients initiated on metformin/DPP 4 inhibitors

Transition state	N_{0M} (%)	$N_{1M} = N_1$ X 0.6X (1-0.34) (%)	$N_{2M} = N_2$ X0.6(1-0.54)(%)	$N_{3M} = N_3$ X0.6X(1-0.37) (%)	D_M=D X0.6X(1-0.07) (%)	Totals (%)
N_{0M} (%)	98.3(98.5-98.1)	0.7(0.7-0.8)	0.03(0.03-0.06)	0.04(0-0.04)	0.78(0.72-0.84)	100
N_{1M} (%)	1.6(1.5-1.8)	95.92(97.82-95.97)	0.7(0.69-0.88)	0.11(0.04-0.15)	1.67(1.45-1.90)	100
N_{2M} (%)	0	0	96.57(95.69-97.43)	0.86(0.57-1.13)	2.57(2.0-3.18)	100
N_{3M} (%)	0	0	1.10(1.16-1.55)	88.11(84.83 – 91.04)	10.71(7.8-13.61)	100
D (%)	0	0	0	0	100	100
Totals (%)	100	100	100	100	115.73	

The transition probabilities to the various transition states have been highlighted in Table 3.1 and Table 4.16 for patients on metformin monotherapy and for those on metformin/DPP 4 inhibitors respectively.

4.3.1 Calculation of Incremental Cost Effectiveness Ratio(ICER).

The cycle profile of transition probabilities for a 25 year time frame was determined using equation 1. The redistribution of patients with diabetic nephropathy for the 25 year timeframe are attached in appendix 5 and 6 for metformin monotherapy and metformin/DPP 4 inhibitors respectively.

The crude life expectancy, obtained using equation 2 in section 3.3.7.2 for the patients on metformin was found to be twenty oneyears while that of those taking the dual therapy of metformin and dipeptidyl peptidase 4 inhibitors was twenty three years. The cost of starting treatment for patients with metformin monotherapy was found to be IUD 42,225 per patient. Conversely, the cost of dual therapy of metformin/Dipeptidyl Peptidase Inhibitors was IUD55,814. The incremental Cost Effectiveness Ratio was IUD 7138 for each extra year of the crude life expectancy.

4.3.2 Sensitivity analysis

Asensitivity analysis was done to test the robustness of the obtained ICER. A plot of the percentage of people alive against time was plotted. This survival curves demonstrated the impact of the variation in transition probabilities. This is demonstrated in the Figure 8-10 below.

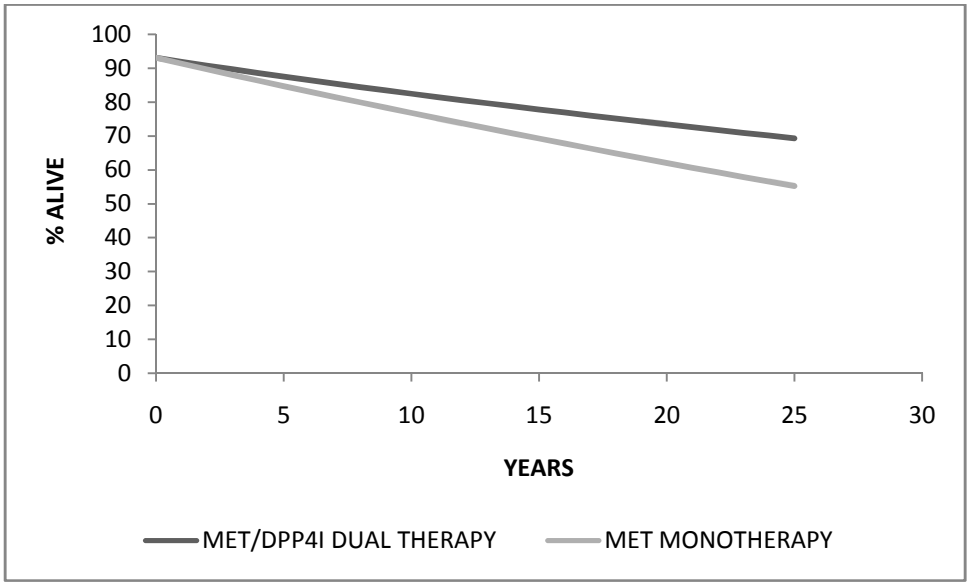


Figure 8 A survival curve showing the results obtained from the mean reported transition probability.

