Utilization Of Oral Anti-diabetic Medications:

Examining Adherence To Clinical Guidelines

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THESIS

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
IHD	Ischemic Heart Disease
DCCT	Diabetes Control and Complications Trial
UKPDS	United Kingdom Prospective Diabetes Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes
EASD	European Association for Study of Diabetes
UIMCC	University of Illinois Medical Center at Chicago
ESRD	End stage renal disease
FPG	Fasting Plasma Glucose
MI	Myocardial Infarction
TZD	Thiazolidinedione
FDA	Food and Drug Administration
IDF	International Diabetes Federation
HR	Hazard Ratio
OR	Odds Ratio
CHF	Congestive Heart Failure
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ICD-9 CM	International Classification of Disease – 9 Clinical Modification
PCOS	Polycystic Ovary Syndrome
EGFR	Estimated Glomerular Filtration Rate
AHRQ	Agency for Healthcare Research and Quality

SUMMARY

In recent years several new drugs have been approved by the US FDA for the treatment of type 2 diabetes mellitus. Each class of drug is known to have its benefits, disadvantages and undesired effects in patients with pre-existing clinical conditions that may preclude its use in these patients. The American Diabetes Association published a treatment algorithm for first line and second line drug therapy as a guide for physicians in treatment of type 2 diabetes mellitus. Several studies have evaluated the treatment patterns using claims data analysis. However the level of concordance between clinical practice and the ADA guidelines has not been investigated. Also the effect of lab based evidence - impaired renal and liver function on physician prescribing behavior is not known. The aim of this study was to determine the degree of compliance of physician practice with the ADA guidelines and asses factors influencing these decisions.

A retrospective cohort study of patients with diabetes managed at one of the clinics that provide routine diabetes care in University of Illinois Medical Center at Chicago was conducted for period from January 2007 to October 2010. Patients newly starting drug therapy at any one of these clinics (Appendix A) were included in the study. Data from electronic prescription medication orders for diabetes was collected. Laboratory data collected included serum creatinine, creatinine clearance, alanine aminotransferase, aspartate aminotransferase and hemoglobinA1c levels. Patient demographics and all diagnosis data were also collected.

Descriptive analysis of the data showed that physicians at UIMCC were compliant with the ADA guidelines about 72% of the time when they prescribed metformin as first line therapy adjusting for any liver or renal impairment status of the patient. The next most widely used drug as first line therapy was sulphonylureas followed by Insulin. A mixed effect regression model to identify predictors for prescribing metformin demonstrated that renal function, type of clinic and hemoglobin A1c levels were statistically significant variables. Liver function markers ALT/AST were perfectly correlated with metformin prescription and hence not included in the model Patients with impaired liver function never got metformin. Patients with impaired renal function and higher haemoglobinA1c levels were less likely to receive metformin. Patients seen at the family medicine clinic were more likely to receive metformin than those seen at internal medicine or geriatric clinic.

This single site study is the first to document the compliance of physicians with the ADA guidelines and assess the effects of patient's clinical condition on prescribing behavior. It shows that physicians consider label information in their decision making process. Understanding these factors can help in defining the second line therapy towards a more streamlined management of diabetes.

1 INTRODUCTION

1.1 Overview

Type 2 diabetes is a chronic metabolic disorder that has several implications on the overall health of an individual. It is known to have many sequelae and hence effective control of blood glucose levels takes precedence in the realm of chronic care. Several oral medications and injectable drugs have been used over the years, each class having its own benefits and disadvantages. Moreover inter-individual variation in response to a medication and its dose necessitates the need to change or frequently adjust the dose to meet targeted blood levels of glucose. The American Diabetes Association, a national organization engaged in conducting continuing education and research in diabetes, released evidence based guidelines to assist practitioners in their prescribing strategy. While the guidelines for initiating drug therapy are well defined, they do not provide a clear strategy for achieving and maintaining glycemic goals when initial treatment fails. Also not much is known about the extent to which physicians incorporate these guidelines in their practice. The goal of this study was to1) investigate compliance of physician prescribing behavior with current ADA treatment guidelines 2) characterize the pattern of drug use, and 3) identify predictors of drug use. The results from this study will help in learning the real world prescribing behavior and the importance of clinical evidence behind the practice.

1.2 Background

The scientific advancement in treatment strategies for acute communicable diseases combined with lifestyle changes has resulted in a shifting of the leading cause of death from acute to chronic diseases.[1] Diabetes, heart disease, arthritis, stroke and some types of cancer are the most common preventable chronic diseases observed in the United States (US).[1] Chronic

disease accounts for 7 out of every 10 deaths in the US.[2] Diabetes was reported to be the seventh leading cause of death in 2007 with 23.6 million or 7.8% of the entire US population being afflicted with the disease. The incidence and prevalence of diabetes continues to grow with 1.6 million new cases being detected in 2007. Patients with diabetes have twice the risk of death compared to patients without diabetes at the same age. It is also the leading cause of blindness among older adults (age > 75 years), kidney failure and foot amputations in adults.[3]

The economic cost associated with diabetes in 2007 in the US was $174 billion. Of this, $116 billion was attributable to direct medical costs while $58 billion was attributable to indirect costs including lost workdays, restricted activity and disability.[4] Expenditures incurred by patients with diabetes are 2.3 times higher than those without diabetes and amount to an average amount of $11,744 per year with $6,649 being spent specifically on treating patients with diabetes. Every fifth dollar of health care expenditure is spent on a diabetic patient.[4] Racial and ethnic differences in the prevalence of diabetes are observed with a higher prevalence in Hispanics (10.4%) and non-Hispanic blacks (11.8%) compared non-Hispanic whites (6.6%) and Asians (7.5%).[3] A recent report by the Center for Disease Control and Prevention (CDC) estimates that the aging of the population and increase in high risk minority groups will result in 1 out of every 3 Americans suffering from diabetes by 2050.Currently, 1 in 10 Americans suffers from the disease.

Diabetes, which is characterized by hyperglycemia, has a significant impact on morbidity and mortality. It is a major risk factor for macrovascular and microvascular complications such as retinopathy, nephropathy, neuropathy, ischemic heart disease (IHD), stroke and peripheral vascular diseases. It is also associated with a decreased quality of life and life expectancy.[5-7]

Chronic debilitating diseases associated with the progression of the disease have made effective glycemic control a priority for physicians.[8]

Several clinical trials have been conducted to evaluate the effects of intensive glycemic control versus standard glycemic control in patients with type 1 and type 2 diabetes. The Diabetes Control and Complications Trial (DCCT) was conducted to compare the effects of intensive therapy and conventional therapy on the progression of diabetic retinopathy, neuropathy and nephropathy in patients with insulin dependent diabetes mellitus. The study found that intensive treatment retarded the progression of microvascular complications; however there was a two to three fold increase in the reporting of severe hypoglycemic events.[9] Although this was a type 1 study and may not predict outcomes in type 2 patients, it demonstrated that intensive control of diabetes helped slow down the advancement of sequelae of diabetes mellitus.

The United Kingdom Prospective Diabetes Study (UKPDS) was conducted in patients newly diagnosed with type 2 diabetes and had a follow up period of 10 years. The study sought to determine the effects of intensive therapy on the reduction of microvascular and macrovascular diabetes complications and the therapeutic advantages or disadvantages between different classes of drugs. The goal of the intensive therapy arm was to maintain median glycosylated hemoglobin (HbA1c) of 7.0% while that of the conventional therapy arm was a median of 7.9%. As with the DCCT study, the UKPDS concluded that lowering blood glucose levels (9% to 8% HbA1c) was associated with a reduction (35%) in microvascular events. There was a non-statistically significant reduction in diabetes induced CV mortality ($p=0.052$) Patients starting therapy on metformin had a beneficial effect in terms of reduced cardiovascular complications, all cause and diabetes specific deaths by about 33% ($P < 0.0023$) while sulphonylureas and insulin had no effect. This is possibly related to weight gain which is one of

the main disadvantages of using sulphonylurea or insulin therapy.[6, 7] While this study demonstrated a continuous association between reduction in blood glucose levels toward normal levels and risk of complications it did not determine any particular cut-off values.

A similar Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial sought to determine the effect of intensive therapy (HbA1c < 6.0%) and standard therapy (HbA1c 7.0%-7.9%) on microvascular events. The intensive therapy intervention was stopped before the trial ended since higher mortality due to cardiovascular complications was observed and patients were reassigned to the standard treatment arm. During the reassignment, it was observed that advanced nephropathy, diabetic eye complications and peripheral neuropathy were not statistically significantly different between the groups. Micro and macroalbuminuria events were significantly lower in the intensive group at reassignment and at end of the study. A 0.27% per year increase in all-cause mortality in intensive treatment arm led to cessation of treatment. The study concluded that the benefits of reduction in microvascular events should be considered in the light of adverse events such as increased all-cause mortality and a two to three fold increase in hypoglycemia incidents.[10, 11]

Although the above trials do not reach a consensus on glycemic goals to be achieved by therapy, they demonstrate the importance of sustaining glucose levels close to non-diabetic range with the long-term benefits of reducing diabetes related complications. The American Diabetes Association (ADA) in consensus with the European Association for Study of Diabetes (EASD) released a statement in 2006 outlining ideal blood glucose levels and treatment strategies to maintain them at goal to reduce the morbidity burden associated with diabetes. The ADA recommends maintaining HbA1c level < 7% for the population with the aim of keeping it “as close to normal (<6%) as possible without significant hypoglycemia”.[8, 12]

The many available treatment options and addition of newer classes of anti-diabetic drugs in the last decade has led to increased ambiguity regarding the appropriate treatment approach. While there have been a number of studies that have compared the mechanism of action, benefits and disadvantages of various drugs within a class, there have been insufficient clinical trials comparing the effectiveness of drugs between different classes that could serve as a strong foundation for evidence-based practice.

Several studies have been directed toward maintaining glycemic levels within normal HbA1c levels with a goal of retarding the progression of complications from hyperglycemia. A study conducted to compare failure rates as an outcome defined by change in therapy after the commencement of initial therapy reported that there existed an association between the initial therapy and failure rates.[13] A study conducted in Scotland sought to determine the initial and continual use of sulphonylureas and biguanides. It also determined the time between the first anti-diabetic prescription and the first insulin prescription.[14] Another study on a large prescription data set in the Netherlands classified initial oral therapy into five broad categories and described the proportions that resulted in any change from baseline therapy.[15]

1.3 Purpose of the Study

However the studies described above did not take into account the influence of compromised liver function or renal function on selection of initial therapy or the need to switch, change or discontinue medication following initial therapy. The thiazolidinedione class of drugs is metabolized by the liver and is contraindicated in patients' with reduced liver function.[16, 17] Metformin is primarily eliminated by the kidneys and is contraindicated in patients with renal impairment due to the risk of lactic acidosis.[16-19] Presence of these preconditions significantly affects the rationale for prescribing particular oral diabetic medications in patients with type 2

diabetes.. The American Diabetes Association (ADA) and the European Association for the study of diabetes published its recommendations for first line therapy in the year 2006 and updated it with minor modifications in the year 2009. While it strongly advocates the use of metformin as initial therapy, the guidelines for second line treatment are ambiguous. Although not mandatory, these guidelines help direct practitioners with a uniform treatment strategy.[8, 12] The purpose of this study was to investigate physician compliance of prescribing behavior in type 2 diabetes with the ADA guidelines and describe drug utilization patterns.

Research questions

1. To what extent are physicians at University of Illinois Medical Center at Chicago (UIMCC) compliant with existing ADA guidelines in initial treatment of patients with type 2 diabetes?

2. What observable individual patient characteristics predict assignment to initial drug therapy in patients with type 2 diabetes?

3. What is the pattern of utilization pattern of oral diabetes drugs after initial prescription?

4. What observable individual patient characteristics predict assignment to secondary drug therapy in patients with type 2 diabetes?

Objectives and Hypotheses

The objectives of this study and the supporting hypotheses are described below.

1. The first objective was to determine level of concordance between ADA prescribing guidelines for initiating drug therapy and current practice in University of Illinois Medical Center at Chicago (UIMCC)

2. The second objective was to identify individual patient characteristics that predict assignment to metformin as initial drug therapy.

Hypothesis 1 (H_1): Individual patient characteristics of renal impairment and liver impairment, are negatively associated with use of metformin as initial therapy.

(H_{a1}): Individual patient characteristics of renal impairment and liver impairment, are not statistically associated with use of metformin as initial therapy.

3. The third descriptive objective of the study was to characterize the utilization patterns of oral diabetic drugs after treatment failure with metformin

1.4 Significance of the Study

Previous studies focused on oral diabetic medication use have shown that a quite a significant proportion of newly diagnosed patients are required to change, add or discontinue the initial therapy within the first year.[14, 15] However these evaluations only describe the variation in prescribing pattern from a select few possible baseline therapies. Moreover they do not specify the class or combination of drugs to which the initial prescription changed. In this study we examine the initial drug selection as well as the drug choices that follow the initial prescription.

