Use, Safety, and Effectiveness of Diabetes Medications in Older Nursing Home Residents

By

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This dissertation by Andrew R. Zullo is accepted in its present form by the Department of Health Services, Policy, and Practice as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

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Andrew Zullo graduated from Rutgers University Ernest Mario School of Pharmacy, *magna cum laude*, with a Doctor of Pharmacy in 2012. At Rutgers University, he earned the Academic Merit, John and Josephine Calasibetta, Alumni Association, and Ernest Mario Endowed Scholarships. He was also elected to the Phi Lamba Sigma Leadership Honor Society, and given two leadership awards: the New Jersey Pharmacists Association Outstanding Leadership Award and the United States Public Health Service Excellence in Public Health Pharmacy Practice Award. He then received a Master of Science degree in epidemiology at the Brown University School of Public Health in 2015. For his master's thesis, Andrew worked on a study of the effect of health insurance on personal prescription drug importation. For his work on drug importation, Andrew earned both the Nora Kahn Piore Award and a grant from the Brown University Population Studies and Training Center.

Dr. Zullo entered the PhD program in Health Services Research at Brown University in August 2012 (while simultaneously pursing the Master of Science degree in Epidemiology) to pursue interests in the fields of pharmacoepidemiology and pharmaceutical health services research. Outside of the classroom, he has worked on research projects with Drs. Vincent Mor and David D. Dore. During his training at Brown, Andrew was award the 2016 American Geriatrics Society Scientist-in-Training Research Award. His research has been presented at conferences for the American Geriatrics Society and AcademyHealth. He has lead or contributed to publications in geriatrics, gerontology, diabetes, cardiology, comparative effectiveness, and clinical pharmacy.

Preface and Acknowledgements

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Introduction

Overview

Little evidence exists to guide selection of medicines to treat geriatric patients with type 2 diabetes mellitus (T2D). The extensive evidence for younger, healthier individuals does not apply to older persons with T2D because they have complex medical problems, are more susceptible to hypoglycemia and its consequences, and have greater functional disability.[1,2] The need for evidence pertaining to frail elderly persons is critical, especially among nursing home (NH) residents. This population is frequently affected by impairments in cognitive or physical function. These impairments are associated with increased risk of premature death[3,4], poorer quality of life[5,6], reduced adherence to self-care[7], and increased health expenditures in an aging United States (U.S.) population[8-12]—and may be exacerbated by diabetes treatment.[1,2,13] Individuals with T2D have more functional disability than those without[13,14] and the prevalence of T2D in the NH increased from 16 to 23 percent from 1995 to 2004.[15] Preserving cognitive and physical function is increasingly recognized as a primary goal of T2D therapy since many elders prefer drugs that improve their ability to maintain independence in daily life rather than extend lifespan by reducing the risk of fatal macrovascular complications.[16] Furthermore, emphasizing functioning, which can be improved in the short term with conservative prescribing, over long-term vascular outcomes like major adverse cardiovascular (CV) events (myocardial infarction, unstable angina pectoris, heart failure) and stroke,[17] may be more appropriate for elderly NH residents. Long-stay NH residents, who generally require extensive and ongoing care, have a median life expectancy of less than 2.5 years.[12,18,19 2,20]

The overall objectives of this dissertation were 1) to understand how treatments for T2D are selected for older adults in the NH setting, and 2) to quantify the effects of treatments for T2D on cognitive and physical functioning as well as CV-related and serious hypoglycemic events in older NH residents. Our central hypothesis was that sulfonylureas (SUs) worsen functioning, increase hypoglycemic events, and have no beneficial effect on CV events compared to dipeptidyl peptidase-4 (DPP-4) inhibitors. The rationale for this work was that T2D treatments may improve functioning through a reduction in CV symptoms/events[17,21,22] and may worsen functioning by causing hypoglycemic episodes, but the net effects of these treatments on day-to-day functioning remain unknown.[23-25] Large randomized trials of pharmacologic therapies for T2D have generally not measured CV or functional outcomes and have also excluded frail older persons.[20,26-28] Additionally, little is known about current practice patterns and utilization of T2D medications in the NH.

This dissertation will provide the clinical guidance for selecting T2D therapies for long-stay NH residents that accounts for cognitive and physical functioning in addition to the more commonly considered hypoglycemia and vascular endpoints.

Specific Aims

Aim 1: To quantify the frequency and determinants of initiating sulfonylureas over metformin with the aim of understanding the impact of the boxed warnings on metformin use in a nationally representative cohort of NH residents, with a focus on conditions included in the FDA-labeled boxed warning for metformin.

Aim 2: To compare the effect of DPP4Is versus SUs on mortality, adverse glycemic events, and cardiovascular events among long-stay NH residents age 65 and older

Aim 3: To compare effect of DPP4Is versus SUs on cognitive functioning, altered mental status events, and physical functioning among long-stay NH residents age 65 and older

Data Source and Analytic Sample

We analyzed a secondary database that includes all U.S. Medicare fee-for-service beneficiaries who are NH residents for ≥90 days between 2007 and 2010. The data includes the Minimum Data Set (MDS) for NH resident assessment linked to Medicare Parts A, B, and D claims data. These data include validated assessments of cognitive and physical functioning (MDS) and serious hypoglycemia[29,30], stroke[31], heart failure,[32] and CV events (myocardial infarction, unstable angina)[33,34] (claims).

CHAPTER 1: METFORMIN SAFETY WARNINGS AND DIABETES DRUG PRESCRIBING PATTERNS FOR OLDER NURSING HOME RESIDENTS

Abstract

Background: Diabetes mellitus is common in U.S. nursing homes (NH), and the mainstay treatment, metformin, has U.S. Food and Drug Administration (FDA) boxed warnings indicating safety concerns in those with advanced age, heart failure, or renal disease. Little is known about the selection of treatments in this setting, especially for metformin.

Objectives: To quantify prescribing of sulfonylureas over metformin and associated patient characteristics in older NH residents.

Design: National retrospective cohort.

Setting: U.S. NHs.

Participants: Long-stay NH residents age ≥65 years who initiated metformin or sulfonylurea monotherapy following a period of ≥6 months with no glucose-lowering treatment use between 2008 and 2010 (N=7,295).

Measurements: Measures of patient characteristics were obtained from linked national Minimum Data Set assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare claims. Odds ratios (ORs) comparing patient characteristics and treatment initiation were estimated using univariable and multivariable multilevel logistic regression models with NH random intercepts.

Results: Of the 7,295 residents in the study population, 3,066 (42%) initiated metformin and 4,229 (58%) initiated a sulfonylurea. In multivariable analysis, several factors were associated with sulfonylurea initiation over metformin initiation, including heart failure (OR = 1.2, 95% confidence interval (CI) 1.1-1.4) and renal disease (OR=2.1, 95%CI 1.7-2.5). Compared to those aged 65 to <75 years, residents 75 to <85 (OR=1.3, 95%CI 1.2-

1.5, 85 to <95 (OR=2.0, 95%CI 1.7-2.3), and ≥95 (OR=4.3, 95%CI 3.2-5.8) years old were more likely to initiate sulfonylureas over metformin.

Conclusion: Advanced age, and the presence of heart failure or renal disease were predictive of initiating sulfonylureas over metformin among older NH residents with diabetes. Providers in the NH consider FDA safety warnings when prescribing medications.

Introduction

Approximately one million older U.S adults live in a nursing home (NH) and 25% of all adults spend the final stages of their lives in these settings.[35] Between 25% and 35% of elderly NH residents have diabetes mellitus; mainly type 2 diabetes (T2D).[36-38] Metformin is endorsed in diabetes treatment guidelines as first-line therapy due to its low cost, favorable safety profile (e.g., low hypoglycemia risk) and potential cardiovascular benefits.[38-40] Since metformin is cleared unchanged by the kidneys, its product label has included a U.S. Food and Drug Administration (FDA) boxed warning since its approval that cautions prescribers to monitor renal function in elderly recipients of the drug.[41,42] This warning was included because of distinct concern that patients with poor renal function may be at higher risk of developing lactic acidosis, a rare but potentially fatal condition, secondary to metformin accumulation.[43] Initial guidelines stated that metformin was contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/minute/1.73 m^2.[42] However, the level of concern about lactic acidosis diminished over time since empirical evidence largely does not support an increased risk with metformin treatment, and the FDA relaxed the restrictions in early

2016 to indicate the acceptability of metformin use in patients with an eGFR of 30-60 mL/minute/1.73 m^2.[43,44]

Initiation of metformin or sulfonylurea monotherapy is common in the U.S. NH setting.[45,46] Sulfonylureas have been used for over 60 years and commonly cause hypoglycemia, which is particularly detrimental in frail older adults.[24,47,48] It is possible that in response to FDA warnings, providers initiated frail, older NH residents on a drug class with a known, common adverse event (hypoglycemia with sulfonylureas) rather than a drug with tenuous evidence to support an association with a rare adverse event (lactic acidosis with metformin).[24,43] In this study, we quantified the frequency and determinants of initiating sulfonylureas over metformin with the aim of understanding the impact of the boxed warnings on metformin use in a nationally representative cohort of NH residents, with a focus on conditions included in the FDA-labeled boxed warning for metformin. We hypothesized that common conditions included in the warning would be associated with more sulfonylurea initiation.

Methods

Data Sources

The study cohort consisted of NH residents identified from a random 20% national sample of Medicare Fee-For-Service beneficiaries. We linked data for this sample from Medicare Parts A (inpatient), B (physician and supplier), and D (prescription drug) claims with the Minimum Data Set (MDS) for the years 2007 to 2010 and obtained information about beneficiaries' NHs from the Online Survey, Certification, And Reporting (OSCAR) data.

The Medicare claims data provided information on demographics, Medicare eligibility, hospitalizations, and dispensings of prescription drugs for each patient. Medicare Part D provided information on drug name, dosage, route of administration, formulation (immediate or extended release), quantity dispensed, and days supplied. Approximately 81% of NH residents were enrolled in Part D in 2006.[49]

The MDS is a federally-mandated health assessment tool that captures information on cognitive, physical, and psychosocial functioning; active clinical diagnoses and health conditions; and services. NH staff assess each resident at least annually for all MDS measures, at three-month intervals for many measures, and at any time that a significant change in resident status occurs.[50] We used the MDS 2.0, which has been found generally reliable and valid for measuring domains when used by trained staff.[51] In cases when information was not available on certain comorbidities in the MDS, we used diagnoses from Part B coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The MDS was preferred over claims data for clinical information because the MDS assessments contain information on active clinical conditions and are often used by physicians in patient care management and prescribing decisions, whereas claims data are not.[51]

The OSCAR database consists of facility-level information collected at NHs for the purpose of certification for Medicare and Medicaid programs.[52] The OSCAR data permitted us to identify each patients' NH facility at the time of metformin or sulfonylurea initiation.

Study Population

Our study cohort comprised long-stay NH residents 65 years or older who initiated either metformin or a second-generation sulfonylurea (glimepiride, glipizide, or glyburide) as monotherapy between January 1, 2008 and December 31, 2010. Users were identified through the National Drug Codes (NDCs) in Medicare Part D claims. We defined long-stay residents as those with 90 or more consecutive days in a NH. Residents lived in all 50 U.S. states, the District of Columbia, Puerto Rico, and the Virgin Islands. We defined the date of each resident's first eligible prescription as the index date. We excluded residents who were prescribed any glucose-lowering medication (including insulin) in the six months preceding the index date (prevalent users). These exclusions were made to isolate individuals initiating sulfonylurea monotherapy as an alternative to metformin monotherapy, the accepted first-line treatment.[38-40]

All patients were required to have maintained continuous Medicare insurance eligibility for the six months preceding the index date and could not have Medicare Advantage coverage. To preserve real-world prescribing patterns and avoid exclusion of participants due to imperfect documentation of diabetes (a known challenge from prior pharmacoepidemiology studies [53]), residents were not required to have a specified diagnosis of diabetes to be in our study sample. However, 6,631 (91%) of those in our study sample had a diagnosis of diabetes on at least one MDS assessment before initiating metformin or a sulfonylurea. Glucose-lowering medications are not routinely prescribed for indications other than diabetes in older adults.

Resident Characteristics

To ascertain the presence of clinically-active conditions, comorbidities, and geriatric conditions as potential predictors, we primarily used the MDS 2.0 data in the one year prior to the initiation of a glucose-lowering medication. Of particular interest were the conditions included in the FDA boxed warning about lactic acidosis in metformin package labeling between 2007 and 2010 or that were previously removed from the label, but still likely to have an influence during that time.[41,42] These included age ≥80 years, renal impairment, and heart failure. Liver impairment, excessive alcohol use, and sepsis are also all mentioned in the metformin boxed warning and were evaluated, but are less common. Age at the time of glucose-lowering medication initiation was available in the Medicare enrollment file. Heart failure, renal impairment, alcohol use, and sepsis were all measured in the MDS. Since liver disease was not assessed by the MDS, we used ICD-9 codes from Medicare Part B claims in the one year prior to the initiation of metformin or sulfonylurea.[54]

Geriatric conditions and the NH resident functional status were also of interest as predictors because they could affect diabetes management decisions.[39] We calculated the MDS Activities of Daily Living (MDS-ADL) score using seven ADLs (bed mobility, transfer, locomotion, dressing, eating, toilet use, and personal hygiene), each ranging from 0 (total independence) to 4 (total dependence).[55] The sum of the seven items forms a 28-point scale, where higher scores indicate greater physical impairment.[55] Cognitive function was measured using the MDS Cognitive Performance Scale (MDS-CPS) score, which ranges from 0 (intact) to 6 (severe impairment).[56] The CPS score was recoded into a three-category variable: cognitively intact to mild impairment (CPS 0-2), moderate impairment (CPS 3), and moderate-severe to very severe impairment (CPS 4-6).[56] The

MDS Changes in Health, End-Stage Disease, Signs, and Symptoms (CHESS) Scale was used as a validated measure of overall health stability and frailty, where 0 indicates no health instability/frailty and 5 indicates very high instability/frailty.[57,58] Values of three to five on the CHESS scale were collapsed into a single category representing moderate to very high health instability.[57,58] Concomitant medication use up to 12 months prior to the index date was assessed.

