Factors Associated with Initiation of Glucose-lowering Agents among Medicare Beneficiaries with Newly Diagnosed Type 2 Diabetes, 2007 – 2017

by

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Abstract

Patients with type 2 diabetes (T2D) endure significant clinical and economic burdens. Early initiation of a pharmacologic agent can help achieve better glycemic control and reduce the risk of diabetes-related complications. Professional society guidelines recommend initiating metformin at the time of diagnosis, while others recommended newer drug classes depending on patients' clinical characteristics. Little is known about the proportion of and timing of initiation of glucose-lowering agents among Medicare beneficiaries newly diagnosed with T2D. As the initiation and the selection of glucose-lowering agents are based on a myriad of clinical characteristics and patient preferences, it also remains unclear which factors are associated with treatment initiation and therapeutic class selection. In this study, we sought to understand the patterns and factors associated with the initiation of pharmacological treatment after T2D diagnosis and the selection of therapeutic class.

Using 2006-2018 Medicare claims data, we identified patients newly diagnosed with T2D in 2007-2017 and assessed the initiation of a glucose-lowering agent within the first year of diagnosis and time from diagnosis to initiation. Independent variables included patient demographics, social factors, clinical characteristics, and healthcare utilization. Adjusted Cox Proportional Hazard models were constructed to identify factors associated with time to treatment initiation.

We found that only 13.7% of Medicare beneficiaries with newly diagnosed T2D initiated a glucose-lowering agent within the first year after diagnosis, and this remained relatively constant from 2007-2017. In the adjusted model, increasing age (HR 0.92, 95%CI 0.91-0.93 for 10-year increase) and female gender (HR 0.89, 95% CI 0.87-0.91) were associated with a lower likelihood of initiation within one year of diagnosis. Black race was associated with a lower hazard of initiation than White race (HR 0.92, 95% CI 0.89-0.96) in the adjusted model. Antihypertensive drug use (HR 1.23, 95% CI 1.20-1.26) and statin use (HR 1.17, 95% CI 1.14-1.20) were associated with increased hazards of glucose-lowering agent initiation, whereas a history of CVD (HR 0.86, 95% CI 0.84-0.88) and chronic kidney disease (HR 0.84, 95% CI 0.82-0.87) were associated with a reduced likelihood of initiation. There was a large variation in T2D treatment initiation across regions and states, being lowest in Hawaii (6.35 cases per 100 persons-year) and highest in North Dakota (20.17 cases per 100 persons-year).

Of those who initiated an antidiabetic drug within the year of T2D diagnosis, 54.2% and 21.5% of patients received metformin and sulfonylureas in 2007, while 84.4% and 6.0% initiated metformin and sulfonylureas in 2017, respectively. After adjustment, older age (OR 0.67, 95% CI 0.65-0.70 for ten years of increase), Black race (OR 0.80, 95% CI 0.72-0.90), chronic kidney disease (OR 0.44, 95% CI 0.40-0.48) and CDV disease (OR 0.76, 95% CI 0.71-0.82) were associated with lower odds of initiating metformin compared to sulfonylureas, while female gender (OR 1.15 95% CI 1.07-1.23) was associated with higher odds of receiving metformin compared to sulfonylureas.

Our findings describe the real-world initiation of glucose-lowering agents following the first T2D diagnosis in older adults and carry important implications for quality prescribing

initiatives. Further investigation is needed to investigate the barriers of the low initiation rate and nonconformity with the guidelines.

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Preface

I cannot begin to express my gratitude to all the members of my thesis committee, Dr. Inmaculada Hernandez, Dr. Serena Guo, and Dr. Sandra Kane-Gill. I wanted to thank Dr. Kane-Gill for providing insightful comments on my research project. And thank Dr. Guo for the research input and all the invaluable advice and experiences on topics of endocrine diseases. This project would not have been possible without the help, support, and guidance from you. I would like to express my most profound appreciation to my academic advisor, Dr. Hernandez. I really appreciate your mentorship on both coursework and research throughout my academic journey. Without you, I would not have the opportunity to work on such meaningful topics with these extraordinary healthcare researchers in your group.

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Finally, I wish to thank my family for their unwavering love and encouragement in all of my pursuits.

1.0 Introduction

1.1 Epidemiology of Type 2 Diabetes

Diabetes is a chronic, metabolic disease characterized by elevated blood glucose levels due to impairment of insulin secretion, deficient insulin action, or both[1,2]. It is one of the four major noncommunicable diseases[3], with 422 million people worldwide now living with diabetes[4]. In the United States, diabetes affects 10.5% of Americans, with nearly 34.2 million people of all ages have diabetes[5].

Type 2 diabetes (T2D) is the most prevalent type of diabetes[2]. The development of T2D is complicated, with the primary pathogenesis being pancreatic β-cell dysfunction and insulin resistance in target organs[6]. In the United States, T2D accounts for 91.2% of patients with diabetes[7]. Although T2D is most prevalent in people over 45 years of age[1], the prevalence of T2D in adolescents and young adults has increased dramatically due to sedentary lifestyle, obesity, and family history[8,9].

1.2 The Burden of T2D

1.2.1 Clinical Burden of T2D

The immediate and long-term complications associated with diabetes carry a major burden in morbidity and mortality[10]. Even though acute complications such as hyperglycemic

hyperosmolar state (HHS) and diabetic ketoacidosis are uncommon and mostly preventable for patients with T2D, these complications account for increased morbidity and mortality[10-12]. Since 2010, significant increases in hospitalizations for and death from HHS have been reported by the United States Diabetes Surveillance System[10]. Macrovascular complications of diabetes, including coronary heart disease, stroke, peripheral vascular disease, and microvascular complications, such as diabetic kidney disease, retinopathy, and neuropathy, are responsible for much of the burden of T2D[13]. Notably, diabetes is a crucial risk factor for cardiovascular disease (CVD) and mortality[14-17]. Patients with diabetes have an 1.5-4 times increased risk of stroke. They also had a two- to four-fold higher risk of hospitalization for major CVD events[18] and increased mortality compared to those without diabetes[19]. Other complications such as peripheral neuropathy and retinopathy can lead to a potentially disabling situation, which profoundly affects their physical well-being and health-related quality of life[20-22]. In fact, diabetic retinopathy is the leading cause of blindness among US adults[23]. In addition, patients with diabetes are at about 15 times higher risk of lower-extremity amputations than nondiabetic individuals[24].

1.2.2 Economic Burden of T2D

T2D imposes substantial economic costs on patients and the health care system. In the US, patients with T2D have medical expenditures 2.3 times higher than patients without T2D[25,26] due mainly to the high costs associated with management of diabetic complications, which accounts for 48%-64% of total medical costs[27-29]. In 2010, a study estimated annual medical costs for the approximately 16.5 million T2D patients in the US at $159.5 billion[30]. Data from 2017 estimated the annual national cost of diagnosed diabetes at $327 billion, including $237 billion in direct

medical costs and $90 billion in reduced productivity[25]. The clinical and economic burden of T2D will continue to increase as the prevalence of T2D rises.

1.3 Pharmacotherapy for T2D

The goal of T2D management is centered on glycemic control, the prevention or delay of complications, and the maintenance of a good quality of life[31,32]. To achieve the glycemic target, the approaches to T2D management for newly diagnosed patients usually involve lifestyle management such as weight management, physical activity, and medical nutrition therapy, as well as the use of glucose-lowering medications[33-36]. Although lifestyle interventions have shown effects in maintaining glycemic targets[35,37,38], the addition of pharmacologic therapy contributes to achieving glycemic control and reduction in the risk of complications[31,36,39-43]. In the UK prospective Diabetes Study (UKPDS), intensive treatment with metformin was associated with a 32% reduction in the risk of diabetes-related complications and death, and treatment with sulfonylureas or insulin with a 12% reduction[44].

The pharmacotherapy of T2D has become complex with the approval of numerous agents belonging to several therapeutic classes in the last two decades. Table 1 lists the main classes of glucose-lowering agents available in the US and their characteristics.

Table 1 Properties of Main Classes of Glucose-Lowering Agents for T2D Available in the US

Class		Earliest Approval Year in the US	Agents (Route of Administration)	Mechanisms and Physiological Actions	Characteristics and Considerations*
Non-insulin	Biguanides	1995 (metformin)	Metformin Metformin ER (oral)	Activates AMP-kinase; reduces hepatic glucose production	• High HbA1c efficacy • Low risk of hypoglycemia • Reduced CVD events among overweight patients • Contraindications: eGFR <30mL/min/1.73m^2 • GI side effects, Lactic acidosis (rare)
	Sulfonylureas (second generation)	1999 (Glimepiride)	Glimepiride Glipizide Glyburide (oral)	Closes K_{ATP} channels on β-cell plasma membranes; increases insulin secretion	• High HbA1c efficacy • Reduce microvascular risk • Might increase risk of CVD and mortality • Common hypoglycemia • Weight gain
	Thiazolidinediones	1999 (Pioglitazone, Rosiglitazone)	Pioglitazone Rosiglitazone (oral)	Activates the nuclear transcription factors PPAR-γ; increases insulin sensitivity	• High HbA1c efficacy • Low risk of hypoglycemia • Weight gain, edema, heart failure caused by fluid retention • Bone fractures • Not recommended in patients with renal impairment • **FDA Black Box warning**: risk of congestive heart failure
	GLP-1 receptor agonist	2005 (Exenatide)	Exenatide Exenatide ER Albiglutide Dulaglutide Liraglutide Lixinsenatide (SC injection) Semaglutide (oral)	Activates GLP 1 receptors; increases insulin secretion, and reduces glucagon secretion, slows gastric emptying, induces satiety	• High HbA1c efficacy • Low risk of hypoglycemia • Weight loss • Some agents have cardiovascular and renal benefits • **FDA Black Box warning**: risk of thyroid C-cell tumors in rodents, human relevance not determined
	DPP-4 inhibitors	2009 (Saxagliptin)	Saxagliptin Alogliptin Linagliptin Sitagliptin (oral)	Inhibits DPP-4 activity by increasing postprandial incretin (GLP-1, GIP) concentrations; increases insulin secretion and decreases glucagon secretion	• Relatively high HbA1c efficacy • Low risk of hypoglycemia • Well tolerated • Some agents increase risk of heart failure • Acute pancreatitis has been reported but causality has not been established

Table 1 Continued

Non-insulin	SGLT-2 inhibitors	2013 (Canagliflozin)	Canagliflozin Dapagliflozin Empagliflozin (oral)	Inhibits SGLT-2 in the proximal nephron; blocks glucose reabsorption in the kidney, increasing glucosuria	• Relatively high HbA1c efficacy • low risk of hypoglycemia • Weight loss • Reduce blood pressure • Most agents have cardiovascular and renal benefits • Risk of DKA (rare), hypotension, and genitourinary infections
Insulin	Rapid-acting Insulin	1992 (Insulin Lispro)	Insulin Lispro Insulin Glulisine Insulin Aspart (SC injection)	Supplement to the endogenous insulin	• Highest HbA1c efficacy • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) compared to insulin analogs.
	Short-acting Insulin	1991	Insulin Regular Human (SC injection /inhaled)		
	Intermediate-acting insulin	1982	Insulin Human NPH (SC injection)		
	Long-acting insulin	2000 (Insulin Glargine)	Insulin Glargine Inuslin Degludec Insulin Detemir (SC injection)		

Abbreviations: ER = extended release; AMP = adenosine monophosphate; HbA1c = glycated hemoglobin A1c; CVD: cardiovascular disease; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; K_{ATP} = adenosine triphosphate-sensitive potassium channel; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GIP= glucose-dependent insulinotropic polypeptide; SC = subcutaneous; SGLT-2 = sodium glucose cotransporter 2; DKA = diabetic ketoacidosis; PPAR = peroxisome proliferator activated receptor; NPH = neutral protamine Hagedorn;

* Please refer to instructions for use for full list of contraindications, warnings, precautions and adverse event of a specific agent.

