ROLE OF GLYCEMIC CONTROL IN DEVELOPMENT OF ATRIAL FIBRILLATION IN VETERANS WITH TYPE 2 DIABETES MELLITUS

by

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a well-known risk factor for atrial fibrillation (AF). The role of glycemic control in the development of AF is not clear in these patients. This study was conducted to find the association between glycemic control and AF in patients with T2DM receiving care through the US Veteran's Affairs system.

A case-control study was designed using US Veteran's Affairs data in patients with T2DM receiving care between 2000 and 2014. The study included patients with T2DM as identified by diagnostic criteria or diabetes medication therapy, and with a minimum of two HbA1c values before the index date. Index date was defined as the AF diagnosis date for cases; for control patients, it was +/- 90 days of case's index date. Incidence density sampling was used to select control patients who were matched with cases on diabetes duration and calendar year of T2DM diagnosis. Cases were defined as patients who were diagnosed with AF and controls were defined as patients who were not diagnosed with AF before the time period they were selected as control patients. A prior 12 month period before the index date was used to assess HbA1c values. HbA1C < 7% was defined as controlled glycemia. A logistic regression model was used to find the association between glycemic control and AF in patients with T2DM.

After controlling for confounders, compared to patients who had a mean HbA1c < 7% in the preindex observation period, patients with mean HbA1c 7-9% were 0.94 times

(95% CI 0.90, 0.99; $p = 0.010$), patients with HbA1c 9-11% were 0.95 times (95% CI 0.86, 1.04; $p = 0.261$) and patients with HbA1c > 11% were 0.96 times (95% CI, 0.81, 1.14; $p = 0.642$) as likely to be associated with AF. Numerous comorbidities were also associated with AF including congestive heart failure (OR: 2.29, 95% CI 2.20, 2.38; $p < 0.001$), coronary heart disease (OR: 1.72, 95% CI: 1.67, 1.78; $p < 0.001$), hypertension (OR: 2.03, 95% CI 1.96, 2.10; $p < 0.001$), myocardial infarction (OR: 1.97, 95% CI 1.80, 2.16; $p < 0.001$), left ventricular hypertrophy (OR: 1.51, 95% CI 1.38, 1.65; $p < 0.001$), and chronic kidney disease (OR: 1.14, 95% CI 1.09, 1.18; $p < 0.001$). We conclude that glycemic control is not associated with AF in patients with T2DM.

This dissertation is dedicated to my family especially my brother, Mayank Singhal, who trusted me more than I did myself.

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CHAPTER 1

INTRODUCTION

Atrial Fibrillation

Atrial fibrillation (AF) is a common cardiac rhythm disorder (arrhythmia) with increasing incidence and prevalence.[1,2] In 2010, prevalence of AF in the United States was estimated to be 5.2 million,[3] and it is expected to increase to 12.1 million by 2050.[2] The annual economic burden associated with AF in the United States is approximately $7.7 billion (reported in 2011 dollars) including hospitalization, outpatient care, and medication costs.[4]

AF is associated with irregular atrial electrical activity and disorganized atrial contraction that eventually leads to disruption in atrial blood flow. The major complications associated with AF are stroke and heart failure. In AF, when the atria do not fully pump blood to the ventricles, residual blood pools and forms a clot (thrombus). A stroke can occur when the thrombus breaks loose and travels distally (embolus), causing an arterial obstruction. Thus, antithrombotic drugs such as aspirin and warfarin are recommended for stroke prevention in AF.[5,6]

AF is classified into three types: paroxysmal, persistent, and permanent.[5,6] Paroxysmal AF is a temporary irregularity in heart rhythm that lasts less than one week. Persistent AF lasts longer than one week and may cease due to medical intervention or on

its own. In permanent AF, normal sinus rhythm cannot be restored through drug treatment. The repeated occurrence of both persistent and paroxysmal AF leads to permanent AF, which is characterized by an irregularity in heart rhythm lasting more than 1 year.[5,6] Symptoms of AF include palpitations, shortness of breath, weakness, chest pain, dizziness or fainting, fatigue, and confusion. AF can be asymptomatic before diagnosis. In the Framingham study, 24% of patients had a stroke as their first symptom of AF.[7] Paroxysmal AF is less frequent and often asymptomatic compared to permanent AF; 90% of paroxysmal AF cases are asymptomatic.[7,8] In order to detect AF in the early stages, screening through electrocardiogram (ECG) can be a helpful approach. According to a study, patients with systematic screening are more likely to be diagnosed with AF compared to routine practice.[9]

The most common AF risk factors are advanced age, being male, being White and comorbidities including high blood pressure, heart failure, coronary heart disease (CHD), rheumatic heart disease, mitral valve prolapse, pericarditis, congenital heart defects, sick sinus syndrome, surgery, hyperthyroidism, obesity, lung disease, and diabetes.[10]

Diabetes mellitus is one of the most common concomitant diseases in patients with AF.[11] Evidence from population-based studies[12-14] suggest that there may be an independent association between Type 2 diabetes mellitus (T2DM) and AF.[12] Some common risk factors for both diseases include increasing age, obesity, high blood pressure, atherosclerosis, nonalcoholic fatty liver disease, increased pulse pressure, and sleep apnea.[15,16] Several theories exist regarding the link between T2DM and AF:

1) Elevated blood glucose has been associated with cardiac conduction abnormalities, which can lead to AF.[17,18]

2) Impaired glucose tolerance has been shown to affect the thickness of the atrium and ventricle size, which can lead to the development of AF.[19]
3) Elevated C-reactive protein (C-RP) and interleukin (IL)-6, markers of inflammation, are also linked to both diseases.[20-22]

A description of links between hyperglycemia, impaired glucose tolerance, and inflammation are described in Figure 1 and the pathophysiology section below.

Type 2 Diabetes Mellitus

Diabetes affects 29.1 million people in the United States and T2DM is the most common form, constituting 90-95% of the overall population with diabetes.[1,2,23] Diabetes is currently the seventh leading cause of death in the United States and the mortality rate is found to be higher for patients with cardiovascular diseases including myocardial infarction (MI), CHD, and congestive heart failure (CHF).[24-26]

Diabetes is a metabolic disorder caused by inadequate secretion of insulin and/or receptor insensitivity to endogenous insulin, leading to hyperglycemia.[27] Glycemic control is important in reducing microvascular complications in patients with T2DM.[28] Glycated hemoglobin (HbA1c) is the most commonly used test for measuring longitudinal glycemic control.[29] A target HbA1c of <7% is considered appropriate for most patients with T2DM. A less strict HbA1c target is chosen for certain patients such as those with shorter life expectancy, severe hypoglycemia, advanced micro/macro vascular complications or comorbidities, and at risk elderly, dementia patients, or young children.[30]

Pharmacologic management of T2DM includes the use of metformin as first line therapy; however, T2DM often requires combination therapy, including insulin due to a

persistent reduction of insulin secretion from Beta cells.[31] Other medications include glucagon-like peptide-1 (GLP-1) agonists (exenatide, liraglutide), sulphonylureas (glipizide, glyburide), and thiazolidinediones (TZDs) (pioglitazone) (See Appendix A).

Pathophysiologic Links Between Glycemic Control, Inflammation, and AF in Patients with T2DM

Hyperglycemia has been associated with cardiac conduction abnormalities in T2DM. Autonomic neuropathy, damage to the autonomic nerves in both sympathetic and parasympathetic neurons, is commonly seen in patients with diabetes mellitus.[32,33] A correlation between autonomic neuropathy and QT interval prolongation has also been noted. Studies have further proposed an association between QT interval prolongation and increased mortality, ventricular arrhythmia, and sudden cardiac death. [34,35] Also, there is a higher prevalence of A-V block, which can cause conduction abnormalities in patients with T2DM compared to patients without diabetes.[36] These links between T2DM and cardiac conduction abnormalities may explain in part the association between T2DM and AF.

The association between impaired glucose tolerance with atrium thickness and ventricular hypertrophy is known. Studies have found greater thickness in the left atrium epicardial adipose tissue and left atrial pericardial adipose tissue in patients with persistent AF compared to those with paroxysmal AF.[37,38] An accumulation of epicardial adipose tissue and pericardial adipose tissue in the cardiac region has been documented in patients with T2DM as well.[39,40] The proportional relationship between T2DM and left ventricle (LV) mass has been demonstrated in many studies and similarly, a number of studies have shown that impaired glucose tolerance has an effect on left ventricular mass.[19,41,42] An

increased thickness of LV has been associated with some cardiovascular diseases including CHDs, congestive heart disease, stroke, and transient ischemic attack.[43] The thickness of the myocardium is altered with the accumulation of adipocytes and can lead to disturbances in atrial conduction. The change in conduction due to a thickening of myocardium may explain the association between T2DM and AF.[18,44]

AF and T2DM are linked by the presence of inflammatory markers such as C-RP and IL-6.[20-22] Studies have also suggested that the pathologic process of DM may be due to an inflammatory response.[21,45,46] Elevated C-RP is commonly observed in patients with T2DM[47] and has been found to directly correlate with HbA1c values.[48] In a multivariable logistic adjusted model, increased C-RP was observed in patients with high HbA1c values (OR 1.20 for each 1-unit increase in HbA1c, 95% CI 1.07-1.34).[48] The likelihood of having an elevated C-RP level (> 0.30 mg/dl) was more pronounced for patients with HbA1c > 9.0% (OR 2.15, 95% CI 1.07-4.32 and > 11.0% (4.40, 1.87-10.38).[48] Studies have found increased C-RP and IL-6 along with marked inflammatory infiltrates in atrial biopsies of patients with AF.[21,46] In one study, serum C-RP concentrations were two times greater in AF than in a control group without atrial arrhythmia.[45]

Theory of Antidiabetes Drugs with Anti-inflammatory Properties (ADAIP) and Inflammation

Based on the evidence of inflammation in the development of AF and increased glucose level, it can be hypothesized that antidiabetes drugs with anti-inflammatory properties (ADAIP), metformin, and TZDs,[49,50] can decrease the likelihood of developing AF in T2DM patients. Chang et al. found that metformin lowered the risk of AF in patients

with T2DM compared to patients who were not using any other antidiabetes (AD) medication.[49,51] TZDs also independently lowered the risk of AF in a population with T2DM.[50]

Metformin has shown anti-inflammatory (AI) effects by inhibiting proinflammatory responses in smooth muscle cells and endothelial cells. It has also been found to prevent secretion of the proinflammatory cytokines IL-6 and IL-8.[52] Studies have suggested that metformin lowers inflammatory markers such as macrophage migration inhibitory factor, C-RP, soluble intercellular adhesion molecule, and vascular adhesion molecule-1 in plasma.[53-55] AF is also considered an inflammatory disease due to elevated inflammatory biomarkers.[21] In a previous study, metformin lowered the risk of AF in patients with T2DM.[51] Thus, inflammatory properties of metformin may potentially affect AF risk.

TZDs have AI properties that may favorably affect the risk of AF in patients with T2DM.[56] TZDs work as ligands to the peroxisome proliferator-activator receptor γ (PPAR γ), which inhibits production of cytokines such as tumor necrosis factor α (TNF-α), IL-2, -6, -8, matrix metalloproteinases (MMPs), and other inflammatory mediators in diabetic and non-diabetic patients.[57,58,59] Increased C-RP and IL-6 have been demonstrated in patients with AF.[21]

Other Drugs with Anti-inflammatory (AI) Properties

Due to the possible involvement of inflammation in the etiology of AF, it is important to consider any drug with AI properties. Cardio-protective drugs, including statins, fibrates, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II

receptor blockers (ARBs) have been shown to have AI effects.[60-62] Statins are commonly used to lower low-density lipoprotein (LDL) cholesterol and are recommended for patients with cardiovascular diseases including those with T2DM. The American Diabetes Association (ADA) suggests the use of statins in T2DM patients with elevated LDL (> 100 mg/dl).[63] Statin therapy significantly reduces C-RP.[64,65] Fibrates are prescribed to lower triglyceride levels in patients with atherosclerosis and dyslipidemia and affect the expression of genes that give rise to inflammatory cytokines.[66] Angiotensin II receptors play a major role in blood pressure and fluid metabolism. This receptor also has proinflammatory effects on the vascular system. The angiotensin I (AT1) receptor is activated by the angiotensin II receptor in hypertension, which causes secretion of pro inflammatory substances, especially cytokines and aldosterone.[67] ACE-Is and ARBs are also commonly used in patients with T2DM for their cardiovascular and renal protective effects. ARBs have been shown to reverse inflammatory effects in animal studies.[68] Also, ARBs exert AI effects on the peripheral vasculature.[69] Similarly, ACE-Is are widely used in hypertension and following MI and also possess AI effects.[70]

Other commonly used medications with AI properties include corticosteroids, polyunsaturated fatty acids (PUFA), and nonsteroidal anti-inflammatory drugs (NSAIDs). Acute and chronic use of corticosteroids has been shown to reduce C-RP levels and also decrease AF recurrence.[71,72] PUFA, including omega-3 fatty acids (commonly called fish oil), are well known for their inflammatory properties.[73-75] Studies have shown reduction in the risk of AF with the use of PUFA.[76,77] NSAIDs are widely used to treat pain and a variety of inflammatory conditions. Recent studies have shown an increased risk of AF with the use of NSAIDs.[78-80] Adverse renal effects associated with NSAIDs, including

blood pressure destabilization, fluid retention, and electrolyte disturbance may increase risk of AF.[78,79]

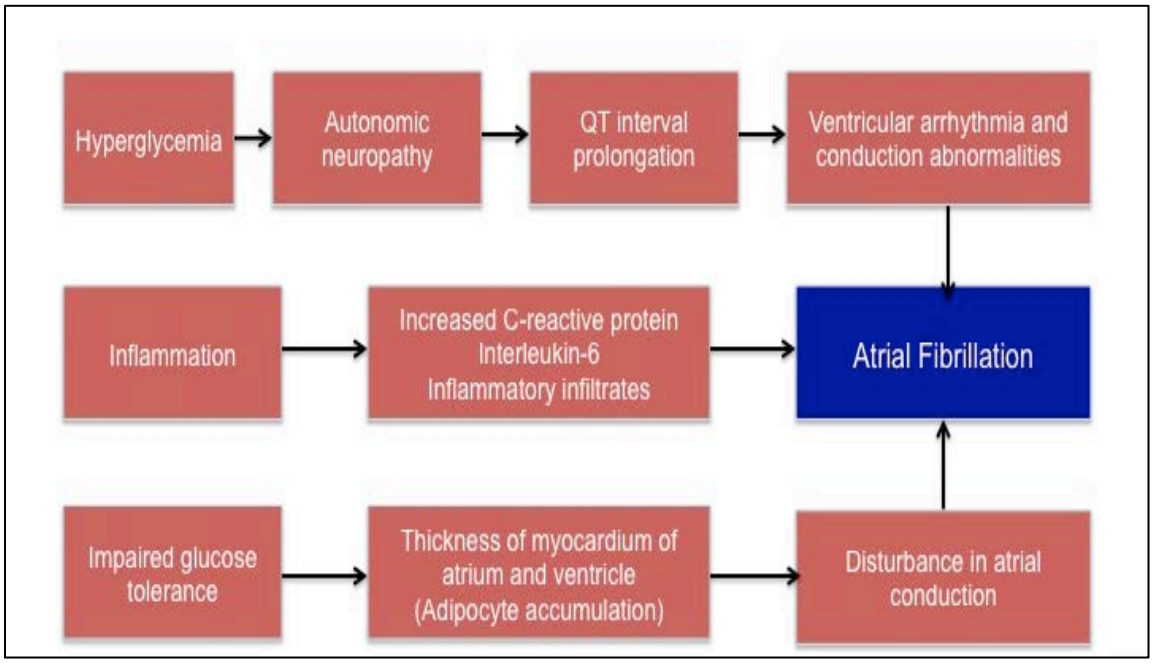

Figure 1. Effect of glycemic control and inflammation on pathophysiology of AF.

CHAPTER 2

LITERATURE REVIEW

Glycemic Control and AF in T2DM Patients

Dublin et al.[81] conducted a population-based case-control study aimed at describing the association between diabetes and AF. The secondary goal was to describe the association of AF with glycemic control and diabetes duration. A database in this study was initially prepared to conduct four studies with a shared control group and previous studies examined hormone replacement therapy and antihypertensive medications. Therefore, the study population was restricted to post- and perimenopausal women, and men with pharmacologically-treated hypertension. The analysis included people aged 30-84 with at least four visits to a group health (GH) plan. Patients were excluded if they had a pacemaker or missing data on BMI. AF cases were identified from the electronic health records between October 1, 2001 and December 31, 2004. Diabetes was considered present if a physician diagnosis was recorded in the medical record and classified as pharmacologically treated for those receiving antidiabetic medications. Multivariate regression was used to calculate odds ratios for the risk of AF associated with controlled versus uncontrolled glycemic level adjusting for age, sex, calendar year, treated hypertension, and BMI.

The study identified 1,410 cases and 2,203 controls. Patients with an average

HbA1c > 7% in the preindex period were more likely to develop AF.[81] Compared to patients without diabetes, the odds of AF increased with worsening glycemic control: OR 1.06 (95% CI 0.74, 1.51) for HbA1c ≤ 7%, OR 1.48 (95% CI 1.09, 2.01) for HbA1c 7%-≤ 8%, OR 1.46 (95% CI 1.02, 2.08) for HbA1c 8-≤ 9, and OR 1.96 (95% CI 1.22, 3.14) for HbA1c > 9%. Compared to patients without diabetes, the risk for AF also increased with duration of diabetes, ≤ 5 years (OR 1.07 [95% CI 0.75, 1.51]), > 5-≤ 10 years (OR 1.51 [95% CI 1.05, 2.16]), and > 10 years (OR 1.64 [95% CI 1.22, 2.20]).

The study has limitations including a narrowly defined population (post- and perimenopausal women and hypertensive men).[81] In addition, patients with diabetes, who likely were evaluated more frequently which increases the likelihood of detecting AF, were compared to patients without diabetes. Also, generalizing results from 2001-2004 to current populations may not be appropriate as there have been many improvements in technologies for the detection of AF and in diabetes management.[82,83,84]

Huxley et al[85] conducted a prospective cohort study to determine the risk of AF in patients with diabetes compared to unaffected patients and to examine the relationship between disease severity markers (fasting serum glucose [FSG], fasting insulin, and HbA1c) and AF incidence. Patients were categorized into three categories (based on FSG, HbA1c, AD drug history, and physician diagnosis codes): 1) patients with diabetes, 2) patients with prediabetes, 3) patients without diabetes. The study included White or African American individuals between the ages of 45 and 64 years. Information on educational level, income, cigarette smoking, and use of antihypertensive and AD drugs was obtained from questionnaires. The age-adjusted method was used to calculate AF incidence in all groups. The models were adjusted for age, study site, income, education, prevalent CHD,

BMI, systolic blood pressure, antihypertensive medications, and smoking. A sensitivity analysis was conducted after excluding patients with prevalent CHD. Restricted cubic spline was used to find the association between glycemic control and AF risk. After confirming the linearity of diabetes markers and AF, a Cox Proportional Hazards model was used to find the association between AF and measures such as FSG, HbA1c level, and fasting insulin.

In total, 13,025 patients were identified, including 33.7% without diabetes, 51.4% with prediabetes, and 14.9% with diabetes. A total of 1,311 AF cases were diagnosed during a mean 14.5 years of follow-up. Compared to unaffected patients, those with diabetes were 35% more likely to develop AF (HR 1.35 [95% CI 1.14, 1.60]). In patients with diabetes, for each 1% increase in HbA1c, the risk of AF increased by 13% (HR 1.13 [95% CI 1.07, 1.20]). After excluding patients with prevalent CHD (n = 642), the result was unchanged. (HR 1.14; $p < 0.001$) The duration of diabetes was also positively associated with increased risk of AF – 25% [95% CI 1% to 56%] in patients who self-reported diabetes of < 5 years and 58% [95% CI 17% to 113%]) in patients with self-reported diabetes > 10 years. ($p < 0.001$).

The study conducted by Huxley et al.[85] concluded that there was a higher risk of AF in patients with diabetes compared to patients without diabetes. Potential limitations include the fact that only patients aged 45-64 years, and non-White and non-African Americans were excluded, which limits generalizability. In addition, some variables including educational level, income, cigarette smoking, and use of antihypertensive and AD drugs were obtained through a questionnaire, which introduces the possibility of recall bias. Finally, only 14.9% of study patients had diabetes, and there were limited variables

used for adjustment in the multivariate regression model. Two studies have found that there is a relationship between AI drugs to both diabetes[86] and AF.[70] Therefore, it is important to adjust the model for drugs with AI properties since they are both associated with both T2DM and AF.

Fatemi et al.[87] prospectively examined the outcome of incident AF in relation to glycemic control in patients with diabetes using data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.[88] Subjects were required to be AF-free at baseline and to have had either cardiovascular disease or an age between 55 and 79 years with anatomic evidence of atherosclerosis, albuminuria, left ventricular hypertrophy (LVH), or ≥ 2 additional cardiovascular risk factors (dyslipidemia, hypertension, current smoking status, or obesity). Patients were randomly assigned to intensive care targeting HbA1c < 6 % and standard therapy targeting HbA1c 7-7.9%.

In total, 10,082 patients were included with a median follow-up of 4.68 years. AF incidence was 5.9 vs. 6.4 per 1,000 patient-years in the intensive and standard therapy groups, respectively (p = 0.52). Age, weight, diastolic blood pressure, heart rate, and previous heart failure predicted AF in patients with diabetes. Patients who developed AF were at increased risk of morbidity and mortality (nonfatal MI, stroke, or cardiovascular death HR 2.40 [95%CI 1.71-3.36]; all-cause mortality HR 2.65 [95% CI 1.81-3.86]; and cardiovascular mortality HR 3.76 [95%CI 2.34-6.05]). The authors concluded that there is no relationship between glycemic control and incidence of AF.

This study may have included AF patients in the baseline cohort because no information regarding cardioversion or techniques used to control rhythm was available. Information on anticoagulants was not available and patients at high stroke risk and those

with AF at baseline may have been included, biasing the results toward the null hypothesis. The study only compared patients with HbA1c < 6% vs. 7-7.9%, and included sicker patients (35% had previous cardiovascular events), which limited generalizability. The study was also not powered to detect differences in morbidity and mortality. Unlike the other studies, this study showed no association between glycemic control and AF.

ADAIP and AF

Metformin and AF

Chang et al.[51] conducted a retrospective cohort study using the Taiwan National Health Research Institute (NHRI) Longitudinal Cohort of Diabetes Patients Database (LHDB) to assess whether metformin may prevent new onset of AF in patients with T2DM.[51] Cox proportional hazard models were used to report hazards ratios and incidence rates for metformin-exposed and unexposed populations.

The mean followup duration was 5.4 years. The mean age (SD) of the metformin users was 57.0 (14.8) and was 58.6 (17.1) years for nonusers. There were 49.8% males in nonusers and 48.2% in metformin users. Metformin users had more hypertension diagnosis (63.4% vs. 53.7%) and were on antihypertensive (70.8% vs. 61.6%) and statins medications (37.5% vs. 17.9%). The study followed 645,710 patients for 13 years and 9,983 patients developed AF (incidence rate 1.5% [287 per 100,000 person-years]). The AF incidence rate was lower in metformin users (245 per 100,000 person-years) vs. nonusers (293 per 100,000 person-years) $p < 0.001$. After adjusting for comorbidities including age, sex, hypertension, CHF, CKD, asthma, MI, ischemic stroke, peripheral arterial diseases, antihypertensive drugs, and statins, metformin users were 19% less likely

to develop AF than nonuser groups (HR 0.81, 95% CI 0.76-0.86, $p < 0.001$).

As the study was conducted in the Taiwanese population, the results may not be generalizable to other populations. The study included only those using metformin monotherapy, which possibly limited patients to the early stage of T2DM. Moreover, the comparison group was non-AD users, which does not reflect a real world scenario. Lack of HbA1c values limited the researcher's ability to examine the effect of varying levels of glycemic control on the incidence of AF.

TZDs and AF

Chao et al.[50] conducted a population-based cohort study using the Taiwan National Health Insurance Research Database (NHIRD). The primary goal of the study was to evaluate the effect of TZDs on AF in patients with T2DM. The study population consisted of patients diagnosed with T2DM in Taiwanese hospitals from 2000-2007. The study used a 2-tailed *t*-test, a Mann-Whitney rank sum test for normal and skewed variables, and a chi-square for testing categorical variables. A Cox Proportional Hazards model was used and event free survival was plotted in survival curves.

The study included 12,065 patients with T2DM including 4,137 TZD users and 7,928 non-TZD users. The mean age (SD) of TZD users was 53.7 (12) and 54.1(12.2) for nonusers. There were 52.9% and 53.6% males in TZD and non-TZD groups, respectively. TZD users had fewer comorbidities including hypertension (38.1% vs. 44.5%), coronary artery disease (16.9% vs. 18.4%), chronic renal disease (6.3% vs. 7.3%), and CHF (4.1% vs. 4.7%). The distribution of AD drugs was similar across the groups except alpha-glucosidase inhibitors (40.4% vs. 20.7%). The incidence of AF in the TZD group was lower

than non-TZD users (1.2% vs. 1.8%; *p* value = 0.008). After multivariable analysis adjusted for demographics and comorbidities, patients TZD users were 31% less likely to have AF than non-TZD users (HR 0.69, 95% CI 0.49-0.91, *p* value = 0.028).

The results may not be generalizable to non-Taiwanese populations. The study included only patients receiving prescription of rosiglitazone; therefore, association of pioglitazone was not assessed. Information on smoking status and BMI was not available to be included in the adjusted analysis.

Other AI Drugs and AF

In addition to ADAIP, there are few other drugs with AI properties that can potentially affect the association between glycemic control and AF. As explained in the role of inflammation in AF and glycemic control, other drugs with AI properties can act as confounders affecting the association of glycemic control and AF. A number of studies have established an association between glycemic control and inflammation biomarker – C-RP (C-RP).[89-92] Studies of AF associated with exposure to drugs with AI properties are described below.