Statistical Analysis

We first described nursing home resident characteristics and their daily medication dose [(tablet strength × quantity) ÷ days supply] at initiation using descriptive statistics. We then evaluated univariable associations between potential predictors and metformin versus sulfonylurea initiation using logistic regression to estimate odds ratios (OR) with 95% confidence intervals (CI). To test our hypothesis that certain individual factors were independently associated with prescribing sulfonylureas over metformin, we used a multilevel multivariable logistic regression model.[59] Because residents are clustered within NHs, we included NH random intercept to obtain more accurate standard errors and CIs.[60]

We conducted sensitivity analyses. First, since an interaction between age and congestive heart failure was plausible based on *a priori* knowledge, one model contained that interaction. Second, we removed age from the model to check for multicollinearity with comorbidities. Lastly, we performed two additional sensitivity analyses to examine whether patient characteristics and conditions included in the FDA boxed warning for metformin were associated with greater initiation of dipeptidyl peptidase-4 inhibitors and

thiazolidinediones, which are oral glucose-lowering therapies that are believed to have a lower risk of hypoglycemia than sulfonylureas.[47,61] Data were analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) software. The Institutional Review Board of Brown University reviewed and approved this study.

Results

The 7,295 residents in our study cohort had a mean age of 82 years; 37% were male, 82% were non-Hispanic white race, and 29% were obese (Table 1.1; Table 1.5). Extensive or greater assistance with ADLs was required by 70% of the cohort and moderate or more severe cognitive impairment was present in 64%. Most residents (94%) had at least three comorbidities. The number of residents in each of the 5,339 NHs in our study ranged from 1 to 8, with an average of 1.4 residents per NH. With regard to the FDA boxed warning conditions in the metformin package labeling: advanced age (≥80 years) was present in 66%, heart failure in 28%, renal impairment in 9%, use of alcoholic beverages at least weekly in 2.8%, sepsis in 0.7%, and liver disease in 0.6% of the overall cohort. There were 2,485 NH residents in the cohort (34%) without any of the conditions listed in the FDA boxed warning for metformin, 3,206 (44%) with one, 1,365 (19%) with two, and 239 (3%) with three or more.

Dose and Formulation of Metformin and Sulfonylureas at Initiation

Of the 7,295 residents in the study population, 3,066 (42%) initiated metformin and 4,229 (58%) initiated a sulfonylurea (Table 1.2). Among sulfonylurea initiators, 847 (20%) were prescribed glimepiride, 2,257 (53%) glipizide, and 1,125 (27%) glyburide.

Approximately 6% of metformin users and 30% of glipizide users were prescribed extended release formulations. The most common daily dose of metformin was 1000 mg for the immediate release formulation and 500 mg for the extended release. The most common daily dose of glipizide was 5 mg for both immediate release and extended release formulations.

Predictors of Initiating Sulfonylureas over Metformin

In univariable analyses (Table 1.3; Table 1.4; Table 1.6), the most common conditions included in the FDA-labeled boxed warning for metformin were strong predictors of initiating sulfonylureas over metformin: advanced age (≥95 versus 65 to <75, OR=3.67, 95%CI 2.83-4.73); renal disease (OR=2.34, 95%CI 1.95-2.80); and CHF (OR=1.57, 95%CI 1.41-1.74). Sepsis in the prior year was not associated with use of sulfonylureas over metformin (OR 1.18, 95%CI 0.67-2.10).

In multivariable analyses (Table 1.3; Table 1.4; Table 1.6), the strongest predictors of initiating sulfonylureas over metformin were common conditions contained in the FDA boxed warning for metformin, including CHF (OR=1.24, 95%CI 1.09-1.41), renal disease (OR=2.05, 95%CI 1.67-2.52), and dialysis use (OR=5.69, 95%CI 2.47-13.08), and advanced age (≥95 versus 65 to <75, OR=4.32, 95%CI 3.21-5.82). There were few other notable predictors of initiating sulfonylureas over metformin, with the exception of obesity (compared to normal weight, OR=1.25, 95%CI 1.09-1.44) and having any emergency department visit, physician visit, or hospitalization for hypoglycemia up to one year prior to treatment initiation (OR=1.23, 95%CI 1.04-1.46).

In the sensitivity analyses, an interaction between age and CHF was not observed (p-value for interaction = 0.17), and removing age from the model had no influence on the observed associations between predictors and initiation of sulfonylureas versus metformin. The observed associations between predictors and initiation of DPP-4 inhibitors or thiazolidinediones over metformin were similar to those for sulfonylureas (Table 1.7; Table 1.8).

Discussion

In this national sample of older NH residents, patient conditions included in the FDA boxed warning were the strongest predictors of initiating monotherapy with sulfonylureas over metformin.[42-44] These conditions included advanced age, heart failure, and renal disease. Few other patient characteristics were strong predictors of initiating sulfonylureas over metformin despite our large sample size.

Little prior information is available regarding the factors that drive selection of glucose-lowering treatments for diabetes in the NH. The most comparable study was a cohort of adults aged 65 years and older in Alberta, Canada using 1998-2010 Alberta Blue Cross insurance data.[62] Advanced age, renal disease, and heart failure were shown to be associated with more frequent initiation of sulfonylurea versus metformin monotherapy. In a less comparable cohort study of younger community-dwelling U.S. patients in 2006-2008 CVS Caremark data, younger age (<70 years) was predictive of receiving metformin as initial oral glucose-lowering therapy.[63] Finally, in a national German cohort study using 2004 data from 5 million patients 20 years and older, patients were less likely to initiate metformin if they had a diabetes complication, which included

heart failure and dialysis among other conditions, or if they were aged 75 years or older.[64] Overall, these findings from non-NH populations are consistent with our data in the U.S. NH setting.

In combination with identifying predictors of the glucose-lowering treatment decision, the initial dose prescribed may indicate providers' perceptions of NH residents' risk of adverse effects. Despite the concerns about adverse drug effects (e.g., gastrointestinal side effects, hypoglycemia) among frail older adults in the NH setting, many individuals were started on higher doses than recommended by the American Medical Directors Association (AMDA) and other organizations.[40] The AMDA-recommended daily dose of immediate-release metformin is 500 mg daily, yet many patients were initiated on metformin at higher doses, putting them at greater risk of gastrointestinal side effects.[40] Although the American Geriatrics Society Beers Criteria recommendation to avoid glyburide use among older adults due to the risk of prolonged hypoglycemia was first released in 2012, among patients prescribed glyburide before 2012, one might expect lower daily starting doses of 1.25 to 2.5 mg.[65-67] However, many NH residents were initiated on glyburide at doses of 5 mg daily or greater.

This study has some limitations. First, our data did not contain information on the duration of an individual's diabetes. Such measures would have been desirable since duration of diabetes and associated declines in beta cell function may influence treatment selection. Second, measures of glycemic control (fasting plasma glucose, hemoglobin A1c) and patient preferences for treatment were not available in the data, but could influence treatment selection.[2,40,68] Third, while DPP-4 inhibitors and thiazolidinediones represented an alternative to metformin between 2007 and 2010, they were used less

often than sulfonylureas.[45,46] In recent years, these medication classes may be substituted for metformin more often, especially given mounting evidence that they are not associated with adverse cardiovascular effects as previously thought.[69-71] Lastly, some patients may have a long history of using glucose-lowering medications not captured by the data (i.e., before the six month period of glucose-lowering medication non-use that preceded metformin or sulfonylurea initiation) or with intermittent gaps of more than six months. If that were the case, providers might favor the drug and regimen last observed in their long-term medication history. Similarly, treatment decisions could be influenced by prior therapeutic failures or adverse effects associated with one of the treatments. The unexpected finding that history of hypoglycemia was associated with sulfonylurea over metformin initiation is consistent with this possibility since it may serve as a proxy for long-term medication use history.

In response to FDA warnings, providers initiated frail, older NH residents on a drug class with a known, common adverse event (hypoglycemia with sulfonylureas) rather than a drug with tenuous evidence to support an association with a rare adverse event (lactic acidosis with metformin). It is possible that this practice induces more harm than it prevents. In light of the 2016 FDA warning updates that ease restrictions on metformin use in the presence of renal impairment, providers are advised to maintain metformin as the preferred first-line glucose-lowering medication among older NH residents with renal impairment provided that the eGFR is greater than 30 mL/minute/1.73 m^2, in the absence of other contraindications. While little empirical evidence exists for NH residents, the lower hypoglycemia risk observed in younger patients with DPP-4 inhibitors, thiazolidinediones, and the more recently developed sodium-glucose co-transporter 2

inhibitors suggests that these may be preferred alternatives when metformin is contraindicated.

Chapter 1 Tables

Table 1.1. Demographic and Clinical Characteristics of Nursing Home Residents Initiating Metformin or Sulfonylureas (N=7,295)

Characteristic	n (%)
Demographics	
Age in years, mean (SD)	82 (8)
65 to <75	1,425 (20)
75 to <85	2611 (36)
85 to <95	2864 (39)
≥95	395 (5)
Male	2,683 (37)
Race/ethnicity	
White, non-Hispanic	5,995 (82)
Black, non-Hispanic	840 (12)
Hispanic	307 (4)
Other[1]	153 (2)
Clinical Characteristics	
Comorbidities	
Atherosclerotic heart disease	1,195 (16)
Cardiovascular disease (unspecified type)	1,879 (26)
Renal disease	665 (9)
Liver disease	42 (1)
Congestive heart failure	2,049 (28)
Number of comorbidities (prior year), mean (SD)	6 (2)
Geriatric Syndromes	
Cognitive performance	
Cognitively intact to mild impairment	2575 (35)
Moderate impairment	2647 (36)
Moderate-severe to very severe impairment	2073 (28)
Activities of daily living status	
Independent to limited supervision	2,163 (30)
Extensive assistance required	2,842 (39)
Dependent or totally dependent	2,290 (31)
Leaves ≥25% of food uneaten at most meals	2,602 (36)
Medications (prior year)	
Statins	1,397 (19)
Angiotensin converting enzyme inhibitors	1,330 (18)
Angiotensin receptor blockers	367 (5)
Beta blockers	1,737 (24)
Antiplatelet agents	511 (7)
Warfarin	506 (7)
Number of medications (prior year), mean (SD)	13 (5)
History of hypoglycemia	788 (11)

SD, standard deviation.
[1]Other race/ethnicity includes American Indian/Alaskan Native/Asian Pacific Islander.
See Table 1.5 for a complete list of characteristics.

Table 1.2. Daily Dose at Initiation of Metformin or Sulfonylureas among Long-stay Nursing Home Residents (N=7,295)

Drug	Any Formulation	Immediate Release Formulation	Extended Release Formulation
Metformin, n (%)[a]	3,066 (100)	2,880 (93.9)	186 (6.1)
Daily dose, milligrams			
Mean (SD)	1044.8 (589.1)	1056.7 (588.9)	861.2 (562.5)
Median (IQR)	1000 (500-1000)	1000 (500-1016.1)	500 (500-1000)
Mode	1000	1000	500
Glimepiride, n (%)[a]	847 (100)	847 (100)	0 (0)
Daily dose, milligrams			
Mean (SD)	2.5 (1.9)	2.5 (1.9)	NA
Median (IQR)	2 (1-4)	2 (1-4)	NA
Mode	2	2	NA
Glipizide, n (%)[a]	2,257 (100)	1,571 (69.6)	686 (30.4)
Daily dose, milligrams			
Mean (SD)	7.8 (17)	8.3 (20)	6.7 (5.8)
Median (IQR)	5 (2.5-10)	5 (4.6-10)	5 (2.5-10)
Mode	5	5	5
Glyburide, n (%)[a]	1,125 (100)	1,125 (100)	0 (0)
Daily dose, milligrams			
Mean (SD)	5.9 (7.8)	5.9 (7.8)	NA
Median (IQR)	5 (2.5-7.5)	5 (2.5-7.5)	NA
Mode	2.5	2.5	NA

Abbreviations: NA, not applicable.
[a] Percentages are row percentages.

Table 1.3. Univariable and Multivariable Multilevel Logistic Regression Analysis of Demographic Characteristics and Geriatric Syndromes Associated with Sulfonylurea versus Metformin Initiation among Long-stay Nursing Home Residents (N=7,295)

Characteristic	Sulfonylurea Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI)[1,2]
	4,229/7,295 (58)		
Age in years			
65 to <75	685/1,425 (48)	Reference	Reference
75 to <85	1,426/2,611 (55)	1.30 (1.14-1.48)	1.33 (1.15-1.54)
85 to <95	1,813/2,864 (63)	1.86 (1.64-2.12)	1.96 (1.67-2.29)
≥95	305/395 (77)	3.67 (2.83-4.73)	4.32 (3.21-5.82)
Sex			
Male	1,536/2,683 (57)	Reference	Reference
Female	2,693/4,612 (58)	1.05 (0.95-1.15)	0.91 (0.82-1.02)
Health stability			
No health instability	2,506/4,432 (57)	Reference	Reference
Minimal health instability	1,040/1,758 (59)	1.11 (1.00-1.25)	1.01 (0.89-1.15)
Low health instability	444/719 (62)	1.24 (1.06-1.46)	1.02 (0.85-1.23)
Moderate to very high health instability	239/386 (62)	1.25 (1.01-1.55)	1.05 (0.82-1.35)
Cognitive performance			
Cognitively intact to mild impairment	1,500/2,575 (58)	Reference	Reference
Moderate impairment	1,517/2,647 (57)	0.96 (0.86-1.07)	0.94 (0.83-1.07)
Moderate-severe to very severe impairment	1,212/2,073 (59)	1.01 (0.90-1.13)	1.00 (0.85-1.17)
Activities of daily living			
Independent to limited assistance	1,181/2,163 (55)	Reference	Reference
Extensive assistance	1,683/2,842 (59)	1.21 (1.08-1.35)	1.09 (0.96-1.25)
Dependent or totally dependent	1,365/2,290 (60)	1.23 (1.09-1.38)	1.14 (0.98-1.34)
Leaves ≥25% of food uneaten at most meals			
No	2,711/4,693 (58)	Reference	Reference
Yes	1,518/2,602 (58)	1.02 (0.93-1.13)	0.92 (0.81-1.03)
History of Falls			
No	2,776/4,853 (57)	Reference	Reference
Yes	1,453/2,442 (60)	1.10 (1.00-1.21)	1.07 (0.96-1.20)
Weight loss			
No	3,805/6,548 (58)	Reference	Reference
Yes	424/747 (57)	0.95 (0.81-1.10)	0.85 (0.70-1.03)

[1]Multivariable analyses also adjusted for a wide range of variables not shown here, including demographic characteristics, clinical conditions, baseline medications, geriatric syndromes, and nursing home characteristics; see Table 1.6 for complete list.
[2]Includes a random intercept for nursing home facility at the time of medication initiation to account for clustering of residents within nursing facilities.
[3]Measured using the Changes in Health, End-Stage Disease, Signs, and Symptoms Scale score

Table 1.4. Univariable and Multivariable Multilevel Logistic Regression Analysis of Comorbidities and Medications Associated with Sulfonylurea versus Metformin Initiation among Long-stay Nursing Home Residents (N=7,295)