The present study will document the nature of the variation and identify possible clinical and demographic variables that may be associated with prescribing variation. Results from this study will help describe the current trends in prescribing decisions in type 2 diabetes, investigate the basis for these decisions and lay the foundation for larger studies in medical practice external to UIC. It will help evaluate the extent to which physicians follow recommended guidelines and identify potential reasons for deviating from guidelines. The long term goal of the project is to contribute to improving the safety, effectiveness and cost effectiveness of drug therapy for type 2 diabetes.

2 LITERATURE REVIEW

Diabetes is broadly classified into type 1, type 2 and gestational diabetes. Diabetes type 1 or juvenile diabetes or insulin-dependent diabetes is an auto immune disorder that manifests in childhood or adolescents. It results when the body's immune system damages the pancreatic cells that produce insulin. Type 1 is more commonly associated with genetic, environmental or autoimmune disorders unlike type 2 that is associated with obesity, family history of diabetes, sedentary lifestyle or age as risk factors and can develop at any time irrespective of an individual's age. Gestational diabetes is a temporary condition that is observed in pregnant women usually during advanced stages of pregnancy due to hormonal imbalance.[20-22] Since the aim of this study was to study the patterns of oral anti- diabetic medication use in patients suffering from type 2 diabetes, this section will cover various topics related to type 2 diabetes.

2.1 Type 2 diabetes

Diabetes mellitus type 2 or non-insulin dependent or adult onset diabetes is a metabolic disorder where in blood glucose level exceeds normal values. The physiology, epidemiology, some sequelae and some co-morbidities associated with the condition are described in following subsections.

2.1.1 Definition, physiology and epidemiology

Food is converted to glucose by the body and is circulated by the blood. Insulin is a hormone produced and secreted by the beta cells of Islets of Langerhans in the pancreas. Insulin helps in regulating the conversion of carbohydrates and fats into glucose and uptake of glucose by cells in the body.[17, 22] Type 2 diabetes results when inadequate amount of insulin is secreted by the pancreas, commonly known as insulin deficiency, or when the body is unable to use the

circulating insulin, a condition known as insulin resistance. Both conditions result in increased glucose circulating in the blood stream and manifest as diabetes. The condition may go unnoticed for several years as the intensity of hyperglycemia and its symptoms may not be noticeable in the early stage of disease development.[23]

The current WHO criterion for diagnosis of diabetes is fasting plasma glucose level of ≥ 126mg/dl or 2 hour plasma glucose level ≥ 200mg/dl.[24] Glycosylated hemoglobin is an accurate method of monitoring plasma glucose levels over a period of 3-4 months. It is a reflection of the overall glucose control over a period of time and is not strongly affected by sporadic changes in diet or missed prescription doses. It is an irreversible process in which glucose reacts with hemoglobin to form glycosylated hemoglobin. These levels tend to be higher (greater than 7%) in patients with diabetes than in healthy individuals.[23, 25, 26]The most recent report published by American Diabetes Association in 2010 states the criterion for diagnosis of diabetes is HbA1c ≥ 6.5% or fasting plasma glucose level of ≥ 126mg/dl or 2 hour plasma glucose ≥ 200mg/dl.[27, 28] The ADA recommends initiation or change of therapy when the HbA1c levels ≥ 7% with the goal of maintaining it at levels < 7%. In a non-diabetic individual the HbA1c levels is on an average ≤ 6.0% with 6.1% being the upper limit. The final goal of a therapeutic regimen is to maintain glucose levels as close to the non-diabetic range as long as it does not induce or potentiate the risk of hypoglycemia.[8, 12]

About 90%-95% of diabetes cases can be attributed to type 2 diabetes due to insulin deficiency or insulin resistance. Obesity, family history of diabetes, sedentary lifestyle, prior history of gestational diabetes mellitus, glycosuria and diagnosis of Polycystic Ovary Syndrome (PCOS) are considered as risk factors for type 2 diabetes.[27] Progression of the disease and

gradual destruction of beta cell functions requires some patients to switch from oral agents to insulin therapy.[8, 23]

2.1.2 Co-morbidities and sequelae associated with diabetes

Heart disease and stroke

In 2004 diabetic patients are 2-4 times at a higher risk of death due to heart disease than non-diabetic patients. Heart disease was reported 68% of the time and stroke was reported 16% of the time on diabetes-related death certificates.[3, 21]

High blood pressure

Seventy-five percent of diabetic patients in 2003-2004 had blood pressure greater than or equal to 130/80 mmHg or tend to be on prescription medications for high blood pressure.[3, 21]

Blindness

Diabetes is responsible for 12,000 to 24,000 cases of blindness each year due to retinopathy. [3, 21]

Kidney disease

End stage renal disease (ESRD) is one of the most complicated irreversible manifestations of diabetes. In 2005 alone, 178,689 people were on chronic dialysis as a result of ESRD due to diabetes. [3, 21]

Nervous system disease

Nervous system damage occurs in 60% to 70% of diabetic patients although the intensity differs from mild to moderate. Thirty percent of diabetic people aged 40 years have impaired nerve sensation in their feet. Progression of the disease can lead to amputation of extremities.[3, 21]

Amputations

About 71,000 lower-limb amputation operations were conducted in diabetic patients in the year 2007. [3, 21]

Dental disease

CDC reports that, on average, diabetics are at twice the risk of periodontal disease compared to non-diabetics. Diabetics with worse control over A1c levels (A1c > 9%) are three times more likely to suffer from severe periodontal disease than non-diabetics.[3, 21]

Complications of pregnancy

Poor glycemic control during initial stages of pregnancy can cause birth defects or spontaneous abortions while in later stages of pregnancy may lead to larger than normal babies resulting into a risk for the mother and the baby.[3, 21]

Other complications

Other life threatening complications of diabetes are ketoacidosis, hyperosmolar coma, reduced immunity to pneumonia and influenza. Persons aged over 60 years are 2-3 time more likely to demonstrate reduced physical stamina in their daily activities than those without diabetes at the same age.[3, 21]

The UKPDS, DCCT (although type 1) , and ADVANCE studies have demonstrated the importance of glucose control and compared the effects of intensive vs. conventional and less intensive glucose control on microvascular and macrovascular outcomes.[29 30, 31] A comparison of tight glucose control with insulin or sulphonylurea (FPG < 6 mmol/L) to conventional treatment with diet alone showed that intensive control reduced risk of diabetes related clinical endpoints (fatal or nonfatal MI, stroke, renal failure, peripheral vascular disease) by 12% (p=0.029) compared to the conventional treatment group. Overall it reduced the microvascular outcomes

but did not have any effect on macrovascular outcomes.[31] A sub analysis of the UKPDS comparing clinical endpoints between metformin and intensive treatment (mean fasting plasma glucose < 6mmol/L) with sulphonylurea or insulin in overweight patients showed a statistically significant reduction in all-cause mortality (p=0.021), any diabetes related endpoint (p=0.0034) and stroke (p=0.032). In addition it was not related with any hypoglycemic events or significant weight gain.[32] The ADVANCE trial reported the results of intensive therapy (mean HbA1c≤ 6.5%) with modified release gliclazide compared to any standard therapy HbA1c= 7.3%) that the patient was initially assigned. The study found that addition of modified release gliclazide reduced the incidence of microvascular events (HR=0.86, P=0.01) and combined microvascular and macrovascular event (HR= 0.90, P=0.01) but had no effect on macrovascular outcomes when compared to standard treatment.[29]

2.2 Management of type 2 diabetes - Lifestyle modifications

Advancing age, obesity and history of diabetes in the family have been identified as a major risk factors for diabetes in a study conducted by National Institute of Diabetes and Digestive and Kidney Diseases. Although not highly correlated, gender and lack of sufficient exercise were also found to be risk factors for diabetes.[33] Surgical interventions such as gastric bypass surgery in highly obese people have demonstrated that it helps in maintaining weight and glucose levels close to normal in patients with diabetes.[34] Weight loss also helps in improving hypertriglyceridemia, and hyperuricemia and maintaining these benefits over time.[35] A weight loss of more than 20kgs over time had almost a curative effect on the subjects.[8] Intensive lifestyle along with metformin therapy is found to reduce the need for drug therapy for management of comorbidities like hypertension and hyperlipidemia in patients with diabetes when compared to treatment with metformin and placebo.[36] Intensive dietary control has also

shown that it is an effective treatment in patients recently diagnosed with diabetes and can be used in the initial stages instead of oral medications or insulin.[37] These studies emphasize the important role of weight loss in reducing the risk associated with diabetes mellitus.. A life style intervention with weight loss, exercise regimen and diet control is often the first step in treatment of patients with newly diagnosed with diabetes and recommended by the ADA. Pharmacological therapy is often started immediately with lifestyle interventions if the glycosylated hemoglobin is high.

2.3 Management of type 2 diabetes—Drugs used in diabetes

Failure to maintain weight loss and progressive loss of beta cell functions requires the use of anti-diabetic agents in most patients for sustained maintenance of glycemic goals. The choice of an anti-diabetic drug and its dose depends on drug-related factors such as its effectiveness in lowering glucose levels, its side effects, safety profile, cost and patient related factors such as baseline severity of hyperglycemia, other associated comorbidities, allergies, contraindications and tolerability. Since it dependent on several patient factors, the drug and dose needs to be individually titrated to achieve stable levels at initiation and during the course of the treatment.[8, 12] The most commonly accepted strategy is to use a drug with rapid action and higher glucose lowering property when HbA1c > 8.5% and a drug with slower onset and lower glucose reducing property when HbA1c < 7.5%.[8, 12] The following sections describe the hypoglycemic agents that are used in treatment of diabetes in the U.S.

2.3.1 Biguanides

Galega officinalis was used in the early twentieth century in Europe due to its ability to lower glucose levels attributed to a compound guanidine. However toxicity associated with use of guanidine led to clinical investigation of related biguanide derivatives phenformin, buformin

and metformin. Phenformin and buformin were withdrawn from many countries including U.S. owing to lactic acidosis as a major adverse event. Metformin is not only an inexpensive drug but also has several other beneficial pharmacologic effects which include weight stabilization/reduction, improvement in lipid profile, reduced chances of hypoglycemia and other beneficial vascular effects. Metformin has several pharmacological pathways that make it favorable as first line therapy. It requires the presence of insulin and primarily acts by reducing gluconeogenesis i.e. the production of glucose from noncarbohydrate sources as well as glycogenolysis i.e. glucose production from glycogen and oxidation of fatty acids in the liver. It decreases HbA1c levels by 1%-2%.[17, 38-40]

Pharmacokinetics and Contraindications:

Metformin has a bioavailability of 50%-60% and reaches peak plasma concentrations in 2 hours. It is absorbed from the small intestine and has a half-life of 2-5 hours. Since most of the drug is eliminated unchanged in the urine it is typically not prescribed in patients with more than mild renal impairment. .[17-19, 39-41] Although the relationship between metformin as a cause of lactic acidosis has not been established, it is can precipitate the risk of lactic acidosis in the presence of other conditions. Metformin increases the conversion of glucose to lactate and this action is potentiated in presence of liver dysfunction. Hence it is contraindicated in patients with impaired liver function. [17]It is also given in combination with drugs from other classes. Renal excretion is competitively inhibited when administered simultaneously with cimetidine, resulting in increased levels of metformin in the blood. Hence it should be used carefully in patients on cimetidine. It is also contraindicated in patients with cardiac insufficiency, alcohol abuse or presence of metabolic acidosis. Metformin can decrease the absorption of cyanocobalamin when used over a long period of time. Although it does not have a potential to cause anemia, annual

examination of hemoglobin levels is recommended along with measurement of creatinine clearance.[17, 39]

2.3.2 Sulphonylureas

Sulphonylureas (SU) belong to insulin secretagogues class of drugs and acts by stimulating the release of insulin from β cells of Islets of Langerhans in the pancreas. It binds to sulphonylurea receptor on β cells of the pancreas which results in depolarization and opening of the calcium channels. The influx of calcium causes insulin to be released due to its action on calcium dependent proteins. Since the release of insulin by sulphonylureas is not regulated by levels of blood glucose, hypoglycemia is a common side effect associated with this class of drugs especially in patients with irregular eating habits and tightly controlled blood glucose. It is used in patients who are not responsive to increased glucose levels but have retained their ability to secret insulin.[17, 39, 42] It is effective in reducing the HbA1c levels by 1%-2%.[8, 17] The first generation SU include tolbutamide, chlorpropamide, tolazamide and acetohexamide while second generation SU include glyburide, glipizide and glimepiride.

