Clinical Outcomes Associated with Second-line Medications for the Treatment of Type 2 Diabetes

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CHAPTER I

INTRODUCTION

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend metformin and lifestyle modification as first-line treatment for type 2 diabetes.[1] Many patients remain on metformin monotherapy for long periods of time, with adequately controlled blood glucose levels. However, patients often add a second agent to achieve better glycemic control, or switch to a different agent due to comorbidities such as kidney disease.[2] The ADA and EASD guidelines are very nonspecific in their recommendations for what the optimal add-on therapy should be. They recommend tailoring therapy for each patient, which leaves providers with insufficient guidance on appropriate second-line therapy.

The long-term clinical outcomes of second-line drugs are not fully understood, and recommendations on choosing the optimal regimen for patients with different clinical characteristics are not clear. Sulfonylureas and insulin are among several drugs recommended as second-line treatment, and are often added to metformin to achieve glycemic goals.[1] Despite the recent introduction of newer hypoglycemic agents and the advantages they provide, sulfonylureas and insulin are still widely used because they are effective in lowering blood glucose levels and are less costly compared to the newer agents. However, both drugs are associated with hypoglycemia and weight gain, which could potentially lead to poor long-term outcomes. As part of this dissertation work, I used data from a large national Veterans Health Administration (VHA) diabetes cohort to 1) validate algorithms used to identify hypoglycemia events in large scale studies; 2) evaluate whether metformin adherence is associated with risk of

hypoglycemia in the year following intensification with sulfonylureas; and 3) assess weight gain and hypoglycemia as potential mediators in the causal pathway between insulin as an add-on therapy to metformin (compared to sulfonylurea) and death.

Identifying Hypoglycemia Cases in Epidemiologic Studies

Importance of evaluating hypoglycemia as an outcome measure of type 2 diabetes treatment

Both sulfonylureas and insulin can cause hypoglycemia, an important short-term clinical outcome which is usually preventable and has a large impact on patient quality of life.[3] Hypoglycemia events not only lead to impaired quality of life but are also associated with an increased risk of serious clinical outcomes such as acute cardiovascular events, long-term neurological impairment, and death.[3–8] Hypoglycemia due to insulin and oral hypoglycemic agents were found to account for greater than 25% of all hospitalizations that were due to adverse drug events, and hospitalizations due to hypoglycemia have been increasing over the last 10 to 20 years.[4,9,10]

The incidence of hypoglycemia is often perceived to be low overall in patients receiving treatment for type 2 diabetes, especially in clinical trial settings where patients at highest risk for hypoglycemia are excluded. However, there are significant differences in the incidence of hypoglycemia depending on the treatment regimen. Up to 20-50% of patients on sulfonylureas or insulin reported experiencing hypoglycemia symptoms annually in clinical practice.[3]

Many recent studies suggest that there may be a direct relationship between hypoglycemia and acute cardiovascular outcomes through several possible mechanisms including myocardial ischemia or infarction, arrhythmia, and cerebral ischemia or stroke.[11–16]

Biologically, hypoglycemia can induce responses such as increase in beta cell insulin and pancreatic glucagon secretion, and an increase in sympathoadrenal response (catecholamine release) which can induce direct cardiovascular effects including ischemia in the myocardium, QT interval prolongation, and increased blood pressure.[5–8,17] Hypoglycemia can also induce inflammatory responses, coagulation and endothelial dysfunction.[7,18–20] All of these biologic effects are possible mechanisms for an increase in acute cardiovascular risk when hypoglycemia occurs, especially among high risk patients who have existing cardiovascular disease.[21–25]

Large clinical trials have found that intensive glucose control targeting a glycosylated hemoglobin (HbA1c) of less than 6.5% did not lead to cardiovascular benefit and may be associated with increased mortality.[26–29] It is hypothesized that this may partly be explained by the increased risk of hypoglycemia in patients who received intensive glucose treatment, although it was unclear whether hypoglycemia was the direct cause of cardiovascular events or deaths in the studies.[30] Observational studies have also found associations between hypoglycemia and cardiovascular events.[31–35] However, hypoglycemia could also be a marker of other comorbid conditions such as patient frailty, disability, or a function of failing health which could partially explain the relationship between hypoglycemia and death.[36,37]

Various definitions of hypoglycemia in epidemiologic studies

Identifying patients with hypoglycemic events in epidemiologic studies is challenging because mild to moderate events may go unnoticed or are resolved quickly with self-intervention. Patients may require assistance from a family member if they experience a significant hypoglycemia episode but still not seek healthcare intervention, and self-reported events can be unreliable. There is consensus that serious hypoglycemia events are ones in which

third party assistance is needed. In previous epidemiologic studies examining the outcome of hypoglycemia, investigators used administrative data to identify serious events which led to emergency room visits or hospitalizations through various combinations of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes (**Table 1.1**).[38]

In a population-based retrospective cohort study of Tennessee Medicaid patients, Shorr and colleagues used administrative claims data to identify potential serious hypoglycemia events which occurred in the outpatient setting and led to an emergency department visit, hospitalization, or death among patients using hypoglycemic drugs.[39] Discharge diagnoses or death certificate underlying cause of death with the following ICD-9-CM codes were used: 251.0 (hypoglycemic coma), 251.1 (functional hypoglycemia syndrome), 251.2 (hypoglycemia, unspecified), 250.3 (diabetes with other coma), and 962.3 (therapeutic misadventure). Once potential events were identified, medical records were reviewed to further identify serious events with documented symptoms and a blood glucose level of less than 50 mg/dL outside the hospital. Other studies have used different sets of codes to identify hypoglycemia events (**Table 1.2**).

Table 1.1. ICD-9-CM codes used for hypoglycemia and their descriptions

ICD-9 code	*Description*
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia, unspecified
250.3	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.8	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
270.3	Disturbances of branched-chain amino-acid metabolism
775.0	Syndrome of "infant of a diabetic mother"
775.6	Neonatal hypoglycemia
962.3	Poisoning by insulins and antidiabetic agents

Table 1.2. ICD-9-CM codes used to identify hypoglycemia events in previous studies

Author	*Journal*	*ICD-9-CM codes*
Shorr RI et al.[39]	Arch Int Med. 1997	250.3, 251.0, 251.1, 251.2, 962.3
Johnson ES et al.[40]	J Clin Epid. 2002	250.3, 250.8, 251.0, 251.1, 251.2, 962.3
Ginde AA et al.[41]	BMC Endo Dis. 2008	250.8, 251.0, 251.1, 251.2, 270.3, 775.0 (infant), 775.6 (neonatal), and 962.3, excluding 259.8, 272.7, 681.XX, 682.XX, 686.9, 707.1-707.9, 730.0-730.2, 731.8 or 250.3
Johnston SS et al.[42]	Diabetes Care. 2011	250.8, 251.0, 251.1, 251.2
Zhao Y et al.[33]	Diabetes Care. 2012	250.8, 251.0, 251.1, 251.2

Variation in blood glucose thresholds that define hypoglycemia

In addition to ICD-9-CM codes, some clinical trials and observational studies with laboratory data or documented glucometer data available have defined hypoglycemia using blood glucose measurements. While any blood glucose measurement lower than 70 mg/dL is low, many patients with glucose levels lower than that threshold experience no symptoms, and mild symptoms may quickly resolve with self-intervention. Investigators interested in more clinically significant hypoglycemia often want to exclude such mild cases and identify cases which were likely to be accompanied by symptoms. Most studies have defined hypoglycemia using a glucose threshold ranging from 50-70 mg/dL (**Table 1.3**), although it was common for studies conducted in critical care settings to use an even lower threshold. Some studies also add a criterion such as the requirement of third party assistance.

Validation of hypoglycemia definitions

The use of administrative data to identify hypoglycemia events could lead to misclassification of events, including false negative or missed events that were not captured by encounters or were coded differently, or false positive events where the coding of hypoglycemia

was used incorrectly. Some nonspecific ICD-9-CM codes can be used for diabetes-related complications other than hypoglycemia. Two studies have validated codes and algorithms for identifying hypoglycemia events and estimated their positive predictive values by comparing against chart reviews as the reference standard.

Table 1.3. Examples of different glucose threshold levels used in various clinical studies

Author/Journal	*Study Type*	*Hypoglycemia definition*	*Setting*
Damci. BMC Endocr Disord. 2014 [43]	Prospective cohort	<56 mg/dL	Outpatient
Kinnare. J Acad Nutr Diet. 2013 [44]	Retrospective cohort	<60 mg/dL	Inpatient
Boucai. Am J Med. 2011 [45]	Retrospective cohort	≤70 mg/dL	Inpatient
Brustman. Obstet Gynacol. 2011 [46]	Prospective cohort	<50 mg/dL	Outpatient
Hermanides. Crit Care Med. 2010 [47]	Retrospective cohort	<45 mg/dL	Inpatient
Mortensen. Am J Med Sci. 2010 [48]	Retrospective cohort	<70 mg/dL	Inpatient
Egi. Mayo Clin Proc. 2010 [49]	Retrospective cohort	<81 mg/dL	Inpatient
Bonds. BMJ. 2010 [50]	Retrospective analysis of a randomized controlled trial (RCT)	<50 mg/dL	Outpatient
Zoungas. NEJM. 2010 [37]	RCT	<50 mg/dL	Outpatient
Miller. BMJ. 2010 [51]	RCT	<50 mg/dL	Outpatient
Kosiborod. JAMA. 2009 [52]	Retrospective cohort	<60 mg/dL	Inpatient
Mellbin. Heart. 2009 [24]	RCT	<60 mg/dL	Inpatient
UK Hypoglycemia Study Group. Diabetologia. 2007 [53]	Prospective cohort	<54 mg/dL	Outpatient
Vriesendorp. Crit Care Med. 2006 [54]	Retrospective cohort	<45 mg/dL	Inpatient
Miller. Arch Intern Med. 2001 [55]	Cross-sectional	<60 mg/dL	Outpatient
McLaughlin. Ann Emerg Med. 2000 [56]	Retrospective cohort	<60 mg/dL	Inpatient
Burge. JAMA. 1998 [57]	RCT	<60 mg/dL	Outpatient

Johnson and colleagues described the positive predictive values of different ICD-9-CM discharge codes which may identify potential events in administrative claims databases, as part of a study which estimated the population-based incidence and trends overtime for serious hypoglycemia.[40] Among health maintenance organization (HMO) members within a single

healthcare group who have diabetes, investigators examined claims for emergency department services and inpatient hospital services, restricting the search to primary hospital discharge diagnosis codes for hypoglycemia which resulted in hospitalization. Events were confirmed if notes from outpatient medical records indicated presentation with hypoglycemia (any symptoms or laboratory values consistent with hypoglycemia), and they were excluded if inconsistent with hypoglycemia or if there was insufficient information. Of 269 potential events identified through claims data, 203 were consistent with hypoglycemia based on record review. Positive predictive values for each of the ICD-9-CM codes were estimated; the overall positive predictive value was 75%, with those for individual codes ranging from 62% (250.3) to 100% (251.1 and 962.3).

Ginde and colleagues created a different ICD-9-CM coding algorithm to identify hypoglycemia events in the emergency department setting, and validated the algorithm in three medical centers against a reference standard method (chart review).[41] They used a broader set of ICD-9-CM codes to identify potential events (**Table 1.2**), and for the nonspecific code 250.8 (diabetic complications) they evaluated a set of co-diagnoses that would likely exclude hypoglycemia as a diagnosis. In contrast to previous studies, they documented potential events with 250.3 (diabetes with coma) but excluded it from their final algorithm because of its inability to distinguish between diabetic ketoacidosis and hypoglycemia. Charts were reviewed for all potential cases identified through the algorithm, and events were confirmed if they had a documented pre-hospital or emergency department glucose measurement of 3.9 mmol/L (equivalent to 70 mg/dL) or if there was a documented physician discharge diagnosis of hypoglycemia. They reviewed 679 charts with complete information and confirmed 436 hypoglycemia events (overall positive predictive value 64%). Positive predictive values for individual codes ranged from 54% (962.3) to 100% (250.3 and 775.6). There was one case with

the code 250.3 which was a confirmed hypoglycemia case, so the positive predictive value for that code was 100%. Similar to the Johnson study, they found that the majority of confirmed events (83%) were coded as 250.8. Interestingly, 250.8 had a positive predictive value of 62% overall but when the specified co-diagnoses were absent, the positive predictive value increased to 92%. Excluding events identified through 250.8 with co-diagnoses led to an overall positive predictive value of 89%, significantly improving the accuracy of the algorithm.

Based on the high positive predictive value demonstrated by this new algorithm, our research group adapted the algorithm to identify hypoglycemia cases in our large pharmacoepidemiologic studies.[58,59] In two recently published studies, we used a similar algorithm to identify hypoglycemia events which led to emergency department visits. We did not use the codes 775.0 or 775.6 because all patients in the cohort were adults. In addition, we used a modified version of the algorithm to identify hospitalizations which occurred due to hypoglycemia, and also identified outpatient events based on any outpatient laboratory glucose values of less than 60 mg/dL. For hypoglycemia hospital admissions, we identified events with primary discharge diagnosis codes 251.0-2, 270.3, or 962.3, and excluded any events that included 250.3.

It is possible that the administrative codes used for hypoglycemia may vary depending on the provider, facility, year of hospitalization or emergency department visit, or geographic location, therefore the results of validation studies which were previously conducted may not be applicable in other settings or populations. Accuracy of individual codes may also vary from study to study. As an example, the code 251.1 (other unspecified hypoglycemia) had a positive predictive value of 100% in the Johnson study but only 67% in the Ginde study. Since our group decided to use a modified version of the algorithm for identifying inpatient events and also added

outpatient events, further validation of these definitions was warranted. We also used blood glucose measurements to define outpatient hypoglycemia events, and it was unclear whether the identified events were symptomatic or asymptomatic hypoglycemia episodes. Our study population and setting in the VHA is predominantly elderly males and can differ from other healthcare systems, so it would be important to evaluate the performance of the hypoglycemia algorithms for future studies of hypoglycemia.

Our research group has prior experience validating administrative codes used to identify outcome events in pharmacoepidemiologic studies, including stroke or acute myocardial infarction hospitalizations among diabetes patients in the VHA.[60] Similar to previous validation studies, we assembled a convenience sample of diabetes cohort patients who met the hypoglycemia definition at the Tennessee Valley Healthcare System site, and conducted chart reviews to evaluate the positive predictive values for our definitions of hypoglycemia in Study 1.

Antidiabetic Medication Adherence and the Risk of Hypoglycemia

Medication adherence is suboptimal among patients with chronic diseases

Even though medications are an important part of chronic disease management, adherence and persistence to medications are often suboptimal among patients with various chronic diseases. Hypoglycemic medication adherence rates among patients with type 2 diabetes is estimated to be 60-85%, and lower rates have been reported for antihypertensive medication adherence among patients with hypertension.[61–63] Studies report that approximately 50% of patients who are prescribed antihypertensive medications and 33% of patients who are prescribed metformin discontinue the drug within a year.[63–65]

Many factors have been found to be associated with poor medication adherence or persistence, including complex medication regimens, the number and type of medications, cost, side effects, communication with providers, and other sociodemographic factors.[66,67] Patients may often unintentionally miss doses because they forget, or they may intentionally miss doses due to fear of side effects, mistrust of their provider, high medication costs, or negative beliefs about medications.[66,67] Others may change the daily dosing without the recommendation of the provider. Patients with high blood pressure may take half of their prescribed dose on days when they exercise or find that their blood pressure is lower than usual, and those with diabetes may choose to take their sulfonylurea only on days when they eat heavy meals. Patients may also discontinue their medications completely without consulting with their provider.

Measuring medication adherence in clinical studies

According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group, medication adherence and persistence are separate constructs.[68] Adherence, also referred to as compliance, is defined as the degree to which the patient conforms to the provider recommendations regarding the dose, frequency, and timing of medication use. Adherence is usually reported as a percentage and is measured over a defined time period using various methods. Persistence is defined as the duration of medication use, from the time of first fill to discontinuation, and is usually reported as number of days. In clinical studies, authors may predefine a gap period allowed between refills to define whether the patient is persistent.[68]

Studies have used various methods to measure adherence. While there is currently no gold standard for measuring medication adherence, there are many direct and indirect ways of

estimating it. Direct measures of medication adherence include serum or urine concentrations of medications or other biomarkers that reflect medication use. These methods are usually costly and may not be feasible for many studies.[69] There are also indirect measures of adherence that utilize questionnaires or pill counts, which are often used by prospective studies or clinical trials. There are several validated questionnaires such as the Adherence to Refills and Medications Survey (ARMS), and the Morisky 4-item Medication Adherence Questionnaire.[70,71] Pill counts is a method commonly used in clinical trials to track adherence, where patients are required to bring pill bottles at each visit.

In studies that utilize retrospective databases, pharmacy prescription refill data can be used to indirectly estimate adherence in the study population. The use of pharmacy prescription refill data assumes that gaps in refills indicate nonadherence. This approach can be advantageous since it is noninvasive, objective data are available, and it allows researchers to evaluate adherence in large epidemiologic studies. There are limitations to this method in that actual ingestion cannot be monitored, and adherence may be underestimated if patients utilize multiple pharmacies where refill data are not available in the study database.[69] However, refill compliance has been shown to approximate actual use in many validation studies and could be more accurate than self-report.[72,73]

Refill data can be used to estimate adherence through various methods, but two methods are used most commonly in retrospective studies: the medication possession ratio (MPR) or the proportion days covered (PDC).[69] The MPR is calculated as the total days' supply dispensed divided by the number of days the patient should have been taking the medication. The PDC is calculated as the number of days on which the patient has medication on hand divided by the total number of days in the measurement period. The MPR can be greater than 100% and

overestimate adherence if the patient fills extra days' supply during the time period, while the PDC cannot be greater than 100% since it measures the proportion of days the patient has medication available during that time period.

High adherence has often been defined as a MPR or PDC of 80% or greater in previous research.[69,72] For studies of chronic disease such as hypertension and diabetes, researchers found that 80% is a reasonable choice that may predict clinical outcomes. However, optimal cutoff points may be different for other conditions and treatments.

Medication Adherence and its association with clinical outcomes

High adherence to chronic disease medications has been associated with improved short-term and long-term clinical outcomes and reduced healthcare costs.[73–80] In previous studies of patients with hypertension, those with high adherence were more likely to achieve blood pressure control.[81] In a recent cohort study, Kim and colleagues found that adherence to antihypertensive treatments was associated with improved cardiovascular mortality.[63]

Similarly, among patients with type 2 diabetes, high medication adherence has also been associated with improved glycemic control, and several studies have examined adherence as it relates to clinical outcomes. Adherence is an important component of strict control of blood glucose levels, which in turn is related to reduction in diabetes complications. Higher adherence to oral antihyperglycemic drugs was shown to be associated with better attainment of target HbA1c.[82–85] With regards to long-term outcomes, investigators have found that high adherence (>80% MPR or PDC) was associated with a lower risk of hospitalization and emergency department visits.[74,79,86] Lau and colleagues found in a retrospective cohort study of 900 patients in a managed care organization that nonadherence or a medication possession ratio of less than

80% was associated with higher odds of hospitalization due to diabetes or cardiovascular/ cerebrovascular causes (odds ratio [OR] 2.53, 95% confidence interval [CI] 1.38-4.64).[87] Ho et al. also found in a retrospective cohort study of 11,532 patients, that high adherence (PDC >80%) was associated with a lower risk of mortality (OR 1.81, 95% CI 1.46-2.23).[78] However, many of these studies may need to be interpreted with caution because patients who are highly adherent to their medications likely also have other healthier behaviors compared to those who are not adherent.[75]

Relationship between adherence and treatment intensification

Medication adherence is an important part of clinical response to medications, and any problems with adherence should ideally be addressed prior to intensifying therapy. However, in clinical practice providers may often make the decision to intensify therapy based on physiologic or laboratory measurements, regardless of the level of medication adherence. There may be challenges or barriers to reviewing patients' pharmacy fill data or asking the patient about adherence issues during encounters. Little data exists on this concept in the diabetes literature but there are multiple examples with another chronic disease, hypertension.

In a retrospective study of hypertensive patients conducted by Heisler and colleagues, intensification of antihypertensive medications occurred in 30% of the study population with elevated blood pressure, with no difference among patients who had high, intermediate, or low adherence (adherence was evaluated based on prescription fill records).[88] However, in a different study Rose and colleagues found that antihypertensive treatment intensification improved blood pressure control similarly among patients with different levels of adherence.[89] The authors argue that while addressing adherence is important, it may not be a necessary step prior to intensifying

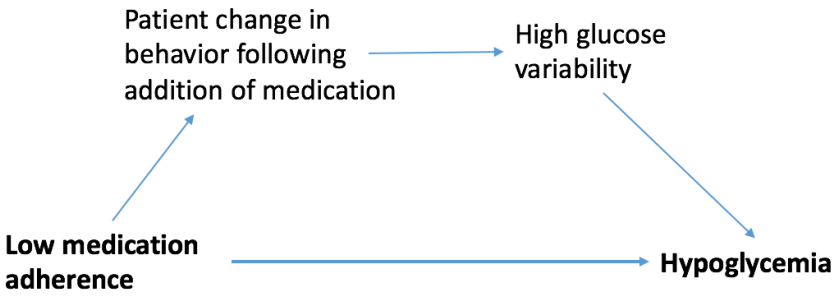
therapy for hypertension. Similarly, for antihyperglycemic drug therapy among type 2 diabetes patients, clinicians may intensify treatment based on HbA1c or glucose measurements before addressing adherence issues, and whether that impacts certain clinical outcomes, including adverse side effects such as hypoglycemia, is unclear.

Relationship between medication adherence and hypoglycemia

The association between strict adherence to antihyperglycemic agents and medication-related safety outcomes such as hypoglycemia is less clear compared to the relationship between antihypertensive agents and cardiovascular outcomes. As discussed above, patients with poor adherence to hypoglycemic medications may appear to have lower response to therapy or higher HbA1c leading prescribers to adjust the dosage or add medications when adherence to current therapy was suboptimal. These patients may also have highly variable glucose levels due to inconsistent or irregular dosing of their medications. These clinical situations could place low adherence patients at higher risk for hypoglycemia if they changed their behavior and started taking medications all at once, leading to more glucose fluctuations and blood sugar variability. However, low adherence patients could also be taking a lower dose of medication overall and are therefore less likely to develop hypoglycemia. This is a challenging question to address, because adverse events of a drug may occur with a higher frequency among those with higher adherence and more regular dosing and also with lower adherent patients. Nonetheless, with antihyperglycemic therapy, irregular intake of medications and inconsistent dosing, in addition to being prescribed a more intensive regimen than needed are concerning because they could potentially lead to greater glycemic variability and a higher risk of adverse clinical outcomes including hypoglycemia.

High glucose variability during the day has been shown to be associated with hypoglycemia in type 2 diabetes patients.[90,91] Several studies suggest that glucose variability is a risk factor for mortality and cardiovascular disease, although the mechanism remains unknown.[92,93] Rapid changes in HbA1c and HbA1c variability have also been linked to increased risk of cardiovascular disease outcomes such as acute myocardial infarction and stroke, in addition to hypoglycemia.[94,95] If patients who are nonadherent to metformin are started on an intensified treatment with a sulfonylurea and they initiate both of their medications, this could potentially lower their baseline glucose and increase the risk for hypoglycemia (**Figure 1.1**).

