THE IMPACT OF ORAL ANTIDIABETICS ON WEIGHT IN THE ELDERLY WITH TYPE 2 DIABETES MELLITUS IN THE AMBULATORY SETTING

by

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STATEMENT OF THESIS APPROVAL

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ABSTRACT

Comparison of data gathered in an electronic medical record (EMR) database on Type 2 Diabetes Mellitus (T2DM) patients age 65 years and older with oral antidiabetics (OAD) agent prescription and recorded body mass index (BMI)/weight was performed.

A retrospective review of the General Electric Centricity Medical Quality Improvement Consortium (MQIC) research database containing the ambulatory health records of US patients was conducted. T2DM patients age 65 and older were identified by diagnosis, OAD prescription or both. Six months of continuous OAD activity was required; 395 days pre-index-date (index date was defined by first OAD prescription) clinical activity was required. Two BMI and weight readings were mandated, at baseline, closest to index date and follow-up, closest to 6 months after initiation of OAD activity. A historical, longitudinal cohort design was used and data were analyzed using analysis of variance (ANOVA) with Tukey test for adjustment of the differences in the means between the groups for continuous variables; Pearson's Chi-square test was used to test association for categorical variables.

The overall mean age for all of the OAD groups was 72.7 years. The values of the baseline diastolic blood pressure (DBP) differed ($p=0.0009$), as well as age ($p< 0.001$); DBP indicated patients were in Hypertension Stage 1. The baseline A1C level was shown to be statistically significant between the groups ($p< 0.001$) with the highest mean value in sulfonylureas group (7.7). Significant differences between the OAD groups were also found in respect to race and smoking status ($p=0.004$ and < 0.0001).

In comparison between the baseline and the follow-up values, statistical significance was found in both of the outcomes and a drop of 0.7 BMI units was initiated among all of the OAD groups. The overall mean BMI value among all of the OAD groups was 29.08 kg/m^2. The change in BMI after 6 months of monotherapy demonstrated that meglitinides had the biggest decrease in BMI (-1.27), followed by the metformin group (-1.06) and the sulfonylureas showed the least BMI drop (-0.14). Weight as the secondary outcome variable demonstrated an average 3.97 lb weight loss between all of the OAD groups. Major weight loss was found in the meglitinides users (-7.82lb), pursued by the metformin group (-6.41lb); the sulfonylureas group reported the least weight loss (-0.89lb).

EMR data demonstrated an association between the OAD user and BMI/weight and associated conditions consistent with elderly T2DM patients in a real-world setting. The likelihood of weight loss was somewhat consistent with the previous literature, except in the case of the TZD group, where the literature showed the expected weight gain and this study does not support these findings.

To Djordje and my parents for their love and support

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CHAPTER 1

INTRODUCTION

Diabetes is a chronic condition that impairs or destroys the body's ability to regulate the level of glucose in the body. Also, diabetes mellitus can be defined as group of metabolic diseases characterized by high levels of blood glucose (hyperglycemia)[7]. It occurs as the result of defects in the body's ability to produce and secrete insulin, or the ability to use insulin, in some cases both. There are two major types of the metabolic disorder, Type 1 and Type 2 diabetes mellitus. Type 1 diabetes occurs when the body stops producing insulin [11]. Type 2 diabetes occurs when the body develops insulin resistance, or a decreased sensitivity to the action of insulin, thus, the body does not effectively use the insulin it produces [12]. Type 2 is the most prominent form and accounts for 90%-95% of all diabetes cases in the U.S. This type of diabetes most commonly presents in adulthood and is associated with obesity and patients can generally survive without exogenous insulin. Usually, diabetes is associated with multiple complications that lean to morbidity and early mortality. The major group of complications varies from arteriosclerosis of the major arteries in the body, called macrovascular complications; these can lead to coronary artery disease, myocardial infarction and stroke [13]. Events like this are responsible for 65% of the deaths among patients with Type 2 diabetes; roughly 50% are due to heart attack and 15% die from stroke [11].

Over 40% of people living with Type 2 diabetes are over the age of 65. The condition represents a significant health burden for such patients and the care of this population is a considerable cost for society overall. There are several lines of evidence to suggest that Type 2 diabetes in elderly adults has a strong genetic predisposition [2-4]. Elderly patients with a family history of diabetes are more likely to develop the disease as they age. Prevalence of diabetes is to a great extent higher in some ethnic groups, especially Native Americans, followed by Hispanics, African Americans and Micronesians. The demographic scale of people age 60 years and older living with diabetes is as follows: male population accounts for 12.0 million (11.2%) and female population, 11.5 million (10.2%). Based on ethnicity, non-Hispanic whites account for 14.9 million (or 9.8% of all non-Hispanic whites aged 20 years or older have diabetes) and non-Hispanic blacks, 3.7 million (14.7 %) [9]. The value of body mass index (BMI) potentially can impact quality of life and life style habits among the elderly population (65 years and older) with Type 2 diabetes [27].

The American Diabetes Association (ADA), has explicitly recommended that care of patients 65 years of age and older be individualized and a key component of individualizing diabetes care should be the acknowledgment of a patient's perceptions of the quality-of-life effects of different types of therapy [1]. BMI (low, normal or high) can be affected by: patients' diet, daily exercise, total fat intake and quality of life. Patients who present with Type 2 diabetes may be started on therapeutic nutrition management and exercise to reduce weight and obtain control over the A1C level and degree of insulin resistance [25, 27]. However, if the patients on diet and exercise fail to achieve and maintain glycemic control, pharmacotherapy is recommended.

The purpose of the study is to explore the association of oral antidiabetics (OAD) classes and BMI/weight change over 6 months in Type 2 diabetes (T2DM) elderly patients in ambulatory setting. This study was conducted utilizing the real-world data in the GE EMR

database; therefore, it provides more evidence to support or deviate from the clinical trial's findings. The proposed study investigated the distribution of T2DM elderly patients in the General Electric Electronic Medical Records (GE EMR) database in regards to:

1. BMI and weight trends in elderly with diabetes patients using OAD medication
2. OAD use in elderly with diabetes patients and baseline clinical variables

CHAPTER 2

LITERATURE REVIEW

Type 2 diabetes is a common disease in the elderly population. By the age of 75, approximately 20% of the population is afflicted with this illness. From 1980 through 2006, the number of Americans with diabetes tripled (from 5.6 million to 16.8 million) [28]. People aged 65 years or older account for approximately 37% of the population with diabetes. Diabetes in elderly adults is metabolically distinct from diabetes in the younger patient population, and the approach to therapy needs to be different in this age group[29]. Diabetes is associated with considerable morbidity, mainly from macro- and microvascular complications, depression, kidney failure and weight gain. Several lines of evidence suggest that optimal glycemic control and risk factor modification can substantially reduce the risk of complications in elderly patients [29]. A study by Brixner D. et al. 2007, indicates that BMI and lab values are the key source for recognition of the cardiovascular metabolic syndrome and therefore risk of later developing diabetes [30].

In the past, treatment options were limited. Currently, numerous treatments are available for use in older patients with diabetes. Recent studies have described several new and exciting therapeutic opportunities for elderly patients with diabetes. Regardless of the most suitable drug therapy, patients still experience various complications; one of the most commonly recurring is weight change [31]. Considering the slowness in metabolism as

people age and the association of Type 2 diabetes and weight gain, there are newer oral antidiabetic drugs (OADs) designed to purposely either cause weight loss and/or cause less weight gain, presented as BMI change.

A model developed at the National Institutes of Health (NIH) showed that regular measurement and tracking of BMI over time in diabetic patients can help better control A1C level; therefore the better Type 2 diabetes disease management, as well as compared with non-BMI control for patients with the onset of diabetes at 65 years and older [4, 5]. Most OADs, except metformin, have shown moderate increase in patients' weight by 1 to 3 kg [31]. Also, metformin did not show an effect on weight change in placebo-controlled trials either [21, 22]. Sulfonylureas are well known as agents associated with weight gain in elderly patients [32]. Thiazolidinediones (TZD) caused similar gain in weight (1 to 2.5 kg) compared to sulfonylurea. In one of the most important studies regarding diabetes, the UK Prospective Diabetes Study (UKPDS), second-generation sulfonylureas, such as glibenclamide and chlorpropamide, had an effect on weight gain [14].

A study by Asche et al. studied the adverse events (AE) rates with OAD use in the elderly and concluded the findings differed from those seen in clinical trials, particularly for weight gain and hypoglycemia. AEs related to sulfonylurea therapy were in the same range as in clinical trials for weight gain; AEs related to thiazolidinediones therapy were more common than in clinical trials and lower for hypoglycemia and edema [33].

Some of the literature is not consistent with what has been previously discussed. The results found by Cohen et al. showed that weight gain does not essentially accompany treatment of T2DM. The OAD therapy is related with some weight gain, in certain drug classes, where it is mostly due to modification of glycemia and improvement of weight loss prior to the OAD treatment [19]. Significant decrease in levels of triglycerides, low-density lipoprotein, total cholesterol and A1C were associated with use of metformin and TZD

(rosiglitozone). Also, metformin showed significant decrease in body weight, and was as effective in normal and overweight individuals as it is in those who are obese; there are evidence-based data to support metformin use in obese individuals with T2DM [20, 21]. Metformin is particularly appropriate for overweight patients with high fasting blood-glucose levels [22]. An open randomized cross-over study compared metformin with glibenclamide over one year in non-insulin-dependent patients. Equivalent effect on glycemic control was found, but, in contrast to glibenclamide, metformin reduced body weight [23].

The literature also showed that TZDs caused a significant weight change among elderly patients in the EMR database, which somewhat supports findings from previous studies with regard to combination therapy of rosiglitazone with metformin or sulfonylurea [25, 26]. The literature indicates that rosiglitazone in combination with other OAD agents is a cost-effective intervention for the treatment of normal weight, overweight and obese patients with T2DM when compared with conventional care [24]. Additionally, Shearer et al. concluded that after adjusting for the baseline weight, TZD still showed 1.12lb weight loss, which conflicts with the current literature findings. A few assumptions have to be addressed regarding previously mentioned results: 1) no patients' lifestyle data were reported or 2) missing prescription refill data, therefore no record of patients' therapy compliance. Importantly, in older adults with T2DM, the TZDs should be used cautiously; and in patients with heart failure, TZDs are absolutely contraindicated. Contraindicated heart failure is 2.5 times more frequent in users of TZDs and insulin compared with insulin users alone, the risk of heart failure is 4.5% in patients taking TZDs compared with 2.6% for non-TZD users [25]. TZDs have a lesser role in treating T2DM in older patients because of their significant cardiovascular-related concerns, association with increased fracture risk and rosiglitazone's potential to cause macular edema [26].

Following patients BMI is of great importance to try to improve not only patients' weight but also compliance rates. For aging patients (50 years of age or older) and at disease onset, there is a sustainable difference in BMI trends compared to those who are between 60-70 years old [24]. The study by Rezende FA et al. 2006, proved that there is an association between inadequate metabolic profile and the excess of body weight and/or central obesity, evidencing the need for a nutritional and clinical intervention in the Type 2 diabetes patients, in order to reduce the risk of future chronic complications [34].

Preliminary studies

One of the few essential studies on diabetes care that looked at the relationship between glycemic control (as measured by glycosylated hemoglobin or A1C) and diabetic complications, as well as potential reduction of those complications, is the United Kingdom Prospective Diabetes Study (UKPDS). The UKPDS looked at the adult population of Type 2 diabetes to compare intensive pharmacologic therapy versus conventional therapy with diet [14]. The study showed that second-generation sulfonylurea, such as glibenclamide and chlorpropamide, were associated with minor weight gain, 2.4 kg on average. The newest sunfonylurea agent, glimiperide, has shown better outcomes regarding A1C, lower insulin levels in conditions of low blood glucose and certain weight loss. After 4 months of treatment with glimiperide, patients lost up to 1.9 kg, after 1 year, -2.9 kg and after 1.5 years, -3.0 kg. Greater decrease in BMI was found in males compared to females and there was evidence that menopause did not have any significant influence on the results. UKPDS researchers found that as A1C levels reached normal, each 1% improvement reduced the risk of all diabetes complications, including heart attack, stroke and amputation [15].

Oral antidiabetics agents studied

Generally, patients are initiated on an oral antidiabetic agent (OAD). In fact 70% of Type 2 diabetes patients are treated with oral OADs. Currently, five different classes of hypoglycemic agents are available, each class displaying unique pharmacologic properties [17]. These classes are as they appear: *sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors* and *dipeptidyl-peptidase 4 inhibitors* (see Table 1). In the case of the patients who do not tend to manage adequate glucose control with diet and exercise, single OAD therapy can be attempted. When choosing an agent, it is of the greatest importance to consider both patient- and drug-specific characteristics. If adequate blood glucose control is not attained using a single OAD, a combination of agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control and at the same time improve patients' BMI goal. However, over a third of new Type 2 diabetes patients change OAD medication within the first year for reasons such as therapy failure and side effects [16]. Thus, it is important to understand the efficacy, safety and cost effectiveness of OADs in the initial treatment of Type 2 diabetes. From a patients' perspective and even from that of payers', as well, there is still the question to be addressed: What first-line OAD strategy will be the most cost effective in treating new patients to achieve the recommended glycemic goal with minimal side effects, in the proposed study weight gain/loss?

Table 1. Oral antidiabetic agents

Class of Agent	Contraindications	Side Effects
Sulfonylureas	Renal failure	Hypoglycemia
	Hepatic insufficiency	Weight gain
	DKA	
Meglitinides	Hepatic insufficiency	Hypoglycemia
	DKA	
Biguanide	Predisposition to lactic acidosis	Gl upset
	Poor peripheral perfusion	Lactic acidosis
	Hypoxic states, Sepsis	
Thiazolidinediones	Congestive heart failure	Fluid retention
	Liver disease	Peripheral edema
	DKA	
Alpha-glucosidase Inh*	Small-bowel disease	Flatulence
	Severe renal insufficiency	Diarrhea
	DKA	Gl upset
DPP-4 inhibitors*	DKA	Headache
		Nausea, vomiting
		Diarrhea

*Alpha-glucosidase inhibitors and DPP-4 inhibitors decrease the hemoglobin A1C level 0.5% to 1%; other classes of agents decrease it by 1% to 2%.
Source: References 19, 22, 23, 27.
Abbreviations: CrCl = Creatinine clearance, DKA = Diabetic ketoacidosis, DPP-4 = Dipeptidyl-peptidase-4, GI Gastrointestinal

CHAPTER 3

STUDY DESIGN AND METHODS

Study design

This study employed a cross-sectional cohort design to evaluate the association between the use of oral anidiabetics agents (OAD) and change in BMI and weight utilizing data from January 1, 1997, through December 31, 2008.

The cohort included an elderly population age 65 years and older at the date of first OAD prescription within the GE EMR database, who had ≥ 12 months of continuous pre-index-date activity; index date was defined as first OAD prescription.

Persons excluded were individuals who were diagnosed with depression, cancer, HIV, protein-calorie malnutrition, hypothyroidism and weight loss medications (see Appendix A for ICD-9 codes).

Variables

The primary dependent variable was Body Mass Index (BMI), measured at baseline and follow up, and presented as the BMI change. In addition, the weight, as the secondary outcome variable, was measured at baseline, follow-up and presented as change in weight.

Primary independent or predictor variables were OAD classes, age, race, glycated hemoglobin (A1C), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total

cholesterol (TC), triglycerides (TG), comorbid condition (see Appendix D), insurance type, age, and drugs/ drug classes known to be associated with Type 2 diabetes (see Appendix C).

Procedures

Data used in the proposed study were gathered through the General Electric Centricity Electronic Medical Record (GE EMR, GE Healthcare, Waukesha, WI) research database from 1996 to present. It is a longitudinal patient database containing, but not limited to, demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems. Patients in the EMR database are similar in age and racial/ethnic subgroups to the US population based on the 2005 United States (US) Census estimates. Patients 65 years and older were representative of 16.6% of the patients within the GE EMR which is somewhat consistent with US Census national population estimates of 13.6%. The main reason for this difference is that frailer, sicker elderly will be presented more in the EMR than in the general population of the same age. The prevalence of Type 2 diabetes in the GE EMR identified by diagnosis codes was 6.55% in 2007. The important fact is that the GE EMR database has a higher representation of women compared to national estimates (58.1% female in EMR vs. 50.8% in the US). Patient data are available for only 35 of 50 US states, with a higher representation of Northeastern, Midwestern and Southern States, 24.27%, 33.13% and 29.94%, respectively.