The second generations SU differ from the first generation SU essentially in their potency, dose, duration of action and the extent to which they cause hypoglycemia. The SU currently in use in the U.S. are chlorpropamide, glyburide, glipizide and glimepiride.[39, 42] Sulphonylureas are commonly used first-line oral anti-diabetic therapy. The dose needs to be titrated individually after careful monitoring of blood glucose levels on initiation of therapy. Since the duration of action of different sulphonylureas ranges from 12 to >24 hours therapy often involves combination of different sulphonylureas or combination with drugs from other classes to obtain optimal and stable HbA1C levels. SU treatment is effective as long as β cell

function is intact. Progression of β cell impairment requires the need to switch to another class of drug or insulin treatment.[17]

Pharmacokinetics and Contraindications:

SU has a high volume of distribution as it is bound to plasma protein albumin. They are metabolized in the liver and eliminated by the kidneys on conversion to active or inactive metabolites.[39] The pharmacokinetic properties of drugs in this class are described in the table I

Table I Pharmacokinetics of sulphonylureas

Sulphonylureas	Equivalent dose (mg)	Half-life (t ½ hour)	Duration of action (hours)
First generation			
Tolbutamide	1000	4.5-6.5	6-12
Chlorpropamide	250	36	Up to 60
Tolazamide	250	7	12-14
Acetohexamide	500	6-8	12-18
Second generation			
Glyburide	5	1.5-3	Up to 24
Glipizide	5	4	Up to 24
Glimepiride	2	2-3	Up to 24

Source: Foye WO, Lemke TL, Williams DA. Foye's Principles of Medicinal Chemistry. Sixth ed: Wolters Kluwer; 2008.

SU are contraindicated in patients suffering from type 1 diabetes due to their inability to produce insulin and in type 2 diabetes patients scheduled for surgery as insulin is generally used to maintain glucose levels. Although not contraindicated, it is not recommended in obese patients as it leads to weight gain. Allergic reactions are rare. Alcohol-induced facial flushing reaction maybe observed in patients on chlorpropamide.[40] Several drugs are known to have the capability to induce hypoglycemia when co-administered with SU necessitating dose adjustment. Warfarin, monoamine oxidase inhibitors (MOI), chloramphenicol, phenylbutazone decrease the metabolism of SU, while salicylates, probenecid, allopurinol reduces the renal excretion. Some

drugs also cause displacement of SU from plasma proteins and hence the dose needs to be titrated individually in patients.[17]

2.3.3 Thiazolidinediones

Thiazolidinedine (TZD) class of drugs includes troglitazone, rosiglitazone and pioglitazone. Troglitazone was withdrawn almost immediately upon introduction (1997) in the UK and in 2000 in the US due to hepatotoxicity. Since then rosiglitazone and pioglitazone have been used in treatment of diabetes since no hepatotoxicity was observed in the newer drugs.[17, 43] Increasing evidence on adverse events led to the FDA recently placing restriction on the use of rosiglitazone and complete withdrawal from the European market.[44] TZD's require the presence of insulin and its main mechanism of action is to increase glucose uptake by stimulating peroxisome proliferator-gamma receptors in adipose tissue and increasing insulin sensitivity. It also reduces gluconeogenesis and increases lipogenesis which further increases glucose utilization. TZD's can be used as monotherapy or in combination with metformin, SU or insulin.[17, 45] They are effective in reducing HbA1c levels by 0.5%-1.5%.[46]

Pharmacokinetics and Contraindications:

Rosiglitazone and pioglitazone are rapidly metabolized in the liver and reach peak plasma concentration in 1-2 hours. Rosiglitazone is eliminated in the urine while pioglitazone is eliminated in bile. They are highly protein bound however the low concentrations do not result in displacement or interaction with any other drugs. They are metabolized by cytochromes that do not interfere significantly with metabolism of other drugs. In Europe, they are used as primary therapy in patients who have a contraindication for metformin. Glitazones have been known to cause fluid retention resulting in increased plasma volume and subsequent reduction in hemoglobin levels. Hence they are contraindicated in patients suffering from congestive heart

failure and regular evaluations of hemoglobin levels are suggested.[16, 17, 47] Since they are metabolized extensively by the liver and troglitazone was associated with fatal hepatotoxicity, periodic liver function tests are highly recommended. Some studies demonstrated a higher risk for edema in patients receiving TZD's in combination with insulin. Although not contraindicated caution should be exercised when administering a combination therapy of TZD and insulin. It is also not recommended during pregnancy unless the benefits outweigh the risks. TZD's may resume ovulation in women suffering from polycystic ovary syndrome and result in preganacy.[16, 17]

2.3.4 α Glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose and miglitol act by delaying the process of digestion and thereby absorption of carbohydrates from the intestinal lumen. α-Glucosidase inhibitors act by inhibiting the α-glucosidase enzymes from breaking complex carbohydrates into monosaccharide and hence temporarily interrupt the digestion and absorption process thereby preventing post-prandial hyperglycemia. It is taken before meals with a diet rich in complex carbohydrates.[8, 12, 17] It reduces the HbA1c levels by 0.4%-0.8%. These drugs have a fairly high rate of discontinuation (25%-45%) owing to flatulence as a common side effect.[39, 48]

Pharmacokinetics and Contraindications:

These drugs are not systematically absorbed into the bloodstream as they are only responsible in delaying the absorption of carbohydrates from the intestine. It is degraded by the enzymes in the small intestine and the metabolites absorbed into the bloodstream are eliminated in the urine. It is contraindicated in patients with significant renal impairment, inflammatory bowel disease and ulcers in the colon.[17, 39]

2.3.5 Glinides

Repaglinide and nateglinide are commonly used to control post-prandial hyperglycemia. It is a rapid acting insulin releaser with insulin released within 15-20 minutes of administration and having pharmacological effect lasting for about 3 hours. Hence these are taken about 15-20 minutes before meals and commonly used in patients who are otherwise on non-pharmacological methods for insulin control. It is also administered with drugs from other classes of oral anti-diabetics; however not with SU since both classes of drugs use the same biological pathway as calcium channel opening agents whilst binding to different receptors.[17] There is no impact on weight change and lesser chances of drug induced hypoglycemia due to shorter duration of action**.** However it requires more frequent administration when administered as monotherapy. It is a viable option when used with metformin.[40]

Pharmacokinetics and Contraindications:

Glinides have rapid onset of action with plasma peak concentrations being achieved in 60 minutes and 20 minutes with repaglinide and nateglinide respectively. The drugs are metabolized by the liver and excreted in bile. The reduction in HbA1c levels is comparable to that achieved by SU (1%-2%) without inducing any hypoglycemia.[17, 40, 49]

2.3.6 Glucagon like peptide 1 (GLP-1) agonists

Exenatide injection is administered in patients who are not sufficiently stable on metformin or sulphonylurea. GLP-1 is an incretin hormone secreted by endocrine L cells in the small intestine. GLP-1 is released when there an increase in the plasma glucose levels. It stimulates the release of insulin, inhibits the release of glucagon and retards gastric emptying.[39, 40] However it is very short acting (t ½ = 90 seconds) and the release stops when glucose serum levels are restored. Moreover it is actively degraded by dipeptidyl peptidase IV enzyme resulting

in the short half-life. Exenatide is homologous to human GLP-1 and mimics its actions while having a longer duration of action. It is administered twice a day and results in 0.5%-1.0% reduction in HbA1c levels. It is typically used in conjunction with SU, metformin and/or TZD.[50-52]

2.3.7 Dipeptidyl peptidase 4 inhibitors (DPP-4 Inhibitors)

As mentioned in the previous section DPP-4 is responsible for rapid degradation and inactivation of GLP-1. Sitagliptin and saxagliptin are inhibitors of DPP-4 and help in prolonging the action of GLP-1. Sitagliptin is an oral DPP-4 inhibitor that was approved by the FDA in October 2006. It is recommended for use as monotherapy or in combination with metformin or TZD's.[39, 40] Several clinical trials were conduction to compare the efficacy of Sitagliptin as monotherapy. It was found that the drug was well tolerated and did not lead to any adverse hypoglycemic events or significant weight gain. The overall reduction in HbA1c levels was consistent in the trials and typically ranged from 0.4%-0.9%.[53-56]. Many randomized clinical trials have assessed the effect of adding sitagliptin to existing metformin, TZD or SU therapy. All trials found a statistically and clinically significant reduction in HbA1c levels when compared to existing therapy without sitagliptin.[56-61] Saxaglitin is currently in the investigational phase as an supplemental drug, however clinical trials have demonstrated it to be promising future drug with 0.7%-0.8% decrease in HbA1c levels.[8, 12, 56]

2.3.8 Amylin agonists

Amylin is an amino acid peptide that is secreted along with insulin during ingestion of meals. It is found that patients with type 2 diabetes secrete insufficient quantities of this peptide which retards the rate of gastric emptying and reduces the quantity of glucagon released by the liver thereby alleviating hyperglycemic conditions. Pramlitide injection is an analogue of amylin

that is approved for use with insulin or its analogues. It has shown to reduce HbA1c levels by 0.5-0.7% with nausea being the only reported side effects which improves with the course of the therapy.[8, 39, 40, 62, 63]

Pharmacokinetics and contraindications:

Pramlitide reaches peak levels in about 20 minutes with a half-life of 29 minutes and is eliminated by the kidneys. Owing to its rapid onset of action and short duration of action, it is administered just before meals. It has not demonstrated any contraindications till date.[8, 39, 64]

2.3.9 Insulin and its analogues

Human insulin and its analogues is the standard treatment used in type 1 patients. Failure of oral hypoglycemic agents to maintain HbA1c levels and progressive loss of β cell function requires the use of insulin in type 2 diabetes patients. Structurally insulin is composed of two amino acid chains A and B connected by two disulphide bonds. Human insulin is synthesized by inserting the genes responsible for formation of the amino acids into Escherichia coli and subsequent fermentation.[39, 65] Analogues of insulin chiefly differ in their duration of action. Faster acting analogues show peak pharmacological effect in 2-4 hours of administration and have duration of action of 6-8 hours. Longer acting analogues comparatively have duration of action for up to 24 hours. They are formulated injectable suspensions to release the drug uniformly over extended period of time thereby reducing the possibility of hypoglycemic events compared to faster acting analogues.[39, 40]

Pharmacokinetics and contraindications:

Insulin is primarily metabolized in the liver and eliminated by the kidneys. Although not contraindicated, hypoglycemia is the most common adverse event associated with its use.[9, 39, 66, 67] Severe hypoglycemia can lead to significant permanent brain damage. Ingestion of alcohol by

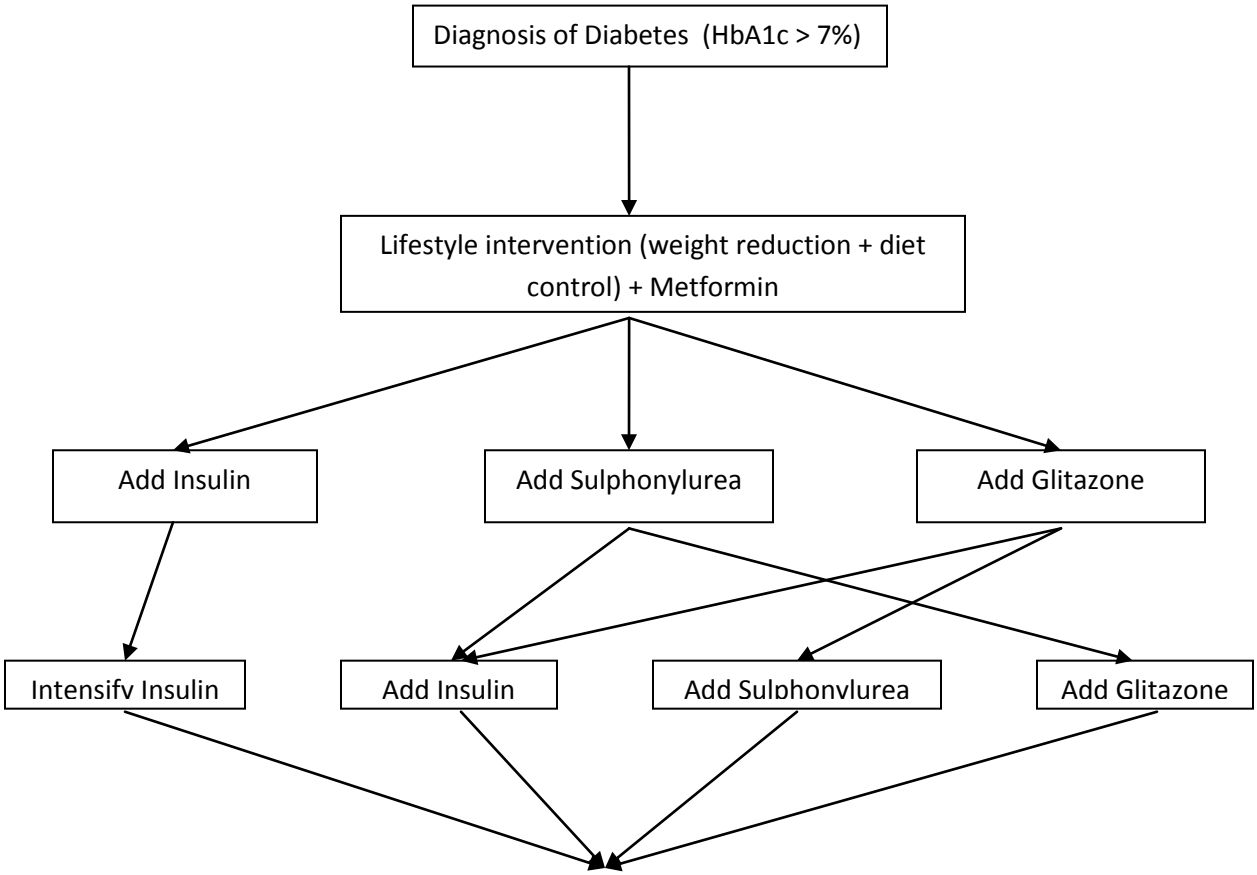
patients on insulin can trigger hypoglycemic events as alcohol inhibits gluconeogenesis. Patients are advised to follow regular eating habits and avoid sudden strenuous exercise.[39, 40]