A meta-analysis conducted by Ozaydin[70] examined the association between statins, PUFAs, corticosteroids, angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) and the risk of AF. The authors concluded that ACEi and ARBs were associated with a decreased risk of AF. However, these results conflict with previous studies.[93-96] The demonstrated association between statins and AF also conflicted with other studies.[97-100]

A large prospective cohort study evaluating the association between AF incidence

and NSAID use concluded that current NSAID use increased the risk of AF by 76% compared to those who never used NSAIDs (HR 1.76, 95% CI 1.07-2.88) during a mean of 12.9 years of follow-up.[101] The study included 8,423 patients with a mean (SD) age of 68.5 (8.7) years. A Cox proportional hazards model was used to find the association between NSAIDs and incidence of AF. The study adjusted the model for age, sex, and other variables including left ventricular end-diastolic dimension, systolic blood pressure (SBP), diastolic blood pressure (DBP), MI, and diabetes. The study concluded that the use of NSAIDs increases the risk of AF. The study did not collect information on any other drugs with AI properties. Lack of this information could change the findings in this study.

A large case-control study was conducted by Schmidt et al.[80] on 2,925 cases and 21,871 controls matched on age and sex. The study used conditional logistic regression to examine the association between the use of NSAIDs or selective cyclo-oxygenase (COX) 2 inhibitors and AF. The study used risk set sampling to capture controls. Age and sex were used to match cases and controls. Exposure to NSAIDs at the time of admission was defined as new users and patient use before that period was defined as recent users. Patients who used NSAIDs were at a 33% increased risk of developing AF and a 50% increased risk if they used COX-2 inhibitors compared to patients with no drugs (OR 1.33, 95% CI 1.26, 1.41). The study concluded that NSAIDs could increase the risk of AF. Therefore, AF should be added as a risk factor in cardiovascular comorbidities when prescribing NSAIDs.

Prescription records were used to extract drug exposure information. However, some over-the-counter drugs, including ibuprofen, may have been overlooked. This misclassification bias could have moved the effect estimate towards the null. The study did

not include smoking and BMI information. Therefore, the effect estimates were not adjusted for smoking and BMI. Moreover, the study included only NSAIDs and COX 2 inhibitors. There were a few other drugs with AI properties not captured in the studies including PUFAs and corticosteroids. These drugs may have an effect on the risk of AF.

Gap Summary

In summary, a number of studies have studied the association of diabetes with risk of AF and found diabetes to be a significant independent risk factor for AF. The level of glycemic control in patients with T2DM is not commonly studied. Many limitations exist in the studies where glycemic control and the association with AF were studied. Data on the effect of NSAIDs is more consistent, showing an increased incidence of AF. However, there is little data on other drugs with AI properties. We addressed the limitations of the previous studies as follows:

1) Studies conducted earlier had their limitations (as discussed above) such as poor external validity caused by limited age group[85] or ethnicity,[85] focusing exclusively on hypertensive and perimenopausal women,[81] or on patients with high cardiovascular related comorbidities.[87] The current study included a national representative dataset – electronic medical record (EMR) data from the US Department of Veteran Affairs (VA), aiming to address the aforementioned limitations. However, the VA data also has generalizability issues because of its overrepresentation of males in the veteran population.
2) Studies have also found contradictory results for the association between level of glycemic control and risk of AF.[81,85,87] It is necessary to find the relationship using

more robust data, such as the national VA population. A study with a large sample size should produce a more reliable result. The VA data provide a relatively larger sample size and, in addition, provide long-term follow-up records in the dataset, which enables researchers to extract the history and previous prescription information.

3) None of the previous studies was designed to understand the effect of short-term or immediate glycemic control on the incidence of AF in patients with T2DM. Therefore, this study was highly focused on finding the association of immediate glycemic control vs long-term and AF in contrast to the previous studies.
4) Inflammation is involved in both glycemic control and AF. None of the previous studies controlled for drugs with AI properties that can potentially affect both the variables, when assessing the association between level of glycemic control in patients with T2DM and AF, which could have led to confounding bias. The current study controls for a range of drugs with AI properties to reduce the risk of confounding.
5) The incidence of AF in T2DM in VA patients overall has not been reported in the literature. Thus, study reports AF incidence rates in the VA population.

This study used a case-control study design with patients treated in the VA to examine the relationship between glycemic control and AF in patients with T2DM. In addition, the study reported the use of ADAIP in the population and its association with the development of AF in patients with T2DM. We also conducted an additional analysis to report incidence rates of AF in overall and T2DM cohorts.

Objectives

The first objective of this dissertation was to establish incidence rates of AF in the overall veteran population and then report incidence rates of AF in veterans with and without T2DM. Secondly, a case-control study was designed to quantify the relationship between glycemic control and the likelihood of developing AF in veterans with T2DM. The final objective was to examine the influence of ADAIP on the likelihood of developing AF in veterans with T2DM.

Specific Aims

1) Quantify the incidence rate of AF in the veteran affairs population from 2000-2014.
    a. Report crude incidence rate of AF during 14-years of follow-up in three separate cohorts – all veterans, veterans with T2DM, and veterans without T2DM.
    b. Compare incidence rates of AF between patients with and without T2DM.
    c. Report incidence rates of AF in all three cohorts separately, in high-risk subsets such as older and male veterans.

    Hypothesis: The crude incidence rate of AF will be higher in patients with T2DM compared to patients without diabetes. Also, the incidence rate of AF will be higher in males and older veterans.
2) Determine if glycemic control during the previous 12 months is associated with developing AF in veterans with T2DM.

    Hypothesis: Patients with AF will be more likely to have uncontrolled glycemia in the preceding 12 months compared to patients without AF.

3) Examine the influence of being prescribed ADAIP and developing AF in VA patients with T2DM.
    a. Calculate the odds of developing AF in patients with T2DM who were and were not prescribed with ADAIP in the previous 12 months.
    b. Determine the role of glycemic control in the relationship between ADAIP and AF.

Hypothesis: Being prescribed ADAIP will lower the odds of developing AF in patients with T2DM and where glycemic control is not a confounder, but a mediating variable in the association between ADAIP and AF.

CHAPTER 3

METHODS

Study Design and Timeline

We conducted descriptive, historical cohort, and case-control studies using data from patients receiving care in the VA health system. The dataset used in this study was from 2000-2014.

For Objective 1, a cohort study design was used to calculate incidence rates for AF in the overall veteran population receiving routine care in the VA system between 2000 and 2014. Incidence rates of AF were reported separately, in the T2DM and non-T2DM populations.

For Objective 2, a case-control study design was used to estimate the relationship between AF and exposure to inadequate glycemic control over the prior 12 months with glycemic control defined as HbA1C < 7.0%. All patients with a diagnosis of T2DM in the VA system were considered eligible for inclusion in the study.

A case-control study design was used to address Objective 3. In this objective, we measured the association between ADAIP and AF and we examined the role of glycemic control in this association. The study was conducted on the T2DM population receiving care in the VA setting from 2000 to 2014. We used a 12 month period to capture baseline information, HbA1c values to estimate glycemic control, and ADAIP use. The study was

approved by the VA and University of Utah Institutional Review Boards. A schematic of the study design is outlined in Figure 2.

Data Collection and Data Source

The Department of VA is the largest integrated health system in the United States. The VA electronic health record (EHR) contains data on over 20 million patients across the US. Veterans Health Information Systems and Technology Architecture (VistA) captures all aspects of patient EHR information for the VA nationwide. Utilization records include pharmacy, inpatient, outpatient, and laboratory encounters; eligibility data includes demographics; and clinical data includes vital signs, laboratory results, radiology reports, etc. The records are linkable to death records with scrambled social security numbers (SCRSSN).

We used data from several VA datasets, hosted in the Veterans INformatics and Computing Infrastructure (VINCI) environment. VINCI is an initiative to improve researchers' access to VA data and to facilitate the analysis of that data while ensuring veterans' privacy and data security. VINCI is a partner with the VA's Corporate Data Warehouse (CDW) and hosts all data available through CDW. Researchers received data for this study in VINCI along with the tools for reporting and analysis in a secure workspace. The requested components of the dataset were:

1) SCRSSN of patients in a VA system (cohort)
2) Corporate data warehouse (CDW): CDW contains electronic health records of patients. CDW dataset was used to extract demographics, vital signs, and pharmacy fill data.
3) Medical statistical analysis system (MEDSAS): Inpatient and outpatient encounters

were extracted from MEDSAS datasets. Diagnosis of AF and other co-morbidities was collected from outpatient and inpatients diagnosis files from MEDSAS.

4) Decision support system (DSS): DSS was used to extract lab data from the VA system including lipid values. Also, primary exposure – HbA1c values, were captured from the DSS data file.

Strengths of the VA Data

The VA dataset includes information from the integrated health systems that include VA hospitals and clinics. These data provide both clinical parameters and utilization records of veterans in the United States. In this study, we are using clinical variables such as HbA1c and drug use as primary exposures. The utilization data such as pharmacy fill records provide information on prescriptions filled by patients. Unlike prescription orders, pharmacy fill data reflect medication adherence of patients whereas prescription orders are limited to physician's prescribing behavior. As a result, using prescription orders as a measure of medication use can introduce information bias in the study. Thus, pharmacy-dispensing data in the VA records minimize the information bias as seen in other electronic medical records (EMRs).

The other advantage of using the VA dataset is its larger population and longer duration of patient follow-up relative to other US datasets. We were interested in identifying newly diagnosed T2DM patients as a source population and then incident cases of AF. Furthermore, patients with T2DM with a longer duration of diabetes are at a greater risk of developing AF than shorter follow-up.[81] Therefore, a longer follow-up of patients and larger sample size would help to capture enough patients to conduct analyses.

Along with these strengths, the VA dataset has some limitations. First, the VA is a predominantly male population, which limits the generalizability of the dataset to the US population. In our study, over 95% of patients were male versus 49.6% in the entire US population.

A majority of the study population is older than 65 years, which makes this population eligible to receive benefits from Medicare as well as the VA. We believe that we may underestimate medication use in this population. If a patient is filling medication from an external source through Medicare Part D eligibility, this patient may not have a record in the VA pharmacy dataset.

Selection of the Study Cohort

Population to be Studied

The study used patients receiving care in the VA system between 2000 and 2014. To capture AF incidence rates in the overall population, an entire VA dataset was used. For the other two objectives, patients diagnosed with T2DM between 2001 and 2013 were used to capture cases and controls. The study population of all three objectives is explained in detail below.

Objective 1

Separate cohorts were created to report the overall incidence rate of AF or atrial flutter in all patients, patients with T2DM, and patients without T2DM.

An overall cohort of patients regardless of T2DM status

To report the incidence rate of AF or atrial flutter in the national cohort of veterans, all patients enrolled in the VA system receiving routine care, defined by two encounters within 12 to 24 months of each other, between 2000 and 2014, were used. AF or atrial flutter incidences were identified based on ICD-9 codes.

The index date of patients in the overall cohort was defined as the second encounter – 12 to 24 months after the first encounter in the observation period in a national VA EMR dataset. Patients were required to have 12 months or more of EMR activity before the index date. EMR activity was defined as any inpatient or outpatient encounter in the VA system. Eligible patients were drawn from the entire population of VA users. Inclusion criteria were the following.

1) Patients with at least two VA encounters within the interval of 12-24 months between 2000 and 2014.
2) Age $\geq$ 18 years on the index date.
3) With EMR activity of at least 12 months before the index date.

Exclusion criteria were the following.

1) Patients with AF diagnosis before the index date were excluded.
2) Any patient using anticoagulant or antiarrhythmic drugs for a longer period can have a potential AF diagnosis. Thus, patients using these medications for > 28 days in the 12 months before the index date were excluded from the study.

A Cohort of Patients With T2DM

Patients with newly diagnosed T2DM were identified from the national cohort of VA users described previously. The following criteria were used to identify newly T2DM diagnosed patients:

1) T2DM patients were identified by any of the three criteria: 1) ICD-9 code for T2DM, 2) HbA1c ≥ 6.5%, 3) AD medication use.
2) EMR activity in the 12 months before the T2DM diagnosis date.
3) Patients with no AD drug use in the 12 months prior to the T2DM diagnosis date were included.
4) In order to prevent misclassification of T1DM patients in the T2DM cohort, patients with only insulin use and no other AD medication use in the 12 months prior to T2DM diagnosis were assumed to be T1DM patients and hence excluded from the study population.

After identifying the cohort of patients with newly diagnosed T2DM, the following criteria were applied to select study cohort.

1) Age ≥ 18 years on T2DM diagnosis date.
2) Patients with one or more encounters after T2DM diagnosis date were included.
3) Patients with a diagnosis of AF or atrial flutter in the 12-month period before T2DM diagnosis were excluded.
4) Patients with > 28-days of anticoagulants or antiarrhythmic drugs use in the 12-month period before the T2DM diagnosis date were assumed to have AF and therefore were excluded.

A Cohort of Patients Without T2DM

This cohort included the population that was used in the overall cohort mentioned above. The index date was defined as the 2nd activity in the VA system within 12-24 months after the first activity during the observation period. Because this cohort was used to calculate incidence rates of AF in the non-T2DM cohort, patients were censored when they developed T2DM during the follow-up. In other words, these patients contributed their person-time in the cohort until they developed T2DM. Patients were also censored if we lost them in follow-up or if they developed an outcome of interest. In addition to the inclusion and exclusion criteria described above in the overall population, patients who developed T2DM on the second encounter (index-date) were excluded from the study.

Objectives 2 and 3

Selection of the Case Group

The identified cohort included patients in the VA system initially diagnosed with T2DM between 2001 and 2014. T2DM diagnosis was identified by at least one ICD-9 code or at least one HbA1c > 6.5% or at least one prescription for AD medications (Appendix A) in the observation period. 12 months of EHR activity in the database, defined by inpatient or outpatient encounters, prior to the first diagnosis of T2DM were used to identify newly diagnosed patients. The prior 12 month period was used to confirm no AD drugs use. (Figure 2)

For cases, the index date was defined as the date of first AF diagnosis between January 1, 2002 and December 31, 2014. The baseline period was defined as 12 months prior to the index date, to identify any treatment or medication in patients with diabetes.

Co-morbidities, defined by ICD-9 codes, were captured for all patients during the baseline period. (Appendix B)

Patients were followed backward in time for 12 months from the index date to identify HbA1c values and medication use, including ADAIP. Other covariates were captured in the same time frame as discussed below.

Inclusion criteria

1) At least one ICD-9 code diagnosis of AF (427.31) or atrial flutter (427.32) between January 1, 2002 and December 1, 2014.
2) Diagnosed with AF/atrial flutter 12+ months after T2DM diagnosis.
3) Age ≥ 18 years on the index date.
4) 12 + months EMR activity prior to initial T2DM diagnosis.
5) No diabetes medication use in the 12 months prior to initial T2DM diagnosis.
6) Patients with a minimum of two HbA1c values with a gap of at least 90 days between readings in the 12 months before the index date.

Exclusion criteria

1) AF diagnosis before the first diagnosis for T2DM.
2) T1DM diagnosis only.
3) Patients with only insulin use and no T2DM diagnosis and no oral AD drug use.
4) With > 28-day supply of anticoagulants or antiarrhythmic drugs use in the 12 months prior to the index date.

Selection of the Control Group

Controls were selected based on incidence density (risk-set) sampling:

1) Control patients were selected from the same source population from which cases were selected.
2) Control patients were selected, independent of exposure status, to approximate the source population exposure distribution.
3) Every patient was eligible to be selected as a control patient before developing AF.
4) Every patient had a varying risk of developing AF at different time of follow-up so a control patient was eligible to be selected multiple times.
5) Sampling of control patients was conducted based on the predefined risk factors.
6) Duration of T2DM and calendar year of T2DM diagnosis were used to define risk factors and, therefore, used to match cases with controls.

The index date for control patients was defined as an inpatient or outpatient encounter in the VA facility within +/- 90 days of the case's index date.

Inclusion criteria

1) With 12+ months EMR activity before T2DM diagnosis.
2) No diabetes drug use in the 12 months prior to T2DM diagnosis.
3) Without AF diagnosis (427.31) or atrial flutter (427.32) in inpatient or outpatient setting – identified based on ICD-9 codes within 12 months of T2DM diagnosis.
4) Age $\geq$ 18 years on the index date.
5) Minimum of 2 HbA1c values with a difference of at least 90 days between readings in the 12 months prior to the index date.

Exclusion criteria

1) AF diagnosis before the index date.
2) T1DM diagnosis only.
3) Patients with only insulin use and no T2DM diagnosis and no oral AD drug use in 12 months.
4) Patients with > 28 days of anticoagulation drug or antiarrhythmic drug use in the 12 months prior to the index date.

Matching

Duration of diabetes was used as a surrogate for disease severity and was also used as patient's contribution to risk in the study. Cases and controls were matched based on the duration of diabetes. Duration of diabetes was the time between T2DM diagnosis date and the index dates for both cases and controls. We used a window of 2 months to match controls with cases.

In addition, calendar year of T2DM diagnosis was used to match cases and controls. Due to changes in treatment patterns from 2001 to 2014, matching patients on calendar year of diagnosis of T2DM helped to select controls with similar treatment patterns.

Sampling Ratio

In case-control studies, there is more likelihood of selection bias in estimating the effect estimate than with cohort studies. During sampling, a loss in statistical precision is expected in the estimation of odds ratios. Having more than 1 control for each case can minimize this loss in precision and maximize power of case-control studies and the

probability of selecting more random controls reduces selection bias. Thus, we used 4 controls for each case in our study; cases/control sets with fewer than 4 matched controls were not included.

Outcome Variable

AF or atrial flutter, identified by ICD-9 codes (ICD-9 427.31, 427.32), were the dependent variable(s) for all three objectives.

For Objective 1, the incidence rates of AF were reported in the overall VA cohort and T2DM and non-T2DM cohorts. A patient who was lost in follow-up or diagnosed with AF was censored. Patients in the non-T2DM cohort developing T2DM prior to AF diagnosis were also censored. For the other objectives, the study outcome was a new AF (ICD-9 427.31) or atrial flutter (ICD-9 427.32) diagnosis in patients with T2DM.

Independent Variables

Objective 1

AF incidence rates were stratified by age (< 65, 65-69, 70-74, 75-79, 75-79, 80-84, ≥ 85 years), and sex in the overall, T2DM, and non-T2DM populations.

Objectives 2 and 3

The primary independent variable in Objective 2 was HbA1c, which measures glycemic control over the previous 3 months. Patients were required to have a minimum of two HbA1c values in the 12 months prior to the index date with a gap of at least 90 days between all measures.

The first HbA1c value was chosen as the closest HbA1c value to the index date (-305-days/+30-days). The second HbA1c value was selected as 90 or more days prior to the first HbA1c values. Similarly, a 90-day gap was considered to capture prior HbA1c readings. With this definition of a gap of 90 days or more, a patient can have a maximum of 4 HbA1c values in a 12-month period. Any HbA1c values between 90-day intervals were ignored. However, additional variables were created – number of HbA1c readings, average HbA1c through a year – to capture all the HbA1c readings.

We assumed that each HbA1c value represents the average blood glucose exposure over the prior 3 months.[102] The ADA recommends HbA1c < 7% in most patients to reduce microvascular complications of diabetes and maintaining this range immediately after T2DM diagnosis is helpful in reducing long term macrovascular complications.[31] Therefore, we classified patients into two Hb1c categories as recommended by the ADA[30,103-105] HbA1c < 7%, defined as controlled, and HbA1c ≥ 7%. Patients were required to have two to four HbA1c values in a year. We used the following definitions of controlled glycemia:

1) Patients with all HbA1c values < 7% were defined as controlled. Uncontrolled glycemia was subcategorized as HbA1c 7% to < 9%, 9% to < 11% and ≥ 11%. Patients with one or more HbA1c between 7 and < 9 were categorized in 7% to < 9%, patients with HbA1c value between > 9 and < 11 were categorized as 9% to 11% and patients with one or more HbA1c value ≥ 11% were categorized into the > 11% category. If a patient fell into two or more categories, the highest HbA1c value was considered to classify the patient.
2) Patients with the weighted arithmetic mean value of all the past available HbA1c values

in the prior 12 months < 7% were defined as controlled. Uncontrolled glycemia was subcategorized as 7% to < 9%, 9% to < 11%, and ≥ 11% based on the arithmetic mean.

3) Patients with the last measured HbA1c < 7% defined as controlled. Uncontrolled glycemia was subcategorized as 7% to < 9%, 9% to < 11%, and ≥ 11% based on the last measured HbA1c.

For the secondary analysis, the association between having AF/atrial flutter and AD exposure to drugs with AI properties, including metformin and TZDs, was examined. We assumed that patients took the drugs as documented by days of supply per dispensing data. A dummy variable was created to identify patients as ADAIP users in the same dataset as described above. A patient with a > 28-day prescription of metformin or TZDs was classified as a user and those with a ≤ 28-day prescriptions were considered as nonusers.

Covariates

For Objective 1, included covariates were age, sex, and race.

Demographics, Vital Signs and Clinical Variables

The included demographic variables for Objectives 2 and 3 were mean age and age categorized as < 65, 65-69, 70-74, 75-79, 75-79, 80-84, ≥ 85 years; sex; race; and geographic region. Age was the difference in years between date of birth and index-date. Weight and height were captured to calculate body mass index (BMI). No time limit was applied to capture height, and a 90-day window from 12 months prior to the index date was used to capture weight. The mean (SD) of BMI was reported and the proportion was categorized into five categories: < 25 kg/m2, 25-30 kg/m2, 30 to < 35 kg/m2, 35 to < 40

kg/m2 and ≥ 40 kg/m2.

Other clinical variables included SBP and DBP, a -90/+30-day window from 12 months prior to the index date was used to capture blood pressures. SBP was reported as mean (SD) and was also categorized as < 130 mmHg and ≥ 130 mmHg. For DBP, mean (SD) was reported and was categorized as < 80 mmHg and ≥ 80 mmHg. For baseline low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), values measured in the 12-month preindex period were used. Mean (SD) was reported for all lipid values. HDL-C was also subcategorized as < 40mg/dL and ≥ 40 mg/dL, LDL-C as < 100 mg/dL and ≥ 100 mg/dL and TG as < 150 mg/dL and ≥ 150 mg/dL.

The total mean (SD) and median (IQR) number of HbA1c values (not limited to four HbA1c values) in the baseline period were reported. The average days of gap between each HbA1c reading in the baseline period were recorded. The study also captured HbA1c values beyond baseline period. Four years prior to the baseline period were used to collect information on all HbA1c values. A mean (SD) HbA1c was captured for every year, in all four years prior to the baseline period.

A mean (SD) and median (IQR) number of office visits in the 12 months before the index date were also captured. The office visits were categorized as 1-5, 6-10, 11-15, 16-20, and > 20.

Medication Use

Diabetes medication use in the past 12 months from the index date were captured based on dispensing data. These medications include metformin, sulphonylurea, TZDs,

DPP-4, GLP-1RA, insulin and other AD drugs such as alpha-glucosidase inhibitor, meglinitinide analogue and pramlintide. Drugs with AI properties including statins,[100,106] fibrates,[100,107] ACE inhibitors,[108,109] ARBs,[110,111] corticosteroids,[112,113] poly unsaturated fatty acids (PUFA) and NSAIDs[80,114] were also captured because they have effects on glycemic control and AF.

Comorbidities

Comorbidities were identified by ICD 9 codes and assessed with two different timelines – at the baseline period and documented any time before the index date. These comorbidities include CHD, cerebrovascular disease, CHF, hypertension, dyslipidemia, stroke, MI, LVH, chronic kidney disease (CKD), retinopathy and neuropathy, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), hypoglycemic events and nonalcoholic liver disease.

Severity Index

All comorbidities were identified based on ICD-9 codes listed in Appendix B. There are several comorbidity indices used in the literature to measure the intensity of a patient's health condition, including the Charlson comorbidity index (CCI), Elixhauser index (EHI), and the diabetes complication severity index (DCSI). The Charlson comorbidity index includes comorbidities that occurred in narrowly defined clinical trial populations, which restricts it to a few comorbidities.[115] The Elixhauser index includes a much broader list of diseases.[116] Moreover, the scale is tested on a large administrative dataset similar to the national data proposed for this study. In a predictive study, the

Elixhauser scale performed better than the Charlson comorbidity index.[117] The DCSI is a scale developed for diabetes-specific patients and has been validated as a good predictor of hospitalization and mortality in patients with diabetes.[118] Therefore, we considered the DCSI as the preferred scale to measure comorbid complications in diabetes patients. A list of included comorbidities is attached in Appendix C. The DCSI includes additional diseases that are related to diabetes.[116] Baseline diabetes treatments were recorded and described by diabetes drug class (Appendix C). Anti-diabetes drugs were used to adjust the multivariable regression model.

Sensitivity Analysis

Previous studies[81,85] have shown that poor glycemic control increases the risk of developing AF. Thus, a sensitivity analysis was conducted to evaluate different HbA1c cut-off values as controlled vs. uncontrolled. According to the ADA, a different cut-off is recommended for selective populations such as patients with limited life expectancies, very young children, and older adults or individuals with more comorbidities.[31] Thus, we defined controlled and uncontrolled patients based on HbA1c values as 8% and 9% instead of 7%. We reported the association with these 2 cut off values.

Statistical Analysis

All statistical analyses for this study were conducted using SAS 9.2 (SAS institute, Cary, NC). A level of significance of 5% was used to reject the null hypotheses. No adjustments were made for multiple comparisons.

Objective 1

Descriptive statistics were used to report the demographic characteristics and baseline clinical characteristics between the T2DM and non-T2DM cohort. The population was compared using student's *t*-tests and Chi-square tests. The statistical analyses were done using SAS 9.2 (SAS institute, Cary, NC). A level of significance of 5% was used to reject the null hypothesis.