Figure 1.1. Causal diagram showing possible associations between adherence, glucose variability, and hypoglycemia



Two studies have specifically explored the relationship between antihyperglycemic medication adherence and the outcome of hypoglycemia. In a retrospective cohort study of adult patients with type 2 diabetes who were new users (no antidiabetic drug filled in prior 6 months) of metformin, a sulfonylurea, or a thiazolidinedione, Quilliam and colleagues used the initial 6 months of therapy to define patients' adherence category based on the medication possession ratio and any change in initial regimen (metformin ≥80% adherence; metformin <80%

adherence; sulfonylurea ≥80% adherence; sulfonylurea <80% adherence; thiazolidinediones ≥80% adherence; thiazolidinediones <80% adherence; switching to a new class; adding on therapy; and switching to two or more different classes of medication).[64] The patients were followed until 12 months after initiation of therapy, change in regimen, or first hypoglycemic event. All inpatient and outpatient hypoglycemia events were identified using the ICD-9-CM code algorithm developed by Ginde et al.[41] The algorithm was also used to identify events during the baseline period (first 6 months of therapy). Based on Cox proportional hazards models adjusting for age, gender, Charlson comorbidity index, microvascular and macrovascular diabetes complications, self-monitoring of blood glucose, and fluoroquinolone or benzodiazepine use, the risk of hypoglycemia was significantly higher among patients switching to combination therapy compared to metformin users with ≥80% adherence (adjusted hazard ratio [HR] 1.32, 95% CI 1.07, 1.64). Thiazolidinedione users with ≥80% adherence had a significantly lower risk of hypoglycemia compared to adherent metformin users (adjusted HR 0.67, 95% CI 0.46, 0.98). All other categories of adherence did not have a significantly different risk of hypoglycemia compared to adherent metformin users. In a separate model, the authors found that hypoglycemia during the baseline period was strongly associated with hypoglycemia during the follow-up period (HR 42.3, 95% CI 36.0, 49.5). The findings from this study suggest that early intensification of initial hypoglycemic drug regimen is linked to higher risk of hypoglycemia, but adherence levels may not be strongly associated with a higher risk. Among sulfonylurea users, patients who were less adherent (<80%) did have a numerically higher crude rate of hypoglycemia (168.8 per 10,000 person-years) compared to those who were adherent (142.3 per 10,000 person-years), although the difference was not statistically significant. The findings of this study are interesting because the overall rates of hypoglycemia were similar among

metformin and sulfonylurea initiators, which is contradictory to the findings of previous studies. There were also many fewer sulfonylurea initiators and their baseline characteristics could have differed significantly from those of metformin users, so residual confounding could have been a limitation.

Hsu and colleagues recently conducted a cross-sectional analysis as part of a cohort study examining the association between self-reported medication adherence and adverse safety events including hypoglycemia among patients with reduced renal function (estimated glomerular filtration rate [GFR] <60 ml/min).[96] Adherence was quantified using a 3-question survey, adjusting for the total number of drugs the patient was taking on a daily basis, and categorized into high or low adherence. Among several composite safety outcomes, hypoglycemia was captured through a baseline self-reported questionnaire (low blood sugar during prior 12 months). Lower adherence by self-report was associated with more adverse safety outcomes by self-report (prevalence ratio [PR] 1.21, 95% CI 1.04, 1.76), but the specific results for hypoglycemia were not separately reported. Interpreting the findings of this study is limited because it was a cross sectional analysis with self-reported exposure and outcome information and the sample size was small (of 293 participants, 185 had self-reported diabetes). Also, the temporal relationship between adherence and hypoglycemia could not be established.

Adherence patterns and risk of hypoglycemia among metformin users adding a sulfonylurea

The VA diabetes cohort is an ideal population to study medication adherence because most patients receive their medications through the VA pharmacy and there are detailed records of prescription medication fills for all cohort patients. Using prescription fill data, we could

estimate the adherence for a large national cohort of patients and evaluate how it relates to clinical outcomes such as hypoglycemia.

In Study 2, I evaluate whether medication adherence behaviors during metformin monotherapy (baseline period) are associated with an elevated risk of early hypoglycemia events after intensifying therapy with sulfonylurea. In contrast to the Quilliam study which examined all oral antihyperglycemic drug monotherapy initiators, I focus on a group of patients who are at higher risk of developing hypoglycemia (those intensifying with an agent known to cause hypoglycemia) which addresses a more clinically important and practical question. I was also able to account for more potential confounders in the analysis compared to previous studies. I hypothesized that low baseline adherence would be associated with higher risk of hypoglycemia following intensification.

Mediators in the Association between Insulin Therapy and Risk of Death

Intensive glucose control and macrovascular outcomes

Observational studies and clinical trials have shown that intensive glucose control can improve microvascular outcomes.[97] Based on these results, providers have been targeting therapy with more aggressive HbA1c goals, and other outcomes such as hypoglycemia have been considered unavoidable side effects due to the benefits on major outcomes. However, current evidence does not support that intensive glucose control can improve macrovascular outcomes.[98–100]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with existing type 2 diabetes and cardiovascular disease were randomized to receive either intensive

glucose control therapy targeting a HbA1c lower than 6%, or standard care targeting a HbA1c between 7.0% and 7.9%.[26] The objective of the trial was to determine whether targeting a lower HbA1c would be more effective in reducing cardiovascular events. A total of 5128 patients were randomized to the intensive therapy group, and 5123 patients were randomized to the standard therapy group. The trial was stopped early in February 2008 when it was found during an interim analysis that there was an elevated risk of all-cause mortality in the intensive glucose control group (5.0% vs. 4.0%; HR 1.22, 95% CI 1.01, 1.46). While the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular cause did not differ between the two groups (6.9% vs. 7.2%; HR 0.90, 95% CI 0.78, 1.04), the rate of nonfatal myocardial infarction was lower in the intensive control group (3.6% vs. 4.6%; HR 0.76, 95% CI 0.62, 0.92), and the rate of death from cardiovascular causes was higher in that group (2.6% vs. 1.8%; HR 1.35, 95% CI 1.04, 1.76).

Importantly, intensive glucose control in the ACCORD trial was also associated with higher rates of severe hypoglycemia, fluid retention, and weight gain.[26] Specifically, the proportion of patients with hypoglycemia requiring medical assistance was 10.5% and 3.5% in the two groups, respectively; and those with weight gain of greater than 10 kg compared to baseline was 27.8% and 14.1%, respectively. Blood pressure was slightly lower in the intensive therapy group. The investigators report that more patients in the intensive control group had frequent regimen changes and multiple drugs in different classes were often initiated to achieve the lower HbA1c target. Among patients on intensive glucose control, 77.3% were prescribed insulin, compared to 55.4% of those receiving standard care. The use of thiazolidinediones was also notably higher in the intensive glucose control group (91.7% vs. 58.3%). A post-hoc analysis revealed evidence of effect modification: among those without a baseline cardiovascular

event history or among those with a baseline glycated hemoglobin level ≤8.0% there was no difference in the risk of death between the two treatment groups. This suggests that the increased risk of death is specific to those with advanced cardiovascular disease and those who may have had poor glycemic control prior to entering the trial.

In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial which randomized 12,537 patients to either insulin glargine or standard care, the investigators found no difference in cardiovascular death, myocardial infarction, or stroke between the two groups after 6 years of follow up (HR 1.02, 95% CI 0.94, 1.11).[101] In the standard care group, only 11% of patients received insulin. However, the rate of hypoglycemia and weight gain were higher in the insulin glargine group, similar to the ACCORD trial.

Other large clinical trials such as the UK Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and VA Diabetes Trial (VADT) have also failed to show that intensive glucose control leads to improved cardiovascular or mortality outcomes compared to standard therapy (**Table 1.4**),[29,102,103] although a post-trial monitoring of the UKPDS found that microvascular benefits persisted and macrovascular and mortality outcomes emerged after 10 years of follow-up since the trial.[28] All of these trials demonstrated that intensive glucose therapy led to a significantly higher risk of hypoglycemia and weight gain, both of which are unwanted and adverse side effects from a patient perspective and negatively impact quality of life.

Table 1.4. Randomized controlled trials which investigated how intensive glucose control may impact cardiovascular disease and death

Study	*N*	*Years*	*Treatment arms*	*Results*
ACCORD [26]	10,251	3.5	Intensive therapy (HbA1c target <6.0%) vs. standard therapy (7.0-7.9%)	Primary outcome composite nonfatal MI, stroke, CVD death: 6.9% vs. 7.2%, HR 0.90 (95% CI 0.78-1.04); Cardiovascular death: HR 1.35 (1.04-1.76); All-cause death: 5.0% vs. 4.0%, HR 1.22 (1.01-1.46)
ORIGIN [101]	12,537	6.2	Insulin glargine vs. standard care	Primary outcome nonfatal MI, stroke, CVD death: 2.94 vs. 2.85 per 100 PY, HR 1.02 (0.94-1.11)
UKPDS [102]	3867	10	Intensive therapy (insulin or sulfonylurea) vs. standard therapy	MI: HR 0.84 (0.71-1.00); Stroke: HR 1.11 (0.81-1.51); All-cause death: HR 0.96 (0.70–1.33)
ADVANCE [29]	11,140	5	Intensive glucose control (target HbA1c <6.5%) vs. standard glucose control	Primary outcome nonfatal MI, stroke, CVD death: 10.0% vs. 10.6%, HR 0.94 (0.84-1.06); Death: 8.9% vs. 9.6%, HR 0.93 (0.83-1.06)
VADT [103]	1791	5.6	Intensive therapy (HbA1c reduction 1.5%) vs. standard therapy	Composite MI, stroke, CVD death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene: 29.5% vs. 33.5%, HR 0.88 (0.74-1.05); Death: HR 1.07 (0.81-1.42)

Chronic exogenous insulin use associated with increased risk of death

There are many factors which could account for the increased risk of death associated with intensive glucose control in the ACCORD trial, including but not limited to: the differences in achieved HbA1c level, rapid rate of change in HbA1c, the rate of hypoglycemia, weight gain,

and other adverse effects or drug interactions from using multiple classes of drugs.[104,105] The ACCORD investigators also considered the possibility of a chance finding. Post-hoc analyses of clinical trials have not been able to point to any specific mechanisms that could have led to the results. One potentially important factor that may be linked to some of the other suggested factors might be the differences in drug regimens and dosages including the use of insulin. Although post-hoc analyses of the ACCORD and ORIGIN trials have failed to demonstrate that insulin dose was associated with cardiovascular mortality after adjusting for baseline factors,[101,106] further studies are warranted to investigate whether higher insulin use may have led to higher mortality outcomes through various mechanisms.

In a recent cohort study, our research group found that insulin was associated with a greater risk of all-cause death compared to sulfonylureas when added to metformin.[107] In a large retrospective cohort of adult veterans with type 2 diabetes who initiated therapy with metformin and later added sulfonylurea or insulin, the investigators compared the time to cardiovascular disease or death (composite acute myocardial infarction, stroke, or all-cause death) using 1:5 propensity score matching to balance confounders in the two exposure groups. After propensity score matching, there were a total of 2436 metformin + insulin and 12,180 metformin + sulfonylurea users included in the analysis. The investigators originally hypothesized that insulin would be associated with a lower risk of the primary outcome because of its ability to achieve better glycemic control. However, they found that the risk of the composite primary outcome was higher in the insulin group compared to the sulfonylurea group (42.7 vs. 32.8 events per 1000 person-years; adjusted HR 1.30, 95% CI 1.07, 1.58). The differences in rate of cardiovascular disease were not significant, but all-cause mortality was higher among insulin users (33.7 and 22.7 per 1000 person-years; adjusted HR 1.44, 95% CI 1.15, 1.79). Because the

study was an observational study, the investigators conducted many sensitivity analyses to verify the robustness of their findings. They also estimated that any unmeasured confounder would have to be 30% higher in insulin users for the main results to become nonsignificant, and 70% higher for the all-cause mortality results to become nonsignificant. In other words, the unmeasured confounder would have had to be considerably different in the comparison groups in order to yield different study results. While a causal relationship could not be established due to the observational nature of the study, considering the advanced methods used to account for confounding (i.e. new user design, propensity score matching, sensitivity analyses), it is possible that exogenous insulin compared with sulfonylurea as an add-on to metformin might lead to a higher risk of death through mechanisms which are not yet well understood.

In addition to this study, other observational studies have also shown that insulin may be associated with an increased risk of cardiovascular events and mortality compared to other agents especially in patients with existing cardiovascular disease, although confounding by indication is a larger possibility in some of those studies (**Table 1.5**).[108–111] Insulin users are typically older and have a longer history of diabetes, and often they may be more insulin-resistant. On the other hand, other studies have also suggested that insulin has macrovascular benefits despite an increase in risk of hypoglycemia.[99] Meta-analyses of clinical trials have also shown inconsistent results.[112]

Understanding the mechanisms through which insulin may lead to poor outcomes

Despite the ability of exogenous insulin to improve glycemic control in patients with type 2 diabetes, observational studies have not been able to demonstrate a consistent benefit on long-term cardiovascular outcomes, and there appears to be some evidence of an increased risk of

death. The factors which account for this observed increased risk are not well understood and will not likely be evaluated in clinical trials in the near future.

Table 1.5. Observational studies evaluating the relationship between exogenous insulin use and cardiovascular and/or mortality outcomes

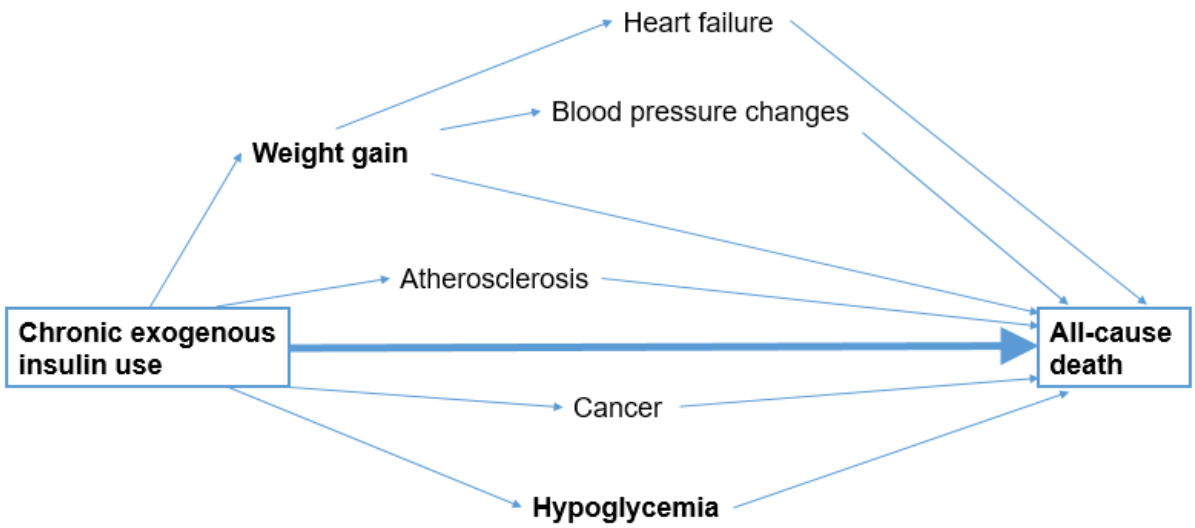
Author, year	*Study population*	*Comparison groups*	*Results*
Currie, 2013 [109]	UK General Practice Research Database; n=84,622	Insulin vs. metformin	First major adverse cardiac event, first cancer, or mortality: 58.9 vs. 36.6 per 1000 PY, aHR 1.81 (95% CI 1.63-2.01)
Gamble, 2010 [108]	Saskatchewan Health; n=12,272	High/moderate/low insulin exposure vs. no insulin	All-cause mortality (high vs. none): 95 vs. 40 per 1000 PY, aHR 2.79 (2.36-3.30)
Holden, 2015 [114]	UK Clinical Practice Research Datalink; n=6484	Insulin exposure (units/kg/day)	All-cause mortality: aHR for 1-unit increase 1.54 (1.32-1.78); MACE: aHR 1.35 (1.04-1.75)
Roumie, 2014 [107]	Veterans Health Administration, n=42,938	Metformin + insulin vs. metformin + sulfonylurea	Composite AMI, stroke, all-cause death: 42.7 vs. 32.8 per 1000 PY, aHR 1.30 (1.07-1.58); Death: 33.7 vs. 22.7 per 1000 PY, aHR 1.44 (1.15-1.79)
Smooke, 2005 [111]	Single medical center; advanced heart failure; n=554	Insulin-treated diabetes vs. nondiabetic patients	All-cause mortality: aHR 4.30 (1.69-10.94)
Stoekenbroek, 2015 [115]	Dutch Pharmo database; n=836	High/intermediate vs. low dose of insulin	Cardiovascular event hospitalization: OR 3.00 (1.70-5.28) and OR 2.03 (1.17-3.52)

Weight gain and hypoglycemia

As reviewed in the prior section, all of the trials conducted demonstrated an increased risk of weight gain and hypoglycemia with insulin use. Both weight gain and hypoglycemia are linked to cardiovascular outcomes and death. Improved glycemic control and microvascular outcomes from insulin initiation have suggested that weight gain and hypoglycemia may be

inevitable side effects of treatment.[113] However, it is possible that weight gain and hypoglycemia could impact macrovascular and mortality outcomes (**Figure 1.2**).

Figure 1.2. Causal diagram showing the potential mediators in the association between insulin therapy and all-cause death



Many argue that insulin itself is potentially weight neutral, and that selecting the optimal regimen can prevent weight gain, especially when combined with strategies to increase insulin sensitivity such as diet, exercise, and the concomitant use of metformin. In a retrospective cohort study of 58 patients, Larger and colleagues tested the hypothesis that type 2 diabetes patients starting insulin will eventually return to their pre-diabetes weight.[116] They found that weight gain of 8.0 ± 5.3 kg occurred during the first 2 years of insulin therapy, but stabilized in the third year and remained lower than maximum weight prior to starting insulin therapy. The majority of patients had lost weight from pre-diabetes to the time of diagnosis. The authors argue that insulin

did not cause weight gain but reversed the weight loss associated with poor glycemic control due to onset of diabetes.

However, patients who initiate insulin often do progressively gain significant weight overtime. In large clinical trials and observational studies, patients who received intensive glucose control with the use of insulin had significantly greater weight gain compared to those receiving standard therapy or other agents.[26,27,29,101,102,117,118] There are several possible mechanisms of insulin-associated weight gain, including reversal of hyperglycemia and hyperglycosuria, change in metabolism of free fatty acids and protein, increase in dietary calorie intake due to fear of hypoglycemia, inflammatory changes through influx of macrophages into the adipose tissue, and modulation of appetite related signals in the central nervous system.[113,119,120] The degree of weight gain has been shown to be related to the insulin dose requirements or intensity of treatment, as well as the specific regimen that is used; NPH insulin has been associated with higher weight gain compared to detemir and basal insulin regimens.[117] Other predictors of weight gain include diabetes-related distress and age.[121] Weight gain in type 2 diabetes patients is undesirable since weight is related to cardiovascular risk and increased insulin resistance and may outweigh the benefits of improved glycemic control.

Hypoglycemia is a predictor of all-cause mortality.[31,122,123] As discussed previously, it is also linked to cardiovascular outcomes. In a post-hoc analysis of the ACCORD trial, investigators found that the risk of death was higher among patients with hypoglycemic events in both the intensive control and standard care arms.[26] However, hypoglycemia could not seem to explain the differences in mortality outcomes between those two groups.[50] It is possible that hypoglycemia does not directly lead to cardiovascular events or death most of the time, but is rather a marker of other unmeasured conditions such as frailty, which is associated with an

increased risk of death. Older adults are often over-treated, even though the risks of hypoglycemia may outweigh the benefits of intensive glycemic control.[124] Also, patients with many comorbidities and complex clinical conditions are more likely to experience severe hypoglycemia.[125]

Other potential pathways

In a review article, Bittencourt discusses potential biologic mechanisms of how insulin may directly cause cardiovascular harm, via pathways that do not involve weight gain or hypoglycemia.[109,114,125] Higher doses of insulin and serum insulin levels, which could be a sign of insulin resistance, have been associated with risk of cardiovascular disease, independent of whether glucose levels are elevated. There is debate about whether the insulin resistant state itself is associated with cardiovascular disease, or whether excess insulin directly causes pro-atherogenic effects in the endothelium through insulin signaling pathways.[126,127] Holden and colleagues conducted a retrospective study in which they found that higher insulin doses were associated with increased risk of all-cause mortality and cancer.[114]

The potential effects of exogenous insulin therapy on the risk of cancer have been reported in recent studies.[114,128–130] In a population-based cohort study, Bowker et al. found that insulin use was associated with a higher risk of cancer-related mortality compared to metformin use (adjusted HR 1.9, 95% CI 1.5, 2.4).[129] However, it remained uncertain whether the results meant that metformin was protective, or if the association was due to unmeasured confounding by indication. Expanding on their original cohort study, the authors also found that increasing insulin doses (measured by standardized number of fills per year) were associated with an increasing risk of cancer mortality.[130] Karlstad and colleagues conducted a meta-analysis of

observational studies to examine the types of cancer which may be associated with insulin use.[128] Overall, the review suggested that insulin use (compared to no insulin use) may be associated with an increased risk of pancreas, liver, kidney, stomach, and lung cancer, and when compared to use of other oral antihyperglycemic drugs, insulin use was associated with a higher risk of any cancer, pancreatic, and colorectal cancer. However, the heterogeneity, limited sample size, and methodological flaws in many of the included studies were a large concern. It remains largely uncertain whether exogenous insulin use could increase incidence of cancer or worsen the progression of existing cancer.

Understanding the mechanisms which are responsible for the observed increased risk of mortality associated with insulin use can be clinically important for the medical community, as it will impact how type 2 diabetes treatment should be individualized to achieve the best outcomes in patients with different risk factors. Prospective studies are needed to clarify the mechanisms and impact of chronic exogenous insulin use on the incidence and progression of cardiovascular disease or cancer. However, it is uncertain whether these studies could be carried out due to practical and ethical concerns.

Mediation analyses to better understand potential causal pathways

Using mediation analysis methods in Study 3, I evaluate whether two potentially important mediators, weight gain and hypoglycemia, are able to explain some proportion of the association between insulin use and death. This study may provide further hypotheses on which key clinical pathways play a large role in the increased risk of mortality with insulin.

When conducting mediation analyses in a survival context, there are several options one could consider.[131,132] First, the traditional "difference method" could be used by comparing the differences in coefficients for the outcome models with and without the mediator of interest. This

method is more commonly used in epidemiologic studies. The alternative "product method" can also be considered, where the indirect effect is estimated from the product of the exposure coefficient from the exposure mediator model and the mediator coefficient from the mediator outcome model. When the outcome is rare, the two methods will coincide, but when the outcome is common, they will produce different results. The product method can generally allow testing of whether there is any mediated effect.