2.4 Guidelines on treatment of type 2 diabetes

The many available treatment options and the approval of newer drugs in the last decade have increased uncertainty regarding the best treatment approach. The American Diabetes Association (ADA), in consensus with European Association for Study of Diabetes (EASD) released a statement in 2006 outlining treatment strategies for diabetes to help direct practitioners into a uniform treatment pathway. While it strongly advocates use of metformin as initial therapy, the guidelines for second line treatments are ambiguous.[8, 12] Moreover contraindication associated with metformin necessitates the use of other oral agents as initial therapy when lifestyle modification interventions fail to maintain HbA1c levels at goal. The International Diabetes Federation (IDF) published its guidelines in 2005 and updated it in 2007. The two institutions differ not only in the targeted glycemic goal (ADA 7.0% vs. IDF 6.5%) but also their treatment recommendations.[68]

The algorithm developed by ADA in 2006 is described in Fig 1. ADA recommends evaluation of HbA1c levels every 3 months following diagnosis until HbA1c < 7% and then every 6 months.[8, 12]

Figure 1. American Diabetes Association 2006 guidelines

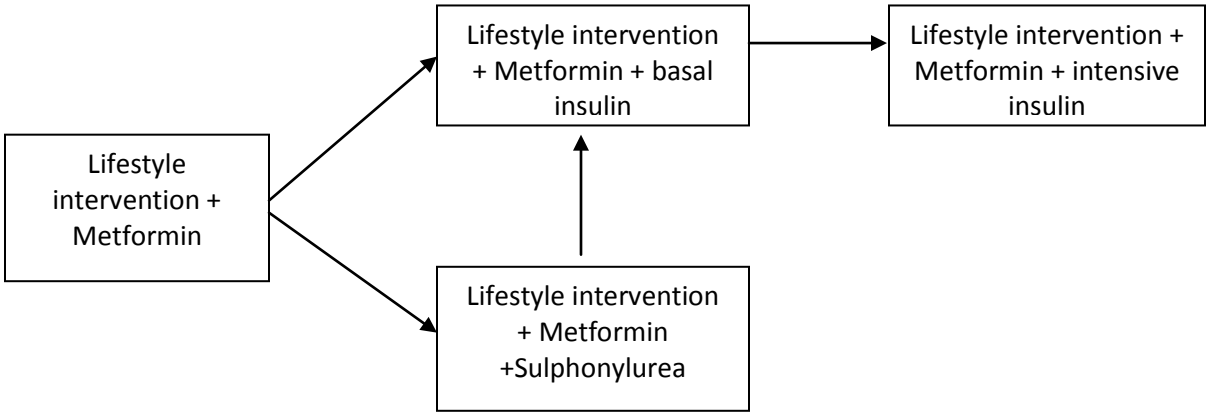


Source: Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. Aug 2006;49(8):1711-1721.

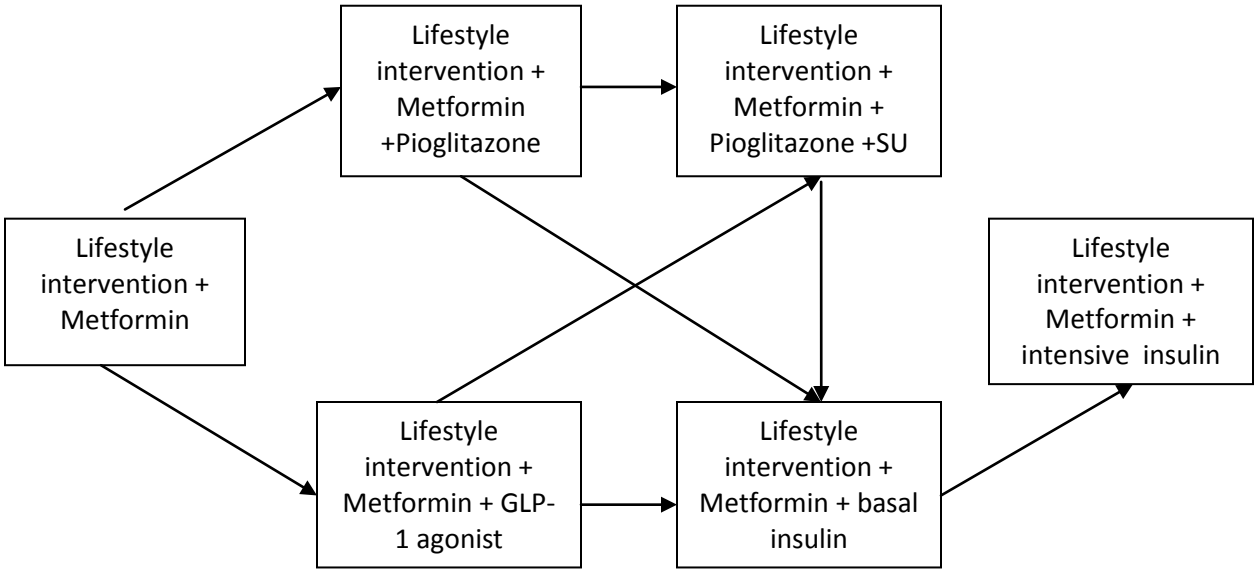
As shown in Fig 1. The ADA guidelines propose commencement of treatment on metformin, with addition of insulin, SU or Glitazone as supplemental drugs. Patients should be started on low dose metformin and the dose gradually increased once GI side effects, if any, have stabilized. The algorithm does not provide any guidance on the use of pramlintide, exenatide, glinides or α-glucosidase inhibitors due to shorter duration of action, lower effectiveness and cost.[8]

Figure 2. Updated ADA algorithm - 2009

Tier 1.



Tier 2.



Source: Nathan DM BJ, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2008;31(12):1-11.

The guidelines were updated in 2009 to classify the treatment options into Tier 1 (well validated core therapies) and Tier 2 (less validated core therapies). Tier 1 included initiation of therapy on metformin accompanied by lifestyle interventions followed by addition of basal insulin or SU as deemed appropriate by the physician. Tier 2 included initiation of therapy on metformin and lifestyle interventions followed by addition of pioglitazone or GLP-1 agonist. Addition of SU to metformin and pioglitazone or basal insulin to metformin can be implemented if targeted glycemic levels (HbA1c < 7%) are not achieved. The last step in managing hyperglycemia when all other combinations fail is the use of metformin with insulin.[12]

The statement drew some criticism on its publication in 2009 for suggesting the introduction of insulin as an add on drug when secondary failure was observed with metformin and the conflicts of interest between authors due to their affiliation with the pharmaceutical industry. A study demonstrating the safe use of insulin early during the course of therapy and longstanding reputation of the authors helped justify the algorithm.[68-70]

The IDF guidelines in comparison with ADA guidelines are vague and directed towards management of post meal surge in glucose levels. Also IDF has a more aggressive target of HbA1c < 6.5%. It suggests the use of alpha-glucosidase inhibitors, amylin analogues, DPP-4 inhibitors, glinides, GLP-1 agonists and rapid-acting insulin to achieve these targets.[5, 71, 72] The document does not provide any algorithm unlike the ADA document or outline methods to initiate or titrate the dose for each individual.[68]

2.5 Issues in current treatment selection

Metformin is eliminated by the kidneys. It is contraindicated in patients with renal impairment (creatinine ≥ 1.5 in men, ≥ 1.4 in women) due to risk of lactic acidosis. However there are reports of metformin being prescribed in patients about 25% of the time even after

diagnosis of this contraindication.[18] Several studies conducted to determine the association between metformin and lactic acidosis did not find any causal relationship and attributed lactic acidosis to causes other than metformin.[16]. However renal failure leads to accumulation of metformin and hence is contraindicated in renal dysfunction.[73-76] In patients with metformin contraindication, there are no specific recommendations for alternate initial therapy. Practitioners must use their knowledge, past experience and instinct to make appropriate decisions. The most common second line drugs are sulphonylureas, but studies have consistently demonstrated hypoglycemia and weight gain as adverse events associated with their use.[16, 42] Inability to maintain stable levels of HbA1c requires addition of other antidiabetic agents or a switch between different classes of drugs such as thiazolidinediones (TZD's), glinides, α-glucosidase inhibitors or the more expensive alternatives such as glucagon like peptides, amylin agonists and dipeptidyl peptidase 4 inhibitors.. TZD's are contraindicated in patients with liver dysfunction and have recently been under close scrutiny due to results from a meta-analysis concluding an approximately 55% increased risk for congestive heart failure and fluid retention compared to patients not on TZD's.[16, 17, 43, 47] A retrospective cohort study by Delea et al. studying the effect TZD's on heart failure found that patients on TZD's had a HR of 1.76 for heart failure compared to patients on oral diabetic medications other than TZD's.[77] A meta-analysis by Nissen et al. assessed the effect of rosiglitazone on cardiovascular mortality and morbidity. Odds ratio for MI was reported to be 1.43 (95% CI = 1.03, 1.98; p=0.03) while odds ratio (OR) for death from cardiovascular death was reported to be 1.64 (95% CI = 0.98, 2.74; p=0.06) for rosiglitazone group versus control group.[78] Increasing evidence on adverse events led to the FDA recently placing restriction on the use of rosiglitazone and complete withdrawal from the European market.[44]

2.6 Current treatment patterns and study of factors affecting utilization of diabetes drugs

Donnan et al. focused on determining the changes in oral antidiabetic therapy and time required to switch from oral anti diabetic therapy to insulin therapy in a cohort of patients suffering from type 2 diabetes. The study included patients with a new prescription during the two and half year study period. About 72% of patients continued on the therapy they were initiated through the study period, but 17% of patients on oral anti-diabetics (11% of sulphonylurea users and 6% of metformin users) switched to insulin, and 9% of the entire study population died during the follow up period. The median time to switch therapy was 6 months while rate of switching to insulin was reported at 5.84% per year.[14]

A Canadian study using Saskatchewan heath outpatient prescription database assessed the effectiveness of starting on a metformin therapy versus sulphonylurea therapy. Effectiveness was measured as a delay in onset of secondary failure defined by change in therapy to a combination therapy or any other monotherapy. Patients starting on metformin monotherapy were found to progress to combination (HR 0.79 CI = 0.71-0.87) or insulin therapy (HR 0.65 CI = 0.51-0.82) much later than those starting on sulphonylurea therapy as indicated by a lower hazard ratio. Hence initial therapy with metformin may be responsible for retarding the loss of β cell function. Also metformin users were more likely to switch therapies compared to SU monotherapy group (HR 1.43, CI = 1.17-1.75). However this was more likely because the practice pattern during the study period in the early nineties favored the use of SU rather than the drug effects as indicated by the number newly diagnosed patients (71%) on SU.[13]

Plat et al, using a data from PHARMO record linkage system data on patients in Netherlands, showed that metformin and sulphonylurea monotherapies were the most frequently prescribed initial therapy followed by TZD monotherapy. The number of patients who continue

with the initial therapy varies by drug class (46% of TZD users and 60% of SU users). The most important observation was that more than 40% of patients change their medication in the first year. Of the patients who were initiated on monotherapy 15-25% needed an add-on drug to maintain stable HbA1c levels while 16-25% discontinued the initial monotherapy drug.[15]

A Dutch study in a general healthcare center setting by Spoelstra et al. sought to determine factors associated with switching from oral anti diabetic drugs to insulin therapy. This four and half year longitudinal study included comorbidity, laboratory results and medication use data on 152 patients concluded that younger age at diagnosis, multiple health problems especially cardiovascular problems, and worse metabolic control were associated with switching to insulin therapy. One fifth (20.4%) of enrolled subjects switched from an oral anti diabetic drug to insulin during the study period.[79]

The above studies primarily focused on utilization patterns of initial therapy in diabetes prior to the release of ADA guidelines in European and Canadian patients. Management of diabetes is fairly complex in nature and requires frequent dose adjustment, addition or change in medications based on individual response and preexisting conditions. Although not prescriptive in nature, the ADA recommendations are based on evaluation of several studies comparing the advantages, disadvantages and success rates of different drug therapies and serve as a guideline for physicians. This study is aimed at measuring adherence of physicians prescribing behavior with the guidelines. Study of actual utilization pattern of these anti-diabetic drugs taking into account any contraindicating conditions justified by laboratory tests will help in designing interventions that are evidence based. This can possibly lead to studies that address improving adherence to prescription regimen thereby achieving better clinical and patient reported

outcomes. It will help identify potential factors that influence prescribing decisions and contribute to the long term safety, efficacy and effectiveness of drug therapy in type 2 diabetes patients.