Characteristic	Sulfonylurea Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI)[1,2]
	4,229/7,295 (58)		
Congestive heart failure			
No	2,884/5,246 (55)	Reference	Reference
Yes	1,345/2,049 (66)	1.57 (1.41-1.74)	1.24 (1.09-1.41)
Atherosclerotic heart disease			
No	3,486/6,100 (57)	Reference	Reference
Yes	743/1,195 (62)	1.23 (1.09-1.40)	1.02 (0.89-1.18)
Cardiovascular disease (unspecified type)			
No	3,065/5,416 (57)	Reference	Reference
Yes	1,164/1,879 (62)	1.25 (1.12-1.39)	1.13 (1.00-1.28)
Renal disease			
No	3,730/6,630 (56)	Reference	Reference
Yes	499/665 (75)	2.34 (1.95-2.80)	2.05 (1.67-2.52)
Liver disease			
No	4,204/7,253 (58)	Reference	Reference
Yes	25/42 (60)	1.07 (0.57-1.98)	0.98 (0.50-1.95)
Comorbidity burden			
0-4	1,260/2,420 (52)	Reference	Reference
5-6	1,532/2,587 (59)	1.34 (1.20-1.50)	1.07 (0.93-1.22)
≥7	1,437/2,288 (63)	1.55 (1.38-1.75)	0.98 (0.81-1.17)
Statins			
No	3,433/5,898 (58)	Reference	Reference
Yes	796/1,397 (57)	0.95 (0.85-1.07)	0.90 (0.78-1.05)
Antiplatelets			
No	3,919/6,784 (58)	Reference	Reference
Yes	310/511 (61)	1.13 (0.94-1.36)	1.01 (0.81-1.25)
Warfarin			
No	3,909/6,789 (58)	Reference	Reference
Yes	320/506 (63)	1.27 (1.05-1.53)	1.16 (0.93-1.45)
Number of Medications			
0 to 9	897/1,657 (54)	Reference	Reference
10 to 14	1,631/2,815 (58)	1.17 (1.03-1.32)	1.11 (0.97-1.27)
≥15	1,701/2,823 (60)	1.28 (1.14-1.45)	1.13 (0.98-1.31)
History of hypoglycemia			
No	3,732/6,507 (57)	Reference	Reference
Yes	497/788 (63)	1.27 (1.09-1.48)	1.23 (1.04-1.46)

[1]Multivariable analyses also adjusted for a wide range of variables not shown here,

including demographic characteristics, clinical conditions, baseline medications, geriatric syndromes, and nursing home characteristics; see Table 1.6 for complete list.

[2]Includes a random intercept for nursing home facility at the time of medication initiation to account for clustering of residents within nursing facilities.

Table 1.5. Complete Set of Demographic and Clinical Characteristics of Nursing Home Residents Initiating Metformin or Sulfonylureas (N=7,295)

Characteristic	n (%)
Demographics	
Age in years, mean (SD)	82 (8)
65 to <75	1,425 (20)
75 to <85	2611 (36)
85 to <95	2864 (39)
≥95	395 (5)
Male	2,683 (37)
Race/ethnicity	
White, non-Hispanic	5,995 (82)
Black, non-Hispanic	840 (12)
Hispanic	307 (4)
Other[1]	153 (2)
Region of residence	
Northeast	2,008 (28)
Midwest	2,115 (29)
South	2,092 (29)
West	947 (13)
Caribbean	133 (2)
Body mass index	
Underweight (<18.5)	321 (4)
Normal weight (18.5 to <25)	2,544 (35)
Overweight (25 to <30)	2,330 (32)
Obese (≥30)	2,100 (29)
Pain	
No pain	5,089 (70)
Pain less than daily	1,640 (23)
Pain daily	566 (8)
Clinical Characteristics	
Comorbidities	
Atrial fibrillation	2,260 (31)
Atherosclerotic heart disease	1,195 (16)
Cardiovascular disease (unspecified type)	1,879 (26)
Hypertension	5,690 (78)
Peripheral vascular disease	1,256 (17)
Stroke	1,779 (24)
Renal disease	665 (9)
Liver disease	42 (1)
Depression	4,079 (56)
Congestive heart failure	2,049 (28)
Number of comorbidities (prior year), mean (SD)	6 (2)
Geriatric Syndromes	

Cognitive performance	
Cognitively intact to mild impairment	2575 (35)
Moderate impairment	2647 (36)
Moderate-severe to very severe impairment	2073 (28)
Activities of daily living status	
Independent to limited supervision	2,163 (30)
Extensive assistance required	2,842 (39)
Dependent or totally dependent	2,290 (31)
Leaves ≥25% of food uneaten at most meals	2,602 (36)
History of falls	2,442 (34)
CHESS score (overall health stability)	
No instability	4,432 (61)
Minimal instability	1,758 (24)
Low instability	719 (10)
Moderate to very high instability	386 (5)
Medications (prior year)	
Statins	1,397 (19)
Angiotensin converting enzyme inhibitors	1,330 (18)
Angiotensin receptor blockers	367 (5)
Beta blockers	1,737 (24)
Calcium channel blockers	1,032 (14)
Thiazide diuretics	551 (8)
Antiplatelet agents	511 (7)
Warfarin	506 (7)
Number of medications (prior year), mean (SD)	13 (5)
Any inpatient hospitalization	5,095 (70)
History of hypoglycemia	788 (11)
History of sepsis	50 (1)
Any dialysis use	73 (1)
Alcohol use weekly	204 (1)

SD, standard deviation; CHESS, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, emergency department.
[1]Other race/ethnicity includes American Indian/Alaskan Native/Asian Pacific Islander.

Table 1.6. Complete Set of Univariable and Multivariable Multilevel Logistic Regression Analyses of Characteristics Associated with Sulfonylurea versus Metformin Initiation among Long-stay Nursing Home Residents (N=7,295)

Characteristic	Metformin Initiation (n/N, %)	Sulfonylurea Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI)[1,2]
	3,066/7,295 (42)	4,229/7,295 (58)		
Demographics				
Age in years				
65 to <75	740/1,425 (52)	685/1,425 (48)	Reference	Reference
75 to <85	1,185/2,611 (45)	1,426/2,611 (55)	1.30 (1.14-1.48)	1.33 (1.15-1.54)
85 to <95	1,051/2,864 (37)	1,813/2,864 (63)	1.86 (1.64-2.12)	1.96 (1.67-2.29)
≥95	90/395 (23)	305/395 (77)	3.67 (2.83-4.73)	4.32 (3.21-5.82)
Sex				
Male	1,147/2,683 (43)	1,536/2,683 (57)	Reference	Reference
Female	1,919/4,612 (42)	2,693/4,612 (58)	1.05 (0.95-1.15)	0.91 (0.82-1.02)
Body mass index				
Underweight (<18.5)	157/321 (49)	164/321 (51)	0.78 (0.62-0.99)	0.69 (0.53-0.90)
Normal weight (18.5 to <25)	1,091/2,544 (43)	1,453/2,544 (57)	Reference	Reference
Overweight (25 to <30)	963/2,330 (41)	1,367/2,330 (59)	1.07 (0.95-1.19)	1.13 (0.99-1.28)
Obese (≥30)	855/2,100 (41)	1,245/2,100 (59)	1.09 (0.97-1.23)	1.25 (1.09-1.44)
Comorbidities				
Congestive heart failure				
No	2,362/5,246 (45)	2,884/5,246 (55)	Reference	Reference
Yes	704/2,049 (34)	1,345/2,049 (66)	1.57 (1.41-1.74)	1.24 (1.09-1.41)
Atherosclerotic heart disease				
No	2,614/6,100 (43)	3,486/6,100 (57)	Reference	Reference
Yes	452/1,195 (38)	743/1,195 (62)	1.23 (1.09-1.40)	1.02 (0.89-1.18)
Cardiovascular disease (unspecified type)				

No	2,351/5,416 (43)	3,065/5,416 (57)	Reference	Reference
Yes	715/1,879 (38)	1,164/1,879 (62)	1.25 (1.12-1.39)	1.13 (1.00-1.28)
Peripheral vascular disease				
No	2,564/6,039 (42)	3,475/6,039 (58)	Reference	Reference
Yes	502/1,256 (40)	754/1,256 (60)	1.11 (0.98-1.25)	0.94 (0.82-1.08)
Stroke				
No	2,327/5,516 (42)	3,189/5,516 (58)	Reference	Reference
Yes	739/1,779 (41)	1,040/1,779 (59)	1.03 (0.92-1.14)	1.06 (0.93-1.20)
Renal disease				
No	2,900/6,630 (44)	3,730/6,630 (56)	Reference	Reference
Yes	166/665 (25)	499/665 (75)	2.34 (1.95-2.80)	2.05 (1.67-2.52)
Liver disease				
No	3,049/7,253 (42)	4,204/7,253 (58)	Reference	Reference
Yes	17/42 (40)	25/42 (60)	1.07 (0.57-1.98)	0.98 (0.50-1.95)
CHESS Score (overall health stability)				
No health instability	1,926/4,432 (43)	2,506/4,432 (57)	Reference	Reference
Minimal health instability	718/1,758 (41)	1,040/1,758 (59)	1.11 (1.00-1.25)	1.01 (0.89-1.15)
Low health instability	275/719 (38)	444/719 (62)	1.24 (1.06-1.46)	1.02 (0.85-1.23)
Moderate to very high health instability	147/386 (38)	239/386 (62)	1.25 (1.01-1.55)	1.05 (0.82-1.35)
Comorbidity burden (MDS comorbidities)				
0-4	1,160/2,420 (48)	1,260/2,420 (52)	Reference	Reference
5-6	1,055/2,587 (41)	1,532/2,587 (59)	1.34 (1.20-1.50)	1.07 (0.93-1.22)
≥7	851/2,288 (37)	1,437/2,288 (63)	1.55 (1.38-1.75)	0.98 (0.81-1.17)
Geriatric Syndromes				
Cognitive performance				
Cognitively intact to mild impairment	1,075/2,575 (42)	1,500/2,575 (58)	Reference	Reference
Moderate impairment	1,130/2,575 (43)	1,517/2,647 (57)	0.96 (0.86-1.07)	0.94 (0.83-1.07)

Moderate-severe to very severe impairment	861/2,073 (41)	1,212/2,073 (59)	1.01 (0.90-1.13)	1.00 (0.85-1.17)
Activities of daily living				
Independent to limited assistance	982/2,163 (45)	1,181/2,163 (55)	Reference	Reference
Extensive assistance	1,159/2,842 (41)	1,683/2,842 (59)	1.21 (1.08-1.35)	1.09 (0.96-1.25)
Dependent or totally dependent	925/2,290 (40)	1,365/2,290 (60)	1.23 (1.09-1.38)	1.14 (0.98-1.34)
Leaves ≥25% of food uneaten at most meals				
No	1,928/4,693 (42)	2,711/4,693 (58)	Reference	Reference
Yes	1,084/2,602 (42)	1,518/2,602 (58)	1.02 (0.93-1.13)	0.92 (0.81-1.03)
History of Falls				
No	2,077/4,853 (43)	2,776/4,853 (57)	Reference	Reference
Yes	989/2,442 (40)	1,453/2,442 (60)	1.10 (1.00-1.21)	1.07 (0.96-1.20)
Weight loss				
No	2,743/6,548 (42)	3,805/6,548 (58)	Reference	Reference
Yes	323/747 (43)	424/747 (57)	0.95 (0.81-1.10)	0.85 (0.70-1.03)
Medications (prior year)				
Statins				
No	2,465/5,898 (42)	3,433/5,898 (58)	Reference	Reference
Yes	601/1,397 (43)	796/1,397 (57)	0.95 (0.85-1.07)	0.90 (0.78-1.05)
Antiplatelets				
No	2,865/6,784 (42)	3,919/6,784 (58)	Reference	Reference
Yes	201/511 (39)	310/511 (61)	1.13 (0.94-1.36)	1.01 (0.81-1.25)
Warfarin				
No	2,880/6,789 (42)	3,909/6,789 (58)	Reference	Reference
Yes	186/506 (37)	320/506 (63)	1.27 (1.05-1.53)	1.16 (0.93-1.45)
Angiotensin converting enzyme inhibitors				
No	2,526/5,965 (42)	3,439/5,965 (58)	Reference	Reference
Yes	540/1,330 (41)	790/1,330 (59)	1.03 (0.98-1.08)	0.97 (0.84-1.12)

Angiotensin receptor blockers				
No	2,919/6,928 (42)	4,009/6,928 (58)	Reference	Reference
Yes	147/367 (40)	220/367 (60)	1.07 (0.95-1.21)	0.89 (0.69-1.14)
Beta blockers				
No	2,398/5,558 (43)	3,160/5,558 (57)	Reference	Reference
Yes	668/1,737 (38)	1,069/1,737 (62)	1.21 (1.09-1.36)	1.12 (0.97-1.28)
Number of Medications (last MDS assessment)				
0 to 9	760/1,657 (46)	897/1,657 (54)	Reference	Reference
10 to 14	1,184/2,815 (42)	1,631/2,815 (58)	1.17 (1.03-1.32)	1.11 (0.97-1.27)
≥15	1,122/2,823 (40)	1,701/2,823 (60)	1.28 (1.14-1.45)	1.13 (0.98-1.31)
History of hypoglycemia				
No	2,775/6,507 (43)	3,732/6,507 (57)	Reference	Reference
Yes	291/788 (37)	497/788 (63)	1.27 (1.09-1.48)	1.23 (1.04-1.46)
History of sepsis				
No	3,047/7245 (42)	4,198/7,245 (58)	Reference	Reference
Yes	19/50 (38)	31/50 (62)	1.18 (0.67-2.10)	0.87 (0.45-1.66)
Any dialysis use				
No	3,059/7,222 (42)	4,163/7,222 (58)	Reference	Reference
Yes	7/73 (10)	66/73 (90)	6.93 (3.17-15.12)	5.69 (2.47-13.08)
Alcohol use weekly				
No	2,969/7,091 (42)	4,122/7,091 (58)	Reference	Reference
Yes	97/204 (48)	107/204 (52)	0.79 (0.60-1.05)	0.95 (0.70-1.30)

Abbreviations: CHESS, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

[1]Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tacchyarrhythmias, do not resuscitate and hospitalize preferences, calendar time, and use of the following medications: calcium channel blockers, potassium-sparing diuretics, loop diuretics, anxiolytics, and antidepressants.

[2]Includes a random intercept for nursing home facility at the time of medication initiation to account for clustering of residents within nursing facilities.