The counterfactual framework method can be used to estimate natural direct and indirect effects, which will allow estimation of the proportion of the total effect mediated through the mediator of interest when interaction between the exposure and mediator are present.[131,132] If a proportional hazards model is used, this method requires that the outcome is rare and the confounding assumptions hold.[133] The "no confounding" assumptions require that there is no unmeasured confounding in the exposure and outcome relationship, the exposure and mediator relationship, and the mediator and outcome relationship, in addition to no mediator-outcome confounder that is an effect of the exposure.[131] Using a weighting approach with the proportional hazards model can allow for the estimation of natural direct and indirect effect on the log hazards scale, even when the outcome is common. Using other survival models is also an option, such as the accelerated failure time model and additive hazard model. These models are generally more flexible, and also do not require the rare outcome assumption.[131,133]

In Study 3, I use the difference method described above to examine whether there is any mediating effect by weight gain or hypoglycemia in the causal pathway between insulin use and all-cause death. I first estimate the indirect effect and the proportion of the total effect mediated through the mediator. Bootstrapping methods are then used to obtain a 95% confidence interval for the indirect effect and proportion mediated. There are many methodological strengths to this

mediation analysis, including the use of data from a large cohort and the use of Cox proportional hazards models to evaluate the outcome model with and without the mediators. I also evaluate the mediator change in BMI using restricted cubic splines, allowing for nonlinear associations with the outcome, which has not been commonly done in other studies. Finally, bootstrapping methods were used to obtain 95% confidence intervals for the proportion mediated by each potential mediator, which requires significant computational resources.

CHAPTER II

VALIDATION OF A COMPOSITE CASE DEFINITION FOR HYPOGLYCEMIA

Introduction

Hypoglycemia is a common side effect associated with insulin and sulfonylureas, which are second-line antihyperglycemic medications used to treat type 2 diabetes.[1] Hypoglycemia due to antihyperglycemic therapy is associated with poor quality of life, high healthcare costs, and adverse clinical outcomes such as cardiovascular disease and death.[3,4,6,37] Experts recommend monitoring patients for hypoglycemia and including this outcome when evaluating diabetes treatment effectiveness.[134] However, monitoring hypoglycemia events accurately in a patient population is challenging because events range from mild to severe, often go unnoticed, can be self-treated at home, and are underreported to healthcare providers. There is agreement among providers and researchers that any hypoglycemia event requiring hospitalization or emergency care is a severe event. Nonetheless, a low glucose measurement at any given time can be clinically meaningful due to its potential physiologic effects, even when the patient reports no typical symptoms.[13]

Observational studies and clinical trials studying the adverse effects of antihyperglycemic drugs have identified hypoglycemia events in study patients through various definitions. While it is challenging to capture all hypoglycemic events in a study population, studies have used varying definitions to identify clinically meaningful or severe hypoglycemia cases. In previous cohort studies, our group used administrative data and laboratory data to define hypoglycemia as

a composite of events including: 1) hospitalization due to hypoglycemia, 2) emergency department visit due to hypoglycemia, and 3) an outpatient blood glucose measurement less than 60 mg/dL.[58,59] These specific definitions were chosen based on prior studies and have not been validated in the VA patient population. Hospitalizations and emergency department visits are identified through an algorithm of discharge diagnosis codes using administrative data, and the accuracy can vary depending on the institution and time period. With the availability of laboratory data, additional outpatient events could be captured using our definition, but this method has not been validated and it is unknown what proportion of those patients experience symptoms or receive further care.

The objective of this validation study was to estimate the accuracy of our composite hypoglycemia definition by reviewing the charts of a sample of case patients within the VA Tennessee Valley Healthcare System.

Methods

Study design and data sources

We performed a validation study of hospital and emergency department visits and outpatient episodes of hypoglycemia identified through *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*[38] algorithms and outpatient laboratory data (**Table 2.1**) among veterans with diabetes. The descriptions for each code are provided in **Table 2.2**. This study was nested within a retrospective cohort constructed using national Veterans Health Administration (VHA) databases including administrative, clinical and laboratory data linked through identifiers designed for research (scrambled social security numbers) from

October 1, 2001 to September 31, 2014. The local charts of all cohort patients who met the hypoglycemia definitions for hospitalizations were reviewed, in addition to a random sample of patients who met the emergency department event definition or outpatient event definition within the VA Tennessee Valley Healthcare System. For all chart reviews, a structured chart abstraction tool (**Appendix A**) was used to assess the occurrence of a true hypoglycemia event and determine the specific classification of the hypoglycemia event. The institutional review boards of VHA Tennessee Valley Healthcare System and Vanderbilt University approved the study.

Table 2.1. Definitions of hypoglycemia events that were validated in this study

Hypoglycemia Event	*Definition*
1. Hospitalization	ICD-9 CM codes 251.0, 251.1, 251.2, 962.3, or 270.3 in primary position
2. Emergency Department	ICD-9 CM codes 251.0, 251.1, 251.2, 962.3, 270.3, or 250.8 without co-existence of 259.8, 272.7, 681.X, 682.X, 686.9, 707.1-707.9, 730.0-730.2, or 731.8 in any position, and concurrent CPT codes 99281, 99282, 99283, 99284, 99285, or 99288
3. Outpatient	Outpatient blood glucose measurement <60 mg/dl

Table 2.2. Hypoglycemia event diagnosis codes

ICD-9-CM code	*Description*
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia, unspecified
962.3	Poisoning by insulins and antidiabetic agents
270.3	Disturbances of branched-chain amino-acid metabolism
250.8*	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
*Without coexistence of:	
259.8	Other specified endocrine disorders
272.7	Lipidoses
681.X	Cellulitis and abscess of finger and toe
682.X	Other cellulitis and abscess
686.9	Unspecified local infection of skin and subcutaneous tissue
707.1-707.9	Chronic ulcer of skin
730.0-730.2	Osteomyelitis
731.8	Other bone involvement in diseases classified elsewhere

Study population and selection of patients with hypoglycemia for chart review

The source population was veterans 18 years of age or older who received care at the VA Tennessee Valley Healthcare System between October 1, 2001 and September 31, 2012. Patients who met one of the three definitions for hypoglycemia (**Table 2.1**) were eligible for inclusion in the validation study. There were only 15 events that met the hospitalization definition at the local site during the timeframe, so all hospitalization events were reviewed. In addition, a random sample of 110 emergency department visits and 210 outpatient events were selected for chart review. Because hypoglycemia events were randomly selected, multiple events could be reviewed for some patients if they had more than one event during the timeframe.

Validation and chart abstraction

A biostatistician assembled the eligible study population and potential hypoglycemia cases identified through the current definitions. A trained chart abstractor and I reviewed each of the encounters linked with the events using a standardized chart abstraction form which was developed by our research group to verify the diagnosis of hypoglycemia. Both chart abstractors were blinded to administrative data such as diagnoses and medications prior to conducting each chart review.

As part of the chart abstraction protocol, information on hypoglycemia related symptoms, treatment of symptoms, symptom improvement, history of present illness, potential contributors to the event, documented glucose measurements, antihyperglycemic medications at time of event, smoking status and aspirin use were collected (**Appendix A**). Information available in the patient electronic charts including history and physical notes, discharge summaries, consult notes, medication records and laboratory records were utilized for data collection. Based on the

information collected, each hypoglycemia event was classified as either a true event (severe, documented symptomatic, or asymptomatic/atypical events) or a false positive event (probable symptomatic event or not a true event) (**Table 2.3**). These classifications are modified from the American Diabetes Association (ADA) workgroup definitions of hypoglycemic events.[135]

Table 2.3. Classification of hypoglycemia events

	Event Classification		*Definition*
1.	Not a hypoglycemia event	***False positive***	Did not have typical symptoms, and did not have a confirmed glucose measurement <60 mg/dL
2.	Probable symptomatic hypoglycemia	***False positive***	Had typical symptoms, but did not have a confirmed glucose measurement <60 mg/dL
3.	Asymptomatic or atypical hypoglycemia	***True positive***	Was asymptomatic or had atypical symptoms, but had a confirmed glucose measurement <60 mg/dL
4.	Documented symptomatic hypoglycemia	***True positive***	Had typical symptoms with a confirmed glucose measurement <60 mg/dL
5.	Severe hypoglycemia	***True positive***	Had typical symptoms with a confirmed glucose measurement <60 mg/dL, and was seen in the emergency department or hospitalized due to the event

For a 20% random sample of all charts, both abstractors independently performed reviews, to assess the interrater agreement rate. In cases where there was disagreement, a third abstractor reviewed the chart to determine the appropriate classification for the hypoglycemia event.

Analysis

The positive predictive values (PPV) and 95% confidence intervals (CI) were calculated using the Wilson method for each specific ICD-9 code, each type of event (inpatient, emergency department, or outpatient), and the overall definition for any hypoglycemia event. The interrater

agreement was estimated using the kappa statistic for 20% of the charts reviewed by the two abstractors.[136] The kappa statistic was calculated as follows:

$$\kappa = \frac{Observed\ agreement\ rate - 0.5}{1 - 0.5}$$

where 0.5 represents the chance agreement rate in this study.

Results

A total of 335 potential hypoglycemia events were selected for chart review. Of the selected events, chart abstractions were completed for 321 (214 individual patients), including 15 hospitalizations, 103 emergency department visits, and 203 outpatient glucose measurements (**Figure 2.1**). The number of events reviewed per patient ranged from 1 to 10. The median age was 65 years, and 98% had a diagnosis of type 2 diabetes at the time of the event (**Table 2.4**). There were 72 outpatient events (definition 3) that occurred in a nursing home or long-term care facility associated with the VA. There were 15 events with a laboratory appointment only, with no associated clinic visit on the event date. In addition, 77 outpatient events were suspected to have been identified from blood tests that potentially required fasting (54 had a lipid panel tested on the same day).

Hospitalization events (definition 1)

For the hospitalization events, the PPV was 80.0% (95% CI 54.8%, 93.0%) (**Table 2.5**). Hospitalization events examined ICD-9 discharge diagnosis codes in the primary position only. For individual ICD-9 diagnosis codes (primary position only), 251.1 had a PPV of 100%, 251.2 had a PPV of 100%, and 962.3 had a PPV of 67%. Two patients had no evidence of

hypoglycemia but were admitted to the hospital because they intentionally overdosed on metformin. One patient was admitted due to hypokalemia.

Figure 2.1. Identification of potential hypoglycemia cases that were selected for chart review and validation

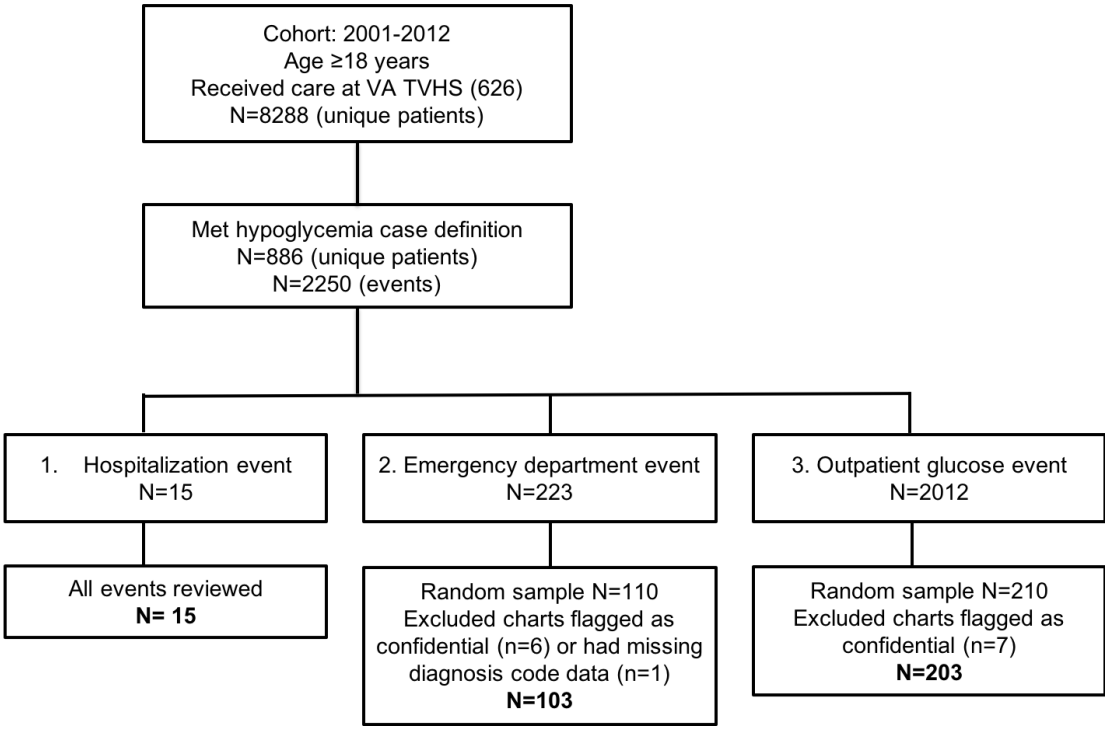


Table 2.4. Characteristics of potential hypoglycemia cases reviewed

Characteristic	*Study sample N=321*
Age, median (IQR)*	65 (58, 77)
Male (%)	307 (96%)
Race, (%)	194 (60%)
White	
Black	108 (34%)
Hispanic/ Other	3 (1%)
Missing	16 (5%)
Diagnosed with diabetes, %	311 (97%)
Event type	
Hospitalization	15
Emergency department visit	103
Outpatient glucose measurement <60 mg/dL	203
Had typical symptoms (%)	102 (32%)
Had atypical symptoms (%)	21 (7%)
Blood glucose (mg/dL) at time of event, median (IQR)	53 (42, 59)
Had prescription for antidiabetic drug	290 (90%)
Had prescription for sulfonylurea or insulin, %	276 (86%)
Aspirin use, %	174 (54%)
Smoking, %	112 (35%)

Table 2.5. Positive predictive value of hypoglycemia definitions and diagnosis codes

	ICD-9-CM code	*Potential cases*	*Confirmed cases*	*PPV (%) (95% CI)*
All		321	256	80 (75, 84)
1. Hospitalizations		15	12	80 (55, 93)
	251.0	0	0	-
	251.1	2	2	100 (34, 100)
	251.2	4	4	100 (51, 100)
	962.3	9	6	67 (35, 88)
	270.3	0	0	-
2. Emergency department visits		103	49	48 (38, 57)
	251.0	0	0	-
	251.1	0	0	-
	251.2	68	47	69 (57, 79)
	962.3	1	1	100 (21, 100)
	270.3	0	0	-
	250.8*	36	3	8 (3, 22)
3. Outpatient glucose		203	195	96 (92, 98)

* without co-existence of 259.8, 272.7, 681.X, 682.X, 686.9, 707.1-707.9, 730.0-730.2, or 731.8 in any position

Emergency department events (definition 2)

For emergency department events, the PPV was 48% (95% CI 38%, 57%). Of 103 charts reviewed, 49 cases were true hypoglycemia events (43 severe, 1 documented symptomatic, 5 asymptomatic), and 54 cases were not true events (**Table 2.5**). Of the 54 false positive events, 11 were possible hypoglycemia events with no documented glucose measurement <60 mg/dL. Among the 45 events with no evidence of hypoglycemia, 24 (53%) were hyperglycemia events that were coded incorrectly; 6 (13%) were related to other potential diabetes complications such as foot ulcer or cellulitis that were coded incorrectly; 3 (7%) were hypoglycemia events that occurred in the emergency department during a visit with another primary indication and did not meet our case definition which required hypoglycemia as the primary reason for the visit; 1 (2%) had glucose <70 mg/dL; and 11 (24%) came to the emergency department for other reasons. Examining individual ICD-9 codes (any position), 251.2 had a PPV of 69% (n=68; 95% CI 57%, 79%); 962.3 had a PPV of 100% (n=1; 95% CI 21%, 100%), and 250.8 had a PPV of 8.3% (n=36; 95% CI 2.9%, 21.8%). In the study sample, the PPV for emergency department events improves to 70% if the ICD-9 code 250.8 is excluded from the case definition. Of 69 cases with either code 251.2 or 962.3, 47 were a true hypoglycemia event. Of 36 cases with the code 250.8, 2 also had 251.2. Only one case with 250.8 and no other code was a true hypoglycemia event. Thus only 1 of 49 true events would be missed by excluding this code.

As a sensitivity analysis, we classified the 3 hypoglycemia events that occurred during an emergency department (due to another primary cause) as true cases. These cases had documented low glucose measurements <60 mg/dL, with or without symptoms. This led to an overall PPV of 50% (95% CI 41%, 60%) for emergency department events.

Outpatient glucose events (definition 3)

For outpatient events, the PPV was 96% (95% CI 92, 98) (**Table 2.5**). Cases that were not a true hypoglycemia event were: hypoglycemia that occurred during a hospitalization that were incorrectly identified as outpatient events (n=3), no glucose measurement record of <60mg/dL found in chart (n=4), and hypoglycemia that occurred during an emergency department visit due to another primary cause (n=1). Of 195 cases that had a true hypoglycemia event with a confirmed blood glucose <60 mg/dL (out of 203 total cases reviewed), 15% had typical symptoms (3% were severe events that led to an emergency department visit or hospitalization), while 81% had no symptoms or symptoms were not noted in the chart. The median blood glucose measurement for those with severe events was 39 mg/dL (IQR 28, 44); median blood glucose for documented symptomatic events was 46 mg/dL (IQR 39, 56); and median blood glucose for asymptomatic or unknown events was 52 mg/dL (IQR 47, 57).

Overall algorithm and interrater agreement

The overall PPV for the composite of all 3 definitions of hypoglycemia was 80% (95% CI 75, 84). When the code 250.8 and its exclusion criteria were removed from the algorithm, the overall PPV increased to 89% (95% CI 85%, 93%).

The two abstractors both independently reviewed 65 charts. There were 6 charts for which they disagreed on whether the event was a true hypoglycemia event. For 7 additional charts, they agreed on whether it was a true versus false event but disagreed on the specific type of hypoglycemia event (e.g. one abstractor assigned the event as “asymptomatic” while the other abstractor assigned it as “documented symptomatic”). The resulting kappa statistic for interrater

agreement was 0.79 for the overall identification of true hypoglycemia events. For assignment of specific hypoglycemia classification, the kappa statistic was 0.61.

Discussion

In this study, the overall positive predictive value of the composite hypoglycemia definition was estimated to be 80% in a sample of veterans with type 2 diabetes. The specific positive predictive values were 80% for hospitalization events, 48% for emergency department events, and 96% for outpatient events. Adjusting the emergency department event definition to exclude ICD-9 code 250.8 resulted in higher positive predictive values for that specific definition (70%) and the overall algorithm (89%) in the study sample. Excluding 250.8 from the algorithm led to missing only one of 48 true events, which further justifies excluding this code in future studies.

In a previous validation study, Ginde and colleagues found that their emergency department algorithm performed well with a positive predictive value of 89%.[41] We had adapted their algorithm for the VA population, but found that the positive predictive value was much lower. There are many possible explanations for these results, including differences in administrative coding at institutions, study period, and validation methods. Importantly, the ICD-9 code 250.8 is a nonspecific code, so it is plausible that different institutions used this code differently.

Our study also differs from previous validation studies of hypoglycemia in that it evaluated a composite definition including hospitalizations, emergency department visits, and outpatient events. Because we thought it would be important to be able to identify serious events

that result from medications used in the outpatient setting, we excluded hospitalizations and emergency department visits in which hypoglycemia occurred after presentation or was not the primary reason for admission. Hospitalized patients may have different physiologic responses and/or receive different antihyperglycemic treatment due to their acute conditions. For emergency department events, we conducted a sensitivity analysis with and without cases where hypoglycemia occurred during the visit. For outpatient events, however, we did not examine the primary cause of visit, but only considered records of point of care or laboratory blood glucose measurements to identify true events.

Typical symptoms were not required for any of the definitions, but a documented blood glucose of less than 60 mg/dL was required to be considered a true event. Not all of the hospitalizations and emergency department events had associated symptoms; some patients were sent to the emergency department or hospitalized due to a low glucose measurement but did not report symptoms. Among all outpatient events, 15% had documentation of hypoglycemia-related symptoms or sought further treatment for hypoglycemia. These patients had lower median blood glucose measurements compared to those who had no record of further treatment.

One limitation of this validation study is that only the algorithm-positive events were reviewed, so only the positive predictive values could be estimated. To determine the sensitivity, specificity, and negative predictive values, we would have to conduct chart reviews on a sample of patients who were not identified as having a hypoglycemic event. This would have greatly increased the data collection burden and created additional challenges with regards to control sampling. Another limitation which is common to many studies evaluating the outcome of hypoglycemia, is that many true cases are still likely to be missed even though we included an outpatient definition to capture more events.

In summary, we found that our composite definition for hypoglycemia performed moderately well in identifying true hypoglycemia cases in a large cohort of veterans with type 2 diabetes. However, the nonspecific ICD-9 code 250.8 from the emergency department event definition captured many false positive events. Excluding this code from the definition improved the positive predictive value of the algorithm in our study population.

CHAPTER III

ANTIDIABETIC MEDICATION ADHERENCE AND THE RISK OF HYPOGLYCEMIA

Introduction

Antihyperglycemic medications are an important part of diabetes management. However, patient compliance to these medications has been shown to be suboptimal. Antihyperglycemic medication adherence rates among patients with type 2 diabetes is estimated to be 60-85%, and up to a third of patients who are prescribed metformin discontinue the drug within one year.[61–63] Many factors could be associated with medication adherence, including complexity of medication regimens, perceived side effects, beliefs about medications, relationship with provider, medication costs, and other socioeconomic factors.[66,67]

The level of adherence to antihyperglycemic medications can have an impact on both short-term diabetes treatment goals and long-term clinical outcomes. Higher adherence to oral antihyperglycemic drugs is associated with better attainment of target glycosylated hemoglobin (HbA1c).[82–85] In one study, nonadherence, defined as a medication possession ratio of <80%, was associated with higher odds of hospitalization due to diabetes or cardiovascular/cerebrovascular causes.[87]

One important potential issue with nonadherence is that providers are often unaware of its impact on their patients. This may lead healthcare providers to intensify antihyperglycemic therapy by adding another agent to the patient's current regimen, even when the underlying cause of their suboptimal glycemic levels was due to nonadherence. However, patients with low

medication adherence may become more adherent (or motivated to adhere to their diabetes regimen) shortly following an outpatient visit where a new medication is added. This could lead to greater glucose variability and increase the possibility of hypoglycemic events. For example, if a patient was only 50% adherent on his metformin monotherapy, the physician who is unaware of his low adherence might add a sulfonylurea (a medication with potent hypoglycemic effects) to his regimen because his HbA1c is high. Following this clinic visit, the patient may start taking both his metformin and sulfonylurea more regularly, which will lower his baseline glucose levels further, and the addition of sulfonylurea may place them at a higher risk for hypoglycemic events.

We conducted a retrospective cohort study to evaluate whether low adherence to metformin monotherapy immediately prior to intensification was a risk factor for early hypoglycemia events following intensification of therapy with a sulfonylurea.