Participants are selected from a network of outpatient private physician practices that uses an ambulatory EMR, known as Centricity Office from General Electric Healthcare Information Technology (GEHC IT). All data in this database are de-identified (DI) according to HIPAA standards. For each patient, the EMR begins with demographic information followed by details regarding medications and prescriptions, symptoms,

physical examination findings, laboratory and radiology results and diagnoses. In addition, this database includes information such as weight, height, blood pressure, and glucose and cholesterol level, HDL, LDL, triglycerides and smoking status. After this part is done, a reporting data set is created for analysis. These data sets are used for primary care research, health system research and, in particular, for quality of health care studies. Following HIPPA standards, medical practices that use this EMR can decline participation in MQIC (Medical Quality Improvement Consortium) studies, and their patients' records are going to be excluded from the research data sets.

The values of the GE EMR database are as follows: 1) Centricity EMR is used by over 100 clinical practice sites to manage 30 million patient records in 35 states, 2) the GE EMR research database contains longitudinal ambulatory electronic health data for over 10 million patients of all ages (but not limited to demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems), and 3) variety of practice types are represented in the consortium ranging from solo practitioners to community clinics, academic medical centers, and large integrated delivery networks. Approximately 60% of the participating clinicians practice primary care.

This EMR allows the use of combinations of clinical data, such as chief complaint data, comprehensive laboratory values, and vital signs.Therefore, these parameters identify patients, which can be valuable in maximizing the identification of patients; such data also enable research of treatment outcomes.

Patients were selected from the GE EMR database according to the following selection criteria:

1. Age 65 or older on index date
2. No OAD prescription prior to index date (naive diabetic patients)
3. Indication of Type 2 diabetes based on meeting at least one of the following requirements:

a. Diagnosis of Type 2 diabetes based on an ICD-9 codes of 250.X0 or 250.X2, or

b. At least one prescription order for an oral antidiabetic drug (OAD) (Index Date) (see Appendix A and Table 1). All patients need to have only one OAD prescription at date prescribed, excluding the fixed dose combinations.

Within this historic cohort study design, the patients were followed for 6 months (+30 days) from the index date. The study required that included patients have at least a year of continuous pre-index-date activity (see Figure 1).

4. Continuously active in the database for a minimum of 365 days (+/-30days) prior to index date

5. Continuously active in the database for at least 6 months (+30 days) post-index-date

6. Naïve patient population- no other OAD, insulin per med list entry naïve prior to index date

7. Comorbid conditions- Exclusion of the patients with cancer, HIV, depression, protein-calorie malnutrition, hypothyroidism, hyperthyroidism, and weight loss medications (see Appendix A for ICD-9 codes)

8. Number of patients with diagnose of Type 1 Diabetes (exclusion criteria)

9. Number of patients with no other added-on OAD or insulin in 210 days (180 days+30 days) post-index-date

10. Baseline BMI reading (Index date +/- 30 days) for 210 days data

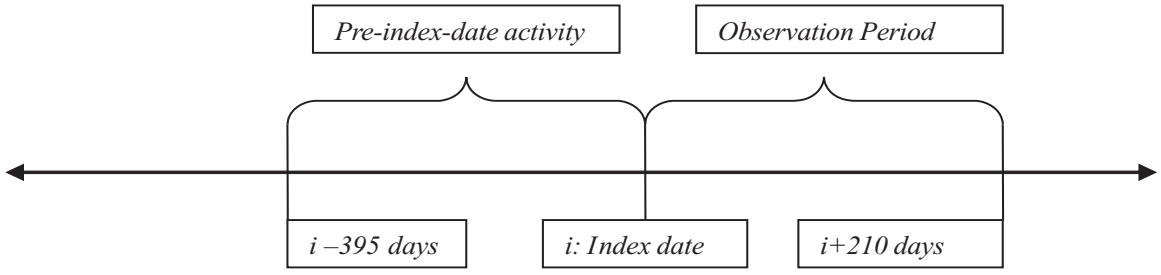

Figure 1. Study timeline

11. Follow-up BMI reading for 180 days (+30 days) post-index-date, completed the final number of patients (study population). Patient population was stratified based on diabetes treatment on index date and divided into 6 study groups:

- MET monotherapy
- SU monotherapy
- TZD monotherapy
- Alpha Glucose inhibitors monotherapy (later excluded due to the lack of number of patients)
- DPP-4 inhibitor monotherapy
- Meglitinides monotherapy

Data were entered into SAS Proprietary Software 9.2 (SAS Institute Inc., Cary, NC, USA) for analysis. Demographics information that included age, ethnicity, region, insurance type, smoking and alcohol status for the population and each group was recorded, and presented in a tabular format. Clinical baseline characteristic and comorbidities were also recorded, namely, blood pressure, A1C, LDL, HDL, TG, TC, hypertension, acute myocardial infarction, cardiovascular disease, cerebrovascular disease and kidney disease. Prescription orders for the covariate medication of the study population were also recorded, namely: 1) dyslipidemias, antipsychotics, antiretrovirals, hormone replacement therapy, glucocorticoids and 2) hyperglycemia/ Glucose Intolerance, such as, atypical antipsychotics, glucocorticoids, thyroid hormone, oral contraceptives and nicotinic acid. For a full description of the prescription medication see Appendix B. Results were presented in tabular format, reporting baseline demographics with percentage of certain OAD users.

The following characteristics of the patients' were captured to portray the OAD study population and afterward employed as variables in the Analysis of Variance (ANOVA) with Tukey test performed to explain the differences in study groups.

- Demographic data
  - Age (65-69, 70-74, 75-80, ≥80)
  - Gender (Male, Female)
  - Race/ethnicity (Caucasian, African-American, Hispanic, Other, Unknown)
  - Region (Northeast, South, Midwest, West)
  - Insurance status (Commercial, Medicare, Medicaid, Self-pay, Not Reported)
- Baseline clinical characteristics
  - A1C; continuous and categorical (<7.0, ≥7.0 - <9.0, ≥9.0)
  - BP; mean SBP and mean DBP (≤ 130/80, ≥ 130/80)
  - BMI (systematically calculated by EMR based on height and weight); continuous and categorical [under or normal (BMI < 24.9), overweight (BMI 25-29.9), obese (BMI 30-34.9), very obese (35.0-39.9), extremely obese (BMI>40).]
  - Weight (continuous)
  - Smoking status; current, former, nonsmoker, other
  - Alcoholism- cirrhosis, alcohol dependence, severe alcohol abuse (defined by ICD-9 codes as appears: 303, 571.2 and V11.3)
  - Lipid levels
    - TGs; continuous and categorical (<150 mg/dl, ≥150 mg/dl)
    - HDLs; continuous and categorical (<40 mg/dl, ≥40 mg/dl)
    - LDLs; continuous and categorical (< 100 mg/dl, ≥100 mg/dl)
    - TC; continuous and categorical (<240 mg/dl, ≥240 mg/dl)
  - Covariate drugs: other therapy drugs influences studied outcomes (see Appendix B.)
- Comorbidities
  - Charlson Comorbidity Index at time of study entry (see Appendix C)

o Individual comorbid conditions: hypertension, acute MI, cardiovascular disease, cerebrovascular disease and kidney disease (see Appendix C)

The A1C level on baseline and after 6 months from index date was captured for individual patients. There was a need for acknowledging the recordings of the change in A1C level after 6 months for a certain OAD monotherapy, and an attempt was made to describe and if possible to strengthen the impact of the OAD on the diabetes clinical outcomes. The results of the change in A1C level were presented by drug level, where change in A1C level after six months for each OAD medication was measured; these readings tried to accompany the previously shown change in clinical outcomes (BMI and weight).

The primary outcome variables was the BMI (unit and percent change), and change in weight (unit and percent change). Change was measured from baseline to 6 months for all patients with 6 month (+30 days) follow-up BMI or weight readings.

Statistical methods

Descriptive statistics were utilized to describe the baseline demographic and clinical characteristics for elderly Type 2 diabetes patients. Tests for statistically significant differences in baseline characteristics by baseline treatment was conducted using analysis of variance (ANOVA), which is used for comparison among two and more groups of interest, for continuous variables and Pearson's chi-square test for categorical variables. Any present small sample cell size (<5) was analyzed by using the Fisher exact test. The ANOVA was accompanied by the Tukey test, used to find which means are significantly different from one another. It compares all possible pairs of means with multiple-comparison adjustment. Changes in BMI and weight from baseline for the 6 months follow-up analyses were reported for patients overall and by index diabetes treatment. The sample power calculation

was not performed, since the presented analysis is the Post-hoc analysis of variances, where it is not suggested to do the power calculation. These outcomes analyses were accounted for the patients in each outcome that have baseline and follow-up data.

In addition to ANOVA, general linear models were developed to estimate the mean change in outcomes for patients by baseline drug treatment for subjects with baseline and follow-up readings of the individual outcome measures at 6 months. The model controlled for patient baseline BMI and weight values, some of the demographic and clinical characteristics that differ between patients that could impact outcomes, for the addition of covariate drugs.

Mean change in outcomes, BMI and weight, was estimated utilizing coefficients derived from the ANOVA. Also the general linear model was used to assess the differences in outcomes between patients; p-value with 95% confidence intervals was reported. The results were presented as units change for both outcomes, also the statistical significant comparisons betwen OAD groups were shown. All statistical tests were performed at a 0.05 significance level using SAS Proprietary Software 9.2 (SAS Institute Inc., Cary, NC, USA).

CHAPTER 4

RESULTS

Study population

From the total population of 11,071,328 within the EMR database, 428,456 people had an OAD prescription-Index date (first OAD prescription in EMR database from 1996 though 2008). For the purposes of the study, we included only patients 65 years of age and older at or after the date of first OAD prescription (n=1,440,198). Monotherapy OAD, including the patients who were prescribed with one OAD medication during the study period, limited the population to 122,780 patients (1.1% of the overall EMR database). Then, 46,776 patients had 395 days of pre-index-date activity, where 61.9% of the patients were lost due to the insufficient (fewer than 395 days) activity prior to index date. An additional 6.4% patients were excluded due to the lack of 6 months activity after index date. Another 16% of unique patients were excluded from the 46,776 patients group based on the criterion of including only naive antidiabetic agent users. Based on the diagnosis exclusion criteria, 7.6% patients were excluded from the study. This included 158 patients due to the Type 1 diabetes, 9383 with ICD9 code (cancer, HIV, hypothyroidism, hyperthyroidism, protein-calorie malnutrition) and 208 patients with prescriptions for weight loss medications. From the index date, 8,004 (1.5% lost) patients were followed for the 6 months (+30 days) of continuous OAD monotherapy with no add-on or switches on the therapy. Baseline BMI and

weight readings (+/- 30 days from the index date) were captured for 5,162 unique patients (2.3% patients were excluded due to the lack in BMI readings). This resulted in a study population of 2721 patients (1.9% lost) who had follow-up BMI and weight readings, 6 months + 30 days from the index date (see Figure 2). Additionally one patient was excluded due to the deficient power in the Alpha Glucose Inhibitors group (group contained one patient, therefore was dropped from further analysis), which brought the final study population to

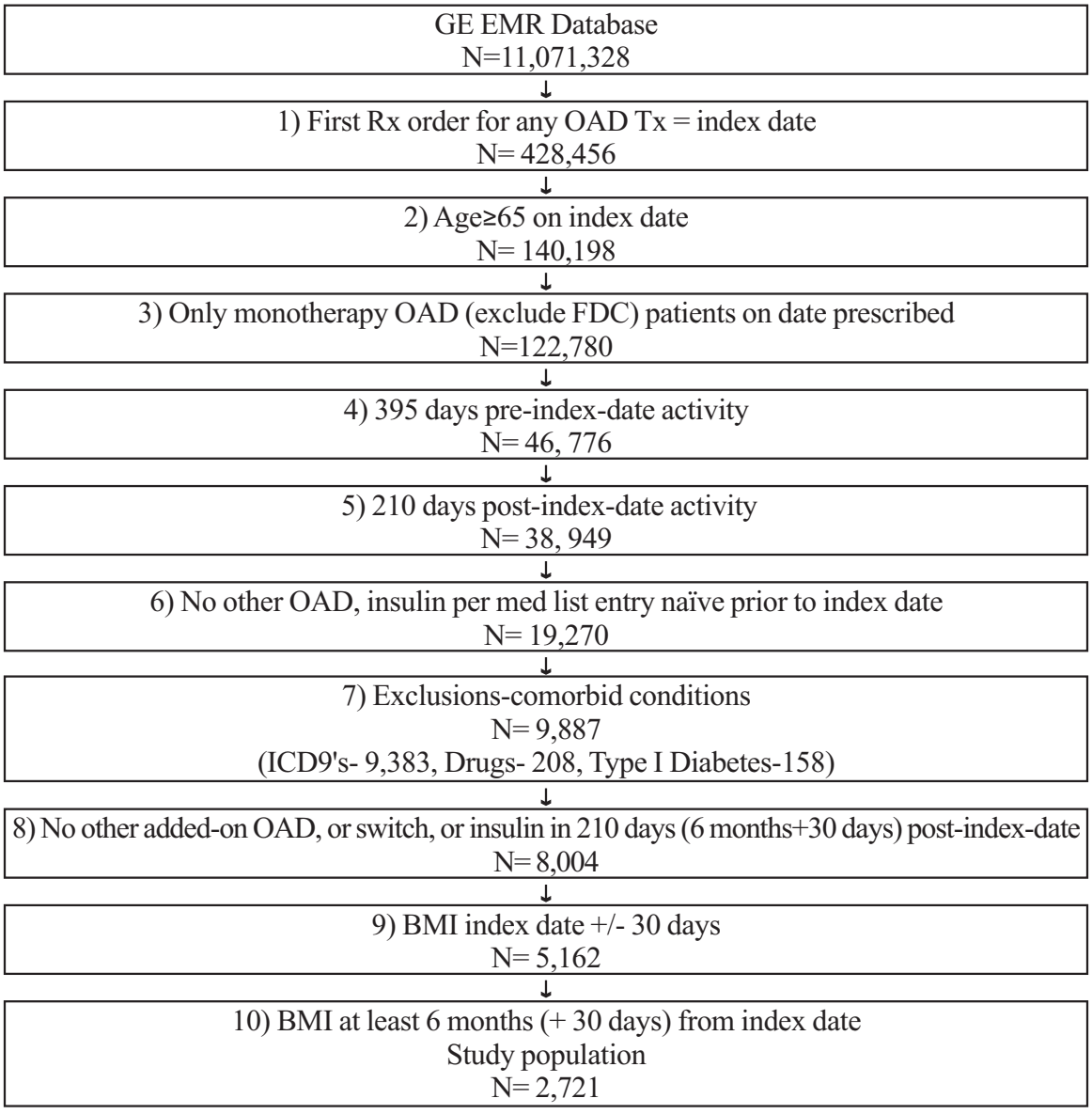

Figure 2. Study population flowchart

2720 unique patients, where from the initial 122,780 collection, 97.7% patients were excluded.

Of the monotherapy study population (N=122,780), 38.1% patients had a year pre-index-date activity; 8004 patients had a 6 months monotherapy OAD activity and of those, 2, 721 patients had at least two BMI and weight readings (baseline and follow-up). This study has a lesser sample size, accordingly to the rigorous patient selection criteria and excluding the major diseases and covariate therapies that were shown to be associated with weight and elderly Type 2 Diabetic patients. Table 2 shows the baseline characteristics of the study population by OAD groups (study cohorts). The study population was somewhat evenly distributed across the age categories (65-69, 70-74, 75-79 years of age) within OAD groups, with the exception of the DPP-4 Inhibitors group (11%, 15% and 74%). Ethnicity data were not reported for the majority of patients (55%, 56%, 49%, 67% and 70%, respectively). The Caucasian group represented the most reported ethnicity (38%, 34%, 44%, 26% and 18%, respectively). Gender distribution difference was found only in the metformin group, male vs. females, 45% and 55%, respectively. The included patients were 65 years of age or older, therefore the majority was insured though Medicare: 67%, 67%, 74%, 70% and 79%. Data were gathered mostly from the Northeast region of the United States (34%, 30%, 33%, 37% and 36%); the West region was underrepresented in the study. Reported baseline BP showed the patients were mainly, regardless of the OAD group, in Hypertension Stage 1 (blood pressure from >130/80 mmHg to 159/99 mmHg). There were many missing observations in the following baseline variables: HDL, LDL, total cholesterol, triglycerides, alcohol and smoking status. From the total study population, hypertension (16%, 16%, 17%, 11% and 15%) and cardiovascular disease (8%, 13%, 8%, 7% and 6%) accounted for the majority of the comorbidities within the study population.