1.3.1 Metformin

Since its debut on the US market in the 1990s, metformin remains one of the most commonly prescribed drugs for T2D worldwide, either alone or in combination with other glucose-lowering therapies. Metformin suppresses hepatic glucose production and improves insulin sensitivity[45]. Literature showed that patients treated with metformin had a significantly reduced mean fasting plasma glucose and Hemoglobin A1c (HbA1c) level at 29 weeks[46]. It remains unclear whether metformin has cardiovascular benefits. However, metformin monotherapy has been associated with decreased risk of myocardial infarction and all-cause mortality compared to lifestyle management among overweight patients with newly diagnosed T2D[47]. Metformin is also associated with minimal hypoglycemia risk and is safe to be used in combination with other glucose-lowering agents [36,48]. Metformin is contraindicated in patients with impaired kidney function, as defined by a glomerular filtration rate (eGFR) < 30mL/min/1.73m^2. This is because metformin is associated with an increased risk of lactic acidosis[49,50].

1.3.2 Sulfonylureas

Sulfonylureas were the pillar of T2D treatment in the 2000s. Sulfonylureas stimulate insulin release by binding to the sulfonylurea receptor on the adenosine triphosphate-sensitive potassium channel on the beta cell membrane[51]. Sulfonylureas monotherapy can efficaciously lower the HbA1c level[52-54]. However, sulfonylureas appeared to be associated with an increased risk of composite cardiovascular events and all-cause mortality, especially among those with a

CVD history[55,56]. Moreover, the use of sulfonylureas has been linked to a greater risk of hypoglycemia because of its insulin secretagogue effects[57,58].

1.3.3 Thiazolidinediones

Thiazolidinediones activate the transcription process associated with peroxisome proliferator-activated receptor, promote insulin sensitivity in adipocytes, muscles, and liver[59]. They have a similar effect on reducing HbA1c levels compared to metformin[59]. However, they are associated with risk of fluid retention, leading to weight gain, edema, and heart failure[59]. For this reason, they have a lower priority in the treatment guideline and are rarely used nowadays[36].

1.3.4 Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists stimulate the GLP-1 receptor and regulate the endogenous incretin hormone[60]. Most of the GLP-1 receptor agonists are administered through the subcutaneous route. Overall, GLP-1 receptor agonists have demonstrated high potency in lowering HbA1c[61], along with bodyweight reductions and low risk of hypoglycemia[60]. However, differences within class exist in terms of the magnitude of effect on HbA1c level and adverse effects[62-64]. Gastrointestinal disorders are the most common side effects associated with GLP-1 receptor agonists, although they vary by agent and formulation[61]. GLP-1 receptors are associated with a significantly decreased risk of atherosclerotic cardiovascular disease (ASCVD) in patients with T2D[61,65].

1.3.5 Dipeptidyl Peptidase-4 (DDP-4) Inhibitors

DPP-4 inhibitors also act through regulating the endogenous incretin by reducing the degradation of the incretin hormones GLP-1 from DPP-4 and normalize the secretion of insulin and glucagon[66]. Extensive clinical evidence has shown that these agents can achieve sustainable reductions in HbA1c level[60] with a low risk of hypoglycemia[67]. Outcome clinical trials have shown a neutral cardiovascular effect of DPP-4 inhibitors. Because of their good tolerability, DPP-4 inhibitors are efficaciously used as monotherapy and are available in combination with commonly prescribed glucose-lowering agents.

1.3.6 Sodium-glucose Cotransporter-2 (SGLT-2) Inhibitors

SGLT-2 inhibitors target the kidney to promote urinary glucose and calorie excretion, reducing plasma glucose level and addressing hyperglycemia[68]. Because their effect is independent of insulin, SGLT-2 inhibitors can be used in combination with any class of glucose-lowering agents at any stage of disease[36,48]. SGLT-2 inhibitors have been proven to have good hypoglycemic effects[69] and have been associated with cardiovascular and renal benefits[70,71].

1.3.7 Insulin

Insulin remains the most potent glucose-lowering therapy of all the agents, particularly for patients with poor glycemic control[72]. If patients are not able to achieve glucose target, presenting with blood glucose level over blood glucose levels 300 mg/dL (16.7 mmol/L) or HbA1c level of over 10% (86 mmol/mol), or abnormal catabolic conditions, initiating insulin therapy is especially

critical[36]. However, compared with other glucose-lowering agents, there is a substantial risk of hypoglycemia and weight gain associated with insulin therapy[72,73].

1.3.8 Professional Society Recommendations

Since the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) made the first consensus recommendations in 2006, metformin has always been the primary glucose-lowering agent for patients with T2D. Though the guidelines for initial therapy for T2D in the US have remained unchanged over the last decade, the selection of glucose-lowering agents has become more patient-centered, given the number of available glucose-lowering agents and the clinical and patient factors taken into consideration increased. Table 2 shows the list of established guidelines for and their recommendations for initial therapy of T2D. According to the Standards of Medical Care in Diabetes 2021 by ADA, metformin remains the preferred pharmacologic treatment for patients newly diagnosed with T2D and should be initiated at the time of T2D diagnosis irrespective of the HbA1c value. If metformin is contraindicated or not tolerated, a patient-centered approach should guide the choice of the pharmacologic agent[36]. While the ADA still recommends metformin as the initial therapy, the European Society of Cardiology, together with the EASD, went one step further in altering their treatment guidelines to include newer classes of glucose-lowering agents. SGLT-2 inhibitors and GLP-1 receptor agonists are now recommended as first-line therapy for patients with established ASCVD or high cardiovascular risk, independent of HbA1c value, whereas metformin is considered as the first line in patients without CVD and at moderate cardiovascular risk.

Table 2 Well-Recognised Guidelines or Consensus Reports for the Treatment of T2D and Their Recommendations for Initial Therapy

Professional Society Guidelines	Year	Recommendations for Initial Therapy	
American Diabetes Association (ADA): Standards of Medical Care in Diabetes - 2021	2021	Metformin is the preferred initial pharmacologic agent for the treatment of T2D. It should be started at the time T2D is diagnosed unless there are contraindications.	[36]
American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE): Consensus Statement by the AACE and ACE on The Comprehensive Type 2 Diabetes Management Algorithm – 2020	2020	Metformin is generally preferred. Patients with established ASCVD or high risk, CKD 3, or HFrEF, start with LA GLP-1 receptor agonist or SGLT-2 inhibitors with proven efficacy irrespective of glycemic control.	[74]
Canadian Diabetes Association: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update	2020	For treatment of people with newly diagnosed T2D, metformin may be introduced at the time of diagnosis, in conjunction with healthy behavior interventions.	[75]
ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the ADA and the EASD	2019	First line therapy is metformin with comprehensive lifestyle management.	[31]
European Society of Cardiology (ESC)/EASD: ESC Guidelines on Diabetes, Prediabetes, And Cardiovascular Diseases Developed in Collaboration with the EASD	2019	Patients with diabetes should be classified according to three accepted levels of cardiovascular risk and treated accordingly, independent of baseline hba1c. Patients with T2D and ASCVD should be treated with an SGLT-2 inhibitor or a GLP-1 receptor agonist, independent of HbA1c.	[76]
International Diabetes Federation: Recommendations for Managing Type 2 Diabetes in Primary Care	2017	Metformin is the preferred choice to start monotherapy. When metformin is not tolerated, other glucose-lowering agent can be used, preferably sulfonylureas (except glibenclamide/glyburide), AGI or DPP-4 inhibitor.	[77]

Abbreviations: T2D = type 2 diabetes; ASCVD= atherosclerotic cardiovascular disease; CKD 3= stage 3 chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; LA = long-acting (⩾24 hour duration); GLP-1 = = glucagon-like peptide-1; SGLT-2 = sodium glucose cotransporter 2; HbA1c = glycated hemoglobin; AGI= Alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase-4;

1.4 Significance of Therapy Initiation for T2D

It has been shown in the UKPDS trial that early initiation of pharmacologic agents can significantly improve glycemic control without leading to increase hypoglycemia or weight

gain[44,47]. Nichols et al. showed that among patients who are newly diagnosed with T2D, initiating metformin within three months of diagnosis was associated with fulfillment of the general target HbA1c level set by the ADA (≤7.0%) compared to lifestyle management[78,79]. Early initiation was also associated with decreased risk of microvascular events, myocardial infarction events, and mortality in patients with newly diagnosed T2D[44,47,80]. Given these benefits, ADA/EASD recommended that metformin should be initiated at the time of T2D diagnosis[31].

However, many patients with newly diagnosed T2D remained untreated with glucose-lowering agents for an extended period of time[81-84]. A UK study assessed the time to initiation among patients with newly diagnosed T2D and reported that the 180-day, 1-year, and 2-year initiation rate was 36%, 42%, and 51%, respectively[85]. Another study in the US explored the time to initiation among the younger and older population (below and over 65 years old) and found that 43% of older adults with T2D would initiate therapy within two years after T2D diagnosis[86], whereas the 2-year initiation rate for younger patients was 59%. Low initiation rates of pharmacologic agents are concerning because the associated hyperglycemia increases the risk for both micro- and macrovascular complications of diabetes.

1.5 Gaps in Evidence

Data are scarce about the real-world trends in the initiation of glucose-lowering therapy after the first T2D diagnosis during the last decade in the US. Prior studies investigating the factors associated with therapy initiation only included a limited range of factors. Specifically, Spoelstra et al. assessed the effect of the diabetes severity as defined by the fasting blood glucose level at diagnosis on the initiation of glucose-lowering therapy[81]. Zhang et al. and Sinclair et al. explored

how age, HbA1c value, baseline as well as follow-up comorbid disease conditions, and co-medications can affect the initiation of the treatment[85,86] However, these studies did not examine associations between social factors or health care utilization and treatment initiation, which have been described to be important in the initiation of other chronic therapies[87].

While quantifying prescribing patterns of treatment initiation is an essential part of assessing the quality of pharmaceutical care and identifying barriers to treatment access[36,88,89], limited studies have explored the current prescribing patterns for initial therapy of T2D among US Medicare beneficiaries. Little is known regarding factors associated with the selection of glucose-lowering drug classes.

2.0 Objective

This study aimed to describe the trends in the initiation of a glucose-lowering agent and the time from diagnosis to the initiation among patients newly diagnosed with T2D between 2017-2017. We sought to identify the factors associated with the timing of initiation and the choice of drug class, including demographics, clinical characteristics, social determinants, and health care utilization factors. We further explored temporal trends in the choice of the initial therapeutic class and the factors associated with therapeutic class selection.

3.0 Methods

3.1 Dataset and Study Design

We used 2006-2018 claims data from a 5% random sample of Medicare beneficiaries provided by the Centers for Medicare and Medicaid Services (CMS). We identified patients who were newly diagnosed with T2D in 2007-2017. Newly diagnosis of T2D was defined as having at least one inpatient or outpatient claim with an International Classification of Disease, Ninth Revision (ICD-9) or International Classification of Disease, Tenth Revision (ICD-10) code for T2D diagnosis (ICD-9: 250.x0, 250.x2; ICD-10: E11) for the first time in 12 months and no prescriptions for any glucose-lowering agent 12 months before the index date (Figure 1). The index date was defined as the date of T2D diagnosis.