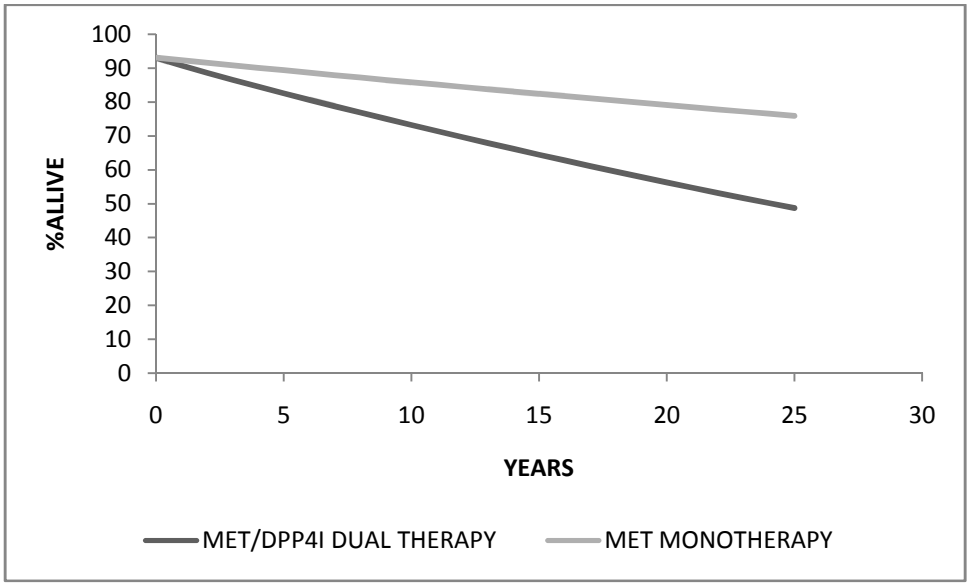


Figure 9 a Survival curve for patients with diabetic nephropathy using the highest transition probabilities.

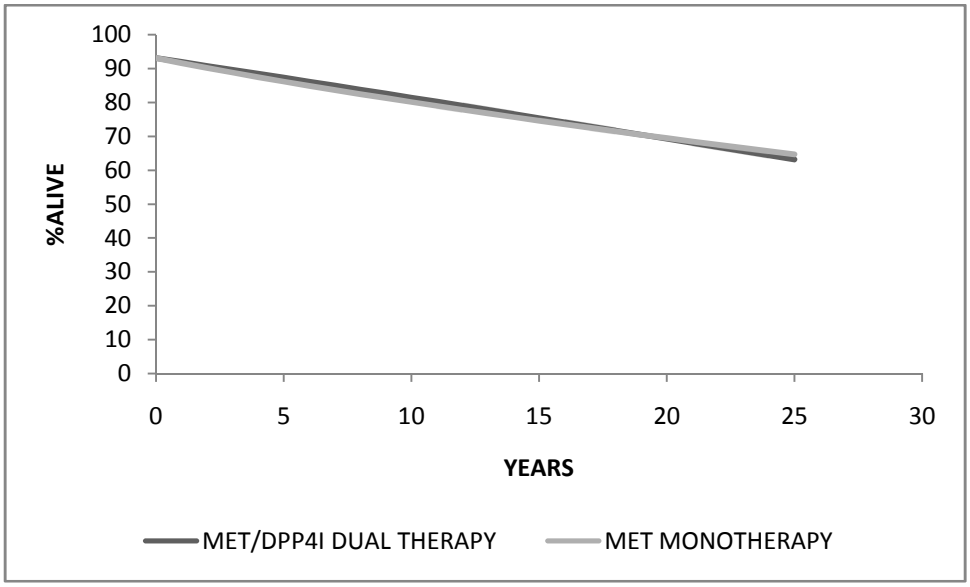


Figure 10: survival curve of the impact of the transition probabilities on the proportions of clients surviving.

4.3.7 Output table of the analysis.

Table 4.17 is a summary of the findings of the Markov process.

Table 4.17output table of Markov process.

Intervention	**Cohort cost(IUD) per person per year**	**Crude life expectancy**
Metformin Monotherapy	42225	21
Metformin/DPP 4 Inhibitor.	55814	23
Cost difference	13588	2
ICER	7138	N\A

5.0 CHAPTER FIVE:

DISCUSSION AND RECOMMENDATIONS

5.1 Price survey of Metformin monotherapy and metformin/DPP 4 inhibitor dual therapy

From this study, the factors affecting the price of metformin were the pack size of the drugs and the country from which the drugs had been imported. This is consistent with studies that have highlighted that generics are cheaper than branded products since originator drugs are priced so as to recover the cost incurred during research and development.(42) It can also be attributed to the brand premium that originator or branded generics attract (42). This is also consistent with the WHO report on price, affordability and availability (42). The national pharmaceutical policy in Kenya does not require regulation of drug prices. Pharmacists are compensated through a tariff system that attaches a markup on the wholesale price of the drug. This further increases the drug prices. It therefore creates a perverse incentive that encourages drug sales for profit.

The WHO/HAI measures the affordability of drugs in terms of the number of days the lowest paid unskilled government worker (LPGW) should work so as to pay for medication (45). In Kenya, to buy metformin, 2 days are required for the LPGW and 16 days to buy DPP 4 inhibitors .The prices at which the drugs are sold makes them unaffordable, unavailable and hence inaccessible. This measure does not reflect the real situation in Kenya since 9.2% of the population is unemployed, the gross domestic product is $3099 per capita but with a Gini index of 0.47 reflecting a nation that is in the lower middle income bracket with very high inequality. The country is also ranked 147th among 187 countries In terms of the human development index which is a composite statistics of life expectancy, education and per capita income.