Methods

Study design and data sources

We used national Veterans Health Administration (VHA) databases which include administrative, clinical and laboratory data linked through identifiers designed for research (scrambled social security numbers) to construct a retrospective cohort of veterans with type 2 diabetes. Sources of data include: VHA dispensed medication information, including fill date, days supply, and number of pills; demographic data; diagnostic and procedure information from inpatient and outpatient encounters coded as *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*[38]; and laboratory test results and vital signs (blood

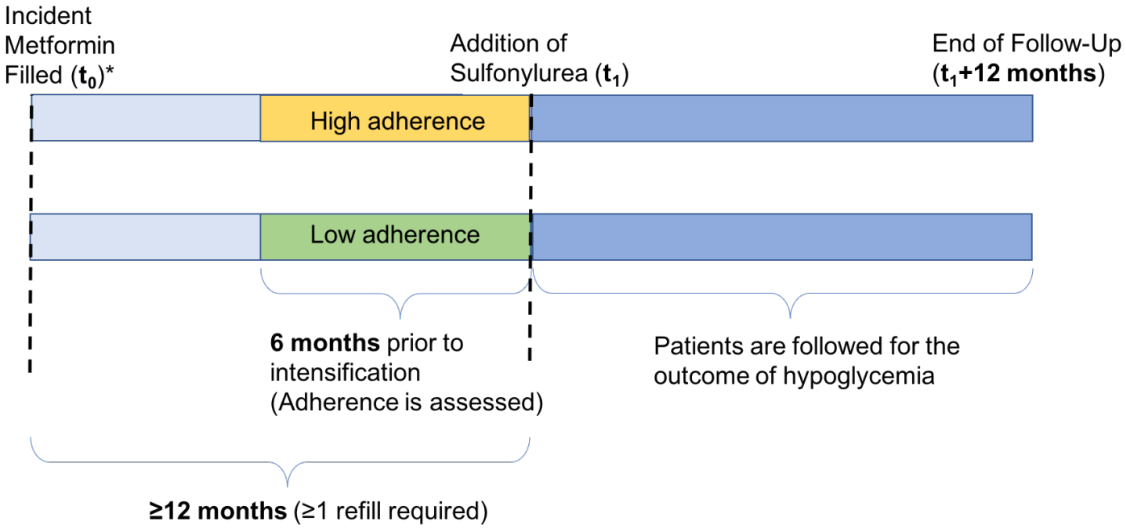
pressure, height and weight measurements) from standard clinical sources. For VHA cohort patients who are also enrolled in Medicare or Medicaid, data on additional encounters, Part D prescription fill records, and self-reported demographics (race/ethnicity) were obtained from the Centers for Medicare and Medicaid Services (CMS) through the VHA's interagency exchange agreement.[137] Dates of death were obtained from the National Death Index (NDI) data prior to 2011, and VHA vital status files were used as a supplement to identify subsequent dates of death from 2011 to 2012. More specific details of the data sources and datasets can be found in **Appendix B**. The institutional review boards of VHA Tennessee Valley Healthcare System and Vanderbilt University approved this study.

Study population

The study population included veterans aged 18 years or older who received regular care at VHA. Regular care was defined as having at least one inpatient or outpatient encounter or a prescription fill every 360 days in the prior 2 years. New users of metformin from October 2001 to September 2011, with at least 365 days of baseline data and no antihyperglycemic drug fill during the past 180 days, were identified. The time of first ever metformin fill is referred to as "global first" (t_0). Patients were excluded if they did not refill metformin at least once during the initial 12 months of therapy. This criterion was added to exclude patients who may not have tolerated metformin well. Metformin "global first" initiators who refilled their medication at least once became eligible for the intensification cohort when they filled their first sulfonylurea (glyburide, glipizide or glimepiride) prescription (t_1) (**Figure 3.1**). The time from t_0 to t_1 was required to be at least 12 months so that adherence could be assessed and defined based on a

sufficient time period for all study patients. However, persistence on metformin prior to t_1 was not required, as long as metformin was refilled at least once during the first 12 months.

Figure 3.1. Timeline showing the periods during which the exposure (adherence) and outcome (hypoglycemia) were assessed in the study population



Patients receiving hospice care or dialysis at the time of intensification (t_1) were excluded because their medication administration schedule and hypoglycemia risk may be inherently different than the included clinical population (**Appendix C**). Patients with missing birthdate or gender were also excluded.

Exposures

The main exposure of interest was antihyperglycemic medication adherence behavior at the time of metformin intensification with sulfonylurea. This was operationalized using a proxy measure, metformin monotherapy adherence, which was first defined as a continuous variable representing the proportion of days with metformin on hand (proportion of days covered

[PDC][68]) during the 6-month period prior to t_1, the time of intensification (addition of sulfonylurea). We limited the study population to those who had the opportunity to take metformin for at least 12 months before intensification, so that all study patients could have adherence calculated based on the same length of pre-intensification time (**Figure 3.1**). The proportion of days covered was calculated as the proportion of days with metformin on hand based on prescription fill records. Patients were expected to have highly variable total durations of metformin use, but adherence was calculated based on the 6-month period immediately prior to intensification for all patients.

Many prior studies have defined high adherence as proportion of days covered (PDC) or medication possession ratio (MPR) of 80% or greater.[68,72] Clinically, a patient with 80% adherence would be missing approximately one dose per week on average. We applied this definition to our study and compared the outcome among patients with low adherence (<80%) and high adherence (≥80%) at the time of intensification (t_1).

Follow-up of the exposure groups in the intensification cohort patients began immediately after intensification (**t_1**) and continued for up to 1 year until study outcome, regimen change (addition of a third agent), loss to follow-up (181 days without VHA contact), death, or end of study (September 30, 2012) (**Figure 3.1**).

Primary outcome: Hypoglycemia

The main outcome of interest was an early hypoglycemia event occurring within one year of metformin intensification with a sulfonylurea. Hypoglycemia was defined as a composite event of 2 types: hospitalization due to hypoglycemia, or an outpatient blood glucose measurement of less than 60 mg/dL based on the accuracy and positive predictive value (PPV) of

the validation of hypoglycemia performed in Study 1. Hospitalization for hypoglycemia was identified by a primary discharge diagnosis of hypoglycemia or poisoning by insulin or other antidiabetic agents (ICD-9-CM codes 251.0, 251.1, 251.2, 270.3 or 962.3 in the primary position only). Hypoglycemia events identified through emergency department visits were not included as events in this study, due to the low positive predictive value of the administrative code algorithm found in our previous validation study.

Patients were followed for the hypoglycemia outcome for up to a year after intensification of metformin monotherapy. Only first hypoglycemia events occurring after intensification were counted as the outcome in this analysis. Recurrent events were not considered in the study; therefore, follow-up was discontinued once the patient had the outcome or reached study end (1 year after intensification).

Secondary outcomes

As a secondary outcome, the median HbA1c measurements among low and high adherence patients at baseline and 12 months after intensification were explored. The absolute change in HbA1c measurements between the time of intensification (t_1) and 12 months after intensification (t_1+12 months) was also examined for patients who survived during that period.

Covariates

Baseline covariate information was collected from up to 730 days prior to intensification (t_1 baseline). Covariates included age, sex, race (white, black, other), year of metformin initiation, indicators of healthcare use (hospitalized during past year, nursing home use, number of outpatient visits, Medicare or Medicaid utilization), physiologic variables (body mass index

[BMI], blood pressure, HbA1c level, low-density lipoprotein [LDL] level, proteinuria, serum creatinine, and calculated estimated glomerular filtration rate [eGFR] using the Chronic Kidney Disease Epidemiology Collaboration formula), duration of metformin monotherapy (proxy for diabetes duration), selected medications, smoking, and selected comorbidities (See **Appendix D** for further details).

Two important covariates also included in the analysis were the type and dose of sulfonylurea added at t_1. Sulfonylurea types included glipizide, glyburide, and glimepiride. Defined daily doses (DDD) of the sulfonylurea were captured at t_1 for each patient and was used to define the covariate *sulfonylurea dose*. One defined daily dose for each specific sulfonylurea agent were: 10mg for glipizide, 10mg for glyburide, and 2mg for glimepiride according to the World Health Organization (WHO).[138] Multiple imputation was conducted for missing covariates using an iterative Markov chain Monte Carlo (MCMC) method for both the construction of propensity scores and for the final outcome model. First, 30 imputation datasets were created, and propensity score models were built separately in each of the imputed datasets to obtain 30 propensity scores for each study patient. The mean of the 30 propensity scores was calculated for each patient and was used for the propensity score weighting in the main analysis. Second, 30 imputation datasets were created once again for covariate-adjustment in the final outcome model. For continuous variables, restricted cubic splines were included in the outcome model to account for nonlinearity.

Data cleaning and quality control

For blood glucose values obtained in the outpatient setting, we excluded non-numeric values (such as “high” or “low”) and converted non-absolute values to absolute values so that a

blood glucose value >400 would be coded as 400, and a blood glucose value <70 would be coded as 70. If a patient had hypoglycemia based on the outpatient blood glucose which led to a hospitalization within 48 hours, the event was counted as a single event attributed to the hospitalization. Any implausible values for HbA1c (<3% and >30%), height (<48 inches and >90 inches), and weight (<50 pounds and >700 pounds) were excluded and considered missing.

Statistical analyses

The primary analysis evaluated whether the risk of early hypoglycemia following intensification was higher among patients with low adherence versus high adherence. Propensity scores were created and modeled the probability of low adherence based on covariate information and service network of care. Results of the propensity score models are presented in separate figures and tables (**Appendix E**). A time-to-event analysis was conducted using a weighted Cox proportional hazards model adjusting for baseline covariates, where propensity score matching weights from the propensity score were applied.[139]

For the secondary analysis, we described the change in HbA1c from baseline to 12 months after intensification among patients who survived, to examine whether there are greater decreases in HbA1c among patients with low adherence.

Subgroup and sensitivity analyses

We examined whether the association between low adherence and risk of hypoglycemia differed by two potential effect modifiers, sulfonylurea type and dose, which were determined a priori. Subgroup analyses were conducted for patients who intensified treatment with glyburide

versus glipizide or glimepiride, and also for those who added a high dose of sulfonylurea (≥1 DDD) versus low dose of sulfonylurea (<1 DDD).

As part of sensitivity analysis, we modeled medication adherence as a continuous variable using restricted cubic splines in a Cox proportional hazard model adjusting for key baseline covariates. This analysis was performed to examine whether there was a nonlinear or tipping point association between adherence and the hypoglycemia outcome.

Results

Study population

We identified 187,267 patients who initiated metformin monotherapy. Of those patients, 49,617 patients intensified therapy with a sulfonylurea after being on metformin monotherapy for at least one year and did not meet other exclusion criteria (**Figure 3.2**). The intensification cohort patients were 96% male, 84% White, and the median age was 63 years (interquartile range [IQR] 57, 72). The median metformin adherence in the 6 months prior to intensification was 87% (IQR 50, 100) (**Figure 3.3**); 47% (IQR 16, 63) among low adherence patients and 100% (IQR 94, 100) among high adherence patients. A total of 21,554 patients (43%) had low adherence, which was defined as <80%. Low adherence patients were slightly younger (age 62 vs. 64), had a lower proportion of white patients (77% vs. 86%), were on a shorter duration of metformin monotherapy (25 vs. 30 months), had higher baseline HbA1c levels (7.5 vs. 7.3%), and were on fewer outpatient medications (11 vs. 13) (**Table 3.1**).

Figure 3.2. Flowchart of eligible study patients

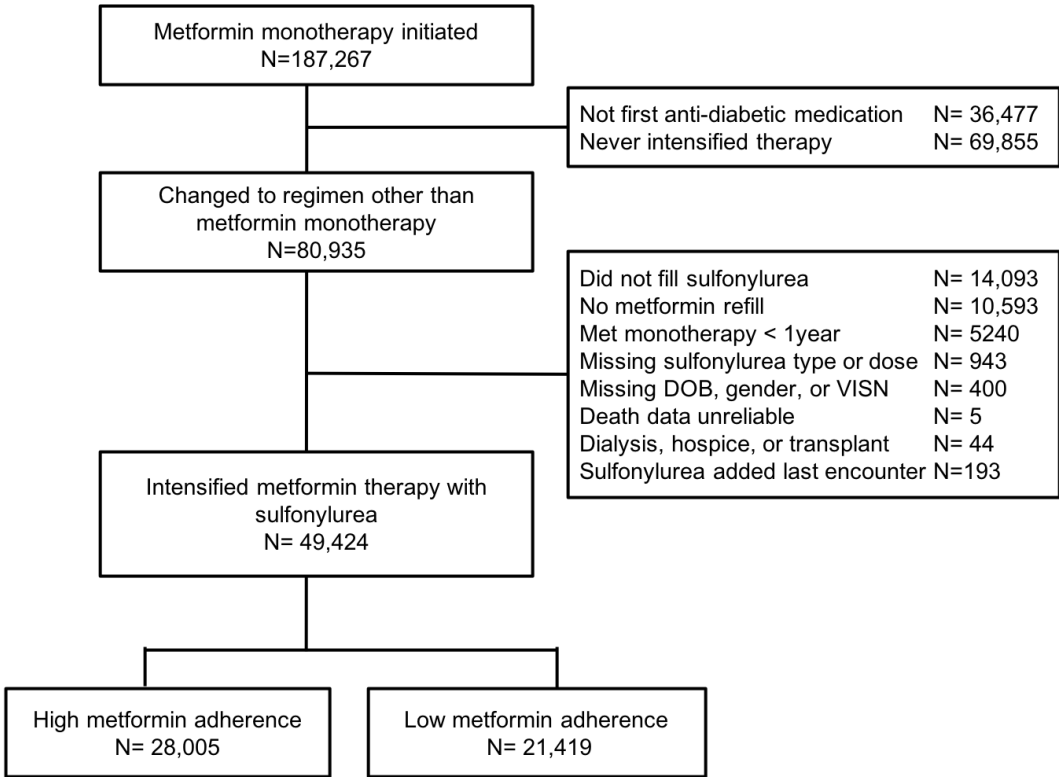


Figure 3.3. Distribution of adherence in the study population

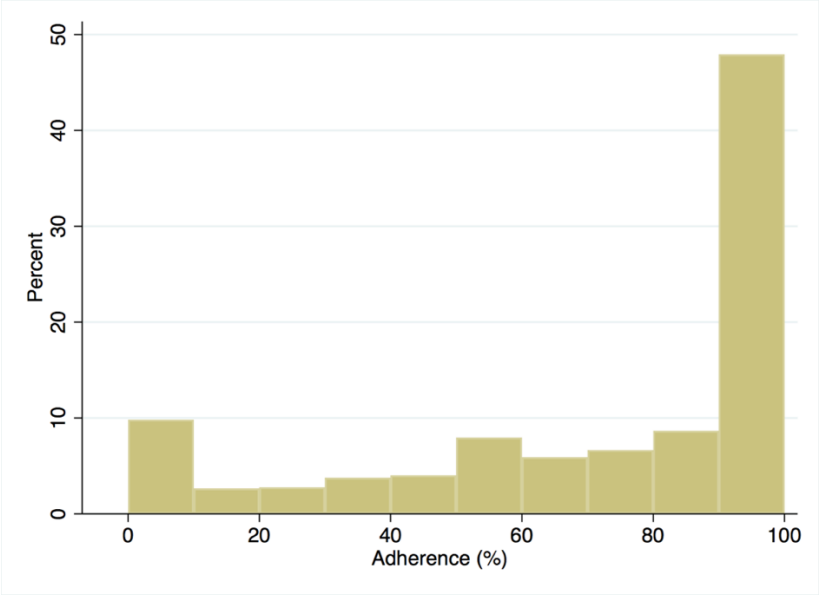


Table 3.1. Characteristics of study patients

Characteristic	*Full cohort N=49,424*		
	Low Adherence N= 21,419	*High Adherence N= 28,005*	*SD†*
Age, median (IQR)*	62 (56, 71)	64 (59, 72)	-0.16
Male (%)	95.1	96.4	0.7
Race, (%)†			
White	78.6	87.3	-0.23
Black	16.2	9.1	0.21
Hispanic/ Other	5.3	3.6	0.08
Available %	91.3	92.2	0.03
Months on sulfonylurea monotherapy, median (IQR)‡†	25 (9, 45)	30 (16, 49)	-0.21
Initiated glyburide (%)	36.5	38.8	0.05
Sulfonylurea initial dose (DDD), median (IQR)	0.5 (0.5, 1.0)	0.5 (0.3, 1.0)	0.08
HbA1c, %	7.5 (6.8, 8.6)	7.3 (6.7, 8.0)	0.24
Available %	90.7	92.5	0.07
Low density lipoprotein mg/dL, median (IQR)	94 (73, 120)	83 (67, 102)	0.33
Available %	82.7	86.2	0.10
Glomerular filtration rate (ml/min), median (IQR)	82 (66, 99)	80 (65, 95)	0.10
Available %	88.2	89.4	0.04
Creatinine mg/dL, median (IQR)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	-0.03
Proteinuria, (%)			
Negative	49.5	51.1	-0.03
Trace through 4+	18.5	17.9	0.02
Available %	68.0	69.0	0.02
Systolic blood pressure (mm/Hg), median (IQR)	133 (122, 144)	132 (121, 142)	0.08
Diastolic blood pressure (mm/Hg), median (IQR)	77 (69, 84)	76 (68, 82)	0.13
Available %	98.4	98.9	0.04
Body mass index (kg/m^2), median (IQR)†	31.9 (28.3, 36.2)	32.1 (28.6, 36.4)	-0.03
Available%	97.5	98.3	0.06
Baseline Co-morbidities (%)			
Malignancy	5.7	6.4	-0.03
Liver/ respiratory failure†	1.3	0.9	0.03
HIV†	0.3	0.3	0.02
Congestive heart failure	6.2	5.9	0.01
Cardiovascular disease	22.8	25.3	-0.06
Serious mental illness	18.1	18.0	0.001
Smoking	13.6	12.4	0.04
Obstructive Pulmonary Disease/ Asthma	12.6	13.6	-0.03
Cardiac valve disease	1.6	1.7	-0.01
Arrhythmia	7.8	8.6	-0.03
Parkinson's	0.4	0.5	-0.004
Osteoporosis	2.1	2.2	-0.1
History of falls/ fractures	1.2	0.9	0.04
Oxygen use	0.3	0.3	0.01
Use of Medications (%)			
ACE Inhibitors	59.9	65.2	-0.11
ARBs	10.5	12.9	-0.08
Other anti-hypertensive medications†	22.6	26.5	-0.09
Statin and other lipid lowering agents†	68.6	79.8	-0.26
Anti-arrhythmics, digoxin and inotropes	2.1	2.4	-0.02
Anticoagulants, platelet inhibitors	5.7	7.3	-0.06
Nitrates	10.7	12.6	-0.06

Aspirin	21.3	22.9	-0.04
Loop Diuretics	12.4	14.1	-0.05
Antipsychotics	7.8	8.2	-0.02
Oral glucocorticoids	11.6	13.1	-0.05
Alpha blockers	14.0	17.7	-0.10
Indicators of Healthcare Utilization			
Hospitalized in last year (%)†	13.3	11.4	0.06
Hospitalized in prior 90 days (%)†	5.4	4.7	0.03
Nursing home encounter (%)	0.04	0.04	0.001
Outpatient visits, median (IQR)	6 (3, 10)	6 (4, 10)	-0.04
Medicare utilization	24.6	26.5	-0.04
Medicaid utilization	9.8	8.8	0.03
Number of outpatient medications, median (IQR)	12 (8, 16)	13 (9, 18)	-0.21
Year of Metformin Initiation			
2001-2002	4.4	4.5	-0.01
2003	17.7	17.9	-0.01
2004	19.5	20.4	-0.02
2005	21.2	22.2	-0.02
2006	21.6	20.7	0.02
2007	15.6	14.2	0.04

* Abbreviations: median and interquartile range (IQR), standardized differences (SD), angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB)

† Standardized differences (SD) are reported. Standardized differences are the absolute difference in means or percent divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations.

‡ Time to treatment intensification represents the time on metformin monotherapy and is an approximation of the duration of diabetes since patients were free of all hypoglycemic medications for 180 days prior to starting metformin.

Primary Outcome: Hypoglycemia

There were a total of 1001 hypoglycemia events (11 hospitalizations and 990 outpatient events); 412 among low adherence patients (4 hospitalizations and 408 outpatient events), and 589 among high adherence patients (7 hospitalizations and 582 outpatient events). The unadjusted hazard rates of hypoglycemia per 1000 person-years were 20.9 (95% confidence interval [CI] 19.0, 23.0) and 22.4 (95% CI 20.6, 24.3) for low and high adherence patients, respectively. The risk of hypoglycemia in the low adherence patients was not significantly different compared to high adherence patients (adjusted hazard ratio [HR] 0.95, 95% CI 0.83, 1.09) (**Table 3.2**).

Table 3.2. Adjusted hazard ratio and 95% confidence intervals for the risk of hypoglycemia among low adherence patients versus high adherence patients

	Low adherence N=21,419	*High adherence N=28,005*
First hypoglycemia events		
Hospitalizations and outpatient glucose <60 mg/dL*	412	589
Person-years	19,717	26,331
Unadjusted rate/1000 person-years (95% CI)	20.9 (19.0, 23.0)	22.4 (20.6, 24.3)
Adjusted hazard ratio † (95% CI)	0.95 (0.83, 1.09)	Ref

* Primary analysis does not require persistence on metformin, but patients are censored after 90 days if they fill a third antihyperglycemic agent

† Propensity score weighted (with matching weights), covariate-adjusted hazard is derived from Cox proportional hazards model for time to outcome, adjusting for baseline covariates

Sensitivity and subgroup analyses

When adherence was modeled as a continuous variable using restricted cubic splines, there did not appear to be a significant linear or nonlinear association between different levels of adherence and the risk of hypoglycemia (**Figure 3.4**).

Subgroup analyses results were also consistent with the main findings (**Table 3.3**). The associations between adherence and hypoglycemia did not appear to differ by sulfonylurea type (interaction test p=0.32) or by sulfonylurea dose (interaction test p=0.37).

Relationship between adherence and change in HbA1c

The median baseline HbA1c for low and high adherence patients was 7.5 (IQR 6.8, 8.6) and 7.3 (IQR 6.7, 8.0), respectively. The median HbA1c at 12 months for patients who did not die and had a baseline measurement was 6.9 (IQR 6.3, 7.7) among low adherence patients and 6.8 (IQR 6.3, 7.4) among high adherence patients (**Figure 3.5**). The median absolute HbA1c change from baseline to 12 months was -0.3 (IQR -1.2, 0) among low adherence patients and -

0.3 (IQR -1.0, 0) among high adherence patients who survived during the 12-month follow-up period. Among low adherence patients, 30.5% of patients had a greater than 1% decrease in HbA1c over the first 12 months. Among high adherence patients, 27.2% had a greater than 1% decrease. This difference was statistically significant ($p<0.0001$).