We excluded patients who had a diagnosis for other types of diabetes 12 months before or after the index date using ICD codes (Appendix Table 1). We also excluded patients who filled a prescription for multiple glucose-lowering medication classes on the date of initiation. We limited our sample to patients who had been continuously enrolled in Medicare fee-for-service both 12 months before and after the index date, which enabled us to have complete information to define covariates and outcomes during the study period. All patients were followed for one year after the index date.

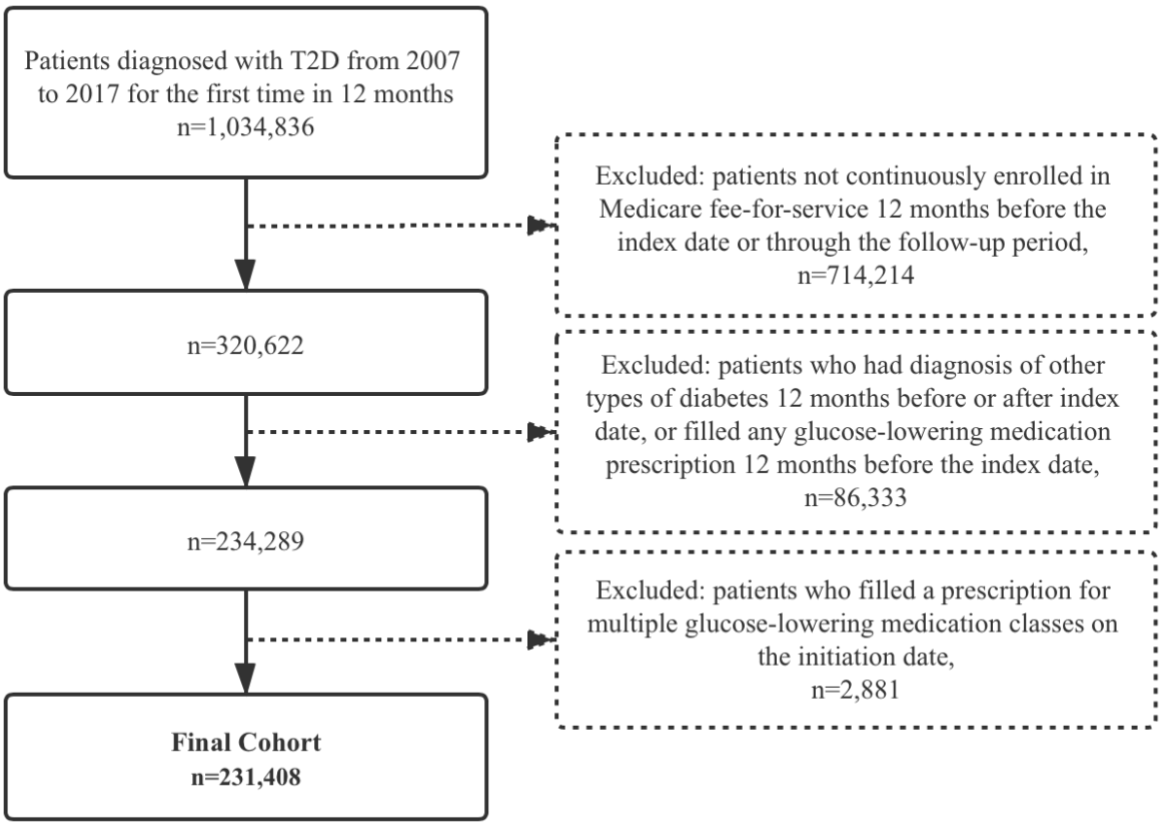


Figure 1 Cohort Flowchart

3.2 Outcomes

The primary outcomes included 1) initiation of a glucose-lowering medication (list in Appendix Table 2) within a year of diagnosis, and 2) time from first T2D diagnosis to the initiation. Patients who initiated a glucose-lowering agent within one year of diagnosis were defined as initiators, whereas those who failed to initiate treatment were defined as non-initiators. The 1-year follow-up period was selected as this period reflects guidelines' recommendations[36,48]. We

examined the class of glucose-lowering medication initiated among the initiators, categorizing them into three groups: metformin initiators, sulfonylureas initiators, and other initiators.

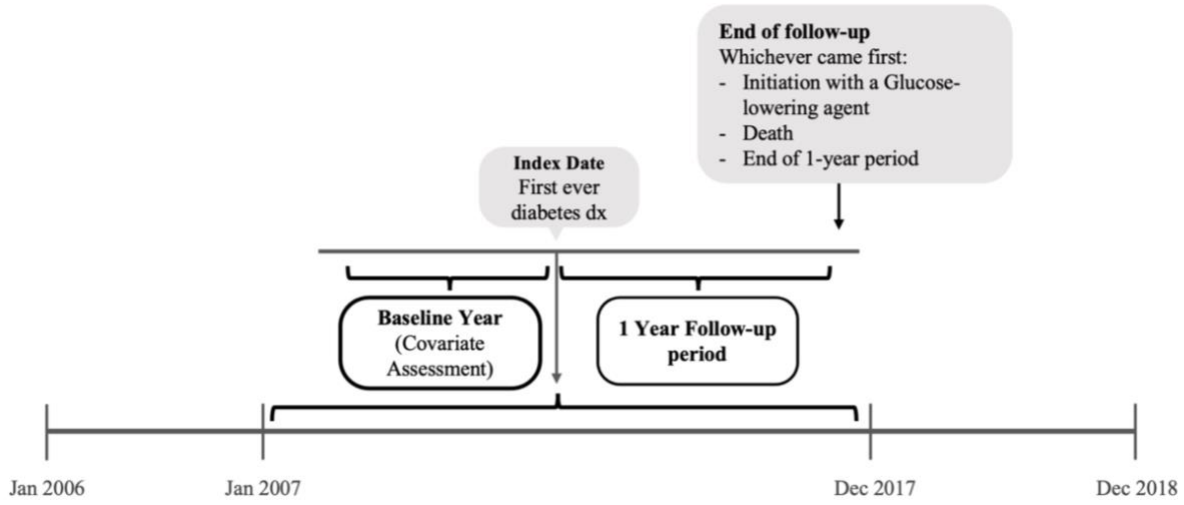


Figure 2 Study Design

Medicare Claims data from 2006 to 2018 were used. Patients with a first-ever T2D diagnosis from January 2007 to December 2017 were included and the index date was defined as the date when patients had their first-ever T2D diagnosis. Patients were assessed for 1 year following the index date for the outcome. Baseline characteristics of the beneficiaries are assessed 6 or 12 months prior to the index date.

3.3 Covariates

We included a comprehensive set of covariates in our analysis, including demographics, social factors, clinical characteristics, healthcare utilization factors, and index year.

Demographics included age at the time of diagnosis, sex, and race (White/Black/others). Social factors included eligibility for Medicaid coverage, low-income subsidy, US Census region of residence (Northeast/Midwest/West/South), and residence in a metropolitan/rural area determined using rural-urban continuum codes (RUCC)[90]. Low-income subsidy eligibility served

as an individual-level proxy for socioeconomic status. We obtained information of RUCC at the cross-walked Federal Information Processing Standard (FIPS) code level.

Clinical characteristics included prior comorbidities and co-medications used. Prior comorbidities were defined in the 12 months before the index date and were determined using CMS Chronic Conditions Warehouse definitions. Comorbidities included 1) composite CVD (acute myocardial infarction, ischemic heart disease, or stroke), 2) congestive heart failure, 3) chronic kidney disease, and 4) the number of other comorbidities. Prior co-medications used were assessed using the Part D Event file. They were defined as filling a prescription for specific classes of medication in the six months before the index date, including 1) antihypertensive medications, 2) antiplatelets, and statins. We further measured the number of other medications used in the six months before the index date.

Healthcare utilization factors, including inpatient admission, the number of ER visits, and the number of outpatient visits, were assessed six months prior to the index date. We also collected information regarding health costs, including patients' out-of-pocket spending and total spending on pharmaceuticals. These were calculated as the sum of the costs incurred six months before the index date. Because the health cost variables are not normally distributed, we dichotomized cost variables (top 10% percentile vs. rest).

3.4 Statistical Analysis

For the primary analysis, we first performed descriptive statistical analysis to compare the baseline characteristics of initiators and non-initiators. Student's t-tests were used for continuous variables and chi-square tests for categorical variables. We also plotted the unadjusted initiation

rate and the time to initiation by calendar year to address the initiation patterns. We constructed Cox proportional hazards models to quantify the association between independent variables and time to initiation. We used stepwise and Least Absolute Shrinkage and Selection Operator (LASSO) variable selection methods. The LASSO model was performed using 10-fold cross-validation. The tuning parameter lambda (λ) is chosen by cross-validation, and two λs are calculated, minimum lambda (λ_{min}) and lambda plus one standard error (λ_{1se}). Model performance was assessed using the concordance index. Concordance index is a generalization of the area under the Receiver Operating Characteristic (ROC) curve that can take into account censored data. The variables included in the selection and the variables selected by the Stepwise procedures are presented in Appendix Table 4. In the Penalized Cox model, we used λ_{1se} because it gives the parsimonious model with the best concordance index. The model performance according to the λ values is presented in Appendix Figure 1. We investigated the interaction of race with other patient characteristics (i.e., race and sex, residence in a metropolitan/rural area, and low-income subsidy eligibility) in the Cox model.

Because the effect of composite CVD history might overlap with the effect of use of antihypertensives or statins, we conducted sensitivity analysis to explore the effect of composite CVD history on medication initiation in models that did not include use of antihypertensive drug or statins.

To quantify the geographic variation in initiation rate, we used Poisson regressions to calculate the adjusted incidence density (per 100 person-years) for each state while adjusting for other variables and plotted the incidence density by state[91].

For the secondary analysis, we compared the baseline characteristics between patients initiating with metformin, sulfonylureas, and others using Analysis of variance (ANOVA) or chi-

square tests. We constructed logistic regression models to assess the predictors of initiating metformin compared to sulfonylureas.

The penalized LASSO Cox regression models were performed using Coxnet package[92] in R version 3.6.0 (R Core Team, 2019). All other statistical analyses were conducted using statistical software SAS 9.4 (SAS Institute, INC., Cary, NC, USA).

4.0 Results

4.1 Baseline Characteristics

Our final cohort included 231,408 patients who met all the inclusion criteria (Figure 2). 31,813 (13.7%) patients initiated with a glucose-lowering agent within one year of T2D diagnosis.

Baseline characteristics for the overall cohort and each group by initiation status are shown in Table 3. The mean age of the total cohort was 71.7 years, and 62.2% were female. Age was significantly lower among initiators (67.8 years) than non-initiators (72.3 years, p<.0001). Compared to non-initiators, initiators were less likely to be male (56.6% vs. 63.1%, p<.0001), more likely to be Black (13.3% vs. 12.2%, p<.0001), or be eligible for Medicaid (47.8% vs. 43.0%, p<.0001). The initiators were less likely to be from the Northeast census region (15.3% vs. 23.6%, p<.0001) but were more likely to be from the South region (42.2 vs. 38.7%, p<.0001). Patients with no prior CVD, chronic kidney disease, or a smaller number of other comorbidities at baseline were more likely to initiate a glucose-lowering therapy within a year of diagnosis. Finally, initiators had lower total drug costs and out-of-pocket expenses at baseline than non-initiators and were less likely to have been hospitalized in the year before T2D diagnosis.