Table 1.7. Univariable and Multivariable Multilevel Logistic Regression Analysis of Characteristics Associated with Dipeptidyl Peptidase-4 Inhibitor (DPP4I) versus Metformin Initiation among Long-stay Nursing Home Residents (N=3,351)

Characteristic	Metformin Initiation (n/N, %)	DPP4I Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI)[1,2]
	3,066/3,351 (91)	285/3,351 (9)		
Demographics				
Age in years				
65 to <75	740/787 (94)	47/787 (6)	Reference	Reference
75 to <85	1,185/1,286 (92)	101/1,286 (8)	1.34 (0.94-1.92)	1.50 (1.00-2.25)
85 to <95	1,051/1,177 (89)	126/1,177 (11)	1.89 (1.33-2.67)	2.46 (1.61-3.77)
≥95	90/101 (89)	11/101 (11)	1.92 (0.96-3.84)	2.79 (1.25-6.23)
Sex				
Male	1,147/1,286 (93)	89/1,286 (7)	Reference	Reference
Female	1,919/2,115 (91)	196/2,115 (9)	1.32 (1.01-1.71)	1.33 (0.98-1.79)
Body mass index				
Underweight (<18.5)	157/166 (95)	9/166 (5)	0.68 (0.34-1.38)	0.77 (0.36-1.64)
Normal weight (18.5 to <25)	1,091/1,183 (92)	92/1,183 (8)	Reference	Reference
Overweight (25 to <30)	963/1,051 (92)	88/1,051 (8)	1.08 (0.80-1.47)	1.08 (0.77-1.51)
Obese (≥30)	855/951 (90)	96/951 (10)	1.33 (0.99-1.80)	1.12 (0.78-1.62)
Comorbidities				
Congestive heart failure				
No	2,362/2,546 (93)	184/2,546 (7)	Reference	Reference
Yes	704/805 (87)	101/805 (13)	1.84 (1.42-2.38)	1.51 (1.09-2.10)
Atherosclerotic heart disease				
No	2,614/2,850 (92)	236/2,850 (8)	Reference	Reference
Yes	452/501 (90)	49/501 (10)	1.20 (0.87-1.66)	0.99 (0.67-1.45)
Cardiovascular disease (unspecified type)				

No	2,351/2,558 (92)	207/2,558 (8)	Reference	Reference
Yes	715/793 (90)	78/793 (10)	1.24 (0.94-1.63)	1.11 (0.80-1.54)
Peripheral vascular disease				
No	2,564/2,793 (92)	229/2,793 (8)	Reference	Reference
Yes	502/558 (90)	56/558 (10)	1.25 (0.92-1.70)	1.07 (0.74-1.54)
Stroke				
No	2,327/2,549 (91)	222/2,549 (9)	Reference	Reference
Yes	739/802 (92)	63/802 (8)	0.89 (0.67-1.20)	0.92 (0.65-1.29)
Renal disease				
No	2,900/3,141 (92)	241/3,141 (8)	Reference	Reference
Yes	166/210 (79)	44/210 (21)	3.19 (2.23-4.56)	2.91 (1.78-4.76)
Liver disease				
No	3,049/3,332 (92)	283/3,332 (8)	Reference	Reference
Yes	17/19 (89)	2/19 (11)	1.27 (0.29-5.51)	0.85 (0.16-4.41)
CHESS Score (overall health stability)				
No health instability	1,926/2,106 (91)	180/2,106 (9)	Reference	Reference
Minimal health instability	718/785 (91)	67/785 (9)	1.00 (0.74-1.34)	0.84 (0.60-1.19)
Low health instability	275/294 (94)	19/294 (6)	0.74 (0.45-1.21)	0.56 (0.31-1.00)
Moderate to very high health instability	147/166 (89)	19/166 (11)	1.38 (0.84-2.28)	1.38 (0.72-2.64)
Comorbidity burden (MDS comorbidities)				
0-4	1,160/1,246 (93)	86/1,246 (7)	Reference	Reference
5-6	1,055/1,153 (92)	98/1,153 (8)	1.25 (0.93-1.69)	1.00 (0.69-1.44)
≥7	851/952 (89)	101/952 (11)	1.60 (1.18-2.16)	0.89 (0.55-1.44)
Geriatric Syndromes				
Cognitive performance				
Cognitively intact to mild impairment	1,075/1,207 (89)	132/1,207 (11)	Reference	Reference
Moderate impairment	1,130/1,228 (92)	98/1,228 (8)	0.71 (0.54-0.93)	0.68 (0.49-0.94)

Moderate-severe to very severe impairment	861/916 (94)	55/916 (6)	0.52 (0.38-0.72)	0.52 (0.34-0.80)
Activities of daily living				
Independent to limited assistance	982/1,062 (92)	80/1,062 (8)	Reference	Reference
Extensive assistance	1,159/1,279 (91)	120/1,279 (9)	1.27 (0.95-1.71)	1.46 (1.04-2.06)
Dependent or totally dependent	925/1,010 (92)	85/1,010 (8)	1.13 (0.82-1.55)	1.84 (1.21-2.80)
Leaves ≥25% of food uneaten at most meals				
No	1,928/2,176 (91)	194/2,176 (9)	Reference	Reference
Yes	1,084/1,175 (92)	91/1,175 (8)	0.86 (0.66-1.11)	0.80 (0.59-1.10)
History of Falls				
No	2,077/2,273 (91)	196/2,273 (9)	Reference	Reference
Yes	989/1,078 (92)	89/1,078 (8)	0.95 (0.73-1.24)	0.99 (0.73-1.32)
Weight loss				
No	2,743/2,297 (92)	254/2,297 (8)	Reference	Reference
Yes	323/354 (91)	31/354 (9)	1.04 (0.70-1.53)	1.15 (0.69-1.92)
Medications (prior year)				
Statins				
No	2,465/2,696 (91)	231/2,696 (9)	Reference	Reference
Yes	601/655 (92)	54/655 (8)	0.96 (0.70-1.31)	0.96 (0.65-1.40)
Antiplatelets				
No	2,865/3,127 (92)	262/3,127 (8)	Reference	Reference
Yes	201/224 (90)	23/224 (10)	1.25 (0.80-1.96)	1.27 (0.74-2.17)
Warfarin				
No	2,880/3,135 (92)	255/3,135 (8)	Reference	Reference
Yes	186/216 (86)	30/216 (14)	1.82 (1.21-2.73)	1.57 (0.94-2.62)
Angiotensin converting enzyme inhibitors				
No	2,526/2,767 (91)	241/2,767 (9)	Reference	Reference

Yes	540/584 (92)	44/584 (8)	0.85 (0.61-1.19)	0.89 (0.60-1.33)
Angiotensin receptor blockers				
No	2,919/3,188 (92)	269/3,188 (8)	Reference	Reference
Yes	147/163 (90)	16/163 (10)	1.18 (0.70-2.01)	0.93 (0.49-1.75)
Beta blockers				
No	2,398/2,611 (92)	213/2,611 (8)	Reference	Reference
Yes	668/740 (90)	72/740 (10)	1.21 (0.92-1.61)	1.14 (0.79-1.64)
Number of Medications (last MDS assessment)				
0 to 9	760/806 (94)	46/806 (6)	Reference	Reference
10 to 14	1,184/1,289 (92)	105/1,289 (8)	1.47 (1.02-2.10)	1.42 (0.96-2.10)
≥15	1,122/1,256 (89)	134/1,256 (11)	1.97 (1.39-2.79)	1.85 (1.22-2.79)
History of hypoglycemia				
No	2,775/3,344 (92)	282/3,344 (8)	Reference	Reference
Yes	291/344 (85)	53/344 (15)	2.18 (1.58-3.01)	2.35 (1.59-3.46)
History of sepsis				
No	3,047/3,330 (92)	283/3,330 (8)	Reference	Reference
Yes	19/21 (90)	2/21 (10)	1.13 (0.26-4.89)	0.58 (0.08-4.18)
Any dialysis use				
No	3,059/3,336 (92)	277/3,336 (8)	Reference	Reference
Yes	7/15 (47)	8/15 (53)	12.62 (4.54-35.01)	6.87 (1.72-27.48)
Alcohol use weekly				
No	2,969/3,244 (92)	275/3,244 (8)	Reference	Reference
Yes	97/107 (91)	10/107 (9)	1.11 (0.57-2.16)	1.13 (0.53-2.40)

Abbreviations: CHESS, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

[1]Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tacchyarrhythmias, do not resuscitate and hospitalize preferences, calendar time, and use of the following medications: calcium channel blockers, potassium-sparing diuretics, loop diuretics, anxiolytics, and antidepressants.

[2]Includes a random intercept for nursing home facility at the time of medication initiation to account for clustering of residents within nursing facilities.

Table 1.8. Univariable and Multivariable Multilevel Logistic Regression Analysis of Characteristics Associated with Thiazolidinedione versus Metformin Initiation among Long-stay Nursing Home Residents (N=3,947)

Characteristic	Metformin Initiation (n/N, %)	Thiazolidinedione Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI)[1,2]
	3,066/3,947 (78)	881/3,947 (22)		
Demographics				
Age in years				
65 to <75	740/930 (80)	190/930 (20)	Reference	Reference
75 to <85	1,185/1,509 (79)	324/1,509 (21)	1.06 (0.87-1.30)	1.10 (0.87-1.39)
85 to <95	1,051/1,177 (77)	316/1,367 (23)	1.17 (0.96-1.43)	1.26 (0.99-1.62)
≥95	90/101 (64)	51/141 (36)	2.21 (1.51-3.22)	2.75 (1.74-4.34)
Sex				
Male	1,147/1,446 (93)	299/1,446 (21)	Reference	Reference
Female	1,919/2,501 (91)	582/2,501 (23)	1.16 (0.99-1.36)	1.06 (0.88-1.28)
Body mass index				
Underweight (<18.5)	157/206 (76)	49/206 (24)	1.17 (0.83-1.65)	1.02 (0.69-1.51)
Normal weight (18.5 to <25)	1,091/1,183 (79)	291/1,382 (21)	Reference	Reference
Overweight (25 to <30)	963/1,051 (78)	270/1,233 (22)	1.05 (0.87-1.27)	1.20 (0.97-1.49)
Obese (≥30)	855/951 (76)	271/1,126 (24)	1.19 (0.98-1.43)	1.45 (1.14-1.84)
Comorbidities				
Congestive heart failure				
No	2,362/3,012 (78)	650/3,012 (22)	Reference	Reference
Yes	704/935 (75)	231/935 (25)	1.19 (1.00-1.42)	0.98 (0.79-1.22)
Atherosclerotic heart disease				
No	2,614/3,379 (73)	765/3,379 (23)	Reference	Reference
Yes	452/568 (80)	116/568 (20)	0.88 (0.70-1.09)	0.74 (0.57-0.96)
Cardiovascular disease (unspecified type)				

No	2,351/3,040 (77)	689/3,040 (23)	Reference	Reference
Yes	715/907 (79)	192/907 (21)	0.92 (0.76-1.10)	0.78 (0.63-0.97)
Peripheral vascular disease				
No	2,564/3,288 (78)	724/3,288 (22)	Reference	Reference
Yes	502/659 (76)	157/659 (24)	1.11 (0.91-1.35)	0.95 (0.75-1.21)
Stroke				
No	2,327/2,549 (78)	651/2,978 (22)	Reference	Reference
Yes	739/802 (76)	230/969 (24)	1.11 (0.94-1.32)	1.03 (0.84-1.27)
Renal disease				
No	2,900/3,665 (79)	765/3,665 (21)	Reference	Reference
Yes	166/282 (59)	116/282 (41)	2.65 (2.06-3.40)	2.14 (1.56-2.94)
Liver disease				
No	3,049/3,927 (78)	878/3,927 (22)	Reference	Reference
Yes	17/20 (85)	3/20 (15)	0.61 (0.18-2.10)	0.59 (0.16-2.22)
CHESS Score (overall health stability)				
No health instability	1,926/2,453 (79)	527/2,453 (21)	Reference	Reference
Minimal health instability	718/928 (77)	210/928 (23)	1.07 (0.89-1.28)	1.02 (0.82-1.27)
Low health instability	275/369 (75)	94/369 (25)	1.25 (0.97-1.61)	1.06 (0.77-1.45)
Moderate to very high health instability	147/197 (75)	50/197 (25)	1.24 (0.89-1.74)	0.89 (0.58-1.37)
Comorbidity burden (MDS comorbidities)				
0-4	1,160/1,440 (81)	280/1,440 (19)	Reference	Reference
5-6	1,055/1,366 (77)	311/1,366 (23)	1.22 (1.02-1.46)	1.08 (0.87-1.35)
≥7	851/1,141 (75)	290/1,141 (25)	1.41 (1.17-1.70)	1.19 (0.89-1.61)
Geriatric Syndromes				
Cognitive performance				
Cognitively intact to mild impairment	1,075/1,363 (79)	288/1,363 (21)	Reference	Reference
Moderate impairment	1,130/1,432 (79)	302/1,432 (21)	1.00 (0.83-1.20)	1.00 (0.81-1.25)

Moderate-severe to very severe impairment	861/1,152 (75)	291/1,152 (25)	1.26 (1.05-1.52)	1.22 (0.95-1.57)
Activities of daily living				
Independent to limited assistance	982/1,197 (82)	215/1,197 (18)	Reference	Reference
Extensive assistance	1,159/1,511 (77)	352/1,511 (23)	1.39 (1.15-1.68)	1.28 (1.03-1.60)
Dependent or totally dependent	925/1,239 (75)	314/1,239 (25)	1.55 (1.28-1.88)	1.14 (0.87-1.48)
Leaves ≥25% of food uneaten at most meals				
No	1,928/2,555 (78)	573/2,555 (22)	Reference	Reference
Yes	1,084/1,392 (78s)	308/1,392 (22)	0.98 (0.84-1.15)	0.85 (0.70-1.03)
History of Falls				
No	2,077/2,678 (78)	601/2,678 (22)	Reference	Reference
Yes	989/1,269 (78)	280/1,269 (22)	0.98 (0.83-1.15)	0.94 (0.78-1.13)
Weight loss				
No	2,743/3,516 (78)	773/3,516 (22)	Reference	Reference
Yes	323/431 (75)	108/431 (25)	1.19 (0.94-1.50)	1.15 (0.85-1.57)
Medications (prior year)				
Statins				
No	2,465/3,143 (78)	678/3,143 (22)	Reference	Reference
Yes	601/804 (75)	203/804 (25)	1.23 (1.03-1.47)	1.10 (0.88-1.38)
Antiplatelets				
No	2,865/3,677 (78)	812/3,677 (22)	Reference	Reference
Yes	201/270 (74)	69/270 (26)	1.21 (0.91-1.61)	0.96 (0.69-1.35)
Warfarin				
No	2,880/3,709 (78)	829/3,709 (22)	Reference	Reference
Yes	186/238 (78)	52/238 (22)	0.97 (0.71-1.33)	1.05 (0.72-1.53)
Angiotensin converting enzyme inhibitors				
No	2,526/3,221 (78)	695/3,221 (22)	Reference	Reference