Incidence rates of AF were reported in cases/person-year. Incidence rates were calculated overall and in the subset of patients with T2DM. Incidence rate of AF = Number of new AF cases/Total time experienced for the subjects followed defined as sum of all the time contributed by each patient in the cohort.

Objective 2

Means (SD) were used to report continuous data and frequencies were reported for categorical data. Student's *t*-test for continuous variables and chi-square for categorical data were used to report the significant differences at the baseline period. A conditional logistic regression analysis was conducted to calculate the likelihood of developing AF by glycemic control (controlled vs. uncontrolled diabetes). The potential confounders assessed were age, BMI, race, medication use, DCSI, LVH and other comorbidities. The statistical analyses were done using SAS 9.2 (SAS institute, Cary, NC). 5% was used as a level of significance. No adjustments were made for multiple comparisons.

A number of variables including SBP, DBP, and lipid values were excluded from the regression model due to the possibility of significant collinearity with hypertension and dyslipidemia diagnoses, respectively. Likewise, diseases included in DCSI were also

excluded from the regression model such as cerebrovascular diseases, stroke, and retinopathy and neuropathy. In order to use an entire population in the regression model, missing observations were placed in a "missing" category rather than excluding patients missing these data from the regression analyses. To test the variance explained by the model, R squared (R^2) was used to compare different regression models.

The following covariates were used to control the regression model: Age, sex, race, region, BMI, DCSI, diabetes medications, statins, fibrates, ACE or ARBs, NSAIDs, PUFA, corticosteroids, number of visits in 12 months of the index date, number of HbA1c counts, average number of days between all HbA1c values, and comorbidities such as CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, and smoking.

Objective 3

Descriptive statistics were performed using a student's *t*-test for continuous variables and chi-square for categorical data at the baseline period. Total number of ADAIP users were captured in cases and control patients. Multivariable conditional logistic regression was used to predict the odds of developing AF with ADAIP group compared to non-ADAIP group. The odds ratio was used to report the effect estimate between drugs and AF.

In order to identify the role of glycemic control of ADAIP and AF, we conducted a mediation analysis. We used the following conditions to identify an intermediary variable:

- Exposure is correlated with outcome.

- Exposure is correlated with mediator.
- Mediator is correlated with outcome.
- Mediator is correlated with outcome, controlling for exposure and confounders.

If each criterion was met, we considered that glycemic control mediates the effect of ADAIP and AF. While predicting outcome through mediator and controlling for a mediator, we included confounders that can potentially affect the association of mediator and outcome.

As a result, we controlled our regression model for age, sex, race, region, BMI, diabetes medications (sulphonylurea, DPP-4, GLP-1RA, insulin, and other oral AD drugs), statins, fibrates, ACE or ARBs, NSAIDs, PUFA, and corticosteroids and comorbidities such as CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, and smoking.

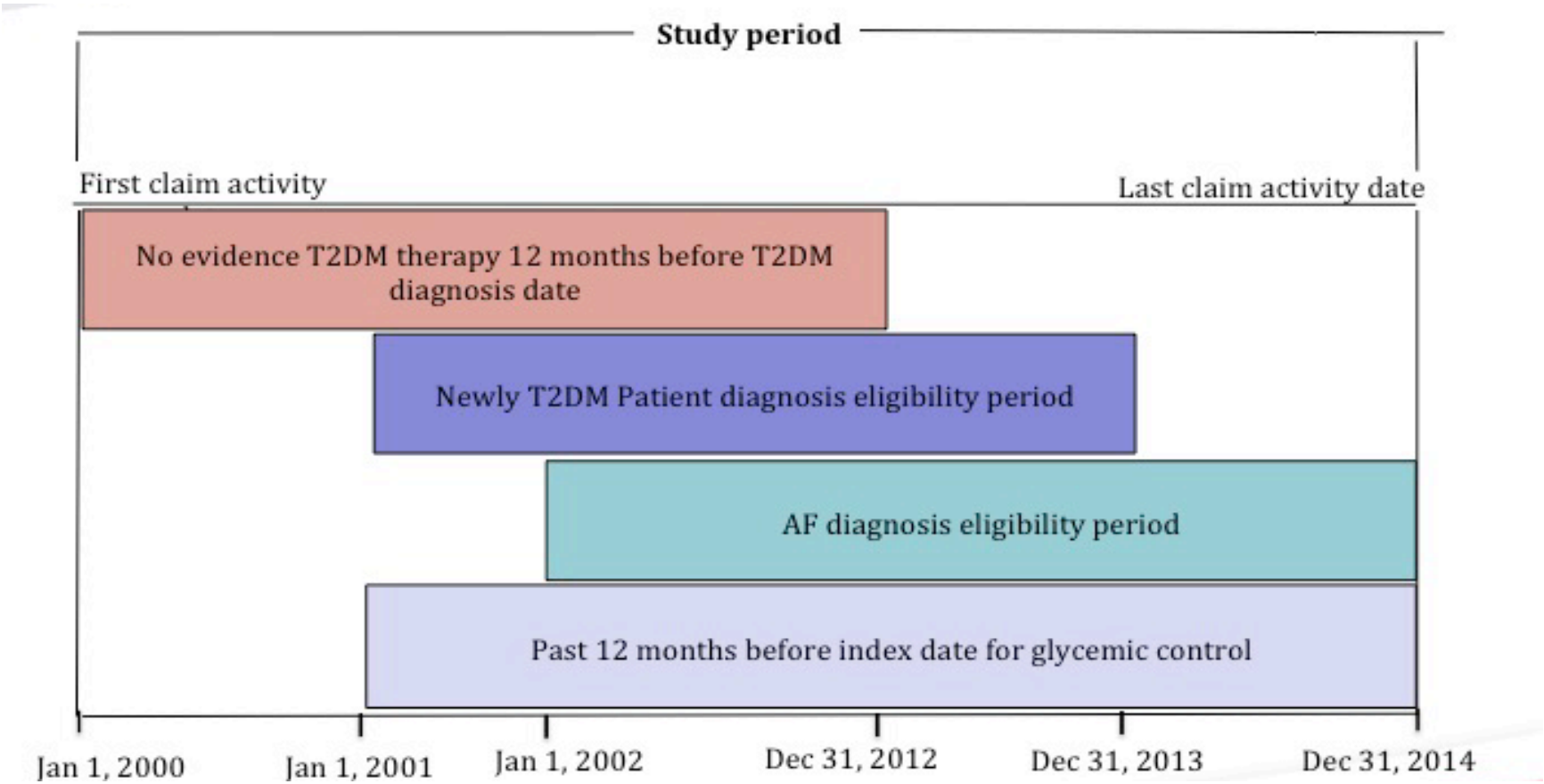

Figure 2. Study design and timeline.

CHAPTER 4

RESULTS

Objective 1

The results of this section describe incidence rates in the overall cohort, and for patients with T2DM and patients without T2DM. This section also reports the incidence rate of AF categorized by age and sex in all the aforementioned cohorts.

A total of 12.7 million patients received care in the VA network between 2000 and 2014. After applying inclusion and exclusion criteria (Figure 3), there were 7,007,752 patients with a minimum of two inpatient or outpatient encounters between 2001 and 2014. In patients with T2DM and without T2DM, the total number was 1,602,696 and 6,987,311, respectively.

Table 1 outlines the baseline demographics of the included population. Patients with T2DM were slightly older than patients without T2DM. The mean age (SD) of an overall cohort was 58.8 (16.1) years, for patients with T2DM it was 63.9 (11.7) years, and for patients without T2DM it was 58.7 (16.1) years, ($p < 0.001$). Of patients with T2DM, 54.3% patients were younger than 65 years compared to patients without T2DM (61.0%) ($p < 0.001$). Of patients with T2DM, 95.9% were male vs. 90.8% in non-T2DM patients. In the overall population, 64.2% were White and 12.7% were African American. The percentage of Whites and African Americans was higher in the T2DM cohort (69.0%

and 15.3%) vs. non-T2DM cohort (64.2% and 12.7%) ($p < 0.001$). However, race information was missing in 10.0% of T2DM cohort vs. 18.0% in non-T2DM cohort.

Incidence Rates of AF in Overall Cohort, T2DM Cohort, and Non-T2DM Cohort

After following the entire cohort, 554,014 patients were diagnosed with AF over a total follow-up of 50,014,922 patient years, as explained in Table 2. The incidence rate of AF in the entire cohort was calculated as 11.07 AF cases per 1,000 patient-years. The incidence rate of AF in patients with T2DM was higher compared to patients without T2DM. In patients with T2DM, 124,131 AF diagnoses occurred over 9,532,798 patient-years for an incidence rate of 13.02 cases per 1,000 patient-years. Similarly, in patients without T2DM 451,639 patients were captured with AF diagnosis over 42,053,329 years for an incidence rate of 10.73 AF cases per 1,000 patient-years.

Incidence Rates of AF in Overall Population and Stratified by T2DM Population Categorized by Age and Sex.

As outlined in Table 3, we reported incidence rates of AF in six age categories: < 65 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years and ≥ 85 years. There was a consistent increase in AF incidence rates with age in the overall cohort. For patients aged < 65, the incidence rate in cases per 1,000 person-years was 5.8 rising to 32.8 in patients aged ≥ 85.

In the cohort of patients with T2DM, a similar trend in AF rates by age groups was observed (Table 3). Patients who were younger than 65 years of age had 8.26 AF cases per

1,000 person-year whereas incidence rates of AF in other groups were 15.0 for aged 65-69 years, 18.3 for 70-74 years, 22.4 for 75-79 years, 26.4 for 80-84 years and 33.4 for ≥ 85 years. (Reported in cases per 1,000 person-year)

The same trend with age was observed in patients without T2DM. The incidence rates per 1,000 person-years in patients without T2DM were as follows: 5.31 for < 65 years, 14.7 for 65-69 years, 19.0 for 70-74 years, 23.7 for 75-79 years, 27.5 for 80-84 years, and 33.0 for ≥ 85 years.

When comparing incidence rates of AF in patients with T2DM and without T2DM categorized by age, we found that for patients with T2DM the incidence rate was higher in the T2DM cohort except for the < 65 years group. The incidence rate of AF per 1000 patient years by age for the T2DM cohort vs. the non-T2DM cohort was 8.2 vs. 5.3 for age < 65 years, 15.0 vs. 14.7 for 65-69 years, 18.3 vs. 18.9 for 70-74 years, 22.4 vs. 23.7 for 75-79 years, 26.4 vs. 27.5 for 80-84 years, and 33.4 vs. 33.0 for 85 years and older group (per 1,000 person-year).

The incidence rates were also reported by sex (Table 4). Females had lower incidence rates compared to males in all three groups. For males in the all-patients cohort, the incidence rate of AF was 11.8 AF cases per 1,000 person-year vs. 2.7 cases per 1000 person-year in females. Similarly, in patients with T2DM, there was an incidence rate of 13.3 AF cases per 1,000 person-year in males compared to females with 5.4 cases per 1,000 person-year. In male patients without T2DM, incidence rates were 11.6 AF cases per 1,000 person-year whereas the incidence rate in female patients without T2DM was 2.5 AF cases per 1,000 person-year.

Objective 2

The result of this section describes the association between glycemic control and AF in patients with T2DM.

Demographics and Vital Signs

There were 2.9 million patients identified with T2DM between 2001 and 2014; after applying inclusion and exclusion criteria, 1.75 million newly diagnosed patients with T2DM were selected as possible cases and controls (Figure 4). Of these, 189,095 patients were included (Figure 5) of which 37,819 cases were matched to 151,276 controls (4:1 matching). The baseline characteristics of cases and controls are detailed in Table 5. The mean age (SD) of the overall group was 67.1 (10.4) years and 96.5% were males.

The mean age (SD) of the patients with AF (cases) was 71.1 (9.7) years, and the cohort was predominantly male (98.2%). The mean age of the population with no AF (controls) was 66.1 (10.4) years, with and 96.1% were male ($p < 0.001$ for both). There was a substantial difference between races for cases and controls. As seen in Table 5, a majority of each cohort was White (80.1% for cases and 72.4% for controls), followed by African American (10.3 vs. 17.3% for cases and controls, respectively, $p < 0.001$). A majority of the population was from the Midwest, constituting 31.7% in cases and 32.4% in controls, and the lowest population was observed in the East region (12.6% and 12.0%, $p < 0.001$).

The mean (SD) BMI for cases and controls was 32.0 (7.1) kg/m2 for cases and 32.2 (6.5) kg/m2 for controls ($p < 0.001$). A greater proportion of patients with BMI 25-30 kg/m2 was observed in cases with $n = 10,808$ (28.6%) whereas, for controls, the highest

proportion of patients was seen as n = 46,317 (30.6%) in the BMI group of 30 -< 35 kg/m2 ($p < 0.001$).

Cases had a mean (SD) SBP of 127.4 (18.6) vs. 130.7 (16.3) for controls. ($p < 0.001$) The proportion with SBP ≤ 130 mmHg in cases was 54.9% whereas in controls, 40.9% of the cohort had SBP ≤ 130 mmHg ($p < 0.001$). Cases and controls had a mean (SD) DBP of 70.5 (11.7) mmHg and 73.5 (10.8), respectively. In cases, a proportion of patients with DBP < 80 mmHg were 76.8% and in controls, it was 59.7% ($p < 0.001$). The missing SBP and DBP values were high for controls (15.2% vs. 1.0%) (All p-value < 0.001).

The mean (SD) HbA1c (%) of 2-4 HbA1c values for the past 1-year was 7.2 (1.3) and the median (IQR) was 6.9 (6.3-7.8) for cases with a mean (SD) of 7.3 (1.4) and median (IQR) of 7 (6.3-8.0) for controls ($p < 0.001$).

Controls had significantly higher mean (SD) lipid values compared to cases including HDL-C at 41.1 (12.4) mg/dL vs. 39.9 (12.3) mg/dL, LDL-C as 80.5 (29.4) mg/dL vs. 86.8 (30.8) mg/dL, and triglycerides as 172.3 (137.3) mg/dL vs. 162.9 (125.9) mg/dL, respectively. ($p < 0.001$ for all) The percentage of patients with baseline HDL-C with ≤ 40 mg/dL was 48.2% for cases, and 46.4% for controls. The percentage of patients in cases and controls with LDL-C ≥ 100 mg/dL was 16.6% and 23.0%, respectively. Cases who had baseline triglyceride level ≥ 150 mg/dL was 35.8% and it was 39.9% for controls (All $p < 0.001$).

Both groups had a similar proportion of patients who smoked. The number of cases who smoked was 14,171 (37.5%) versus 56,856 (37.6%) for controls. ($p = 0.683$)

Diabetes duration was used to match both cases and controls. The mean (SD) diabetes

duration for the groups was 5.4 (2.8) years and 5.4 (2.8) years, respectively ($p = 0.540$). The proportion of patients was highest in the category of 5-10 years diabetes duration for cases (47.7%) than for controls (47.6%) (p = 0.918).

Patients with AF tended to have a greater number of visits during the 1-year observation period, with a mean (SD) of 16.7 (18.9) and median (IQR) of 12 (6-21) compared to patients with no AF with a mean (SD) of 10.9 (11.8) and median (IQR) of 8 (4-14) ($p < 0.001$). 26.2% of the cases and 12.6% of the controls had more than 20 visits ($p < 0.001$).

The proportion of cases with hypertension was 33,158 (87.7%) followed by CHD with 19,181 (50.7%), COPD with 10,766 (28.5%), retinopathy and neuropathy with 9,547 (25.2%), dyslipidemia with 8,283 (21.9%), and CHF with 8,111 (21.4%). For the controls, a lower rate of comorbidities before the index date was observed for hypertension with 109,250 (72.2%) followed by CHD with 38,044 (25.1%), dyslipidemia with 29,958 (19.8%), retinopathy and neuropathy with 15,568(18.7%), and COPD with 23,598 (15.6). The mean (SD) score for DCSI was higher for cases at 3.1 (3.3) versus controls at 1.58 (2.3). The proportion of patients with DCSI score of 5 and more was significantly higher for patients in cases (25.9% vs 9.6%) (All $p < 0.001$).

Use of metformin (43.0% vs. 51.1%; $p < 0.001$) and sulfonylurea (38.8% vs 38.7%; $p = 0899$) was lower in cases than controls, respectively. Insulin use was higher in cases compared to controls (32.8% vs 30.2%; $p < 0.001$). Use of TZD, DPP-4, and GLP-1RA were similar in both the groups. There was a higher use of statins (74.7% vs. 72.3%), ACE or ARBS (73.2% vs. 69.9%), NSAIDs (45.5% vs. 43.4%) and corticosteroid (24.5 vs. 17.2%) in cases versus controls ($p < 0.001$). Fibrates use was lower in cases than controls

(8.7% vs. 9.6%; $p < 0.001$).

Multivariable Regression Analyses

Uncontrolled Glycemia Defined as Minimum 1 HbA1c value ≥ 7%

The logistic regression model (Table 6) that was used to assess the association between AF and glycemic control was adjusted for baseline age, sex, race, region, BMI, CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, smoking, DCSI, diabetes medication use, statins, fibrates, ACE or ARBSs, NSAIDs, PUFA, corticosteroids, number of visits, number of HbA1c counts and average gap in between HbA1c values. Relative to patients who had HbA1c < 7% in prior 12 months of AF diagnosis, patients with HbA1c 7-9%, 9-11% and > 11% were 1.04 (95% CI 1.01, 1.09; $p = 0.030$), 1.08 (95% CI 1.01, 1.17; $p = 0.031$) and 1.24 (95% CI, 1.10, 1.38; $p < 0.001$) times as likely to be associated with AF, controlling for covariates.

Demographics including age, sex, race, and region were significantly associated with AF. Increase in age was directly associated with AF. Compared to patients who were younger than 65 years, patients aged 65-69 years were 1.53 times more likely to have AF (95% CI 1.26, 1.85; $p < 0.001$). Likewise, patients age 70-74 years were 2.26 times more likely to have AF (95% CI, 1.79, 2.84; $p < 0.001$), 75-79 years was 3.13 times (95% CI, 2.44, 4.01; $p < 0.001$), 80-84 years was 3.17 times (95% CI, 2.41, 4.16; $p < 0.001$), and ≥ 85 years was 2.47 times (95% CI 1.79, 3.42; $p < 0.001$). As compared to females, males were 1.57 times as likely to develop AF (95% CI, 1.44, 1.71; $p < 0.001$). African Americans were 0.58 times as likely to be associated with AF compared to Whites (95% CI 0.56, 0.60;

$p < 0.001$). When compared to the West, patients from the South and Midwest were 0.90 (95% CI 0.87, 0.93; $p < 0.001$) and 0.93 (95% CI 0.90, 0.96; $p < 0.001$) times as likely to be associated with AF.

BMI was associated with an increased likelihood of AF. With the reference group of BMI < 30 kg/m2, patients with BMI ≥ 35 - < 40 kg/m2 were 1.11 times (95% CI 1.07, 1.16; $p < 0.001$) and with BMI ≥ 40 kg/m2 were 1.31 times (95% CI 1.25, 1.37; $p < 0.001$) more likely to have AF.

Several baseline comorbidities were associated with AF. Patients with CHD were 1.72 times as likely to be associated with AF (95% CI 1.67, 1.78; $p < 0.001$). Similar results were identified with diagnoses of CHF (OR: 2.29, 95% CI 2.19, 2.38; $p < 0.001$), hypertension (OR: 2.03, 95% CI 1.96, 2.10; $p < 0.001$), MI (OR: 1.97, 95% CI 1.80, 2.16; $p < 0.001$) and LVH (OR: 1.51, 95% CI 1.38, 1.65; $p < 0.001$). Furthermore, CKD (OR: 1.14, 95% CI 1.09, 1.18; $p < 0.001$), COPD (OR: 1.35, 95% CI 1.31, 1.40; $p < 0.001$) and hypoglycemic events (OR: 1.32, 95% CI 1.25, 1.39; $p < 0.001$) were associated with increased odds of developing AF. Along with the comorbidities, severity index (DCSI) was associated with AF in a linear trend. Patients whose DCSI score was 1 were 0.97 times (95% CI 0.93, 1.01; $p = 0.122$), with a score of 2 were 1.18 times (95% CI 1.13, 1.23; $p < 0.001$), with a score of 3 were 1.08 (95% CI 1.02, 1.13; $p = 0.003$), with a score of 4 were 1.21 (95% CI 1.14, 1.28; $p < 0.001$) and with score ≥ 5 were 1.21 (95% CI 1.15, 1.28; $p < 0.001$) times more likely to have AF compared to patients whose DCSI score was 0.

Some medications in the past 12 months were associated with AF. AD medication use was associated with decreased odds of developing AF. In particular, patients on DPP-4 and insulin were 0.76 times (95% CI 0.64, 0.90; $p < 0.001$) and 0.92 (95% CI 0.89, 0.95;

$p < 0.001$) times as likely to be associated with AF compared to patients who were not on DPP-4 and insulin, respectively, In addition to AD drugs, statins (OR 0.89; 95% CI 0.87, 0.92; $p < 0.001$) and corticosteroids (OR 1.05; 95% CI 1.02, 1.08; $p = 0.002$) as compared to patients without statins and corticosteroids use, respectively, were also associated with AF.

The number of office visits a patient had in the past 12 months was associated with AF. Patients who visited VA hospitals and clinics more frequently were more likely to have AF. Compared to patients who visited VA medical facility ≤ 5 times, patients who had 6-10 visits were 1.40 times (95% CI 1.35, 1.45; $p < 0.001$) more likely to have AF. Similarly, patients with VA medical facilities visits of 10-15 were 1.81 times (95% CI 1.74, 1.88; $p < 0.001$), 16-20 visits were 2.01 times (95% CI 1.92, 2.11; $p < 0.001$), and > 20 visits were 2.46 times (95% CI 2.35, 2.57; $p < 0.001$) times more likely to have AF.

Additionally, patients whose HbA1C measurement was taken less frequently were more likely to be associated with AF. Patients with an average gap of 100-199 days between HbA1c measurements during the baseline period were 1.01 (95% CI 0.98, 1.04; $p = 0.477$) times more likely to have AF compared to patients with < 100 days of gap in HbA1c measurements. Patients with an even broader gap in HbA1c measurements, 200-299, were 1.04 (95% CI 1.00, 1.09; $p = 0.039$) times as likely to be associated with AF.

Uncontrolled Glycemia Defined as Mean HbA1c ≥ 7%

In multivariable logistic regression compared to patients who had a mean HbA1c < 7% in the 12 months prior to index date, patients with mean HbA1c ≥ 7.0% were less likely to have AF. By HbA1c category, those with mean HbA1c 7-9% were 0.94 (95% CI 0.90,

0.99; p = 0.010), patients with HbA1c 9-11% were 0.95 (95% CI 0.86, 1.04; p = 0.261) and patients with HbA1c > 11% were 0.96 (95% CI, 0.81, 1.14; p = 0.642) times as likely to be associated with AF than those with a mean HbA1c < 7.0%, controlling for age, sex, race, region, BMI, CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, smoking, DCSI, diabetes medication use, statins, fibrates, ACE or ARBSs, NSAIDs, PUFA, corticosteroids, number of visits, number of HbA1c counts, and average gap in between HbA1c values.

Age, sex, race, and region played an important role in showing how they were interlinked with the occurrence of AF. It was observed that an increase in age was associated with a higher risk of AF. Compared to patients younger than 65 years, those between 65-69 years were 1.51 times more likely to have AF (95% CI 1.25, 1.83; p < 0.001). Similarly, the odds ratio of AF in patients with age group 70-74 years was 2.20 (95% CI, 1.75, 2.77; p < 0.001), 75-79 years was 3.01 (95% CI, 2.35, 3.86; p < 0.001), 80-84 years was 3.0 (95% CI, 2.31, 4.00; p < 0.001) and ≥ 85 years was 2.4 (95% CI 1.72, 3.29; p < 0.001). Compared to females, males were at a 55% increased odds of developing AF (95% CI, 1.44, 1.71; p < 0.001). African Americans were less likely to be associated with AF as compared to Whites (OR: 0.58; 95% CI: 0.56, 0.60; p < 0.001). Southern US patients were less likely to have AF compared to patients in the West. (OR: 0.90; 95% CI: 0.87, 0.93; p < 0.001)

The odds of AF were increased in patients with higher BMI. As compared to patients with BMI < 30 kg/m2, patients with BMI ≥ 35 - < 40 kg/m2 were 1.11 times (95% CI 1.07, 1.16; p < 0.001) and with BMI ≥ 40 were 1.31 times (95% CI 1.25, 1.36; p < 0.001) more likely to have AF.

The comorbidities associated with AF included CHF, CHD, hypertension, MI, LVH, CKD, and COPD. Patients with CHF were over two times more likely to have AF than those without CHF (OR: 2.29, 95% CI 2.20, 2.38; $p < 0.001$). Patients with CHD were 1.72 times likely to have AF (95% CI: 1.67, 1.78; $p < 0.001$) than patients without CHF. Hypertension (OR: 2.03, 95% CI 1.96, 2.10; $p < 0.001$), MI (OR: 1.97, 95% CI 1.80, 2.16; $p < 0.001$) and LVH (OR: 1.51, 95% CI 1.38, 1.65; $p < 0.001$), CKD (OR: 1.14, 95% CI 1.09, 1.18; $p < 0.001$), and COPD (OR: 1.35, 95% CI 1.31, 1.39; $p < 0.001$) were also associated with AF relative to patients without these comorbidities. Documented hypoglycemic events were similarly associated with a higher risk of AF (OR: 1.32, 95% CI 1.25, 1.39; $p < 0.001$). Compared to patients whose DCSI score was 0, the odds ratios of developing AF in patients whose DCSI score 1 was 0.97 (95% CI 0.93, 1.01; $p = 0.124$), with a DCSI score of 2 was 1.18 (95% CI 1.13, 1.23; $p < 0.001$), with a DCSI score of 3 was 1.08 (95% CI 1.02, 1.13; $p = 0.003$), with a DCSI score of 4 was 1.21 (1.14, 1.28; $p < 0.001$) and with DCSI score ≥ 5 was 1.21 (95% CI 1.15, 1.28; $p < 0.001$).