Table 3 Baseline Characteristics of Patients with Newly Diagnosed Diabetes During the Study Period, By Initiation Status

Participant Characteristics	Total (N=231,408)	Non-Initiators (N=199,595)	Initiators (N=31,813)	P-Value[a]
Age, Mean(SD)	71.67 (13.43)	72.29 (13.36)	67.80 (13.21)	<.0001
Age Group, %(N)				
<75	55.98 (129536)	53.75 (107275)	69.97 (22261)	<0.001
≥75	44.02 (101872)	46.25 (92320)	30.03 (9552)	<0.001
Female Sex, %(N)	62.18 (143882)	63.07 (125885)	56.57 (17997)	<0.001
Race/Ethnicity, %(N)				<0.001
White	77.29 (178851)	77.52 (154729)	75.82 (24122)	<.0001
Black	12.36 (28593)	12.21 (24274)	13.25 (4218)	<.0001
Others	10.36 (23964)	10.27 (20491)	14.49 (3473)	0.0004
Census Region Location, %(N)				<.0001
Northeast	22.34 (51695)	23.56 (46825)	15.31 (4870)	<.0001
Midwest	20.01 (46309)	19.32 (38567)	24.34 (7742)	<.0001
South	39.15 (90598)	38.67 (77176)	42.19 (13422)	<.0001
West	18.12 (41923)	18.13 (36190)	18.02 (5733)	0.6338
Medicaid Eligibility, %(N)	43.63 (100968)	42.97 (85775)	47.76 (15193)	<0.0001
Low-Income Subsidy Recipient, %(N)	48.05 (111185)	47.19(94197)	53.4 (16988)	<0.0001
Metro Area Resident[b], %(N)	80.98(187394)	81.97(163606)	74.77 (23788)	<.0001
CVD History[c], %(N)	56.98 (131863)	58.49 (116738)	47.54 (15125)	<.0001
Congestive Heart Failure, %(N)	32.73 (75746)	33.78 (67430)	26.14 (8316)	<0.001
Chronic Kidney Disease History, %(N)	22.15 (51263)	23.05 (46011)	16.51 (5252)	<.0001
Antihypertensive Drug Use[d], %(N)	70.36 (162826)	70.30 (140320)	70.74 (22506)	0.1086
Blood-thinner Use[e], %(N)	10.88 (25184)	11.14 (22242)	9.25 (2942)	<.0001
Statin Use, %(N)	42.43 (98191)	42.08 (83980)	44.67 (14211)	<.0001
No. of Other Comorbidities[f], Mean(SD)	3.58 (2.28)	3.70 (2.29)	2.79 (2.10)	<.0001
No. of Other Co-Medications[g], Mean(SD)	1.00 (1.02)	1.00 (1.01)	1.01 (1.04)	0.124
Hospitalization[h], %(N)	12.19 (28200)	12.44 (24836)	10.58 (3366)	<.0001
No. of Outpatient Visit[i], Mean(SD)	3.25 (7.97)	3.29 (8.22)	3.00 (6.16)	<.0001
No. of ER Visit[j], Mean(SD)	0.0018 (0.0081)	0.002 (0.085)	0.0013 (0.05)	0.1974
Top 10% For Part D Drug Costs %(N)	10.00 (23052)	10.09 (20056)	9.43 (2996)	0.0003
Top 10% For Patients Out of Pocket Costs, %(N)	10.00 (23053)	10.27 (20421)	8.29 (2632)	<.0001
Year of Index, %(N)				
2007	13.13 (30376)	12.88 (25705)	14.68 (4671)	<.0001
2008	12.40 (28691)	12.3 (24560)	12.99 (4131)	0.0006
2009	10.17 (23540)	10.11 (20189)	10.53 (3351)	0.0218
2010	12.61 (29190)	12.68 (25311)	12.19 (3879)	0.0149
2011	9.80 (22667)	9.86 (19672)	9.41 (2995)	0.0139
2012	8.80 (20367)	8.89 (17748)	8.23 (2619)	0.0001
2013	8.08 (18691)	8.17 (16311)	7.48 (2380)	<.0001
2014	8.49 (19647)	8.56 (17092)	8.03 (2555)	0.0016

Table 3 Continued

2015	6.88 (15911)	6.89 (13750)	6.79 (2161)	0.5292
2016	5.33 (12332)	5.27 (10527)	5.67 (1805)	0.0032
2017	4.32 (9996)	4.37 (8730)	3.98 (1266)	0.0013

Notes:
Abbreviation: CVD = cardiovascular disease, ER = Emergency department.
Initiators were defined as patients initiated a glucose-lowering agent within one year of T2D diagnosis, non-initiators were defined as patients failed to initiate a glucose-lowering agent within one year of T2D diagnosis.
[a] p-value was estimated using student's t-test for continuous variables, and chi-square test for categorical variables.
[b] Metro area resident was defined by Rural Urban Continuum Code of beneficiaries' residence area < 4, Rural Urban Continuum Code was obtained using zip-code linking file.
[c] Any occurrence of acute myocardial infarction, ischemic heart disease or stroke 12 months prior to the index date, determined by the corresponding variables in Chronic Conditions Data Warehouse.
[d] Use of antihypertensive medications was defined as filling at least one prescription for these following medications: Angiotensin-converting-enzyme inhibitors, Angiotensin receptor blockers, beta-adrenergic blocking agents, calcium-channel blockers, Angiotensin II receptor blockers, or diuretics 6 months prior to the index date.
[e] Use of blood-thinner was defined as filling at least one prescription for antiplatelets or anticoagulants 6 months prior to the index date.
[f] Including Alzheimer Disease, cataract, chronic obstructive pulmonary disease, glaucoma, hip fracture, depression, osteoporosis, rheumatoid arthritis or osteoarthritis, cancer, anemia, hyperparathyroidism, hypothyroidism, asthma.
[g] Use of other co-medication was defined as filling at least one prescription for these following class of medications: NSAID agent, aldosterone receptor antagonist, anti-platelets agent, anticoagulant, opioids, oral steroids or antidepressants.6 months prior to the index date.
[h] hospitalization was defined as those who has any admission date recorded, and also have an inpatient claim associated with it but exclude those with a charge amount for emergency room services provided 6 months prior to the index date.
[i] Number of outpatient visit was calculated as the sum of unique dates of service 6 months prior to the index date. Outpatient visit was defined as having a value for revenue center code other than 0450, 0451, 0452,0456, 0459, 0981 in Medicare outpatient files.
[j] Number of ER visit was calculated as the sum of unique dates of service 6 months prior to the index date. ER visits was defined as having revenue center codes with 0450, 0451, 0452,0456, 0459, 0981 code in Medicare outpatient files, with an ER charge amount that is larger than 0 and claims are not overlapping with the Medicare carrier line claims on the same day or -/+ day[93].

4.2 Trends for the Crude Incidence Rate and Time to Initiation

Figure 3 shows the proportion of patients newly diagnosed with T2D who initiated treatment within a year of diagnosis by calendar year. The proportion of patients initiating treatment within a year of T2D diagnosis remained stable from 2007 to 2017 and ranged from 12.7% to 15.4%.

The trend in time to initiation among initiators is shown in Figure 4. The proportion of patients who initiated within three months steadily rose from 75.5% to 94.2%, and the proportion of patients initiating within six months increased from 86.5% to 98.0% by 2017.

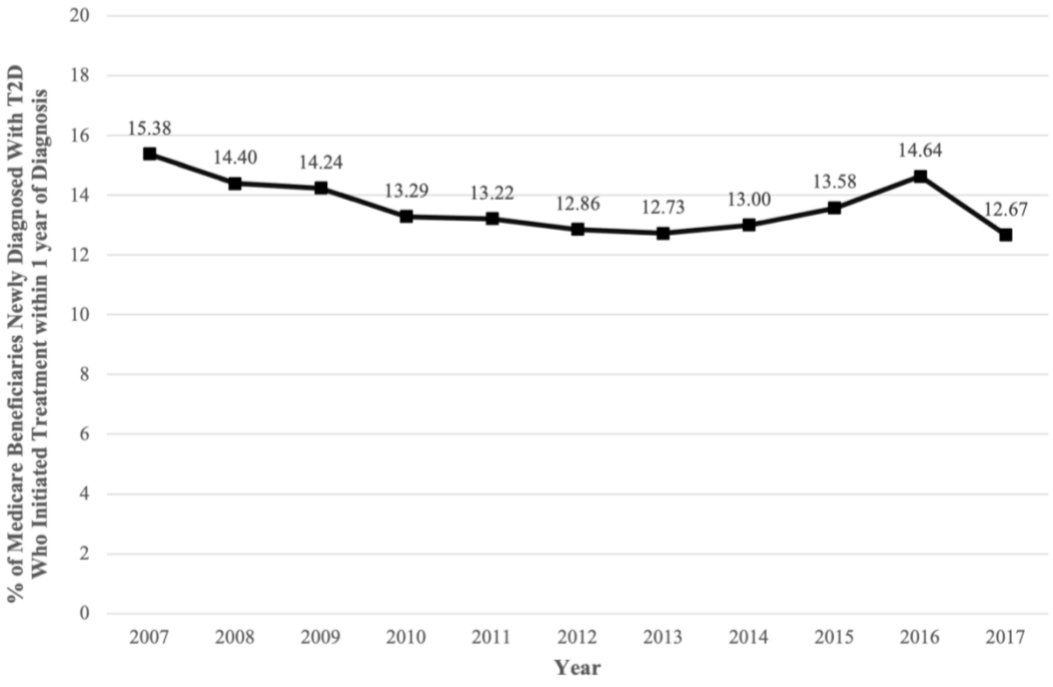


Figure 3 Trends in the Percentage of Medicare Beneficiaries Newly Diagnosed with T2D And Initiated Treatment Within One Year of Diagnosis, By Year, 2007-2017

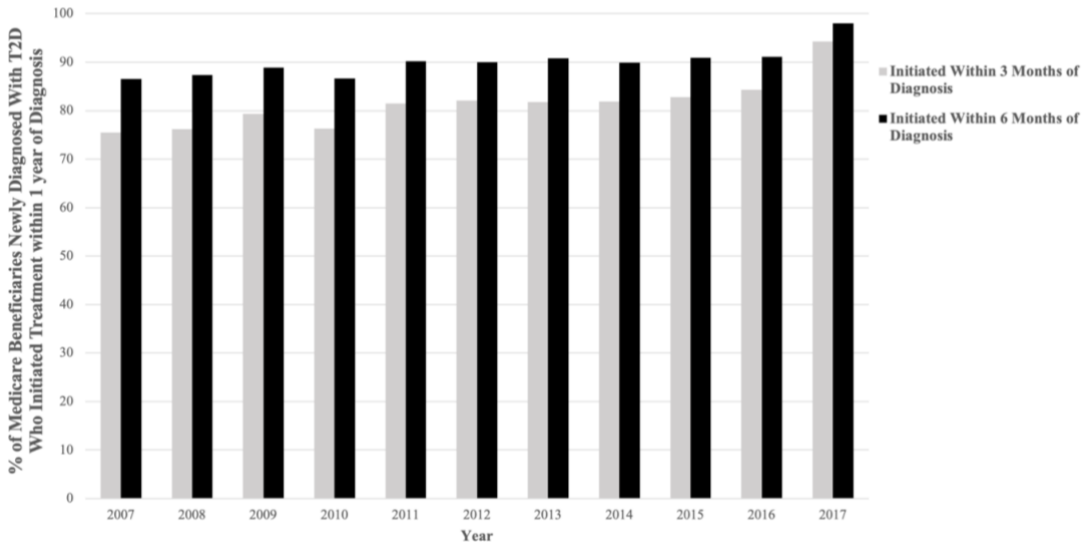


Figure 4 Time to Initiation Among Initiators, By Year

Gray bar shows the proportion of those who initiate within 3 months among initiators by their year of index, black bar shows the proportion of those who initiate within 6 months among initiators by their year of index.