Yes	540/726 (74)	186/726 (26)	1.25 (1.04-1.51)	1.07 (0.85-1.35)
Angiotensin receptor blockers				
No	2,919/3,742 (78)	823/3,742 (22)	Reference	Reference
Yes	147/205 (72)	58/205 (28)	1.40 (1.02-1.91)	1.18 (0.82-1.72)
Beta blockers				
No	2,398/3,067 (78)	669/3,067 (22)	Reference	Reference
Yes	668/880 (76)	212/880 (24)	1.14 (0.95-1.36)	1.00 (0.79-1.25)
Number of Medications (last MDS assessment)				
0 to 9	760/916 (83)	156/916 (17)	Reference	Reference
10 to 14	1,184/1,517 (78)	333/1,517 (22)	1.37 (1.11-1.69)	1.35 (1.06-1.72)
≥15	1,122/1,514 (74)	392/1,514 (26)	1.70 (1.38-2.09)	1.61 (1.25-2.08)
History of hypoglycemia				
No	2,775/3,549 (78)	774/3,549 (22)	Reference	Reference
Yes	291/398 (73)	107/398 (27)	1.32 (1.04-1.67)	1.18 (0.90-1.54)
History of sepsis				
No	3,047/3,922 (78)	875/3,922 (22)	Reference	Reference
Yes	19/25 (76)	6/25 (24)	1.10 (0.44-2.76)	0.46 (0.14-1.52)
Any dialysis use				
No	3,059/3,913 (78)	854/3,913 (22)	Reference	Reference
Yes	7/34 (21)	27/34 (79)	13.82 (6.00-31.84)	10.69 (4.04-28.33)
Alcohol use weekly				
No	2,969/3,824 (78)	855/3,824 (22)	Reference	Reference
Yes	97/123 (79)	26/123 (21)	0.93 (0.60-1.44)	1.13 (0.69-1.86)

Abbreviations: CHESS, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

[1]Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tacchyarrhythmias, do not resuscitate and hospitalize preferences, calendar time, and use of the following medications: calcium channel blockers, potassium-sparing diuretics, loop diuretics, anxiolytics, and antidepressants.

[2]Includes a random intercept for nursing home facility at the time of medication initiation to account for clustering of residents within nursing facilities.

CHAPTER 2: COMPARISON OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS VERSUS SULFONYLUREAS ON MORTALITY, CARDIOVASCULAR, AND ADVERSE GLYCEMIC EVENTS IN OLDER NURSING HOME RESIDENTS

Abstract

Background: Dipeptidyl peptidase-4 inhibitors (DPP4Is) provide similar glycemic control to sulfonylureas (SUs), but might increase the risk of heart failure (HF) in individuals with type 2 diabetes mellitus (T2DM). Studies of the effects of DPP4Is versus SUs on adverse glycemic and cardiovascular outcomes are unavailable for older nursing home (NH) residents.

Objective: To quantify the effect of DPP4Is versus SUs on all-cause mortality, adverse glycemic events, and cardiovascular events among long-stay NH residents age 65 and older.

Design, setting, participants, exposure: New user cohort study of a representative sample of U.S. NH residents in 2008-2010, using national data from the Minimum Data Set and Medicare Parts A, B, and D. We used propensity score matching and Cox regression models to compare outcomes in residents who initiated a DPP4I versus SU.

Main outcomes: All-cause mortality, hypoglycemia or hyperglycemia, major adverse cardiovascular events (MACE), and heart failure within emergency or hospitalization encounters in the first 90 and 180 after DPP4I or SU initiation.

Results: The study cohort included 1008 new DPP4I users matched to an equal number of SU users. Mean age was 81 years. Compared to SU users, DPP4I users had lower 90-day and 180-day risks of hypoglycemic events (90-day, HR=0.89, 95%CI 0.35-2.32; 180-day, HR=0.79, 95%CI 0.40-1.56), but a similar risk of hyperglycemic events (90-day, HR=1.02, 95%CI 0.25-4.07; 180-day, HR=1.26, 95%CI 0.50-3.20). DPP4I users had a lower risk of stroke events at 90 (HR=0.60, 95%CI 0.14-2.52) and 180 (HR=0.39, 95%CI 0.14-1.08) days of follow-up, but a similar risk of other MACE and heart failure events in

all follow-up periods. Users of both medication classes had a similar risk of mortality (90-day, HR=1.12, 95%CI 0.88-1.41; 180-day, HR=1.00, 95%CI 0.84-1.19). Conclusions/relevance: Compared with SUs, DPP4Is may result in a lower risk of hypoglycemic and stroke events, but appear to have little impact on hyperglycemic, MACE, or heart failure events in older NH residents. However, biases from differences in loss to follow-up remains a plausible alternative explanation.

Introduction

Dipeptidyl peptidase-4 inhibitors (DPP4Is) and sulfonylureas (SUs) are recommended second-line treatments for type 2 diabetes mellitus (T2DM) in older nursing home (NH) residents, whose prevalence of T2DM is approximately 30%.[35-38,40,68] These recommendations are based primarily on randomized trials in middle-aged and "young-old" adults.[72-74] There are few data about the comparative effects of these medications among frail elders or NH residents, and the preferred second-line agent for this population remains unclear.

Hypoglycemia occurs frequently in this population and increases the risk of fall, fracture and cardiovascular events.[75,76] Severe acute hyperglycemia is important because it can result in falls, fractures, cardiovascular events, and hyperglycemic hyperosmolar syndrome, a very severe complication.[38,77] Additionally, it remains possible that DPP4Is and SUs differentially affect cardiovascular outcomes and mortality in the NH setting.[72-74,78] Sulfonylureas increase the risk of acute myocardial infarction and stroke in younger adults.[79-81] Furthermore, a large randomized trial showed an increased the risk of heart failure with saxagliptin (a DPP4I).[82] While the uptake of glucagon-like peptide-1 receptor

(GLP-1) agonists has been slow in the nursing home [45], these drugs share aspects of their mechanism of action with DPP4Is and appear to reduce cardiovascular risks.[83] However, studies that directly compare cardiovascular outcomes for DPP4I and SU users are scarce.[84,85] Vulnerable older adults are particularly susceptible to adverse drug effects.[86]

In this study, we compared the effect of DPP4Is versus SUs on mortality, adverse glycemic events, and cardiovascular events among long-stay NH residents age 65 and older.

Methods

Data Sources and Subjects

Data for this retrospective cohort study came from fee-for-service Medicare Parts A (inpatient), B (outpatient), and Part D (prescription drug) claims; the Online Survey Certification and Reporting System (OSCAR), which provides facility-level information on NH characteristics, staffing, and quality indicators; and the Minimum Data Set (MDS) version 2.0, which comprises assessments made on nearly all nursing home residents in the U.S. MDS assessments occur a minimum of every 3 months, and more often for residents with a major recent change in clinical status.[87]

The study population comprised U.S. nursing home residents aged 65 and older who initiated a DPP4I or SU between January 1, 2008 and September 30, 2010, who resided in a nursing home for at least the preceding three months (Figure 2.1). Data from January 1, 2007 to December 31, 2007 was available to ascertain prior glucose-lowering treatment use.

We first identified 166,889 Medicare beneficiaries with at least one NH stay and a dispensing of a DPP4I or SU between 2008 and 2010. We excluded prior recipients of a DPP4I or SU (n=51,448) and individuals who were <65 years old (n=19,149). We also excluded recipients of a glucose-lowering treatment other than metformin within six months of initiation (n=55,409) with the aim of reducing confounding by prior glucose-lowering treatment use. Use of prior glucose-lowering treatments is a high-dimensional space consisting of numerous treatment combinations because NH residents are often treated in ways that inexplicably deviate from clinical guidelines.[88] Since the number of subjects with many of the treatment patterns was often too small to allow estimation of the association between initiation of DPP4Is versus SUs within each treatment pattern subgroup, we instead restricted the sample. Other exclusions were persons discharged from the NH before DPP4I or SU initiation (n=24,466), in the NH for <90 days (n=6,844) and not continuously enrolled in Medicare during the study period or had no Part D claims prior to treatment initiation, and residents who were enrolled in a Medicare Advantage (health maintenance organization) plan at any point during this period (n=349). Finally, we also excluded residents with missing covariate information (n=582), and residents with very poor prognosis at baseline (cancer, n=544; hospice, n=187; comatose, n=10; or fully paralyzed, n=16),[57] Analyses of these study data received expedited review from the Brown University Institutional Review Board.

Measures

Our exposures of interest were new use of DPP4Is (saxagliptin, sitagliptin) or SUs (glimepiride, glipizide, glyburide) in the NH setting.[89] We defined this as a Part D claim

after six months of no glucose-lowering treatment dispensings with the exception of metformin. Metformin was permitted because it is generally the first-line T2DM treatment.[40,90] Residents were not required to already be on metformin because prior literature has demonstrated that many residents are managed on second-line agent monotherapy (without metformin), perhaps due to a contraindication to metformin.[45,88] Medicare Part D covers at least 81% of nursing home residents and in most cases is the sole source of prescription drug coverage.[49]

Our outcomes were all-cause mortality, adverse glycemic events, and MACEs. All of our non-mortality outcomes were defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes on a Part A inpatient hospital claim or a Part B emergency department (ED) claim, though inclusion of ED visits contributed only a small number of additional cases. Adverse glycemic events included hypoglycemia (ICD-9-CM codes 251.0X, 251.1X, or 251.2X; algorithm positive predictive value [PPV], 89%) and hyperglycemia (ICD-9-CM codes 250.02, 250.03, 250.1, 250.2, 250.3; PPV unavailable).[29] The MACE events included acute myocardial infarction (ICD-9-CM code 410.X; PPV, 67-97%)[91-93], stroke (including ischemic stroke [ICD-9-CM codes 433.X1, 434.X excluding 434.X0, or 436], intracerebral hemorrhage [ICD-9-CM code 431], and subarachnoid hemorrhage [ICD-9-CM code 430], but excluded traumatic brain injury [ICD-9-CM codes 800 to 804 and 850 to 854]; PPV, 97% [94]), and heart failure [402.X1, 404.X1, 404.X3, or 428.X; PPV, 90%][95]. We considered each outcome individually. We also included a MACE plus HF composite for the cardiovascular outcomes. We chose a 90-day outcome period because it is long enough to be clinically meaningful, but short enough that many of these highly vulnerable residents

have not yet died, a highly prevalent competing outcome which complicates interpretation of longer-term outcomes in the NH setting. We also examined outcomes at 180 days of follow-up to better understand the longer-term effects of prescribing DPP4Is over SUs. We identified death using the Medicare enrollment file to use it for censoring in the primary analysis, and explore how death might act as a competing risk for our outcomes in sensitivity analyses. Study subjects were censored at the first occurrence of the primary outcomes, end of the study period (December 30, 2010), death, or disenrollment from Medicare.

Information on chronic conditions and characteristics of NH residents were obtained from Medicare Part A and MDS 2.0 data, which has demonstrated reliability[96] and validity[97,98] for assessing the clinical status of NH residents. The MDS 2.0 is also provided data on other patient characteristics including pre-treatment physical functional[55] and cognitive status[56,99], geriatric syndromes, nutrition, social characteristics, care preferences, and proxies for frailty like the Changes in Health, End-stage Disease, Signs, and Symptoms Scale (CHESS) score.[57,100]

We used the validated OSCAR dataset to evaluate a variety of nursing home facility characteristics such as staffing, resident mix and quality indicators.[52]

Analyses

We used propensity score matching methods to identify a subset of SU exposed residents who were comparable, on average, with DPP4I initiators on a range of baseline risk factors. Analogous to an intention-to-treat framework, we defined subjects as new users based on an observed dispensing of a DPP4I or SU.[101]

We estimated the propensity score via a logistic regression model that used 198 covariates to predict use of DPP4Is over SUs. Variables included sociodemographic characteristics, chronic medical conditions, baseline medication use, prior hospitalization history, baseline functional and cognitive status, geriatric syndromes, nutrition and fluid status, and nursing home characteristics (Table 2.1). To evaluate whether our logistic propensity score estimation model might be misspecified and result in inaccurate estimations of the propensity score, we conducted a sensitivity analysis where we estimated the propensity score using generalized boosted regression that attempts to optimize balance on the covariates.[102]

To match DPP4I users with SU users who had similar propensity scores, we first discarded subjects in the top and bottom 1% of the propensity score distribution so as to exclude areas of non-overlap where unmeasured differences in risk are more likely to exist.[103] We then applied a 1:1 greedy (nearest neighbor) 5-to-1 digit matching algorithm without replacement.[104,105] We evaluated the quality of resulting matches by comparing standardized differences between groups for each covariate in our model, and by using t-tests to assess differences in the distribution of propensity scores.[106,107] Our propensity matching yielded good covariate balance, and our primary follow-up period was 90 days, so we did not further adjust for baseline covariates in our models.

We used Cox proportional hazards models with robust standard errors to determine the impact of DPP4I versus SU use on time to outcomes.[108] The robust sandwich estimator was used to account for the clustering within propensity score-matched pairs and forego the need to assume independence of the observations.[108] In sensitivity analyses we used the method of Fine and Gray (similar to Cox regression) to

evaluate the impact of DPP4I versus SU use on time to the outcomes while accounting for the competing risk of death.[109] At the end of each follow-up period, subjects were classified as alive without one of the outcomes of interest, having had outcome documented on a hospital or ED claim in that period, or having died without evidence of an outcome event.

To help determine whether exclusion of individuals with missing data on any covariate may have influenced our results, we assumed the information was missing at random and performed multiple imputation to impute the missing covariate information in a sensitivity analysis.[110] To understand the impact of model misspecification, we also applied logistic regression in a sensitivity analysis. Lastly, since metformin is often the preferred first-line medication used to treat type 2 diabetes mellitus, we restricted our study cohort and reanalyzed the data in this subset.

Results

Our initial cohort included 1064 new DPP4I users and 6,821 new SU users. Before matching, new DPP4I users were more likely to have a high medication burden, have used other glucose-lowering treatments, and to have received clopidogrel, statins, and fibrates in the prior 12 months than new SU users (Tables 2.1 and 2.2). Additionally, DPP4I users were more likely to have a prior hospitalization for heart failure, hypoglycemia, or hyperglycemia, but less likely to have a do not resuscitate order.