Table 2. Baseline demographics characteristics

Variable	MET (N=1602)	SU (N=819)	TZD (N=239)	DPP-4 Inhibitors (N=27)	Meglitinides (N=33)
Age					
65-69	40%	23%	31%	11%	24%
70-74	34%	43%	38%	15%	39%
75-79	26%	34%	31%	74%	36%
Total N for Age					
Gender					
Male	45%	50%	51%	52%	45%
Female	55%	50%	49%	48%	55%
Race					
Caucasian	38%	34%	44%	26%	18%
African-American	4%	5%	5%	7%	6%
Hispanic	1%	3%	0%	0%	3%
Other	1%	2%	1%	0%	3%
Unknown	55%	56%	49%	67%	70%
Region					
Northeast	34%	30%	33%	37%	36%
South	25%	26%	33%	33%	36%
Midwest	27%	30%	23%	22%	12%
West	14%	14%	12%	7%	15%
Insurance					
Commercial	16%	17%	14%	15%	12%
Medicare	67%	67%	74%	70%	79%
Medicaid	0%	0%	0%	0%	0%
Self-pay	0%	0%	0%	0%	0%
Other/Unknown	16%	16%	12%	15%	9%
Blood Pressure					
Normal	30%	29%	33%	33%	42%
Hypertension-stage1	64%	63%	64%	63%	55%
Hypertension-stage2	5%	6%	3%	4%	3%
A1C					
<7.0	29%	18%	25%	30%	42%
7.0-8.9	32%	34%	29%	26%	27%
>9.0	5%	8%	6%	0%	0%
Number of nonmissing observations	1,060	484	143	15	23
Tryglicerides					
<150 mg/dl	17%	11%	24%	22%	15%
<150 mg/dl	20%	17%	19%	15%	18%
Number of nonmissing observations	590	232	102	10	11
HDL					
<40 mg/dl	18%	17%	16%	15%	15%
>40 mg/dl	35%	25%	42%	26%	33%
Number of nonmissing observations	850	346	140	11	16

Table 2 continued

Variable	MET (N=1602)	SU (N=819)	TZD (N=239)	DPP-4 Inhibitors (N=27)	Meglitinides (N=33)
LDL					
<100 mg/dl	19%	15%	23%	11%	6%
>100 mg/dl	22%	15%	20%	15%	30%
Number of observations	663	247	104	7	12
Total cholesterol					
<240 mg/dl	49%	40%	51%	30%	45%
>240 mg/dl	5%	5%	6%	7%	6%
Number of nonmissing observations	868	365	138	10	17
Smoking status					
Current	6%	4%	3%	4%	0%
Former	15%	11%	11%	30%	12%
Not current	6%	4%	10%	7%	6%
Unknown	19%	16%	14%	7%	18%
Number of nonmissing observations	722	279	98	13	12
Alcohol status					
Not an alcoholic	100%	100%	100%	100%	100%
Alcoholic	0%	0%	0%	0%	0%
Covariate lipid medication					
no drug	86%	83%	88%	93%	88%
drug	14%	17%	12%	7%	12%
Covariate glusoce medications					
no drug	86%	82%	83%	85%	82%
drug	14%	18%	17%	15%	18%
Comobridity-Hypertension					
no diagnosis	84%	84%	83%	89%	85%
diagnosis	16%	16%	17%	11%	15%
Comobridity-Acute MI					
no diagnosis	100%	99%	100%	100%	100%
diagnosis	0%	1%	0%	0%	0%
Comorbidity-CVD					
no diagnosis	92%	87%	92%	93%	94%
diagnosis	8%	13%	8%	7%	6%
Comorbidity-CRVD					
no diagnosis	97%	96%	98%	100%	97%
diagnosis	3%	4%	2%	0%	3%
Comorbidity-Kidney Disease					
no diagnosis	99%	97%	97%	93%	97%
diagnosis	1%	3%	3%	7%	3%

Table 3 illustrates the frequency of the individual OAD agents among the elderly Type 2 Diabetic patients. Of the total of 2720 patients, the most prescribed OAD agent was metformin with 1602 users (58.9%), followed by the glipizide, 395 users (14.52%) and pioglitazone, 156 (5.74%). Glipizide was the most prescribed in the class of sulfonylureas followed by the glimepiride with 211 users (7.76%) and glyburide, 198 (7.28%) of the total 2720 elderly diabetic patients.

Table 4 describes the baseline characteristics of the categorical variables. The differences were assessed using a Chi-square test. The rates of comorbid conditions differed between the treatment groups (acute MI, CVD and KD with p-values 0.0357, 0.0007 and 0.0001, respectively). Significant differences between the OAD groups were also found with respect to race and smoking status ($p=0.004$ and < 0.0001).

Table 3. Frequency of the OAD use among the elderly Type 2 diabetes

Prescribed drug	Number of patients	Percent (%)
GLIMEPIRIDE	211	7.76
GLIPIZIDE	395	14.52
GLYBURIDE	198	7.28
GLYBURIDE MICRONIZED	13	0.48
METFORMIN HCL	1602	58.9
NATEGLINIDE	20	0.74
PIOGLITAZONE HCL	156	5.74
REPAGLINIDE	13	0.48
ROSIGLITAZONE MALEATE	83	3.05
SITAGLIPTIN PHOSPHATE	27	0.98
TOLBUTAMIDE	2	0.07
Total	2720	100.00

Table 4. Baseline characteristics of the categorical variables

Categorical variables at Baseline		
Variable	**F**	**P-Value**
Gender	7.9	0.092
Race	34.6	0.0044*
Region	18.1	0.1127
Insurance	8.5	0.9327
Smoking status	53.4	<.0001*
Alcohol status	2.1	0.7181
Covariate lipid medication	6.5	0.1608
Covariate glusoce medications	6.9	0.1398
Comobridity-Hypertension	0.6	0.9631
Comorbidity-Acute MI	10.3	0.0357*
Comorbidity-CVD	19.3	0.0007*
Comorbidity-CRVD	4.7	0.3225
Comorbody-Kidney Disease	22.7	0.0001*

Table 5 illustrates the characteristics of continuous variables at baseline. The overall mean age in the OAD groups was 72.7 years. The values of the baseline diastolic blood pressure (DBP) differed (p=0.0009), as well as age (p< 0.001); also, DBP indicated that the patients were in Hypertension Stage 1. The A1C level was shown to be statistically significant (p< 0.001) with the highest mean value in the sulfonylureas group (7.7).

Table 6 describes the characteristics of the outcome variables (BMI and weight) at the baseline, closest reading to the Index date, and at the 6 months follow-up period. In comparing the baseline and follow-up values, statistical significance was found in both of the outcomes, BMI and the weight. The mean baseline BMI for all OAD groups was 29.78 kg/m², where the metformin users had the highest baseline BMI value (31.24 kg/m²); lowest baseline BMI was found among the DPP-4 Inhibitors patients (29.07 kg/m²). After the closest sixth month reading considering the monotherapy OAD, the overall mean BMI value was 29.08 kg/m². Further, the overall mean change in BMI among all of the OAD groups was - 0.7 BMI units (data show the weight loss among patients). The change in BMI after 6 months of

Table 5. Baseline characteristics of the continuous variables

Countinucs variables at baseline			Blood Pressure						
Variable		Age	Systolic	Diastolic	A1C	TG	HDL	LDL	TC
MET	Mean	71.2	134.8	75.5	7.3	179.9	46.3	105.3	184.3
	Lower	71.0	133.9	74.9	7.2	171	45.4	102.8	181.6
	Upper	71.4	135.9	75.9	7.3	188.9	47.2	107.9	187
SU	Mean	72.5	134.7	73.9	7.7	221.8	44.3	103.5	185.5
	Lower	72.2	133.4	73.3	7.5	197.7	42.9	99	180.9
	Upper	72.7	135.9	74.7	7.8	245.8	45.7	107.9	190.1
TZD	Mean	71.7	132.1	73.9	7.5	170.5	47.5	103.3	187
	Lower	71.2	129.7	72.5	7.2	150.1	44.9	95.7	179.6
	Upper	72.2	134.4	75.4	7.7	190.8	50.1	110.9	194.4
DPP-4 Inhibitors	Mean	75.4	135.1	74.1	7.1	145.1	47.8	121.3	193.6
	Lower	73.8	128.7	70.5	6.7	81.4	37.8	75.8	162.7
	Upper	77.0	141.5	77.6	7.5	208.7	57.8	166.7	224.5
Meglitinides	Mean	72.8	130.7	70.9	6.7	159.1	44.4	128.6	186.7
	Lower	71.3	123.9	67.4	6.4	111.8	38.8	109.7	161.1
	Upper	74.2	137.5	74.5	7.1	206.3	50.1	147.5	212.3
F		18.8	1.6	4.7	8.6	5.1	2.03	1.99	0.26
P-Value		<.0001*	0.1639	0.0009*	<.0001*	0.0004*	0.0885	0.0933	0.9053

* Statistically significant at alpha <0.05

Table 6. Characteristics of the outcome variables at baseline and follow-up

Outcome variables at baseline		BMI			Weight		
Variable		Baseline	Follow up	Change	Baseline	Follow up	Change
MET	Mean	31.24	30.17	-1.06	191.45	185.11	-6.41
	Lower	30.95	29.90	-1.16	189.45	183.14	-6.98
	Upper	31.52	30.45	-0.96	193.44	187.07	-5.85
SU	Mean	29.67	29.53	-0.15	181.23	180.38	-0.89
	Lower	29.30	29.16	-0.27	178.41	177.61	-1.56
	Upper	30.05	29.90	-0.02	184.04	183.15	-0.22
TZD	Mean	29.69	29.43	-0.26	181.59	180.57	-0.97
	Lower	28.99	28.71	-0.50	176.79	175.66	-2.38
	Upper	30.38	30.15	-0.01	186.39	185.47	0.43
DPP-4 Inhibitors	Mean	29.07	28.33	-0.74	173.41	169.70	-3.96
	Lower	26.66	26.00	-1.16	159.43	156.09	-6.35
	Upper	31.49	30.67	-0.32	187.38	183.30	-1.58
Meglitinides	Mean	29.21	27.94	-1.27	173.24	165.25	-7.82
	Lower	26.46	25.38	-3.11	157.91	150.62	-17.30
	Upper	31.97	30.50	0.56	188.58	179.89	1.66
F		12.99	3.8	31.86	11.74	4.56	39
P-Value		<.0001*	0.0044*	<.0001*	<.0001*	0.0011*	<.0001*

*Statistically significant at alpha <0.05

monotherapy showed the meglitinides had the biggest decrease in BMI (-1.27), followed by the metformin group (-1.06) and the sulfonylureas showed the least BMI drop (-0.14).

The secondary outcome was weight, where the mean baseline weight was 180.17 pounds (lb). Patients prescribed with metformin weighed the most (191.45 lb) at baseline. The follow-up weight mean was 176.20 lb; therefore, the 3.97 lb weight loss was reported between all of the OAD groups. Major weight loss was found in the meglitinides users (-7.82lb), followed by the metformin group (-6.41lb). The sulfonylureas group reported the least weight loss (-0.89lb).

Table 7 describes the BMI baseline frequency distribution by the OAD classes. Furthermore, the baseline BMI was stratified by four cohorts: underweight (BMI less than 18 kg/m2), normal (BMI 18-24.9 kg/m2), overweight (25-30 kg/m2) and obese (over 30 kg/m2). Over 58% of the patients were metformin users, and of those, 64.63% were in the obese group. The majority, 41.23% of the sulfonylureas users, were in the normal weight BMI group and a similar trend was observed in the case of DPP-4 Inhibitors and meglitinides (1.54%, 2.46%, respectively).

Table 7. Characteristics of the baseline BMI stratified by underweight/normal/overweight/obese OAD users

OAD Class	Baseline BMI				
	Underweight (%)	Normal (%)	Overweight (%)	Obese (%)	Total (%)
MET	60.00	45.54	54.36	64.63	58.9
SU	30.00	41.23	31.6	26.73	30.11
TZD	5.00	9.23	11.49	7.07	8.79
DPP4-Inhibitors	0.00	1.54	1.10	0.82	0.99
Meglitinides	5.00	2.46	1.44	0.75	1.21
Total	0.74	11.95	33.27	54.04	100

Table 8 illustrates the BMI follow-up frequency distribution by the OAD classes, where the weight reading closest to the 6 months of OAD monotherapy was accounted for. Results are somewhat similar to the BMI baseline frequency distribution. The heaviest elderly diabetic patients were seen in the metformin group, with 62.5% obese patients; weight loss was indicated in these patients, since there were 64.63% patients in the obese group at the baseline and there were 62.50% after 6 months. The sulfonylureas users showed minor weight gain, 28.92% patients in the obese group at the follow-up compared to the 26.73% of the patients in the obese group at baseline.

Table 8. Characteristics of the follow-up BMI stratified by underweight/normal/overweight/obese OAD users

OAD Class	Follow up BMI				
	Underweight (%)	Normal (%)	Overweight (%)	Obese (%)	Total (%)
MET	58.62	54.2	55.88	62.5	58.9
SU	27.59	33.08	30.62	28.92	30.11
TZD	6.9	8.65	11.34	7	8.79
DPP4-Inhibitors	0.0	1.78	0.82	0.9	0.99
Meglitinides	6.9	2.29	1.34	0.68	1.21
Total	1.07	14.45	35.66	48.82	100.0

Differences among the OAD groups

Figure 3, Table 9, Figure 4, Figure 5, Figure 6, Table 10, Figure 7, Table 11, Figure 8, Table 12, Figure 9, Table 13, Figure 10, Table 14, Figure 11, Table 15, Figure 12, Table 16, Figure 13, Table 17, Figure 14, and Table 18, illustrate the association between the baseline levels of BMI, Weight, A1C, Diastolic Blood Pressure (DBP), Triglycerides, Age and study cohorts (OAD classes). Also, the correlation between the follow-up BMI, weight and OAD groups was analyzed. An analysis of variance (ANOVA) is a statistical test in which the observed variance is partitioned into components due to different explanatory variables. The ANOVA describes that the means of several groups are all equal, and therefore generalizes the Student's t-test to more than two groups. The Tukey test, which is used in conjunction with an ANOVA to find which pairs of means are significantly different from one another (and compares all possible pairs of means), was applied in proposed analysis. The statistically significance differences between the pairs of AOD classes were found at alpha < 0.05 at and are presented in the legend, below each figure as they appear. All of the analyses for the variable of interest were performed at OAD class level, except for the change of the A1C level that was done both at class and individual OAD agent level. The reasons for this motion were: 1) there are no OAD agents refill data available in GE EMR and improvement of the A1C level after 6 months of OAD monotherapy could be attributed to the actual OAD medication and 2) to emphasize the impact, of the better A1C controlled OAD therapy, on clinical outcomes (BMI and weight).

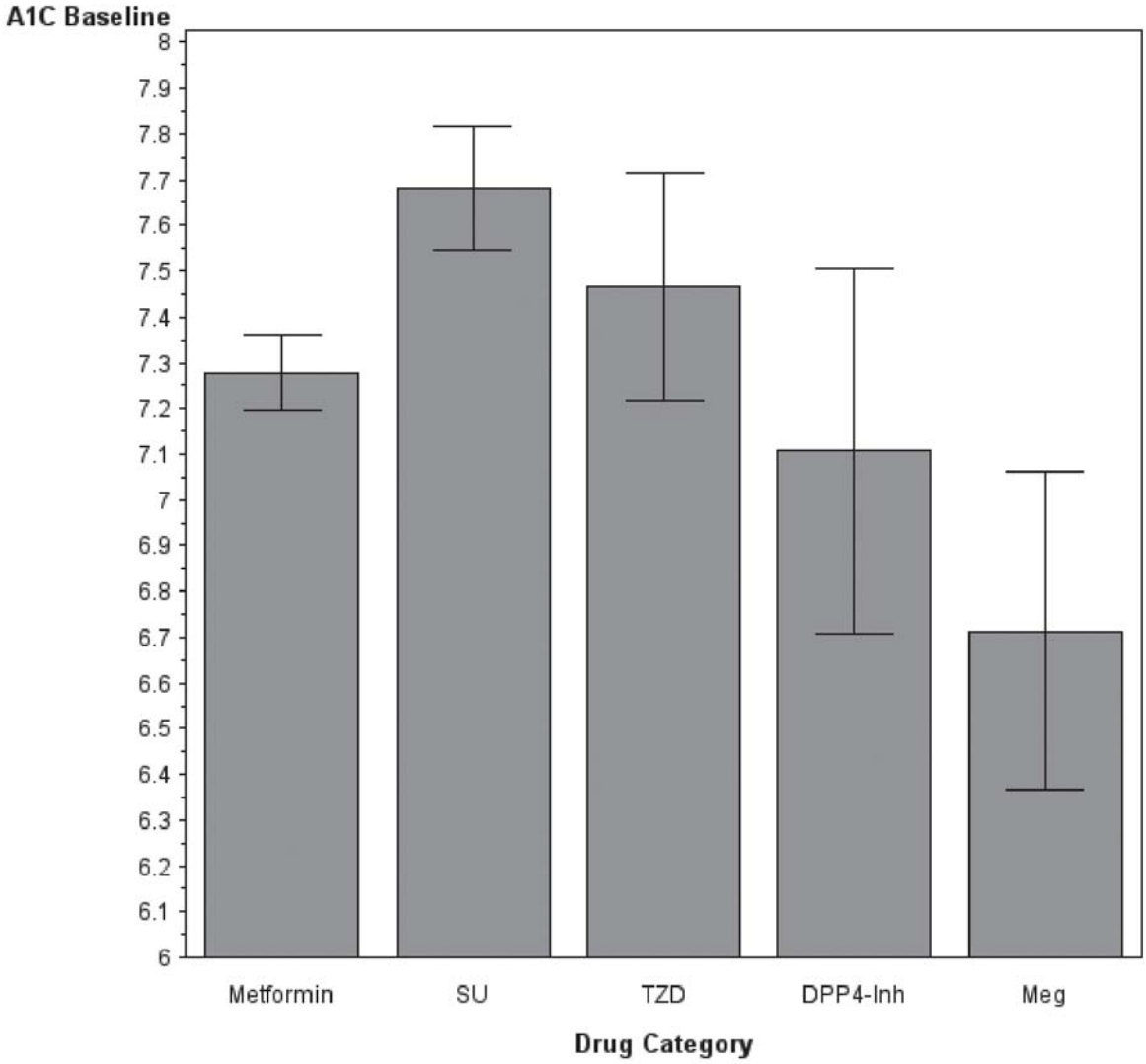

Figure 3. Mean baseline A1C by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas and Sulfonylureas vs. Meglitidines