The pharmaceutical sector in Kenya has many brands of metformin hydrochloride. The intellectual property act CAP 58 (2) which states that “the rights under the patent shall not extend to acts in respect of articles which have been put in Kenya or in any other country or imported into Kenya ” legalizes parallel importation of pharmaceutical products into Kenya(45). This has led to influx of many products at competitive prices. It is for this reason that DPP 4 has a mandated uniform price by the patent holder. The lapse of the patent of DPP 4 inhibitors is expected to be in the year 2019. Studies have shown that parallel importation may lead to lower

prices of pharmaceuticals but incidences of substandard, falsified counterfeit products in a market allowing parallel importation increases(46).

The attitude towards generic drugs in Kenya is poor and there is preference for branded generics or originator products. This has the effect of increasing the brand premium that is attached to products leading to increased prices and inaccessibility of the drugs. It is recommended that pharmacists and pharmaceutical technologists should be made confident of the quality of generic drugs, parallel importation especially of the DPP 4 inhibitors be encouraged and generic brand substitution be practiced so as to make these drugs affordable hence accessible.

The Median Price Ratio of the drugs of metformin 500mg was 1.06 which was a reflection of the similarity of the local prices to the international reference price. The local price of Metformin 850mg was higher than the IRP as was illustrated by the MPR which was 8.05.

This difference in MPR of two products that are similar in form but only differ in strength illustrates a sector that has no regulation. The ratio of the highest local price to the lowest is also higher than the ratio of the highest to lowest price of the International reference prices in spite of the fact that there is more variety in the international market. It is recommended that price regulation be instituted so as to safeguard the vulnerable population from exploitation and to give the stakeholders in the entire supply chain their due. The requirement to conduct pharmacovigilance studies especially for parallel imported products should be legislated and enforced.

5.2 Key informant interview.

A review of literature on dialysis in developing countries highlights the fact that there is a lack of published peer reviewed economic evaluations of dialysis treatment. It would therefore be difficult to assess the cost of dialysis from literature. This study found that the cost of dialysis at the renal unit of Kenyatta National Hospital was KSh 1,871,640 (IUD 20,962) per treatment per year. This was consistent with a systematic review carried out by Lawrentiaet al that found the cost to be IUD 16845 (47). The cost of hemodialysis in Kenya is lower than the cost in Britain ($30000)(46) and in the united states of America ($60 000) but was 10 times higher than the cost

in India ($3000)(47). This cost highlights the fact that dialysis is inaccessible to the Kenyans who require it. A majority of Kenyans use out of pocket payments to fund their health care needs. For those who can afford insurance, only fifty percent of the payment is covered(48). This has led to catastrophic payments hence not achieving one of the major roles of health care financing which is to protect the patient from such payments.

Over 90% of the cost of dialysis was used for purchasing non pharmaceuticals and pharmaceutical items. This is also consistent with studies in South America (Barbados) that indicate that the largest proportion of costs incurred is of pharmaceuticals and non-pharmaceutical items (49). In this study the direct costs accounted for more than 90% of the total cost of dialysis. The policy of the Kenyan government of leasing dialysis equipment to county hospitals as a measure of reducing the congestion in the major referral hospitals by patients on dialysis should consider the fact that the machines account for less than 1% of the costs incurred by the hospital. Other studies have put the cost of machines to be at 14% (49). The disparity can be explained by the efficiency with which the machines are being used in the different settings: in the renal unit of KNH, a machine is used to treat 1000 patients in a year. This reduces the cost per treatment per year to 1500. For successful implementation of the policy, funding of non-pharmaceutical and pharmaceutical items required for dialysis should be considered. The pharmaceutical items were also found to be unavailable. They were only available in specific stores. The procurement procedure was single sourcing of the materials in a particular store. Incentives should be provided for entrepreneurs to either manufacture or procure these items. This can be done by removing the tariffs and taxes imposed on them. The government may also enter into public private partnerships with involvement of Non-Governmental Organizations (NGOs) and set up stand-alone dialysis units so as to enhance accessibility to this service. Some pharmaceutical items were not provided by the hospital. This led to further exploitation of patients, a majority of whom were using out of pocket means of funding their health care needs.

The indirect costs incurred (productivity losses for patients and their care givers) were not included in this study since this was a study done from the health care provider's perspective. However, this formed a major cost category to the patient. The indirect costs were more than the actual cost incurred by the patient in the hospital. Further studies should aim at costing this category of costs.

The intangible costs (costs associated with pain, suffering and impairment of quality of life as well as the value of extending life) were also not considered. This cost category was however the most important to the patient as it was directly associated with the patients quality of life.