3 METHODS

3.1 Study design

This was a retrospective, observational cohort study of patients followed for 3 ½ years in UIMCC. UIMCC serves thousands of patients from different social and ethnic backgrounds. The study population was comprised of patients with diabetes whose medication orders were maintained in UIC's electronic medical record since January 2007.

3.2 Data sources

The Cerner Millennium data repository at UIMCC contains data on patient demographics, prescription and laboratory values. We identified patients with a first prescription for any diabetic drug using UIMCC data. The variables included in the study were based on literature review and expert opinion. Data on all anti-diabetic prescription orders for medications listed in table III were extracted from a computerized physician order entry (CPOE) system. .

Data collected from the Cerner Millennium data repository include:

- Patient demographics: age, gender,
- Prescription data for any diabetes medication: start date, end date, dose and frequency.
- Laboratory data: Aspartate aminotransferase levels (AST), alanine aminotransferase levels (ALT), estimated creatinine clearance, brain natriuretic peptide (BNP), HbA1c levels.

Data collected from the Trendstar billing repository include:

- Admission date, self-declared ethnicity, clinic visit dates, ED visit dates, principal and secondary diagnoses for each encounter.

3.3 Study sample

The study population consisted of all diabetes patients receiving their primary care from UIMCC. Study sample was selected after application of a set of inclusion and exclusion criteria

to overcome inconsistencies in data recording procedures. The final study sample included patients newly treated with medications for type 2 diabetes and had regular follow-up visits. Data were examined to ensure that all patients met the inclusion criteria.

3.3.1 Inclusion criteria

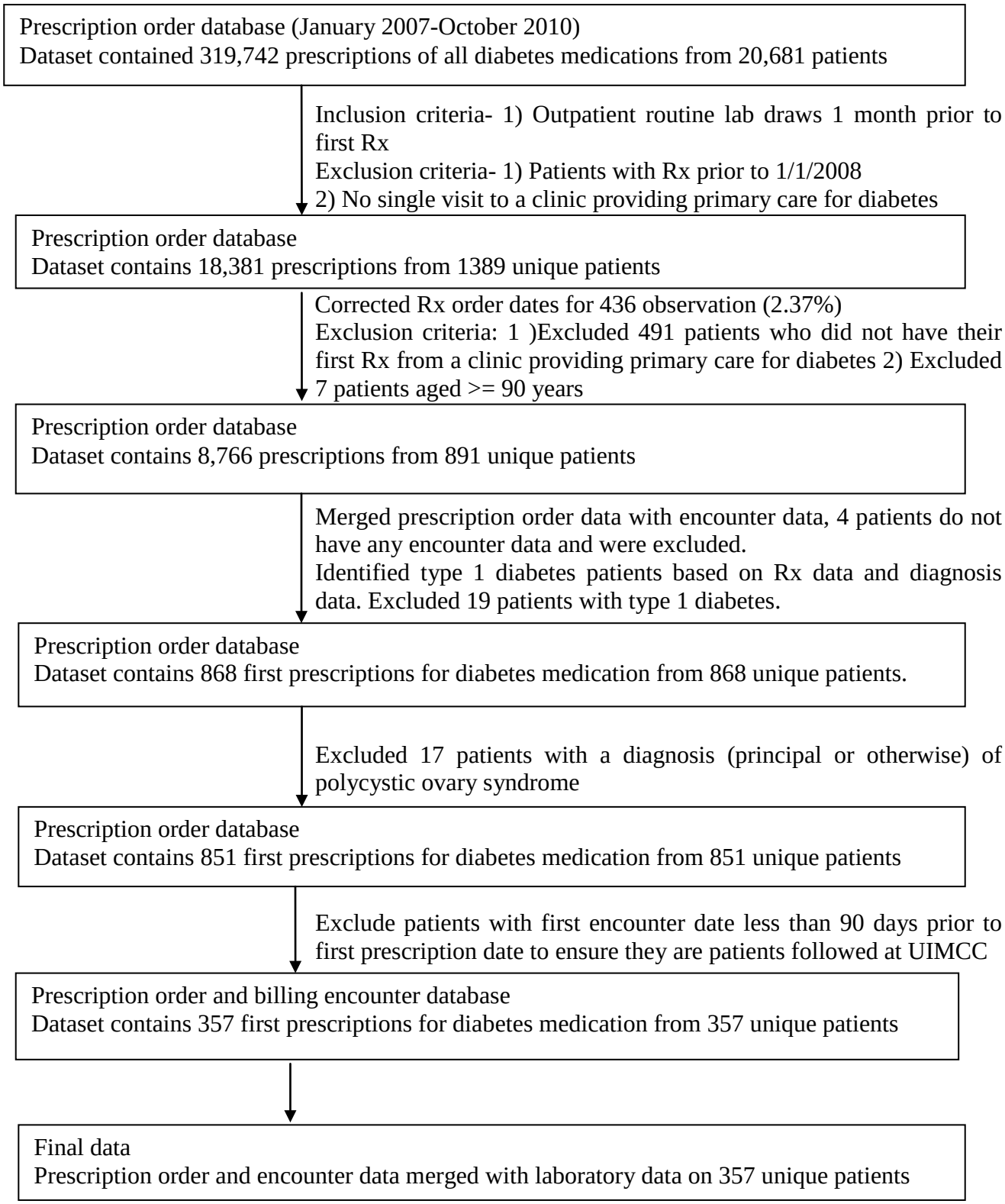
1. All patients aged more than 18 years to less than 90 years were included in the study.
2. All outpatients receiving their medication orders from physicians in UIMCC.
3. Patients must have had at least one outpatient routine laboratory draws for lipid levels, HDL, cholesterol levels, glycosylated hemoglobin levels or any of the basic metabolic panel tests (chem7) prior to their first prescription for a diabetes medication to ensure that they are patients routinely seen at UIMCC

3.3.2 Exclusion criteria

1. Patients with no single visit to a clinic which provides chronic diabetic care were excluded from the study. Clinics in UIMCC that provide chronic diabetes care are enlisted in Appendix A .
2. Patients with a prescription for a diabetic medication prior to January 1, 2008 were excluded from the study because data was not reliably recorded in the Cerner system.
3. Patients who did not have their first diabetes medication prescription from a clinic providing primary care for diabetes listed in appendix A were excluded because we could not ascertain the if the patients were newly treated or patients receiving a continuation in diabetes care.
4. Patients having a diagnosis for polycystic ovary syndrome (PCOS) were excluded because metformin is used in treatment of PCOS patients and hence these patients might be falsely identified as patients with diabetes.

5. Patients with first encounter date for any diagnosis less than 90 days prior to their first diabetes prescription were excluded to ensure they were regularly followed at UIMCC prior to initiation at UIMCC.

Figure 3. Flow chart of data preparation



3.4 Independent and dependent variables/study variables

The dependent variable was a binary variable coded as 1 for patients that started on metformin (either as combination therapy or as monotherapy) and coded as 0 for patients that started on drugs other than metformin..

The independent variables selected were based on patient demographics, relevant laboratory values used to project renal function, liver function and billing encounter data for every diagnosis for each eligible patient. Creatinine clearance was used to determine renal function status while alanine transaminase levels and aspartate aminotransferase levels were used to determine liver function status. Brain natriuretic peptide (BNP) test values and ICD-9-CM codes for congestive heart failure (CHF) were used to create an indicator variable for presence of CHF. The definition for presence of CHF was BNP values greater than 200 pg/ml or ICD-9-CM diagnosis code for CHF codes during the patient's duration of treatment at UIMCC. ALT and AST levels were dummy coded based on upper normal limits definition at UIMCC. ALT was high if recorded chart values were 2.5 times the normal upper value of 50 units/L (125 units/L) while AST was high if recorded chart values were 2.5 times the normal upper value of 40 units/L (100 units/L). Renal function status was determined based on the estimated creatinine clearance and serum creatinine values. Information provided in metformin insert was used to determine abnormal renal function. Patients with moderate (CrCl = 31-60 ml/min) or severe impairment (CrCl = 10-30 ml/min) or an abnormal serum creatinine (creatinine levels $\geq$1.5 mg/dL [males], $\geq$1.4 mg/dL [females] or abnormal creatinine clearance) were classified as renally impaired patients.

All ICD-9-CM codes used to identify CHF, PCOS and diabetes are listed in table II. The variables used in the study are summarized in table III

Table II: ICD-9-CM codes used to identify diabetes and comorbidities[82]

Comorbidity	ICD-9-CM Codes
Type 1 diabetes mellitus	250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92
Type 2 diabetes mellitus	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93
Polycystic ovary syndrome	256.4
Congestive heart failure	428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.43, 428.9, 429.0, 429.1, 429.3, 429.4, 425, 425.0, 425.1, 425.2, 425.3, 425.4, 425.5, 425.7, 425.8, 425.9

Table III: Study variables

Variable	Type of variable	Variable definition and coding
Dependent variable		
Metformin	Dichotomous	1 = Started on metformin 0 = Did not start on metformin
Independent variables		
Age	Continuous	Continuous
Gender	Categorical	0 = Male; 1 = Female
Race/Ethnicity	Categorical	Caucasian, 1 = Yes, 0 = No Hispanic, 1 = Yes, 0 = No, Asian, 1 = Yes, 0 = No, Others, 1 = Yes, 0 = No Reference = African American
Inpatient status	Categorical	1 = Inpatient 0 = Outpatient
Alanine Transaminase	Categorical	1 = High (greater than 125 units/L) 0 = Normal
Aspartate Transaminase	Categorical	1 = High (greater than 100 units/L) 0 = Normal
Renal function (composite function based on creatinine clearance and serum creatinine)	Categorical	1 = Renal impairment 0 = No renal impairment
Renal function based on creatinine clearance	Categorical	Mild (61-90 ml/min), 1 = Yes, 0 = No Moderate (31-60ml/min), 1 = Yes, 0 = No Severe ($\leq$ 30 ml/min), 1 = Yes, 0 = No
HbA1c levels	Categorical	Actual values recorded in charts
Brain natriuretic peptide test	Categorical	Calculated from continuous values as follows: 1 = greater than 200 pg/mL (abnormal) 0 = 0-200 pg/mL (normal)
Congestive heart failure		1 = Presence of CHF 0 = Absence of CHF
Physician training	Categorical	Family Medicine, 1 = Yes, 0 = No Other clinic, 1 = Yes, 0 =No Reference = General Internal Medicine
Type of clinic	Categorical	Resident, 1 = Yes, 0 = No Other, 1 = Yes, 0 = No Reference= Attending Physician

Drug classes and specific drugs within each class used in the study are enlisted in table IV. Drugs listed in combination drug, insulin and its analogues were obtained from the dataset while other drug classes were obtained from literature.

Table IV: Medication data[17, 83, 84]

Drug class	**Medication**
Biguanide	Metformin
Thiazolidinedione	Pioglitazone, Rosiglitazone
Sulphonylureas	Chlorpropamide, Glimepiride, Glipizide, Glyburide,
Glinides	Nateglinide, Repaglinide
α Glucosidase inhibitors	Acarbose, Miglitol
Glucagon like peptide agonists	Exenatide
Dipeptidyl peptidase inhibitors	Saxagliptin, Sitagliptin
Amlyin agonists	Pramlitide
Insulin and its analogues	Insulin aspart, insulin aspart protamine, insulin isophane, insulin glulisine, insulin glargine, insulin detemir, insulin aspart- insulin aspart protamine, insulin regular, insulin lispro- insulin lispro protamine, insulin lispro, insulin isophane- insulin regular
Combination drugs	Glimepiride-pioglitazone, Glimepiride-rosiglitazone, Glipizide-metformin, Glyburide-metformin, Metformin-rosiglitazone, Pioglitazone-metformin, Repaglinide-metformin, Sitagliptin-metformin

3.5 Data preparation and management

All data were imported from Microsoft Excel spreadsheets into SAS version 9.1 (SAS Institute, Cary, NC). Data on medication and prescription dates were extracted in two week segments in order to identify prescription order dates that were recorded incorrectly. Any prescription date that fell out of the two week timeframe in which the data was extracted was

identified and replaced with a date in the center of the 2 week period in which it should have been recorded. In practice, it is not uncommon for a physician to see a patient and start the prescription the day after. Hence to avoid falsely detecting any incorrect start dates we included an extra day after the two week time in the algorithm to identify incorrect dates..