Figure 3.4. Hazard ratios and 95% confidence intervals for hypoglycemia when adherence was modeled as a continuous variable using restricted cubic splines, with median adherence (87%) as the reference

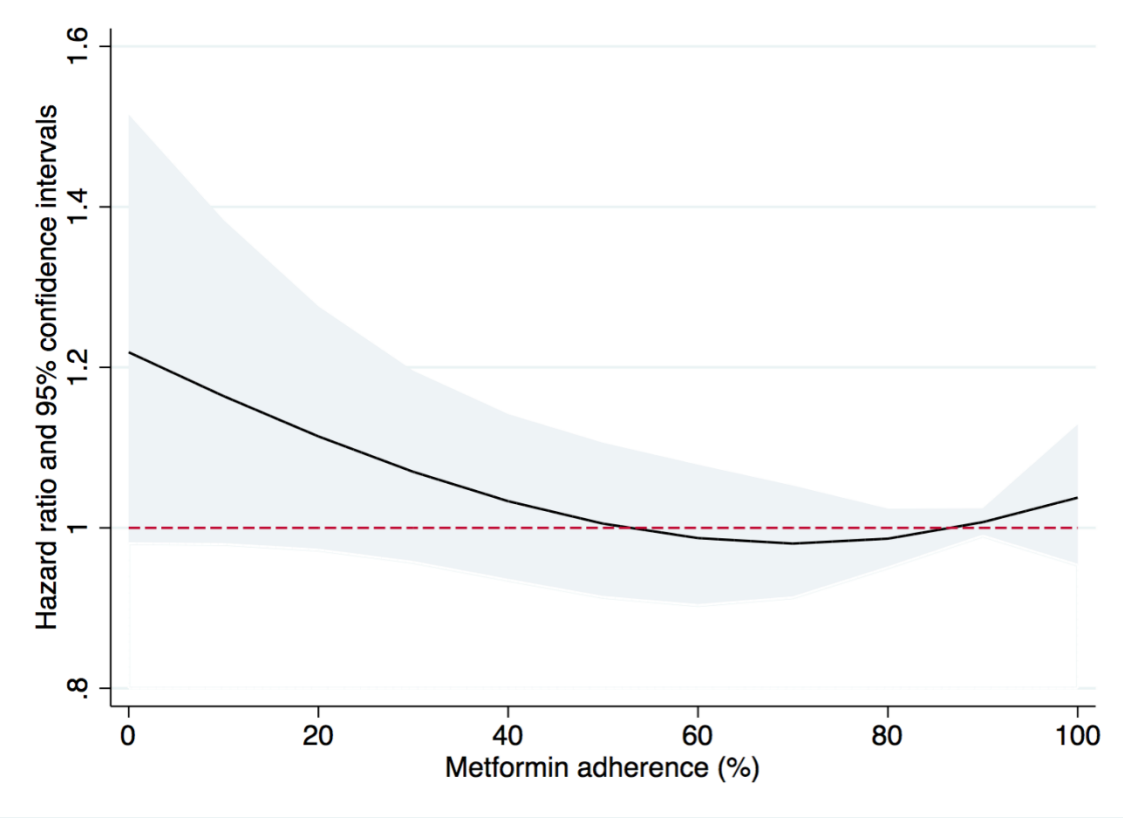
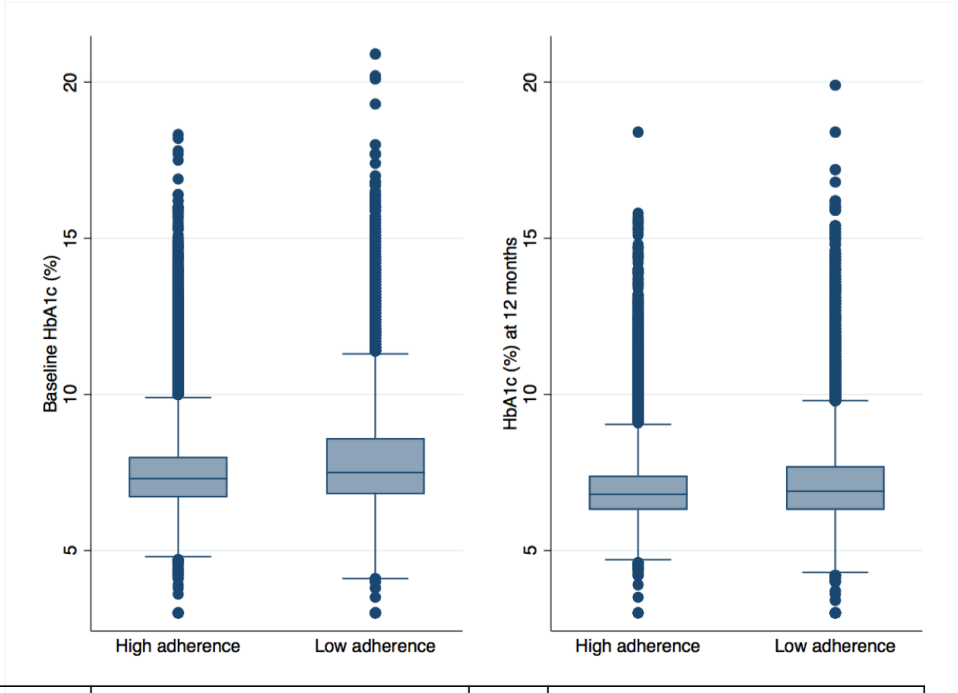


Table 3.3. Subgroup analysis results

	Low adherence	*High adherence*
Sulfonylurea type		
Glyburide	**N=8309**	**N=10,223**
First hypoglycemia events/ person-years	155/7808	231/9789
Unadjusted rate/1000 person-years (95% CI)	19.9 (17.0, 23.2)	23.6 (20.7, 26.8)
Adjusted hazard ratio (95% CI)	0.88 (0.70, 1.10)	Ref
Glipizide or glimepiride	**N=13,110**	**N=17,782**
First hypoglycemia events/ person-years	257/11,909	358/16,542
Unadjusted rate/1000 person-years (95% CI)	21.6 (19.1, 24.4)	21.6 (19.5, 24.0)
Adjusted hazard ratio (95% CI)	1.00 (0.84, 1.20)	Ref
Sulfonylurea dose		
DDD ≥1	**N=7248**	**N=8611**
First hypoglycemia events/ person-years	142/6581	196/8046
Unadjusted rate/1000 person-years (95% CI)	21.6 (18.3, 25.4)	24.4 (21.2, 28.0)
Adjusted hazard ratio (95% CI)	0.97 (0.76, 1.23)	Ref
DDD<1	**N=14,171**	**N=19,394**
First hypoglycemia events/ person-years	270/13,136	393/18,285
Unadjusted rate/1000 person-years (95% CI)	20.6 (18.2, 23.2)	21.5 (19.5, 23.7)
Adjusted hazard ratio (95% CI)	0.95 (0.81, 1.13)	Ref

† Propensity score weighted (using matching weights), covariate-adjusted hazard is derived from Cox proportional hazards model for time to outcome, adjusting for baseline covariates

Figure 3.5. Change in median HbA1c among high and low adherence patients during the first year of intensification



Time since intensification	0 months			12 months	
N	25,916	19,434		24,715	18,111
HbA1c (%), med (IQR)	7.3 (6.7, 8.0)	7.5 (6.8, 8.6)		6.8 (6.3, 7.4)	6.9 (6.3, 7.7)

Discussion

In our study of veterans with type 2 diabetes, we found no evidence that low metformin monotherapy adherence (<80%) increased the risk of developing early hypoglycemia within a year of intensifying treatment with a sulfonylurea. The risk of hypoglycemia across different adherence levels did not appear to vary significantly. Adherence did appear to be related to glucose variability (or decline in HbA1c) during the first year. Among patients who survived, a greater proportion of low adherence patients had a greater than 1% decrease in HbA1c compared to high adherence patients.

We used clinical and administrative data from a large national cohort to determine medication adherence and hypoglycemia events and used advanced survival methods to balance and adjust for potential confounders in the comparison groups. Other studies have examined the association between medication adherence and the outcome of hypoglycemia, but none have addressed this specific question or used similar methods. Qulliam and colleagues previously examined whether the risk of hypoglycemia differed depending on the adherence and change in regimen during the first 6 months of metformin, sulfonylurea, or thiazolidinedione therapy.[64] Using Cox proportional hazards models adjusting for several confounders, they found that the hazard of hypoglycemia was higher among patients switching to combination therapy compared to metformin users who were highly adherent; however, they did not specifically evaluate how adherence could relate to the risk of hypoglycemia after switching to combination therapy. Hsu and colleagues sought to address a similar question, but used a cross-sectional design to examine the relationship between self-reported adherence and adverse safety events including hypoglycemia.[96] They did find that lower adherence by self-report was associated with more adverse safety outcomes by self-report (prevalence ratio [PR] 1.21, 95% CI 1.04, 1.76), but the specific results for hypoglycemia were not reported, and the temporal relationship could not be established due to the cross-sectional nature of the study.

Studying the effect of medication nonadherence on side effects such as hypoglycemia is complex because those with irregular adherence behaviors may truly have more glucose variability and a higher risk of hypoglycemia when they take their medications, but also a lower risk of hypoglycemia on days that they do not take the medication. We had expected that the relationship between adherence and hypoglycemia may be complex, so we modeled adherence as a continuous variable with restricted cubic splines in our sensitivity analyses to capture any

nonlinear effects. It appeared that there may be increasing risk with very low adherence (<30%), but the wide confidence intervals show that we had low power to address this question in this population, and that the risk may not be significantly different from the reference. Another potential explanation for our results is that the risk of hypoglycemia may be more strongly related to other factors, such as high initial sulfonylurea dose or low baseline HbA1c. We found that sulfonylurea dose was slightly higher among low adherence patients, but the baseline HbA1c was also higher in this group which could have led to opposite effects.

Our study had several limitations. We used pharmacy fill data to assess adherence and were only able to capture baseline adherence. Since our hypothesis was that patients with poor adherence to metformin may change their behavior after adding a second drug, it could have been interesting to capture post-intensification metformin and sulfonylurea adherence and compare that to the pre-intensification adherence. However, this was likely difficult to capture in our data because most patients would have gotten a 90-day supply of a sulfonylurea and would have had a higher than 50% adherence during the 6 months following intensification. Another limitation is that hypoglycemia is often missed because patients do not present to the hospital or obtain glucose measurements even when they have a moderate to severe event. In addition, veterans may not receive all care at VHA facilities, so some events may have been missed even if patients presented to the hospital. However, our data are supplemented by Medicare and Medicaid encounter information, which should have reduced missed events. A limitation of the HbA1c analysis is that HbA1c is a measure of glycemic control over three months and variability in HbA1c may not necessarily reflect day to day glycemic variability which may be related to risk of hypoglycemia. Nonetheless, it was meaningful to explore whether adherence was associated with HbA1c variability in this population to inform further research in that direction.

Unmeasured confounders such as severity of diabetes or other health behaviors could have impacted our results, but we were able to balance many potential confounders with the use of propensity score weighting and covariate adjustment. Finally, the study population was mostly white men, which should be considered when generalizing the study results to other settings or populations.

In conclusion, we found no evidence that low metformin monotherapy adherence was a risk factor for early hypoglycemia events following intensification with a sulfonylurea, even though low adherence patients had a greater decline in HbA1c during the first 12 months of intensification. These results were consistent when we examined the risk of hypoglycemia across different levels of adherence.

CHAPTER IV

MEDIATORS IN THE ASSOCIATION BETWEEN INSULIN USE AND DEATH

Introduction

Maintaining adequate glycemic control is an essential part of diabetes management. However, large clinical trials have failed to demonstrate that intensive glucose control, or targeting aggressive glycosylated hemoglobin (HbA1c) goals, can lead to improved macrovascular and mortality outcomes.[26,29,101–103] In fact, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that intensive glucose control compared to standard care led to higher rates of cardiovascular deaths and all-cause deaths, in addition to a higher rate of hypoglycemia and weight gain.[26] The proportion of patients using insulin was higher in the intensive care group compared to the control group in the ACCORD trial. Observational studies have found that insulin use among type 2 diabetes patients may be associated with a higher risk of death compared to other agents.[107–109,114] In a recent large cohort study, the authors found that insulin use had a 44% higher rate of all-cause death compared to sulfonylurea use among patients who also take metformin.[107]

The factors which account for this observed increased risk of death associated with insulin use (or intensive glucose control) are still being investigated. Many previous studies showed that there is an increased risk of weight gain and hypoglycemia among insulin users, both of which are associated with cardiovascular outcomes and death.[58,117,118] Weight gain and

hypoglycemia are predictors of death, but it is unclear whether the association is causal or whether they are markers of other unmeasured conditions which lead to death.[140,141]

Understanding the mechanisms which explain the increased risk of death associated with insulin use will be critical to optimizing treatment guidelines and improving clinical outcomes for diabetes patients. The objective of this study was to use causal mediation analysis methods to evaluate whether two potentially important mediators – weight gain and hypoglycemia – could explain some proportion of the association between insulin use and death. The study results could help provide further hypotheses on which key clinical pathways may play a large role in the increased risk of mortality associated with insulin.

Methods

Study design and data sources

We conducted a retrospective cohort study using data from the Veterans Health Administration (VHA) patient population. Sources of data include: VHA dispensed medication information, including fill date, days supply, and number of pills; demographic data; diagnostic and procedure information from inpatient and outpatient encounters coded as *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*[38]; and laboratory test results and vital signs (blood pressure, height and weight measurements) from standard clinical sources. For VHA cohort patients who are also enrolled in Medicare or Medicaid, data on additional encounters, Part D prescription fill records, and self-reported demographics (race/ethnicity) were obtained from the Centers for Medicare and Medicaid Services through the VHA's interagency information exchange agreement.[137] Dates of death were obtained from the

National Death Index (NDI) data prior to 2011, and VHA vital status files were used as a supplement to identify subsequent dates of death from 2011 to 2012. Further details of the data sources and datasets can be found in **Appendix B**. The institutional review boards of VHA Tennessee Valley Healthcare System and Vanderbilt University approved this study.

Study population

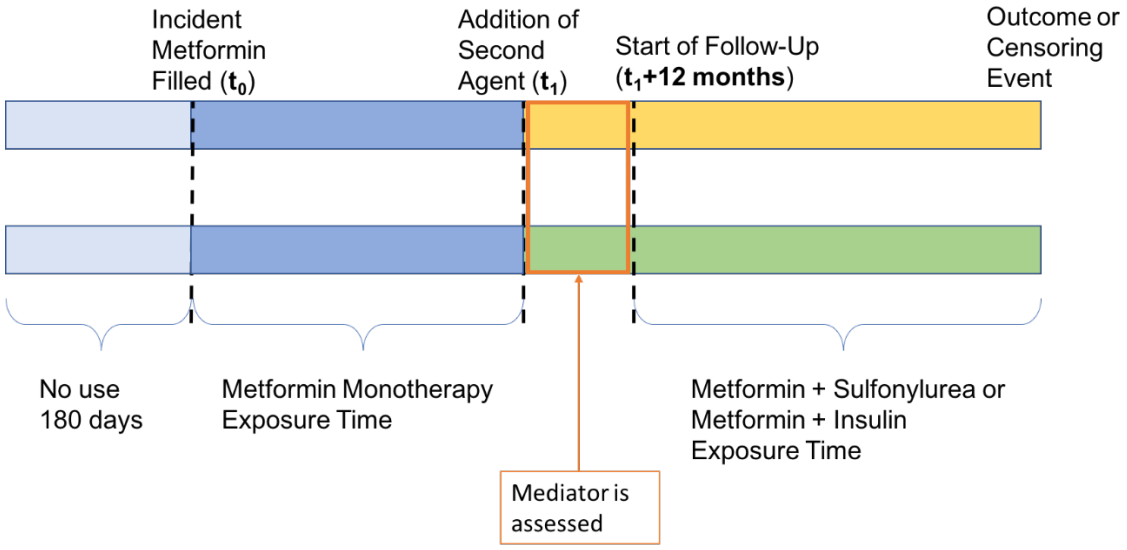
The study population included veterans aged 18 years or older who received regular care at VHA. Regular care was defined as having at least one encounter or prescription fill every 360 days for the last 2 years. New users of metformin between 2001 and 2008 who had not filled any antihyperglycemic drug in the prior 180 days were identified. Metformin monotherapy users became eligible for the intensification cohort if there was a prescription for sulfonylurea or insulin while continuing their metformin therapy; defined as having metformin on hand during the 180 days prior to intensification. Following intensification, we required patients to adhere to their new regimen for at least 12 months, because mediators were measured during the initial 12 months of intensified therapy and follow-up for the study outcome began after this 12-month lag period. Finally, patients needed at least one observed baseline body mass index (BMI) measurement (0-9 months prior to intensification) and at least one observed follow-up BMI measurement (3-12 months after intensification). Hospice and dialysis patients were excluded (**Appendix C**).

Exposures

The two main exposure groups were metformin monotherapy users who added insulin (long-acting, premixed, or short/fast-acting insulin), and those who added a sulfonylurea

(glyburide, glipizide, or glimepiride) to their regimen. Follow-up of cohort patients began 12 months after intensification with these agents, and continued until the study outcome, regimen change including nonpersistence on metformin (180 days without metformin) or initiation of a third antihyperglycemic drug, loss to follow-up (no longer in contact with VHA), or study end (September 30, 2012) (**Figure 4.1**).

Figure 4.1. Diagram showing the start of follow-up time (t_1+12 months) for metformin users adding sulfonylurea or insulin



Mediators

The two mediators of interest in this study were weight gain and hypoglycemia. The mediators were measured during the initial 12 months of intensified therapy. Since the mediator must be measured prior to the outcome in causal mediation studies, follow-up of study patients began after this 12-month lag, and only patients who survived during this period were included in the mediation analysis.

The weight change variable was defined as the absolute change in BMI during the first 12 months of intensification. This was calculated by subtracting the observed baseline BMI (0-9 months prior to t_1) from the observed 12-month follow-up BMI (3-12 months after t_1), which is why observed BMI measurements were required for all study patients.

Hypoglycemia events were identified using the same definition used in previous aims (**Table 2.1**). However, we did not include emergency department events due to the low positive predictive value of the administrative algorithm identified in Study 1. Hypoglycemia as a mediator was defined as the occurrence of one or more hypoglycemic events anytime during the first 12 months after intensification.

Outcome: All-cause death

The primary outcome was all-cause death, which was identified using both NDI data and the Vital Status file for deaths occurring up to 2011, and the Vital Status file for deaths between 2011 and 2012. The Vital Status file determines dates of death from various sources including Medicare, VHA, Social Security, and VHA compensation and pension benefits. When the date of death in the VHA vital status file conflicted with the NDI date of death (<3%), the latter was used (the sensitivity of the VHA vital status file is 98.3% and specificity is 99.8% relative to NDI).[17]

Covariates

Baseline covariate information was collected from 720 days prior to intensification. Covariates included age, sex, race (white, black, other), year, indicators of healthcare use (hospitalized during past year, nursing home use, number of outpatient visits, Medicare or

Medicaid utilization), physiologic variables (blood pressure, BMI, HbA1c level, LDL level, proteinuria, serum creatinine, and calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula)[142], duration of metformin monotherapy (proxy for diabetes duration), selected medications, smoking status, and selected comorbidities (**Appendix D**).

Multiple imputation was conducted for missing covariates using an iterative Markov chain Monte Carlo (MCMC) method based on multivariate normal regression. Thirty imputation datasets were created, and propensity score models were built separately in each of the imputed datasets to obtain 30 propensity scores for each study patient. The mean of the 30 propensity scores was calculated for each patient and was used for the final analysis.

Data cleaning and quality control

For blood glucose values obtained in the outpatient setting, we excluded non-numeric values (such as "high" or "low") and converted non-absolute values to absolute values so that a blood glucose value >400 would be coded as 400, and a blood glucose value <70 would be coded as 70. If a patient had hypoglycemia based on the outpatient blood glucose which led to a hospitalization within 48 hours, the event was counted as a single event attributed to the hospitalization. Any implausible values for HbA1c (<3% and >30%), height (<48 inches and >90 inches), and weight (<50 pounds and >700 pounds) were excluded and considered missing.

Statistical analyses

The difference method was used as the primary mediation analysis method to evaluate whether the insulin use and death association was mediated by change in BMI or hypoglycemia. This method compares the differences in coefficients for the outcome models with and without

the mediator of interest.[131] We also estimated the proportion of the association that was mediated through weight gain and hypoglycemia.

Separate mediation analyses were conducted for the evaluation of each mediator. For each analysis, the associations between the exposure and mediator, and the mediator and outcome were explored. Cox proportional hazards models applying propensity score matching weights were built, under the assumption that the primary outcome of death was rare in the study population.[131,139] The propensity score modeled the probability of receiving insulin treatment in the study population (**Appendix F**). We applied the propensity score weighting without additionally adjusting for baseline covariates in the final models. The first model compared the risk of death among insulin intensifiers vs. sulfonylurea intensifiers, without the mediator variable (Model 1). In the second model, we included the mediator (either BMI or hypoglycemia within the first 12 months of intensification) in the model (Model 2). The indirect effect on the log-hazard scale was estimated by taking the difference in beta coefficients for the effect of insulin use on the death outcome in Model 1 (without the mediator) and Model 2 (with the mediator). The proportion mediated was then estimated by dividing the indirect effect by the total effect (beta coefficient from Model 1).[143] Bootstrapping (1000 samples with replacement) was used to create 95% confidence intervals (CI) for the indirect effect and proportion mediated.[144] For the bootstrapping procedure, 5 imputations were performed for missing covariates to reduce the computational burden. The indirect effect and proportion mediated and corresponding 95% CI were also estimated on the hazard ratio (HR) scale to check the robustness of the results. On the HR scale, the indirect effect was estimated by dividing the hazard ratio of insulin upon death in Model 1 (HR_{total}) by the hazard ratio in Model 2 (HR_{direct}),

and the proportion mediated was estimated using a transformation formula on the ratio scale, which is shown below.[131,143]

$$Proportion\ mediated\ = \frac{HR_{direct}\ (HR_{indirect} - 1)}{HR_{total} - 1}$$

Subgroup and sensitivity analyses

Sensitivity analyses were conducted to check the robustness of the main findings. We used an alternative lag period where the mediator was measured. The main analysis used a 12-month lag period, but in the sensitivity analysis we used a 6-month lag period which increased the size of the cohort. Fewer patients were censored due to death or other causes since the lag period is shorter. However, since there is a shorter period of time during which the mediator is assessed, it may not sufficiently capture the mediator and its impact on the outcome.

Analyses were performed using STATA version 11 (main analyses), and R (cohort construction and bootstrapping).

Results

We identified 187,267 patients who were new users of metformin. Metformin was not the first antidiabetic medication in 19.5% of those patients, and 37.3% never intensified treatment. After applying the inclusion and exclusion criteria, there were 28,892 patients who intensified metformin monotherapy with a sulfonylurea or insulin and remained on the intensified regimen for 12 months with observed BMI measurements at baseline and follow-up. Of these patients, 27,239 patients (94.3%) intensified metformin therapy with a sulfonylurea, and 1653 patients (5.7%) added insulin (**Figure 4.2**).