Table 9. Association between the baseline A1C and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline A1C				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	7.28	7.68	-0.40	-0.6107	-0.1950
Sulfonylureas vs. Metformin	7.68	7.28	0.40	0.1950	0.6107
Sulfonylureas vs. Meglitidines	7.68	6.71	0.97	0.1602	1.7774
Meglitidines vs. Sulfonylureas	6.71	7.68	-0.97	-1.7774	-0.1602

*All of the above comparisons were statistically significant at alpha <0.05

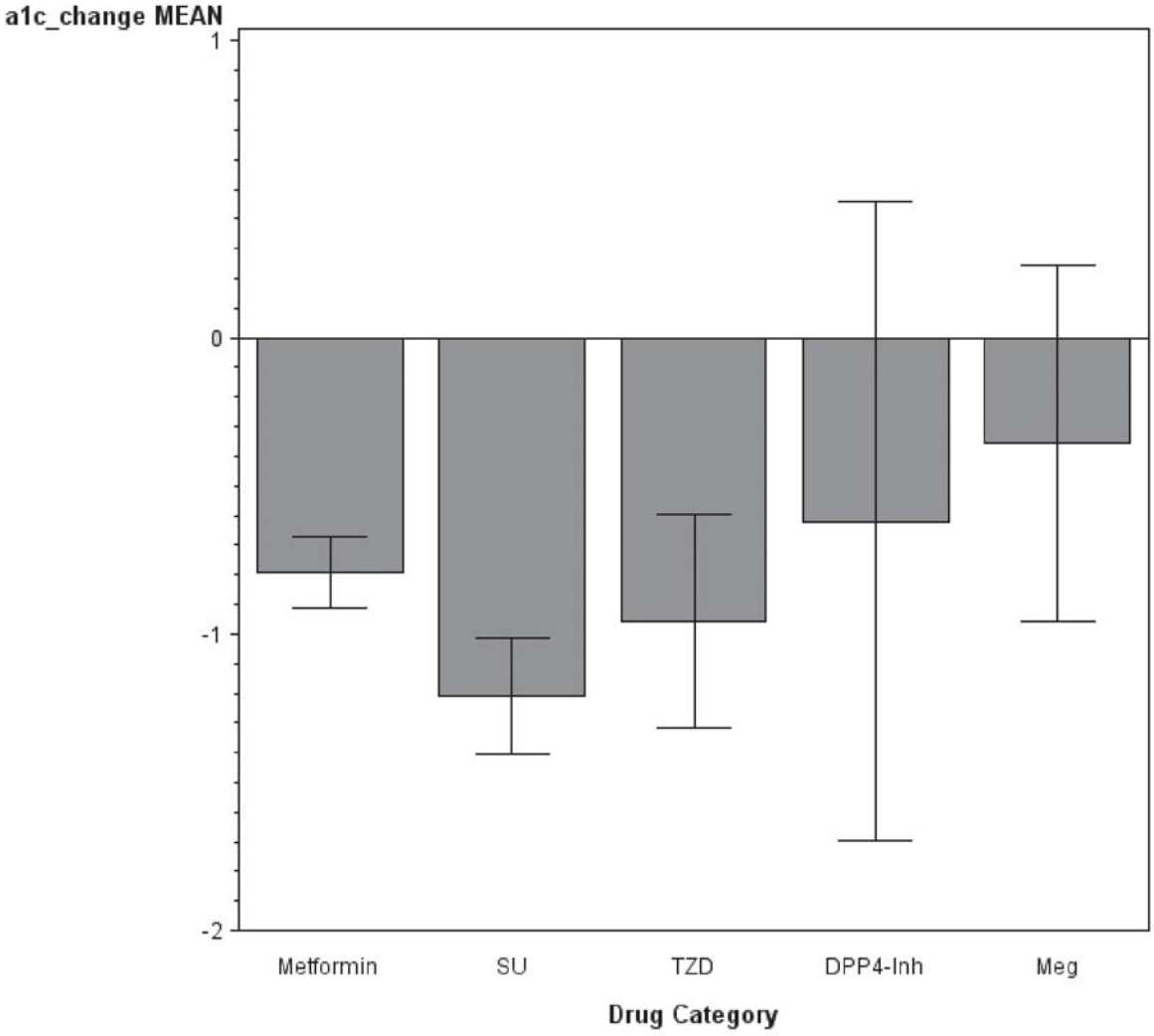

Figure 4. Mean change A1C by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparison: Metformin vs. Sulfonylureas

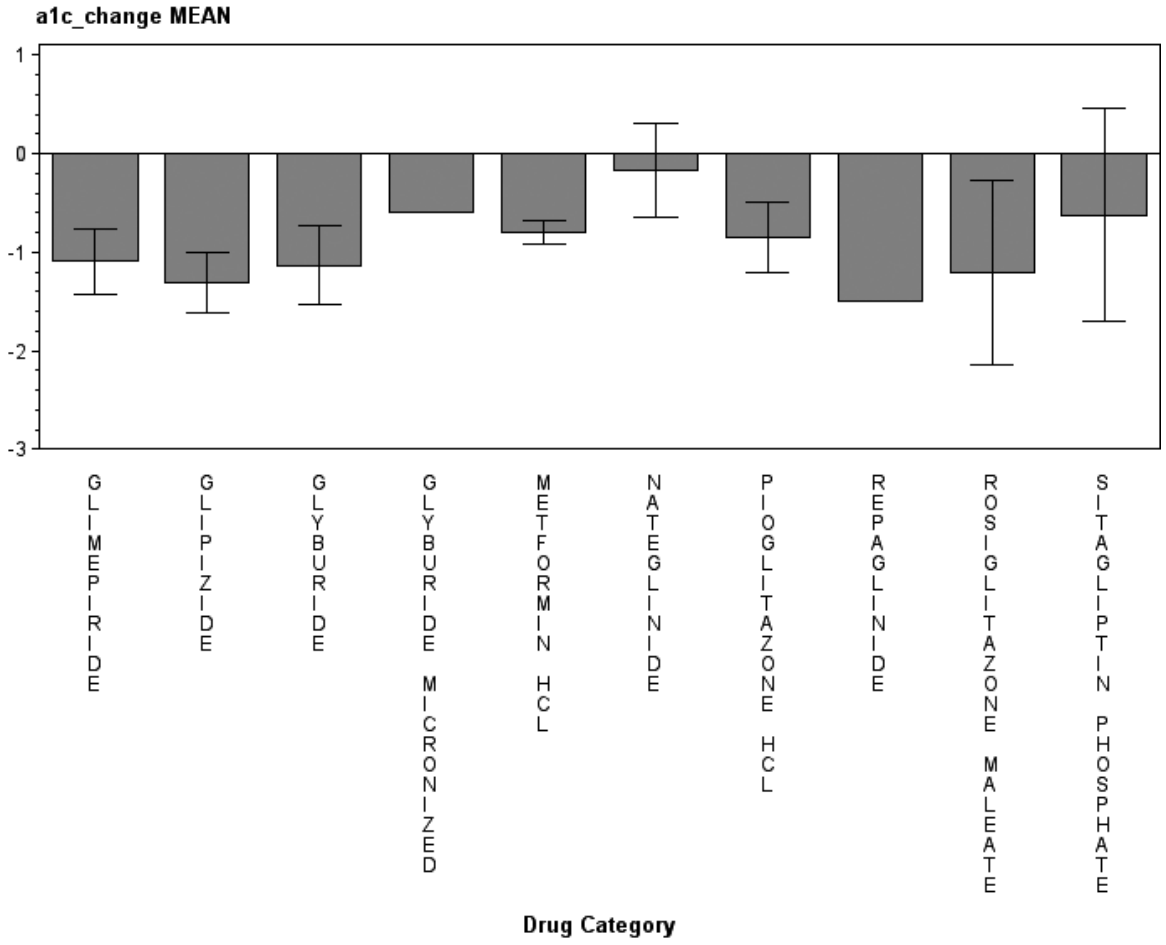

Figure 5. Mean change of A1C by individual OAD medication

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparison: Metformin vs. Glimiperide, Metformin vs. Glipizide and Metformin vs. Glyburide

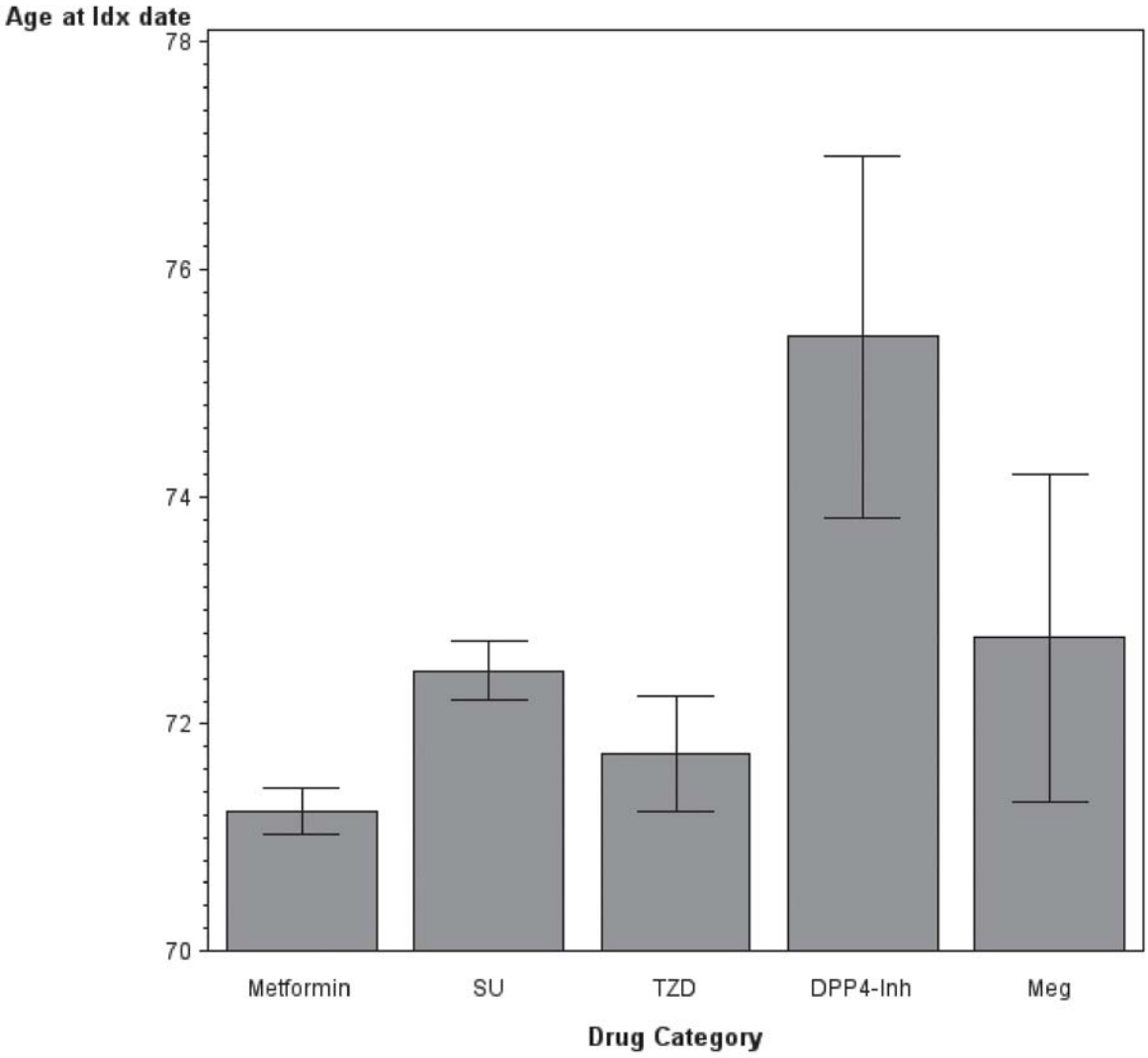

Figure 6. Means age at index date by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas, Metformin vs. DPP-4 Inhibitors and Sulfonylureas vs. DPP-4 Inhibitors, TZD vs. DPP-4 Inhibitors

Table 10. Association between the patient age and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline Age				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	71.232	72.466	-1.23	-1.7099	-0.7585
Metformin vs. DPP4-Inhibitors	71.232	75.407	-4.18	-6.3243	-2.0261
Sulfonylureas vs. DPP4-Inhibitors	72.466	75.407	-2.94	-5.107	-0.7749
Sulfonylureas vs. Metformin	72.466	71.232	1.23	0.7585	1.7099
TZD vs. DPP4-Inhibitors	71.732	75.407	-3.68	-5.9235	-1.4268
DPP4-Inhibitors vs. Metformin	75.407	71.232	4.18	2.0261	6.3243
DPP4-Inhibitors vs. Sulfonylureas	75.407	72.466	2.94	0.7749	5.107
DPP4-inhibitors vs. TZD	75.407	71.732	3.68	1.4268	5.9235

*All of the abovecomparisons were statistically significant at alpha <0.05.

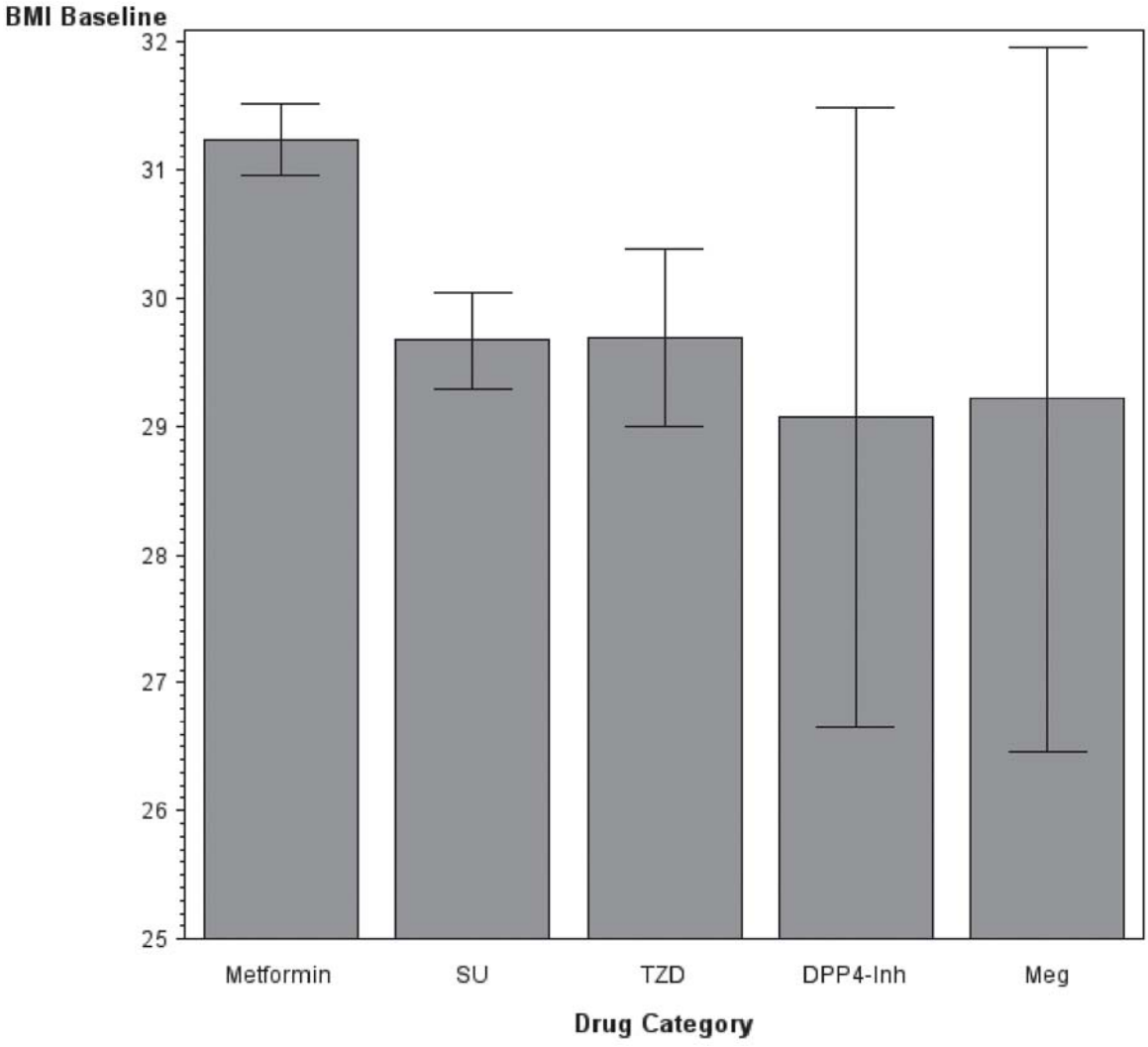

Figure 7. Mean baseline BMI by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas and Metformin vs. TZD

Table 11. Association between the baseline BMI and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline BMI				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	31.24	29.67	1.57	0.8985	2.2328
Metformin vs. TZD	31.24	29.69	1.55	0.4741	2.6279
Sulfonylureas vs. Metformin	29.67	31.24	-1.57	-2.2328	-0.8985
TZD vs. Metformin	29.69	31.24	-1.55	-2.6279	-0.4741

*All of the above comparisons were statistically significant at alpha <0.05.