Propensity score matching yielded 1,008 new DPP4I users and an equal number of SU users (Table 2.2). The mean (SD) age was 81 (8) years. Matching balanced

covariates closely,[106] with all but 2 variables having an absolute standardized mean differences of 0.06 or less (Table 2.1).

DPP4I users appeared less likely than SU users to experience a hypoglycemic event (Table 2.3). In the first 90 days after initiation, the risk of hypoglycemia was 0.89 (95%CI, 0.35-2.32) times lower in DPP4I users than in those receiving SUs (Table 2.4 and Figure 2.1). Results for hypoglycemia were similar at 180 days post-initiation (HR=0.79, 95%CI 0.40-1.56)(Figure 2.2). The risk of hyperglycemia was similar across treatment groups at all follow-up times (Tables 2.3 and 2.4; Figure 2.3).

DPP4I users were less likely than SU users to have a hospitalization or ED visit for stroke (Table 2.4). At 90 days after treatment initiation, the risk of a stroke hospitalization or ED visit was 0.60 (95%CI 0.14-2.52) times lower in DPP4 users than in SU users, though this difference was not statistically significant (Table 2.4 and Figure 2.4). This difference was observed at 180 days (HR=0.39, 95%CI 0.14-1.08) after treatment initiation as well. The risk of AMI (Figure 2.5), heart failure (Figure 2.6), and MACE plus heart failure (Figure 2.7) was similar for DPP4I and SU users across all time points (Tables 2.3 and 2.4).

The main results were generally similar when estimating the propensity score using generalized boosted regression (Table 2.5), implementing multiple imputation of missing baseline covariate information (Table 2.6), employing Fine and Gray models to account for the competing risk of death (Table 2.7), using logistic regression models (Table 2.8), and restricting to metformin users (Table 2.9). Of note, the estimates from the generalized boosted regression propensity score-matched cohort suggested a relative reduction in mortality, and possibly heart failure, events associated with DPP4I use.

Discussion

In this large national cohort study of NH residents, we observed a decreased risk of hospitalization and ED visits for hypoglycemic and stroke events among new users of DPP4Is compared to new users of sulfonylureas. We did not observe any difference in the risk of hyperglycemia, AMI, or heart failure between the two treatment groups. To our knowledge, this is the first study to examine the comparative safety of DPP4Is and SUs for frail older adults in the NH setting.

Although our results differ from other observational studies, our population is distinct, consisting of old-old, frail, and multimorbid NH residents. Consistent with a large nationwide study that used Taiwan's National Health Insurance Research Database to examine the comparative effectiveness of DPP4Is versus SUs as add-on to metformin among adults (mean age of 58) in any care setting, we found that DPP4I users had a lower risk of hypoglycemic and stroke events compared with SU users, but no differential risk of AMI or heart failure events.[84] However, unlike that study, we did not find that DPP4Is were associated with a lower risk of all-cause death and MACE plus heart failure events. Our results also contrasted a pooled subanalysis of younger patients in three studies (mean ages of study populations were 55, 57, and 57) comparing sitagliptin to sulfonylureas, which found a lower incidence and risk of MACE events among sitagliptin versus SU users.[111] Lastly, our study contrasts another using the UK Clinical Practice Research Datalink (CPRD; mean study population age of 60 years), which suggested that DPP4I plus metformin use was associated with a reduction in all-cause death and MACE events compared to sulfonylurea plus metformin use.[78] Differences in the duration of

follow-up and censoring definitions between all of the aforementioned studies is another potential explanation for some of the inconsistent findings.

Regarding the outcome of heart failure specifically, the SAVOR-TIMI 53 trial found an unanticipated association between DPP4I (saxagliptin) use versus placebo and hospitalization for heart failure.[82] Other randomized trials have not detected a difference in the risk of heart failure between DPP4I and placebo users.[112,113] In addition, two large observational studies—the aforementioned study using Taiwan data[84] and another using data from 18 health insurers and health system data partners in the U.S. Food and Drug Administration Mini-Sentinel program—did not find a higher risk of hospitalization for heart failure in users of saxagliptin or sitagliptin compared with sulfonylureas.[85] The findings from our older NH population provide analogous evidence to suggest the absence of an association between DPP4I versus SU use and heart failure.

Our study has several limitations. Because it is an observational study without randomization of treatments, we cannot rule out the possibility of residual confounding by indication. In particular, our study may have benefited from laboratory information on hemoglobin A1c and other measures of glycemic control. However, several factors support the robustness of our findings. We obtained good balance on a wide array of baseline covariates across treatment groups. We obtain consistent results using several alternate analytic approaches. Moreover, DPP4Is and SUs have a similar place in therapy for treatment of T2DM, which reduces the likelihood of confounding by indication. Another important consideration is the size of our final study population and precision of our estimates. Since our outcomes were uncommon, DPP4I use not yet very common during the study period, and post-match sample size modest, our estimates are often

imprecise. These circumstances mandate a more nuanced interpretation of the range of plausible effect estimates, rather than simply seeking to reject or fail to reject the null hypothesis using p-values (i.e., rather than assessing whether estimates are or are not statistically significant).[114,115] In addition to contributing to the imprecision of our estimates through a reduction in sample size, restriction on glucose-lowering treatment history may have reduced the generalizability of our findings. Future work should seek to confirm the findings by adding more recent data so as to increase the number of new DPP4I users available for matching and comparison to SU users in the NH setting. Further, the small number of cases for each outcome did not permit subgroup analyses to examine modification of the DPP4I versus SU effect, so addition of more data would also help to address this limitation. Lastly, there may be under-ascertainment of outcomes. It is likely that many cases of hypoglycemia and hyperglycemia will not require a hospitalization or ED visit because the NH facility is capable of appropriately managing their occurrence. However, provided that the misclassification is non-differential by treatment group and the specificity of claims-based hypoglycemia and hyperglycemia measures is high, relative effect measures are unlikely to be biased.[116] If providers were more attentive to the clinical manifestations of hypoglycemia among sulfonylurea users due to the established relationship, this differential ascertainment may have biased the estimates.

Our study has several strengths. We adjusted for many potential confounders, and had many covariates that are not available in administrative and claims-only databases. Our results were robust under several different analytic approaches, and generally were consistent with those of prior studies in populations outside the NH. Although our

estimates were not as precise as desired, they are some of the only estimates of treatment effects for this population and are likely to be some of the most exact. Our demographically, geographically, and clinically diverse population aids the generalizability of the findings to frail, older adults in long-term care—the most widely treated segment of the elderly population. This strength is particularly important given the systematic exclusion of older NH residents from clinical trials of treatments and the resulting paucity of evidence to guide treatment-decisions, despite the continued need and frequent use of medications in the NH. Nonetheless, our findings must be interpreted within the context of the aforementioned study limitations.

In summary, use of DPP4Is for T2DM among older NH residents may result in a lower risk of hypoglycemia and stroke compared to use of SUs, but was not associated with a differential risk of hyperglycemia, AMI, heart failure, or MACE plus heart failure. Additional studies are often needed to better understand the comparative safety and effectiveness of treatments in the NH setting, including the comparative effects of DPP4Is and SUs for adverse glycemic, cardiovascular, and mortality events. However, given the absence of prior clinical trials that include NH residents and the lack of any planned future ones, to the best of our knowledge, our study provides new critical evidence to guide treatment decisions for NH residents with T2DM. Future research examining DPP4I versus SU use in NH residents should examine outcomes like cognitive and physical functioning. Many NH residents, their families, caregivers, and clinicians value maintaining functioning and quality of life more than extending lifespan or minimizing traditional clinical adverse events, especially given the high competing risk of death in the NH setting.

Chapter 2 Tables

Table 2.1. Standardized differences between dipeptidyl peptidase-4 inhibitor and sulfonylurea users before and after propensity score matching.

			Original Value		Absolute Value	
#	Covariate	Label	Before Matching	After Matching	Before Matching	After Matching
1	carrybladdercont	Bladder incontinence	0.11	0.07	0.11	0.07
2	ppcat	Facility: % of other private pay clients	0.11	0.07	0.11	0.07
3	carrybipol	Bipolar disorder	0.02	0.06	0.02	0.06
4	owner	Facility: Class of ownership (for-profit, non-profit, government)	0.05	0.06	0.05	0.06
5	carrychessscore	Changes in Health, End-	0.06	0.06	0.06	0.06

		Stage Disease, and Signs and Symptoms Score (health instability)				
6	carryovrnghthosp	Number of overnight hospitalizations	0.08	0.06	0.08	0.06
7	hours	Facility: Staff hours per resident	0.09	0.06	0.09	0.06
8	carrycps	Cognitive status (Cognitive Performance Scale score)	0.11	0.06	0.11	0.06
9	carryedvisits	Number of emergency department visits	0.08	0.06	0.08	0.06
10	anypsychotictwelv	Antipsychotics	0.04	0.06	0.04	0.06

11	carrypressulcstage	Pressure ulcers, presence and stage	0.08	0.06	0.08	0.06
12	ichanypartabefore	Intracranial hemorrhage hospitalizatio n	0.05	0.06	0.05	0.06
13	anymoodtwelv	Mood stabilizing or anti-convulsant	0.08	0.06	0.08	0.06
14	anyaspirintwelv	Aspirin or antiplatelet	-0.03	0.05	0.03	0.05
15	carryadlchngninety	Change in ability to perform activities of daily living	0.03	0.05	0.03	0.05
16	carryhearing	Hearing performance	0.03	0.05	0.03	0.05
17	carrysocialengage	Social	0.10	0.05	0.10	0.05

		engagement				
18	carrymedsadlseat	Resisted taking medications, activities of daily living assistance, or eating	0.04	0.05	0.04	0.05
19	anylaopioidtwelv	Long-acting opioids	0.04	0.05	0.04	0.05
20	ichanypartbbefore	Intracranial hemorrhage emergency department visit	0.02	0.04	0.02	0.04
21	carrybehaviorsc	Problem behaviors present	-0.03	0.04	0.03	0.04
22	carrycogabilvary	Cognitive ability varies over time	0.09	0.04	0.09	0.04
23	carrybowelcont	Bowel	0.09	0.04	0.09	0.04

		incontinence				
24	dmrace	Race/ethnicity	0.10	0.04	0.10	0.04
25	caretransitions	Transitions in care setting	0.13	0.04	0.13	0.04
26	carrycommuniscale	Communicati on scale	0.10	0.04	0.10	0.04
27	edcat	Educational Attainment	0.07	0.04	0.07	0.04
28	carryvisionfourc	Vision performance	0.09	0.04	0.09	0.04
29	anydualopioidtwelv	Tramadol	0.05	0.03	0.05	0.03
30	fulldoc	Participation of medical director and/or other physician	0.06	0.03	0.06	0.03
31	anylamorphinetwelv	Long-acting morphine	0.04	0.03	0.04	0.03
32	carryreducesocial	Reduced social	0.01	0.03	0.01	0.03

		interaction				
33	yearoftx	Year of sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.15	0.03	0.15	0.03
34	prov1090	Facility: pharmacist full time equivalents	-0.02	0.03	0.02	0.03
35	carryparticipatefam	Family participation in resident's care	0.05	0.03	0.05	0.03
36	agecat	Age	0.12	0.03	0.12	0.03
37	carrypain	Pain presence and severity	0.07	0.03	0.07	0.03
38	hipfxanypartbbefore	Hip fracture emergency department visit	0.00	0.03	0.00	0.03

39	carrypvd	Peripheral vascular disease	0.03	0.02	0.03	0.02
40	carryresistinfxn	Antibiotic resistant infection	0.01	0.02	0.01	0.02
41	carrybehaviorchng	Behavior status change	0.09	0.02	0.09	0.02
42	hyperglyanypartbbefore	Hyperglycemia emergency department visit	0.10	0.02	0.10	0.02
43	carryhyperthy	Hyperthyroidism	0.03	0.02	0.03	0.02
44	carryRP14B	Dehydration/fluid status care plan implemented	0.07	0.02	0.07	0.02
45	bmicat	Body mass index	0.14	0.02	0.14	0.02
46	anyinsulinintermediatetw	Intermediate-acting insulin	0.06	0.02	0.06	0.02

	elv	6-12 months before initiation				
47	amianypartbbefore	Acute myocardial infarction emergency department visits	-0.01	0.02	0.01	0.02
48	respir	Facility: Percentage of residents receiving respiratory care	0.04	0.02	0.04	0.02
49	antiarrhythmicstwelv	Antiarrhythmics	-0.01	0.02	0.01	0.02
50	alterconsanypartabefore	Altered consciousness hospitalization	0.03	0.02	0.03	0.02
51	carrydiabetes	Diabetes mellitus	0.12	0.02	0.12	0.02

52	carrytasteproblem	Complains about the taste of many foods	0.06	0.02	0.06	0.02
53	anyinsulinshorttwelv	Short-acting insulin 6-12 months before initiation	0.14	0.02	0.14	0.02
54	carryhealthcomplns	Repetitive health complaints presence and frequency	0.03	0.02	0.03	0.02
55	carrylanguage2	Primary language spoken	0.05	0.02	0.05	0.02
56	carryostomy	Ostomy (bowel)	-0.05	0.02	0.05	0.02
57	anysteroidtwelv	Oral steroids	0.01	0.02	0.01	0.02
58	carryalcohol	Customary routine includes alcoholic beverages at	0.00	0.02	0.00	0.02

		least weekly				
59	bisphosphonatestwelv	Bisphosphonates	-0.01	0.02	0.01	0.02
60	carrydonothosp	Do not hospitalize advanced directive documented in the medical record	-0.06	0.02	0.06	0.02
61	psychact	Facility: Percentage of residents receiving psychoactive drugs	-0.01	0.02	0.01	0.02
62	dmsex	Female sex	-0.02	0.02	0.02	0.02
63	carryventilator	Ventilator or respirator	0.03	0.01	0.03	0.01
64	carryfeedrestrict	Feeding restrictions advanced directive	-0.05	0.01	0.05	0.01

		documented in the medical record				
65	alterconsanypartbbefore	Altered consciousness emergency department visit	0.02	0.01	0.02	0.01
66	carrynummeds	Number of medications	0.25	0.01	0.25	0.01
67	durationofpreindexnhstay	Duration of nursing home stay before sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.04	0.01	0.04	0.01
68	carryeatingperform	Eating performance	0.05	0.01	0.05	0.01
69	anyalphablockerstwelv	Alpha blockers	-0.04	0.01	0.04	0.01