Study patients were 96% male and 83% white, and the median age was 61 years (**Table 4.1**). The median time on metformin monotherapy prior to intensification was 23 months. The median change in BMI from baseline to 12 months after intensification was 0.26; 0.26 (interquartile range [IQR] -0.59, 1.05) among metformin + sulfonylurea users and 0.36 (IQR -0.79, 1.59) among metformin + insulin users (p=0.010) (**Figure 4.3**). Hypoglycemia occurred in 538 (1.9%) of the 28,892 patients; 491 (1.8%) among metformin + sulfonylurea users and 47 (2.8%) among metformin + insulin users (p=0.003) (**Table 4.2**).

Figure 4.2. Flowchart of eligible patients

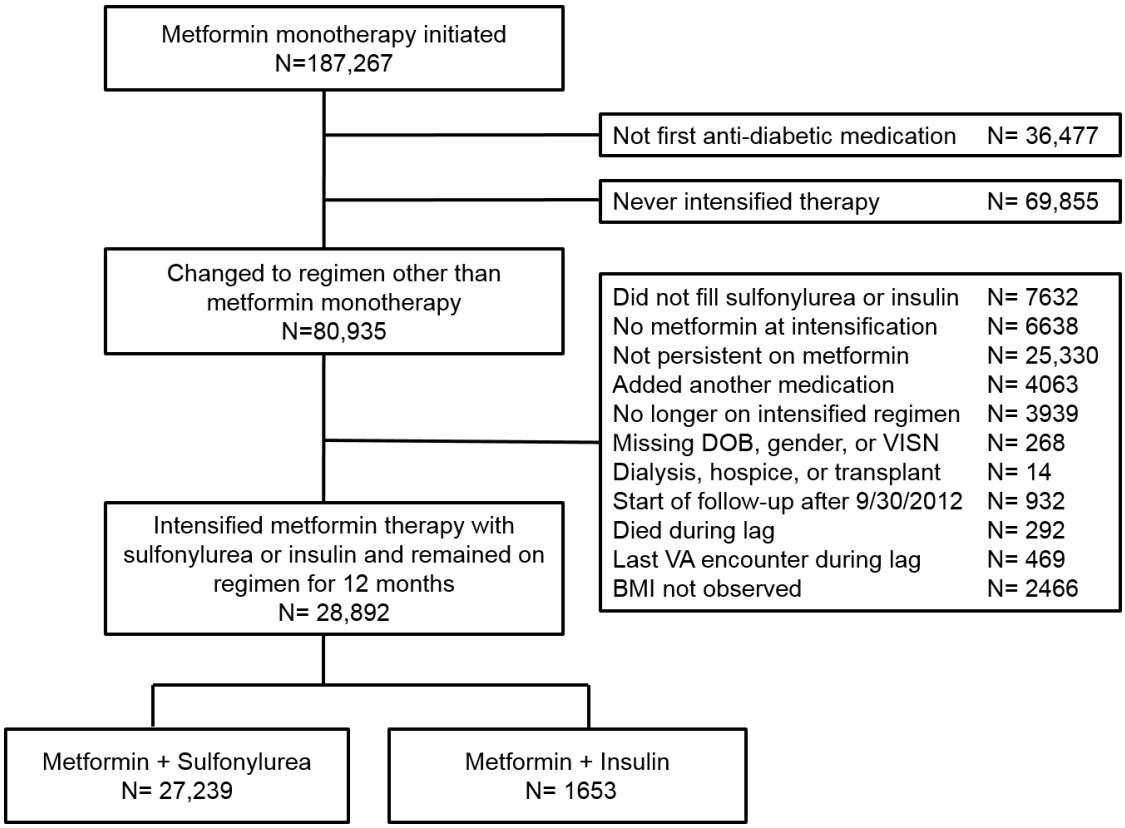


Table 4.1. Characteristics of study patients by intensification regimen

Characteristic	*Full Cohort N=28,892*		
	Metformin + Insulin N=1653	*Metformin + Sulfonylurea N=27,239*	*Std. diff†*
Age, median (IQR)*	59.1	61.8	-0.28
Female (%)	6.4	4.0	0.11
Race, (%)†			
White	66.7	73.9	0.16
Black	19.5	12.1	0.20
Hispanic/ Other	4.1	4.4	-0.02
Available %	90.3	90.4	-0.004
Time (months) to treatment intensification, median (IQR)‡†	26	27	-0.03
HbA1c, %	9.2	8.0	0.56
Available %	91.0	93.1	-0.08
Low Density Lipoprotein mg/dL, median (IQR)	92	91	0.008
Available %	80.7	86.0	-0.17
Glomerular Filtration Rate (ml/min), median (IQR)	92.9	89.0	0.16
Creatinine mg/dL, median (IQR)	1.00	1.01	-0.06
Proteinuria, (%)			
Negative	51.2	52.1	-0.02
Trace through 4+	19.4	17.8	0.04
Available %	70.6	69.9	0.02
Systolic blood pressure mm/Hg, median (IQR)	134	134	-0.01
Diastolic blood pressure mm/Hg, median (IQR)	78	77	0.06
Available %	100	99.9	-0.04
Body mass index (kg/m^2), median (IQR)†	33.9	33.7	0.03
Baseline Co-morbidities (%)			
Malignancy	5.2	4.9	0.01
Liver/ respiratory failure†	1.9	0.9	0.09
HIV†	0.5	0.3	0.03
Congestive heart failure	7.1	3.7	0.15
Cardiovascular disease	26.6	21.5	0.12
Serious mental illness	26.6	19.6	0.17
Smoking	19.2	13.9	0.14
Obstructive Pulmonary Disease/ Asthma	18.2	12.1	0.17
Cardiac valve disease	1.5	1.1	0.03
Arrhythmia	8.3	5.9	0.09
Parkinson's	0.6	0.4	0.03
Osteoporosis	2.7	1.7	0.07
Falls /fractures	1.6	0.8	0.08
Oxygen use	1.0	0.1	0.11
Use of Medications (%)			
ACE Inhibitors or ARBs	69.6	72.6	-0.07
Anti-hypertensive medications†	23.6	22.5	0.03
Statin and other lipid lowering agents†	75.4	82.2	-0.17
Anti-arrhythmics, digoxin and inotropes	2.4	1.7	0.05

Anticoagulants, platelet inhibitors	5.9	5.2	0.03
Nitrates	12.6	10.9	0.05
Aspirin	28.8	22.6	0.14
Loop Diuretics	16.6	10.4	0.18
Antipsychotics	14.1	8.9	0.16
Alpha-blockers	14.5	14.4	0.003
Indicators of health care utilization			
Hospitalized in last year (%)†	28.9	9.9	0.49
Hospitalized in prior 90 days (%)†	19.6	3.0	0.54
Nursing home encounter (%)	0	0.02	-0.02
Outpatient visits, median (IQR)	9	8	0.16
Medicare utilization	23.4	19.2	0.10
Medicaid utilization	13.3	6.0	0.25
No. of outpatient medications, median (IQR)	16	14	0.29

* Abbreviations: median and interquartile range (IQR), standardized % bias (% bias), angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB)

† Standardized mean differences are reported. The standardized mean difference is the difference of the sample means in the treated and non-treated (full or matched) sub-samples as a percentage of the square root of the average of the sample variances in the treated and non-treated groups (formulae from Rosenbaum and Rubin, 1985).

‡ Time to treatment intensification represents the time on metformin monotherapy, and is an approximation of the duration of diabetes since patients were free of all hypoglycemic medications for 180 days prior to starting metformin.

Figure 4.3. Boxplot showing differences in 12-month change in BMI by treatment regimen

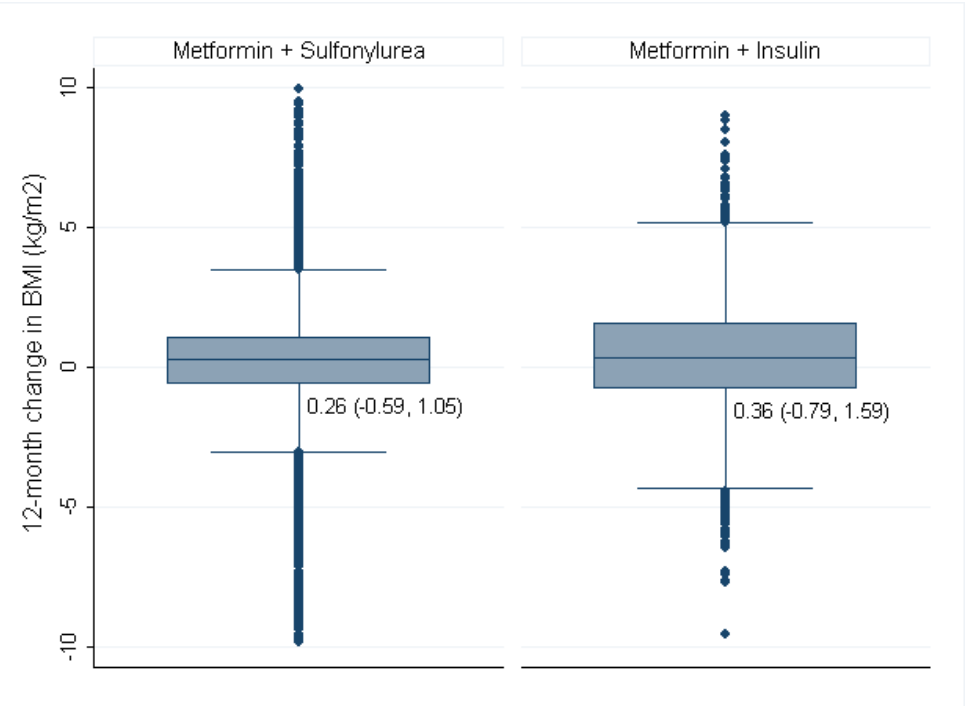


Table 4.2. Risk of hypoglycemia during the first 12 months of intensification by treatment regimen

	Metformin + Sulfonylurea N=27,239	*Metformin + Insulin N=1653*
Hypoglycemia		
Events, N (%)	491 (1.8%)	47 (2.8%)
Unadjusted odds ratio	Ref	1.59 (1.18, 2.16)

Model without mediator

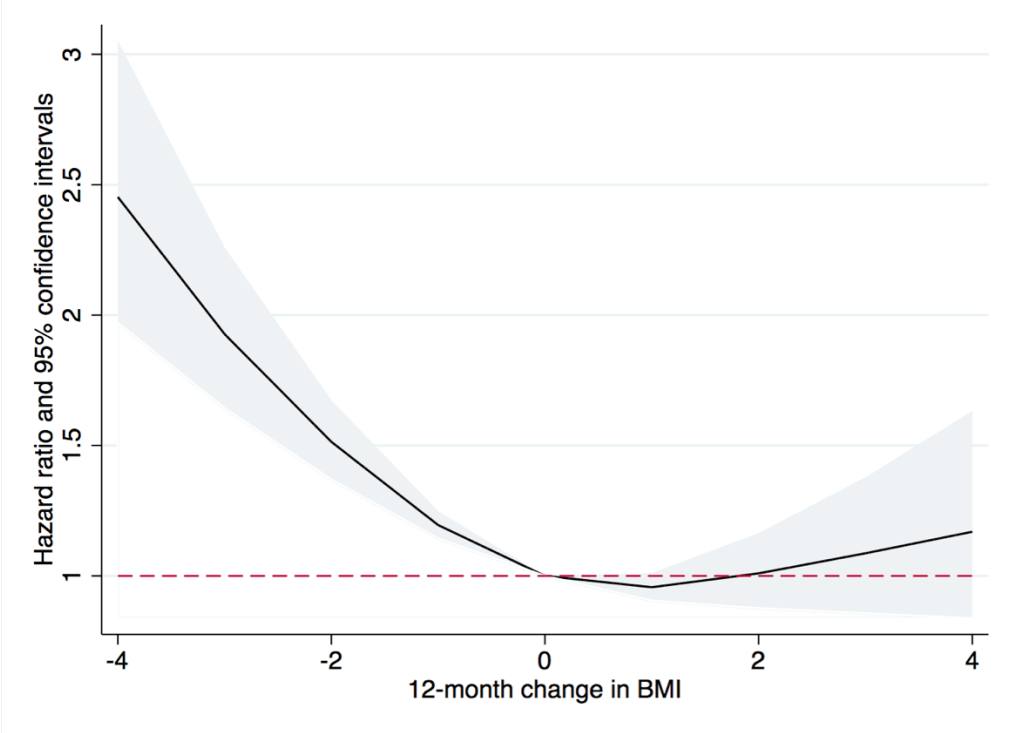
The rate of all-cause death per 1000 person-years was 15.3 (95% CI 11.7, 20.1) among metformin + insulin users, and 9.9 (95% CI 9.1, 10.7) among metformin + sulfonylurea users (**Table 4.3**). The unweighted, unadjusted Cox proportional hazards model showed that the hazard for death was significantly higher among metformin + insulin users compared to metformin + sulfonylurea users (unadjusted hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.17, 2.05). The propensity score modeled the probability of intensifying with insulin and the distributions appeared to differ among metformin + insulin and metformin + sulfonylurea users (**Appendix F**), suggesting that baseline covariates were imbalanced between the comparison groups. When propensity score weighting was added to the model to balance covariates between the two groups, the treatment effect became attenuated was no longer statistically significant (weighted HR 1.14, 95% CI 0.83, 1.57) (**Table 4.3**).

Model with change in BMI as the mediator

The median 12-month change in BMI was higher in the metformin + insulin users, but the difference was small (0.36 vs. 0.26, p=0.010). Change in BMI and death appeared to have a nonlinear association (**Figure 4.4**), where greater weight loss was significantly associated with an increased risk of death compared to no change. When the change in BMI variable was

included in the propensity score weighted Cox proportional hazards model, the hazard ratio remained similar to the model without the mediator (HR 1.12, 95% CI 0.81, 1.54) (**Table 4.3**). On the log hazard scale, the estimated proportion of insulin effect on death mediated through change in BMI was 0.15 (bootstrapped 95% CI -0.56, 2.58). Similarly, on the hazard ratio scale, the estimated proportion mediated was 0.16 (bootstrapped 95% CI -0.53, 2.55).

Figure 4.4. Hazard ratios and 95% confidence intervals for death when change in BMI was modeled as a continuous variable using restricted cubic splines, with zero as the reference



Model with hypoglycemia as the mediator

Hypoglycemia occurred more frequently in the metformin + insulin users (odds ratio 1.59, 95% CI 1.18, 2.16) (**Table 4.2**). When the hypoglycemia variable was included in the propensity score weighted Cox proportional hazards model, the hazard ratio for death comparing metformin + insulin users to metformin + sulfonylurea users also remained similar to the model

without the mediator (HR 1.14, 95% CI 0.83, 1.57) (**Table 4.3**). On the log hazard scale, the estimated proportion of insulin effect on death mediated through hypoglycemia was 0.01, and it was not statistically different significant (bootstrapped 95% CI -0.69, 0.74). Similarly, on the hazard ratio scale, the estimated proportion mediated was 0.01 (bootstrapped 95% CI -0.53, 2.55). In the model adjusting for hypoglycemia, the hazard for death was 3.521 times higher among patients who had hypoglycemia compared to those who did not (95% CI 1.912, 6.484).

Table 4.3. Risk of death among patients who intensified with insulin versus sulfonylurea, and the indirect effect and proportion mediated through change in BMI and hypoglycemia

	Metformin + Sulfonylurea N=27,239	*Metformin + Insulin N=1653*
All-cause death (without mediators)		
Events/ person years	590/59,553	53/3459
Crude rate/1000 person-years (95% CI)	9.9 (9.1, 10.7)	15.3 (11.7, 20.1)
Crude hazard ratio (95% CI)	Ref	1.55 (1.17, 2.05)
PS weighted hazard ratio (95% CI)	Ref	1.14 (0.83, 1.59)
Beta coefficient		0.1331
All-cause death (with change in BMI in model)		
PS weighted hazard ratio (95% CI)	Ref	1.12 (0.81, 1.54)
Beta coefficient		0.1111
Indirect effect (95% CI) – log hazard		0.02 (-0.01, 0.06)
Proportion mediated (95% CI) – log hazard		0.15 (-0.56, 2.58)
Indirect effect (95% CI) – hazard ratio		1.02 (0.99, 1.06)
Proportion mediated (95% CI) – hazard ratio		0.16 (-0.53, 2.55)
All-cause death (with hypoglycemia in model)		
PS weighted hazard ratio (95% CI)	Ref	1.14 (0.83, 1.57)
Beta coefficient		0.1315
Indirect effect (95% CI) – log hazard		0.00 (-0.04, 0.03)
Proportion mediated (95% CI) – log hazard		0.01 (-0.69, 0.74)
Indirect effect (95% CI) – hazard ratio		1.00 (0.96, 1.03)
Proportion mediated (95% CI) – hazard ratio		0.01 (-0.72, 0.75)

Sensitivity analyses

When a 6-month lag was used to assess the mediators, we had a larger cohort of 30,214 patients, including 27,997 metformin + insulin users and 2217 metformin + sulfonylurea users. The median change in BMI during the 6-month period was 0.14 (IQR -0.91, 1.27) and 0.24 (-0.52, 0.97) for metformin + insulin and metformin + sulfonylurea users, respectively. Hypoglycemia still occurred more frequently in the insulin users (unadjusted odds ratio 1.71, 95% CI 1.28, 2.27). The propensity score weighted hazard ratio for the effect of insulin intensification on death was higher in magnitude and statistically significant in this cohort (HR 1.62, 95% CI 1.25, 2.11). However, the mediation analysis results were consistent with the primary analysis. On the log hazard scale, the proportion of the total effect of insulin on death mediated through change in BMI was estimated to be 0.09 (bootstrapped 95% CI -0.02, 0.29), and the proportion mediated through hypoglycemia was estimated to be -0.01 (bootstrapped 95% CI -0.09, 0.03), and both were not statistically different from zero. Results were similar when the estimates were obtained on the hazard ratio scale (**Table 4.4**).

Table 4.4. Risk of death among patients who intensified with insulin versus sulfonylurea, and the indirect effect and proportion mediated through change in BMI and hypoglycemia (6-month observation period)

	Metformin + Sulfonylurea N=27,997	*Metformin + Insulin N=2217*
All-cause death (without mediators)		
Events/ person years	551 / 52,289	93 / 3774
Crude rate/1000 person-years (95% CI)	10.5 (9.7, 11.5)	24.6 (20.1, 30.2)
Crude hazard ratio (95% CI)	Ref	2.33 (1.87, 2.90)
PS weighted hazard ratio (95% CI)	Ref	1.62 (1.25, 2.11)
Beta coefficient		0.4828
All-cause death (with change in BMI in model)		
PS weighted hazard ratio (95% CI)	Ref	1.52 (1.16, 1.97)
Beta coefficient		0.4164
Indirect effect (95% CI) – log hazard		0.04 (-0.01, 0.08)
Proportion mediated (95% CI) – log hazard		0.09 (-0.02, 0.29)
Indirect effect (95% CI) – hazard ratio		1.05 (0.99, 1.08)
Proportion mediated (95% CI) – hazard ratio		0.11 (-0.03, 0.32)
All-cause death (with hypoglycemia in model)		
PS weighted hazard ratio (95% CI)	Ref	1.62 (1.24, 2.10)
Beta coefficient		0.4801
Indirect effect (95% CI) – log hazard		0.00 (-0.03, 0.01)
Proportion mediated (95% CI) – log hazard		-0.01 (-0.09, 0.03)
Indirect effect (95% CI) – hazard ratio		1.00 (0.97, 1.01)
Proportion mediated (95% CI) – hazard ratio		-0.01 (-0.11, 0.04)

Discussion

We found no evidence that change in BMI or hypoglycemia were significant mediators in the association between insulin use and all-cause death. The proportion of the effect of insulin on death mediated through change in BMI was estimated to be 2.4%, and the proportion of effect

mediated through hypoglycemia was 0.1%, which suggests that neither change in BMI nor hypoglycemia were clinically important mediators in the association.

After the ACCORD trial, post-hoc analyses and other epidemiologic studies have sought to identify the mechanisms for the increased risk of death that was observed with intensive glucose control.[50,51,145] These post-hoc analyses have explored various factors that could have contributed to the findings, including HbA1c levels, age-related factors, and episodes of severe hypoglycemia, but none involved conducting a formal mediation analysis. The retrospective cohort study conducted by Roumie et al. suggested that insulin use could have been one of the contributing factors; they observed a higher risk of death among metformin users adding insulin compared to sulfonylurea.[107]

The risk of all-cause death among insulin users was not significantly higher compared to sulfonylurea users in this study. The point estimate was also attenuated compared to what we observed in our previous study, likely due to differences in the study population that was assembled based on additional cohort entry requirements. In order to conduct mediation analyses and have a predefined baseline period to assess the mediators prior to follow-up for the outcome, patients were required to have survived and remain in contact with the VHA for a longer period of time and were also required to have observed BMI measurements at baseline and during the first 12 months. This greatly reduced our sample size for the primary analysis which required a 12-month lag period, and selected a different population compared to the original cohort in our previous study.

For the sensitivity analysis with a 6-month baseline period, the effect of insulin upon death was higher and statistically significant, but the proportion mediated by the mediators remained similar to the primary analysis. This further supports our findings that change in BMI

and hypoglycemia do not appear to be important mediators in the association between insulin use and death. We did find that the estimate of effect of insulin upon death was sensitive to the definition of this "gap" period during which the mediator was assessed and patients were required to survive during that time period to be included in the study follow-up. The effect size was larger and statistically significant when we used a 6-month gap, but the effect was attenuated and became nonsignificant when we applied the 12-month gap, suggesting that a larger proportion of insulin patients die during the initial 6-12 months following intensification, and for those surviving after 12 months, the differences in risk of death may become attenuated. This suggests that the effect of insulin may be more pronounced early on, or it could also indicate some residual confounding by indication where those more likely to die were prescribed insulin, although we accounted for many covariates in our analyses to balance clinical characteristics that may indicate such conditions.

Our study adds important information to the literature, indicating that the mechanism in which insulin might cause death does not appear to be associated with weight gain or hypoglycemia. While we hypothesized that weight gain would explain a large proportion of the effect, the results of the study suggest that other pathways, potentially through cancer or renal impairment, may need to be further investigated. The results could also indicate that uncontrolled residual confounding may have led to the results of our previous study, rather than a true causal relationship. However, a confounding sensitivity analysis had shown that the unknown confounder would have to have a very strong effect in order to result in the effect estimate that we observed.[107] Frailty was potentially an unmeasured confounder in that study, but frailty was estimated to have a minimal effect on confounding after adjustment for the covariates in our data.[146]

This study had some important methodological strengths. Pathway analyses have not been used to assess this clinical question before. We were able to use administrative and clinical data from a large national cohort to estimate the proportion of total effect of insulin upon death that was mediated through two variables. We used appropriate methods to capture the mediators prior to follow-up of patients for the outcome and were able to conduct a time-to-event analysis using Cox proportional hazards models for the mediation analysis, since our outcome was rare (<10%). Bootstrapping was performed to determine the 95% confidence intervals for the proportion mediated, while using propensity score weighting to balance covariates, which was computationally intensive and required significant computing resources. We also modeled one of the mediators, change in BMI, as a restricted cubic spline, which allowed for a nonlinear effect on the outcome in the models. Change in BMI did have a nonlinear effect on the outcome of death, where greater weight loss or weight gain was associated with a higher risk, so it was important to model it using the methods that we used. We had expected that change in BMI would mediate a larger proportion of the effect, but did not find that, potentially due to the observed mediator outcome association in our specific population, which showed that weight loss was highly associated with death whereas weight gain was not. Those who started insulin likely gained more weight.