5.3The long term cost of treating diabetes mellitus in kenya

In this study, the cost of an additional year of life expectancy for the cohort of 10,000 patients on dual therapy of metformin and Dipeptidyl Peptidase inhibitors was found to be IUD 20995 per patient. This cost did not factor in the benefits of the delay to development of other complications that are associated with the incretomimetics dual therapy in comparison with metformin monotherapy. It only considered diabetic nephropathy since this was the only complication that had been characterized interms of transition probabilities in literature. It also did not include the cost incurred due to the adverse effects associated with the drugs. The incremental cost effectiveness ratio is therefore a lower estimate of the expected cost effectiveness of the increto-mimetics. Incretomimetics are a recent discovery. The first analogue(sitagliptin) was approved in the year 2006(14). Therefore there is a pausity of economic evaluation studies. The available studies have factored in all the complications that are likely to occur in diabetic patients. The main outcome in this study was that of mortality as reflected in the crude life expectancy of the various arms in the study. Quality Adjusted Life Years could not be used since this composite measure would require the inclusion of all the complications arising from diabetes Mellitus Type 2.

The key cost drivers in this study were the transition probabilities of the health states. These were obtained from the United Kingdom Prospective Diabetes Study. (UKPDS64). This have been used as the basis of this economic evaluation. This is a major weakness of the study since the population under study was not entirely of an African descent. A search of the best current available evidence did not reveal any study of the African population. Africans have a faster progression to complications as compared to other races. The UKPDS was the only study that had calculated these probabilities using a validated methodology. The study has been referenced in this thesis. The used rates are therefore the best that can be used to undertake an economic evaluation. The impact of the transition probabilities have been depicted by the survival curves which are a plot of the percentage of people alive against the number of years. The curves clearly show that the transition probabilities do not have an effect on these numbers. The two

intervention arms are shown to have no difference depending on the boundary of the confidence interval used.

Another cost driver was the prices of the drugs and cost of dialysis. The defined daily dose of dipeptidyl peptidase inhibitors was undocumented. The prices used in this study were obtained from a key informant interview. In the hierachy of evidence, expert opinion ranks last. The informants therefore provided data that cannot be relied on fully if other superior methods of data collection are conducted.

The incremental cost effectiveness ratio is on the dominant side of the cost effectiveness plane. Most countries would invest in an intervention if it had an ICER that is less than IUD50,000. The ICER obtained in this instance does not take into consideration the number of lives that are saved. The study shows that in a cohort of 10000 years over a 25 year period, using dual combination of Metformin and DPP 4 Inhibitors would result in saving 24,300 people. This is more than 975 people per year. In comparison to the investments made by the government to prevent traffic accidents, IUD 7138 is very affordable.

6.0 CONCLUSION

The factors affecting the price of metformin and DPP 4 inhibitors were the pack size of the drug ($P<0.05$) and the country of importation of the drug ($P<0.05$). The median local price of the daily defined dose of metformin was KSh22.8 (IUD 0.48). The median price ratio of the international median price and the local median price of metformin 500mg tablets and 850mg was 1.3 and 8.4 respectively .The median local price of a daily defined dose of DPP 4 inhibitors was KSh58 (IUD1.22) while that of FDC metformin and DPP 4 inhibitors was KSh122 (IUD 2.58).

The annual cost of dialysis treatment, with the perspective of the health provider, at Kenyatta National Hospital is KSh 1,871,640 (IUD 39,678). The annual cost of treating microalbuminuria and macroalbuminuria was KSh 174,360 (IUD 3696) and KSh 251,160 (IUD 5324).

The crude life expectancy of drug naïve diabetic patients taking metformin was 21 years. Those taking FDC metformin/DPP 4 inhibitors had a crude life expectancy of 23 years. .

The incremental cost effectiveness ratio of FDC metformin/DPP 4 inhibitors compared with metformin monotherapy in drug naïve diabetes patients was found to be 336,698 (IUD 7138) per person per year.

It is therefore more cost effective to manage type two diabetes mellitus on dual therapies of metformin/DPP 4 inhibitors as compared to metformin monotherapy

6.0 REFERENCES

1. **2013**International Diabetes Federation Diabetes Atlas Id. 6-th.International Diabetes Federation

2. **Levitt NS(2008)**: Diabetes in Africa: epidemiology, management and healthcare challenges. *Heart*. 94(11):1376-82.

3. **Bosi E(2009).:** Metformin – the gold standard in type 2 diabetes: what does the evidence tell us? *DiabetesObesityMetabolism*.11 (Suppl. 2):3-8.

4. **Monami M, Iacomelli I, Marchionni N, Manucci E. (2010):**Dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *NutritionMetabolismCardiovascular Disease*.20(4):224-35.

5. **Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al.(2009):**Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 32(1):193 – 203.

6. **Riche DM, East HE, Riche KD (2009):**Impact of sitagliptin on markers of [beta]-cell function: a meta-analysis. *American Journal Medicine Science*. 337(5):321 – 8.