In order to meet the objectives of this study it was necessary to identify newly diagnosed patients with diabetes. Patients with any prescription for a diabetes medication prior to January 1st 2008 (inpatient or outpatient) were excluded from the study. This was primarily done because data were not recorded reliably prior to 2008. It is possible that although the patient was seen for the first time by a primary care clinic in UIMCC, the patient may have been transferred from a different health care provider. To resolve this limitation, patients with outpatient routine laboratory draws at UIMCC at least 1 month prior to first prescription were included in the study. This ensured that they had a clinic visit for any indication at least a month prior to their diabetes prescription and were classified as patients being followed up routinely at UIMCC. Routine laboratory draws included tests for any basic metabolic panel (chem7), lipids, HDL, cholesterol or glycosylated hemoglobin. The Cerner system for prescription order entry records medication data each time a patient visits any clinic in the UIC network. We identified clinics within the UIC network which routinely treat patients with diabetes. These clinics are listed in Appendix A Patients not having a single visit to a clinic that routinely provided diabetes care were excluded from the study. Also patients who did not have their first diabetes medication prescription from any of these clinics were excluded. This strategy was used to eliminate any false positives of patients starting chronic diabetes care at UIMCC. The prescription order data was then merged with billing encounter data for all diagnosis. Patients with missing encounter data (n=4) or a diagnosis for PCOS (n=17) or diagnosis of type 1 diabetes (n=19) were excluded

at this step. A final inclusion criteria of a billing encounter date more than three months prior to the prescription date for first diabetes medication resulted in 357 patients being included in the study cohort. Laboratory dates and values most recent and prior to the corresponding first prescription date was then identified for creatinine clearance, ALT, AST, BNP, HbA1c tests and included in the final dataset.

To study the prescribing pattern after metformin failure, the changes in prescription for a cohort of patients initiated on metformin as monotherapy or in combination therapy with other anti-diabetic drugs were identified. Laboratory test data most recent and prior to the day the prescription changed was determined and included in the final data for identifying factors determining the second line drug therapy .

3.6 Data analysis

All analyses were carried out in SAS version 9.1 (SAS Institute, Cary, NC) and SuperMix (Scientific Software International Inc., Skokie IL). Descriptive statistics on patient characteristics such as gender race and age were computed to show distribution of the patient population. Proportion of patients starting on each class of hypoglycemic agents was calculated. Descriptive statistics on patient characteristics, provider characteristics and laboratory values were reported classified by patients starting on metformin and not starting on metformin. Bivariate histograms were plotted between race, gender, admit status, renal function status, ALT values, AST values, comorbidity and metformin starts.

All descriptive analyses were conducted at the level of patient. For the first objective of determining physician compliance with ADA prescribing guidelines for initiating diabetes drug therapy, we described the number of patients starting on each class of drugs, summary statistics on all the independent variables for selected patient cohort and the percent compliance with

metformin prescription as first line therapy for diabetes. Percent compliance with ADA guidelines was calculated using the following formula:

Compliance = (Number of metformin-eligible patients that got metformin + Number of metformin-ineligible patients that did not get metformin) / Total number of patients

The criterion for determining metformin eligibility was derived from information on metformin package insert. Patients with impaired renal and liver function based on serum creatinine, creatinine clearance, AST or ALT values were classified as metformin ineligible patients. Patients with normal renal and liver function were classified as metformin eligible patients.

For the second objective and hypothesis testing of the effect of renal and liver function status on initial prescription, a mixed effects logistic model was used to fit a model for the binary outcome of metformin use. A mixed effects logistic model is used for analysis of clustered data on a binary or multinomial outcome variable. It adjusts for any random effects introduced by sampling. In this study, a physician could prescribe to more than one patient. Hence patients were clustered within physician and physician was entered as a random effect in the model. All other patient covariates were considered as fixed effects. Modeling procedure was conducted in SuperMix (Scientific Software International Inc. IL). Link function used was logistic with Bernoulli distribution for the outcome variable.

To meet the third objective of characterizing second line drug therapy we analyzed a subgroup of patients starting on metformin monotherapy. Change from initial metformin treatment was defined as an addition of a drug to metformin or a complete switch to a drug other

than metformin. Laboratory values most recent and prior to the date on which the initial prescription changed was determined and summary statistics were reported. Descriptive statistics were conducted to compare patient characteristics before and after change in prescription.

4 RESULTS

This section presents the descriptive statistics, bivariate analyses and plots, and results from mixed effects modeling procedure.

4.1 Descriptive statistics

Patient and physician characteristics are presented in table V. The study sample consisted of 357 patients and 138 physicians. There were 136 males and 221 females from 14 clinics in UIMCC. The clinics were classified based on specialty as endocrinology clinic, family medicine, geriatric clinic and general internal medicine clinic. Overall, about 9% of the sample population was under 35 years of age, 27% were between 36-50 years, 40% were between 51-65 years and 25% of patients were above 65 years of age. The mean age at the first prescription was 53.9 ± 13.5 years for patients starting on metformin and 60.7 ± 13.3 years for patients starting diabetes treatment on drugs other than metformin (P=<0.0001). There were 132 providers across the different clinics. The providers were classified as attending physicians, residents or other (advanced practitioner nurse). The number of patients per provider ranged between 1 and 20. Laboratory data most recent and prior to the first prescription of patients in the study sample is summarized in table VI. Results of bivariate analyses between the outcome variable and each of independent variables are expressed as p values in table V.

Table V: Patient and provider characteristics

Variable	All patients (N=357)				
	Metformin (N=257)		No metformin (N=100)		P value
	N	%	N	%	
Patient characteristics					
Gender					
Female, n (%)	158	61.58	63	63	0.7904
Male, n (%)	99	38.52	37	37	
Race					
Black, n (%)	149	57.98	61	61	
Other, n (%)	9	3.50	1	1	
Hispanic, n (%)	59	22.96	30	30	0.2088
Asian/Pacific Islander, n (%)	9	12.06	2	2	
Caucasian, n (%)	31	3.50	6	6	
Mean age (years), (SD)	53.9 (13.5)		60.7 (13.26)		<0.0001
Admit status					
Inpatient, n (%)	2	0.78	2	2	0.3130
Outpatient, n (%)	255	99.22	98	98	
Number of patients with CHF	26	10.12	16	16	0.1213
Provider characteristics					
Physician training					
Attending physician, n	129	50.59	40	40.80	
Resident	102	39.60	56	57.15	0.0035
Others (APN)	24	9.81	2	2.05	
Type of clinics					
Family medicine, n	90	35.30	13	13.25	
Internal medicine, n	158	62.00	78	79.60	<0.0001
Other , n	7	2.70	7	7.15	

Table VI: Clinical characteristics of patients - Laboratory values

Variable	All patients (N=357)				
	Metformin (N=257)		No metformin (N=100)		P value
	N	%	N	%	
Laboratory data					
Renal function status[a]					
Normal, n (%)	58	26.13	8	9.88	< 0.0001
Mild impairment, n (%)	113	50.90	28	34.57	
Moderate impairment, n (%)	50	22.52	38	46.91	
Severe impairment, n (%)	1	0.45	7	8.64	
Liver function status[b]					
High ALT/AST level, n (%)	0	0.00	3	3.85	0.0195

[a] Renal function status as indicated by creatinine clearance was missing for 54 patients

[b] Liver function tests was missing for 70 patients

Variable	All patients (N=357)				
	Metformin (N=257)		No metformin (N=100)		P value
	N	Mean	N	Mean	
Laboratory data					
Brain natriuretic peptide[c], mean	10	27.25	4	121.60	0.1230
HbA1c (%), mean	257	7.68	100	8.02	0.1527

[c] BNP values were recorded for 14 patients only

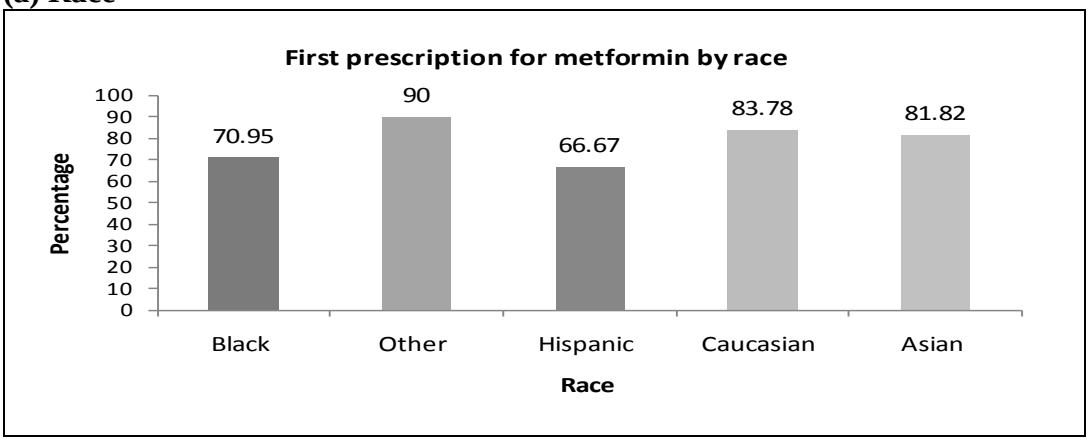
4.2 Bivariate analyses

Bivariate analyses were conducted to test the association between individual independent variables and the outcome variable. Patient age at initiation of medical therapy, physician training, type of clinic, renal function status and liver function status (ALT and AST tests) were significantly associated with the outcome of receiving metformin as first line therapy. Patients who were started on metformin where young (53.9 ± 13.5 years) compared to those who started on other drugs (60.7 ± 13.26 years). Renal function ($p < 0.0001$) and liver function status ($p=0.0195$) were clinically important variables that were found statistically significant and consistent with our hypothesis of being associated with metformin prescription.

Figure 4 illustrates the demographic and clinical characteristics for patients who received metformin. Not much variation was observed in patients receiving metformin by race, gender, admit status, presence of CHF as comorbidity or HbA1c levels. Figure 4 (e) shows that as age increases the proportion of people receiving metformin gradually decrease. Renal function status is a major predictor, as the proportion of patients receiving metformin decreases drastically from normal to severe impairment as demonstrated by figure 4 (f). Patients having impaired liver function as represented by ALT and AST levels never received metformin.

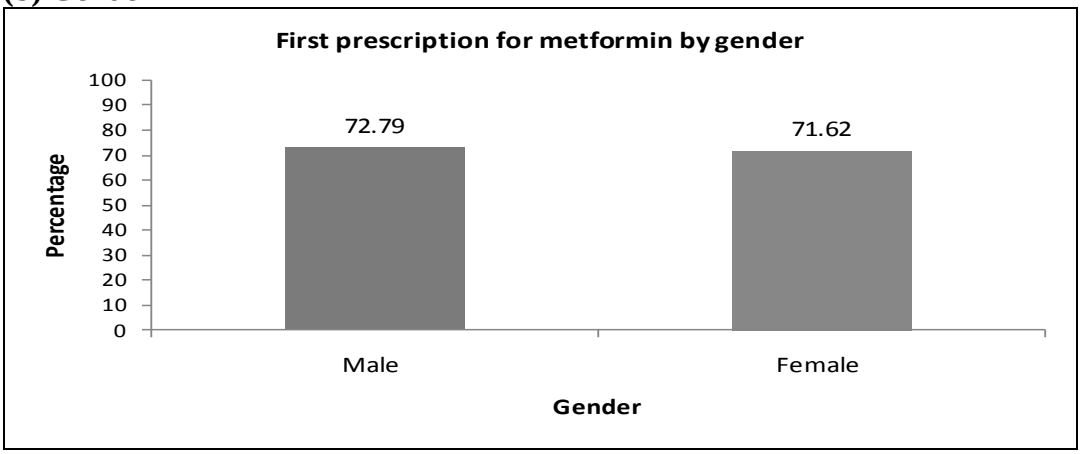
Figure 4. Comparison of metformin use as baseline therapy.