Use of certain medications in the 1-year preindex period was associated with AF. DPP-4 (OR 0.76; 95% CI: 0.64, 0.90; $p = 0.002$) was associated with lower risk of AF, as was insulin (OR 0.93; 95% CI: 0.90, 0.96; $p < 0.001$). Corticosteroids (OR 1.05; 95% CI 1.02, 1.09; $p = 0.002$) and statin (OR 0.89; 95% CI 0.87, 0.92; $p < 0.001$) use were associated with AF.

Patients who visited VA hospitals and clinics more frequently were more likely to have AF. Compared to patients who visited a VA medical facility ≤ 5 times, patients who had 6-10 visits were 1.40 times (95% CI: 1.35, 1.45; $p < 0.001$) more likely to have AF. Similarly, patients with more frequent VA medical facility visits were more likely to have

AF: 10-15 visits (OR: 1.81; 95% CI 1.74, 1.88; $p < 0.001$), 16-20 visits (OR: 2.0; 95% CI 1.92, 2.11; $p < 0.001$), and > 20 visits (OR: 2.5; 95% CI 2.36, 2.58; $p < 0.001$). Likewise, patients with longer gaps in HbA1c measurements – mean 200-299 days compared to patients with < 100 days, were 1.04 (95% CI 1.00, 1.09; $p = 0.040$) times as likely to be associated with AF.

Uncontrolled Glycemia Defined as Last HbA1c Value ≥ 7% Identified Before the Index Date

When the regression model was adjusted for confounders including baseline age, sex, race, region, BMI, CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, smoking, DCSI, AD medication use, statins, fibrates, ACE or ARBs, NSAIDs, PUFA, corticosteroids, number of office visits, number of HbA1c counts, and average day gap between HbA1c values, we found that diabetic patients whose last HbA1c value in the prior 12 months was 7- < 9% were 0.94 (95% CI; 0.11,0.97; $p = 0.002$) times as likely to be associated with AF. Similar to the findings, patients whose last HbA1c was 9- < 11% were 0.91 times (95% CI; 0.85, 0.98; $p = 0.012$) as likely to be associated with AF. However, patients who had HbA1c > 11% were not statistically associated with AF (OR: 0.92; 95% CI; 0.82, 1.04; $p = 0.177$).

As seen in the previous section, demographic variables including age, sex, race, and region were significantly associated with AF. Increase in age was associated with the development of AF. Patients aged 65-69 years were 1.52 (95% CI; 1.25, 1.83; $p < 0.001$), 70-74 years were 2.22 (95% CI; 1.77, 2.80; $p < 0.001$), 75-79 years were 3.05 (95% CI;

2.39,3.91; $p < 0.001$), 80-84 years were 3.09 (95% CI; 2.35, 4.07; $p < 0.001$) and ≥ 85 years were 2.41 (95% CI; 1.75, 3.34; $p < 0.001$) times more likely to be associated with AF compared to patients who were younger than < 65 years. Males were 1.57 times more likely to be associated with AF compared to females (OR: 1.57; 95% CI; 1.44, 1.71; $p < 0.001$). African Americans were 0.59 times more likely to be associated with AF than Whites (OR: 0.59; 95% CI 0.56. 0.60; $p < 0.001$). Patients from the South (OR: 0.90; 95% CI: 0.87, 0.93; $p < 0.001$) and Midwest (OR: 0.93; 95% CI: 0.90, 0.96; $p < 0.001$) were less likely to have AF compared to patients who received care in the West.

An increase in BMI was significantly associated with an increased likelihood of AF. Compared to patients who were overweight (BMI < 30), patients with BMI ≥ 30-35 and ≥ 40 were 1.11 (95% CI; 1.07, 1.16; $p < 0.001$) and 1.31 (95% CI; 1.25, 1.36; $p < 0.001$) times as likely to be associated with AF.

In comorbidities, CHF, MI, and hypertension were strongly associated with an increased likelihood of having AF. The odds of association of CHF were increased by 129% (OR: 2.29; 95% CI: 2.20, 2.39; $p < 0.001$), MI by 97% (OR: 1.97 95% CI: 1.80, 2.16; $p < 0.001$), and hypertension by 103% (OR: 2.03; 95% CI: 1.96, 2.10; $p < 0.001$). Similarly, the odds of developing AF in patients with CHD were increased by 67% (95% CI: 1.67, 1.78; $p < 0.001$). LVH (OR: 1.51; 95% CI; 1.38, 1.65; $p < 0.001$), CKD (OR: 1.14; 95% CI: 1.09, 1.18; $p < 0.001$), COPD (OR: 1.35; 95% CI: 1.31, 1.39; $p < 0.001$) and hypoglycemic events (OR: 1.32; 95% CI: 1.25, 1.39; $p < 0.001$) were positively associated with AF.

Similar to previous findings, DCSI was linearly associated with an increased likelihood of AF. Compared to patients with DCSI score of 0, patients with a score of 2

were 1.18 (95% CI: 1.13, 1.23; $p < 0.001$), with a score of 3 were 1.08 (95% CI: 1.03, 1.13; $p = 0.003$), with a score of 4 were 1.21 (95% CI: 1.14, 1.28; $p < 0.001$) and with a score of ≥ 5 were 1.21 (95% CI: 1.15, 1.28; $p < 0.001$) times more associated with AF.

There were a few medications found to be causing increased likelihood of AF and some were protective. AD medications such as metformin were associated with an increased likelihood of AF (OR: 1.02; 95% CI: 0.99, 1.05; $p = 0.140$). Other drugs such as DPP-4 and insulin were protective against AF. DPP-4 and insulin reduced the odds of developing AF by 24% (OR: 0.76: 95% CI: 0.64, 0.89; $p = 0.002$) and 7% (OR: 0.93; 95% CI 0.90, 0.96; $p < 0.001$), respectively. Likewise, statin use reduced the odds by 11% (OR: 0.89; 95% CI: 0.87, 0.92; $p < 0.001$). On the other hand, corticosteroids increased the odds by 5% (OR: 1.05; 95% CI: 1.02, 1.09; $p = 0.002$).

Patients who frequently visited VA medical facilities were more likely to be associated with increased odds of developing AF. Compared to patients with ≤ 5 visits, patients who had 6-10 visits were 1.40 times (95% CI: 1.35, 1.45; $p < 0.001$) associated with AF and, similarly, patients who had 10-15, 16-20 and > 20 visits had odds ratios of 1.81 (95% CI: 1.74, 1.88; $p < 0.001$), 2.01 (95% CI: 1.92, 2.12; $p < 0.001$), and 2.46 (95% CI 2.36, 2.57; $p < 0.001$), respectively in terms of their likelihood to be associated with AF. Patients who had an average gap of 100-199 days were 1.01 (95% CI: 0.98, 1.04; $p = 0.471$), 200-299-days were 1.04 (95% CI: 1.00, 1.09; $p = 0.040$), and ≥ 300 days were 1.00 (95% CI: 0.93, 1.07; $p = 0.919$) times more likely to be associated with AF compared to patients who had a gap of < 100 days.

Sensitivity Analyses

ADA recommends a less stringent HbA1c cut-off for patients who are elderly with limited life expectancy or with more comorbidities.[31] Therefore, sensitivity analyses were conducted to understand the association between different HbA1c cut-offs and AF. Except for the definition where uncontrolled glycemia was defined as ≥ 1 HbA1c value ≥ 7%, the results were consistent for the other two definitions. When the threshold of defining controlled and uncontrolled glycemia was changed to HbA1c as 6% (Table 7), the result shifted towards the null hypothesis, as there were no differences between blood glucose level and AF. Additionally, with the two different definitions of controlled and uncontrolled depending on the HbA1c values (mean and last HbA1c), none of the odds were statistically significant after adjusting for covariates. However, with one or more HbA1c ≥ 7%, the odds ratio of developing AF were protective. A logistic regression run to find the association between glycemic control and AF was adjusted for covariates including age, sex, race, region, BMI, CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, smoking, DCSI, AD medication use, statins, fibrates, ACE or ARBs, NSAIDs, PUFA, corticosteroids, number of office visits, number of HbA1c counts, and average day gap between HbA1c values. With uncontrolled glycemia defined as any single HbA1c value above 6%, the association between controlled glycemia and AF was 0.95 times. (95% CI: 0.90, 0.99; $p = 0.036$). On the other hand, with mean HbA1C ≥ 6% defining uncontrolled glycemia, the association between HbA1c and AF was 1.01 times (95% CI: 0.96, 1.04; $p = 0.972$), Again, the result was statistically nonsignificant (OR: 1.03: 95% CI 0.99, 1.08; $p = 0.100$) with the third definition of last HbA1c ≥ 6% as uncontrolled glycemia.

After adjusting the model for covariates, when the threshold of defining glycemic control was HbA1c of < 8% (Table 8), uncontrolled glycemia, defined as any one HbA1c value above 8%, was not significantly associated with AF (OR: 0.99; 95% CI: 0.95, 1.04; $p = 0.826$). However, when mean HbA1c and last HbA1c prior to AF of < 8.0% was used to define controlled glycemia, no association was detected (OR: 1.06; 95% CI: 1.01, 1.11; $p = 0.022$ and OR: 1.05; 95% CI: 1.0, 1.10; $p = 0.015$, respectively).

When the threshold was changed to HbA1c as 9% (Table 9), no association between glycemic control and AF was detected by any of the three definitions. A logistic regression model after adjusting for covariates found that patients who had all HbA1c values < 9% in the prior 12 months were 0.97 times (95% CI: 0.92, 1.02; $p = 0.274$) as likely to be associated with AF. Similarly, for the second definition where controlled glycemia was defined as mean HbA1c < 9%, the odds ratio of the association between glycemic control and AF was 0.96 (95% CI: 0.90, 1.02; $p = 0.181$) Likewise, with the third definition as the last HbA1c value < 9%, patients were 1.18 times as likely to be associated with AF (95% CI: 0.96, 1.08; $p = 0.524$).

Objective 3

Objective 3 assessed the association between ADAIP use and AF in patients with T2DM.

Starting with the 1.75 million patients with T2DM, Aim 3 analyses included 97,877 patients who were on ADAIP and 91,218 patients who were not on ADAIP (Figure 6). The baseline characteristics of the study population are detailed in Table 10. The mean age (SD) of the cohort was 67.1 (10.4) years and 96.5% were males. Patient characteristics varied

between patients treated with ADAIP and patients without ADAIP.

Demographics and Vital Signs

The mean age (SD) of the patients treated with ADAIP was 65.2 (9.6) years, with 96.2% being male and 3.8% being female. The mean (SD) age of patients without ADAIP was 69.2 (10.9) years, with 96.9% being males and 3.1% being females ($p < 0.001$ for all). The proportion of White patients in the ADAIP group was 74.8% versus 73.1% of patients without ADAIP. The proportion of African Americans was 15.4% versus 16.5% in ADAIP and non-ADAIP users, respectively ($p < 0.001$). The geographic distribution also varied in patients with ADAIP and patients without ADAIP. The highest proportion was seen in the Midwest region with ADAIP users at 31.6% versus 33.0% for non-ADAIP users ($p < 0.001$).

The proportion of patients with ADAIP and with BMI 30 -< 35 kg/m2 was 30,739 (31.4%) versus 28.7% in patients without ADAIP, which was considerably higher. Whereas, for patients without ADAIP, the highest proportion was seen as 28,491 (31.2%) in patients with BMI as 25-30 kg/m2 ($p < 0.001$).

The number (%) of patients with baseline blood pressure data was 165,671 (87.6%). The proportion of patients with ADAIP whose SBP was ≥ 130mm Hg was 43.7% and for patients without ADAIP was 44.2% ($p = 0.103$). The proportion for ADAIP patients with DBP ≥ 80mm Hg was found to be 26.1% and for patients without ADAIP were 22.7% ($p < 0.001$).

The mean (SD) baseline HbA1c (%), measured as the mean of the 2-4 captured values for each patient during the 1 year prior to the index date was 7.5 (1.4) and the median

(IQR) was 7.1 (6.5-8.1) for patients with ADAIP versus 7.1 (1.4) and a median (IQR) of 6.7 (6.2-7.7) for patients without ADAIP ($p < 0.001$). The mean (SD) number of HbA1c values for the past 1 year were similar for patients with ADAIP and for patients without ADAIP i.e. 2.7(1.0) and 2.7(1.0) along with the median (IQR) values to be 2 (2-3) and 2 (2-3) ($p = 0.031$).

The percentage of patients with baseline HDL-C ≤ 40 mg/dL was 49.6% for patients with ADAIP and 43.7% for patients without ADAIP ($p < 0.001$). There were 20.9% patients with ≥ 100 mg/dL for patients with ADAIP and 22.6% for patients without ADAIP ($p < 0.001$).

Patients with ADAIP were more likely to smoke before the index date as 37,855 (38.7%) compared to 33,172 (36.4%) for patients without ADAIP ($p < 0.001$). The mean (SD) diabetes duration for both the groups was 5.4 (2.8) and 5.4 (2.9), respectively ($p = 0.022$). The proportion of patients was found to be higher in ADAIP users (48.3%) with diabetes duration of 5-10 years than in patients without ADAIP (46.8%) ($p < 0.001$).

The mean number of office visits in patients who used ADAIP was lower compared to patients who used ADAIP (11.3 versus 13.0). The median (IQR) number of office visits in ADAIP users was 8 (5-14) as compared to non-ADAIP users with 8 (5-16) ($p < 0.001$).

The prevalence of baseline comorbidities differed significantly between the ADAIP and non-ADAIP groups except for hypertension (75.2% vs. 75.4%, respectively) ($p = 0.519$). The proportion of ADAIP patients with CHD was 27.1% versus 33.6% for patients without ADAIP ($p < 0.001$). Dyslipidemia in ADAIP users was 20.8% versus 19.6% in non-ADAIP users. The proportion of ADAIP users versus non-ADAIP users diagnosed with retinopathy or neuropathy was 19.2% versus 21.0%, with AF 17.5% versus 22.6%

and with COPD as 16.7% versus 19.7%. The mean (SD) DCSI was lower in patients with ADAIP, 1.44 (2.0%), versus patients without ADAIP, 2.4 (3.0%) ($p < 0.001$). The proportion of patients with a DCSI score of ≥ 5 was higher in patients without ADAIP (17.9%) than those with ADAIP (8.1%) ($p < 0.001$).

Metformin and TZD use was 93,519 (95.6%) and 10,723 (10.9%) in patients with ADAIP. Given the definition of ADAIP, these medications were not used in the non-ADAIP group. Sulphonylureas use was higher in patients with ADAIP compared to patients without ADAIP (48.0% vs 28.8%). Insulin use was lower in ADAIP patients compared to non ADAIP patients (28.0% vs. 33.6%). Use of other drugs with AI properties including statins (79.3% vs. 65.8%), fibrates (11.2% vs. 7.4%), ACE or ARBs (78.2% vs. 62.5%), NSAIDs (47.3% vs. 39.9%), and PUFA (0.4% vs. 0.2%) was higher in patients who were on ADAIP compared to patients who did not use these medications in the baseline period. However, corticosteroids use was higher in patients without ADAIP use (19.8% vs. 17.6%) (all $p < 0.001$).

Mediation Analyses

Univariate and multivariate regression analyses were conducted to determine if glycemic control mediates the effect of ADAIP on odds of having AF. In a univariate logistic regression model (Table 11) where AF (outcome) was predicted by ADAIP (exposure), we found that patients using ADAIP were 0.73 times as likely have AF as compared to the non-ADAIP group (95% CI: 0.72, 0.75; $p < 0.001$). In a second univariate analysis (Table 12) where ADAIP predicted glycemic control (mediator), ADAIP were 0.52 times as likely to have AF (95% CI: 0.51, 0.53; $p < 0.001$). In the third univariate

analysis (Table 13), glycemic control predicted AF and the odds of their association was 1.11 (95% CI; 1.09, 1.14; $p < 0.001$).

ADAIP was not significantly associated with AF (OR: 1.02; 95% CI; 0.99, 1.05, $p = 0.086$) when adjusting for the mediators and potential confounders of age, sex, race, region, BMI, CHD, CHF, hypertension, dyslipidemia, MI, LVH, CKD, rheumatoid arthritis, COPD, hypoglycemic events, nonalcoholic liver disease, smoking, DCSI, diabetes medications, statins, fibrates, ACE or ARBS, NSAIDs, PUFA, and corticosteroids, Table 14. When excluding the mediator variable (glycemic control) from the model, the odds of developing AF did not change (OR: 1.02; 95% CI; 0.98, 1.05, $p = 0.070$) (Table 15). Thus, glycemic control is not mediating any effect in the relationship of ADAIP and AF.

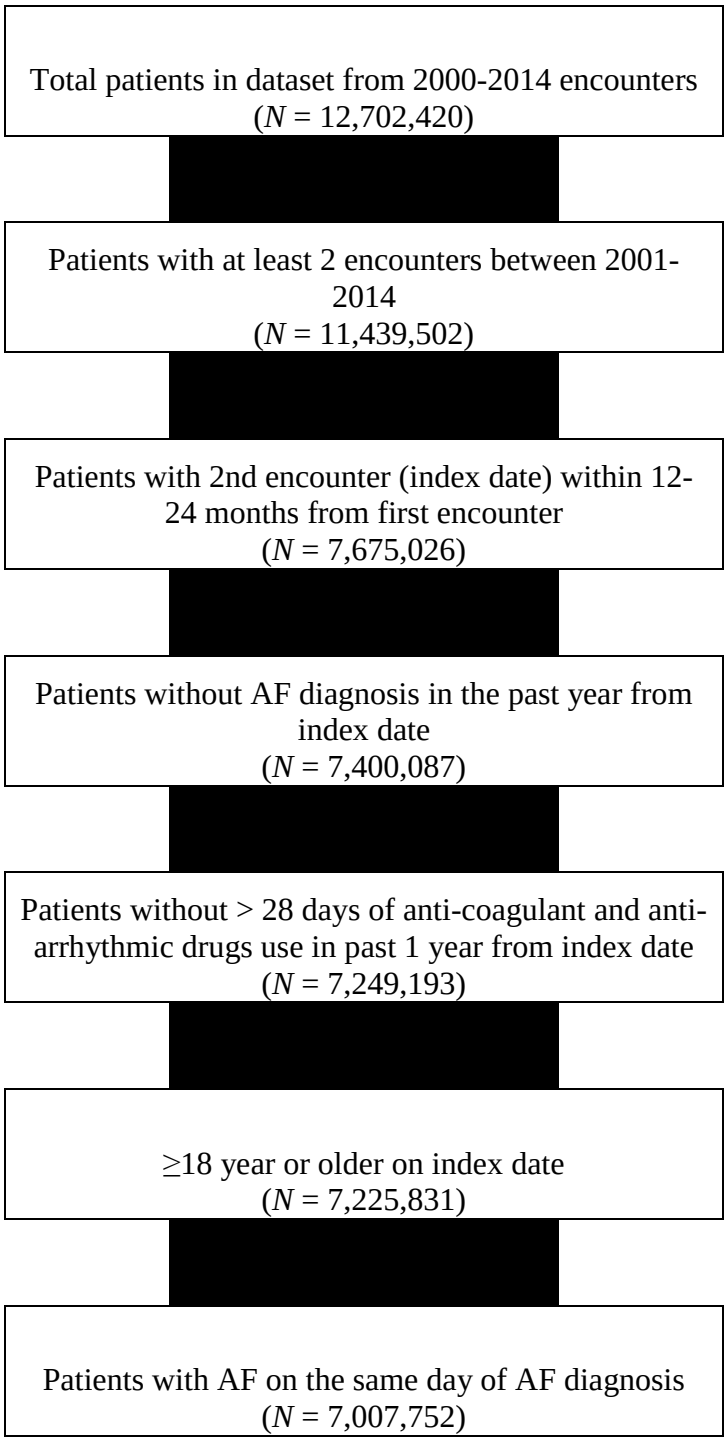

Figure 3. Patient selection chart for calculating the incidence rate of atrial fibrillation in overall veteran cohort.

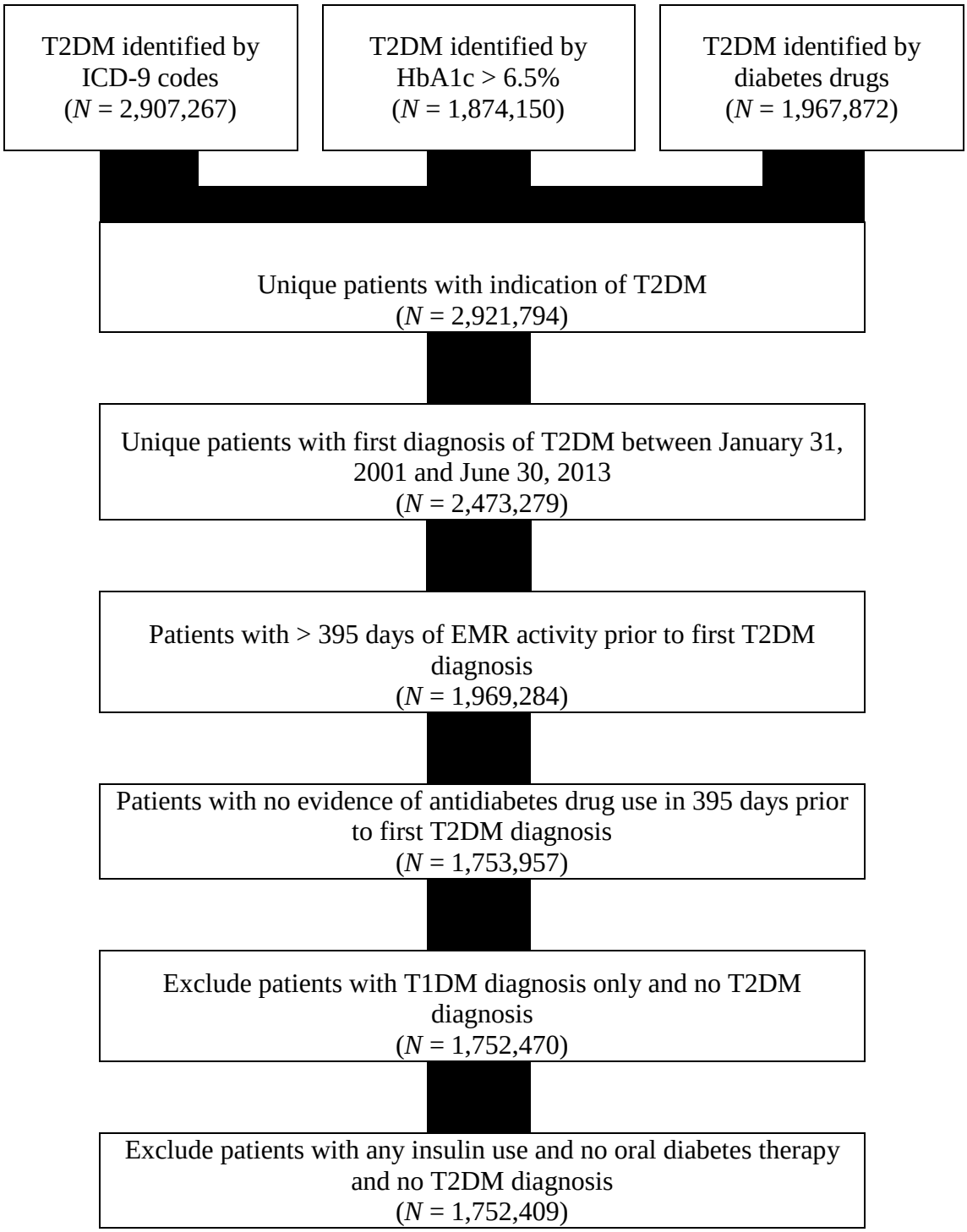

Figure 4. Patient inclusion chart for selecting diabetes cohort.

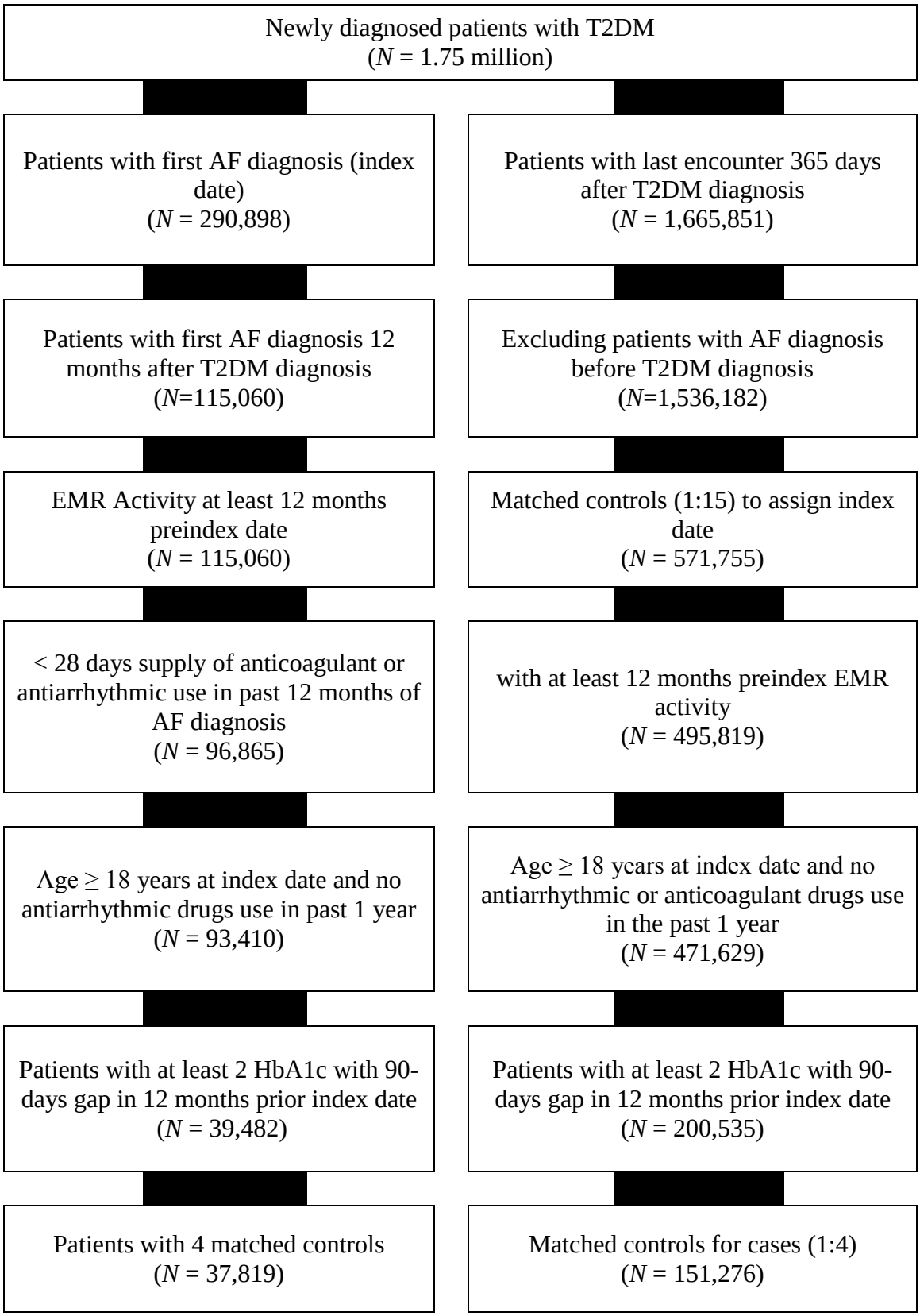

Figure 5. Patient selection criteria for cases and control.