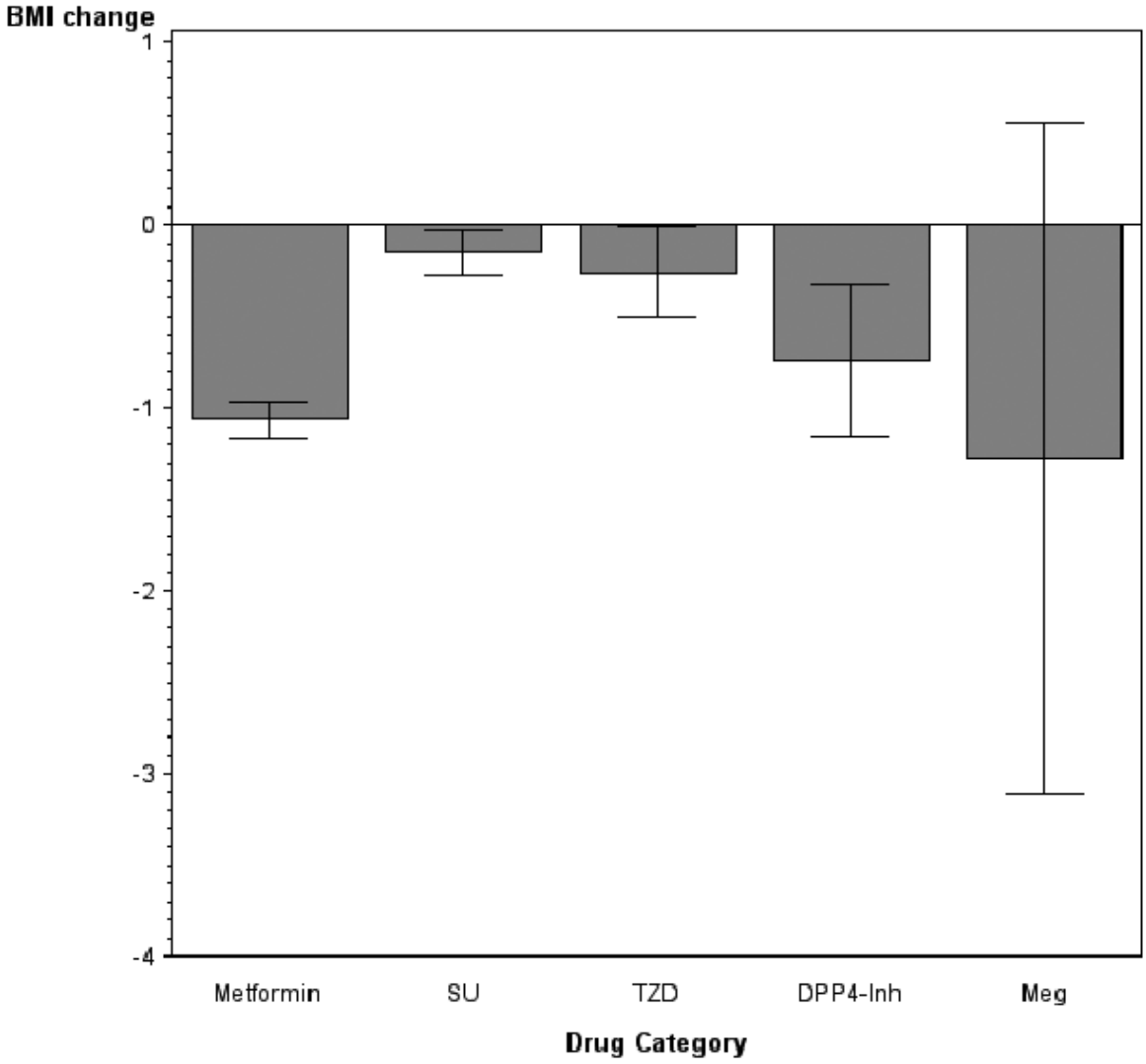

Figure 8. Mean change in BMI by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas, Metformin vs. TZD and Sulfonylurea vs. Meglitinides

Table 12. Association between the change in BMI and the OAD classes
-ANOVA model using Tukey test*

Variable- Change in BMI				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	-1.06	-0.15	-0.92	-1.1540	-0.6803
Metformin vs. TZD	-1.06	-0.26	-0.81	-1.1895	-0.4249
Sulfonylureas vs. Metformin	-0.15	-1.06	0.92	0.6803	1.1540
Sulfonylureas vs. Meglitidines	-0.15	-1.27	1.13	0.1485	2.1063
TZD vs. Metformin	-0.26	-1.06	0.81	0.4249	1.1895
Meglitidines vs. Sulfonylureas	-1.27	-0.15	-1.13	-2.1063	-0.1485

*All of the above comparisons were statistically significant at alpha <0.05.

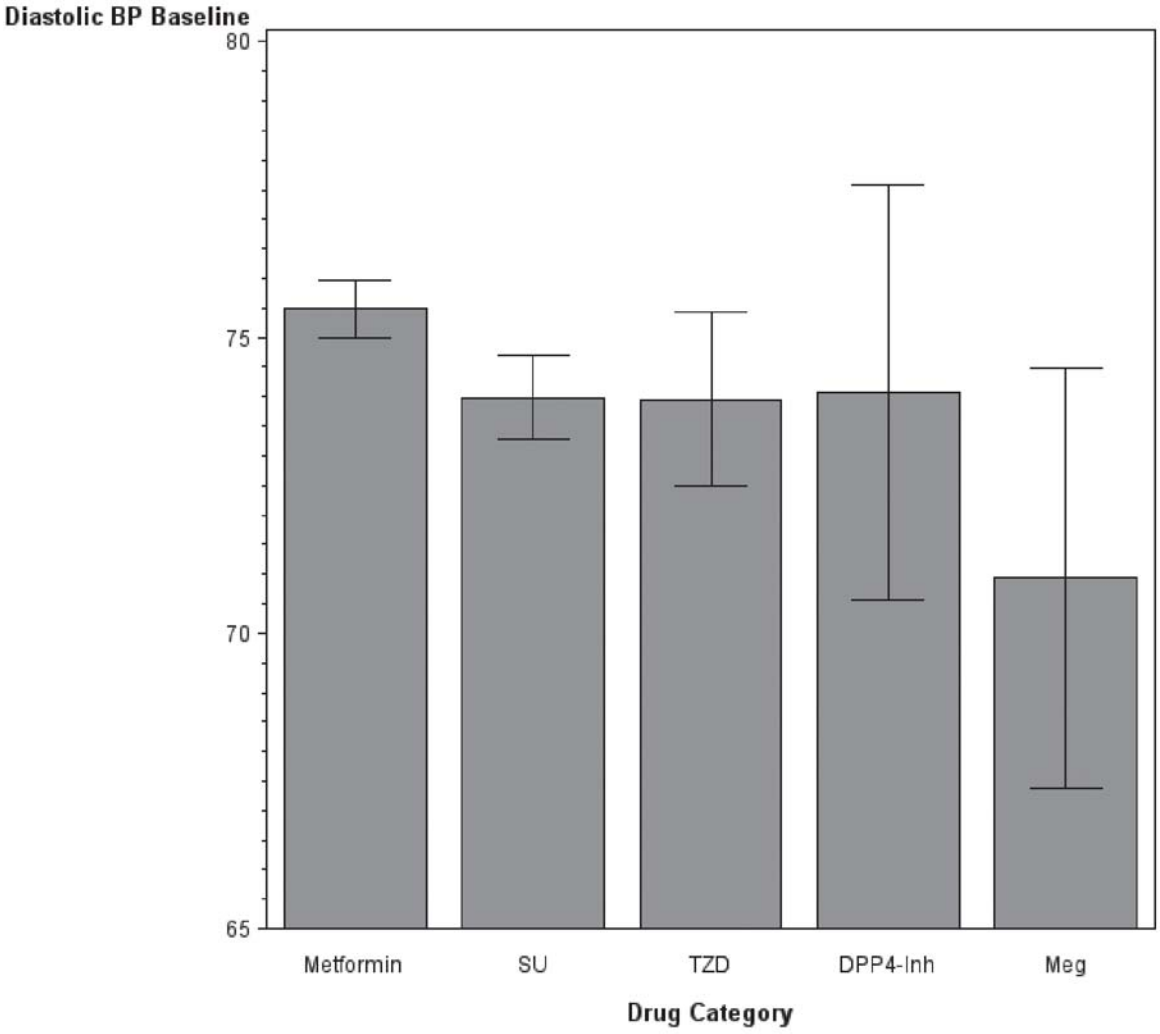

Figure 9. Mean baseline diastolic BP by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas.

Table 13. Association between the baseline diastolic BP and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline Diastolic BP				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	75.49	73.99	1.49	0.2893	2.696
Sulfonylureas vs. Metformin	73.99	75.49	-1.49	-2.696	-0.2893

*All of the above comparisons were statistically significant at alpha <0.05.

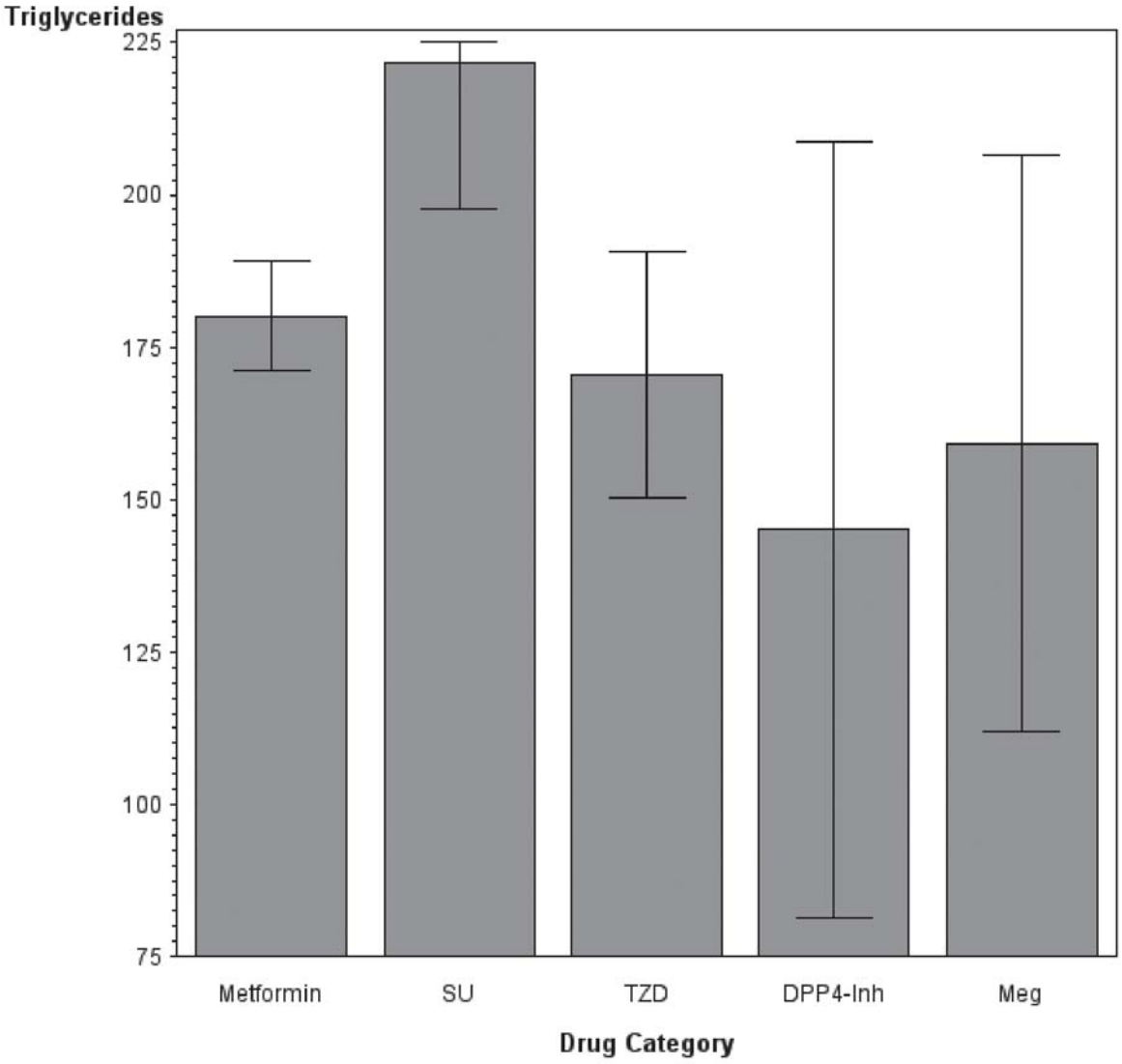

Figure 10. Mean baseline triglycerides by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas and Sulfonylureas vs TZD.

Table 14. Association between the baseline triglycerides and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline Triglycerides				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	179.988	221.7629	-41.78	-69.825	-13.724
Sulfonylureas vs. Metformin	221.763	179.988	41.78	13.724	69.825
Sulfonylureas vs. TZD	221.763	170.47	51.29	8.289	94.296
TZD vs. Sulfonylureas	170.763	221.763	-51.29	-94.296	-8.289

*All of the above comparisons were statistically significant at alpha <0.05.