70	anygabapregabtwelv	Gabapentin or pregabalin	0.08	0.01	0.08	0.01
71	carrycommchange	Change in ability to express, understand, or hear information	0.04	0.01	0.04	0.01
72	carryresponsibfm	Family member responsible for resident	0.00	0.01	0.00	0.01
73	carrytobacco	Customary routine includes use of tobacco at least daily	-0.02	0.01	0.02	0.01
74	carrytxdiet	Therapeutic diet	-0.02	0.01	0.02	0.01
75	carrycdiffinfxn	*Clostridium difficile* infection	0.03	0.01	0.03	0.01

76	painmgmt	Facility: Percentage of residents on a pharmacy pain management program	-0.03	0.01	0.03	0.01
77	carryfootinfxn	Foot infection	0.02	0.01	0.02	0.01
78	carryweightchange	Weight gain or loss of 3 or more pounds	-0.04	0.01	0.04	0.01
79	bedsores	Facility: Percentage of residents with bedsores	0.06	0.01	0.06	0.01
80	calcitonintwelv	Calcitonin	-0.03	0.01	0.03	0.01
81	carrydvt	Deep vein thrombosis	0.00	0.01	0.00	0.01
82	carryRP14A	Dehydration/fluid status resident assessment	0.06	0.01	0.06	0.01

		triggered				
83	carryhearingaidused	Hearing aid present and used	-0.02	0.00	0.02	0.00
84	anystatinstwelv	Statins	0.12	0.00	0.12	0.00
85	carrycatar	Cataracts	0.01	0.00	0.01	0.00
86	carryedema	Edema	-0.01	0.00	0.01	0.00
87	carrybonefracture	Pathological bone fracture	-0.02	0.00	0.02	0.00
88	hipfxanypartabefore	Hip fracture hospitalizations	0.02	0.00	0.02	0.00
89	carrydizziness	Dizziness/vertigo	-0.01	0.00	0.01	0.00
90	anyaglucosidaseinhibstwelv	Alpha-glucosidase inhibitors 6-12 months before initiation	0.05	0.00	0.05	0.00

91	anycalciumchnlblockerstwelv	Calcium channel blockers	0.03	0.00	0.03	0.00
92	anyfibratestwelv	Fibrates	0.11	0.00	0.11	0.00
93	carrynewmeds	Number of new medications	0.05	0.00	0.05	0.00
94	anyinsulinlongtwelv	Long-acting insulin 6-12 months before initiation	0.24	0.00	0.24	0.00
95	carryestabgoals	Established own goals	-0.02	0.00	0.02	0.00
96	carryplnweightprgm	On a planned weight change program	0.04	0.00	0.04	0.00
97	antidep	Facility: Percentage of residents receiving antidepressants	-0.05	0.00	0.05	0.00

98	anyksparingdiureticstwelv	Potassium-sparing diuretics	0.08	0.00	0.08	0.00
99	carrymacdegen	Macular degeneration	0.00	0.00	0.00	0.00
100	carrycutsortears	Skin tears or cuts (other than surgery)	-0.04	0.00	0.04	0.00
101	carryemphcopd	Emphysema/chronic obstructive pulmonary disease	0.03	0.00	0.03	0.00
102	anyezetimibetwelv	Ezetimibe	0.06	-0.01	0.06	0.01
103	carryvisualapp	Glasses, contact lenses, or magnifying glass used	-0.05	-0.01	0.05	0.01
104	carryhipfracture	Hip fracture	-0.01	-0.01	0.01	0.01
105	carryabnormlabs	Abnormal laboratory	0.10	-0.01	0.10	0.01

		values				
106	hyperglyanypartabefore	Hyperglycemia hospitalizations	0.09	-0.01	0.09	0.01
107	raloxifenetwelv	Raloxifene	0.01	-0.01	0.01	0.01
108	hfanypartbbefore	Heart failure emergency department visit	0.09	-0.01	0.09	0.01
109	anynonbenzohypnotwelv	Nonbenzodiazepine hypnotics	0.08	-0.01	0.08	0.01
110	carryrespinfxn	Respiratory infection	0.00	-0.01	0.00	0.01
111	carrypreventfootcr	Received preventative or protective foot care	0.02	-0.01	0.02	0.01
112	carrychewproblem	Chewing problems	-0.02	-0.01	0.02	0.01

113	anybileacidresinstwelv	Bile acid sequestrants	0.02	-0.01	0.02	0.01
114	anyarbstwelv	Angiotensin receptor blockers	0.11	-0.01	0.11	0.01
115	carryaphasia	Aphasia	-0.03	-0.01	0.03	0.01
116	rn100t	Facility: registered nurse full time equivalents per 100 beds	0.03	-0.01	0.03	0.01
117	carrymentaleval	Evaluation by a licensed mental specialist	0.04	-0.01	0.04	0.01
118	carrydiabretinopathy	Diabetic retinopathy	-0.01	-0.01	0.01	0.01
119	hfanypartabefore	Heart failure hospitalizations	0.12	-0.01	0.12	0.01
120	pt100t	Facility: physical	-0.03	-0.02	0.03	0.02

		therapy full time equivalents per 100 beds				
121	carrydialysis	Dialysis	0.02	-0.02	0.02	0.02
122	carryexercisepref	Prefers exercise or sports	-0.02	-0.02	0.02	0.02
123	carrydonotresus	Do not resuscitate advanced directive documented in the medical record	-0.12	-0.02	0.12	0.02
124	surv0690	Facility: medication error rate	-0.02	-0.02	0.02	0.02
125	carryrenaldx	Renal failure	0.03	-0.02	0.03	0.02
126	carryalzheimers	Alzheimer’s disease	-0.03	-0.02	0.03	0.02

127	acuindex2	Facility: acuity of residents (acuity index)	0.05	-0.02	0.05	0.02
128	carryuti	Urinary tract infection	0.06	-0.02	0.06	0.02
129	amianypartabefore	Acute myocardial infarction hospitalizations	0.01	-0.02	0.01	0.02
130	anythiazidediureticstwelv	Thiazide diuretics	0.06	-0.02	0.06	0.02
131	hypoglyanypartbbefore	Hypoglycemia emergency department visit	0.10	-0.02	0.10	0.02
132	carrydepression	Depression	0.00	-0.02	0.00	0.02
133	anyniacintwelv	Niacin medication	0.03	-0.02	0.03	0.02
134	anymetformintwelv	Metformin	0.17	-0.02	0.17	0.02

135	anywarfarintwelv	Warfarin	0.03	-0.02	0.03	0.02
136	anyglucagontwelv	Glucagon	0.10	-0.02	0.10	0.02
137	carryhearingaidnotused	Hearing aid present and not used regularly	-0.06	-0.02	0.06	0.02
138	antianx	Facility: Percentage of residents receiving antianxiety medications	0.02	-0.02	0.02	0.02
139	anyomega3fatwelv	Omega-3 fatty acid medication	0.08	-0.02	0.08	0.02
140	paymcaid	Facility: Percentage of residents covered by Medicaid insurance	0.06	-0.02	0.06	0.02
141	anydepressanttwelv	Antidepressan	0.08	-0.02	0.08	0.02

		t medications				
142	otherhtndrugstwelv	Miscellaneous antihypertensive medications	0.06	-0.02	0.06	0.02
143	carryanx	Anxiety disorder	-0.01	-0.02	0.01	0.02
144	carryhtn	Hypertension	-0.01	-0.02	0.01	0.02
145	cna100t	Facility: nurse aide full time equivalents per 100 beds	-0.02	-0.02	0.02	0.02
146	carrychurch	Customary routine includes usual attendance at church, temple, synagogue, or other place of worship	-0.05	-0.02	0.05	0.02
147	carryglaucoma	Glaucoma	0.05	-0.02	0.05	0.02

148	n_qol_def	Facility: count of quality-of-life deficiencies	0.03	-0.02	0.03	0.02
149	strokeanypartbbefore	Stroke emergency department visits	0.04	-0.02	0.04	0.02
150	carryfalloneight	History of falls	-0.04	-0.02	0.04	0.02
151	carrytwentfiveuneat	Leaves 25% or more of food uneaten at most meals	-0.02	-0.02	0.02	0.02
152	carrystroke	Stroke	0.01	-0.03	0.01	0.03
153	anymuscletwelv	Muscle relaxant medications	0.09	-0.03	0.09	0.03
154	carryparenteralfeed	Parenteral/intravenous feeding	0.05	-0.03	0.05	0.03

155	anyaceistwelv	Angiotensin-converting enzyme inhibitors	0.09	-0.03	0.09	0.03
156	carrysocialcontact	Customary routine includes daily contact with relatives or close friends	-0.05	-0.03	0.05	0.03
157	hypoglyanypartabefore	Hypoglycemia hospitalizations	0.11	-0.03	0.11	0.03
158	carryepilepsy	Seizure disorders	0.02	-0.03	0.02	0.03
159	carrymissinglimb	Missing limb or amputation	-0.03	-0.03	0.03	0.03
160	carrywoundinfxn	Wound infection	0.05	-0.03	0.05	0.03
161	anythiazolstwelv	Thiazolidinediones 6-12 months before	0.21	-0.03	0.21	0.03

		initiation				
162	carrydysrh	Cardiac dysrhythmias	0.00	-0.03	0.00	0.03
163	carrychf	Congestive heart failure	0.06	-0.03	0.06	0.03
164	carryRP12B	Nutrition status care plan implemented	0.09	-0.03	0.09	0.03
165	anyinsulinrapidtwelv	Rapid-acting insulin 6-12 months before initiation	0.23	-0.03	0.23	0.03
166	strokeanypartabefore	Stroke hospitalizatio n	0.03	-0.03	0.03	0.03
167	carryweightloss	Weight loss of 5% or more in the last 30 days or 10% or more in the last 180 days	0.02	-0.04	0.02	0.04

168	carrysidevisprob	Side vision problems or decreased peripheral vision	-0.02	-0.04	0.02	0.04
169	carrychronicprobflare	Any acute episode or a flare-up of a recurrent or chronic health problem	0.08	-0.04	0.08	0.04
170	carryothercvd	Other cardiovascular disease	0.00	-0.04	0.00	0.04
171	protonpumpitwelv	Proton pump inhibitors	0.13	-0.04	0.13	0.04
172	carryRP12A	Nutritional status resident assessment triggered	0.07	-0.04	0.07	0.04
173	carryhallucintns	Hallucinations	-0.02	-0.04	0.02	0.04
174	carrytoothloss	Some or all natural teeth	0.04	-0.04	0.04	0.04

		were lost				
175	anybetablockerstwelv	Beta blockers	0.11	-0.04	0.11	0.04
176	multifac	Facility: part of a nursing home chain	-0.03	-0.04	0.03	0.04
177	carrydem	Dementia other than Alzheimer's disease	-0.04	-0.04	0.04	0.04
178	carryselfinitact	At ease doing self-initiated activities	-0.06	-0.04	0.06	0.04
179	carryRP01A	Delirium resident assessment triggered	-0.07	-0.04	0.07	0.04
180	carryadl	Morris activities of daily living scale (0-28 point)	0.00	-0.05	0.00	0.05

181	anyanxietytwelv	Anti-anxiety medication	0.02	-0.05	0.02	0.05
182	carryosteoporosis	Osteoporosis	0.00	-0.05	0.00	0.05
183	restrain	Facility: Percentage of residents physically restrained	0.04	-0.05	0.04	0.05
184	carryhypotn	Hypotension	-0.03	-0.05	0.03	0.05
185	carrydietsupplement	Dietary supplement between meals	0.02	-0.05	0.02	0.05
186	carrymdvisits	Number of physician visits	0.04	-0.05	0.04	0.05
187	carryhypothy	Hypothyroidism	0.02	-0.05	0.02	0.05
188	carrymdorderchngs	Number of orders changed by	0.11	-0.05	0.11	0.05

		physician				
189	carryarthritis	Arthritis	0.01	-0.05	0.01	0.05
190	anyclopidogreltwelv	Clopidogrel	0.15	-0.05	0.15	0.05
191	prov3330	Facility: Off-site pharmacy	0.04	-0.05	0.04	0.05
192	prov1535	Facility: Organized family group	0.04	-0.05	0.04	0.05
193	carrymechanaltdiet	Mechanically altered diet	-0.01	-0.05	0.01	0.05
194	carryanemia	Anemia	0.04	-0.05	0.04	0.05
195	carryivmeds	Any intravenous medications	0.05	-0.06	0.05	0.06
196	carryskinutrition	Nutrition or hydration intervention to manage skin problems	0.06	-0.06	0.06	0.06
197	carryarterhrtdz	Arterioscleroti	0.07	-0.06	0.07	0.06

		c heart disease				
198	comorbidity_burden	Number of comorbidities	0.05	-0.06	0.05	0.06

Table 2.2. Characteristics of dipeptidyl peptidase-4 inhibitor and sulfonylurea users before and after propensity score matching.

	n (%)			
	Before matching (original cohort)		After matching (analytic cohort)	
	DPP4I users	SU users	DPP4I users	SU users
Characteristic	**(N=1,064)**	**(N=6,821)**	**(N=1,008)**	**(N=1,008)**
Age, mean (SD) years	80.4 (8.1)	81.4 (8.2)	80.5 (8.1)	80.6 (8.1)
Female sex	766 (72.0)	4,816 (70.6)	725 (71.9)	732 (72.6)
Race				
Caucasian	773 (72.7)	5,164 (75.7)	742 (73.6)	726 (72.0)
African-American	165 (15.5)	1,066 (15.6)	159 (15.8)	167 (16.6)
Other	126 (11.8)	591 (8.7)	107 (10.6)	115 (11.4)
Chronic conditions				
Renal disease	115 (10.8)	639 (9.4)	103 (10.2)	108 (10.7)
Peripheral vascular disease	195 (18.3)	1,150 (16.9)	180 (17.9)	171 (17.0)
Diabetic retinopathy	19 (1.8)	132 (1.9)	18 (1.8)	20 (2.0)
Heart failure	338 (31.8)	1,934 (28.4)	315 (31.3)	331 (32.8)