7. **Gao W, Dong J, Liu J, Li Y, Liu F, Yang L, et al (2014):**Efficacy and safety of initial combination of DPP-IV inhibitors and metformin versus metformin monotherapy in type 2 diabetes: a systemic review of randomized controlled trails. *Diabetes ObesityMetabolism*. ;16(2):179 – 85.

8. **Rodboard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al**. (**2009):** Statement by an American Association of Clinical Endocrinologist/American College of Endocrinology consensus panel on type 2 diabetes mellitus: and algorithm for glycemic control. *Journal of American Association of Clinical Endocrinology*. 15(6): 540 – 59.

9. **Alberti KGMM, Zinmet P ft**. (**1998):** Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetes Medicine*. 15(7):539 – 53.

10. **Beulens JW, Grobbee DE, Nealb B, others(2010):**The global burden of diabetes and its complications: an emerging pandemic. *European Journal of Cardiovascular Prevention and Rehabilitation*. 17(1suppl):s3 – 8.

11. **Zhang P, Zhang X, Brown JB, Vistisen D, Sicree RA, Shaw J, et al** (**2010):**. Economic impact of Diabetes. *Diabetes Atlas International Diabetes Federation*.4:1 – 28.

12. **Alder AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR(2003): Development** and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney International Reports-Journal*. 63(1):225 – 32.

13. **Mayer-Davis EJ, Beyer J, Bell RA, Dabelea D, D'Agosino R, Iperatore G, et al.(2009):**Diabetes in African American Youth Study. *Diabetes Care*. 32(Suppl. 2): S112 = 22

14. **Amori RE, Lau J, Pittas AG (2007):**Efficacy and safety in incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*.298(2):194 – 206.

15. **Vaag AA** (**2006):** Glycemic control and prevention of microvascular and macrovascular disease in the Steno 2 study. *Endocrinology Practitioners*. 12:89 – 92.

16. **Nilsson P. (2010):** Action to Control Cardiovascular Risk in Diabetes**(ACCORD)** Studyand risk-factor control in type 2 diabetes. *New England Journal of Medicine*.1628 – 30

17. **RayKK, Seshasai SRK, Wijeruriya S, Sivakumaran R, Nethercott S, Preiss D, et al.(2009):** Effect of intensive control of glucose on cardiovascular outcome and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet*. 373(9677):1765 – 72.

18. **Clarke P, Gray A, Legood R, Briggs A, Holman R**.(**2003**)**:**The impact of diabetes-related complications on healthcare costs; results from the United Kingdom Prospective Diabetes Study (UKPDS Study 65). *Diabetic Medicine*. 20(6):442 – 50.

19. **2013**:Kenya Household Health Expenditure and Utilization Survey

20. **Dr. L W Mbogo et al** (**2009**)**:** Prevalence of risk factors associated with nephropathy in diabetic patients with chronic renal insufficiency as seen in Kenyatta National Hospital. University of Nairobi repository accessed 15 Dec 2014

21. **Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, et al (2000):** Cost effectiveness on an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomized controlled trial (UKPDS 41*)*. *British Medical Journal*.320(7246):1372 – 8.

22. **Huang L, Xi P, Xu M, Liu T, Zeng Z** (**2008**)**:** Crystal Structure of Metformin ethyl N-(3-tossulfonyl)carbamate. *Anaytical Sciences X-ray Structure Analysis Online*. 289 – 90.

23. **Jackson RA, Hawa MI, Japsan JB, Sim BM, DiSilvio L, Featherbe D, et al.**(**1987**)**:**Mechanism of metformin action in non-insulin-dependent diabetes.*Diabetes*.36(5):632 – 40.

24. **Klip A, Leiter LA.(1990):** Cellular mechanism of action of metformin. Diabetes Care. 13(6):696 – 704.

25. **Strack T(2008):** Metformin: a review. *Drugs Today (Barcelona)*.44(4):303- 14.

26. **Group UPDS (UKPDS), others** (**1998**)**:** Effects of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS – 34). *Lancet*.352:854 – 65.

27. **Derosa G, Cabone A, Franzetti I, Querci F, Fogari F, Fogari E, Bianchi L, et al.(2012):**Effects of a combination of stiagliptin plus metformin vs metformin monotherapy on glycemic contrl, β-cell function and insulin resistance in type 2 diabetic patients. *Diabetes Research Clinical Practice*.98(1):51-60

28. **Nauck MA, Visboll T, Gallwitz B, Garber A, Madsbad S. (2009):** Incretin-Based Therapies Viewpoints on The way to consensus. *Diabetes Care*.32(Suppl2):S223 – 31.

29. **Mikhail N (2008).**Incretinmimetics and dipeptidyl peptidase 4 inhibitors in clinical trials for the treatment of type 2 diabetes. *Journal of Expert Opinion on Investigational Drugs* 17(6):845-53.

30. **Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al.(2010):** Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes : a randomized trial. *Lancet*.376(9739):431 – 9.