(a) Race



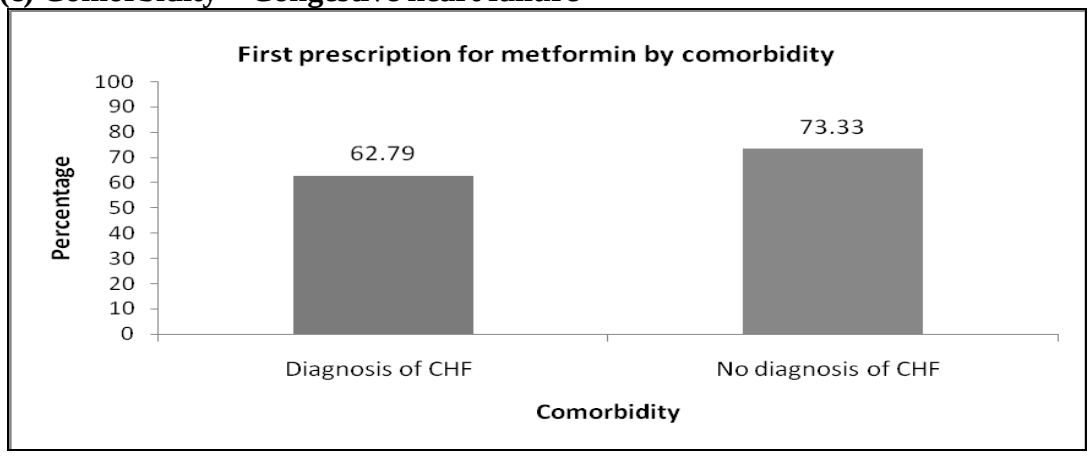
Note. Sample size for African-Americans: n=210; Others n=10; Hispanic n=89; Caucasians n=37; Asian n=11

(b) Gender



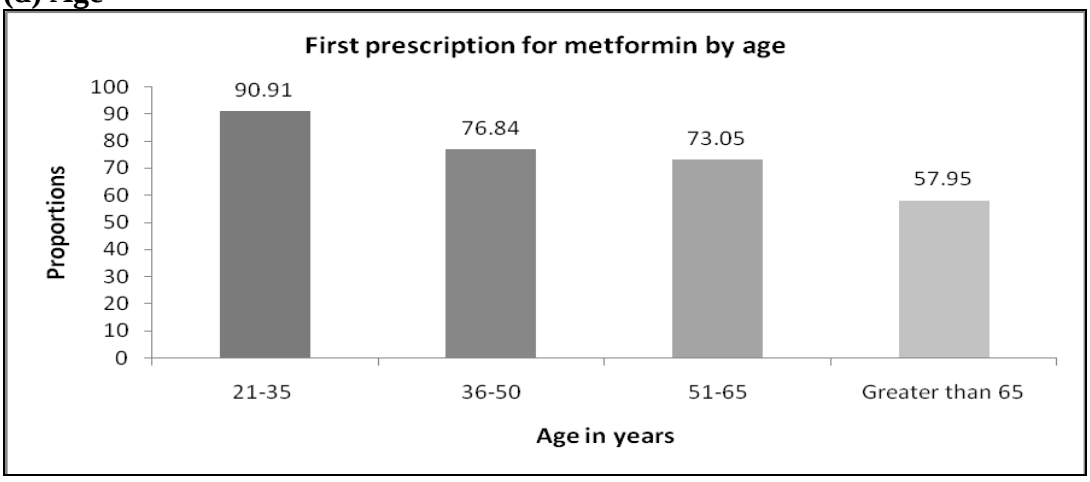
Note. Sample size for males n=136; females n=221

(c) Comorbidity – Congestive heart failure



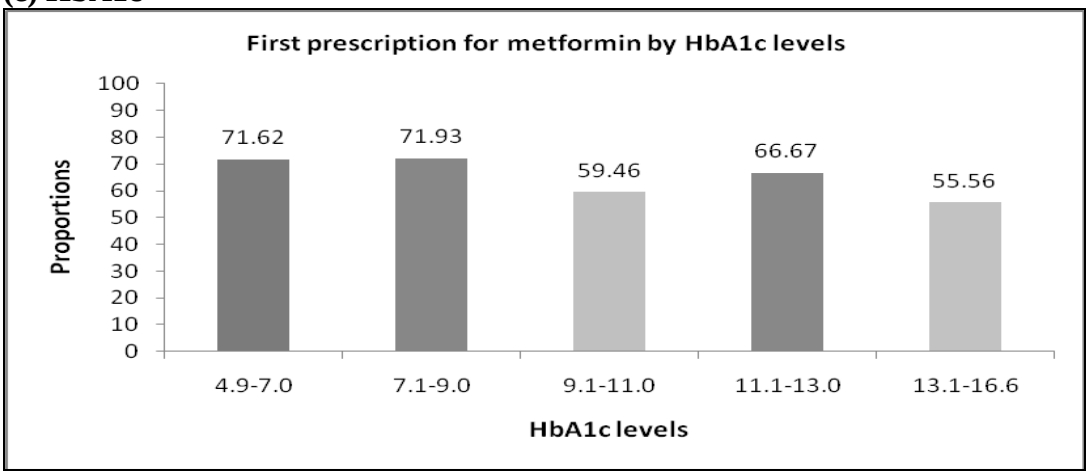
Note. Sample size for patients with CHF n=42; no CHF n=315

(d) Age



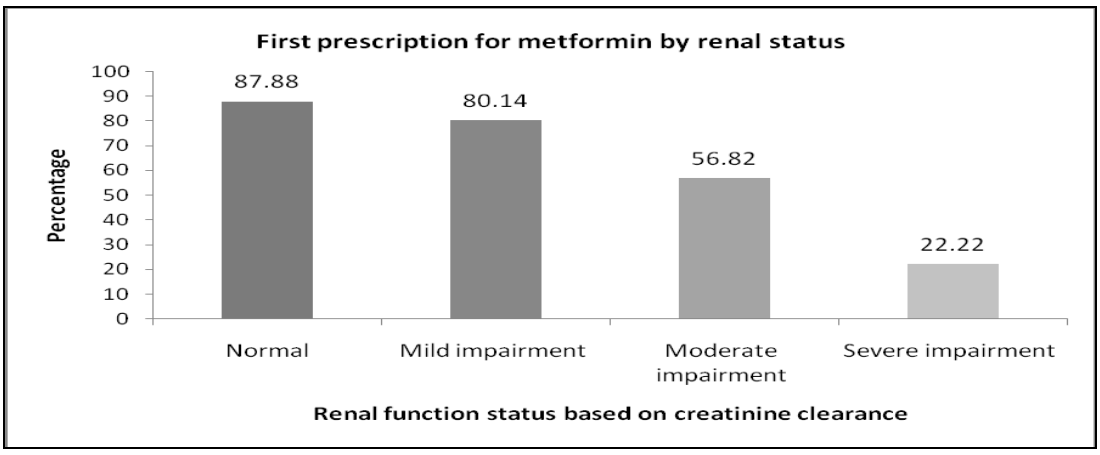
Note. Sample size for age group 21-35years: n=33; 36-50 years: n=95; 51-65 years: n=141; above 65 years: n=88

(e) HbA1c



Note. Sample size for HbA1c levels 4.9-7.0: n=148; 7.1-9.0: n=114; 9.1-11.0: n=37; 11.1-13.0: n=15;13.1 and above: n=9
Values missing for 34 patients

(f) Renal function based on creatinine clearence



Note. Sample size for normal: n=66; mild impairment: n=141; moderate impairment: n=88; severe impairment: n=8
Values missing for 54 patients

4.3 Medication prescription patterns for first line therapy

About 69% of patients were started on metformin as monotherapy. Approximately 3% of patients were started on metformin in combination therapy with either a sulphonylurea or a thiazolidienedione. Sulphonylureas were the next most widely used anti-diabetes medication (15.68% patients) followed by insulin (8.68% patients), TZD (2.24% patients) and other drugs (1.4% patients).

Table VII: Medication utilization patterns of initial anti-diabetes medications

Medication class	Number of patients (N = 357)	
	N	%
Metformin	246	68.90
Sulphonylurea	56	15.68
Insulin	31	8.68
Metformin + Sulphonylurea	8	2.24
TZD	8	2.24
Others	5	1.40
Metformin + TZD	3	0.84

4.4 Compliance with ADA guidelines

Of the 257 patients that started drug therapy on metformin, 202 were found to metformin eligible while 53 of the 100 patients that were not started on metformin were found to be metformin ineligible. Using the previously mentioned formula, physicians at UIMCC were found to be compliant with the ADA guidelines on prescribing metformin as the initial therapy in 71.4% of patients.

4.5 Mixed effects model

A mixed effects logistic model with clinically and demographically relevant covariates was fitted for the binary outcome variable of receiving metformin. The response variable was assumed to have Bernoulli distribution. Since renal function status was missing for 54 patients, we did not include these patients in the model building process. Metformin was not prescribed in patients with high ALT and AST levels, hence there were no positive observations for these variables amongst metformin users. Also ALT and AST levels were highly correlated and hence not included in the model as they were perfect predictors of the outcome. All other variables were included in the model.

The deviance statistic (-2 Log likelihood) value of the final model was 349.97. Renal function status (p=0.0008) and type of clinic (p=0.0205) were significantly associated with getting a prescription for metformin while HbA1c showed a trend towards significance (p=0.0539) Negative parameter estimates for HbA1c and renal function suggest that as that these variables are inversely related to the outcome while a visit to family medicine clinic is positively associated with the outcome of receiving metformin. With a one unit increase in HbA1c level, there was a 13% decrease in the odds of receiving metformin (OR=0.87). Providers in family medicine clinic were more than twice (OR=2.50) as likely to prescribe metformin as first line therapy when compared to providers in Medicine clinic. Results from mixed effects model are summarized in table VIII.

Table VIII Mixed effects logistic model for metformin as initial prescription

Variable	Estimate	Std Err.	OR (95% CI)	P value
Intercept	2.6072	1.0263	13.56 (1.81, 101.36)	0.0111
HbA1c levels	-0.1314	0.0682	0.87 (0.76, 1.00)	0.0539
Renal impairment	-1.0919	0.3259	0.33 (0.17,0.63)	0.0008
Age	-0.0110	0.0127	0.98 (0.96, 1.01)	0.3862
Gender	0.0545	0.2841	1.05 (0.60, 1.84)	0.8477
Family medicine clinic	0.9168	0.3956	2.50 (1.15, 5.43)	0.0205
Other (geriatric or endocrinology) clinic	0.1677	0.6703	1.18 (0.31, 4.39)	0.8025
Inpatient	-1.5139	1.0825	0.22 (0.02, 1.83)	0.1620
CHF	0.0379	0.3887	1.03 (0.48, 2.22)	0.9223
Race-White	0.5452	0.5374	1.72 (0.60, 4.94)	0.3104
Race –Asian	0.8475	0.8686	2.33 (0.42, 12.80)	0.3292
Race - Hispanic	-0.3763	0.3167	0.68 (0.36, 1.27)	0.2347
Race - Other	1.1687	1.1136	3.21 (0.36, 28.54)	0.2940
Training - Resident	0.0425	0.3053	1.04 (0.57,1.89)	0.8893
Other training	0.9324	0.8114	2.54 (0.51, 12.46)	0.2505

4.6 Medication prescription patterns for second line therapy

For the third aim, we studied the change in prescription due to secondary failure with metformin. There were 257 users of metformin; 163 patients either did not change their medication or did not have any follow-up visits while 94 patients had a change in prescription. However, 30 of the identified patients received the order for a change in prescription from a clinic other than the one which started the metformin. These patients were excluded to obtain a final sample population of 54 patients. Overall three quarters of the changed prescriptions were for sulphonylureas (76%) followed by TZD and Insulin (11% each).

Table IX Medication utilization patterns after initiation on metformin

Medication class	Number of patients (N = 54)	
	N	%
Sulphonylurea	41	76
TZD	6	11
Insulin	6	11
Other (Sitagliptin)	1	2

Laboratory data most recent and prior to the day the prescription changed is summarized in table X.

Table X Characteristics of patients at prescription change

	Medication Class (N=54)					
	Sulphonylurea (N=41)		**TZD (N=6)**		**Insulin (N=6)**	
Clinical Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
Age, mean (SD)	56.65 (13.82)	-	55.83 (15.99)	-	52 (9.93)	-
HbA1c Levels, mean (SD)	9.05 (2.32)	-	7.48 (0.86)	-	7.78 (0.76)	-
Number of patients with CHF	4	10.53	1	16.67	2	40.00
Renal function status						
Normal, n (%)	11	30.56	1	16.67	2	40.00
Mild impairment, n (%)	14	38.89	3	50.00	2	40.00
Moderate impairment, n (%)	10	27.78	2	33.33	1	20.00
Severe impairment, n (%)	1	2.78	0	00.00	0	00.00

All patients in the above cohort had normal liver function

Renal function missing for 7 patients

5 DISCUSSION

5.1 Discussion of results

5.1.1 Metformin prescription compliance and determinants of prescribing behavior

Overall, our study found that physicians at UIMCC are compliant with the ADA guidelines for metformin prescription on diagnosis of type 2 diabetes mellitus about three quarters of the time. Our hypothesis was that the compliance would be driven primarily by the renal function and liver function status of the patient. The mixed effects modeling procedure confirmed that renal function along with the type of clinic are statistically significant determinants of receiving a prescription for metformin as the first line therapy. HbA1c levels showed a trend towards significance and is also a clinically significant variable. Liver function status although not included in the mixed model due to its perfect collinear relationship with metformin prescription was found to be significant factor in the bivariate analysis. These factors are not only are statistically significant but also have high clinical implications.