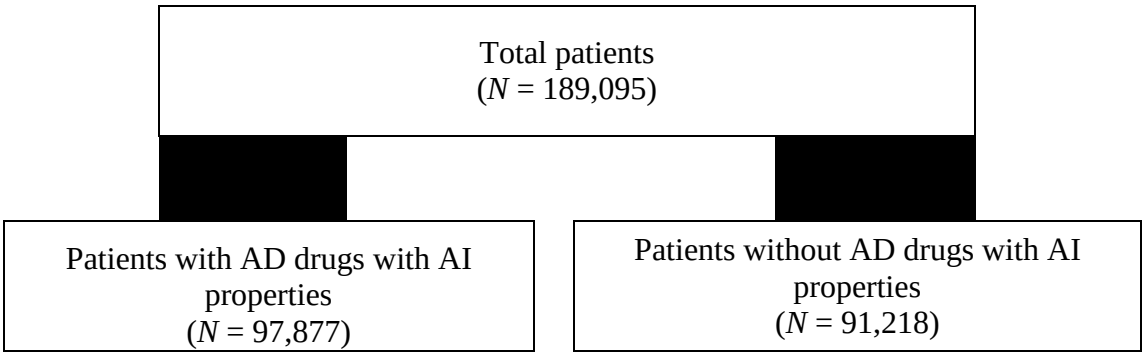

Figure 6. Patient selection criteria for patients with antidiabetes drugs with anti-inflammatory properties and without antidiabetes drugs with anti-inflammatory properties.

Table 1. Baseline characteristics of overall, type 2 diabetes cohort, and non-type 2 diabetes cohort in patients receiving care in veteran affairs facilities between 2000 and 2014.

	Overall (*N* = 7,007,752)		With T2DM (*N* = 1,602,696)		Without T2DM (*N* = 6,987,311)		*P* value*
Variable	N/Mean	SD/%	N/Mean	SD/%	N/Mean	SD/%	
Age, Years							
Mean (SD)	58.75	16.1	63.89	11.7	58.74	16.1	< 0.001
< 65	4,274,714	61.0	869,687	54.3	4,262,813	61.0	< 0.001
65-69	722,173	10.3	221,735	13.8	719,360	10.3	
70-74	692,815	9.9	184,055	11.5	690,387	9.9	
75-79	671,920	9.6	164,750	10.3	669,907	9.6	
80-84	460,164	6.6	110,548	6.9	459,246	6.6	
≥ 85	185,966	2.7	51,921	3.2	185,598	2.7	
Sex (*n*, %)							
Male	6,363,369	90.8	1,536,440	95.9	6,343,479	90.8	< 0.001
Female	644,361	9.2	66,249	4.1	643,810	9.2	
Race (*n*, %)							
White	4,499,132	64.2	1,105,962	69.0	4,484,359	64.2	< 0.001
African American	893,038	12.7	245,124	15.3	890,135	12.7	
Other**	126,589	1.8	32,340	2.0	126,196	1.8	
Unknown	230,207	3.3	51,786	3.2	229,557	3.3	
Missing	1,258,786	18.0	167,484	10.5	1,257,064	18.0	

*Between T2DM population and non-T2DM population

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiians

Table 2. Crude incidence rates of atrial fibrillation of overall, type 2 diabetes, and non-type 2 diabetes cohort in patients receiving care in veterans affair facilities between 2000-2014.

	Total number of patients	Total events	Total months	Total years	Incidence rates per person-year	Incidence rates per 1,000 person-years
All Population	7,007,752	554,014	600,179,074	50,014,922	0.011	11.07
Diabetes	1,602,696	124,131	114,393,576	9,532,798	0.013	13.02
Non-Diabetes	6,987,311	451,639	504,639,956	42,053,329	0.010	10.74

Table 3. Incidence rate of AF categorized by age in patients with T2DM receiving care in veteran affairs facilities between 2000-2014 by categories.

	Total number of patients	Total events	Total year	Incidence rates**	Total number of patients	Total events	Total year	Incidence rates**
	Age < 65 years				Age 65-69 years			
All Population	4,274,714	187,313	32,219,690	5.81	722,173	78,070	5,234,368	14.91
Diabetes	869,687	46,440	5,623,833	8.26	221,735	18,754	1,251,407	14.99
Non-Diabetes	4,262,813	144,715	27,231,362	5.31	719,360	62,469	4,251,846	14.69
	Age 70-74 years				Age 75-79 years			
All Population	692,815	97,254	5,110,398	19.03	671,920	102,494	4,340,951	23.61
Diabetes	184,055	20,262	1,106,053	18.32	164,750	19,789	881,662	22.45
Non-Diabetes	690,387	79,424	4,189,086	18.96	669,907	86,620	3,654,896	23.7
	Age 80-84 years				Age ≥ 85 years			
All Population	460,164	66,843	2,438,077	27.42	185,966	22,040	671,440	32.82
Diabetes	110,548	13,175	498,790	26.41	51,921	5,711	171,053	33.39
Non-Diabetes	459,246	58,393	2,119,662	27.55	185,598	20,018	606,477	33.01

**per 1,000 person-years

Table 4. Incidence rates of AF categorized by sex in patients with T2DM receiving care in veteran affairs facilities between 2000-2014 by categories.

	Males				Females			
	Total number of patients	Total events	Total years	Incidence rates per 1,000 person-year	Total number of patients	Total events	Total years	Incidence rates per 1,000 person-year
All Population	6,363,369	542,390	45,779,190	11.85	644,361	11,622	4,235,572	2.74
Diabetes	1,536,440	122,035	9,145,040	13.34	66,249	2,095	387,708	5.40
Non-Diabetes	6,343,479	441,797	38,149,166	11.58	643,810	9,840	3,904,047	2.52

Table 5. Baseline characteristics of cases and controls (*N* = 189,095).

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N*=151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Age, Years							
Mean (SD)	67.15	10.43	71.12	9.72	66.15	10.36	< 0.001
< 65	80,276	42.45	10,317	27.28	69,959	46.25	< 0.001
65-69	38,126	20.16	7,584	20.05	30,542	20.19	
70-74	23,448	12.4	5,651	14.94	17,797	11.76	
75-79	20,921	11.06	5,723	15.13	15,198	10.05	
80-84	15,965	8.44	4,971	13.14	10,994	7.27	
≥ 85	10,359	5.48	3,573	9.45	6,786	4.49	
Sex (*n*, %)							
Male	182,518	96.52	37,135	98.19	145,383	96.1	< 0.001
Female	6,577	3.48	684	1.81	5,893	3.9	
Race (*n*, %)							
White	139,873	73.97	30,273	80.05	109,600	72.45	< 0.001
African American	30,116	15.93	3,901	10.31	26,215	17.33	
Other**	3,755	1.99	616	1.63	3,139	2.08	
Unknown	7,583	4.01	1,452	3.84	6,131	4.05	
Region (*n*, %)							
West	50,254	26.58	10,819	28.61	39,435	26.07	< 0.001
South	54,923	29.05	10,228	27.04	44,695	29.55	
Midwest	61,018	32.27	11,990	31.7	49,028	32.41	
East	22,899	12.11	4,781	12.64	18,118	11.98	
Visits							
Mean Number of Visits	12.09	13.75	16.69	18.95	10.94	11.82	< 0.001

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Median (IQR)	8	(5-15)	12	(6-21)	8	(4-14)	
1-5	58,461	33.24	7,571	21.1	50,890	36.35	< 0.001
6-10	40,877	23.24	7,176	20	33,701	24.07	
11-15	30,822	17.52	6,799	18.95	24,023	17.16	
16-20	17,575	9.99	4,573	12.74	13,002	9.29	
> 20	26,989	15.35	9,387	26.16	17,602	12.57	
Missing	1,155	0.61	375	0.99	780	0.52	
SBP (mm Hg)							
Mean (SD)	129.99	16.89	127.44	18.63	130.73	16.28	< 0.001
< 130 mmHg (*n*, %)	82,558	43.66	20,753	54.87	61,805	40.86	< 0.001
≥ 130 mmHg (*n*, %)	83,113	43.95	16,672	44.08	66,441	43.92	
Missing (*n*, %)	23,424	12.39	394	1.04	23,030	15.22	
DBP (mm Hg)							
Mean (SD)	72.85	11.11	70.49	11.74	73.53	10.83	< 0.001
< 80 mmHg (*n*, %)	119,296	63.09	29,046	76.8	90,250	59.66	< 0.001
≥ 80 mmHg (*n*, %)	46,312	24.49	8,351	22.08	37,961	25.09	
Missing (*n*, %)	23,487	12.42	422	1.12	23,065	15.25	
Baseline HbA1c (%)							
Past 1 Year							
Mean (SD)	7.29	1.37	7.17	1.28	7.32	1.39	< 0.001
Median (IQR)	6.97	(6.35-7.93)	6.9	(6.3-7.77)	7	(6.35-7.95)	
< 7	94,822	50.15	20,187	53.38	74,635	49.34	< 0.001
7 - ≤ 8	48,926	25.87	9,768	25.83	39,158	25.89	
8 - ≤ 9	24,447	12.93	4,485	11.86	19,962	13.2	

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
≥ 9	20,900	11.05	3,379	8.93	17,521	11.58	
All Baseline HbA1c (%) (Not Limited to 2-4)							
Past 1 Year							
Mean (SD)	7.28	1.35	7.28	1.35	7.28	1.35	1.000
Median (IQR)	6.98	(6.35-7.9)	6.97	(6.35-7.9)	6.98	(6.35-7.9)	
< 7	94,824	50.15	18,981	50.19	75,843	50.14	0.933
7 - ≤ 8	49,510	26.18	9,855	26.06	39,655	26.21	
8 - ≤ 9	24,687	13.06	4,958	13.11	19,729	13.04	
≥ 9	20,074	10.62	4,025	10.64	16,049	10.61	
Number of HbA1c Values Past 1 Year							
Mean (SD)	2.73	1	2.73	1	2.73	1	1.000
Median (IQR)	2	(2-3)	2	(2-3)	2	(2-3)	
2-4	178,275	94.28	35,662	94.3	142,613	94.27	0.03
Mean HbA1c (2-4)	7.29	1.37	7.17	1.28	7.32	1.39	< 0.001
Mean Days Between HbA1c Values	157.16	66.37	157.36	66.49	157.11	66.34	0.525
Median (IQR) Days Between HbA1c Values	147	(106-192)	147	(106-192)	147	(106-191)	
> 4	10,820	5.72	2,157	5.7	8,663	5.73	0.03
Mean HbA1c (> 4)	7.29	1.39	7.18	1.3	7.32	1.41	< 0.001
Mean Days Between HbA1c Values	66.34	15.47	66.24	15.46	66.37	15.47	0.727
Median (IQR) Days	67	(56-78)	67	(56-78)	67	(56-78)	

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Between HbA1c Values							
Mean Past HbA1c							
n	76,661	40.5	14,907	39.4	61,754	40.8	0.708
2 Year	7.46	1.45	7.35	1.39	7.49	1.47	< 0.001
n	77,244	41	15,127	40.1	62,117	41.2	0.708
3 Year	7.39	1.43	7.3	1.37	7.41	1.44	< 0.001
n	73,867	44.6	14,541	38.9	59,326	46.3	0.708
4 Year	7.32	1.4	7.25	1.34	7.34	1.42	< 0.001
n	68,405	36.2	13,389	35.4	55,016	36.4	0.708
5 Year	7.28	1.41	7.23	1.35	7.3	1.42	< 0.001
Baseline HDL-C (mg/dL)							
Mean (SD)	40.85	12.37	39.87	12.33	41.08	12.36	< 0.001
< 40 mg/dL	88,433	46.77	18,217	48.17	70,216	46.42	< 0.001
≥ 40 mg/dL	76,796	40.61	13,672	36.15	63,124	41.73	
Missing (*n*, %)	23,866	12.62	5,930	15.68	17,936	11.86	
Baseline LDL-C (mg/dL)							
Mean (SD)	85.62	30.62	80.52	29.36	86.84	30.79	< 0.001
< 100 mg/dL	118,571	62.7	24,554	64.93	94,017	62.15	< 0.001
≥ 100 mg/dL	41,064	21.72	6,295	16.65	34,769	22.98	
Missing (*n*, %)	29,460	15.58	6,970	18.43	22,490	14.87	
Baseline Triglycerides (mg/dL)							
Mean (SD)	170.47	135.37	162.93	125.86	172.3	137.52	< 0.001
< 150 mg/dL	91,318	48.29	18,717	49.49	72,601	47.99	< 0.001
≥ 150 mg/dL	73,984	39.13	13,559	35.85	60,425	39.94	

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Missing (*n*, %)	23,793	12.58	5,543	14.66	18,250	12.06	
Ever Smoked Before Index Date (*n*, %)							
Yes	71,027	37.56	14,171	37.47	56,856	37.58	0.683
BMI (kg/m2)							
Mean (SD)	32.15	6.6	31.97	7.1	32.2	6.46	< 0.001
< 25	20,149	10.66	5,184	13.71	14,965	9.89	< 0.001
25-30	55,135	29.16	10,808	28.58	44,327	29.3	
30- < 35	56,884	30.08	10,567	27.94	46,317	30.62	
≥ 35- < 40	31,298	16.55	6,108	16.15	25,190	16.65	
≥ 40	20,761	10.98	4,502	11.9	16,259	10.75	
Missing (*n*, %)	4,859	2.57	646	1.71	4,213	2.78	
Diabetes Duration							
Mean (SD)	5.41	2.84	5.42	2.84	5.41	2.84	0.540
< 5 (*n*, %)	80,938	42.8	16,152	42.71	64,786	42.83	0.918
5-10 (*n*, %)	89,964	47.58	18,023	47.66	71,941	47.56	
> 10 (*n*, %)	18,193	9.62	3,644	9.64	14,549	9.62	
Baseline Comorbidities (*n*, %)							
Coronary Heart Disease	57,225	30.26	19,181	50.72	38,044	25.15	< 0.001
Cerebrovascular Disease	13,059	6.91	4,453	11.77	8,606	5.69	< 0.001
Congestive Heart Failure	15,723	8.31	8,111	21.45	7,612	5.03	< 0.001
Hypertension	142,408	75.31	33,158	87.68	109,250	72.22	< 0.001
Dyslipidemia	38,241	20.22	8,283	21.9	29,958	19.8	< 0.001
Stroke	2,804	1.48	1,036	2.74	1,768	1.17	< 0.001
Myocardial Infarction	2,430	1.29	1,383	3.66	1,047	0.69	< 0.001

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Left Ventricular Hypertrophy	2,585	1.37	1,266	3.35	1,319	0.87	< 0.001
Chronic Kidney Disease	23,479	12.42	7,911	20.92	15,568	10.29	< 0.001
Retinopathy and Neuropathy	37,912	20.05	9,547	25.24	28,365	18.75	< 0.001
Rheumatoid Arthritis	1,826	0.97	481	1.27	1,345	0.89	< 0.001
COPD	34,364	18.17	10,766	28.47	23,598	15.6	< 0.001
Hypoglycemic Events	9,270	4.9	2,998	7.93	6,272	4.15	< 0.001
Nonalcoholic Liver Disease	1,472	0.78	311	0.82	1,161	0.77	0.277
Baseline DCSI							
Mean (SD)	1.89	2.57	3.1	3.29	1.58	2.26	< 0.001
0 (*n*, %)	76,095	40.24	9,058	23.95	67,037	44.31	< 0.001
1 (*n*, %)	35,664	18.86	6,171	16.32	29,493	19.5	
2 (*n*, %)	24,922	13.18	5,138	13.59	19,784	13.08	
3 (*n*, %)	17,702	9.36	4,643	12.28	13,059	8.63	
4 (*n*, %)	10,402	5.5	3,003	7.94	7,399	4.89	
≥ 5 (*n*, %)	24,310	12.86	9,806	25.93	14,504	9.59	
Diabetes Medications (365 Days Prior Index Date) (*n*, %)							
Metformin	93,519	49.46	16,271	43.02	77,248	51.06	< 0.001
Sulfonylurea	73,231	38.73	14,657	38.76	58,574	38.72	0.899
TZD	10,723	5.67	1,918	5.07	8,805	5.82	< 0.001
DPP4	1,026	0.54	189	0.5	837	0.55	0.205
GLP-1RA	322	0.17	66	0.17	256	0.17	0.823
Insulin	58,075	30.71	12,397	32.78	45,678	30.2	< 0.001

Table 5. Continued.

	Overall (*N* = 189,095)		Cases (*N* = 37,819)		Controls (*N* = 151,276)		*P* value***
Variable	*N*/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	
Other OAD*	370	0.2	71	0.19	299	0.2	0.696
Drugs with AI Properties (*n*, %)							
Statins	137,595	72.77	28,257	74.72	109,338	72.28	< 0.001
Fibrates	17,759	9.39	3,306	8.74	14,453	9.55	< 0.001
ACE or ARB	133,479	70.59	27,669	73.16	105,810	69.95	< 0.001
NSAIDs	82,700	43.73	17,203	45.49	65,497	43.3	< 0.001
Poly Unsaturated Fatty Acids	582	0.31	122	0.32	460	0.3	0.561
Corticosteroids	35,260	18.65	9,264	24.5	25,996	17.18	< 0.001

* Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide
**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian
****Between cases and controls

Table 6. Likelihood of atrial fibrillation in patients with type 2 diabetes (* all values < 7%, ** ≥ 1 value ≥ 7%)[1], (* Mean < 7%, ** Mean ≥ 7%)[2], (* last value < 7%, **last value ≥ 7%)[3] (*N* = 189,095).

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Controlled Glycemia (< 7%)	Ref					
HbA1c 7 -< 9	1.04 (1.00-1.09)	0.030	0.94 (0.90-0.99)	0.010	0.94 (0.91-0.98)	0.002
HbA1c 9 -< 11	1.08 (1.01-1.17)	0.031	0.95 (0.86-1.04)	0.261	0.91 (0.85-0.98)	0.012
HbA1c ≥ 11	1.23 (1.10-1.38)	< 0.001	0.96 (0.81-1.14)	0.642	0.92 (0.82-1.04)	0.177
Age, Years						
< 65	Ref					
65-69	1.53 (1.27-1.85)	< 0.001	1.51 (1.25-1.83)	< 0.001	1.52 (1.25-1.83)	< 0.001
70-74	2.26 (1.79-2.84)	< 0.001	2.20 (1.75-2.77)	< 0.001	2.22 (1.77-2.79)	< 0.001
75-79	3.13 (2.44-4.00)	< 0.001	3.01 (2.35-3.86)	< 0.001	3.05 (2.39-3.91)	< 0.001
80-84	3.17 (2.41-4.16)	< 0.001	3.04 (2.31-4.00)	< 0.001	3.09 (2.35-4.07)	< 0.001
≥ 85	2.47 (1.79-3.42)	< 0.001	2.38 (1.72-3.29)	< 0.001	2.42 (1.75-3.34)	< 0.001
Sex						
Female	Ref					
Male	1.57 (1.44-1.71)	< 0.001	1.57 (1.44-1.71)	< 0.001	1.57 (1.44-1.71)	< 0.001
Race						
White	Ref					
African American	0.58 (0.56-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001
Other**	0.82 (0.75-0.90)	< 0.001	0.82 (0.75-0.90)	< 0.001	0.82 (0.75-0.90)	< 0.001
Unknown	0.91 (0.85-0.97)	0.003	0.91 (0.85-0.97)	0.003	0.91 (0.85-0.97)	0.003
Missing	0.98 (0.92-1.04)	0.493	0.98 (0.92-1.04)	0.499	0.98 (0.92-1.04)	0.498
Region						
West	Ref					
South	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001
Midwest	0.93 (0.898-0.958)	< 0.001	0.93 (0.90-0.96)	< 0.001	0.93 (0.89-0.95)	< 0.001

Table 6. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
East	0.96 (0.925-1.007)	0.102	0.96 (0.92-1.01)	0.100	0.96 (0.92-1.01)	0.096
BMI (kg/m2)						
< 30	Ref					
30 - < 35	0.99 (0.96-1.02)	0.497	0.99 (0.96-1.02)	0.491	0.99 (0.96-1.02)	0.486
≥ 35 - < 40	1.11 (1.07-1.16)	< 0.001	1.11 (1.07-1.16)	< 0.001	1.11 (1.07-1.15)	< 0.001
≥ 40	1.31 (1.25-1.36)	< 0.001	1.31 (1.25-1.36)	< 0.001	1.31 (1.25-1.36)	< 0.001
Missing	0.64 (0.58-0.70)	< 0.001	0.64 (0.58-0.70)	< 0.001	0.64 (0.58-0.69)	< 0.001
Comorbidities before Index Date						
Coronary Heart Disease	1.72 (1.67-1.78)	< 0.001	1.72 (1.67-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001
Congestive Heart Failure	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001
Hypertension	2.03 (1.95-2.10)	< 0.001	2.03 (1.95-2.09)	< 0.001	2.02 (1.95-2.09)	< 0.001
Dyslipidemia	1.01 (0.98-1.04)	0.492	1.01 (0.98-1.04)	0.498	1.01 (0.98-1.04)	0.497
Myocardial Infarction	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001
Left Ventricular Hypertrophy	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001
Chronic Kidney Disease	1.13 (1.09-1.18)	< 0.001	1.14 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001
Rheumatoid Arthritis	1.02 (0.91-1.15)	0.707	1.02 (0.91-1.15)	0.703	1.02 (0.91-1.14)	0.702
COPD	1.35 (1.31-1.40)	< 0.001	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001
Hypoglycemic Events	1.32 (1.25-1.39)	< 0.001	1.32 (1.25-1.39)	< 0.001	1.31 (1.25-1.38)	< 0.001
Nonalcoholic Liver Disease	0.92 (0.80-1.06)	0.254	0.92 (0.80-1.06)	0.266	0.92 (0.80-1.06)	0.264
Smoking	0.99 (0.96-1.01)	0.385	0.98 (0.96-1.01)	0.390	0.98 (0.96-1.01)	0.398
DCSI						
0	Ref					

Table 6. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
1	0.97 (0.93-1.01)	0.122	0.96 (0.93-1.01)	0.123	0.96 (0.93-1.01)	0.124
2	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001
3	1.08 (1.02-1.13)	0.003	1.08 (1.025-1.13)	0.003	1.07 (1.02-1.13)	0.003
4	1.21 (1.14-1.28)	< 0.001	1.21 (1.141-1.27)	< 0.001	1.20 (1.14-1.27)	< 0.001
≥ 5	1.21 (1.15-1.28)	< 0.001	1.21 (1.151-1.28)	< 0.001	1.21 (1.15-1.28)	< 0.001
Diabetes Medications (395 Days Prior Index Date)						
Metformin	1.02 (0.99-1.04)	0.150	1.02 (0.99-1.05)	0.104	1.02 (0.99-1.04)	0.140
Sulfonylurea	1.04 (1.01-1.06)	0.014	1.04 (1.01-1.07)	0.003	1.03 (1.01-1.06)	0.005
TZD	0.96 (0.91-1.02)	0.193	0.96 (0.91-1.02)	0.234	0.96 (0.91-1.02)	0.205
DPP4	0.75 (0.64-0.90)	0.001	0.76 (0.64-0.90)	0.002	0.75 (0.64-0.89)	0.002
GLP-1RA	0.99 (0.74-1.33)	0.957	0.99 (0.74-1.32)	0.958	0.99 (0.74-1.32)	0.964
Insulin	0.92 (0.89-0.95)	< 0.001	0.93 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001
Other OAD*	0.80 (0.61-1.07)	0.132	0.81 (0.61-1.07)	0.138	0.80 (0.61-1.07)	0.139
Drugs with AI Properties						
Statins	0.89 (0.87-0.92)	< 0.001	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.91)	< 0.001
Fibrates	0.93 (0.89-0.98)	0.002	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003
ACE or ARB	0.99 (0.97-1.03)	0.910	1.00 (0.97-1.03)	0.863	0.99 (0.96-1.02)	0.865
NSAIDs	0.99 (0.97-1.02)	0.750	0.99 (0.97-1.02)	0.736	0.99 (0.97-1.02)	0.760
Poly Unsaturated Fatty Acids	0.98 (0.79-1.22)	0.866	0.98 (0.79-1.22)	0.869	0.98 (0.79-1.21)	0.873
Corticosteroids	1.05 (1.02-1.08)	0.002	1.05 (1.02-1.08)	0.002	1.05 (1.02-1.08)	0.002
Visits in Past 1 Year						
1-5	Ref					
6-10	1.41 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001	1.41 (1.35-1.45)	< 0.001

Table 6. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
10-15	1.80 (1.73-1.88)	< 0.001	1.81 (1.74-1.88)	< 0.001	1.80 (1.74-1.88)	< 0.001
16-20	2.01 (1.91-2.10)	< 0.001	2.01 (1.92-2.11)	< 0.001	2.01 (1.92-2.10)	< 0.001
> 20	2.45 (2.35-2.56)	< 0.001	2.46 (2.36-2.57)	< 0.001	2.46 (2.36-2.57)	< 0.001
Missing	3.23 (2.79-3.73)	< 0.001	3.25 (2.81-3.76)	< 0.001	3.24 (2.81-3.75)	< 0.001
Number of HbA1c counts in Past 1 Year						
2-4	Ref					
> 4	1.03 (0.97-1.09)	0.306	1.03 (0.97-1.09)	0.313	1.03 (0.97-1.09)	0.317
Average Counts of Days Between All HbA1c						
< 100	Ref					
100-199	1.01 (0.98-1.04)	0.477	1.01 (0.98-1.04)	0.476	1.01 (0.98-1.04)	0.471
200-299	1.04 (1.00-1.08)	0.039	1.04 (1.00-1.08)	0.039	1.04 (1.00-1.08)	0.040
≥ 300	0.99 (0.93-1.06)	0.929	0.99 (0.93-1.06)	0.919	0.99 (0.93-1.06)	0.919

* Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 7. Likelihood of atrial fibrillation in patients with type 2 diabetes with sensitivity analysis (HbA1c 6%) (* all values < 6%, ** ≥ 1 value ≥ 6%)[1], (* Mean < 6%, ** Mean ≥ 6%)[2], (* last value < 6%, **last value ≥ 6%)[3] (*N* = 189,095).