4.3 Adjusted Hazard Ratios

4.3.1 Adjusted Hazard Ratios Estimate for the Predictors

Table 4 shows the adjusted hazard ratios for initiating a glucose-lowering agent within one year of T2D diagnosis. Cox regression analysis adjusting for all the baseline characteristics selected in the final model showed that increasing age (Hazard Ratio [HR] 0.92, 95% CI 0.91-0.93 for 10-year increase), female gender (HR 0.89, 95% CI 0.87-0.91), and residence in a metropolitan area (HR 0.78, 95% CI 0.76-0.80) were significantly associated with a higher risk of non-initiation within one year of diagnosis. After adjusting for all the variables, Black race was associated with a lower likelihood of initiation than the White (HR 0.92, 95% CI 0.89-0.96).

Patients who had a composite CVD (HR 0.86, 95% CI 0.84-0.88), chronic kidney disease (HR 0.84, 95% CI 0.82-0.87), or increased number of other comorbidities prior to the index date (HR 0.86, 95% CI 0.86-0.87 for one additional number of comorbidities) were less likely to initiate the treatment, while statin use (HR 1.17, 95% CI 1.14-1.20) and antihypertensive use (HR 1.23, 95% CI 1.20-1.26) were associated with a higher likelihood of treatment initiation. Furthermore, patients who had a hospitalization history prior to the index date had a higher likelihood of treatment initiation (HR 1.07, 95% CI 1.03-1.11).

We identified a significant interaction between race and sex ($p<0.05$): the difference in the hazards of glucose-lowering agent initiation between Black and White was significant in men (HR 0.84, 95% CI 0.80-0.89), but not in women (HR 0.98, 95% CI 0.94-1.03). The interaction between race and low-income subsidy eligibility was also significant ($p<0.05$): the difference in the hazards of initiation between Black to White was more marked in low-income patients (HR 0.91, 95% CI 0.87-0.94) than patients who were not eligible for low-income subsidy (HR 0.96, 95% CI 0.89-1.03).

The results from the sensitivity analysis that assessed the hazard ratios for CVD of initiation of a glucose-lowering agent in different models are presented in Table 5. When the use of antihypertensive drugs and statins was not included in the Cox model, the effect of CVD on initiation moved towards the null. This suggests that the effects of statin and antihypertensive drug use do not fully correlate with the effect of CVD history on initiation with a glucose-lowering agent.

Table 4 Adjusted Hazard Ratio of Initiation of a Glucose-Lowering Agent Within One Year of T2D Diagnosis

Characteristics	Hazard Ratio (95% CI)[a]	p-value
Age (10 years)	0.92 (0.91, 0.93)	<.0001
Female Gender	0.89 (0.87, 0.91)	<.0001
Race/Ethnicity		
White	Ref	
Black	0.92 (0.89, 0.96)	<.0001
Others	1.03 (0.99, 1.07)	0.1172
Census Region Location		
Northeast	Ref	
Midwest	1.67 (1.61, 1.73)	<0.0001
South	1.47 (1.42, 1.52)	<0.0001
West	1.36 (1.31, 1.41)	<0.0001
Low Income Subsidy Recipient	1.20 (1.17, 1.24)	<0.0001
Metro Area Resident[b]	0.78 (0.76, 0.80)	<0.0001
CVD History[c]	0.86 (0.84, 0.88)	<0.0001
Chronic Kidney Disease History	0.84 (0.82, 0.87)	<0.0001
Antihypertensive Drug Use[d]	1.23 (1.20, 1.26)	<0.0001
Statin Use	1.17 (1.14, 1.20)	<0.0001
No. of Other Comorbidities[e]	0.86 (0.86, 0.87)	<0.0001
No. of Other Co-Medications[f]	1.07 (1.06, 1.08)	<0.0001
Inpatient[g]	1.07 (1.03, 1.11)	0.0009
Top 10% For Part D Drug Costs	0.91 (0.87, 0.95)	<0.0001
Year of Index		
2007	Ref	
2008	0.93 (0.90, 0.98)	0.0017
2009	0.91 (0.87, 0.96)	<.0001
2010	1.04 (0.99, 1.09)	0.0934
2011	1.01 (0.96, 1.06)	0.7884
2012	0.97 (0.92, 1.01)	0.1573
2013	0.97 (0.93, 1.03)	0.3083
2014	0.98 (0.93, 1.03)	0.4289
2015	1.01 (0.96, 1.06)	0.7385
2016	1.06 (1.00, 1.12)	0.0604
2017	0.94 (0.88, 1.00)	0.0402

Abbreviations: CVD = cardiovascular disease

[a] Hazard ratios were estimated using Cox proportional hazard models controlled for age, gender, race, census region location, low-income subsidy, metro area resident, chronic kidney disease history, cardiovascular disease history, number of other comorbidities, number of other comedications, statins and antihypertensive use, inpatient visit, top 10% for total drug cost and year of index. Analyses shown do not include interaction terms.

[b] Metro area resident was defined by Rural Urban Continuum Code of beneficiaries' residence area < 4, Rural Urban Continuum Code was obtained using zip-code linking file.

[c] Any occurrence of acute myocardial infarction, ischemic heart disease or stroke 12 months prior to the index date, determined by the corresponding variables in Chronic Conditions Data Warehouse.

[d] Use of antihypertensive medications was defined as filling at least one prescription for these following medications: Angiotensin-converting-enzyme inhibitors, Angiotensin receptor blockers, beta-adrenergic blocking agents, calcium-channel blockers, Angiotensin II receptor blockers, or diuretics 6 months prior to the index date.
[e] Including Alzheimer Disease, cataract, chronic obstructive pulmonary disease, glaucoma, hip fracture, depression, osteoporosis, rheumatoid arthritis or osteoarthritis, cancer, anemia, hyperparathyroidism, hypothyroidism, asthma.
[f] Use of other co-medication was defined as filling at least one prescription for these following class of medications: NSAID agent, aldosterone receptor antagonist, anti-platelets agent, anticoagulant, opioids, oral steroids or antidepressants.
[g] hospitalization was defined as those who has any admission date recorded, and also have an inpatient claim associated with it but exclude those with a charge amount for emergency room services provided

Table 5 Effect of CVD history on Initiation of a Glucose-Lowering Agent Within One Year of T2D Diagnosis in Different Models

Models	Hazard Ratio (95% CI)	p-value
Full model	0.85 (0.83, 0.88)[a]	<.0001
Model without Statin Use	0.87 (0.85, 0.90)[b]	<.0001
Model without Antihypertensive Drugs Use	0.87 (0.85, 0.89)[c]	<.0001
Model without Statin and Antihypertensive Drugs Use	0.90 (0.88, 0.93)[d]	<.0001

Abbreviation: CVD = Cardiovascular disease.
[a] Hazard ratio was estimated using Cox proportional hazard models controlled for age, gender, race, census region location, low-income subsidy, metro area resident, chronic kidney disease history, number of other comorbidities, number of other comedications, statins and antihypertensive use, inpatient visit, top 10% for total drug cost and year of index.
[b] Hazard ratio was estimated using Cox proportional hazard models controlled for age, gender, race, census region location, low-income subsidy, metro area resident, chronic kidney disease history, number of other comorbidities, number of other comedications, statins use, inpatient visit, top 10% for total drug cost and year of index.
[c] Hazard ratio was estimated using Cox proportional hazard models controlled for age, gender, race, census region location, low-income subsidy, metro area resident, chronic kidney disease history, number of other comorbidities, number of other comedications, antihypertensive drugs use, inpatient visit, top 10% for total drug cost and year of index.
[d] Hazard ratio was estimated using Cox proportional hazard models controlled for age, gender, race, census region location, low-income subsidy, metro area resident, chronic kidney disease history, number of other comorbidities, number of other comedications, inpatient visit, top 10% for total drug cost and year of index.

4.4 Geographic Variation in Initiation

The incidence density of initiation therapy within one year of T2D diagnosis was calculated for each state at the average level of all selected covariates using the Poisson regression model. A Choropleth map was created to visualize the geographic variations in the incidence density (Figure 5). The incidence density of initiation with a glucose-lowering medication varied substantially across states. The median was 13.80 cases per 100 person-years (interquartile range [IQR] 11.81-15.58). The incidence density was highest in North Dakota (20.17 cases per 100 persons-year) and lowest in Hawaii (6.35 cases per 100 persons-year).

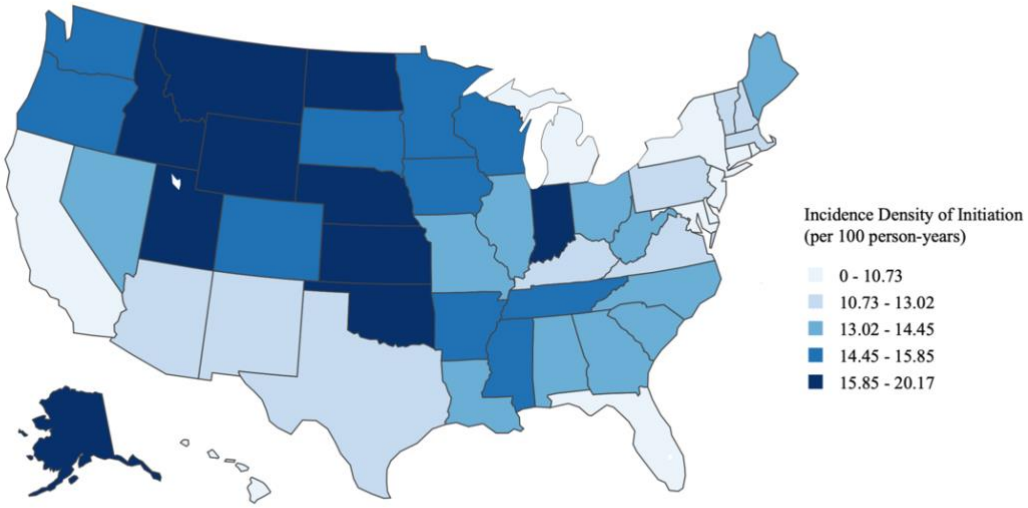


Figure 5 Quintiles for Adjusted Incidence Density of Initiation with A Glucose-Lowering Medication Within One Year of T2D Diagnosis, 2007-2017, by State

The incidence density was estimated using Poisson regression models that adjusted for age, race, sex, comorbidities, co-medications, index year, receipt of the low-income subsidy, prior year hospitalization, rurality, and total drug cost. The darker blue presents a higher incidence density of the first treatment.

4.5 Secondary Analysis

4.5.1 Patient Characteristics for Initiators, By Therapeutic Class

Of the 31,813 initiators, 21753 (68.4%) initiated metformin, 4,712 (14.8%) initiated sulfonylureas, while 5302 (16.7%) initiated other agents. Patient characteristics by the class of glucose-lowering agent initiated are presented below in Table 6. Metformin initiators were significantly younger than sulfonylureas initiators or other initiators (66.27 vs. 71.34 and 70.66, p<.0001). They also had a smaller number of comorbidities (2.61 vs. 29.5 and 3.38, p<.0001) and a lower total drug cost and out-of-pocket drug costs in the baseline year.