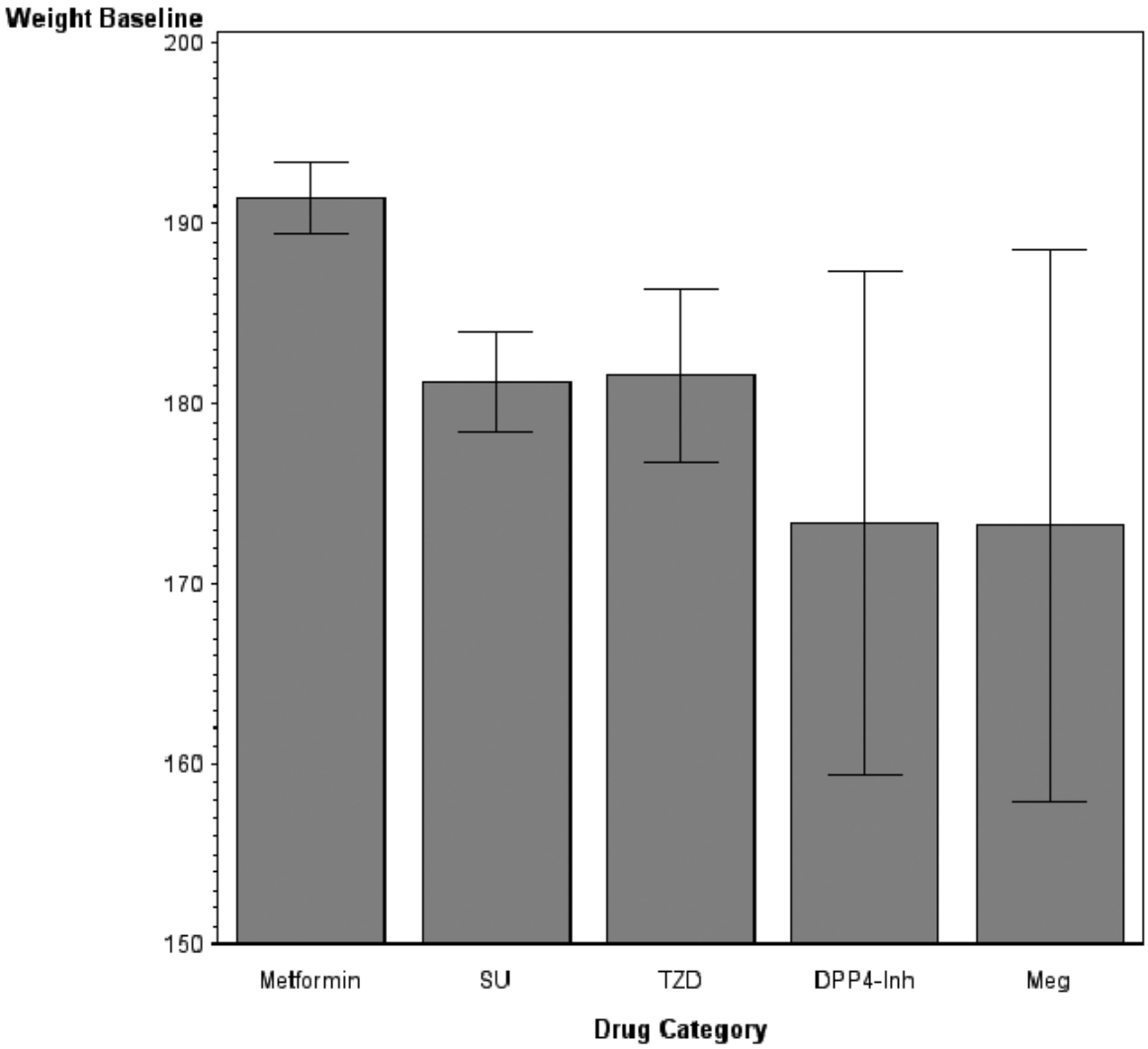

Figure 11. Mean baseline weight by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas, Metformin vs. TZD

Table 15. Association between the baseline weight and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline Weight				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	191.45	181.23	10.22	5.467	14.975
Metformin vs.TZD	191.45	181.59	9.86	2.186	17.528
Sulfonylureas vs. Metformin	181.23	191.45	-10.22	-14.975	-5.467
TZD vs. Metformin	181.59	191.45	-9.86	-17.528	-2.186

*All of the above comparisons were statistically significant at alpha <0.05.

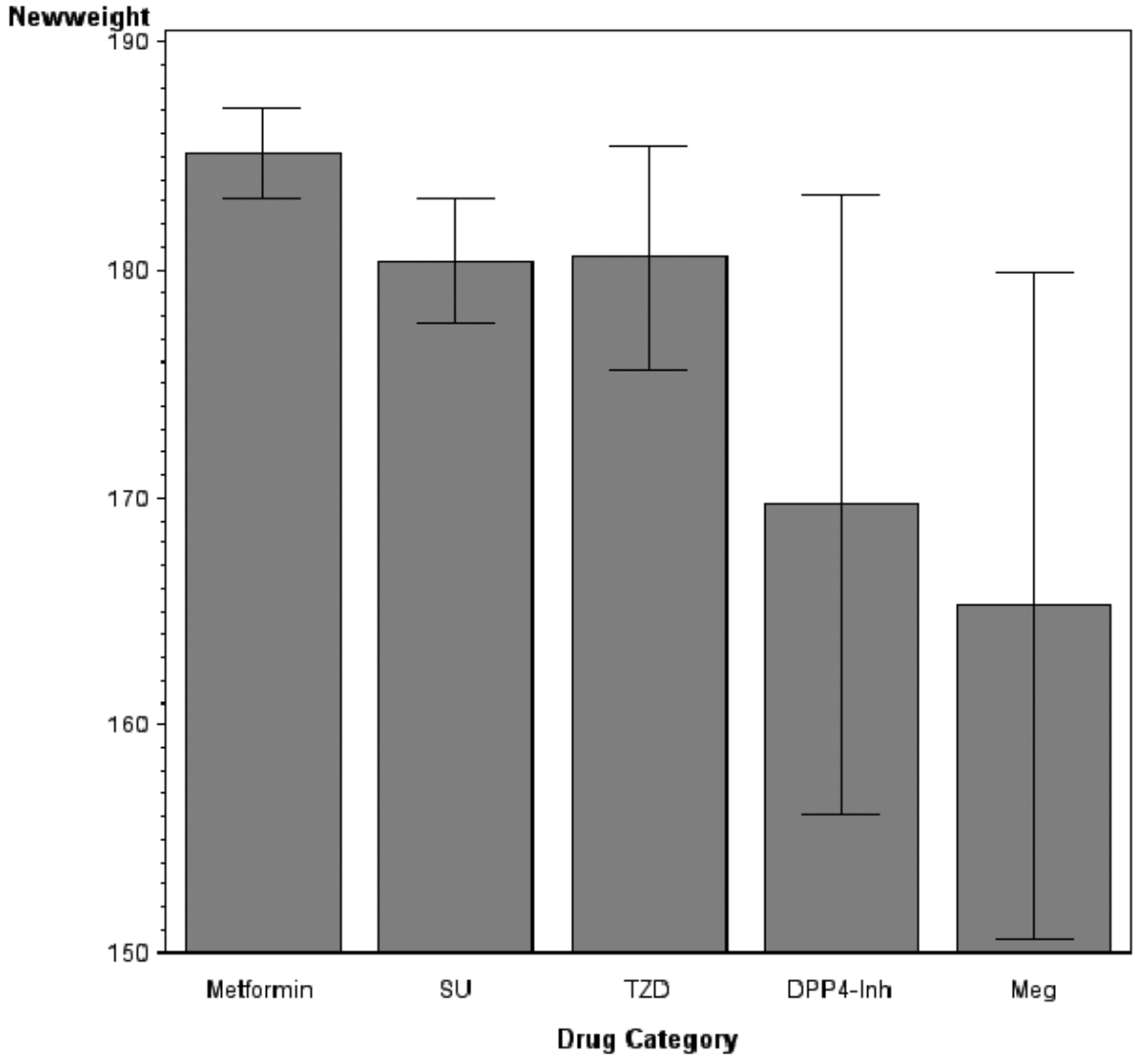

Figure 12. Mean follow-up weight by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylure and Metformin vs. Meglitidines.

Table 16. Association between the follow-up weight and the OAD classes
-ANOVA model using Tukey test*

Variable- Follow up Weight				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	185.11	180.38	4.72	0.025	9.421
Metformin vs. Meglitidines	185.11	165.25	19.85	0.618	39.085
Sulfonylureas vs. Metformin	180.38	185.11	-4.72	-9.421	-0.025
Meglitidines vs. Metformin	165.25	185.11	-19.85	-39.085	-0.618

*All of the above comparisons were statistically significant at alpha <0.05.

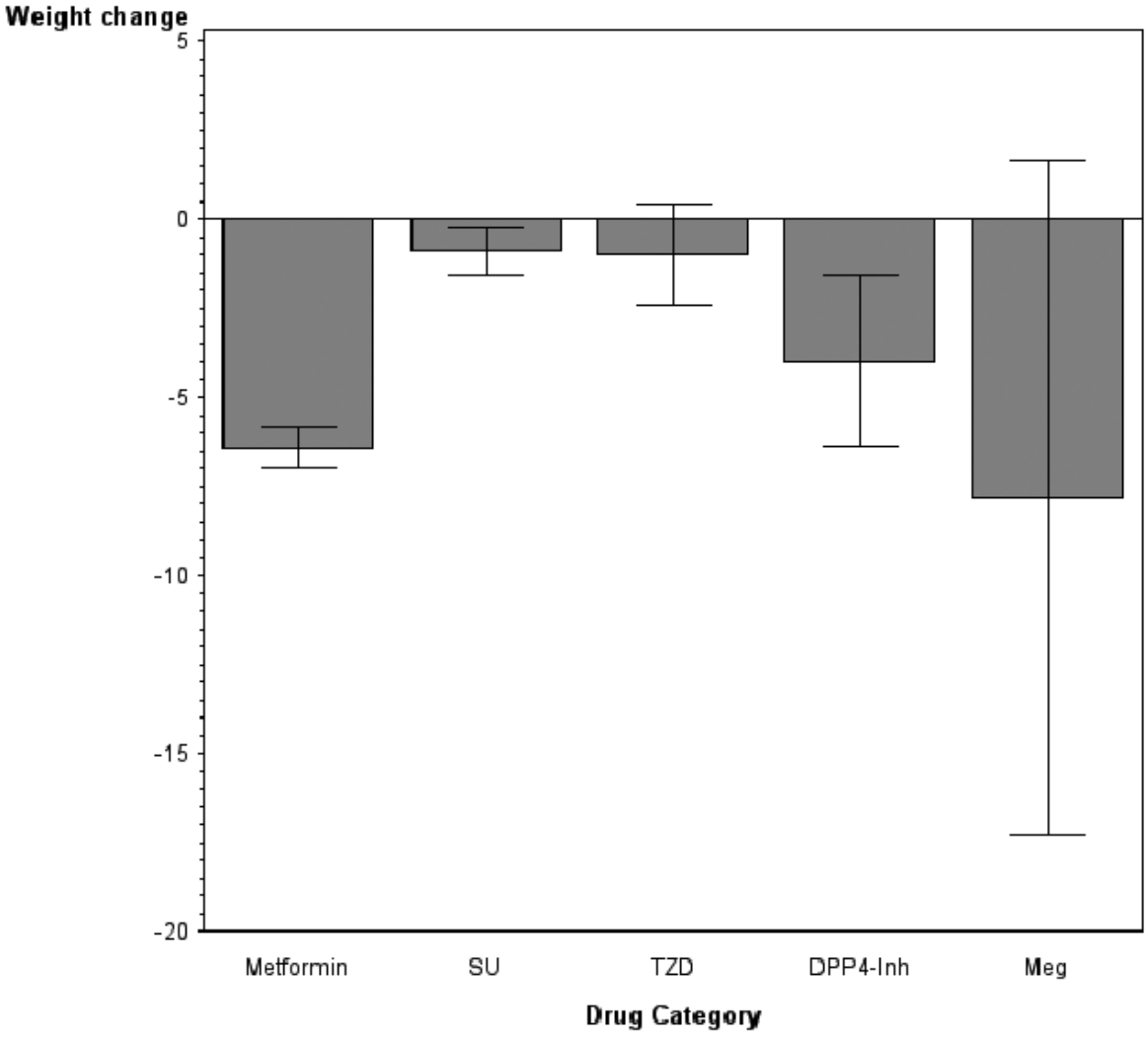

Figure 13. Mean weight change by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas, Metformin vs. TZD, Sulfonylureas vs. Meglitidines and TZD vs. Meglitidines.

Table 17. Association between the change in weight and the OAD classes
-ANOVA model using Tukey test*

Variable- Weight Change				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	-6.34	-0.84	-5.50	-6.808	-4.195
Metformin vs.TZD	-6.34	-1.03	-5.32	-7.4248	-3.2085
Sulfonylureas vs. Metformin	-0.84	-6.34	5.50	4.195	6.808
Sulfonylureas vs. Meglitidines	-0.84	-7.99	7.15	1.7503	12.5465
TZD vs. Metformin	-1.03	-6.34	5.32	3.2085	7.4248
TZD vs. Meglitidines	-1.03	-7.99	6.96	1.3176	12.6094
Meglitidines vs. Sulfonylureas	-7.99	-0.84	-7.15	-12.5465	-1.7503
Meglitidines vs.TZD	-7.99	-1.03	-6.84	-12.5381	-1.1485

*All of the above comparisons were statistically significant at alpha <0.05.

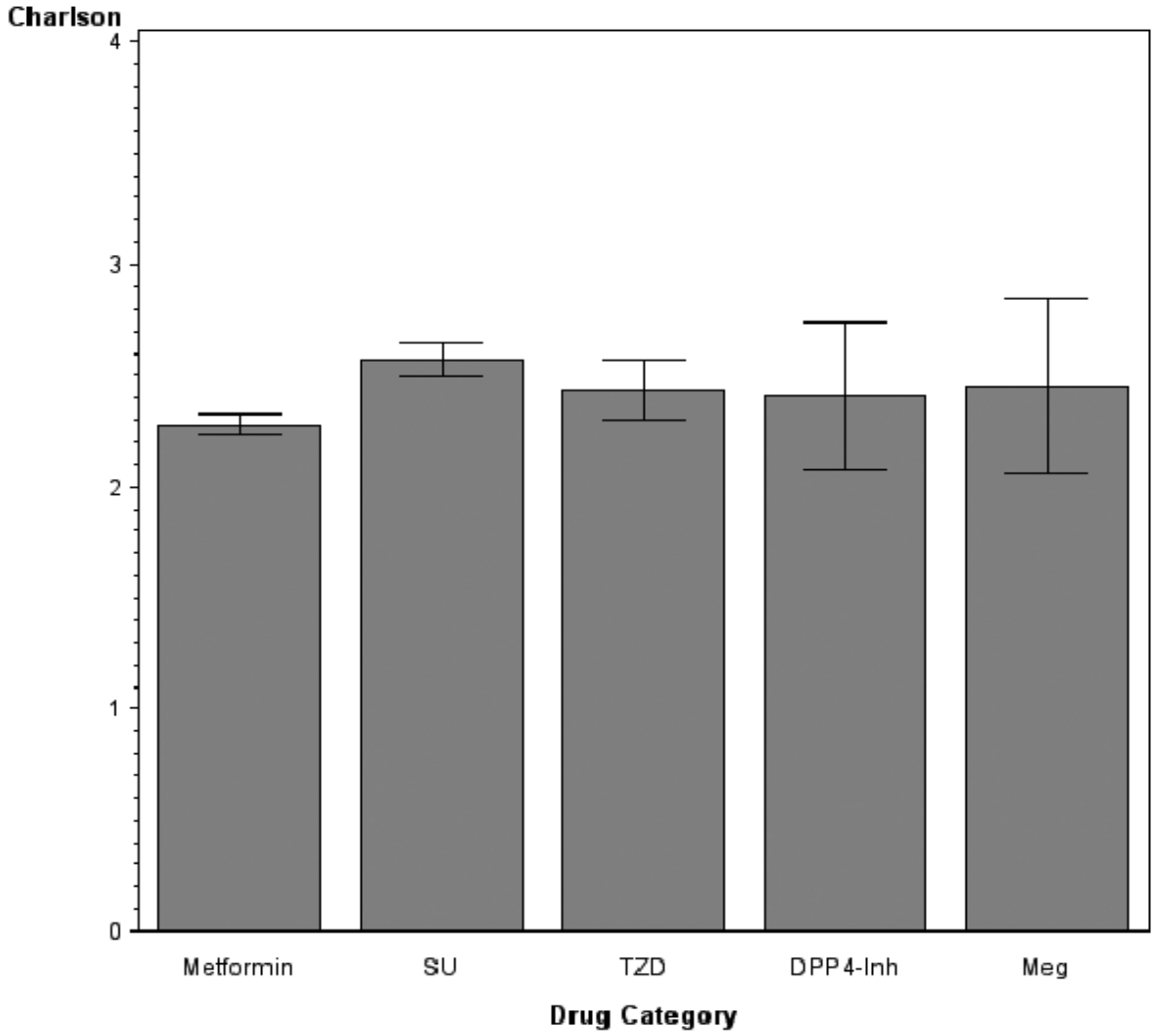

Figure 14. Mean baseline Charlson index by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were found at alpha < 0.05 for the following comparisons: Metformin vs. Sulfonylureas and Sulfonylureas vs.

Table 18. Association between the change in weight and the OAD classes
-ANOVA model using Tukey test*

Variable- Baseline Diastolic BP				95% CI	
Drug categories comparison	Mean 1	Mean 2	Difference in Means	Lower	Upper
Metformin vs. Sulfonylureas	2.27	2.57	-0.29	-0.411	-0.176
Sulfonylureas vs. Metformin	2.57	2.27	0.29	0.1761	0.411

*All of the above comparisons were statistically significant at alpha <0.05.

CHAPTER 5

DISCUSSION

As Type 2 diabetes is a commonly recognized disease in the elderly population, where literature is implying that approximately 20% of the population over 65 years of age is afflicted with this illness, the number of Americans with diabetes tripled (from 5.6 million to 16.8 million) in the last decade [28, 29]. People aged 65 years or older account for approximately 37% of the population with diabetes. Diabetes in elderly adults is metabolically distinct from diabetes in the younger patient population, and the approach to therapy needs to be different in this age group[29]. Diabetes is associated with considerable morbidity, mainly from macro- and microvascular complications, depression, kidney failure and weight gain. Medical care of patients with Type 2 diabetes 65 years of age and older should be individualized and a key component of individualizing diabetes care should be the acknowledgment of a patient's perceptions of the effects of different types of therapy [1]. The ADA 2008 guidelines suggested Type 2 diabetic patients should be given constant access to counseling on increasing physical activity and finally on weight loss of 5–10% of body weight in overweight/obese individuals [35].