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Uncontrolled Glycemia	Ref					
Controlled Glycemia	0.94 (0.90-0.99)	0.036	1.00 (0.96-1.04)	0.972	1.03 (0.99-1.08)	0.100
Age, Years						
< 65	Ref					
65-69	1.54 (1.27-1.87)	< 0.001	1.54 (1.27-1.86)	< 0.001	1.54 (1.27-1.86)	< 0.001
70-74	2.29 (1.82-2.88)	< 0.001	2.28 (1.81-2.87)	< 0.001	2.27 (1.80-2.85)	< 0.001
75-79	3.19 (2.49-4.08)	< 0.001	3.16 (2.47-4.04)	< 0.001	3.13 (2.45-4.00)	< 0.001
80-84	3.25 (2.47-4.27)	< 0.001	3.21 (2.45-4.22)	< 0.001	3.17 (2.42-4.17)	< 0.001
Sex						
Female	Ref					
Male	1.56 (1.44-1.71)	< 0.001	1.57 (1.44-1.71)	< 0.001	1.56 (1.44-1.71)	< 0.001
Race						
White	Ref					
African American	0.58 (0.56-0.60)	< 0.001	0.58 (0.55-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001
Other**	0.82 (0.75-0.90)	< 0.001	0.82 (0.74-0.90)	< 0.001	0.82 (0.75-0.90)	< 0.001
Unknown	0.90 (0.85-0.97)	0.003	0.90 (0.85-0.96)	0.003	0.90 (0.85-0.96)	0.003
Missing	0.98 (0.92-1.04)	0.506	0.97 (0.92-1.04)	0.506	0.98 (0.92-1.04)	0.503
Region						
West	Ref					
South	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001
Midwest	0.93 (0.89-0.96)	< 0.001	0.92 (0.89-0.95)	< 0.001	0.93 (0.89-0.95)	< 0.001
East	0.96 (0.92-1.01)	0.089	0.96 (0.92-1.00)	0.094	0.96 (0.92-1.00)	0.099
BMI (kg/m2)						
< 30	Ref					

Table 7. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
30-< 35	0.99 (0.96-1.02)	0.426	0.98 (0.95-1.01)	0.465	0.99 (0.96-1.021)	0.504
≥ 35- < 40	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.157)	< 0.001
≥ 40	1.30 (1.24-1.36)	< 0.001	1.30 (1.25-1.36)	< 0.001	1.30 (1.25-1.365)	< 0.001
Missing	0.64 (0.58-0.69)	< 0.001	0.63 (0.58-0.69)	< 0.001	0.63 (0.58-0.699)	< 0.001
Comorbidities before Index Date						
Coronary Heart Disease	1.72 (1.66-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001
Congestive Heart Failure	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.39)	< 0.001	2.28 (2.19-2.38)	< 0.001
Hypertension	2.02 (1.95-2.11)	< 0.001	2.02 (1.95-2.15)	< 0.001	2.02 (1.95-2.09)	< 0.001
Dyslipidemia	1.01 (0.98-1.04)	0.499	1.01 (0.98-1.04)	0.490	1.01 (0.98-1.04)	0.483
Myocardial Infarction	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001
Left Ventricular Hypertrophy	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001
Chronic Kidney Disease	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001
Rheumatoid Arthritis	1.02 (0.91-1.15)	0.686	1.02 (0.91-1.15)	0.693	1.02 (0.91-1.14)	0.702
COPD	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001
Hypoglycemic Events	1.32 (1.25-1.39)	< 0.001	1.32 (1.25-1.39)	< 0.001	1.31 (1.25-1.38)	< 0.001
Nonalcoholic Liver Disease	0.92 (0.81-1.06)	0.262	0.92 (0.81-1.06)	0.263	0.92 (0.80-1.06)	0.262
Smoking	0.98 (0.96-1.01)	0.410	0.98 (0.96-1.01)	0.409	0.98 (0.96-1.01)	0.406
DCSI						
0	Ref					
1	0.96 (0.93-1.01)	0.121	0.96 (0.93-1.01)	0.120	0.96 (0.92-1.01)	0.119
2	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001
3	1.07 (1.02-1.13)	0.003	1.07 (1.02-1.13)	0.003	1.07 (1.02-1.13)	0.003
4	1.21 (1.14-1.28)	< 0.001	1.20 (1.14-1.27)	< 0.001	1.20 (1.14-1.27)	< 0.001
≥ 5	1.21 (1.15-1.28)	< 0.001	1.21 (1.15-1.27)	< 0.001	1.21 (1.15-1.28)	< 0.001
Diabetes Medications (395						

Table 7. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Days Prior Index Date)						
Metformin	1.01 (0.99-1.04)	0.191	1.02 (0.99-1.05)	0.149	1.02 (0.99-1.04)	0.127
Sulfonylurea	1.03 (1.01-1.06)	0.012	1.03 (1.00-1.06)	0.010	1.03 (1.00-1.06)	0.009
TZD	0.96 (0.91-1.02)	0.183	0.96 (0.91-1.01)	0.190	0.96 (0.91-1.01)	0.195
DPP4	0.75 (0.64-0.89)	0.001	0.75 (0.64-0.89)	0.001	0.75 (0.63-0.89)	0.001
GLP-1RA	1.00 (0.74-1.33)	0.971	0.99 (0.74-1.32)	0.958	0.99 (0.74-1.32)	0.950
Insulin	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001
Other OAD*	0.80 (0.61-1.06)	0.132	0.80 (0.61-1.06)	0.133	0.80 (0.60-1.06)	0.135
Drugs with AI Properties						
Statins	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.92)	< 0.001
Fibrates	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003
ACE or ARB	0.99 (0.96-1.02)	0.866	0.99 (0.96-1.02)	0.882	0.99 (0.96-1.02)	0.891
NSAIDs	0.99 (0.97-1.02)	0.812	0.99 (0.97-1.02)	0.789	0.99 (0.97-1.02)	0.769
Poly Unsaturated Fatty Acids	0.98 (0.79-1.21)	0.873	0.98 (0.79-1.22)	0.876	0.98 (0.79-1.21)	0.875
Corticosteroids	1.05 (1.01-1.08)	0.002	1.05 (1.01-1.08)	0.002	1.05 (1.01-1.08)	0.002
Visits in Past 1 Year						
1-5	Ref					
6-10	1.40 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001	1.45 (1.35-1.45)	< 0.001
10-15	1.81 (1.73-1.88)	< 0.001	1.81 (1.73-1.88)	< 0.001	1.81 (1.73-1.88)	< 0.001
16-20	2.01 (1.92-2.11)	< 0.001	2.01 (1.92-2.11)	< 0.001	2.01 (1.91-2.10)	< 0.001
> 20	2.46 (2.36-2.57)	< 0.001	2.46 (2.36-2.57)	< 0.001	2.46 (2.37-2.57)	< 0.001
Missing	3.25 (2.81-3.76)	< 0.001	3.25 (2.81-3.75)	< 0.001	3.24 (2.82-3.74)	< 0.001
Number of HbA1c counts in Past 1 Year						
2-4	Ref					
> 4	1.03 (0.97-1.09)	0.313	1.03 (0.97-1.09)	0.311	1.03 (0.97-1.09)	0.311

Table 7. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Average Counts of Days Between All HbA1c						
< 100	Ref					
100-199	1.01 (0.97-1.04)	0.482	1.01 (0.97-1.04)	0.478	1.01 (0.98-1.04)	0.477
200-299	1.04 (1.00-1.08)	0.041	1.04 (1.00-1.08)	0.040	1.04 (1.00-1.08)	0.040
≥ 300	0.99 (0.93-1.06)	0.919	0.99 (0.93-1.06)	0.917	0.99 (0.93-1.06)	0.914

* Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide
**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 8. Likelihood of atrial fibrillation in patients with type 2 diabetes with sensitivity analysis (HbA1c 8%) (* all values < 8%, ** ≥ 1 value ≥ 8%)[1], (* Mean < 8%, ** Mean ≥ 8%)[2], (* last value < 8%, **last value ≥ 8%)[3] (*N* = 189,095).

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Uncontrolled Glycemia	Ref					
Controlled Glycemia	0.99 (0.95-1.04)	0.826	1.06 (1.01-1.11)	0.022	1.05 (1.01-1.10)	0.015
Age, Years						
< 65	Ref					
65-69	1.54 (1.27-1.87)	< 0.001	1.53 (1.27-1.85)	< 0.001	1.53 (1.27-1.85)	< 0.001
70-74	2.28 (1.81-2.88)	< 0.001	2.26 (1.8-2.848)	< 0.001	2.26 (1.82-2.84)	< 0.001
75-79	3.17 (2.47-4.05)	< 0.001	3.14 (2.46-4.02)	< 0.001	3.14 (2.46-4.02)	< 0.001
80-84	3.21 (2.45-4.22)	< 0.001	3.20 (2.44-4.20)	< 0.001	3.19 (2.43-4.19)	< 0.001
≥ 85	2.51 (1.82-3.47)	< 0.001	2.51 (1.82-3.46)	< 0.001	2.49 (1.81-3.45)	< 0.001
Sex						
Female	Ref					
Male	1.56 (1.44-1.71)	< 0.001	1.57 (1.44-1.71)	< 0.001	1.57 (1.44-1.71)	< 0.001
Race						
White	Ref					
African American	0.58 (0.55-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001
Other**	0.82 (0.74-0.90)	< 0.001	0.82 (0.75-0.90)	< 0.001	0.82 (0.75-0.90)	< 0.001
Unknown	0.90 (0.85-0.96)	0.003	0.91 (0.85-0.96)	0.003	0.90 (0.85-0.97)	0.003
Missing	0.97 (0.92-1.04)	0.505	0.98 (0.92-1.04)	0.513	0.98 (0.92-1.04)	0.512
Region						
West	Ref					
South	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001
Midwest	0.92 (0.89-0.95)	< 0.001	0.93 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001
East	0.96 (0.92-1.00)	0.094	0.96 (0.92-1.00)	0.090	0.96 (0.92-1.00)	0.093
BMI (kg/m2)						

Table 8. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
<30	Ref					
30-<35	0.99 (0.95-1.01)	0.464	0.99 (0.96-1.02)	0.444	0.99 (0.95-1.01)	0.459
≥ 35- <40	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.15)	< 0.001
≥ 40	1.30 (1.25-1.36)	< 0.001	1.30 (1.25-1.36)	< 0.001	1.30 (1.25-1.36)	< 0.001
Missing	0.63 (0.58-0.69)	< 0.001	0.64 (0.58-0.70)	< 0.001	0.64 (0.58-0.69)	< 0.001
Comorbidities Before Index Date						
Coronary Heart Disease	1.72 (1.67-1.78)	< 0.001	1.72 (1.67-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001
Congestive Heart Failure	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001
Hypertension	2.02 (1.95-2.15)	< 0.001	2.02 (1.95-2.15)	< 0.001	2.02 (1.95-2.15)	< 0.001
Dyslipidemia	1.01 (0.98-1.04)	0.490	1.01 (0.98-1.04)	0.488	1.01 (0.98-1.04)	0.496
Myocardial Infarction	1.97 (1.80-2.17)	< 0.001	1.97 (1.80-2.17)	< 0.001	1.97 (1.80-2.16)	< 0.001
Left Ventricular Hypertrophy	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001
Chronic Kidney Disease	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001
Rheumatoid Arthritis	1.02 (0.91-1.15)	0.693	1.02 (0.91-1.15)	0.692	1.02 (0.91-1.14)	0.695
COPD	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001
Hypoglycemic Events	1.32 (1.25-1.39)	< 0.001	1.32 (1.25-1.39)	< 0.001	1.31 (1.25-1.39)	< 0.001
Nonalcoholic Liver Disease	0.92 (0.80-1.06)	0.263	0.92 (0.81-1.06)	0.263	0.92 (0.81-1.06)	0.265
Smoking	0.99 (0.96-1.01)	0.409	0.99 (0.96-1.01)	0.415	0.98 (0.96-1.02)	0.412
DCSI						
0	Ref					
1	0.97 (0.93-1.01)	0.120	0.97 (0.93-1.01)	0.120	0.96 (0.93-1.01)	0.122
2	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001
3	1.08 (1.02-1.13)	0.003	1.08 (1.02-1.13)	0.003	1.07 (1.02-1.13)	0.003
4	1.20 (1.14-1.28)	< 0.001	1.21 (1.14-1.27)	< 0.001	1.20 (1.14-1.28)	< 0.001
≥ 5	1.21 (1.15-1.28)	< 0.001	1.21 (1.15-1.28)	< 0.001	1.21 (1.15-1.28)	< 0.001
Diabetes Medications (395 Days Prior Index Date)						

Table 8. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Metformin	1.02 (0.99-1.04)	0.149	1.02 (0.99-1.04)	0.175	1.02 (0.99-1.04)	0.176
Sulfonylurea	1.03 (1.01-1.06)	0.011	1.03 (1.00-1.06)	0.011	1.03 (1.00-1.06)	0.011
TZD	0.96 (0.91-1.01)	0.188	0.96 (0.91-1.01)	0.184	0.96 (0.91-1.02)	0.182
DPP4	0.75 (0.63-0.89)	0.001	0.75 (0.63-0.89)	0.001	0.75 (0.64-0.90)	0.001
GLP-1RA	0.99 (0.74-1.32)	0.957	0.99 (0.74-1.33)	0.979	0.99 (0.74-1.33)	0.963
Insulin	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001
Other OAD*	0.80 (0.61-1.06)	0.133	0.80 (0.61-1.07)	0.137	0.80 (0.61-1.07)	0.134
Drugs with AI Properties						
Statins	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.91)	< 0.001	0.89 (0.87-0.92)	< 0.001
Fibrates	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003
ACE or ARB	0.99 (0.96-1.02)	0.884	0.99 (0.96-1.02)	0.864	0.99 (0.97-1.02)	0.868
NSAIDs	0.99 (0.97-1.02)	0.790	0.99 (0.97-1.02)	0.796	0.99 (0.97-1.02)	0.792
Poly Unsaturated Fatty Acids	0.98 (0.79-1.21)	0.876	0.98 (0.79-1.22)	0.879	0.98 (0.79-1.21)	0.875
Corticosteroids	1.05 (1.01-1.08)	0.002	1.05 (1.01-1.08)	0.002	1.05 (1.02-1.08)	0.002
Visits in Past 1 Year						
1-5	Ref					
6-10	1.40 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001
10-15	1.80 (1.73-1.88)	< 0.001	1.81 (1.74-1.88)	< 0.001	1.81 (1.73-1.88)	< 0.001
16-20	2.01 (1.91-2.10)	< 0.001	2.01 (1.92-2.11)	< 0.001	2.01 (1.92-2.11)	< 0.001
> 20	2.46 (2.36-2.57)	< 0.001	2.46 (2.36-2.58)	< 0.001	2.46 (2.36-2.57)	< 0.001
Missing	3.24 (2.80-3.75)	< 0.001	3.25 (2.81-3.76)	< 0.001	3.25 (2.81-3.76)	< 0.001
Number of HbA1c counts in Past 1 Year						
2-4	Ref					
> 4	1.03 (0.97-1.09)	0.311	1.03 (0.97-1.09)	0.314	1.03 (0.97-1.09)	0.316
Average Counts of Days Between All HbA1c						

Table 8. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
< 100	Ref					
100-199	1.01 (0.97-1.04)	0.478	1.01 (0.97-1.04)	0.480	1.01 (0.98-1.04)	0.478
200-299	1.04 (1.00-1.08)	0.040	1.04 (1.00-1.08)	0.041	1.04 (1.00-1.09)	0.040
≥ 300	0.99 (0.93-1.06)	0.917	0.99 (0.93-1.06)	0.911	0.98 (0.93-1.06)	0.919

* Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 9. Likelihood of atrial fibrillation in patients with type 2 diabetes with sensitivity analysis (HbA1c 9%) (* all values < 9%, ** ≥ 1 value ≥ 9%)[1], (* Mean < 9%, ** Mean ≥ 9%)[2], (* last value < 9%, **last value ≥ 9%)[3] (*N* = 189,095).

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Uncontrolled Glycemia	Ref					
Controlled Glycemia	0.97 (0.92-1.02)	0.274	0.96 (0.90-1.02)	0.181	1.02 (0.96-1.07)	0.524
Age, Years						
< 65	Ref					
65-69	1.54 (1.27-1.86)	< 0.001	1.53 (1.27-1.85)	< 0.001	1.54 (1.27-1.86)	< 0.001
70-74	2.28 (1.81-2.87)	< 0.001	2.26 (1.85-2.84)	< 0.001	2.29 (1.82-2.88)	< 0.001
75-79	3.15 (2.46-4.02)	< 0.001	3.12 (2.44-3.99)	< 0.001	3.18 (2.48-4.06)	< 0.001
80-84	3.19 (2.43-4.19)	< 0.001	3.16 (2.41-4.15)	< 0.001	3.22 (2.46-4.23)	< 0.001
≥ 85	2.49 (1.81-3.44)	< 0.001	2.47 (1.79-3.41)	< 0.001	2.52 (1.83-3.48)	< 0.001
Sex						
Female	Ref					
Male	1.56 (1.44-1.71)	< 0.001	1.56 (1.44-1.71)	< 0.001	1.56 (1.44-1.71)	< 0.001
Race						
White	Ref					
African American	0.58 (0.56-0.60)	< 0.001	0.58 (0.55-0.60)	< 0.001	0.58 (0.56-0.60)	< 0.001
Other**	0.82 (0.74-0.90)	< 0.001	0.82 (0.74-0.90)	< 0.001	0.82 (0.74-0.90)	< 0.001
Unknown	0.90 (0.85-0.96)	0.003	0.90 (0.85-0.97)	0.003	0.90 (0.85-0.96)	0.003
Missing	0.97 (0.92-1.04)	0.501	0.97 (0.92-1.04)	0.505	0.98 (0.92-1.04)	0.507
Region						
West	Ref					
South	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001	0.90 (0.87-0.93)	< 0.001
Midwest	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001	0.93 (0.89-0.96)	< 0.001
East	0.96 (0.92-1.00)	0.096	0.96 (0.92-1.00)	0.097	0.96 (0.92-1.01)	0.093
BMI (kg/m2)						

Table 9. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
< 30	Ref					
30-< 35	0.98 (0.96-1.02)	0.476	0.98 (0.96-1.02)	0.482	0.98 (0.95-1.09)	0.459
≥ 35- < 40	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.15)	< 0.001	1.11 (1.07-1.15)	< 0.001
≥ 40	1.30 (1.25-1.36)	< 0.001	1.30 (1.25-1.36)	< 0.001	1.30 (1.25-1.36)	< 0.001
Missing	0.63 (0.58-0.69)	< 0.001	0.64 (0.58-0.69)	< 0.001	0.63 (0.58-0.69)	< 0.001
Comorbidities Before Index Date						
Coronary Heart Disease	1.72 (1.66-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001	1.72 (1.66-1.78)	< 0.001
Congestive Heart Failure	2.28 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001	2.29 (2.19-2.38)	< 0.001
Hypertension	2.02 (1.95-2.09)	< 0.001	2.03 (1.95-2.09)	< 0.001	2.02 (1.95-2.14)	< 0.001
Dyslipidemia	1.01 (0.98-1.04)	0.491	1.01 (0.98-1.04)	0.489	1.01 (0.98-1.04)	0.492
Myocardial Infarction	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001	1.97 (1.80-2.16)	< 0.001
Left Ventricular Hypertrophy	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001	1.51 (1.38-1.65)	< 0.001
Chronic Kidney Disease	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001	1.13 (1.09-1.18)	< 0.001
Rheumatoid Arthritis	1.02 (0.91-1.14)	0.694	1.02 (0.91-1.14)	0.696	1.02 (0.91-1.14)	0.692
COPD	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001	1.35 (1.31-1.39)	< 0.001
Hypoglycemic Events	1.31 (1.25-1.39)	< 0.001	1.32 (1.25-1.39)	< 0.001	1.32 (1.25-1.39)	< 0.001
Nonalcoholic Liver Disease	0.92 (0.80-1.06)	0.263	0.92 (0.80-1.06)	0.265	0.92 (0.80-1.06)	0.263
Smoking	0.98 (0.96-1.01)	0.401	0.98 (0.96-1.01)	0.400	0.98 (0.96-1.01)	0.413
DCSI						
0	Ref					
1	0.96 (0.92-1.01)	0.121	0.96 (0.93-1.01)	0.120	0.96 (0.92-1.01)	0.120
2	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001	1.18 (1.13-1.23)	< 0.001
3	1.07 (1.02-1.13)	0.003	1.07 (1.02-1.13)	0.003	1.07 (1.02-1.13)	0.003
4	1.20 (1.14-1.27)	< 0.001	1.20 (1.14-1.27)	< 0.001	1.20 (1.14-1.27)	< 0.001
≥ 5	1.21 (1.15-1.28)	< 0.001	1.21 (1.15-1.28)	< 0.001	1.21 (1.15-1.27)	< 0.001
Diabetes Medications (395 Days Prior Index Date)						

Table 9. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
Metformin	1.02 (0.99-1.04)	0.137	1.02 (0.99-1.04)	0.128	1.02 (0.99-1.04)	0.160
Sulfonylurea	1.03 (1.01-1.06)	0.009	1.03 (1.01-1.06)	0.007	1.03 (1.00-1.06)	0.011
TZD	0.96 (0.912-1.01)	0.196	0.96 (0.91-1.02)	0.203	0.96 (0.91-1.01)	0.185
DPP4	0.75 (0.63-0.89)	0.001	0.75 (0.64-0.89)	0.001	0.75 (0.63-0.89)	0.001
GLP-1RA	0.99 (0.74-1.32)	0.949	0.99 (0.74-1.32)	0.955	0.99 (0.74-1.32)	0.963
Insulin	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001	0.92 (0.89-0.95)	< 0.001
Other OAD*	0.80 (0.60-1.06)	0.133	0.80 (0.60-1.06)	0.135	0.80 (0.60-1.06)	0.133
Drugs with AI Properties						
Statins	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.91)	< 0.001	0.89 (0.86-0.92)	< 0.001
Fibrates	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003	0.93 (0.89-0.97)	0.003
ACE or ARB	0.99 (0.96-1.02)	0.887	0.99 (0.97-1.02)	0.879	0.99 (0.96-1.02)	0.881
NSAIDs	0.99 (0.97-1.02)	0.775	0.99 (0.97-1.02)	0.768	0.99 (0.97-1.02)	0.798
Poly Unsaturated Fatty Acids	0.98 (0.79-1.22)	0.878	0.98 (0.79-1.21)	0.872	0.98 (0.79-1.22)	0.877
Corticosteroids	1.05 (1.01-1.08)	0.002	1.05 (1.02-1.08)	0.002	1.05 (1.02-1.08)	0.002
Visits in Past 1 Year						
1-5	Ref					
6-10	1.40 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001	1.40 (1.35-1.45)	< 0.001
10-15	1.81 (1.73-1.88)	< 0.001	1.81 (1.74-1.88)	< 0.001	1.81 (1.73-1.88)	< 0.001
16-20	2.01 (1.92-2.10)	< 0.001	2.01 (1.92-2.10)	< 0.001	2.01 (1.92-2.11)	< 0.001
> 20	2.46 (2.35-2.57)	< 0.001	2.46 (2.35-2.57)	< 0.001	2.47 (2.36-2.58)	< 0.001
Missing	3.24 (2.80-3.75)	< 0.001	3.24 (2.80-3.75)	< 0.001	3.25 (2.81-3.75)	< 0.001
Number of HbA1c counts in Past 1 Year						
2-4	Ref					
> 4	1.03 (0.97-1.09)	0.310	1.03 (0.97-1.09)	0.310	1.03 (0.97-1.09)	0.312
Average Counts of Days Between All HbA1c						

Table 9. Continued.