In this study, we simplified the analysis so that weight gain and hypoglycemia could be defined at a specific time point, which was 12 months after intensification of metformin therapy. One limitation to note in using this simplified approach is that patients who had the primary outcome (death) during the first year were not included in the analysis. Patients who have a hypoglycemic event right after initiating sulfonylurea or insulin, then subsequently died within the first year were not included in the analysis, even though they may represent true clinical

cases where death was mediated through hypoglycemia. Another limitation with the evaluation of hypoglycemia as a mediator is that some events could have been missed. Only severe events that led to a hospitalization, or outpatient events captured through blood glucose measurements during an encounter were identified. BMI was also not measured in regular intervals for all patients, which led to a decreased study sample size since we had to limit the study population to those who had an observed BMI at the time points of interest. Exposure (or treatment) misclassification is a possibility in this study. Pharmacy prescription fill records were used to estimate actual drug use, which have been shown to approximate actual use.[147] We used propensity score matching weights to balance many important covariates between the two treatment groups, however, unmeasured residual confounding may have been present. Similar to the previous aims, the study population was mostly white men, which should be considered in terms of generalizability of the study findings.

In conclusion, we found no evidence that change in BMI or hypoglycemia were important mediators in the association between insulin use and death. Our results suggest that other mediators and pathways may need to be investigated.

CHAPTER V

CONCLUSION

Maintaining adequate glycemic control through medication therapy is an essential part of type 2 diabetes management. Most patients start therapy with metformin and many will add second-line mediations for better glucose control. Newer agents with various mechanisms of action are becoming more widely available, but sulfonylureas and insulin are still commonly used and are preferred by many providers and institutions. While both drugs are highly efficacious in lowering blood glucose and some can be more affordable compared to the newer treatments, there are important concerns over the side effects, particularly weight gain and hypoglycemia.[1] In recent studies, it has also been suggested that insulin use could be associated with a higher risk of death.[107,109] In this work, I aimed to further examine the clinical outcomes of hypoglycemia, weight gain, and death associated with the second-line treatments, sulfonylureas and insulin, using data from a large retrospective national VA cohort.

Hypoglycemia is a serious side effect of sulfonylureas and insulin.[1] Frequent hypoglycemic episodes can lead to poor quality of life, and severe events can lead to long-term health consequences and even death.[3,31] Hypoglycemia should be considered an important clinical outcome measure of antidiabetic treatment, and research should focus on improving the detection and management of hypoglycemia. Epidemiologic studies investigating this outcome have identified events among their study population using various definitions. Although mild events may be missed, investigators aim to capture severe events that required healthcare intervention, such as emergency department care or hospitalization. In Study 1, we validated a computerized composite case definition that we developed for the evaluation of hypoglycemia in

the VA diabetes cohort population, using medical record reviews as the reference standard. Our review of 321 events identified within the Tennessee Valley Healthcare System through the composite definition revealed that hospitalizations identified through ICD-9-CM discharge diagnosis codes were moderately accurate (positive predictive value [PPV] 80%), emergency department visits from CPT procedure codes and ICD-9-CM discharge diagnosis codes were not accurate (PPV 48%) and outpatient events requiring a glucose measurement <60 mg/dL were highly accurate (PPV 96%) in identifying true cases with documented blood glucose measurements. Due to the low performance of the emergency department definition, which was adopted from a previously validated algorithm in a different study population (PPV reported as 87%)[41], we decided to exclude events identified through that definition in our subsequent studies. Specifically, there was one nonspecific code 250.8, which identified many other diabetes-related complications. This study informs other investigators that the performance of the emergency department event algorithm may vary across different study populations and settings, and that they should consider validating it in their study population prior to adoption.

In Study 2, we evaluated a behavioral risk factor, medication adherence, and its potential impact on hypoglycemia after patients on metformin add a sulfonylurea. We hypothesized that when providers intensify treatment with a sulfonylurea for patients who have low metformin adherence, the patient may decide to initiate both drugs, leading to greater glycemic variability and risk of hypoglycemia. The hypothesis was tested in a retrospective cohort study using data from a large VA population with diabetes. Using pharmacy refill data to estimate adherence, we found that among patients on metformin who intensified treatment with a sulfonylurea, those with low metformin adherence (<80% proportion days covered) prior to intensification did not have an increased risk of hypoglycemia during the first year compared to those who were highly

adherent (≥80%) (adjusted hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.83, 1.09). Examining the risk of hypoglycemia across different levels of adherence also did not give us any clear indication of a tipping point or nonlinear association. A descriptive evaluation of the change in HbA1c during the initial 12 months of intensification among those with a baseline measurement, showed that patients with low adherence were more likely to have a greater than 1% decline in HbA1c compared to those with high adherence. Although the association has not been tested analytically, this finding may partially support our hypothesis, that low adherence patients may have greater glycemic variability following intensification, possibly due to initiating two drugs after a period of nonadherence. However, the risk of hypoglycemia still did not differ by baseline metformin adherence. This study evaluated an important behavioral risk factor which is often under-evaluated in the clinical setting. While the study did not find that low metformin adherence led to a greater risk of hypoglycemia following addition of a sulfonylurea, the effects of adherence, HbA1c, and the intensification drug type and dosage may have complex associations which needs to be further evaluated in future studies. Initiating a higher sulfonylurea dose, due to many potential reasons including high HbA1c or low adherence, could lead to a higher risk of hypoglycemia. However, having a higher baseline HbA1c, or continuing to be nonadherent on the new two-drug regimen (as opposed to initiating both drugs) can also be protective factors for the adverse outcome. All of these factors may need to be considered simultaneously when clinicians intensify treatment with a sulfonylurea, so that the risk of hypoglycemia can be minimized.

While Study 2 focused on sulfonylureas, Study 3 focused on the effects of insulin treatment in comparison to sulfonylureas when added to metformin. After the ACCORD trial investigators found that intensive glucose control often involving insulin led to higher risk of

cardiovascular deaths and all-cause deaths, hypoglycemia was suggested as a potential mediator, but formal mediation analyses have not been conducted.[26,104] In a previous cohort study, our group found that insulin compared to sulfonylureas was associated with a higher risk of all-cause death when added to metformin, warranting further investigation of the potential mechanisms.[107] Study 3 compared the risk of all-cause death among patients on metformin who intensified treatment with a sulfonylurea or insulin, and evaluated two potential mediators in the causal pathway: change in body mass index (BMI) and hypoglycemia. This study was also a retrospective cohort study utilizing VA diabetes cohort data, and it used advanced methods to evaluate mediation in a survival context while controlling for confounding. Contrary to our hypotheses, our analyses showed that change in BMI and hypoglycemia did not mediate a significant proportion of the treatment effect on death. While both were shown to be risk factors for death, they did not appear to mediate the pathway from insulin use to death. Our findings still have important clinical and research implications, suggesting that other potential mediators may need to be evaluated, such as cancer or other heart disease to better understand the effects of insulin on clinical outcomes. Future studies could also explore the use of other mediation methods such as additive hazard models, or time varying exposure/mediator models. Another potential direction is to evaluate what other specific unmeasured factors could have contributed to confounding by indication in our previous findings.

In conclusion, this work was able to add valuable evidence to the current literature on the accuracy of identification of hypoglycemia events in epidemiologic studies, and the association of medication adherence and subsequent changes in HbA1c and risk of hypoglycemia among patients adding a sulfonylurea to their regimen. It also contributed an important evaluation of weight change and hypoglycemia as potential mediators in the effect of insulin on death,

addressing a research question that could help advance our clinical knowledge of insulin, in addition to advancing the mediation methods used in pharmacoepidemiologic studies. Finally, this works provides additional directions for future research on improving clinical outcomes for type 2 diabetes patients adding second-line agents such as sulfonylurea and insulin to their treatment regimens.

APPENDIX

Appendix A. Chart Abstraction Tool for Hypoglycemia

1. Medical Record Review Date	(mm/dd/yyyy)	___ / ___ / _____
Reviewer's initials		_____
Same Date of Birth	(0 no, 1 yes)	_____
If no, record below	(mm/dd/yyyy)	___ / ___ / _____
Sex	(1= male 2= female)	_____
Race	(1=AA 2=non-AA)	_____
Age	(years)	_____
DM	(0 no, 1 yes)	_____
Admission/ ED Visit Found ± 24 hrs	(0 no, 1 yes)	_____
Date of admission/encounter	(mm/dd/yyyy)	___ / ___ / _____
Do you have the correct chart?	(0 no, 1 yes)	_____
		(If no, stop here)

2. Exclusion Criteria

Was the patient seen outside TVHS?	(0 no, 1 yes)	_____
Was the patient <18 years old at time of admission?	(0 no, 1 yes)	_____
Was the patient on Dialysis at the time of Hospitalization?	(0 no, 1 yes)	_____

If "Yes" on any of the above exclusion criteria, then stop here.

3. Point of Contact

- ☐ Outpatient visit
- ☐ ED visit (discharged from ED)
- ☐ Hospitalization (admitted through ED or clinic visit)

  Number of hospitalization days (day of admission=1) _____
- ☐ Transfer from outside hospital

  Number of hospitalization days (day of admission=1) _____
- ☐ Other _____

4. Types of Symptoms

1) Typical symptoms

	(0=none, 1=lethargy, confusion, irrational, 2=LOC or hx of LOC, 3=coma)
MS changes	
	(0=no, 1=yes, 2=suspected, 9=unknown)
Seizure	
Sweaty	
Hunger	
Palpitations	
Blurred vision	
Restlessness	
Syncope	
Faintness or lightheadedness	

2) Atypical or questionable symptoms

	(0=no, 1=yes, 2=suspected, 9=unknown)
TIA	
CVA	
Myocardial infarction	
Injury to self or others	
Death	
Other, specify: _____	

5. Treatment Regimen (0=no, 1=yes, 2=suspected, 9=unknown)

Glucagon	
Oral carbohydrates, food, beverages	
D50	
D10 or D20	
D5 or other IV glucose excluding D10, D20, D50	
Other, specify: _____	

6. Symptom Improvement after Treatment _____

(0=no improvement, 1=improvement, 8=no treatment, 9=unknown)

7. History of Present Illness (0=no, 1=yes, 2=suspected, 9=unknown)

N/V, appetite loss, decreased oral intake	
Acute diarrheal illness	
Increase in physical activity in past week	
Intentional hypoglycemia (overdose)	
Unintentional hypoglycemia due to overdose	
Other, specify: _____	

8. Potential Contributory Conditions Noted on Chart or Admission Note

(0=no, 1=yes, 2=suspected, 9=unknown)

Serious mental illness: Dementia, mental retardation, major depression, major life event, schizophrenia, etc	
Alcohol abuse or intoxication, if noted in chart	
Liver disease, specify: _____	
Renal disease *(only record lab values from same encounter)* Creatinine: _____ GFR: _____	
Fever, acute infection, specify: _____	
Prescribed changes in insulin or hypoglycemic (≤4 weeks PTE), specify: _____	
Any patient-initiated changes in DM medication administration, if noted in chart: _____	

9. Glucose Measurements

Admission Glucose: _____ mg/dL

Method Used: _____

(1=glucometer accucheck, 2=lab, 3=unknown)

Performed before treatment: _____

(0=not done prior to the treatment, 1=performed prior to treatment, 2=no treatment, 3=unknown)

10. Medications on Admission (0=no, 1=yes, 9=unknown)

At the time of hypoglycemia event, was the patient taking any antidiabetic agents? _____

If yes, see Supplemental A.

At the time of hypoglycemia event, was the patient taking any aspirin/ antithrombotics? _____

If yes, see Supplemental B.

Smoking (cigarettes/cigars only; do not count electronic cigarettes) _____

(0=Never, 1=Current Smoker, 2=Former Smoker, 3=Smoked, uncertain if current, 4=Not a Current Smoker, uncertain if former, 9=Unknown)

11. Hypoglycemia Coding Validation

Did the patient have a hypoglycemia event only during hospitalization with no mentioning of hypoglycemia as cause of admission? (0 no, 1 yes) _____

Did the patient have some other complication of diabetes? (0 no, 1 yes) _____

Was the hypoglycemia event miscoded? (0 no, 1 yes) _____

**Did the patient have a non-DM hypoglycemia event? (0 no, 1 yes) _____

**Did the patient have other exclusions? (0 no, 1 yes) _____

12. Hypoglycemia Event Classification: _____

Did the patient have typical symptoms?	-	Yes	No	Yes	Yes
Did the patient have a confirmed blood glucose measurement of <60 mg/dL?	No	No	Yes	Yes	Yes
Was the patient hospitalized or seen in the emergency room due to the event?	-	-	-	No	Yes
*Classification of hypoglycemia event:	Not a true hypoglycemia event	Probable symptomatic hypoglycemia	Asymptomatic / atypical hypoglycemia	Documented symptomatic hypoglycemia	Severe hypoglycemia
Code as:	0	1	2	3	4

Supplemental A. Antidiabetic Agents

Antihyperglycemic drug	*Trade Name*	*Total daily dose*	
Metformin	Glucophage		mg
Glipizide	Glucotrol		mg
Glyburide	Micronase		mg
Glimepiride	Amaryl		mg
Chlorpropramide	Diabinese		mg
Rosiglitazone	Avandia		mg
Pioglitazone	Actos		mg
Troglitazone	Resulin		mg
Nateglinide	Starlix		mg
Repaglinide	Prandin		mg
Miglitol	Glyset		mg
Acarbose	Precose		mg
Exenatide	Byetta		mg
Liraglutide	Victoza		mg
Sitagliptin	Januvia		mg
Saxagliptin	Onglyza		mg
Linagliptin	Tradjenta		mg
Alogliptin	Nesina		mg
Canagliflozin	Invokana		mg
Dapagliflozin	Farxiga		mg
Rapid-acting Insulin	Lispro (Humalog) Aspart (Novolog) Glulisine (Apidra)		units
Short-acting Insulin	Humulin R Novolin R		units
Intermediate-acting Insulin	NPH		units
Long-acting Insulin	Glargine (Lantus) Detemir (Levemir)		units
Pre-mix Insulin	Humulin 70/30 Novolin 70/30 Novolog 70/30 Humulin 50/50 Humalog 75/25		units
Unknown			

Supplemental B. Aspirin and Antithrombotic Agents

Drug name	*Total daily dose*	
Aspirin		mg
Clopidogrel (Plavix)		mg
Warfarin (Coumadin)		mg
Enoxaparin (Lovenox)		mg
Fondaparinux (Arixtra)		mg
Heparin		units
Ticlopidine (Ticlid)		mg
Dipyridamole (Persanthine)		mg
Aspirin/dipyridamole (Aggranox)		mg
Prasugrel (Effient)		mg
Ticagrelor (Brilinta)		mg
Rivaroxaban (Xarelto)		mg
Apixaban (Eliquis)		mg
Edoxaban (Lixiana)		mg
Dabigatran (Pradaxa)		mg
Other anticoagulants, specify below: _____		

Appendix B. Description of VHA databases used for research

Database	*Description*
Decision Support Services National Data Extract (DSS NDE)	The DSS NDE contains dispensed prescription information in addition to laboratory test results from the VHA. SAS datasets are available for research purposes. The pharmacy dataset includes inpatient/outpatient prescription fills and prescriptions dispensed by a Consolidated Mail Outpatient Pharmacy, and the data is based on an electronic platform from each facility.
Medical SAS© Datasets	The medical datasets are administrative data for VHA healthcare, maintained by the VHA Office of Information. For our cohort we will access the Patient Treatment File for inpatient care and Outpatient File for outpatient encounters, and datasets which contain data on care provided in non-VA hospitals but were funded by VHA.
VHA-Medicare Data Merge - VA Information Resource Center (VIReC)	VIRec developed an infrastructure to support research linked to Medicare data. Data from Centers for Medicare & Medicaid Services (CMS) are linked through VHA's interagency exchange agreement. We obtained Medicare Part D files to supplement VHA prescription fill data for patients in the cohort.
Vital Signs	The Corporate Data Warehouse (CDW) contains vital signs data from 1999 through present, including data in the VHA electronic platform. We will use data on blood pressure, height and weight measurements.
Vital Status	Vital Status data includes VHA information, social security, compensation, and pension benefits and Medicare. The master file contains vital status for each SSN-date of birth-gender combination, and the date of last healthcare activity.
National Death Index (NDI)	The National Death Index contains death information and causes of death (ICD-10). VHA has an interagency agreement with National Center for Healthcare Statistics to track cause of death. A national file identifying death record information is compiled from state vital statistics. The NDI dataset for VHA is updated annually and provides the date and cause of death for patients in the cohort.

Appendix C. Identification of severe illness for exclusion criteria

Disease	*Definition*
Hospice care	CPT/HCPC: S9126
Renal failure/ dialysis/ severe CKD	ICD9-CM diagnosis codes: 585.6, V56*, V45.1* ICD9-CM procedure codes: 39.95, 54.98 Labs: baseline eGFR <30ml/ min
Transplant (kidney, heart, lung, liver, bone marrow, or pancreas)	ICD9-CM diagnosis codes: V42.0, V42.1, V42.6, V42.7, V42.81, V42.83 ICD9-CM procedure codes: 37.5, 41.0, 50.5, 52.8, 55.6, 33.5, 33.6 CPT/ HCPCS codes: 50320, 50360, 50365, 50370, 50380, 33935,33940, 33945, 32851, 32852, 32853, 323854, 47135, 47136, 38240, 38241, 48554, 48556

Appendix D. Definitions of comorbid conditions and medications, on the basis of codes and prescriptions in 730 days before treatment intensification

Covariate condition	*Inclusive conditions*	*Definition**
Malignancy	Cancer excluding non-melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173)
Liver/ respiratory failure	1. End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X
	2. Respiratory failure	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X
Congestive heart failure	CHF (excluding post procedure-CHF)	ICD 9- CM diagnosis codes: 428.X, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.X
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes:410.X, 412.X, 429.7X
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes:411.X, 413.X, 414.X ICD9-CM procedure codes: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19 CPT procedure codes: 33533-36, 33510-23, 33530, 92980-82,92984, 92995-6, 92974
	3. TIA	ICD 9- CM diagnosis codes: 435.X
	4. Stroke	ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X
	5. Peripheral artery disease revascularization or amputation	ICD 9- CM diagnosis codes:440.2X, 442.2, 443.1, 443.9, 445.0X ICD9-CM procedure codes:38.08-09, 38.18, 38.38, 38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.29, 39.5, 84.1X; 84.10-84.17 CPT procedure codes: 35226,35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 34800, 34802-5
	6. Carotid revascularization	ICD9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28 CPT procedure codes: 35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216 HCPCS procedure code: S2211
	7. Pentoxifylline & related drugs	Medications: Pentoxifylline, Cilostazol, Cyclandelate, Ethaverine HCL, Nicotinyl Alcohol Tartate, Papaverine, Tolazolin
Serious mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82 Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine
	2. Depression,	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0
	3. Schizophrenia,	ICD 9- CM diagnosis codes: 295.X
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89
	5. Post-traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1
Arrhythmia	1. Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X
	2. Arrhythmia and conduction disorder	ICD 9- CM diagnosis codes: 426.X, 427.X

Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 Medications: Varenicline tartrate, Nicotine Replacement therapy (gum, patch, lozenge)
COPD/ asthma		ICD 9- CM diagnoses codes: 491.X, 492.X, 493.X, 496.X, V17.5, V81.3
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08 Medications: Zidovudine, Didanosine, Zalcitabine, Stavudine, Indinavir, Ritonavir, Saquinavir, Nevirapine, Nelfinavir, Delavirdine, Delavirdine, Abacavir, Amprenavir, Efavirenz, Lamivudine-Zidovudine, Ritonavir-Lopinavir, Abacavir-Lamivudine-Zidovudine
Parkinson's Disease		ICD 9- CM diagnosis codes: 332 Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine
Osteoporosis		ICD-9-CM diagnosis code: 733.0X
Falls/ fractures	1. Falls 2. Fractures	ICD-9-CM diagnosis code: E880.X, E881.X, E884.X, E885.9 ICD-9-CM diagnosis code: 733.1X, 800.X-829.X, E887
Home oxygen use		ICD-9-CM diagnosis code: V46.2
Medications		
Antipsychotics	Atypical and typical antipsychotic medications	Lithium, Clozapine, Haloperidol, Loxapine, Lurasidone, Molindone, Olanzapine, Paliperidone, Quetiapine Fumerate; Risperidone, Aripiprazole, Asenapine, Ziprasidone, Chlorpromazine, Fluphenazine, Fluphenazine Deconate, Mesoridazine, Perphenazine, Thioridazine, Thiothixene; Trifluoperazine; Triflupromazine, Asenapine, Chlorprothixene, Iloperidone, Molindone, Promazine, Piperacetazine, Methotrimeprazine, Acetophenazine
ACE inhibitors alone/combination		Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril
ARBs alone/ combination		Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
Beta-blockers		Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotalol, Timolol, Nebivolol
Calcium channel blockers		Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine, Nisoldipine, Bepridil, Amlodipine/Atorvastatin, Clevidipine Butyrate
Thiazide diuretics/ potassium-sparing diuretics		Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Eplerenone; Amiloride, Spironolactone, Triamterene, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Spironolactone, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Hydroflumethiazide, Polythiazide, Quinethazone
Other antihypertensives		Doxazosin, Prazosin, Terazosin, Clonidine, Guanabenz, Guanfacine, Hydralazine, Methyldopa, Metyrosine, Reserpine, Minoxidil, Alfuzosin, Silodosin, Alseroxylon, Cryptenamine,

		Deserpidine, Diazoxide Guanethidine, Iloprost, Mecamylamine, Pargyline, Rescinnamine, Trimethaphan Camsylate
Anti-arrhythmics, digoxin and other inotropes	1. Digoxin	Digoxin, Digitalis
	2. Antiarrythmics	Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, , Procainamide, Propafenone, Ropafenone, Quinidine, Disopyramide, Verapamil, Dofetilide, Mexiletine, Moricizine, Tocainide
Anticoagulants and platelet inhibitors, not aspirin	1. Anticoagulants	Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran
	2. Platelet inhibitors	Clopidogrel, Ticlopidine, Aspirin/Dipyridamole, Dipyridamole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
Statins		Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin/Niacin, Amlodipine/Atorvastatin
Non-statin lipid lowering drugs		Cholestyramine, Colesevelam, Clofibrate, Colestipol, Niacin, Niacinamide, Fish Oil Concentrate, Omega 3 Fatty Acids, Gemfibrozil, Fenofibrate, Fenofibric Acid, Ezetimibe Omacor, Tricor/Fenofibrate, Ezetimibe/Simvastatin
Nitrates		Amyl Nitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Erythrityl Tetranitrate, Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray), Ranolazine
Aspirin		Aspirin, Aspirin/Dipyridamole
Loop diuretics		Furosemide, Ethacrynic acid, Bumetanide, Torsemide
Alpha blockers		Alfuzosin aka Aventis, Uroxatral, Xatral, Prostetrol Tamsulosin aka Flomax, Tamsin Silodosin aka Rapaflo, Silodyx, Rapilif, Silodal, Urief, Doxazosin (Cardura), Carduran, Terazosin (Hytrin), Zayasel, Prazosin (Minipress), Vasoflex, Pressin, Hypovase

Appendix E. Propensity score modeling for Study 2

The propensity score (PS) was defined as the probability of low adherence (<80%), given a particular set of baseline covariates. The PS was estimated using a logistic regression model including restricted cubic splines with 3 knots for continuous variables. Indicator variables for missingness were included. Missing covariate values were imputed from 30 multiple imputation procedures; the imputation model was based on multivariate normal regression. The results of the PS model are shown in **Table E.1**. The average PS from the imputations was used for the propensity score matching weights in the final outcome model. **Figure E.1** shows the distribution of propensity scores by exposure groups (low adherence versus high adherence). **Table E.2** shows the distribution of covariates and mean standardized differences before and after PS weighting. All standardized differences have an absolute value ≤ 0.2, which indicates good balance between the exposure groups.