A study by Brixner D. et al. 2007, indicates that BMI and lab values are the key source for recognition of the cardiovascular metabolic syndrome and therefore risk of later developing diabetes [30]. Majority of the patients presented in this study at baseline were obese (overall

mean BMI at baseline was 29.78 kg/m2) and in the category of hypertension-stage 1 (61.8% overall for all OAD patients). These facts support the severity of the Type 2 diabetes present in examined patients. The National Institutes of Health (NIH) model showed that tracking of BMI over time in diabetic patients can help better control A1C level, therefore the better Type 2 diabetes disease management, as well as compared with non-BMI control for patients with the onset of diabetes at 65 years and older [4, 5]. The results of this research indicate the association between the BMI and A1C level at baseline; the mean of 31.24kg/m2 BMI was captured in the metformin group where the percentage of the patients (34%) with A1C 7.0-8.0 units was the highest. A similar trend was observed for the sunfonylureas and TZD group, with 29.67 kg/m2 BMI and 32% of the sulfonylureas patients, and 29.69 kg/m2 and 29% of the TZD users.

In the past, treatment options were limited. Compared to the past where the treatment options were limited, literature has showed, today, numerous treatments are available for use in older patients with Type 2 diabetes. Still, even with the most suitable drug therapy, various complications will occurr; one of the most commonly recurring is weight change [31]. Considering the major changes in metabolism as people age and the association of Type 2 diabetes and weight gain, there are newer oral antidiabetic drugs (OADs) designed to purposely either cause weight loss and/or cause less weight gain, presented as BMI change. Results of this research reported baseline BMI stratified by the below, normal and above normal weight for the studied OAD agents. The values for the three major OAD classes showed that majority of the metformin users, 64.63%, were obese, 11.49% of the TZD users were overweight; however, most of the sulfonylureas patients, 41.23%, were in the normal weight group. Compared to follow-up BMI for the same three OAD groups, there was a consistent drop in all of the previously mentioned categorizes. Still, most of the metformin users, 62.5%, were obese, 11.34% of the TZD patients were overweight and 33.08% of sulfonylureas users were at normal weight.

Based on the differences in available monotherapy OAD treatments and the distribution of elderly Type 2 diabetes Mellitus (T2DM) patients in the GE EMR database treated with those OAD drugs, a statistically significant weight loss in studied groups was found. Both BMI and weight reduction was associated with the meglitinides users (-1.27 BMI units), followed by the metformin group (-1.06 BMI units) and the sulfonylureas showed the least BMI drop (-0.14). Although the meglitinides group showed a higher weight loss compared to the metformin group, it is important to mention the difference in sample size among these study cohorts (metformin vs. meglitinides, 1601 vs. 33, respectively). Furthermore, there was a significant baseline BMI difference between the metformin and meglitinides users, 31.24 and 29.21, respectively. Results by Cohen et al. showed that weight gain does not essentially accompany treatment of T2DM. The OAD therapy is associated with some weight gain, in certain drug classes, where it is mostly due to modification of glycemia and improvement of weight loss prior to the OAD treatment [1]. Significant decrease in levels of triglycerides, low-density lipoprotein, total cholesterol and A1C were associated with use of metformin and TZD (rosiglitozone) at baseline. Also, metformin showed significant decrease in body weight, as effective in normal and an overweight individual as it is in those who are obese; there are evidence-based data to support metformin use in obese individuals with T2DM [2, 3].. Metformin is particularly appropriate for overweight patients with high fasting blood-glucose levels [4]. An open randomized 1-year cross-over study compared metformin with glibenclamide non-insulin-dependent patients. Equivalent effect on glycemic control was found, but, in contrast to glibenclamide, metformin reduced body weight [5].

The results also showed that TZDs caused a significant weight loss among elderly patients in the EMR database, which somewhat supports findings from previous studies with regard to combination therapy of rosiglitazone with metformin or sulfonylurea. The literature indicates that rosiglitazone in combination with other OAD agents is a cost

-effective intervention for the treatment of normal weight, overweight and obese patients with T2DM when compared with conventional care [6]. Additionally, the study found that after adjusting for the baseline weight, TZD still showed 1.12lb weight loss, which conflicts with the current literature findings. A few assumptions have to be addressed regarding the previously mentioned results compared to presented results: 1) there are no patients' lifestyle data available though the GE EMR database, or 2) prescription refill data, therefore no record of patients' therapy compliance. Importantly, in older adults with T2DM, the TZDs should be used vigilantly; use in patients with heart failure is absolutely contraindicated. Contraindicated heart failure is 2.5 times greater in users of TZDs and insulin compared with insulin users alone. The risk of heart failure is 4.5% in patients taking TZDs compared with 2.6% for non-TZD users [7]. TZDs have a lesser role in treating T2DM in older patients because of their significant cardiovascular-related concerns, association with increased fracture risk, and rosiglitazone's potential to cause macular edema [8].

Limitations

Although studied T2DM patients showed significant weight loss, further research is needed. The existing database limitations, such as missing values in many clinical variables, data entry mistakes and lack of over a year of patients' continuous clinical activity, provide uncertainty in the presented findings. Furthermore, the research had study design limitations:

1) Absence of randomization, which deteriorate the results in regard to differences between the OAD groups; Propensity score matching, or the Heckman method, will prevent potential selection biases.

2) Proposed analysis was statistically limited; the regression model will strengthen the results and provide more precise findings.

In elderly T2DM, treatment aims need to be individualized because of the heterogeneity of the geriatric population. Persons 65 years of age or older with T2DM are often complex to manage given the multitude of comorbid conditions. Older adults often have renal and/or hepatic compromise, thus they respond differently to antihyperglycemic therapies differently than do their younger equivalents, and depending on comorbid conditions, some medication classes may be more appropriate than others.

APPENDIX A

INCLUSION AND EXCLUSION – DIAGNOSIS,

PHARMACOTHERAPEUTIC AGENTS

Table 19. Diagnoses indicative of diabetes

ICD-9 Code	Description
250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stared as uncontrolled
250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled

Table 19. continued

250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
250.92	Diabetes with unspecified complication, type II or unspecified type, not uncontrolled

Table 20. Oral antidiabetic drugs for study inclusion

GPI_CATEGORY_2	GPI_CATEGORY_3	GPI_CATEGORY_4
ALPHA-GLUCOSIDASE INHIBITORS	ALPHA-GLUCOSIDASE INHIBITORS	ACARBOSE
ALPHA-GLUCOSIDASE INHIBITORS	ALPHA-GLUCOSIDASE INHIBITORS	MIGLITOL
MEGLITINIDE ANALOGUES	MEGLITINIDE ANALOGUES	NATEGLINIDE
BIGUANIDES	BIGUANIDES	METFORMIN HCL
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS	DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS	SITAGLIPTIN PHOSPHATE
INSULIN SENSITIZING AGENTS	THIAZOLIDINEDIONES	PIOGLITAZONE HCL
INSULIN SENSITIZING AGENTS	THIAZOLIDINEDIONES	ROSIGLITAZONE MALEATE
MEGLITINIDE ANALOGUES	MEGLITINIDE ANALOGUES	REPAGLINIDE
SULFONYLUREAS	SULFONYLUREAS	ACETOHEXAMIDE
SULFONYLUREAS	SULFONYLUREAS	CHLORPROPAMIDE
SULFONYLUREAS	SULFONYLUREAS	GLIMEPIRIDE
SULFONYLUREAS	SULFONYLUREAS	GLIPIZIDE
SULFONYLUREAS	SULFONYLUREAS	GLYBURIDE
SULFONYLUREAS	SULFONYLUREAS	GLYBURIDE MICRONIZED
SULFONYLUREAS	SULFONYLUREAS	TOLAZAMIDE
SULFONYLUREAS	SULFONYLUREAS	TOLBUTAMIDE

Table 21. List of exclusion criteria

296.2, 296.3, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36 296.21, 296.22, 296.23, 296.24, 296.25, 296.26	Major depression, single and recurrent episode
244.0, 244.1, 244.2, 244.3. 244.8, 244.9	Hypothyroidism
262	Protein-calorie malnutrition
GPI_CATEGORY_1	Weight loss medication, 'ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREXIANTS'
42, 79.53 795.71	HIV
140.0-140.9, 141.0-141.9, 142.0-142.0-142.2, 142.8, 142.9, 143, 143.1, 143.8, 143.9, 144, 144.1, 144.8, 144.9, 145.0-145.9, 146.0-146.9, 147.0-147.3, 147.8, 147.9…148.0-239.8	Cancer
250.X1, 250.X3	Type 1 Diabetes

APPENDIX B

COVARIATE MEDICATIONS

Table 22. Covariate drugs

Drug/Therapeutic Class	GPI_Code	GPI Level
Dyslipidemias		
Antispyschotics, antiretrovirals, HRT, glucocorticoids	ANTIPSYCHOTICS	1
	ANTIRETROVIRALS	2
	ESTROGENS	1
	PROGESTINS	1
	GLUCOCORTICOSTEROIDS	2
Hyperglycemia/ Glucose Intolerance		
Atypical antipsychotics, glucocorticoids, thyroid hormone, oral contraceptives, nicotinic acid,	BENZISOXAZOLES	2
	DIBENZAPINES	2
	ZIPRASIDONE	4
	GLUCOCORTICOSTEROIDS	2
	THYROID HORMONES	2
	COMBINATION CONTRACEPTIVES – ORAL	2
	NICOTINIC ACID DERIVATIVES	2

APPENDIX C

DIAGNOSIS CODES

Table 23. Comorbid cardiovascular diseases

ICD-9 Code	Description
Hypertension	
401.XX	Essential hypertension
402.XX	Hypertensive heart disease
404.XX	Hypertensive heart and kidney disease
405.X	Secondary hypertension
Acute MI	
410.XX	Acute myocardial infarction
Cardiovascular Disease	
411.XX	Other acute and subacute forms of ischemic heart disease
414.XX	Other forms of chronic ischemic heart disease
428.X	Heart failure
429.X	Ill-defined descriptions and complications of heart disease
413.X	Angina pectoris
440.X	Atherosclerosis
Cerebrovascular Disease	
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease
437.2	Hypertensive encephalopathy
437.3	Cerebral aneurysm, nonruptured
430.X	Subarachnoid hemorrhage
434.X	Occlusion of cerebral arteries
431.X	Intracerebral hemorrhage
432.X	Other and unspecified intracranial hemorrhage
433.X	Occlusion and stenosis of precerebral arteries
434.X	Occlusion of cerebral arteries
436.X	Acute, but ill-defined, cerebrovascular disease
437.X	Other and ill-defined cerebrovascular disease
438.X	Late effects of cerebrovascular disease
997.02	Iatrogenic cerbrovascular infarction or hemorrhage
Kidney Disease	
403.XX	Hypertensive kidney disease
404.XX	Hypertensive heart and kidney disease
585.X	Chronic kidney disease (CKD)

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) encompasses 19 medical conditions (ICD-9) weighted 1–6. From the weighted conditions, a sum score can be tallied to yield the total comorbidity score (see Table A.6). To account for increasing age, one point is added to the CCI score for each decade of life over the age of 50 (1 point for 60s, 2 points for 70s, 3 for 80s.) Thus, possible CCI scores range from 0 to 36.

Table 24. Charlson Comorbidity Index (CCI)

Comorbidity	D'Hoore ICD-9 Codes	Charlson Weight
Myocardial Infarction	410, 411	1
Congestive Heart Failure	398, 402, 428	1
Peripheral vascular disease	440-447	1
Cerebrovascular disease	430-433, 435	1
Dementia	290, 291, 294	1
Chronic obstructive pulmonary disease	491-493	1
Rheumatologic disease	710, 714, 725	1
Peptic ulcer disease	531-534	1
Mild liver disease	571, 573	1
Diabetes	250 (excluding 250.4-250.6)	1
Hemiplegia or paraplegia	342, 434, 436, 437	2
Moderate or severe renal disease	403, 404, 580-586	2
Diabetes + complications	250.4-250.6	2
Malignancy	200, 202, 203	2
Moderate or severe liver disease	070, 570, 572	3
Metastatic solid tumor	196-199	6
AIDS	042-044	6

APPENDIX D

DESCRIPTION OF PRIMARY VARIABLES

Table 25. Primary variables

Variable Name	Description	Format
PT_ID	Unique patient identifier	Numeric
DII	Type 2 Diabetes, dichotomous	0=no 1=yes
PT_IDX_DT	Index date	Mmddyyyy
PT_RX_DT	Date for prescription or prescription order	Mmddyyyy
PT_DX_DT	Patient first diagnosis	Mmddyyyy
PT_RX_CAT	Patient first OAD prescription order, 5 classes of OADs of interest	1= MET 2= SU 3= TZD 4= Alpha Glucose Inhibitors 5= DPP-4 Inhibitors 6= Meglitinides
PT_AGE_ IDX	Age of patient in years at index date	Numeric
PT_AGE_IDX_ CAT	Categorical value for index age	1= 65-69 2= 70-74 3= 75-79 4= ? 80
PT_ GEND	Patient gender	0=male 1=female
PT_RACE	Patient Race	1=Caucasian 2=African-American 3=Hispanic 4=other 99=unknown
PT_REGION	Patient geographic region of residence	1=Northeast 2=South 3=Midwest 4=West
PT_INS	Insurance Status	1=commercial 2=Medicare 3=Medicaid 4=self-pay 5=other/unknown

*All the clinical variables are occurring on baseline +/- 30 days of Index date; also for follow-up variable 6 months +/- 30 days

Table 25. continued

Variable Name	Description	Format
BMI_BL	Baseline BMI, continuous, 30 days +/- of index date	Numeric (XX)
BMI_BL_CAT	Baseline BMI, categorical	1=<18.5 2=18.5-24.9 3=25-29.9 4=30-39.9 5=?40
BMI_FL	Follow up BMI, continuous, 6 months +/- 30 days	Numeric (XX)
BMI_FL_CAT	Follow up BMI, categorical	1=<18.5 2=18.5-24.9 3=25-29.9 4=30-39.9 5= ?40
BMI_CHG	Change in BMI from baseline to 6 months follow-up (null if baseline and follow-up readings not available.)	Numeric (XX)
WT_BL	Baseline weight occurring on index date +/- 30 days	Numeric (XX)
WT_ FU	Follow-up WT value (180 days ± 30 days)	Numeric (XX)
WT_ CHG	Change in WT from baseline to 6 months follow-up (null if baseline and follow-up readings not available.)	Numeric (XX)
A1C_BL	Baseline, A1C value	Numeric (XX)
A1C_BL_CAT	Baseline A1C value, categorical	1=<7.0 2=7.0-8.9 3=?9.0
A1C_CHG	Change in BMI from baseline to 6 months follow-up (null if baseline and follow-up readings not available.)	Numeric (XX)
BP_BL_CAT	Baseline mean BP, categorical variable	1= Normal, <130/80 2= ?130/80 to 169/99= Stage 1 (Hypertension) 3= Hypertension, ? 170/100= Stage 2 (Hypertension)
SBP_BL	Baseline systolic blood pressure, numerical variable	Numeric (XX)
DBP_BL	Baseline diastolic blood pressure, categorical variable	Numeric (XX)
TG_BL	Baseline triglyceride level	Numeric (XX)
TG_BL_CAT	Baseline triglyceride level, categorical	1=<150 mg/dl 2=?150 mg/dl
HDL_BL	Baseline HDL level	Numeric (XX)
HDL_BL_CAT	Baseline HDL level, categorical	1=<40 mg/dl 2=?40 mg/dl
LDL_BL	Baseline LDL level	Numeric (XX)
LDL _BL_CAT	Baseline LDL level, categorical	1=<100 mg/dl 2=?100 mg/dl
TC_BL	Baseline total cholesterol level	Numeric (XX)
TC _BL_CAT	Baseline total cholesterol level, categorical	1=<240 mg/dl 2=?240 mg/dl

*All the clinical variables are occurring on baseline +/- 30 days of Index date; also for follow-up variable 6 months +/- 30 days