Table 6 Patient Characteristics, By Class of Glucose-Lowering Agent Initiated

	Metformin (N=21753)	**Sulfonylurea (N=4712)**	**Others[a] (N=5302)**	**p-value[b]**
Age, Mean (SD)	66.27 (12.83)	71.34 (12.77)	70.66 (13.65)	<.0001
Age <75 Years Old, %(N)	75.70 (16467)	57.60 (2714)	57.58 (3053)	<.0001
Female Gender, %(N)	56.67 (12327)	55.24 (2603)	57.28 (3037)	0.1026
Race/Ethnicity, %(N)				
White	77.33 (16821)	74.38 (3505)	70.95 (3762)	<.0001
Black	12.24 (2663)	13.77 (649)	16.96 (899)	<.0001
Others	10.43 (2269)	11.84 (558)	12.09 (641)	0.0002
Medicaid Eligibility, %(N)	45.16 (9824)	49.04 (2311)	57.64 (3056)	<.0001
Low-Income Subsidy Recipient, %(N)	51.17 (11131)	54.61 (2573)	61.90 (3282)	<.0001
CVD History[c], %(N)	42.21 (9181)	56.88 (2680)	61.09 (3239)	<.0001
Chronic Kidney Disease History[d], %(N)	10.9 (2372)	25.47 (1200)	31.61 (1676)	<.0001
No. of Other Co-medications[e], Mean (SD)	0.99 (1.03)	0.98 (1.04)	1.09 (1.09)	<.0001
No. of Other Comorbidities[f], Mean (SD)	2.61 (1.97)	2.95 (2.19)	3.38 (2.39)	<.0001
Top 10% For Part D Drug Costs %(N)	8.75 (1904)	8.89 (419)	12.69 (673)	<.0001
Top 10% For Patients Out of Pocket Costs, %(N)	7.62 (1658)	9.23 (435)	10.17 (539)	<.0001

Abbreviations: CVD = cardiovascular disease

[a] Others include Thiazolidinediones, DPP-4 Inhibitors, GLP-1 Receptor Agonists, SGLT-2 inhibitors, Meglitinides, α-glucosidase Inhibitors, and insulins.

[b] p-value was estimated by ANOVA for continuous variables or chi-square test for categorical variables

[c] Any occurrence of acute myocardial infarction, ischemic heart disease or stroke 12 months prior to the index date, determined by the corresponding variables in Chronic Conditions Data Warehouse.
[d] Chronic kidney diseases was determined by the corresponding variables in Chronic Conditions Data Warehouse
[e] Including Alzheimer Disease, cataract, chronic obstructive pulmonary disease, glaucoma, hip fracture, depression, osteoporosis, rheumatoid arthritis or osteoarthritis, cancer, anemia, hyperparathyroidism, hypothyroidism, asthma.
[f] Use of other co-medication was defined as filling at least one prescription for these following class of medications: NSAID agent, aldosterone receptor antagonist, anti-platelets agent, anticoagulant, opioids, oral steroids, antidepressants.

4.5.2 Trend of Initiation with Each Drug Class

Figure 6 shows the proportion of initiators that initiated each class of glucose-lowering agents by year. The proportion of metformin initiators increased from 54.2% in 2007 to 84.4% in 2017 (p-value for trend < 0.0001) whereas the proportion of patients initiating with sulfonylureas reduced from 21.5% in 2007 to 6.0% in 2017 (p < 0.0001). The proportion of patients initiating with other medications relative to the number of initiators experienced a fluctuated trend, ranging from 7.8% to 24.3%.

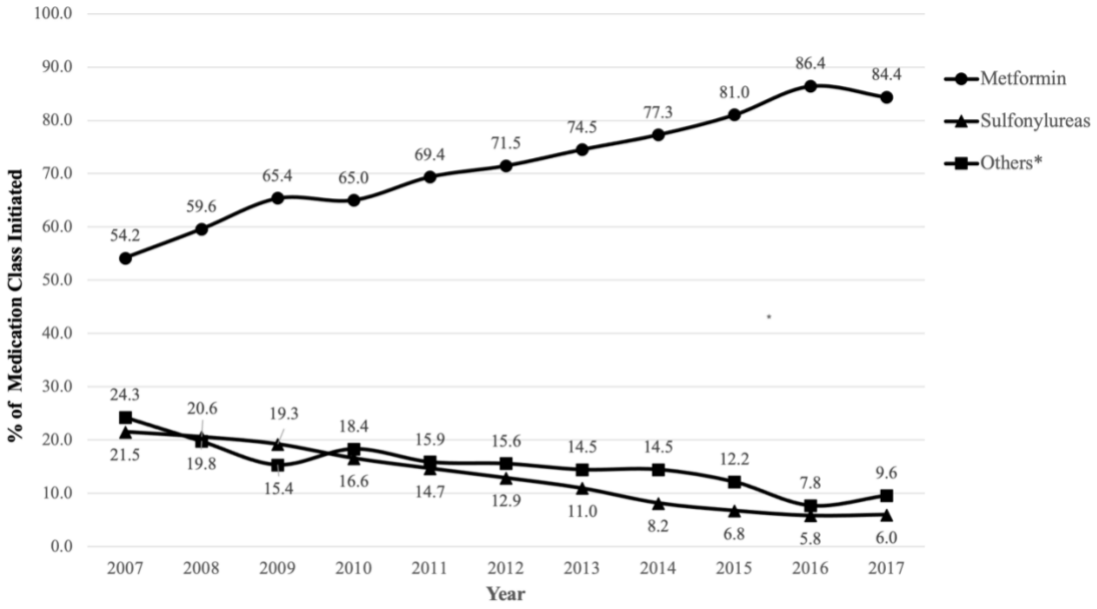


Figure 6 Proportion of Beneficiaries Initiating Each Class of Glucose-lowering Agent, By Year, 2007-2017

[*] Others include Thiazolidinediones, DPP-4 Inhibitors, GLP-1 Receptor Agonists, SGLT-2 inhibitors, Meglitinides, α-glucosidase Inhibitors, and insulins.

4.5.3 Predictors of Metformin Initiation, Compared to Sulfonylurea Initiation

After adjusting for selected baseline covariates (Table 7), age (Odds Ratio [OR] 0.67, 95% CI 0.65-0.70 for ten-years increase), Black race (OR 0.80, 95% CI 0.72-0.90 compared to White race), chronic kidney disease (OR 0.44, 95% CI 0.40-0.48) and cardiovascular disease (OR 0.76, 95% CI 0.71-0.82) were associated with decreased odds of metformin initiation, whereas female gender (OR 1.15 95% CI 1.07-1.23), and residence in the West census region (OR 1.17, 95% CI 1.04-1.31 compared to Northeast region) were associated with increased odds of metformin initiation.

Table 7 Predictors of Receiving Metformin Compared to Sulfonylureas as Initial Therapy

Patient Characteristics	Adjusted Odds Ratio[a] (95% CI)	p-value
Age (10 Years)	0.67 (0.65, 0.70)	<.0001
Female Gender	1.15 (1.07, 1.23)	<.0001
Race		
White	Ref	
Black	0.80 (0.72, 0.90)	<.0001
Others	0.91 (0.81, 1.02)	0.092
Region		
Northeast	Ref	
Midwest	0.90 (0.81, 1.00)	0.055
South	0.95 (0.86, 1.05)	0.235
West	1.17 (1.04, 1.31)	0.005
Low-Income Subsidy Recipient	0.66 (0.61, 0.71)	<.0001
CVD History[b]	0.76 (0.71, 0.82)	<.0001
Chronic Kidney Disease History[c]	0.44 (0.40, 0.48)	<.0001
No. of Other Comorbidities[d]	1.07 (1.05, 1.09)	<.0001
No. of Other Co-Medications[e]	1.01 (0.97, 1.04)	0.823
Hospitalization[f]	0.54 (0.49, 0.61)	<.0001
Top 10% For Part D Drug Costs	0.86 (0.76, 0.98)	0.019

Abbreviation: CVD = Cardiovascular Disease

[a] Adjusted odds ratios were estimated using Logistic regression models controlled for age, gender, race, low-income subsidy, chronic kidney disease, chronic kidney disease history, cardiovascular disease history, number of other comorbidities, number of other comedications, in patient visit and top 10% for total drug cost.

[b] Any occurrence of acute myocardial infarction, ischemic heart disease or stroke 12 months prior to the index date, determined by the corresponding variables in Chronic Conditions Data Warehouse.

[c] Chronic kidney diseases was determined by the corresponding variables in Chronic Conditions Data Warehouse

[d] Including Alzheimer Disease, cataract, chronic obstructive pulmonary disease, glaucoma, hip fracture, depression, osteoporosis, rheumatoid arthritis or osteoarthritis, cancer, anemia, hyperparathyroidism, hypothyroidism, asthma.

[e] Use of other co-medication was defined as filling at least one prescription for these following class of medications: NSAID agent, aldosterone receptor antagonist, anti-platelets agent, anticoagulant, opioids, oral steroids, antidepressants.

[f] hospitalization was defined as those who has any admission date recorded, and also have an inpatient claim associated with it but exclude those with a charge amount for emergency room services provided 6 months prior to the index date

5.0 Discussion

In this study, we examined trends in the rate of initiation of glucose-lowering therapy among Medicare beneficiaries newly diagnosed with T2D. Our study yielded four main findings: First, we observed that only 13.7% of patients newly diagnosed with T2D initiated glucose-lowering therapy within one year of T2D diagnosis. Second, among the initiators, the rate of metformin initiation increased over time, while sulfonylureas initiation decreased. Third, age, female gender, and prior use of medications were associated with an increased likelihood of therapy initiation. In contrast, comorbidities and Black race were associated with decreased risk of therapy initiation. Additionally, age, Black race, and history of chronic kidney disease or CVD were associated with decreased odds of metformin initiation compared to sulfonylureas. Fourth, significant geographic variation exists in the initiation of pharmacotherapy after T2D diagnosis.

To our best knowledge, our study is the first to examine the trends in the rate of initiation of glucose-lowering therapy among Medicare beneficiaries newly diagnosed with T2D. Our findings add to the limited evidence on the rate of initiation of glucose-lowering therapy in older adults newly diagnosed with T2D. We analyzed the rate of initiation among Medicare beneficiaries and found that one-year initiation rate was 13.7%, which is lower than shown in prior work. Previously, Spoelstra et al. assessed the incidence of initiation in a Dutch cohort and found that the one-year cumulative incidence of initiation after diagnosis was 71%[81]. However, their study utilized a highly selective cohort in the general practice setting, with a relatively small sample size. Zhang et al. also explored the time to initiation in the US and reported that the two-year initiation rate was 43% of adults over 65 years old with newly diagnosed T2D[86]. Nevertheless, this work

used electronic medical records, which contained prescriptions ordered by providers and not prescriptions actually filled. The gap between orders of prescriptions and filling rates may explain differences in our estimates. Additionally, it is worth noting that our cohort was from the Medicare beneficiaries, which is the main source of insurance in the US for patients over the age of 65. The lower initiation rates among older adults could also be due to the high prevalence of cardiorenal comorbidities.

ADA has recommended initiation of metformin at the time of T2D diagnosis since 2006[94]. Our study found that, among initiators, the time between diagnosis to initiation decreased over time. This represents an improved awareness of the clinical relevance of early initiation of glucose-lowering therapy. However, our study results suggested that a large proportion of patients remained untreated. This is concerning because hyperglycemia increases the risk for both micro- and macrovascular complications of T2D.