	Odds ratio (95 %CI)[1]	*P* value	Odds ratio (95 %CI)[2]	*P* value	Odds ratio (95 %CI)[3]	*P* value
< 100	Ref					
100-199	1.01 (0.97-1.04)	0.478	1.01 (0.97-1.04)	0.478	1.01 (0.98-1.04)	0.477
200-299	1.04 (1.00-1.08)	0.040	1.04 (1.00-1.08)	0.040	1.04 (1.00-1.08)	0.040
≥ 300	0.99 (0.93-1.06)	0.922	0.99 (0.93-1.06)	0.916	0.99 (0.93-1.06)	0.917

* Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 10. Baseline characteristics of diabetes patients with or without antidiabetes drugs with anti-inflammatory properties (*N* = 189,095).

Variable	Overall (*N* = 189,095)		Patients with AD drugs with AI Properties (*N* = 97,877)		Patients without AD drugs with AI Properties (*N* = 91,218)		
	N/Mean	SD/%	*N*/Mean	SD/%	*N*/Mean	SD/%	*P* value
Age, Years							
Mean (SD)	67.15	10.43	65.24	9.58	69.19	10.9	< 0.001
< 65	80,276	42.45	48,137	49.18	32,139	35.23	< 0.001
65-69	38,126	20.16	21,587	22.06	16,539	18.13	
70-74	23,448	12.40	11,381	11.63	12,067	13.23	
75-79	20,921	11.06	8,651	8.84	12,270	13.45	
80-84	15,965	8.44	5,410	5.53	10,555	11.57	
≥ 85	10,359	5.48	2,711	2.77	7,648	8.38	
Sex (*n*, %)							
Male	182,518	96.52	94,167	96.21	88,351	96.86	< 0.001
Female	6,577	3.48	3,710	3.79	2,867	3.14	
Race (*n*, %)							
White	139,873	73.97	73,204	74.79	66,669	73.09	< 0.001
African American	30,116	15.93	15,022	15.35	15,094	16.55	
Other**	3,755	1.99	2,082	2.13	1,673	1.83	
Unknown	7,583	4.01	4,078	4.17	3,505	3.84	
Missing	7,768	4.11	3,491	3.57	4,277	4.69	
Region (*n*, %)							
West	50,254	26.58	26,705	27.28	23,549	25.82	< 0.001
South	54,923	29.05	29,177	29.81	25,746	28.22	
Midwest	61,018	32.27	30,902	31.57	30,116	33.02	
East	22,899	12.11	11,093	11.33	11,806	12.94	

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
Visits							
Mean Number of Visits	12.09	13.75	11.29	10.21	12.96	16.69	< 0.001
Median (IQR)	8	(5-15)	8	(5-14)	8	(5-16)	
1-5	58,461	33.24	29,250	32.26	29,211	34.28	< 0.001
6-10	40,877	23.24	22,622	24.95	18,255	21.43	
11-15	30,822	17.52	16,835	18.57	13,987	16.42	
16-20	17,575	9.99	9,357	10.32	8,218	9.65	
> 20	26,989	15.35	12,375	13.65	14,614	17.15	
Missing	1,155	0.61	238	0.24	917	1.01	
SBP (mm Hg)							
Mean (SD)	129.99	16.89	129.86	16.22	130.13	17.59	0.001
< 130 mmHg (*n*, %)	82,558	43.66	42,959	43.89	39,599	43.41	0.103
≥ 130 mmHg (*n*, %)	83,113	43.95	42,819	43.75	40,294	44.17	
Missing (*n*, %)	23,424	12.39	12,099	12.36	11,325	12.42	
DBP (mm Hg)							
Mean (SD)	72.85	11.11	73.64	10.77	72.00	11.4	< 0.001
< 80 mmHg (*n*, %)	119,296	63.09	60,182	61.49	59,114	64.81	< 0.001
≥ 80 mmHg (*n*, %)	46,312	24.49	25,572	26.13	20,740	22.74	
Missing (*n*, %)	23,487	12.42	12,123	12.39	11,364	12.46	
Baseline HbA1c (%)							
Past 1 Year							
Mean (SD)	7.29	1.37	7.46	1.36	7.1	1.36	< 0.001
Median (IQR)	6.97	(6.35-7.93)	7.15	(6.5-8.1)	6.75	(6.2-7.7)	
< 7	94,822	50.15	42,212	43.13	52,610	57.68	< 0.001

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
7 - ≤ 8	48,926	25.87	28,936	29.56	19,990	21.91	
8 - ≤ 9	24,447	12.93	14,465	14.78	9,982	10.94	
≥ 9	20,900	11.05	12,264	12.53	8,636	9.47	
All Baseline HbA1c (%) (Not Limited to 2-4)							
Past 1 Year							
Mean (SD)	7.28	1.35	7.27	1.35	7.28	1.35	0.107
Median (IQR)	6.98	(6.35-7.9)	6.97	(6.35-7.9)	6.98	(6.35-7.9)	
< 7	94,824	50.15	49,155	50.22	45,669	50.07	0.520
7 - ≤ 8	49,510	26.18	25,541	26.09	23,969	26.28	
8 - ≤ 9	24,687	13.06	12,848	13.13	11,839	12.98	
≥ 9	20,074	10.62	10,333	10.56	9,741	10.68	
Number of HbA1c Values							
Past 1 Year							
Mean (SD)	2.73	1	2.74	1.01	2.73	1	0.031
Median (IQR)	2	(2-3)	2	(2-3)	2	(2-3)	
2-4	178,275	94.28	92,245	94.25	86,030	94.31	0.533
Mean HbA1c (2-4)	7.29	1.37	7.46	1.36	7.1	1.36	< 0.001
Mean Days Between HbA1c Values	157.16	66.37	157.07	66.35	157.26	66.4	0.534
Median (IQR) Days Between HbA1c Values	147	(106-192)	147	(106-192)	147	(106-191)	
> 4	10,820	5.72	5,632	5.75	5,188	5.69	0.532
Mean HbA1c (> 4)	7.29	1.39	7.46	1.38	7.11	1.37	< 0.001
Mean Days Between HbA1c Values	66.34	15.47	66.19	15.61	66.51	15.31	0.283
Median (IQR) Days Between	67	(56-78)	67	(55-78)	67	(56-78)	

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
HbA1c Values							
Mean Past Hba1c							
n	76,661	40.5	40,642	41.5	36,019	39.5	0.381
2 Year	7.46	1.45	7.58	1.42	7.33	1.48	< 0.001
n	77,244	41.0	40,645	41.6	36,599	40.3	
3 Year	7.39	1.43	7.5	1.39	7.27	1.46	< 0.001
n	73,867	44.6	38,924	45.4	34,943	43.7	
4 Year	7.32	1.4	7.42	1.36	7.22	1.45	< 0.001
n	68,405	36.2	36,014	36.8	32,391	35.5	
5 Year	7.28	1.41	7.35	1.37	7.2	1.45	< 0..001
Baseline HDL-C (mg/dL)							
Mean (SD)	40.85	12.37	40.11	11.62	41.66	13.1	< 0.001
< 40 mg/dL	88,433	46.77	48,523	49.58	39,910	43.75	< 0.001
≥ 40 mg/dL	76,796	40.61	38,436	39.27	38,360	42.05	
Missing (*n*, %)	23,866	12.62	10,918	11.15	12,948	14.19	
Baseline LDL-C (mg/dL)							
Mean (SD)	85.62	30.62	84.69	30.37	86.64	30.86	< 0.001
< 100 mg/dL	118,571	62.70	63,387	64.76	55,184	60.50	< 0.001
≥ 100 mg/dL	41,064	21.72	20,454	20.90	20,610	22.59	
Missing (*n*, %)	29,460	15.58	14,036	14.34	15,424	16.91	
Baseline Triglycerides (mg/dL)							
Mean (SD)	170.47	135.37	179.75	143.89	160.16	124.41	< 0.001
< 150 mg/dL	91,318	48.29	44,739	45.71	46,579	51.06	< 0.001
≥ 150 mg/dL	73,984	39.13	42,276	43.19	31,708	34.76	

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
Missing (*n*, %)	23,793	12.58	10,862	11.10	12,931	14.18	
Ever Smoked Before Index Date (*n*, %)							
Yes	71,027	37.56	37,855	38.68	33,172	36.37	< 0.001
BMI (kg/m2)							
Mean (SD)	32.15	6.6	32.85	6.59	31.4	6.52	< 0.001
< 25	20,149	10.66	7,948	8.12	12,201	13.38	< 0.001
25-30	55,135	29.16	26,644	27.22	28,491	31.23	
30-< 35	56,884	30.08	30,739	31.41	26,145	28.66	
≥ 35- < 40	31,298	16.55	17,984	18.37	13,314	14.60	
≥ 40	20,761	10.98	12,334	12.60	8,427	9.24	
Missing (*n*, %)	4,859	2.57	2,225	2.27	2,634	2.89	
Diabetes duration							
Mean (SD)	5.41	2.84	5.43	2.81	5.4	2.87	0.022
< 5 (*n*, %)	80,938	42.80	41,403	42.30	39,535	43.34	< 0.001
5-10 (*n*, %)	89,964	47.58	47,243	48.27	42,721	46.83	
> 10 (*n*, %)	18,193	9.62	9,231	9.43	8,962	9.82	
Comorbidities Before Index Date (*n*, %)							
Atrial fibrillation	37,819	20.00	17,175	17.55	20,644	22.63	< 0.001
Coronary Heart Disease	57,225	30.26	26,544	27.12	30,681	33.63	< 0.001
Cerebrovascular Disease	13,059	6.91	5,649	5.77	7,410	8.12	< 0.001
Congestive Heart Failure	15,723	8.31	5,558	5.68	10,165	11.14	< 0.001
Hypertension	142,408	75.31	73,651	75.25	68,757	75.38	0.519
Dyslipidemia	38,241	20.22	20,351	20.79	17,890	19.61	< 0.001
Stroke	2,804	1.48	1,204	1.23	1,600	1.75	< 0.001

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
Myocardial Infarction	2,430	1.29	1,027	1.05	1,403	1.54	< 0.001
Left Ventricular Hypertrophy	2,585	1.37	1,126	1.15	1,459	1.60	< 0.001
Chronic Kidney Disease	23,479	12.42	5,748	5.87	17,731	19.44	< 0.001
Retinopathy and Neuropathy	37,912	20.05	18,784	19.19	19,128	20.97	< 0.001
Rheumatoid Arthritis	1,826	0.97	830	0.85	996	1.09	< 0.001
COPD	34,364	18.17	16,382	16.74	17,982	19.71	< 0.001
Hypoglycemic Events	9,270	4.90	4,064	4.15	5,206	5.71	< 0.001
Nonalcoholic Liver Disease	1,472	0.78	851	0.87	621	0.68	< 0.001
DCSI							
Mean (SD)	1.89	2.57	1.44	2.04	2.36	2.96	< 0.001
0 (*n*, %)	76,095	40.24	44,323	45.28	31,772	34.83	< 0.001
1 (*n*, %)	35,664	18.86	20,413	20.86	15,251	16.72	
2 (*n*, %)	24,922	13.18	12,431	12.70	12,491	13.69	
3 (*n*, %)	17,702	9.36	8,322	8.50	9,380	10.28	
4 (*n*, %)	10,402	5.50	4,467	4.56	5,935	6.51	
≥ 5 (*n*, %)	24,310	12.86	7,921	8.09	16,389	17.97	
Diabetes Medications (365 Days Prior Index Date) (*n*, %)							
Metformin	93,519	49.46	93,519	95.55	-	0.00	< 0.001
Sulfonylurea	73,231	38.73	46,983	48.00	26,248	28.78	< 0.001
TZD	10,723	5.67	10,723	10.96	-	0.00	< 0.001
DPP4	1,026	0.54	722	0.74	304	0.33	< 0.001
GLP-1RA	322	0.17	255	0.26	67	0.07	< 0.001
Insulin	58,075	30.71	27,427	28.02	30,648	33.60	< 0.001
Other OAD*	370	0.20	231	0.24	139	0.15	< 0.001

Table 10. Continued.

Variable	Overall (*N* = 189,095) *N*/Mean	SD/%	Patients with AD drugs with AI Properties (*N* = 97,877) *N*/Mean	SD/%	Patients without AD drugs with AI Properties (*N* = 91,218) *N*/Mean	SD/%	*P* value
Drugs with AI Properties (*n*, %)							
Statins	137,595	72.77	77,595	79.28	60,000	65.78	< 0.001
Fibrates	17,759	9.39	11,004	11.24	6,755	7.41	< 0.001
ACE or ARB	133,479	70.59	76,499	78.16	56,980	62.47	< 0.001
NSAIDs	82,700	43.73	46,329	47.33	36,371	39.87	< 0.001
Poly Unsaturated Fatty Acids	582	0.31	370	0.38	212	0.23	< 0.001
Corticosteroids	35,260	18.65	17,220	17.59	18,040	19.78	< 0.001

*Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 11. Univariate analysis of antidiabetes drugs with anti-inflammatory properties and AF (*N* = 189,095).

	Odds ratio	Confidence Interval		*P* value
		Upper	Lower	
AD Drugs with AI Properties	0.728	0.711	0.744	< 0.001

Table 12. Univariate analysis of antidiabetes drugs with anti-inflammatory and glycemic control (*N* = 189,095).

	Odds ratio	Confidence Interval		*P* value
		Upper	Lower	
AD Drugs with AI Properties	0.523	0.513	0.532	< 0.001

Table 13. Univariate analysis of glycemic control and atrial fibrillation (*N* = 189,095).

	Odds ratio	Confidence Interval		*P* value
		Upper	Lower	
Glycemic Control	1.105	1.08	1.13	< 0.001

Table 14. Logistic regression for predicting atrial fibrillation with antidiabetes drugs with anti-inflammatory properties and other covariates (*N* = 189,095).

	Odds ratio (95% CI)	*P* value
AD Drugs with AI Properties	1.02 (0.99-1.05)	0.086
Glycemic Control		
Controlled Glycemia	0.98 (0.95-1.02)	0.303
Age, Years		
< 65	Ref	
65-69	1.49 (1.23-1.81)	< 0.001
70-74	2.13 (1.69-2.68)	< 0.001
75-79	2.84 (2.22-3.64)	< 0.001
80-84	2.91 (2.22-3.83)	< 0.001
≥ 85	2.44 (1.77-3.37)	< 0.001
Sex		
Female	Ref	
Male	1.51 (1.39-1.65)	< 0.001
Race		
White	Ref	
African American	0.83 (0.75-0.91)	< 0.001
Other**	0.90 (0.85-0.96)	0.003
Unknown	0.87 (0.82-0.93)	< 0.001
Missing	0.84 (0.81-0.87)	< 0.001
Region		
West	Ref	
South	0.87 (0.842-0.898)	< 0.001
Midwest	0.91 (0.86-0.93)	< 0.001
East	0.98 (0.95-1.00)	0.160
BMI (kg/m2)		
< 30	Ref	
30 - < 35	1.11 (1.07-1.15)	< 0.001
≥ 35 - < 40	1.31 (1.25-1.36)	< 0.001
≥ 40	0.61 (0.55-0.66)	< 0.001
Missing	1.69 (1.64-1.75)	< 0.001
Comorbidities Before Index Date		
Coronary Heart Disease	2.37 (2.27-2.46)	< 0.001
Congestive Heart Failure	2.06 (1.99-2.13)	< 0.001
Hypertension	1.02 (0.98-1.0)	0.211
Dyslipidemia	2.14 (1.95-2.35)	< 0.001

Table 14. Continued.

	Odds ratio (95% CI)	*P* value
Myocardial Infarction	1.68 (1.53-1.83)	< 0.001
Left Ventricular Hypertrophy	1.17 (1.12-1.22)	< 0.001
Chronic Kidney Disease	1.11 (0.99-1.24)	0.073
Rheumatoid Arthritis	1.43 (1.39-1.48)	< 0.001
COPD	1.43 (1.36-1.51)	< 0.001
Hypoglycemic Events	1.03 (0.89-1.18)	0.679
Nonalcoholic Liver Disease	1.02 (0.99-1.04)	0.195
Smoking	1.01 (0.97-1.05)	0.530
DCSI		
0	Ref	
1	1.29 (1.23-1.34)	< 0.001
2	1.21 (1.15-1.27)	< 0.001
3	1.41 (1.34-1.49)	< 0.001
4	1.52 (1.44-1.60)	< 0.001
≥ 5	1.04 (1.01-1.06)	0.003
Diabetes Medications (395 Days Prior Index Date)		
Sulfonylurea	0.82 (0.69-0.97)	0.023
DPP4	1.10 (0.82-1.47)	0.498
GLP-1RA	1.00 (0.96-1.03)	0.979
Insulin	0.84 (0.64-1.12)	0.242
Other OAD*	0.89 (0.87-0.92)	< 0.001
Drugs with AI Properties		
Statins	0.93 (0.89-0.97)	0.003
Fibrates	1.00 (0.97-1.03)	0.766
ACE or ARB	1.08 (1.05-1.11)	< 0.001
NSAIDs	1.08 (0.87-1.34)	0.463
Poly Unsaturated Fatty Acids	1.20 (1.16-1.24)	< 0.001
Corticosteroids	1.19 (1.16-1.23)	< 0.001

*Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

Table 15. Logistic regression for predicting atrial fibrillation with antidiabetes drugs with anti-inflammatory properties and other covariates, excluding mediator (*N* = 189,095).

	Odds ratio (95 %CI)	*P* value
AD Drugs with AI Properties	1.02 (0.98-1.05)	0.070
Age, Years		
< 65	Ref	
65-69	1.48 (1.22-1.79)	< 0.001
70-74	2.10 (1.67-2.64)	< 0.001
75-79	2.79 (2.19-3.57)	< 0.001
80-84	2.86 (2.18-3.75)	< 0.001
≥ 85	2.41 (1.74-3.30)	< 0.001
Sex		
Female	Ref	
Male	1.51 (1.39-1.64)	< 0.001
Race		
White	Ref	
African American	0.83 (0.75-0.91)	< 0.001
Other**	0.91 (0.85-0.96)	0.003
Unknown	0.87 (0.82-0.93)	< 0.001
Missing	0.84 (0.82-0.87)	< 0.001
Region		
West	Ref	
South	0.87 (0.84-0.89)	< 0.001
Midwest	0.95 (0.86-0.93)	< 0.001
East	0.98 (0.95-1.01)	0.166
BMI (kg/m2)		
< 30	Ref	
30 - < 35	1.11 (1.07-1.15)	< 0.001
≥ 35 - < 40	1.31 (1.26-1.37)	< 0.001
≥ 40	0.61 (0.55-0.66)	< 0.001
Missing	1.69 (1.64-1.75)	< 0.001
Comorbidities Before Index Date		
Coronary Heart Disease	2.37 (2.27-2.47)	< 0.001
Congestive Heart Failure	2.06 (1.99-2.14)	< 0.001
Hypertension	1.01 (0.99-1.00)	0.212
Dyslipidemia	2.14 (1.95-2.34)	< 0.001
Myocardial Infarction	1.68 (1.53-1.83)	< 0.001
Left Ventricular Hypertrophy	1.17 (1.13-1.21)	< 0.001

Table 15. Continued.

	Odds ratio (95 %CI)	*P* value
Chronic Kidney Disease	1.11 (0.99-1.24)	0.073
Rheumatoid Arthritis	1.43 (1.39-1.48	< 0.001
COPD	1.43 (1.36-1.51)	< 0.001
Hypoglycemic Events	1.03 (0.89-1.18)	0.674
Nonalcoholic Liver Disease	1.01 (0.99-1.04)	0.200
Smoking	1.01 (0.97-1.05)	0.526
DCSI		
0	Ref	
1	1.29 (1.23-1.34)	< 0.001
2	1.21 (1.15-1.27)	< 0.001
3	1.42 (1.34-1.49)	< 0.001
4	1.52 (1.44-1.60)	< 0.001
≥ 5	1.04 (1.01-1.07)	0.002
Diabetes Medications (395 Days Prior Index Date)		
Sulfonylurea	0.82 (0.69-0.97)	0.024
DPP4	1.10 (0.82-1.47)	0.499
GLP-1RA	1.00 (0.97-1.03)	0.870
Insulin	0.84 (0.64-1.12)	0.245
Other OAD*	0.89 (0.86-0.91)	< 0.001
Drugs with AI Properties		
Statins	0.93 (0.89-0.97)	0.003
Fibrates	1.00 (0.97-1.03)	0.773
ACE or ARB	1.08 (1.05-1.10)	< 0.001
NSAIDs	1.08 (0.87-1.34)	0.463
Poly Unsaturated Fatty Acids	1.20 (1.16-1.24)	< 0.001
Corticosteroids	1.19 (1.16-1.23)	< 0.001

*Other OADs = alpha-glucosidase inhibitors (acarbose, miglitol), meglinitinide analogues (nateglinide, repaglinide), pramlintide

**American Indians, Asian, Alaska Natives, Pacific Islanders, Native Hawaiian

CHAPTER 5

DISCUSSION

This study was conducted in a large cohort of patients who received care at the VA between 2000-2014 to test the following hypotheses: 1) the incidence rate of AF is higher in patients with T2DM compared to patients without T2DM; 2) In patients with T2DM, poor glycemic control in the prior 12 months is positively associated with AF; 3) ADAIP reduces the odds of developing AF compared to non-ADAIP users in patients with T2DM, when controlling for the glycemic effect of the drugs. This chapter discusses findings in relation to the existing literature, real world relevance and implications, as well as the study's strengths and limitations.

This study found a small association between glycemic control in the prior 12 months and AF in patients with T2DM. While the association was statistically significant, it was not clinically relevant. Statistical significance could be due to the large sample size of the study. However, other comorbidities including CHD, CHF, hypertension, MI, LVH, CKD, and COPD, played much greater roles in the occurrence of AF in patients with T2DM. Based on these results, it is our recommendation that glycemic control may not be associated with AF but other risk factors are important to consider for clinicians, decision-makers, and policy makers when the goal is to reduce the risk of developing AF in patients with T2DM. These results also suggest that patients with these risk factors

Should be managed more frequently, and potentially AF screening should be considered.

Prevention or early detection of AF should be an attractive approach for policy makers in patients with diabetes rather than dealing with its repercussions. AF may lead to various other diseases or emergency events including stroke. The total cost of stroke was estimated to be $73.7 billion in 2010.[119] It is known that strokes in AF patients are more severe and disabling than in patients without AF.[120,121] Overall, it is not easy to estimate the cost of AF since it is associated with many other diseases. However, it can be assumed that the overall burden of AF is considerable in the United States.[122] Thus, it is important to limit the occurrence of AF in the overall population.

In previous studies not limited to T2DM patients,[87] MI,[123] CHF,[123] CHD,[124] hypertension,[123] and LVH[125] were associated with AF. These CV comorbidities were also associated with AF in this current study, which was limited to a diabetes population.

Given an exposure period of 12 months, we used three definitions with different interpretations to define uncontrolled glycemia prior to index date: 1) at least one HbA1c value ≥ 7%; 2) mean HbA1c ≥ 7%; and 3) last HbA1c recorded prior to the index date ≥ 7%. The first definition identifies patients with uncontrolled glycemia at any point during the observation period. Mean HbA1c provides an average glycemic control over the observation period, which could include periods of poor control offset by periods of good control. The third definition discerns if glucose control closest to index date influences the risk of AF. Therefore, odds ratios derived out of these three definitions should be interpreted as appropriate for the specific measure.

The association between AF and HbA1c in the prior 12 months varied, depending on the definition of glycemic control. With the first definition – minimum 1 HbA1c value

above 7% as uncontrolled – patients who had uncontrolled glycemia in the prior 12 months were significantly more likely to have AF than those with controlled glycemia. The association became stronger for patients with ≥ 1 HbA1c between 9% and 11%. In contrast, patients with mean HbA1c 7-9% were significantly less likely to have AF than patients with mean HbA1c < 7%, and the association became nonsignificant in the higher HbA1c categories. Finally, having an HbA1c recorded prior to the index date of 7-9% or 9-11% was significantly protective against developing AF relative to patients whose last HbA1c recorded prior to the index date was < 7%.

Overall results are different[81,85] and similar[87] to the existing literature, depending on the way glycemic control was defined. However, it is important to take study differences into consideration when interpreting these findings relative to prior studies. Only 3 studies have shown an association between glycemic control and AF in patients with T2DM.[81,85,87] None of these studies explored the association between AF and glycemic control by restricting glycemic control exposure to the 12 months prior to diagnosis of AF in patients with T2DM. In the prior studies, glycemic control exposure was defined as a cumulative HbA1c or mean HbA1c over multiple years prior to diagnosis. In one study, HbA1c in patients with T2DM was compared to patients without diabetes in predicting AF.[81] When compared to other studies, the interpretation of glycemic control in our study should be done carefully. Because we limited our exposure to the 12 months prior to the AF event, this reflects near-term glycemic control as opposed to long-term glycemic control presented in other studies. The detailed comparison of this study and other studies is discussed below.

Our results were different compared to the study conducted by Dublin et al., which

found that glycemic control was associated with decreased likelihood of developing AF.[81] In our study, when mean ≥ 7% HbA1c was defined as uncontrolled, glycemic control was not associated with AF. There were differences in population, inclusion criteria, and different comparison groups may explain the disparities in results. Their study used patients without diabetes as a comparison group to show the association of AF and glycemic control. On the other hand, our study investigated the association of AF by comparing poor and good glycemic control in patients with T2DM.

Huxley et al.[85] found a linear association between HbA1c and AF, with AF risk increasing with higher HbA1c. In sensitivity analyses, we used different HbA1c values to see if different cut-off values make any difference in association. Even with different HbA1c values, the result was towards nonsignificance. Differences in study population, design, baseline clinical variables, exposure definition, and approach to adjust the multivariate regression model can help us discern the cause of disparities. Huxley et al. conducted a prospective cohort study that included patients who were between the ages of 45 and 64. The Huxley study adjusted the regression model for the duration of diabetes, whereas we matched cases and controls based on diabetes duration which may have made our comparison groups more similar in terms of duration-related severities and unmeasured confounders. Furthermore, there was a difference in baseline mean HbA1c between studies. In our study, the mean (SD) baseline HbA1c of the study population was 7.3% (1.4) versus 8.3% (3.3) in the Huxley study. They did not adjust their regression model for diabetes severity, which we found as one of the significant risk factors of AF.