31. **Zinman B, Gerich J, Buse JB, Lewn A, Schwaez S, Raskin P, et al.(2009):**Efficacy of the human glucagon-like peptide- 1 analogliraglutide in combination with metformin and thiazolidinedione in patiens with type 2 diabetes (LEAD-4 Me+ Tzd). *Diabetes Care*.32(7):1224 – 30.

32. **Meteucci E, Giampietro O.(2009):** Dipeptidase-4 (CD26): knowing the function before inhibiting the enzyme. *Current Medical Chemistry*. 16(23):2943 – 51.

33. **Ballav C, Gough SC.(2013):**Safety and Efficacy of sitagliptin-metformin in fixed combination for the treatment of type 2 diabetes mellitus. *ClinicalEducation Insights Diabetes*. 20136:25.

34. **Herman LS Schersten B, Bitzen P-O, KjellstromT,Lindogarde F, Malander A**. (**1994):**Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. *Diabetes*.17(10):1100 – 9.

35. **Barlett, JE; Kotrlik, JW, Higgins CC(2001):** Organizational research: Determining appropriate sample size in survey research. *Information TechnologyLearning and Performance Journal*. 19(1):43.

36. **Sandelowski M(1995):** Sample size I qualitative research. *Research in Nursing and HealthJournal*. 18(2):179 – 83.

37. **Leahy JL (2005):** Pathogenesis of type 2 diabetes mellitus. *Archives of Medical Research*. 36(3):197 – 209.

38. **Riche KD(2009):** Impact of stigliptin on markers of [beta]-cell function: a meta-analysis. *American Journal of Medical Science*. 33(5):321 – 8.

39. **Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group.(2005):** Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine*.353(25):2643-53.

40. **Mark M. (2010):** Sample size and saturation in PhD studies using qualitative interviews forum: *Qualitative Social Research*11(3): Art. 8

41. **Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R.** (**2009**): Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis.*Lancet*.373(9659):240–9.

42. **A. I, Wertheimer (1986):**The Defined Daily Dose system (DDD) for drug utilization review.*Hospital Pharmacy*.21(3):233-4, 239-41, 258

43. **Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T (2005):**Diabetic Nephropathy: Diagnosis, Prevention, and Treatment.*Diabetes Care*.28(1): 164-176.

44. **Andalón, M, 2008.** Minimum wages in Kenya**.**

45. **Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, Matthews DR, Stratton IM, Holman RR; UK Prospective Diabetes Study (UKDPS) Group(2004):**A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68).*Diabetologia*.47(10):1747-59.

46. Industrial Property Act (Cap. 509) - Laws of Kenya.

47. **Bale Jr. HE (1998):**The conflicts between parallel trade and product access and innovation: the case of pharmaceuticals.*Journal of international economic law1(4)*637-65348

48. **Khanna U (2009):**The Economics of Dialysis in India. *Indian Journal of Nephrology*.19(1): 1–4

49. **Palmer N, Mueller DH, Gilson L, Mills A, Haines A.(2004):** Health financing to promote access in low income settings—how much do we know? *Lancet*.;364(9442):1365–70.

50. **Adomakoh SA, Adi CN, Fraser HS, Nicholson GD. (2004):**Dialysis in Barbados: the cost of hemodialysis provision at the Queen Elizabeth Hospital. *RevistaPanamericana de SaludPública*. 2004;16(5):350-5

Appendix 1: Price Survey of Metformin and Metformin/DPP 4 inhibitors

Generic names Dosage form Strength	Brand name	Manufacturer	Availability	Pack Size	Pack size found	Price of pack size found	Unit price/tab	Comment
Metformin 500mg								
Metformin 850mg								
Metformin 1000mg								
Metformin ER 500mg								
Metformin ER 750mg								
Metformin 1000mg								
Metformin oral solution								
Sitagliptin phosphate 25mg								
Sitagliptin phosphate 50mg								
Sitagliptin phosphate 100mg								
Saxagliptin 2.5mg								

Saxagliptin 5mg								
Linagliptine 5mg								
Sitagliptin Phosphate +metaformin 50/500mg								
Sitagliptin Phosphate +metaformin 50/500mg								
Sitagliptin Phosphate +metaformin 50/1000mg								
Saxagliptin+ Metformin XR2.5/500mg								
Saxagliptin+metformin XR5/1000mg								
Saxagliptin +metformin XR5/2000mg								

Appendix 2.price component data collection form

Name of data collector……...

Name of distributing outlet……

Product name dosage and strength……

Manufacturer……

Pack size……

Product type:	◯	originator brand	◯	lowest price generic
Production:	◯	imported	◯	locally produced
Type of data:	◯	field	◯	hypothetical

Any additional information about target medicine

……
……
……
……
……
……
……

Stage 1: manufacture

Type of charge	Charge basis	Price to which charge is applied	Amount of charge	comments

Stage 2:Land price.

Type of change	Charge basis	Price to which charge is applied	Amount of charge	comments

Stage 3:Whole or medicine store price

Type of change	Charge basis	Price to which charge is applied	Amount of charge	comments

Wholesaler to retailer discounts and margins……

……

……

Appendix 3: key informant interview.