Table 25. continued

Variable Name	Description	Format
COVMED_LIPID	Dichotomous variable indicating use of a medication that my cause dyslipidemia on or before the index date (see Table 3 in Appendix)	0=no drug 1=drug
COVMED_GLUCOSE	Dichotomous variable indicating use of a medication that my cause hyperglycemia on or before the index date (see Table 3 in Appendix)	0=no drug 1=drug
SMOKE_STAT	Smoking status, categorical variable, as currently as most	1=Current 2=Former 3=Non-smoker 4=Unknown
ALCOH_STAT	Alcohol status, dichotomous variable, date (395 days pre Index date)	1= no 2=yes
BL_CCI	Baseline Charlson's comorbidity index, see Appendix 2; valid values = 0 – 36) based on ICD-9 codes occurring on or before index date (395 days pre Index date)	Numeric (XX)
COM_HTN	Hypertension diagnosis, as Comorbid condition, (see Appendix 2, table 1), 395 days pre or on Index date	0=no diagnosis 1=diagnosis
COM_AMI	Acute MI diagnosis, as Comorbid condition, (see Appendix 2, table 1), 395 days pre or on Index date	0=no diagnosis 1=diagnosis
COM_CVD	Cardiovascular disease diagnosis, as Comorbid condition, (see Appendix 2, table 1), 395 days pre Index date	0=no diagnosis 1=diagnosis
COM_CRVD	Cerebrovascular Disease diagnosis, as Comorbid condition, (see Appendix 2, table 1), 395 days pre or on Index date	0=no diagnosis 1=diagnosis
COM_KD	Kidney disease diagnosis, as Comorbid condition, (see Appendix 2, table 1), 395 days pre or on Index date	0=no diagnosis 1=diagnosis

*All the clinical variables are occurring on baseline +/- 30 days of Index date; also for follow-up variable 6 months +/- 30 days

APPENDIX E

BASELINE CHARACTERISTICS BY DRUG CLASS

-Statistically insignificant variables

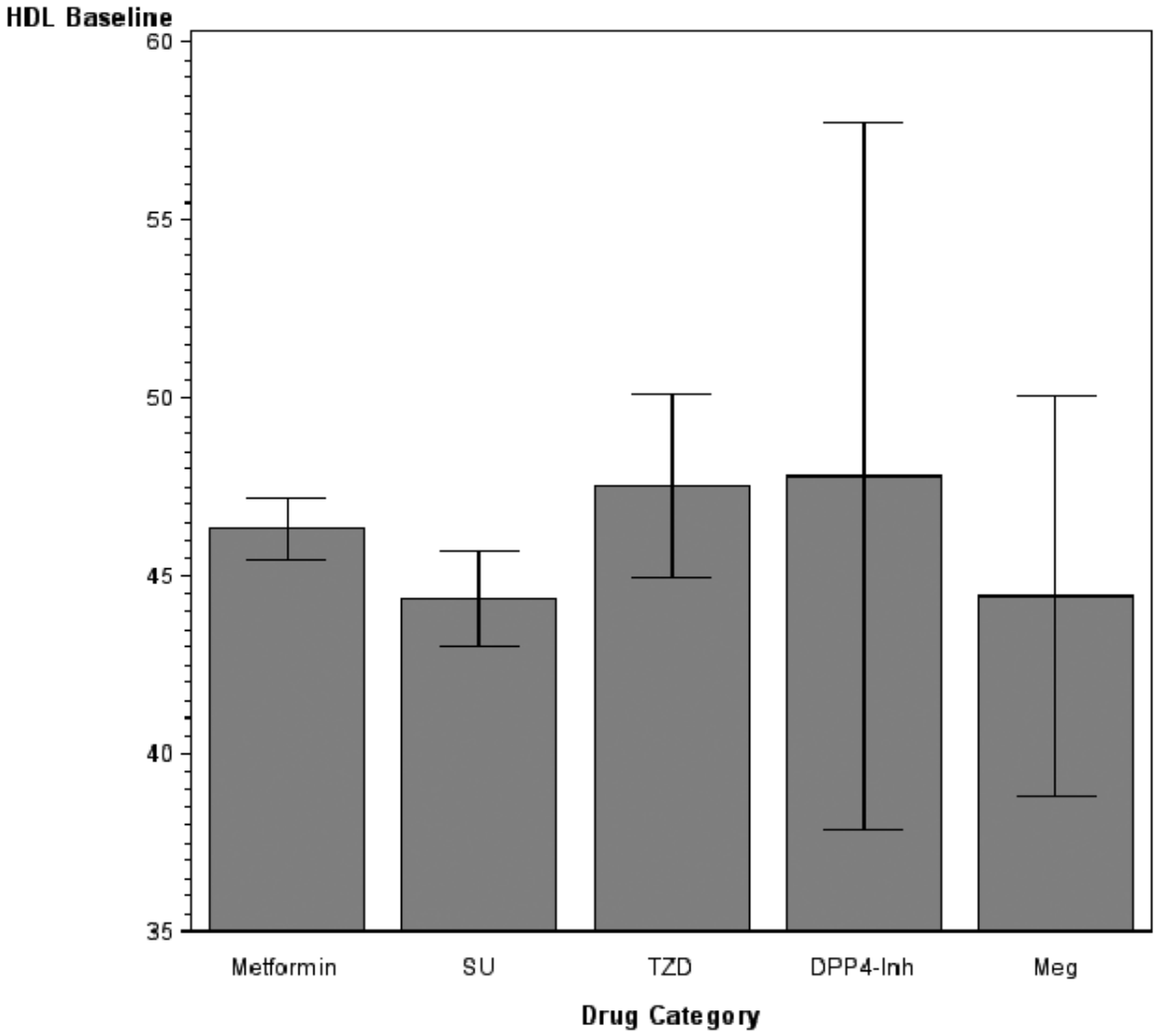

Figure 15. Mean baseline HDL by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were not found at alpha < 0.05 between the studied OAD classes.

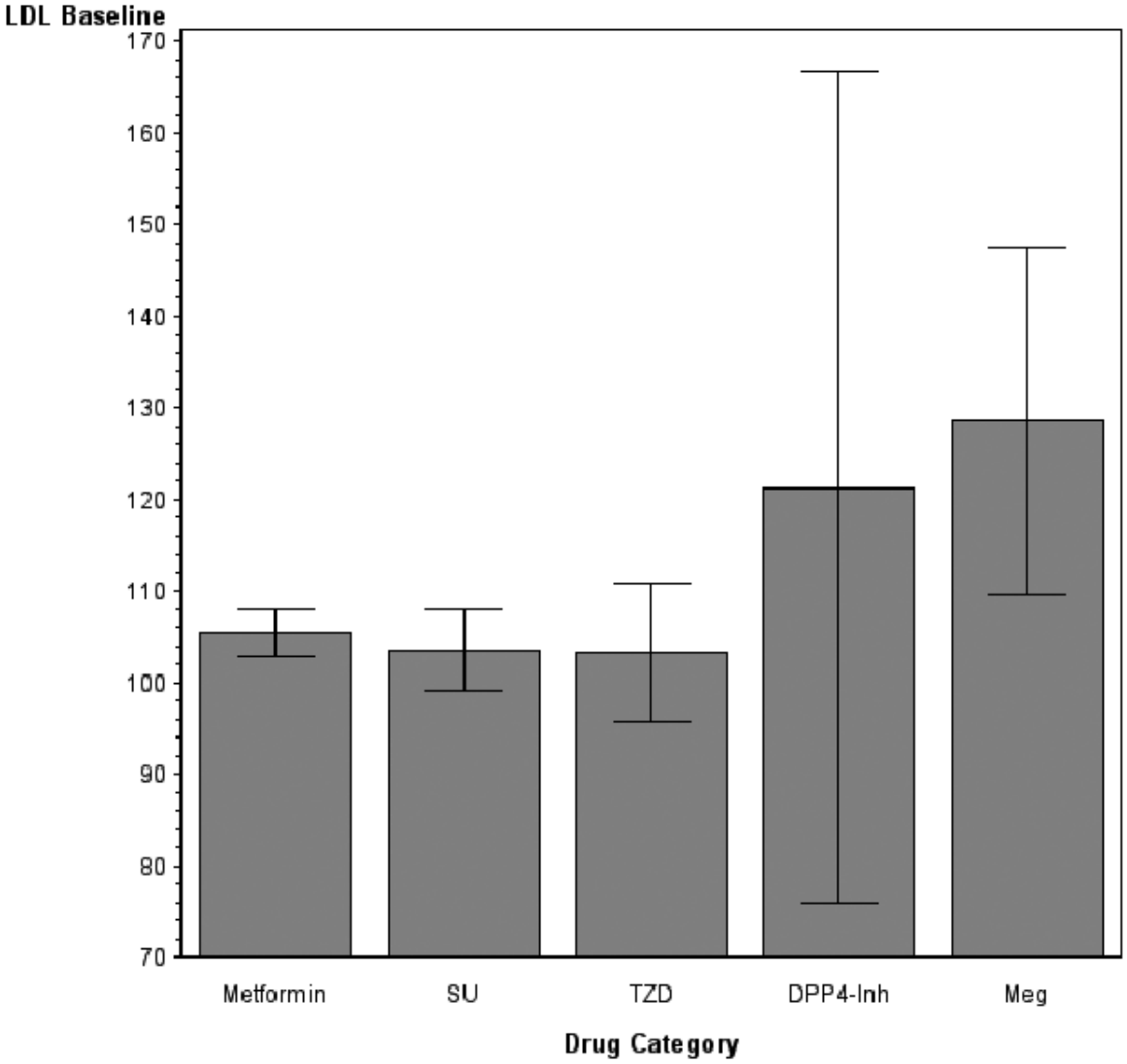

Figure 16. Mean baseline LDL by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were not found at alpha < 0.05 between the studied OAD classes

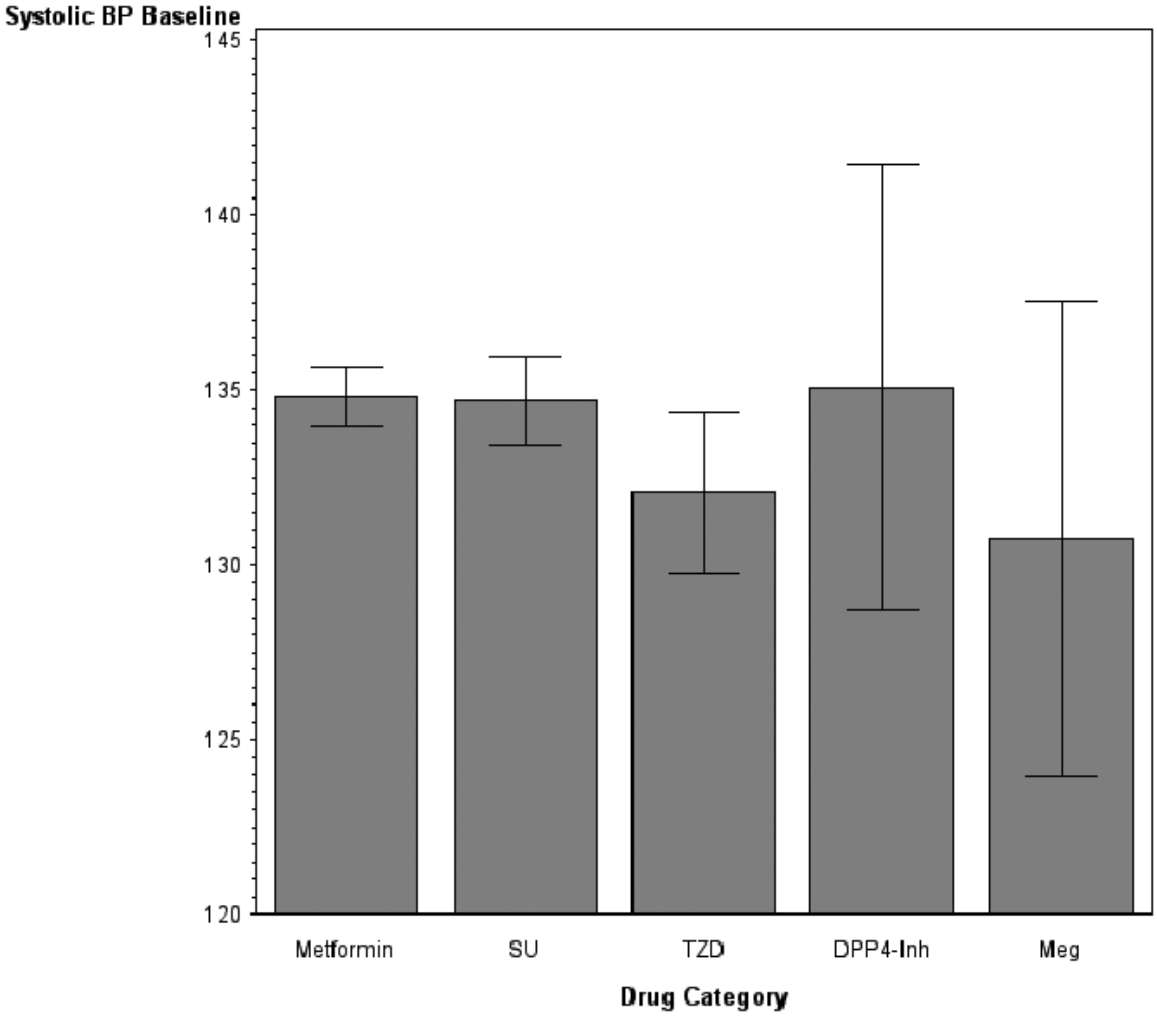

Figure 17. Mean baseline systolic BP by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were not found at alpha < 0.05 between the studied OAD classes

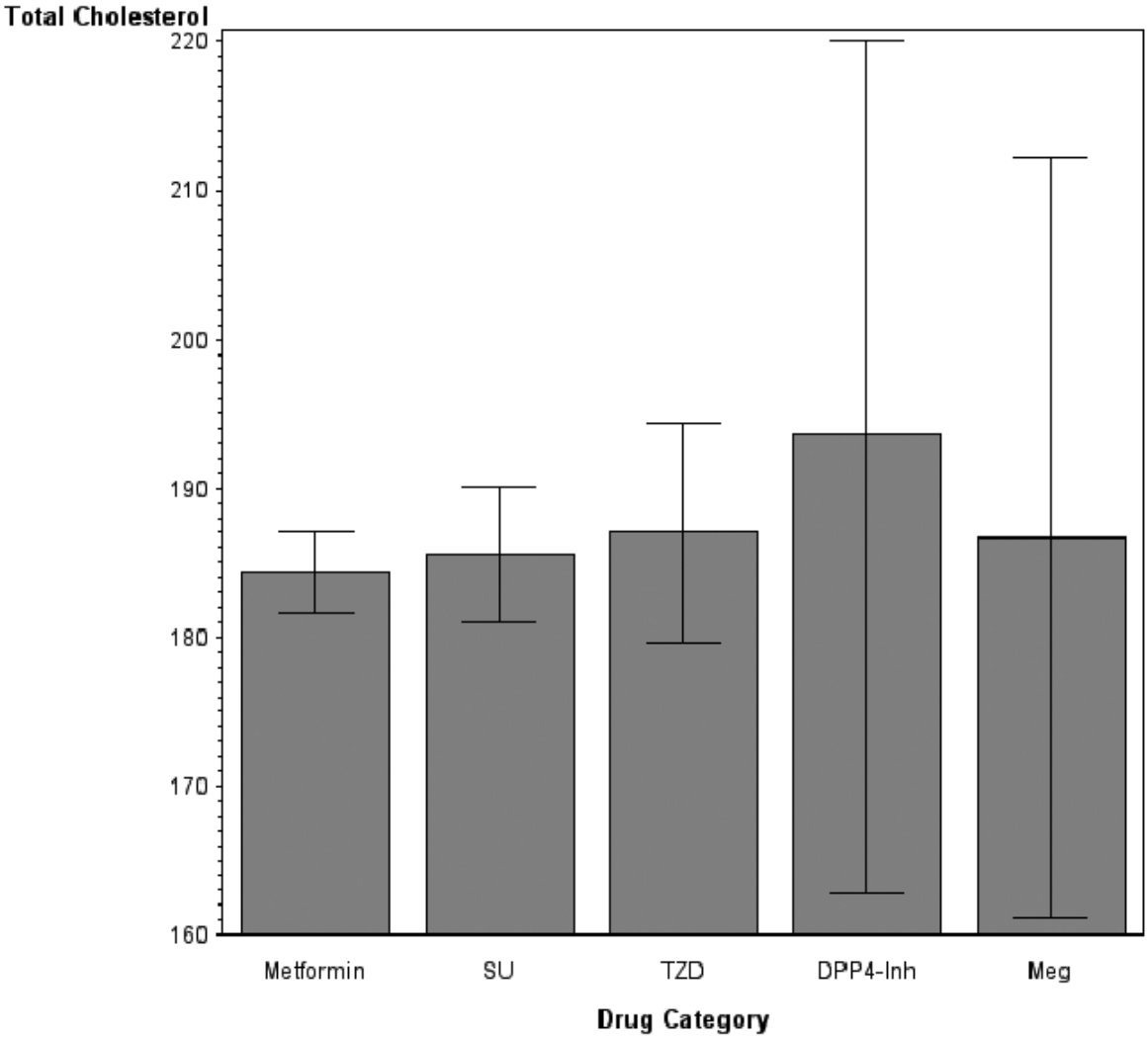

Figure 18. Mean baseline total cholesterol by OAD categories

*Based on the ANOVA model using the Tukey test, significance differences were not found at alpha < 0.05 between the studied OAD classes

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