Figure E.1. Distribution of propensity scores by adherence

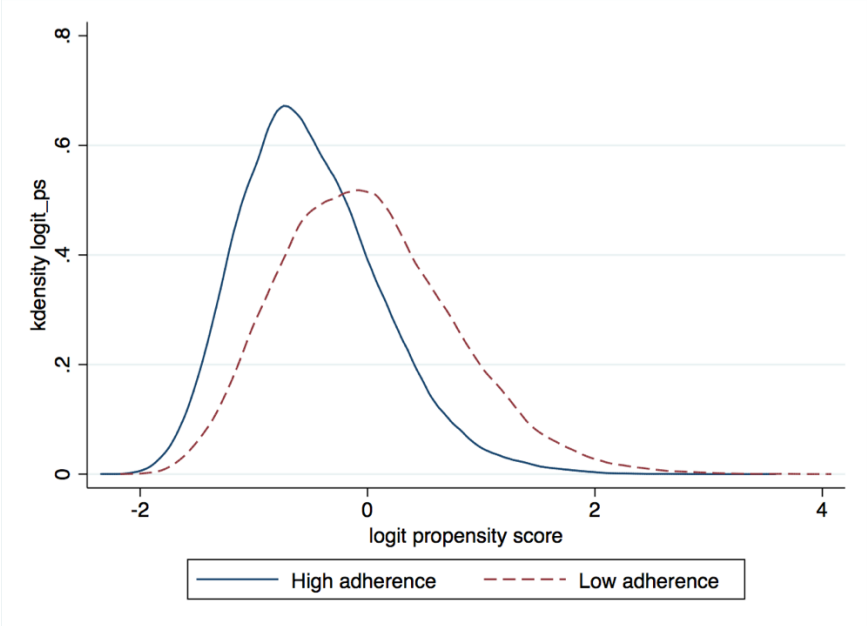


Table E.1. Logistic regression model for the probability of having low adherence

Characteristic	*Odds Ratio*	*95% CI*	
Comorbidities			
Malignancy	0.97	0.90	1.05
Liver failure	1.12	0.94	1.33
Congestive heart failure	1.16	1.05	1.28
Cardiovascular disease	1.11	1.04	1.17
Serious mental illness	1.01	0.95	1.07
Cardiac valve disease	1.02	0.87	1.19
Arrhythmia	1.07	0.99	1.16
Smoking	1.11	1.04	1.17
Chronic obstructive pulmonary disease/ asthma	1.04	0.98	1.10
HIV	0.91	0.64	1.30
Parkinson's Disease	1.07	0.82	1.41
Osteoporosis	1.01	0.88	1.16
Falls/ fractures	1.48	1.21	1.80
Home oxygen use	1.32	0.95	1.85
Indicators of health care utilization			
Hospitalized in last year (VA)	1.39	1.26	1.53
Hospitalized in last year (Medicare)	1.00	0.87	1.15
Hospitalized in last year (Medicaid)	0.99	0.54	1.82
Hospitalized in month of incident diabetes prescription (VA)	1.05	0.92	1.21
Hospitalized in month of incident diabetes prescription (Medicare)	0.73	0.61	0.87
Hospitalized in month of incident diabetes prescription (Medicaid)	0.75	0.32	1.77
Nursing home encounter in last year	0.94	0.37	2.41
Number of medications	0.93	0.93	0.93
Number of medications'	1.06	1.04	1.08
Outpatient visits in past year	0.98	0.96	1.00
Outpatient visits in past year'	1.02	1.00	1.04
Medicare encounters in last year	1.05	0.99	1.11
Medicaid encounters in last year	1.20	1.09	1.32
Demographics			
Race Black	2.03	1.88	2.20
Race Other	1.48	1.34	1.63
Gender Female	0.97	0.85	1.11
Age	0.98	0.98	0.98
Age'	1.02	1.02	1.02
Incident metformin therapy year			
2003	1.01	0.92	1.11
2004	1.01	0.92	1.11
2005	1.03	0.93	1.14
2006	1.11	1.00	1.22
2007	1.14	1.03	1.26
Clinical and laboratory			
HbA1c	1.03	0.99	1.07
HbA1c'	1.13	1.06	1.20
Systolic blood pressure	1.00	1.00	1.00
Systolic blood pressure'	1.01	1.01	1.01
Diastolic blood pressure	1.00	1.00	1.00
Diastolic blood pressure'	1.01	1.01	1.01
Body mass index	0.98	0.98	0.98
Body mass index'	1.01	1.01	1.01
Low density lipoprotein	1.00	1.00	1.00
Low density lipoprotein'	1.01	1.01	1.01
Creatinine	0.36	0.19	0.67

Creatinine’	2.41	1.26	4.60
Estimated glomerular filtration rate	0.99	0.99	0.99
Estimated glomerular filtration rate’	1.01	1.01	1.01
Urine protein trace	1.04	0.96	1.13
Urine protein 1+	1.05	0.97	1.14
Proteinuria present at 2+,	1.13	0.98	1.29
Proteinuria present at 3+,	1.05	0.81	1.36
Proteinuria present at 4+	1.45	0.66	3.17
Medications			
ACE Inhibitors	0.87	0.84	0.90
ARBs	0.90	0.84	0.95
Calcium Channel Blockers	0.96	0.92	1.00
Beta Blockers	0.95	0.91	0.99
Thiazide and K sparing	0.93	0.90	0.97
Other antihypertensive medications	0.95	0.88	1.03
Statin lipid lowering agents	0.73	0.71	0.76
Anti-arrhythmics, digoxin and inotropes	1.06	0.93	1.22
Anticoagulant	0.89	0.80	0.98
Nitrates	1.01	0.95	1.07
Aspirin	1.01	0.95	1.07
Loop Diuretics	1.04	0.98	1.10
Antipsychotics	0.88	0.81	0.95
Oral glucocorticoids	1.02	0.96	1.08
Alpha blockers	1.01	0.93	1.09
Sulfonylurea defined daily dose	1.06	1.02	1.10
Glyburide	0.86	0.74	1.01
Indicators of Missing covariates imputed			
HbA1c missing	1.07	0.99	1.16
LDL missing	1.09	1.03	1.16
Glomerular filtration rate missing	1.04	0.96	1.13
Blood pressure missing	1.00	0.78	1.29
Body mass index missing	1.23	0.99	1.53
Race missing	1.12	1.03	1.21
Urine protein testing missing	1.03	0.99	1.07
Location of care versus VISN 1			
VISN 2	0.94	0.81	1.10
VISN 3	1.20	1.02	1.40
VISN 4	1.02	0.91	1.15
VISN 5	1.00	0.85	1.17
VISN 6	1.06	0.94	1.19
VISN 7	1.09	0.97	1.23
VISN 8	1.13	1.00	1.27
VISN 9	0.85	0.76	0.96
VISN 10	1.04	0.91	1.19
VISN 11	0.92	0.80	1.06
VISN 12	1.00	0.87	1.15
VISN 15	1.11	0.96	1.27
VISN 16	1.07	0.95	1.21
VISN 17	1.26	1.10	1.44
VISN 18	1.13	0.98	1.29
VISN 19	1.02	0.89	1.17
VISN 20	1.02	0.89	1.17
VISN 21	1.30	1.13	1.49
VISN 22	1.34	1.17	1.53
VISN 23	0.84	0.75	0.95

* Continuous variables were included as restricted cubic splines with 3 knots in the model (indicated by ’)

Table E.2. Characteristics of patients after propensity score weighting

Characteristic	*Weighted cohort N=49,424*		
	Low Adherence N= 21,419	*High Adherence N= 28,005*	*SD†*
Age, median (IQR)*	63	64	-0.10
Female (%)	4.9%	4.2%	0.03
Race, (%)†			
White	78.6%	83.1%	-0.12
Black	16.2%	12.4%	0.11
Hispanic/ Other	5.3%	4.5%	0.04
Available %	8.7%	8.5%	0.01
Months on sulfonylurea monotherapy, median (IQR)‡†	29.7	31.7	-0.09
Initiated glyburide (%)	38.8%	37.8%	0.02
Sulfonylurea initial dose (DDD), median (IQR)	0.68	0.66	0.05
HbA1c, %	7.9	7.6	0.16
Available %	9.3%	8.7%	0.02
Low density lipoprotein mg/dL, median (IQR)	98.0	92.0	0.17
Available %	17.3%	16.1%	0.03
Glomerular filtration rate (ml/min), median (IQR)	83.8	82.1	0.06
Available %	11.8%	11.5%	0.01
Creatinine mg/dL, median (IQR)	1.09	1.09	-0.02
Proteinuria, (%)			
Negative	49.5%	50.1%	-0.01
Trace through 4+	18.5%	18.2%	0.01
Available %	32.0%	31.7%	0.01
Systolic blood pressure (mm/Hg), median (IQR)	134	134	0.04
Diastolic blood pressure (mm/Hg), median (IQR)	1.6%	1.4%	0.02
Available %	77	76	0.07
Body mass index (kg/m^2), median (IQR)†	32.717	32.758	-0.01
Available%	2.5%	2.1%	0.03
Baseline Co-morbidities (%)			
Malignancy	5.7%	6.1%	-0.02
Liver/ respiratory failure†	1.3%	1.1%	0.02
HIV†	0.3%	0.3%	0.01
Congestive heart failure	6.2%	6.3%	0.00
Cardiovascular disease	22.8%	24.3%	-0.04
Serious mental illness	18.1%	18.1%	0.00
Smoking	13.6%	13.1%	0.01
Obstructive Pulmonary Disease/ Asthma	12.6%	13.1%	-0.02
Cardiac valve disease	1.6%	1.7%	-0.01
Arrhythmia	7.8%	8.4%	-0.02
Parkinson's	0.4%	0.5%	0.00
Osteoporosis	2.1%	2.2%	-0.01
History of falls/ fractures	1.2%	1.1%	0.02
Oxygen use	0.3%	0.4%	0.00
Use of Medications (%)			
ACE Inhibitors	59.9%	62.4%	-0.05
ARBs	10.5%	11.5%	-0.03
Other anti-hypertensive medications†	22.6%	23.9%	-0.03
Statin and other lipid lowering agents†	68.6%	73.9%	-0.12
Anti-arrhythmics, digoxin and inotropes	2.1%	2.2%	-0.01
Anticoagulants, platelet inhibitors	5.7%	6.4%	-0.03
Nitrates	10.7%	11.7%	-0.03

Aspirin	21.3%	21.7%	-0.01
Loop Diuretics	12.4%	13.4%	-0.03
Antipsychotics	7.8%	7.8%	0.00
Oral glucocorticoids	11.6%	12.2%	-0.02
Alpha blockers	14.1%	15.4%	-0.04
Indicators of Healthcare Utilization			
Hospitalized in last year (%)†	13.4%	12.8%	0.02
Hospitalized in prior 90 days (%)†	5.4%	5.1%	0.01
Nursing home encounter (%)	0.0%	0.0%	0.00
Outpatient visits, median (IQR)	8	8	-0.02
Medicare utilization	24.6%	26.2%	-0.04
Medicaid utilization	9.8%	9.6%	0.01
Number of outpatient medications, median (IQR)	13	13	-0.08
Year of Metformin Initiation			
2003	17.7%	17.7%	0.00
2004	19.5%	19.8%	-0.01
2005	21.2%	21.6%	-0.01
2006	21.6%	21.4%	0.01
2007	15.6%	15.0%	0.02

Appendix F. Propensity score modeling for Study 3

The propensity score (PS) was defined as the probability of intensification with insulin, given a particular set of baseline covariates. The PS was estimated using a logistic regression model including restricted cubic splines with 3 knots for continuous variables. Indicator variables for missingness were included. Missing covariate values were imputed from 30 multiple imputation procedures; the imputation model was based on multivariate normal regression. The results of the PS model are shown in **Table F.1**. The average PS from the imputations was used for the propensity score matching weights in the final outcome model. **Figure F.1** shows the distribution of propensity scores by exposure groups (low adherence versus high adherence). **Table F.2** shows the distribution of covariates and mean standardized differences before and after PS weighting. All standardized differences have an absolute value ≤ 0.1, which indicates good balance between the exposure groups.

Figure F.1. Distribution of propensity scores by treatment

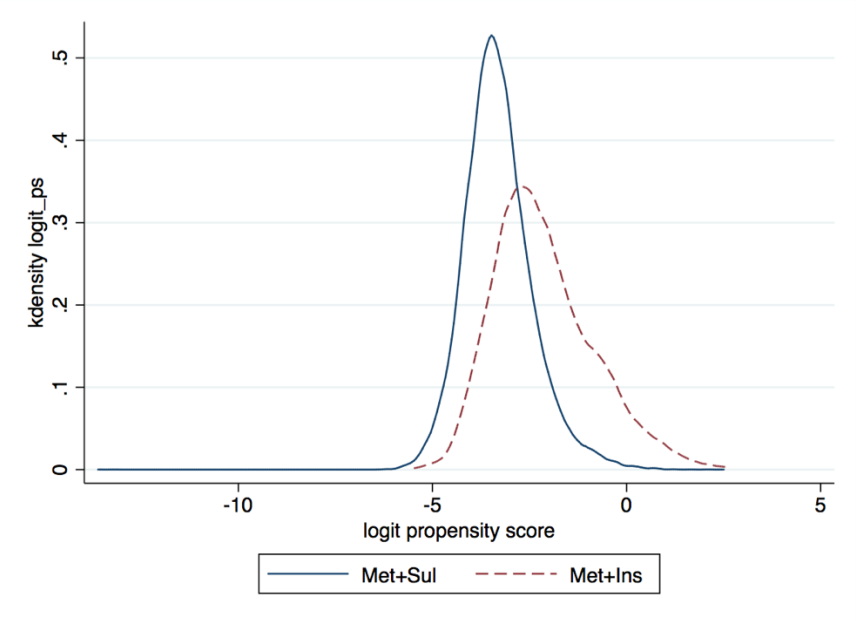


Table F.1. Logistic regression model for the probability of intensification with insulin

Characteristic	*Odds Ratio*	*95% CI*	
Comorbidities			
Malignancy	1.09	0.85	1.39
Liver failure	1.26	0.83	1.90
Congestive heart failure	1.08	0.84	1.39
Cardiovascular disease	1.41	1.22	1.64
Serious mental illness	1.00	0.87	1.15
Cardiac valve disease	0.91	0.56	1.47
Arrhythmia	1.10	0.87	1.40
Smoking	0.98	0.85	1.13
Chronic obstructive pulmonary disease/ asthma	1.06	0.90	1.24
HIV	1.02	0.47	2.19
Parkinson's Disease	1.42	0.69	2.93
Osteoporosis	1.14	0.81	1.61
Falls/ fractures	1.42	0.91	2.23
Home oxygen use	3.13	1.63	6.00
Indicators of health care utilization			
Hospitalized in last year (VA)	1.04	0.80	1.34
Hospitalized in last year (Medicare)	0.97	0.67	1.40
Hospitalized in last year (Medicaid)	0.84	0.18	3.97
Hospitalized in month of incident diabetes prescription (VA)	5.27	3.96	7.02
Hospitalized in month of incident diabetes prescription (Medicare)	2.22	1.48	3.33
Hospitalized in month of incident diabetes prescription (Medicaid)	0.95	1.09	8.22
Number of medications	1.21	1.06	1.38
Outpatient visits in past year	0.83	0.74	0.93
Medicare encounters in last year	1.36	1.15	1.60
Medicaid encounters in last year	1.70	1.31	2.19
Demographics			
Race Black	1.21	0.98	1.50
Race Other	0.97	0.73	1.27
Gender Female	1.22	0.85	1.76
Age	0.67	0.59	0.75
Incident metformin therapy date	1.37	1.25	1.51
Clinical and laboratory			
HbA1c	1.09	1.00	1.18
Systolic blood pressure	1.07	0.98	1.17
Diastolic blood pressure	0.91	0.83	0.99
Body mass index	0.93	0.86	1.00
Low density lipoprotein	0.92	0.86	0.98
Creatinine	0.91	0.70	1.16
Estimated glomerular filtration rate	0.83	0.60	1.16
Urine protein trace	0.95	0.78	1.16
Urine protein 1+	1.12	0.91	1.37
Proteinuria present at 2+	0.99	0.70	1.41
Proteinuria present at 3+	1.68	0.89	3.16
Proteinuria present at 4+	1.43	0.27	7.65
Medications			
ACE Inhibitors	0.96	0.85	1.08
ARBs	1.07	0.89	1.28
Calcium Channel Blockers	1.06	0.94	1.21
Beta Blockers	0.87	0.77	0.98
Thiazide and K sparing	1.01	0.90	1.14
Other antihypertensive medications	1.04	0.86	1.27
Statin lipid lowering agents	0.75	0.66	0.84

Anti-arrhythmics, digoxin and inotropes	1.03	0.72	1.47
Anticoagulant	0.90	0.69	1.17
Nitrates	0.88	0.73	1.06
Aspirin	1.07	0.94	1.22
Loop Diuretics	1.35	1.14	1.61
Antipsychotics	1.10	0.92	1.31
Oral glucocorticoids	1.23	1.05	1.44
Alpha blockers	0.99	0.79	1.24
Indicators of Missing covariates imputed			
HbA1c missing	1.28	1.04	1.59
LDL missing	1.43	1.23	1.65
Glomerular filtration rate missing	1.03	0.85	1.25
Body mass index missing	1.23	0.99	1.53
Race missing	1.12	0.93	1.35
Urine protein testing missing	0.94	0.84	1.10
Location of care versus VISN 16			
VISN 1	1.00	0.72	1.38
VISN 2	1.09	0.75	1.58
VISN 3	0.64	0.40	1.01
VISN 4	1.25	0.94	1.66
VISN 5	1.29	0.87	1.89
VISN 6	1.42	1.09	1.84
VISN 7	1.14	0.88	1.50
VISN 8	0.70	0.53	0.94
VISN 9	1.20	0.92	1.57
VISN 10	1.30	0.96	1.75
VISN 11	1.47	1.11	1.94
VISN 12	1.28	0.94	1.74
VISN 15	1.04	0.74	1.46
VISN 17	1.09	0.80	1.48
VISN 18	1.19	0.86	1.64
VISN 19	1.45	1.03	2.03
VISN 20	1.67	1.26	2.21
VISN 21	0.80	0.54	1.19
VISN 22	0.91	0.64	1.28
VISN 23	1.26	0.95	1.68

Table F.2. Characteristics of patients after propensity score weighting

Characteristic	*Weighted cohort N=28,892*		
	Metformin + Insulin N=1653	*Metformin + Sulfonylurea N=27,239*	*Std. diff†*
Age, median (IQR)*	59.1	59.1	0.000
Female (%)	6.4%	6.2%	0.008
Race, (%)†			
White	66.7%	67.0%	-0.007
Black	19.5%	18.7%	0.023
Hispanic/ Other	4.1%	4.2%	-0.008
Missing %	9.7%	10.0%	-0.012
Time (months) to treatment intensification, median (IQR)‡†	26.4	26.1	0.017
HbA1c, %	9.2	9.1	0.045
Missing %	9.0%	9.0%	-0.001
Low Density Lipoprotein mg/dL, median (IQR)	91.6	92.0	-0.010
Missing %	20.3%	20.2%	0.001
Glomerular Filtration Rate (ml/min), median (IQR)	92.9	92.9	-0.003
Creatinine mg/dL, median (IQR)	1.00	1.00	0.003
Missing %	10.6%	10.6%	0.001
Proteinuria, (%)			
Negative	51.2%	51.0%	0.005
Trace through 4+	19.4%	19.3%	0.002
Missing %	29.4%	29.7%	-0.007
Systolic blood pressure mm/Hg, median (IQR)	134	134	-0.004
Diastolic blood pressure mm/Hg, median (IQR)	78	78	-0.002
Available %	0.0%	0.1%	-0.039
Body mass index (kg/m^2), median (IQR)†	33.9	33.8	0.014
Baseline Co-morbidities (%)			
Malignancy	5.2%	5.0%	0.007
Liver/ respiratory failure†	1.9%	1.7%	0.022
HIV†	0.5%	0.5%	0.010
Congestive heart failure	7.1%	6.9%	0.010
Cardiovascular disease	26.6%	26.0%	0.013
Serious mental illness	26.6%	25.9%	0.017
Smoking	19.2%	18.5%	0.019
Obstructive Pulmonary Disease/ Asthma	18.2%	17.6%	0.016
Cardiac valve disease	1.5%	1.4%	0.004
Arrhythmia	8.3%	8.2%	0.007
Parkinson's	0.6%	0.6%	-0.002
Osteoporosis	2.7%	2.8%	-0.002
Falls /fractures	1.6%	1.5%	0.015
Oxygen use	1.0%	0.8%	0.026
Use of Medications (%)			
ACE Inhibitors or ARBs	69.6%	69.2%	0.008
Anti-hypertensive medications†	23.6%	23.7%	-0.002
Statin and other lipid lowering agents†	75.4%	75.4%	0.001

Anti-arrhythmics, digoxin and inotropes	2.4%	2.3%	0.005
Anticoagulants, platelet inhibitors	5.9%	5.9%	0.001
Nitrates	12.6%	12.4%	0.008
Aspirin	28.8%	27.9%	0.021
Loop Diuretics	16.6%	16.5%	0.003
Antipsychotics	14.1%	14.2%	-0.004
Alpha-blockers	16.6%	16.0%	0.018
Indicators of health care utilization			
Hospitalized in last year (%)†	28.9%	25.5%	0.086
Hospitalized in prior 90 days (%)†	19.6%	16.5%	0.100
Nursing home encounter (%)	0.0%	0.0%	-0.016
Outpatient visits, median (IQR)	9.4	9.3	0.011
Medicare utilization	23.4%	23.4%	0.001
Medicaid utilization	13.3%	13.0%	0.010
No. of outpatient medications, median (IQR)	15.9	15.6	0.035
Year of Metformin Initiation			
2004	17.7%	18.0%	-0.006
2005	21.6%	21.2%	0.011
2006	23.2%	22.9%	0.008
2007	18.1%	18.0%	0.002

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