Key informant interviewer on the resource input in the treatment of diabetes nephropathy.

SECTION ONE: STUDY ELIGILITY CHECKLIST.

Inclusion criteria:(if any of the criteria is marked NO the participant is of eligible for the interview)

1. Participant has been an employee in KNVH for the last six months.

YES **NO**

2. Participant has been working been working in the renal unit of KNH for at least 6 months.

YES **N**

3. participant deals with procurement and utilization of commodities at the renal unit.

YES **NO**

4. participant has signed the informed consent form.

YES **NO**

Exclusion criteria:(if any of the criteria is marked YES participants is not eligible for the interview)

1. Participant does not offer clinical services at the unit.

YES **NO**

2. Participant does not work at the renal unit.

YES

SECTION TWO: STAFF INTERVIEW

2A.interview on resource input during dialysis in end stage renal failure

1. What are the methods of dialysis used in KNH?
   PERITONEAL ◯ HEMODIALYSIS ◯ OTHER ◯

2. What are the pharmaceutical items and the non-pharmaceutical items required during dialysis?
3. What is the cost and frequency of maintenance of machines used during dialysis?
4. How many members of staff are required to perform a single procedure of dialysis?
5. What is the frequency with which a patient can undergo dialysis in a month?
6. How frequency are the non-pharmaceutical and pharmaceutical items replenished in a month?
7. What is the cost per procedure of dialysis?

2B.treatment of macroalbuminuria.

1. What are the test required in the treatment of macroalbuminuria?
2. What laboratory machines are used in the diagnosis of macroalbuminuria?
3. What are the drugs used in the treatment of macroalbuminuria?
4. What are the cost per patient per month of treating with macroalbuminuria?

2C. Treatment of microalbuminuria

1. What laboratory tests are required for diagnosis of microalbuminuria
2. What laboratory reagents and machines are used in the diagnosis of microalbuminuria?
3. What drugs are used in the treatment of microalbuminuria?

Appendix 4 Consent information document

Informed consent form for the staff at KNH who are to be recruited for the key informant interview: **Key informant interview consent form.**

Consent for interview in the study

Permeable

You are being asked to volunteer freely to be interviewed in this study. Before you consent, I would like to provide you with information about this study. This document is a consent form it has information about the study and it will be discussed with you by the interviewer. Please study it carefully and feel free to seek for any clarification. If you agree to join this study, you will be asked to sign this consent form and a copy of it will be given to you for safe keeping.

Purpose of study

The main purpose of this study is to compare the cost effectiveness of metformin monotherapy and dual therapy of metformin/DPP 4 inhibitors in drug naïve type two diabetes patients. Metformin/DPP 4 inhibitors have shown superior efficacy and have no worse adverse effects compared to metformin monotherapy. This study investigates the cost effectiveness at initiation of drug treatment in type 2 diabetes mellitus.

Study methodology

The key informant interview will be conducted with staff in KNH at the renal unit. The key will be asked a set of questions with goal of determining the resource input in the treatment of diabetic nephropathy in type 2 diabetes mellitus. Permission to have voice data recorded during the interview will be sought and if granted the record will be destroyed after transcription within 24 hours. The obtained data will then be analyzed.

Benefits

The benefits of this research work are to be realized during the formulation of policy and guidelines on the treatment of type 2 diabetes mellitus in Kenya. A rational decision can be made when the policy formulators are aware of increment cost effective ratio of metformin/DPP 4 inhibitors compared to standard therapy.

Confidentiality

The researcher will take utmost care to keep your participation in this study confidential. Your voice data will be destroyed in 24 hours by the lead supervisor of this study. Your names will not be used anywhere during the publication or presentation of this study. Your name will only be known by the principle investigator.

Voluntary participation

The decision to be interviewed in this study is your choice. You may freely choose to take part and you may change your mind about taking part at any time.

Risks and discomfort

There are no anticipated risks in taking part in this study. The only discomfort may be the time it takes to conduct the interview which will be at least 30 minutes.

Eligibility

All health workers who are employees of KNH for more than 6 months and have a role in the procurement and utilization of commodities in the renal unit are eligible.

Financial incentives

No financial incentive will be provided during this study. No interviewee will be coerced to participate in the study.

Further information

Further information about this study you may contact Dr. WaraOcheing Gerald, who is the principal investigator as well as a Masters of Pharmacy student studying Pharmacovigilance and Pharmacoepidemiology at the School of Pharmacy University of Nairobi.

Phone number 0717738345

Email grldwara@gmailcom.

The contacts of the lead supervisor are: Name: Dr. Faith A. Okalebo

School of Pharmacy.Departmetn of Pharmacology and Pharmacognosy

Phone number: 0737434204

Email address: f-okalebo@yahoo.com

For questions related to your rights as a volunteer in this research work; you may contact Pro M. L. Chindia, secretary to the Kenyatta National Hospital ethics and research committee. (knh-erc) telephone number 726300-9 fax 725272 email: uonknh-erc@uonbi.ac.ke.