The prescribing trends of glucose-lowering medications observed are consistent with prior literature[95-98]. Particularly, Montvida et al. explored the trends in first-line treatment of T2D and found similar trajectories of increased use of metformin and decreased use of sulfonylureas using the US Centricity Electronic Medical Records 2005-2016[99]. This increase in the proportion of patients initiating metformin after the first T2D diagnosis conforms with the guideline recommendations by ADA[36]. Our study also showed a significant reduction over time in the use of sulfonylureas, which are associated with increased risk of hypoglycemia, CVD, and mortality[55,56]. The steep decrease in sulfonylureas use may reflect a growing recognition by providers that sulfonylureas are associated with substantial risks. A small proportion of patients initiated glucose-lowering agents other than metformin or sulfonylureas. Furthermore, a rise of

other glucose-lowering agents was seen in the later years, suggesting an increased market share of newer classes of glucose-lowering agents such as GLP-1 receptor agonist and SGLT-2 inhibitors.

Our study found that patient characteristics are associated with the initiation of glucose-lowering therapy as well as the selection of drug classes. Many of these patterns seem appropriate and may reflect some amount of patient-centered prescribing. Patients with CVD or chronic kidney disease are less likely to initiate the treatment. Given their medical history and the limited experience with the newer classes of glucose-lowering agents that are more often recommended to be used among patients with these comorbidities (e.g., GLP-1 receptor agonists and SGLT-2 inhibitors), the prescriptions of a glucose-lowering agent were more carefully reviewed by the physicians. Thus, the initiation could be delayed. On the contrary, the use of anti-hypertensive medications and statins was associated with an increased likelihood of glucose-lowering therapy initiation. This is not surprising, as hypertension and dyslipidemia can increase the risk of diabetes-related complications[100,101].

However, there are cases that these glucose-lowering medications were not prescribed accordingly to the patients' characteristics. The increasing age was associated with decreasing odds of initiating sulfonylureas over metformin. The lower cost of and the broad experience with sulfonylureas may be the reasons for the wide use. These findings contradict the recommendations of the American Geriatrics Society's Beers Criteria[102], which recommended against the use of long-acting sulfonylureas in elderly patients due to risks of hypoglycemia. Sulfonylureas are associated with increased CVD risk and mortality, especially for patients with CVD history, but it has been prescribed more in patients with CVD history compared to metformin in our study.

Our analysis also reveals an important relationship between sociodemographic factors and the initiation of a glucose-lowering agent. For example, race/ethnicity was a particularly important

factor associated with non-initiation and drug class selection. After adjusting, Black race was associated with a lower likelihood of initiating a glucose-lowering therapy than White race. Additionally, Black patients had a higher likelihood of initiating sulfonylureas over metformin. This suggests that providers of care for Black patients may be less likely to follow guidelines than those prescribing therapy for White patients and is a testament to racial disparities in access to high-quality diabetes care. We found that the rate of initiation varied across US census regions. This geographic variation persisted after adjustment and was as high as 3-fold across states. These differences could be explained by variations in prescribing behavior. Our study could serve as a preliminary advancement in guiding the combination of individual and region-level factors on diabetes management. Further research is needed to examine the underlying causes regarding the geographic differences.

Our study has several notable strengths. We analyzed data from a nationally representative sample of Medicare Part D beneficiaries, which provides real-world evidence of medication initiation among older US adults. The large sample size and the longitudinal nature of Medicare claims data made it possible to study initiation patterns over time. We included a comprehensive list of baseline covariates, including demographics, clinical characteristics, social factors, and healthcare utilization. Our research contributes to understanding how these variables are associated with the initiation of glucose-lowering therapy in T2D.

However, several limitations should be considered when interpreting the results. Notably, we could not access laboratory or test results such as the HbA1c, eGFR, and body mass index. Some of these are critical indicators and often determine the severity of T2D or associated with the drug selection for initial therapy. Thus, our findings are likely to be subjected to confounding by indication. Though we have identified and collected many covariates, our study did not account

for provider characteristics. Obesity is another diabetes-related condition that might be under-detected in Medicare claims data due to lack of coding. Pharmacy fill data only provide an indirect measure of initiation, and we cannot be certain that patients actually took medications as directed in the prescriptions. Claims data do not capture medications that are filled without insurance coverage, for example, generics obtained through $4 generic programs or samples[103]. Therefore, the rate of initiation might be underestimated. Finally, our cohort only represents Medicare beneficiaries in the US. Thus, our findings have limited generalizability to younger patients.

Using data from nationally representative Medicare populations, we examined the initiation of a glucose-lowering agent among patients with newly diagnosed T2D over the past decade. These findings identify alignments and gaps between guideline recommendations and real-world prescribing practice and expand the limited evidence on early diabetes management in elderly patients. Our study presents a significant opportunity for quality improvement initiatives that address incomplete conformity with the guidelines and optimize the prescribing practice.

Appendix A Definitions for Covariates

Appendix Table 1 Diagnosis Code for Inclusion, Exclusion Criteria and Diabetes Related Conditions

Variable	ICD-9	ICD-10
Inclusion Criteria		
Type 2 Diabetes	250.x0, 250.x2	E11
Exclusion Criteria		
Type 1 Diabetes	250.x1, 250.x3	E10
Gestational diabetes	648.0, 648.8	O24
Secondary diabetes	249	E8, E9, E13
Hemochromatosis	275.01, 275.02, 275.03	E83.11
Acromegaly	253	E22.0
Cystic fibrosis	277.0x	E84

Abbreviation: ICD-9= International Classification of Diseases, Ninth Revision; ICD-10= International Classification of Diseases, Tenth Revision

Appendix Table 2 D Generic Names for Each Class of Glucose-lowering Agents

Drug Class	Generic name and variable value
Biguanides	METFORMIN HCL
Sulfonylureas	GLIMEPIRIDE
	GLYBURIDE
	GLYBURIDE, MICRONIZED
	CHLORPROPAMIDE
	GLIPIZIDE
	TOLBUTAMIDE
	TOLAZAMIDE
	GLYBURIDE/METFORMIN HCL
	GLIPIZIDE/METFORMIN HCL
Thiazolidinediones	PIOGLITAZONE HCL
	ROSIGLITAZONE MALEATE
	PIOGLITAZONE HCL/METFORMIN HCL
	ROSIGLITAZONE/METFORMIN HCL
	ROSIGLITAZONE/GLIMEPIRIDE
	PIOGLITAZONE HCL/GLIMEPIRIDE
DPP-4 Inhibitors	SITAGLIPTIN PHOSPHATE
	SAXAGLIPTIN HCL
	ALOGLIPTIN BENZOATE
	LINAGLIPTIN
	ALOGLIPTIN BENZ/PIOGLITAZONE
	SITAGLIPTIN PHOS/METFORMIN HCL
	LINAGLIPTIN/METFORMIN HCL
	ALOGLIPTIN BENZ/METFORMIN HCL
	SAXAGLIPTIN HCL/METFORMIN HCL
GLP-1 Receptor Agonists	EXENATIDE
	EXENATIDE MICROSPHERES
	ALBIGLUTIDE
	DULAGLUTIDE
	LIRAGLUTIDE
	LIXISENATIDE
SGLT-2 Inhibitors	CANAGLIFLOZIN
	DAPAGLIFLOZIN PROPANEDIOL
	EMPAGLIFLOZIN
	CANAGLIFLOZIN/METFORMIN HCL
	DAPAGLIFLOZIN/METFORMIN HCL
	EMPAGLIFLOZIN/METFORMIN HCL
	EMPAGLIFLOZIN/LINAGLIPTIN
Meglitinides	REPAGLINIDE
	NATEGLINIDE
Alpha-Glucosidase Inhibitors	MIGLITOL
	ACARBOSE
Amylin Analog	PRAMLINTIDE ACETATE
Insulins	INSULIN REGULAR, HUMAN
	INSULIN NPH HUMAN ISOPHANE
	INSULIN LISPRO
	INSULIN GLULISINE
	INSULIN ASPART
	INSULIN DETEMIR
	INSULIN GLARGINE,HUM.REC.ANLOG
	INSULIN GLARGINE,HUM.REC.ANLOG
	INSULIN DEGLUDEC

INSULIN NPH HUM/REG INSULIN HM
INSULIN LISPRO PROTAMIN/LISPRO
INSULIN ASPART PROT/INSULN ASP

Appendix Table 3 List of Co-Medication Classes and their Generic Names

Co-Medication Class	Generic Names
Angiotensin-Converting-Enzyme Inhibitors	BENAZEPRIL HCL','BENAZEPRIL/HYDROCHLOROTHIAZIDE', 'ENALAPRIL MALEATE', 'ENALAPRIL/HYDROCHLOROTHIAZIDE','ENALAPRILAT DIHYDRATE', 'FOSINOPRIL SODIUM', 'FOSINOPRIL/HYDROCHLOROTHIAZIDE', 'PERINDOPRIL ERBUMINE', 'PERINDOPRIL ARG/AMLODIPINE BES', 'QUINAPRIL HCL', 'QUINAPRIL/HYDROCHLOROTHIAZIDE', 'CAPTOPRIL', 'CAPTOPRIL/HYDROCHLOROTHIAZIDE', 'LISINOPRIL', 'LISINOPRIL/ HYDROCHLOROTHIAZIDE', 'RAMIPRIL', 'MOEXIPRIL HCL', 'MOEXIPRIL/HYDROCHLOROTHIAZIDE', 'TRANDOLAPRIL', 'TRANDOLAPRIL/VERAPAMIL HCL',
Angiotensin II Receptor Blockers	AMLODIPINE BES/OLMESARTAN MED', 'AMLODIPINE/VALSARTAN', 'AMLODIPINE/VALSARTAN/HCTHIAZID', 'AZILSARTAN MED/CHLORTHALIDONE', 'AZILSARTAN MEDOXOMIL', 'CANDESARTAN CILEXETIL', 'CANDESARTAN/HYDROCHLOROTHIAZID', 'EPROSARTAN MESYLATE', 'IRBESARTAN', 'IRBESARTAN/HYDROCHLOROTHIAZIDE', 'LOSARTAN POTASSIUM', 'LOSARTAN/HYDROCHLOROTHIAZIDE', 'OLMESARTAN MEDOXOMIL', 'OLMESARTAN/AMLODIPIN/HCTHIAZID', 'OLMESARTAN/HYDROCHLOROTHIAZIDE', 'TELMISARTAN', 'TELMISARTAN/AMLODIPINE', 'TELMISARTAN/HYDROCHLOROTHIAZID', 'VALSARTAN', 'VALSARTAN/HYDROCHLOROTHIAZIDE', 'SACUBITRIL/VALSARTAN'
Diuretics (Loop Diuretics, Thiazide Diuretics, Potassium Sparing Diuretics)	TORSEMIDE','FUROSEMIDE','BUMETANIDE', 'HYDROCHLOROTHIAZIDE','CHLORTHALIDONE','INDAPAMIDE', 'METOLAZONE','METHYCLOTHIAZIDE', 'AMILORIDE HCL','AMILORIDE/HYDROCHLOROTHIAZIDE', 'ETHACRYNIC ACID', 'TRIAMTERENE', 'TRIAMTERENE/HYDROCHLOROTHIAZID', 'SPIRONOLACTONE','SPIRONOLACT/HYDROCHLOROTHIAZID',
Nonsteroidal Anti-Inflammatory Drugs	DICLOFENAC EPOLAMINE','DICLOFENAC POTASSIUM','DICLOFENAC SODIUM','DICLOFENAC', 'SODIUM/MISOPROSTOL','HYDROCODONE/IBUPROFEN','IBUPROFEN','IBUPROFEN/DIPHENHYDRAMINE','IBUPROFEN/FAMOTIDINE', 'IBUPROFEN/OXYCODONE HCL','IBUPROFEN/PSEUDOEPHEDRINE HCL','NAPROXEN', 'NAPROXEN SODIUM', 'NAPROXEN SODIUM/P-EPHED HCL', 'NAPROXEN/ESOMEPRAZOLE MAG', 'KETOPROFEN', 'FENOPROFEN CALCIUM', 'FLURBIPROFEN', 'OXAPROZIN', 'PIROXICAM', 'MELOXICAM','MEFENAMIC ACID','INDOMETHACIN'
Aldosterone Receptor Antagonists	EPLERENONE','SPIRONOLACTONE','SPIRONOLACT/HYDROCHLOROTHIAZID'
Statin	ATORVASTATIN CALCIUM','AMLODIPINE/ATORVASTATIN', 'EZETIMIBE/SIMVASTATIN', 'EZETIMIBE', 'FLUVASTATIN SODIUM','LOVASTATIN', 'PITAVASTATIN MAGNESIUM','PITAVASTATIN CALCIUM','PRAVASTATIN SODIUM', 'ROSUVASTATIN CALCIUM','SIMVASTATIN'
Antiplatelets	ASPIRIN/DIPYRIDAMOLE', 'ANAGRELIDE HCL','CILOSTAZOL', 'CLOPIDOGREL/BISULFATE','DIPYRIDAMOLE',