Fatemi et al.[87] did not find a relationship between glycemic control and new onset of AF. While we found that glycemic control was associated with AF, the association was

weak and was not consistent across definitions of glycemic control. Patients included in the Fatemi et al. study were comparatively younger and included higher proportions of White and female patients than our study. Also, baseline mean HbA1c in the Fatemi study was 8.3% (1.0) compared to HbA1c mean 7.3% (1.4) in our study.

In addition to CV risk factors previously discussed, age, sex, and race were significantly associated with AF, which is consistent with existing literature.[124] We found that an increase in age was independently associated with AF in patients with T2DM. However, the trend consistently increased with every 5-year incremental category except for patients who were older than 85 years. The potential reason could be due to a healthy survivor bias in which a healthy patient who has lived for a longer time reached the cohort.[126] Additionally, males and Whites were more likely to be associated with AF compared to female and African Americans, respectively.[124,127]

CKD develops in patients with long-term poorly managed diabetes. In this study, CKD was significantly associated with AF. In a previous study, CKD and AF were also associated.[128] The association between CKD and AF can be explained by the fact that these two diseases share a number of common risk factors.[129-131] Additionally, CKD and AF are linked by elevated inflammatory biomarkers, which can again potentially link these two diseases.[46,132,133]

COPD was associated with an increased likelihood of having AF. The possible cause of this association could be that they share common risk factors including age, gender, smoking, blood pressure, and BMI.[134,135] Furthermore, treatments used for COPD patients, including long-term glucocorticoid use, are associated with left atrial enlargement[113] which in turn is associated with AF.

DCSI was a significant predictor of AF. None of the previous studies used a severity index (CCI, DCSI, or EHI) to predict AF. DCSI has been previously validated for prediction of mortality and hospitalization in patients with diabetes.[118] DCSI could be significantly associated in part due to inclusion of comorbidities that were independently identified as AF risk factors including atherosclerosis and MI.

Hypoglycemic events were associated with an increased likelihood of AF. A prior study also identified this association,[136] which could be explained by cardiac repolarization and alteration in cardiac autonomic activity associated with AF.[136] An alternate explanation of this finding could be similarity in the symptoms of hypoglycemia and AF. Symptoms of hypoglycemia, such as rapid heartbeat, lightheadedness, sweating and fatigue, may have prompted physicians to order a precautionary ECG test, which could have led to more frequent and earlier detection of AF in these patients.

We found that cases had a higher mean number of office visits than controls. The higher number of visits in cases indicates that these patients were more closely and frequently managed by their physicians. If a patient is visiting VA facilities more frequently, this patient can potentially have more frequent AF screenings, and hence may be more likely to be diagnosed with AF.[9] As a result, we adjusted the odds ratios in this study for number of office visits. More frequent visits can also indicate poorer health with other comorbidities. This finding was confirmed as cases had higher comorbid conditions including CHD, CHF, dyslipidemia, and hypertension – indicating poorer health. This may have led patients to visit VA facilities more frequently.

There is no consensus as to the appropriate HbA1c threshold for differentiating between controlled or uncontrolled glycemia. The ADA recommends higher treatment

goals for a specific set of patients in which the risks of hypoglycemia exceed the benefits of tighter glycemic control such as patients with limited life expectancies, and older adults or individuals with more comorbidities.[31] Given that our study population had a mean age of 67.2 years, 75.3% had hypertension and 30.3% had CHD, HbA1c < 7% may not be a valid threshold to define glycemic control. As a result, we conducted sensitivity analyses using 8% and 9% as threshold values. However, we did not find significant associations between glycemic control and AF by increasing the HbA1c threshold.

We realize that T2DM is a chronic disorder and accumulated poor glycemic control may be a more important factor than near-term control in regards to theorized or real associations between glycemic control and AF. We therefore gathered HbA1c values for an additional 4 years before the 12-month primary exposure period. However, past HbA1c values did not materially alter the regression model results.

Unlike the aforementioned studies conducted to find the association between glycemic control and AF,[81,85,87] this study adjusted for potential confounding by medications with AI properties in the association between glycemic control and AF. While estimating the association between glycemic control and AF, we adjusted the multivariate regression model with ADAIP including fibrates and statins in the prior 12 months. We found that ADAIP was not associated with AF after adjusting for potential confounders. However, the result was not consistent with existing literature.[50,51]

In prior studies, ADAIP – metformin and TZD – were associated with a decreased risk of AF.[50,51] The exposure comparison and population difference may explain the difference in results. The metformin study, however, compared metformin users with AD-treatment-naive patients. We compared patients who were on metformin alone or in

combination with other AD therapies to those who were on other AD medications without metformin. Metformin is a first line therapy for patients with T2DM, which means if a patient is using other diabetes medications but not metformin, they may have used metformin earlier. Limiting medication exposure to 12 months may have underestimated the association between prior metformin and TZD use and AF in this cohort of patients with T2DM. Additionally, both of the prior studies were conducted in the Taiwanese population who had less comorbidity and had less diabetes medication use.

We hypothesized that statins, fibrates, and corticosteroids, which have AI properties,[61,62] reduce the risk of AF. We found that statins and fibrates were protective but corticosteroids were associated with an increased risk of AF in patients with T2DM, which is consistent with the literature.[137]

This is the first study to report AF incidence rates in a national cohort of veterans. The incidence rate of AF reported in this study is higher than a similar study conducted on data described as large, commercial, or Medicare Advantage health plans – which represented 5% of the U.S. population.[3] In our study, we found the incidence rate of AF was 11.07 cases per 1,000 person-years in the overall population. In the other study, the age and gender adjusted incidence rate of the overall population was low, estimated at 3.30 AF cases per 1,000 person-years in 2007.[3] There are several reasons that could potentially explain the differences between these incidence rates. Overall, AF risk is higher in males and also increases with age. While the other study of insured patients did not report demographics of the included population, we speculate that the predominantly older male population in our study may explain the higher AF incidence rates. Furthermore, the incidence rate was age and sex adjusted in the other study while we did not adjust for age

and sex in our study.

Our results were consistent with previous studies in patients ≥ 65 year old.[124] In a prospective cohort study that included only noninstitutionalized ≥ 65 year old patients with three years of follow-up, the incidence rate was 19.2 cases per 1,000 person-years.[124] The crude incidence rate in our study for ≥ 65-year-old was 20.7 cases per 1,000 person-years. Similar to our findings, the same study also found that males had higher rates of AF than females and that AF incidence rate in both sexes increased with age.

In a prospective study conducted on the Atherosclerosis Risk in Communities (ARIC) cohort,[138] the incidence rate of AF in < 65-year-old patients with T2DM and non-T2DM was consistent with our findings.[85] Age adjusted incidence rates of AF in T2DM and non-T2DM age < 65 years were 9.02 versus 4.51 cases per 1000 person versus and it was 8.26 versus 5.31 cases per 1,000 person-years in patients age < 65 in our study.

Understanding AF risk in patients with T2DM and the lacking association between glycemic control and AF can give insight and motivation to clinicians, decision makers, and patients to pay special attention to other AF risk factors to reduce the risk of developing AF and its associated complications. Given a weak association between glycemic control and the occurrence of AF, special attention can be given to patients with other risk factors such as MI, CHD, and LVH for an early diagnosis of AF in patients with T2DM. Since the health burden of a late diagnosis of AF is high, early AF screening and detection in susceptible patients may lower the risk of complications associated with developing AF. Management of glycemic control is a cornerstone of managing diabetes for its protective effects on development of microvascular complications, and has growing evidence for reducing risk of macrovascular complications. However, this study reinforces the

importance of managing CV risk factors in this population.

To date, this is the first study to examine the association between the level of glycemic control of T2DM in the past 12 months and incidence of AF. Furthermore, none of the prior studies adjusted their multivariable models for AI drugs, which can be a confounder that modifies the association between glycemic control and AF.

A case-control study design can be a challenging design to understand and warrants cautious interpretation of HbA1c when predicting AF due to a number of reasons. Causality cannot be established with a case-control study, thus this study would evaluate an association but not a causal relationship between glycemic control and AF. In a case-control study, selection bias can occur when an inappropriate sampling technique is used to select controls. Based on the several sampling methods used in case-control studies, this study used incidence density sampling for selection of controls, which approximates rate ratios. Rate ratios provide a better effect estimate when risk of exposure in a population is required. Methodologically, this study may not be as robust as a cohort study; however, this sampling technique makes this study a strong case-control study.

Patients classified as not having AF may not have severe enough disease to result in regular visits, which can possibly create selection bias in the study. However, incidence density sampling reduces selection bias in case-control studies and enabled us to mimic the estimate of cohort studies. In this study, we randomly selected controls from the same population from which we selected cases and all patients had the same probability of becoming a control patient before their AF diagnosis.

The study used 15 years of data to identify cases and controls. The long-term data allowed us to capture a large number of AF cases in the VA system. The large sample from

this long-term period made this the largest study to date to examine the association between glycemic control and AF in patients with T2DM. The large sample also allowed matching cases with 4 controls, which improves precision and estimates.

Along with strengths, the study has some limitations. The VA population is predominantly male which limits the generalizability to other populations. Diabetes progresses with time and accumulated poor glycemic control is responsible for many diabetes-related complications. Previous studies have taken all HbA1c values before AF diagnosis into account to identify the association between glycemic control and AF.

Approximately 57% of the population was 65 years and older, and these patients may have Medicare prescription drug coverage and filled their prescriptions outside the VA system. Further, some drugs with AI properties can be taken without prescriptions, such as aspirin and ibuprofen, and the study was not able to capture those over-the-counter medications. Both of these scenarios could lead to misclassification bias.

There are other potential causes of misclassification bias in this study. We assumed that the first ICD-9 code of AF in the system was the first day of the diagnosis in the VA. However, there were some patients on antiarrhythmic drugs before their first AF diagnosis, which means that these patients already had arrhythmic episodes. Therefore, we excluded patients who filled their prescriptions of antiarrhythmic drugs in VA facilities, in the 12 months prior to AF diagnosis, to minimize the risk of AF misclassification. However, if patients obtained prescription of antiarrhythmic drugs from pharmacies outside the VA before their first diagnosis of AF then we may have captured an incorrect AF diagnosis date.

We may have introduced selection bias by restricting exposure to only those

patients with a minimum of 2 documented HbA1c values in the prior 12 months. This could show that patients who are getting their blood glucose test performed twice in a year could either be healthy or vigilant or probably sicker compared to the general population.

The study contributes the evidence of the association between near-term glycemic control and AF in a national VA cohort, considering the effect of ADAIP and drugs with AI properties. This study tested a hypothesis that patients with T2DM and poor glycemic control in the prior 12 months had an increased likelihood of developing AF compared to those with good glycemic control. We conclude that glycemic control in the prior 12 months in patients is, at best, a modest predictor of AF. The more compelling elements that significantly predicted AF were CHF, hypertension, MI, CHD, and LVH. Therefore, these multiple factors should be considered for managing AF risk and facilitating early diagnosis in patients with T2DM. For future research, a thorough investigation related to CV comorbidities and AF in patients with T2DM using causal inference method can provide a better understanding of additional risk factors in these patients.

APPENDIX A

ANTIDIABETIC DRUGS

Table 16. List of drugs used in diabetes.

Gpi_Category_2	Gpi_Category_3	Gpi_Category_4
Oral Agents		
Biguanides	Biguanides	Metformin Hcl
Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Sitagliptin Phosphate
Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Saxagliptin Hcl
Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Alogliptin Benzoate
Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors	Linagliptin
Insulin Sensitizing Agents	Thiazolidinediones	Pioglitazone Hcl
Insulin Sensitizing Agents	Thiazolidinediones	Rosiglitazone Maleate
Sulfonylureas	Sulfonylureas	Chlorpropamide
Sulfonylureas	Sulfonylureas	Glimepiride
Sulfonylureas	Sulfonylureas	Glipizide
Sulfonylureas	Sulfonylureas	Glyburide
Sulfonylureas	Sulfonylureas	Glyburide Micronized
Sulfonylureas	Sulfonylureas	Tolazamide
Sulfonylureas	Sulfonylureas	Tolbutamide
Alpha-Glucosidase Inhibitors	Alpha-Glucosidase Inhibitors	Acarbose
Alpha-Glucosidase Inhibitors	Alpha-Glucosidase Inhibitors	Miglitol
Antidiabetic - Amylin Analogs	Antidiabetic - Amylin Analogs	Pramlintide Acetate
Meglitinide Analogues	Meglitinide Analogues	Nateglinide
Meglitinide Analogues	Meglitinide Analogues	Repaglinide
Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Canagliflozin
Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Dapagliflozin Propanediol
Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Empagliflozin
Insulin		
Insulin	Human Insulin	Insulin Aspart
Insulin	Human Insulin	Insulin Glulisine
Insulin	Human Insulin	Insulin Lispro (Human)
Insulin	Human Insulin	Insulin Regular Human
Insulin	Human Insulin	Insulin Detemir
Insulin	Human Insulin	Insulin Glargine

Table 16. Continued.

Gpi_Category_2	Gpi_Category_3	Gpi_Category_4
Insulin	Human Insulin	Insulin Isophane Human
Combination Insulin		
Insulin	Human Insulin	Insulin Lispro Prot & Lispro
Insulin	Human Insulin	Insulin Aspart Prot & Aspart
Insulin	Human Insulin	Insulin Isophane & Regular
Injectable Agents		
Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Exenatide
Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Liraglutide
Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Albiglutide
Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Incretin Mimetic Agents (Glp-1 Receptor Agonists)	Dulaglutide
Combination Products		
Antidiabetic Combinations	Dipeptidyl Peptidase-4 Inhibitor-Biguanide Combinations	Alogliptin-Metformin Hcl
Antidiabetic Combinations	Dipeptidyl Peptidase-4 Inhibitor-Biguanide Combinations	Linagliptin-Metformin Hcl
Antidiabetic Combinations	Dipeptidyl Peptidase-4 Inhibitor-Biguanide Combinations	Saxagliptin-Metformin
Antidiabetic Combinations	Dipeptidyl Peptidase-4 Inhibitor-Biguanide Combinations	Sitagliptin-Metformin Hcl
Antidiabetic Combinations	Dpp-4 Inhibitor-Hmg Coa Reducctase Inhibitor Comb	Sitagliptin-Simvastatin
Antidiabetic Combinations	Dpp-4 Inhibitor-Thiazolidinedione Combinations	Alogliptin-Pioglitazone
Antidiabetic Combinations	Meglitinide-Biguanide Combinations	Repaglinide-Metformin Hcl
Antidiabetic Combinations	Sulfonylurea-Biguanide Combinations	Glipizide-Metformin Hcl
Antidiabetic Combinations	Sulfonylurea-Biguanide Combinations	Glyburide-Metformin
Antidiabetic Combinations	Sulfonylurea-Thiazolidinedione	Pioglitazone Hcl-Glimepiride

Table 16. Continued.

Gpi_Category_2	Gpi_Category_3	Gpi_Category_4
Antidiabetic Combinations	Sulfonylurea-Thiazolidinedione Combinations	Rosiglitazone-Glimepiride
Antidiabetic Combinations	Thiazolidinedione-Biguanide Combinations	Pioglitazone Hcl-Metformin Hcl
Antidiabetic Combinations	Thiazolidinedione-Biguanide Combinations	Rosiglitazone-Metformin
Antidiabetic Combinations	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors-Biguanide Combinations	Canagliflozin-Metformin
Antidiabetic Combinations	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors-Biguanide Combinations	Dapagliflozin Propanediol-Metformin
Antidiabetic Combinations	Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors-Biguanide Combinations	Empagliflozin-Linagliptin

Drugs marketed as of Dec 31, 2014; includes all combinations of the above products.

APPENDIX B

DISEASE WITH ICD-9 CODES

Table 17. A list of diseases used in the study.

Condition	ICD-9 Codes	Description
T2DM		
ICD-9	250.X0	Type II DM without mention of complication
	250.X2	Type II DM, uncontrolled
Biometric HbA1c		> 6.5%
T1DM		
ICD-9	250.X1	Type II DM without mention of complication
	250.X3	Type II DM, uncontrolled
Biometric		HbA1c > 6.5%
Gestational Diabetes		
ICD-9	648.8X	Abnormal glucose tolerance
Pregnancy		
ICD-9	630.XX-679.XX	Pregnancy-related diagnosis codes
V-codes	V22.X	Normal pregnancy
	V23.X	Supervision of high-risk pregnancy
	V24.X	Postpartum care and examination
	V27.X	Outcome of delivery
Gastroparesis	536.3	Gastroparesis
Hypoglycemia	251.2	Hypoglycemia, unspecified
	250.8* without 707-10-707.9, 731.8)	Diabetes with other complications
Hypertension		
ICD-9	401.XX	Essential hypertension
	402.XX	Hypertensive heart disease
	404.XX	Hypertensive heart and kidney disease
	405.X	Secondary hypertension
Biometric Blood Pressure		Two consecutive readings ≥ 130/80 mmHg
Acute MI		
ICD-9	410.XX	Acute myocardial infarction
Coronary Heart Disease		
ICD-9	411.XX	Other acute and subacute forms of ischemic heart disease

Table 17. Continued.

Condition	ICD-9 Codes	Description
	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
Hyperlipidemia		
ICD-9	272.0-	Pure hypercholesterolemia
	272.1	Pure hyperglyceridemia
	272.2	Mixed hyperlipidemia
TG		≥ 150 mg/dl
LDL		≥ 100 mg/dl
HDL		< 40 mg/dl
Cerebrovascular Disease		
ICD-9	437	Cerebral atherosclerosis
	437.1	Other generalized ischemic cerebrovascular disease
	437.2	Hypertensive encephalopathy
	437.3	Cerebral aneurysm, nonruptured
	433.X0	Occlusion and stenosis of precerebral arteries without infarct
	434.X0	Occlusion of cerebral arteries without infarct
	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 cerebrovascular infarction or hemorrhage
Stroke		
ICD-9	430.X	Subarachnoid hemorrhage
	431.X	Intracerebral hemorrhage
	432.X	Other and unspecified intracranial hemorrhage
	433.X1	Occlusion and stenosis of precerebral arteries
	434.X1	Occlusion of cerebral arteries with infarct
Chronic Kidney Disease		

Table 17. Continued.

Condition	ICD-9 Codes	Description
ICD-9	250.4X	Diabetes with renal manifestations
	403.XX	Hypertensive kidney disease
	404.XX	Hypertensive heart and kidney disease
	585.X	Chronic kidney disease (CKD)
Microvascular Complications	250.6	Diabetes with neurological manifestations
ICD-9	362.01-362.07	Diabetic retinopathy
	337.1	Peripheral autonomic neuropathy NOS
	354. XX, 355. XX	Mononeuropathy of upper/lower limb
	357.2	Polyneuropathy in diabetes
	713.5	Neurogenic arthropathy
	443.81	Peripheral angiopathy

APPENDIX C

DIABETES COMPLICATION SEVERITY INDEX (DCSI) AND LIST OF COMPLICATIONS, ICD-9 CODES AND LABORATORY DATA[118]

Table 18. A list of diseases used to score diabetes complication and severity of disease.

Complications	ICD-9 Diagnosis	ICD-9 Code	DSCI Score*
Retinopathy	Diabetic ophthalmologic disease	250.5x	1
	Background retinopathy	362.01	1
	Other retinopathy	362.1	1
	Retinal edema	362.83	1
	CSME	362.53	1
	Other retinal disorders	362.81, 362.82	1
	Proliferative retinopathy	362.02	2
	Retinal detachment	361.xx	2
	Blindness	369.xx .00-.99	2
	Vitreous hemorrhage	379.23	2
Nephropathy	Diabetic nephropathy	250.4	1
	Acute glomerulonephritis	580	1
	Nephrotic syndrome	581	1
	Hypertension, nephrosis	581.81	1
	Chronic glomerulonephritis	582	1
	Nephritis/nephropathy	583	1
	Chronic renal failure	585	2
	Renal failure NOS	586	2
	Renal insufficiency	593.9	2
	Urine protein ≥ 30 mg/g of creatinine, or (+) dipstick protein or serum creatinine ≥ 1.5 mg/dL		1
	Serum creatinine > 2.0 mg/dL		2
Neuropathy	Diabetic neuropathy	356.9, 250.6	1
	Amyotrophy	358.1	1
	Cranial nerve palsy	951.0, 951.1, 951.3	1
	Mononeuropathy	354.0-355.9	1
	Charcot's arthropathy	713.5	1
	Polyneuropathy	357.2	1
	Neurogenic bladder	596.54	1
	Autonomic neuropathy	337.0, 337.1	1
	Gastroparesis/diarrhea	564.5, 536.3	1
	Orthostatic hypotension	458.0	1
Cerebrovascular	TIA	435	1
	Stroke	431, 433, 434, 436	2
Cardiovascular	Atherosclerosis	440.xx	1
	Angina pectoris	413	1

Table 18. Continued.

Complications	ICD-9 Diagnosis	ICD-9 Code	DSCI Score*
	Other chronic IHD	414	1
	Myocardial infarction	410	2
	Ventricular fibrillation, arrest	427.1, 427.3	2
	Atrial fibrillation, arrest	427.4, 427.5	2
	Other ASCVD	429.2	1
	Old myocardial infarction	412	2
	Heart failure	428	2
	Atherosclerosis, severe	440.23, 440.24	2
	Aortic aneurysm/dissection	441	2
Peripheral vascular disease	Diabetic PVD	250.7	1
	Other aneurysm, LE	442.3	1
	PVD	443.81, 443.9	1
	Foot wound + complication	892.1	1
	Claudication, intermittent	443.9	1
	Embolism/thrombosis (LE)	444.22	2
	Gangrene	785.4	2
	Gas gangrene	0.40	2
	Ulcer of lower limbs	707.1	2
Metabolic	Ketoacidosis	250.1	2
	Hyperosmolar	250.2	2
	Other coma	250.3	2

*Severity index is based on a scale ranging from 0-2 for each complication as follows: 0 = no abnormality, 1 = some abnormality, 2 abnormalities.

ICD-9 indicates International Classification of Diseases, Ninth Revision; CSME, cystoid macular edema/degeneration; NOS, not otherwise specified; TIA, transient ischemic attack; IHD, ischemic heart disease; ASCVD, atherosclerotic cardiovascular disease; PVD, peripheral vascular disease; LE, lower extremity.

APPENDIX D

ANTI-INFLAMMATORY DRUGS

Table 19. A list of drugs with anti-inflammatory properties.

	Class	Generic Names	Brand Names
Cardio-protective agents	Statins	Atorvastatin	Lipitor
		Fluvastatin	Lescol
		Lovastatin	Altoprev
			Mevacor
		Pitavastatin	Livalo
		Pravastatin	Pravachol
		Rosuvastatin	Crestor
		Simvastatin	Zocor
	Fibrates	Gemfibrozil	Lopid
		Fenofibrate	Tricor
			Fibricor
	ACE inhibitors	Captopril	Capoten
		Enalapril	Vasotec
		Fosinopril	Monopril
		Lisinopril	Zestril
			Prinivil
		Perindopril	Aceon
		Quinapril	Accupril
		Ramipril	Altace
		Trandolapril	Mavik
		Benazepril	Lotensin
		Moexipril	Univasc
		Quinapril	Accupril
	Angiotensin receptor blockers	Candesartan	Atacand
		Losartan	Cozaar
		Valsartan	Diovan
		Irbesartan	Avapro
		Olmesartan	Benicar
		Telmisartan	Micardis
		Eprosartan	Teveten
Drug affecting insulin sensitivity	Biguanides	Metformin	Glucophage
			Glucophage XR
			Glumetza
			Fortamet
			Riomet
	Glitazones (Thiazolidinediones)	Pioglitazone	Actos
		Rosiglitazone	Avandia
Poly Unsaturated Fatty Acids		Omega-3 polyunsaturated fatty acids	Lovaza
			Fish oil
			Omega-3
			Omacor

Table 19. Continued.

	Class	Generic Names	Brand Names
Corticosteroids	Glucocorticoids	Betamethasone	Celestone
			Celestone Soluspan
			Celestone Phosphate
			Beta-Phos/AC
		Budesonide	Pulmicort
		Cortisone	Cortone acetate
		Dexamethasone	Decadron
			Dexamethasone Intensol
			Hexadrol
		Hydrocortisone	Cortef
			Cortifoam
			Hydrocortone
		Methylprednisolone	Medrol
		Prednisolone	Prelone
			Orapred
			PediaPred
			Millipred
		Prednisone	Deltasone
			Rayos
			Orasone
			Meticorten
NSAIDS	Non-COX-2	Ibuprofen	Motril
			Advil
		Naproxen	Aleve
			Anaprox
			Naprelan
			Naprosyn
		Ketoprofen	Ketoprofen
		Dexibuprofen	
		Piroxicam	Feldene
		Tolfenamic acid	Clotam
			Clotan
			Dolfenax
			Fenamic
			Flocur
			Gantil
			Migea
			Purfalox
		asprin	Ecotrin
	Older and newer COX-2	Diclofenac	Voltaren
			Cataflam

Table 19. Continued.

Class	Generic Names	Brand Names
		Voltaren-XR
		Cambia
		Zipsor
		Zorvolex
	Etodolac	Lodine
	Nabumetone	Relafen
	Meloxicam	Mobic
	Celecoxib	Celebrex
	Rofecoxib	vioxx
	Valdecoxib	Bextra
	Parecoxib	Dynastat
		Tunisia
		Rayzon
	Etoricoxib	Biocoz
		Coxet
		Coxifact
		Ebov
		Ecoxib
		Eldoflam
		Eloxib
		Eteron
		Etody
		Etom
		Etori
		Etorica
		Etosym
		Etozox
		Hireto
		Torcoxia
	Indomethacin	Indocin
	Oxaprozin	Daypro
	Salsalate	Disalsate
		Amigesic
	Sulindac	Clinoril

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