Appendix 5 statement of consent

I have read this consent form. I have had a chance to discuss this research study with the investigator. I have had my questions answered. The discomforts and benefits have been explained to me. I understand that my participation in this study is voluntary. I freely participate in this research study.

By signing this consent form, I have not given up any of the legal rights I have as a participant in this research study.

I agree to participate in this study: **YES** ◯ **NO** ◯

I agree to be interviewed for the purpose of this study:

NO ◯ **YES** ◯

PARTICPANTS

SIGNATURE…….DATE……

PARTICIPANTS

NAME……

I, the undersigned have fully explained the relevant details of this research study to the participant named above and I believe that the participant has understood and has knowingly given his consent.

NAME: GERALD OCHIENG WARA

DATE……

SIGNATURE……

ROLE: PRINCIPAL INVESTIGATOR

Appendix5.Twenty five year cycle profile of a cohort of 10,000 patients on metformin showing their redistribution to the various health states.

N0	N1	N2	ESRF	DEATH	YEAR(MET)
10000	0	0	0	0	0
9640	200	10	10	140	1
9294.16	379.4	24.95	18.55	283.34	2
8961.847	539.8634	43.88781	25.99461	429.5495	3
8642.459	682.929485	65.97736	32.5945	578.2211	4
8335.428	810.0223963	90.49318	38.54508	728.9965	5
8040.213	922.4594634	116.807	43.99127	881.5565	6
7756.3	1021.458941	144.3761	49.0391	1035.613	7
7483.202	1108.147196	172.7328	53.76492	1190.902	8
7220.456	1183.565376	201.4762	58.22255	1347.179	9
6967.621	1248.675611	230.2635	62.44893	1504.219	10
6724.278	1304.366759	258.8038	66.46844	1661.809	11
6490.031	1351.459755	286.8516	70.29637	1819.746	12
6264.498	1390.712563	314.2016	73.94146	1977.843	13
6047.321	1422.824787	340.6838	77.40797	2135.917	14
5838.154	1448.441938	366.1594	80.69717	2293.798	15
5636.671	1468.159408	390.5168	83.80846	2451.323	16
5442.56	1482.52615	413.6686	86.74027	2608.336	17
5255.523	1492.048096	435.5484	89.49065	2764.69	18
5075.276	1497.191332	456.108	92.05773	2920.247	19
4901.55	1498.38504	475.3155	94.43998	3074.872	20
4734.084	1496.024234	493.1527	96.63647	3228.442	21
4572.633	1490.472292	509.6134	98.64693	3380.84	22
4416.961	1482.063313	524.7018	100.4719	3531.953	23
4266.843	1471.104296	538.431	102.1126	3681.679	24
4122.063	1457.877169	550.8215	103.571	3829.922	25
172130.1	29850.179	7455.542	1709.938	49480.99	Totals

Appendix 6. Twenty five year cycle profile of a cohort of 10,000 patients on metformin/DPP 4 inhibitor dual therapy showing their redistribution to the various health states.

N0	N1	N2	ESRF	DEATH	YEAR(MET/DPP
10000	0	0	0	0	0
9830	70	3	4	78	1
9664.01	135.954	6.3405	7.5592	156.3485	2
9501.897	198.0551	9.982217	10.73009	234.9708	3
9343.534	256.4878	13.88859	13.55875	313.7988	4
9188.797	311.4278	18.0256	16.08561	392.7708	5
9037.571	363.0431	22.36165	18.34614	471.8303	6
8889.741	411.494	26.8674	20.37147	550.9257	7
8745.199	456.9332	31.51563	22.1889	630.0099	8
8603.842	499.5067	36.28115	23.82238	709.0396	9
8465.568	539.3537	41.14061	25.29291	787.9752	10
8330.283	576.6071	46.07245	26.61891	866.78	11
8197.894	611.3935	51.05678	27.81653	945.4205	12
8068.312	643.8339	56.07526	28.89992	1023.866	13
7941.452	674.0437	61.111	29.88151	1102.087	14
7817.232	702.1329	66.1485	30.77218	1180.058	15
7695.574	728.2065	71.17356	31.58148	1257.753	16
7576.4	752.3647	76.17316	32.3178	1335.151	17
7459.639	774.703	81.13544	32.98846	1412.231	18
7345.221	795.3126	86.0496	33.59993	1488.972	19
7233.077	814.2804	90.90581	34.15785	1565.356	20
7123.143	831.6893	95.6952	34.66721	1641.367	21
7015.357	847.6183	100.4098	35.13238	1716.989	22
6909.657	862.143	105.0423	35.55718	1792.207	23
6805.988	875.3352	109.5863	35.94502	1867.008	24
6704.291	887.2634	114.0362	36.29886	1941.379	25
213493.7	14619.18	1420.075	648.1907	25462.29	Totals