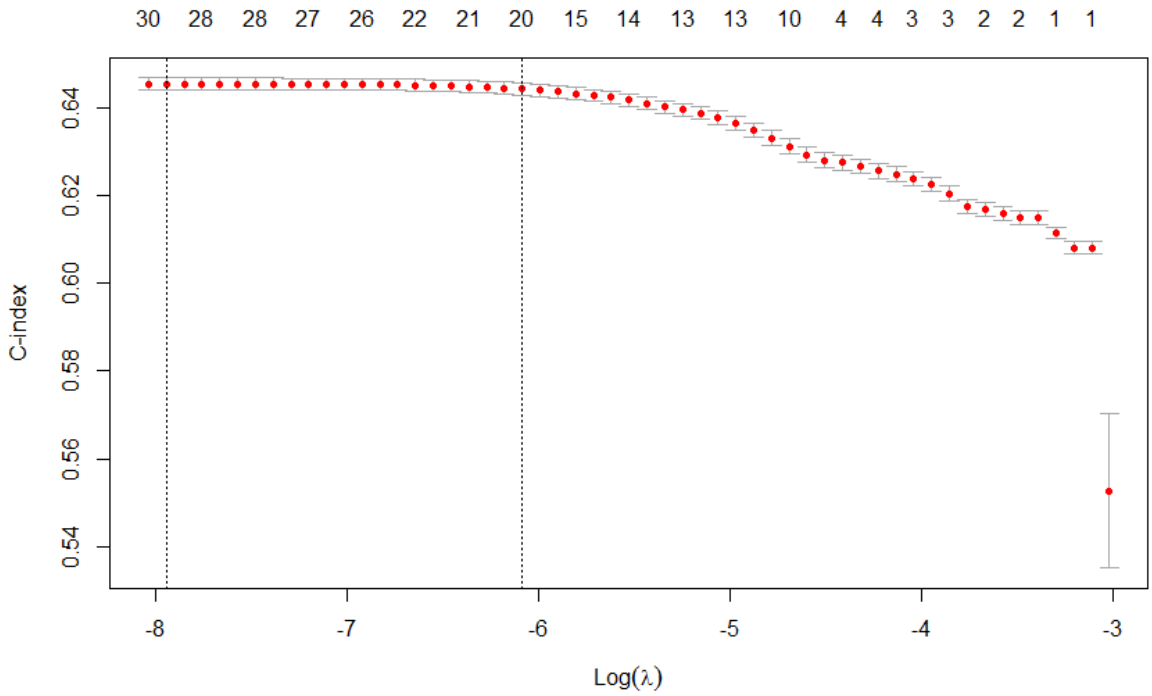
	'PRASUGREL HCL','TICAGRELOR', 'VORAPAXAR SULFATE',
Anticoagulants	APIXABAN','BETRIXABAN MALEATE', 'DALTEPARIN SODIUM, PORCINE','DABIGATRAN','DABIGATRAN ETEXILATE MESYLATE', 'EDOXABAN TOSYLATE','ENOXAPARIN SODIUM','FONDAPARINUX SODIUM', 'HEPARIN SODIUM, PORCINE','HEPARIN SODIUM, PORCINE/PF', 'HEPARIN SOD,PORK IN 0.45% NACL','HEPARIN SODIUM, PORCINE/D5W', 'RIVAROXABAN','WARFARIN SODIUM'
Opioids	BUTORPHANOL TARTRATE','CODEINE SULFATE','CODEINE/BUTALBITAL/ASA/CAFFEIN', 'FENTANYL CITRATE','FENTANYL', 'HYDROCODONE','HYDROCODONE/ACETAMINOPHEN','HYDROCODONE/CHLORPHEN P-STIREX', 'HYDEOCODONE BIT/HOMATROP ME-BR', 'HYDROCODONE/IBUPROFEN','HYDROMORPHONE BITARTRATE', 'MEPERIDINE HCL','MEPERIDINE HCL/PF','METHADONE HCL','MORPHINE SULFATE', 'MORPHINE SULFATE/PH','MORPHINE SULFATE/NALTREXONE', 'OXYCODONE HCL','OXYCODONE HCL/ACETAMINOPHEN','OXYCODONE HCL/ASPIRIN','OXYCODONE MYRISTATE', 'PROMETHAZINE HCL','ASPIRIN/CAFFEIN/DIHYDROCODEINE', 'ACETAMINOPHEN/CAFF/DIHYDROCOD','ACETAMINOPHEN WITH CODEINE','BUTALBIT/ACETAMIN/CAFF/CODEINE','CARISOPRODOL/ASPIRIN/CODEINE'
Oral Steroids	BUDESONIDE','BECLOMETHASONE DIPROPIONATE', 'CORTISONE ACETATE','CICLESONIDE','DEXAMETHASONE', 'HYDROCORTISONE ACETATE','FLUDROCORTISONE ACETATE', 'FLUTICASONE PROPION/SALMETEROL','FLUTICASONE FUROATE','FLUTICASONE PROPIONATE', 'FLUTICASONE/UMECLIDIN/VILANTER','FLUTICASONE/VILANTEROL', 'METHYLPREDNISOLONE ACETATE','METHYLPREDNISOLONE','MOMETASONE/FORMOTEROL', 'PREDNISONE','PREDNISOLONE SODIUM PHOSPHATE','PREDNISOLONE ACETATE','TRIAMCINOLONE ACETONIDE'
Calcium Channel Blockers	AMLODIPINE BESYLATE','AMLODIPINE BESYLATE/BENAZEPRIL','AMLODIPINE BES/OLMESARTAN MED', 'AMLODIPINE BESYLATE/VALSARTAN','AMLODIPINE/VALSARTAN/HCTHIAZID','AMLODIPINE/ATORVASTATIN', 'CLEVIDIPINE','DILTIAZEM HCL','FELODIPINE','ISRADIPINE', 'NICARDIPINE','NIMODIPINE','NIFEDIPINE','NISOLDIPINE','VERAPAMIL HCL'
Beta-Adrenergic Blocking Agents	ACEBUTOLOL','ATENOLOL','ATENOLOL/CHLORTHALIDONE', 'BISOPROLOL FUMARATE','BISOPROLOL/HYDROCHLOROTHIAZIDE', 'BETAXOLOL HCL','CARTEOLOL HCL','CARVEDILOL','CARVEDILOL PHOSPHATE','LABETALOL HCL', 'METOPROLOL SUCCINATE','METOPROLOL SU/HYDROCHLOROTHIAZ','METOPROLOL TARTRATE', 'METOPROLOL/HYDROCHLOROTHIAZIDE','NEBIVOLOL HCL','NEBIVOLOL HCL/VALSARTAN', 'NADOLOL','NADOLOL/BENDROFLUMETHIAZIDE', 'PROPRANOLOL HCL','PROPRANOLOL/HYDROCHLOROTHIAZID','PINDOLOL', 'SOTALOL HCL','TIMOLOL MALEATE','TIMOLOL MALEATE/PF'

Antidepressants	AMITRIPTYLINE HCL','AMITRIPTYLINE/CHLORDIAZEPOXIDE','AMOXAPINE', 'BUPROPION HCL','BUPROPION HBR', 'CITALOPRAM HYDROBROMIDE','CLOMIPRAMINE HCL', 'DESIPRAMINE HCL','DOXEPIN HCL','DULOXETINE HCL','DESVENLAFAXINE','DESVENLAFAXIN SUCCINATE', 'ESCITALOPRAM OXALATE','FLUOXETINE HCL','FLUVOXAMINE MALEATE', 'IMIPRAMINE HCL','IMIPRAMINE PAMOATE','ISOCARBOXAZID', 'LEVOMILNACIPRAN HCL','LURASIDONE HCL', 'MIRTAZAPINE','NEFAZODONE HCL','NORTRIPTYLINE HCL', 'OLANZAPINE','OLANZAPINE/FLUOXETINE HCL', 'PHENELZINE SULFATE','PERPHENAZINE/AMITRIPTYLINE HCL','PROTRIPTYLINE HCL', 'PAROXETINE HCL','PAROXETINE MESYLATE','QUETIAPINE FUMARATE', 'SERTRALINE HCL','SELEGILINE','TRANYLCYPROMINE SULFATE','TRIMIPRAMINE MALEATE',"TRAZODONE HCL', 'VORTIOXETINE HYDROBROMIDE','VILAZODONE HCL','VENLAFAXINE HCL',

Appendix B Results from Regression Models with Feature Selection Methods

Appendix Table 4 Regression Coefficients for The Stepwise and Least Absolute Shrinkage and Selection Operator (LASSO) Selection Process

Variables to Be Selected	Stepwise	LASSO
Age	-0.083	-0.082
Female Gender	-0.116	-0.085
Race		
White	ref	ref
African American	-0.098	-0.031
Others	0.021	NS
Region		
Northeast	ref	ref
Midwest	0.514	0.363
South	0.386	0.244
West	0.305	0.154
Medicaid Eligibility	NS	NS
Metro Resident	-0.259	-0.258
Low-Income Subsidy Recipient	0.184	0.133
Cardiovascular Disease History	-0.160	-0.131
Chronic Kidney Disease History	-0.173	-0.124
Congestive Heart Failure History	NS	NS
Blood Thinner Use	NS	NS
Statin Use	0.159	0.125
Antihypertensive Drug Use	0.210	0.162
No. of Other Comorbidities	-0.148	-0.136
No. of Other Co-Medications	0.066	0.048
Hospitalization	0.063	NS
Top 10% For Patients Out of Pocket Costs	NS	NS
Top 10% For Part D Drug Costs	-0.100	-0.024
Year of Index		
2007	ref	ref
2008	-0.043	-0.004
2009	-0.060	-0.016
2010	0.073	0.008
2011	0.042	NS
2012	0.000	NS
2013	0.010	NS
2014	0.016	NS
2015	0.049	NS
2016	0.097	0.013
2017	-0.025	NS



Appendix Figure 1 Tuning Parameter (λ) Selection in LASSO Selection Process Using 10-Fold Cross-Validation and The Corresponding C-Index

The LASSO selection was performed using 10-fold cross validation. The tuning parameter lambda is chosen by cross validation. When lambda is small, the result is the least squares estimates. Figure shows how the C-index changes accordingly to the tuning parameter λ in the penalized Cox model. The C-index is used to measure the probability of concordance between predicted and observed observations with censored data. If C = 0.5, the prognostic model is a perfectly random prediction. If C = 0 or 1, the model has a perfectly discriminating capability.

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