The negative parameter estimates for dichotomous renal impairment variable clearly suggests that these patients are less likely to receive metformin as initial drug therapy. Similarly patients who had impaired liver function were never started on metformin. Since the categorization of variables was based on package information for metformin, these results shows that label information plays a significant role in the physician's decision making process. Of the numerous anti-diabetic drugs available today, metformin is one the most inexpensive drugs having temporary gastric disturbances as side effects which can be resolved by gradually increasing the initial dose to required therapeutic levels as symptoms subside. It is also the most widely studied drug with longstanding evidence that has demonstrated significant improvement in cardiovascular outcomes and mortality rate without inducing hypoglycemia or weight gain.

Since approximately 90% of the absorbed drug is eliminated unchanged in the urine, renal function is a major decision criteria for physicians. The label for metformin indicates that in presence of moderate to severe renal impairment a C_{max} value 4 times the regular levels is achieved versus 1.86 times in presence of mild impairment due to reduced renal clearance.[85] Although a causal relation has not been established, high metformin levels could act as a risk factor for lactic acidosis especially in patients with other metabolic conditions. The label also indicates that metformin should not be prescribed in patients with liver disease as it can lead to accumulation of lactate which is one of the metabolites of metformin.[85]. Hence in context of these clinical findings physicians are justified in not prescribing metformin in patients with compromised renal and liver function. This is congruent with our findings as summarized in descriptive tables.

Several studies including a post marketing safety surveillance by the US FDA following introduction of the drug in US market evaluated metformin associated lactic acidosis and acidosis in non-metformin group found there was no increased risk in the metformin group. Metformin is in fact known to have cardio protective effects independent of the anti-hyperglycemic property and also reduce overall mortality.[19, 30, 86] A Cochrane review of 347 trials and studies did not find any cases of fatal or non-fatal lactic acidosis between metformin and non-metformin groups.[87, 88]

Recently there has been considerable controversy on the use of metformin in patients with renal impairment and the potential benefits outweighing the risks involved.

A recent observational study in a UK based hospital assessed the incidence of lactic acidosis in patients with and without diabetes and those on a prescription of metformin or any

other anti-diabetic drug.[89] The authors concluded that incidence of lactic acidosis was higher in patients with diabetes than patients without diabetes but attributed it to co-existing factors such as acute cardio respiratory disease, renal impairment and sepsis rather than metformin administration. The incidence did not differ between the metformin and non-metformin groups (p=0.31) amongst patients with diabetes.[89] Sambol et al. investigated the relationship of age and renal impairment on metformin pharmacokinetics and found that renal clearance of metformin was 74%-78% lower in subjects with moderate to severe renal impairment and about 23-33% lower in subjects with mild impairment than in healthy young or middle aged group. Healthy elderly subjects a similar reduced clearance (35-40%) compared to the younger population group.[90] These findings demonstrate that metformin can be safely administered in patients with mild renal impairment with minor dose adjustments and risks being similar to healthy aged population. Vasisht et al. evaluated and compared the use of metformin in patients with renal impairment on a national level using National Health and Nutrition Examination Survey (NHANES) and a diabetes center in a university setting. They found that metformin use was more prevalent than expected in patients with reduced glomerular filtration rate (30 <eGFR< 60) but recommended discontinuation when eGFR < 30 ml/min/1.73m^2 due to significant reduced clearance.[30, 91] These suggestions are also concurrent with current NICE guidelines.[86] The above literature concluded that complete withholding of metformin may not be warranted in patients with stable kidney function. In addition the UK-PDS study demonstrated that use of metformin was associated with improved cardiovascular outcomes such as reduced MI, stroke and peripheral vascular disease.[86]

The conflicting opinions on risks and benefits of metformin make it difficult to select the best treatment strategy in patients with co-existing conditions. The decision to prescribe metformin in a patient with renal impairment should be taken after careful examination of each case at the discretion of the physician.

Although not one of the main covariates, the study found that family medicine clinic at UIMCC was more than twice likely to give orders for metformin as initial therapy than general internal medicine clinic or other clinics (geriatrics and endocrinology). A sub analysis of type of medication (insulin, metformin, other) by the type of clinic using a fisher exact test found a statistically significant difference between the groups (p=0.0001). A higher number of insulin prescriptions were written by internists in general medicine clinic than other providers. A possible explanation for this incidental finding is the unobserved severity of patients seen at the general internal medicine clinic and familiarity of internists with the current clinical knowledge rather than reliance on guidelines. This is an interesting observation that warrants further investigation..

Another clinically relevant finding was the decrease in odds of receiving metformin as HbA1c increased as indicated by a negative parameter estimate -0.1314 (OR= 0.87). When HbA1c levels were plotted as a categorical variable (figure 4) against the outcome variable, we see approximately 10% decrease in proportion when HbA1c levels were greater than 9%. This is consistent with some of the findings from a nested case control study in Netherlands which found that patients with HbA1c > 9% were not adequately controlled on metformin. The authors recommended increasing the dose and dosing frequency before addition of a second line agent.[92] This can be attributed to the fact that metformin is currently one of the drugs with least adverse

event profile of hypoglycemia without causing any weight gain with secondary cardiovascular benefits.[83, 93-96] High HbA1c (> 9.0%) might prompt physicians to prescribe insulin or a sulphonylurea as monotherapy or in combination due to its ability to reduce glucose levels within a shorter duration of time on therapy.

5.1.2 Characteristics associated with change in prescription

The study demonstrated that overall 36.5% (94) of patients who started on metformin changed their medication during the study period. Of these 54 patients were considered eligible for studying patient characteristics. The ADA and EASD recommends addition of sulphonylureas or Insulin as a part of the tier 1 well validated core therapy. Although the sample size was small, our finding were consistent with the recommendations with majority of changed prescriptions for sulphonylureas (76%) and followed by Insulin (11%). One of the major possible reasons being patient's preference for an oral agent over an injectable and relatively lower cost. Tier 2 less validated therapy recommends addition of thiazolidinedione or a GLP-1 agonist. Our study showed that thiazolidinedione was used as frequently Insulin. An interesting finding was a higher mean HbA1c levels in the sulphonylurea group (9.05%) compared to thiazolidinedione group (7.48%) or insulin group (7.78%) at the time of change in prescription (p=0.1473). Although this was not statistically significant and not sufficiently powered due to small sample size we can speculate that physicians preferred to use a sulphonylurea over other classes of medications when the HbA1c levels were very high. Results from Agency for Healthcare Research and Quality (AHRQ) sponsored study on comparative effectiveness of different anti-diabetes medications showed that there was no evidence to prefer any one class of medication as all drugs decreased HbA1c by an average of 1%. Combination therapies were more effective

than monotherapies, however the side effect profiles were also considered additive in nature.[97, 98] Since we could not distinguish between a switch and add-on therapy it is hard to speculate the reason to favor Sulphonylurea when glucose control was worse. Since the first change in drug therapy that was identified, it is possible that an oral medication was preferred over insulin. Also thiazolidinediones are associated with adverse events of congestive heart failure and fractures. However as previously mentioned these results could be biased as they were driven by a small samples size. renal function did not influence the change in prescription and no patients showed evidence of impaired liver function.

5.2 Study limitations

To ensure we studied only newly diagnosed diabetes patients, we excluded patients having an encounter date for any diagnosis less than 90 days from their first prescription for diabetes medication. This conservative exclusion criterion reduced our sample size by more than 50% for studying the first line drug therapy and subsequently for studying medication utilization of second line therapy. However a higher validity was deemed more appropriate for meeting the objective of the study rather than higher sample size. Due to time restrictions, we could not open charts for all subjects to determine their eligibility based on follow-up visits. The external validity in terms of the patient sample is a limitation as UIMCC has a predominant African-American patient population. Moreover, this was a single site study conducted at UIMCC. Hence it may not be generalizable to any national population estimate. However the clinically important patient characteristics we measured are independent of demographics and hence do not expect any major influence of these factors on physician prescribing behavior. Also none of the patient demographic characteristics were found to be statistically significant.

The main limitation of the study was the inability to distinguish between addition and a complete switch to a new medication as second line therapy. The drawback is attributed to the way Cerner system records the data and hence could not be corrected.

5.3 Study strengths and implications

In this study we have characterized the first line therapy, predictors of first line therapy and utilization pattern of second line therapy. Although we could not model predictors of second line therapy due to small sample size we have compared the patient characteristics at onset of diabetes treatment and change in therapy. To our knowledge, this the first study to identify determinants of physician prescribing behavior in diabetes and compliance with the ADA guidelines. Previous studies have described the medication utilization patterns in diabetes and identified predictors of medication adherence. Many of these descriptive studies were conducted in European countries and hence followed different guidelines pertinent to specific regions. We have attempted to add to the existing knowledge of medication utilization and investigate clinical laboratory values that are relevant to a physician in their daily practice. Drug labels and package inserts are the most important source of information for patients as well as physicians. While the ADA has outlined treatment pathways, they are not mandatory and individual physicians make decisions based on their experience. Numerous studies have also been conducted to establish the relation between renal function, lactic acidosis and metformin. This study aimed at translating the knowledge from the literature and drug information to a defined modeling strategy to obtain the direction and magnitude of effects affecting prescribing.

We have used the methods to adjust for any possible clustering effect of physicians and hence the results are more accurate to study settings than previously published descriptive

analysis. Although the results cannot be extrapolated to any national population, they are consistent with the proposed hypothesis and conceptual basis of the study i.e. initial prescription is driven by renal and liver function status of the patient. Also hyperglycemia as indicated by HbA1c levels is a vital laboratory result considered when prescribing. Although not the primary aim, we also found that physicians in family medicine clinic at UIC are more likely to prescribe metformin. This shows that there are certain clinic related characteristics that may also be influential to a physician. Further studies on a larger sample size over a longer period of time including practice setting and physician characteristics can help in establishing the external validity of this study.

6 CONCLUSION

6.1 Compliance with ADA guideline

Most physicians in UIMCC were found to be compliant with the ADA recommendations for first line drug therapy in diabetes. Metformin monotherapy was widely used as initial therapy. Sulphonylureas, thiazolidinediones and insulin was used as second line therapy either in addition to metformin or as monotherapy. Use of sulphonylureas dominated over other classes of drugs.

6.2 Determinants of first line drug therapy in diabetes

Use of metformin as initial drug therapy in diabetes was contingent on the renal function, liver function and blood glucose levels of the patient and type of clinic. Majority of physicians at UIMCC are compliant with tier 1 2009 ADA guidelines and the drug label information. Future research on identification of factors influencing second line drug therapy could include individual physician characteristics and further analysis of patient comorbidities. This would possibly explain the differences in metformin prescription by different clinics. Understanding these characteristics would also assist in defining second line treatment strategy in diabetes. Readers should be cautious of generalizing these results to any other patient population.

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Appendix A

List of clinics providing routine diabetes care at UIMCC

1. FAMILY MED
2. MS-HLTH CNTR
3. PILSEN GERIATRICS
4. MS-JAMES JOR
5. PRIMARY CARE
6. GERIATRICS C
7. MS-NEAR WES
8. INT MED GEN
9. MS-NEAR WEST
10. SP MED ENDO
11. MS-HLTH CNT
12. MS-SOUTH SHO

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ABSTRACTS/ POSTERS: **Rao S,** Amatya A, Patel P. "Predictors of Computed Tomography scan use in Coronary Artery Disease (CAD) patients in emergency departments in United States" Value in Health. 2010; 13(3) (Abstract). Poster presentation at 15th Annual International Meeting, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Atlanta, May 15-19, 2010

. **Rao S**, Touchette DR, Schumock GT, Masica AL, Dolor RJ, Smith SR. "Reconciliation of reported drug related problems by Medication Therapy Management in Medicare beneficiaries" Podium presentation at Midwest Social and Administrative Conference, Iowa City, Iowa, July 28-30, 2010

Rao S, Patel V, Yu S, Lin F, Olaitan O, Touchette DR. "A decision modeling approach to evaluate the cost-effectiveness of prasugrel vs. clopidogrel in patients with planned percutaneous coronary intervention" Poster presentation at UIC College of Pharmacy research day 2011, Poster presentation at 16th Annual International Meeting, ISPOR, Baltimore, May 21-25, 2011