Ischemic heart disease	198 (18.6)	1,039 (15.2)	177 (17.6)	204 (20.2)
Depression	596 (56.0)	3,818 (56.0)	566 (56.2)	575 (57.0)
Chronic Obstructive Pulmonary Disease	230 (21.6)	1,365 (20.0)	215 (21.3)	217 (21.5)
Hypertension	812 (76.3)	5,261 (77.1)	774 (76.8)	783 (77.7)
Hip fracture	17 (1.6)	121 (1.8)	17 (1.7)	18 (1.8)
Number of comorbidities, median, (IQR)	6 (4-8)	5 (4-7)	6 (4-7)	6 (4-8)
ADL score, mean (SD)*	15.8 (7.6)	15.8 (7.7)	15.8 (7.6)	16.1 (7.4)
CPS score, mean (SD)*	2.4 (1.6)	2.6 (1.6)	2.5 (1.6)	2.5 (1.6)
CHESS score, mean (SD)	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)
Number of medications prior to treatment initiation, mean (SD)	14.1 (5.2)	12.7 (4.8)	13.9 (5.0)	13.8 (5.0)
Medication use*				
Metformin	401 (37.7)	1,992 (29.2)	370 (36.7)	379 (37.6)
Statins	487 (45.8)	2,680 (39.3)	450 (44.6)	448 (44.4)
Clopidogrel	214 (20.1)	959 (14.1)	194 (19.3)	215 (21.3)
Warfarin	169 (15.9)	1,015 (14.9)	161 (16.0)	168 (16.7)
Antipsychotics	330 (31.0)	2,000 (29.3)	313 (31.1)	279 (27.7)

Steroids	138 (13.0)	857 (12.6)	128 (12.7)	122 (12.1)
Angiotensin-converting enzyme inhibitors	455 (42.8)	2,578 (37.8)	423 (42.0)	437 (43.4)
Angiotensin receptor blockers	169 (15.9)	758 (11.1)	146 (14.5)	151 (15.0)
Beta blockers	543 (51.0)	3,063 (44.9)	507 (50.3)	528 (52.4)
Length of nursing home stay before treatment initiation, median (IQR) days	647 (296-1,305)	589 (273-1,181)	649 (295-1,296)	640 (294-1,225)
Any physician visits in prior two weeks	639 (60.0)	3,948 (57.9)	595 (59.0)	589 (58.4)
Number of physician order changes in prior two weeks, mean (SD)	2.1 (2.0)	1.9 (1.8)	2.0 (1.9)	2.1 (1.9)
Any overnight hospitalizations in prior 90 days	335 (31.5)	2,011 (29.5)	316 (31.4)	319 (31.7)
Any ED visits in prior 90 days	80 (7.5)	541 (7.9)	76 (7.5)	73 (7.2)
Nursing Home Facility Characteristics				
Ownership				
For profit	771 (72.5)	4,835 (70.9)	735 (72.9)	758 (75.2)
Non-profit	231 (21.7)	1,514 (22.2)	215 (21.3)	189 (18.8)
Government	62 (5.8)	472 (6.9)	58 (5.8)	61 (6.1)
Quality indicators				
% of residents restrained, median (IQR)	1.9 (0.0-5.1)	1.8 (0.0-4.7)	2.0 (0.0-5.1)	1.9 (0.0-5.1)

No. of quality-of-life deficiencies, mean (SD)	4.1 (6.1)	3.8 (6.9)	4.0 (6.1)	4.2 (10.0)
% of residents with pressure sores, mean (SD)	6.9 (4.3)	6.6 (4.2)	6.8 (4.3)	6.8 (4.5)
Staffing				
Direct care hours/resident/day, mean (SD)	2.9 (1.2)	2.9 (1.3)	2.8 (1.2)	2.9 (1.2)

* ADL status was measured by the Morris 28-point ADL score, where higher values indicate greater dependency in ADLs. Cognitive status was measured by Cognitive Performance Scale (CPS), where higher values indicate greater cognitive impairment.

CHESS stands for Changes in Health, End-Stage Disease, Signs, and Symptoms.

Table 2.3. Outcome Events, Person-Years, and Rates Stratified by Dipeptidyl Peptidase-4 Inhibitors and Sulfonylurea Use.

			Unmatched			Matched		
Follow-up Period	**Outcome**	**Treatment**	**Events**	**Person-Years**	**Rate***	**Events**	**Person-Years**	**Rate***
90 days	Hypoglycemia	DPP4I	9	233.7	38.5	8	230.7	34.7
		SU	54	1,540.9	35.0	9	232.3	38.7
	Hyperglycemia	DPP4I	4	234.3	17.1	4	231.2	17.3
		SU	36	1,542.5	23.3	4	232.8	17.2
	Stroke	DPP4I	3	234.5	12.8	3	231.4	13.0
		SU	30	1,534.0	19.6	5	232.6	21.5
	Acute Myocardial Infarction	DPP4I	10	234.0	42.7	10	230.9	43.3
		SU	48	1,542.3	31.1	10	232.5	43.0
	Heart Failure	DPP4I	44	230.7	190.7	43	227.7	188.9
		SU	225	1,528.1	147.2	33	230.7	143.0
	Major Adverse	DPP4I	50	236.4	211.5	49	227.3	215.6

	Cardiovascular Events + Heart Failure	SU	264	1,541.7	171.2	42	230.2	182.5
	Death	DPP4I	159	244.1	651.4	147	231.4	635.3
		SU	875	1,571.5	556.8	133	233.1	570.6
180 days	Hypoglycemia	DPP4I	16	432.6	37.0	15	427.2	35.1
		SU	105	2,877.0	36.5	19	429.2	44.3
	Hyperglycemia	DPP4I	10	433.5	23.1	10	428.1	23.4
		SU	76	2,881.7	26.4	8	430.8	18.6
	Stroke	DPP4I	6	434.6	13.8	5	429.2	11.7
		SU	63	2,884.5	21.8	13	430.7	30.2
	Acute Myocardial Infarction	DPP4I	13	433.9	30.0	13	428.4	30.4
		SU	76	2,884.5	26.3	14	430.6	32.5
	Heart Failure	DPP4I	78	424.9	183.6	77	419.7	183.5
		SU	399	2,839.1	140.5	62	424.9	145.9
	Major Adverse	DPP4I	87	428.5	203.0	85	423.2	200.9

	Cardiovascular Events + Heart Failure	SU	473	2,841.8	166.4	76	423.3	179.5
	Death	DPP4I	290	451.4	642.5	266	429.2	619.8
		SU	1,640	2,941.7	557.5	268	432.0	620.4

*Per 1,000 person-years of follow-up.

Table 2.4. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	90 days	1.10 (0.54-2.23)	0.89 (0.35-2.32)
	180 days	1.01 (0.60-1.72)	0.79 (0.41-1.54)
Hyperglycemia	90 days	0.73 (0.26-2.06)	1.02 (0.25-4.07)
	180 days	0.88 (0.45-1.69)	1.26 (0.50-3.20)
Stroke	90 days	0.66 (0.20-2.16)	0.60 (0.14-2.52)
	180 days	0.63 (0.27-1.46)	0.39 (0.14-1.08)
Acute Myocardial Infarction	90 days	1.38 (0.70-2.72)	1.01 (0.42-2.42)
	180 days	1.14 (0.63-2.05)	0.94 (0.44-1.99)
Heart Failure	90 days	1.30 (0.94-1.79)	1.32 (0.84-2.07)
	180 days	1.31 (1.02-1.66)	1.26 (0.90-1.76)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.25 (0.93-1.70)	1.18 (0.79-1.77)
	180 days	1.23 (0.98-1.54)	1.13 (0.83-1.54)
Death	90 days	1.17 (0.99-1.39)	1.12 (0.88-1.41)
	180 days	1.15 (1.02-1.31)	1.00 (0.84-1.19)

Table 2.5. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Using Generalized Boosted Regression to Estimate the Propensity Score.

Outcome	Follow-up	Hazard Ratio (95% Confidence Interval)
Hypoglycemia	90 days	0.79 (0.31-2.00)
	180 days	0.98 (0.48-2.00)
Hyperglycemia	90 days	0.49 (0.17-1.44)
	180 days	0.70 (0.31-1.57)
Stroke	90 days	0.50 (0.05-5.47)
	180 days	0.65 (0.18-2.30)
Acute Myocardial Infarction	90 days	1.13 (0.41-3.12)
	180 days	0.75 (0.33-1.72)
Heart Failure	90 days	0.92 (0.59-1.44)
	180 days	0.89 (0.64-1.25)
Major Adverse Cardiovascular Events + Heart Failure	90 days	0.97 (0.63-1.48)
	180 days	0.89 (0.65-1.22)
Death	90 days	0.89 (0.70-1.13)
	180 days	0.83 (0.70-0.99)

Footnote: Since misspecification of the propensity score estimation model is a possibility that can influence the results of our study, we employed generalized boosted regression as an alternative propensity score estimation approach. There were 895 new SU users

matched to 895 new DPP4I users. The distribution of propensity scores was nearly identical between the matched groups (P=0.82); the mean (SD) was 0.19 (0.07) in both the SU and DPP4I users.

Table 2.6. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Using Multiple Imputation of Missing Pretreatment Covariate Information.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	90 days	0.95 (0.45-1.99)	0.72 (0.25-2.05)
	180 days	0.97 (0.58-1.64)	0.75 (0.37-1.49)
Hyperglycemia	90 days	0.99 (0.42-2.34)	0.82 (0.25-2.68)
	180 days	1.04 (0.58-1.86)	0.82 (0.37-1.82)
Stroke	90 days	0.64 (0.20-2.11)	0.50 (0.10-2.43)
	180 days	0.62 (0.27-1.43)	0.51 (0.16-1.58)
Acute Myocardial Infarction	90 days	1.30 (0.65-2.60)	1.08 (0.32-3.64)
	180 days	1.14 (0.64-2.03)	1.05 (0.40-2.79)
Heart Failure	90 days	1.39 (1.02-1.89)	1.35 (0.70-2.62)
	180 days	1.37 (1.08-1.73)	1.29 (0.85-1.98)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.33 (0.99-1.78)	1.21 (0.71-2.07)
	180 days	1.27 (1.02-1.580	1.17 (0.81-1.70)
Death	90 days	1.14 (0.96-1.35)	1.11 (0.86-1.43)
	180 days	1.12 (0.99-1.27)	1.06 (0.86-1.30)

Footnote: We were concerned about the sample size reduction due to missing pretreatment covariate information. We were also concerned that pretreatment covariate

information might be missing for a reason related to the outcomes we studied. Therefore, we used multiple imputation to impute the missing information for covariates that were used to estimate the propensity score. No outcome information was imputed. We assumed that the covariate information was missing at random. We used the fully conditional specification method (also known as iterative chained equations) with the discriminant function and logistic regression to impute the missing values because many covariates must only take on specific values. We multiply imputed 10 datasets. No auxiliary covariates were included in the imputation model, but all covariates used in the propensity score estimation model were included. Covariate information was missing for 111 covariates. The covariates with the greatest proportion of missing values were the number of quality of life deficiencies in the nursing home (n=213, 2.5%), the highest educational level attained by the resident (n=171, 2.0%), whether care was needed for fluid maintenance or dehydration (n=153, 1.8%), and the primary language used by the resident (n=101, 1.2%). All but 11 covariates had a proportion of values missing that was $\leq$0.005 (0.5% missing). To obtain the propensity score-matched estimates, we followed our primary analytic approach and performed the propensity score estimation and matching in each multiply imputed complete dataset. We then estimated the outcome model in each imputed dataset, and pooled the parameter estimates across the datasets using the formulas previously developed by Rubin.

Table 2.7. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Adverse Glycemic and Cardiovascular Outcomes Using Fine and Gray Models for the Competing Risk of Death.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	90 days	1.17 (0.56-2.19)	0.89 (0.33-2.32)
	180 days	1.09 (0.64-1.75)	0.79 (0.39-1.55)
Hyperglycemia	90 days	0.99 (0.38-2.16)	1.00 (0.24-4.23)
	180 days	1.06 (0.56-1.83)	1.25 (0.49-3.28)
Stroke	90 days	0.62 (0.15-1.74)	0.60 (0.12-2.44)
	180 days	0.60 (0.23-1.28)	0.38 (0.12-1.02)
Acute Myocardial Infarction	90 days	1.34 (0.64-2.53)	1.00 (0.41-2.44)
	180 days	1.18 (0.64-2.02)	0.93 (0.43-1.99)
Heart Failure	90 days	1.36 (0.98-1.83)	1.31 (0.84-2.08)
	180 days	1.36 (1.07-1.71)	1.25 (0.90-1.75)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.31 (0.97-1.74)	1.17 (0.78-1.78)
	180 days	1.28 (1.02-1.59)	1.13 (0.83-1.54)

Footnote: Death is common in the nursing home setting and can preclude the observation of other events like adverse glycemic and cardiovascular outcomes. This creates two potential problems when using the Cox proportional hazards regression model. First, the independent censoring assumption that the future risk of those whose follow-up has

ended can be represented by nursing home residents who are followed longer. Such an assumption may be too bold for frail older individuals in the nursing home setting. Second, the Cox proportional hazards regression models attempt to project forward the experience of a censored nursing home resident by representing their experience with those residents who were followed longer. To extrapolate to a setting where death is not possible would be to project to a new population or the ability to extend lives, which alters the underlying conditions of the study. Therefore, we can acknowledge death as another possible outcome and end follow-up for other outcomes rather than attempt to project experience beyond nursing home residents' lifetimes. Since exposure to dipeptidyl peptidase-4 inhibitors versus sulfonylureas might be related to unmeasured confounding covariates that increase the risk of death, we were interested in examining outcomes on the cumulative incidence scale. To do so, we employed Fine and Gray regressions. These regressions adapt the essence of the Cox proportional hazards model to the cumulative incidence formulation by modeling a different kind of rate function. The Fine and Gray counts nursing home residents who die in the denominator of the rate. In doing so, the model acknowledges that individuals who succumb to a competing risk (like death) will not develop the event of interest and more importantly, does not require extrapolation to a setting where death is not possible.

Table 2.8. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Using Logistic Regression.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	90 days	1.17 (0.59-2.30)	0.89 (0.34-2.31)
	180 days	1.09 (0.66-1.80)	0.79 (0.40-1.56)
Hyperglycemia	90 days	0.99 (0.42-2.34)	1.00 (0.25-4.01)
	180 days	1.06 (0.59-1.91)	1.25 (0.49-3.19)
Stroke	90 days	0.62 (0.19-2.03)	0.60 (0.14-2.51)
	180 days	0.60 (0.26-1.39)	0.38 (0.14-1.07)
Acute Myocardial Infarction	90 days	1.34 (0.68-2.66)	1.00 (0.41-2.41)
	180 days	1.18 (0.67-2.10)	0.93 (0.43-1.98)
Heart Failure	90 days	1.36 (0.99-1.87)	1.32 (0.83-2.09)
	180 days	1.38 (1.08-1.75)	1.26 (0.89-1.78)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.31 (0.97-1.77)	1.18 (0.77-1.79)
	180 days	1.28 (1.02-1.62)	1.13 (0.82-1.56)
Death	90 days	1.19 (0.99-1.43)	1.12 (0.87-1.45)
	180 days	1.18 (1.02-1.37)	0.99 (0.81-1.21)

Footnote: When the follow-up period is short and the outcome is rare, estimates from logistic regression models approximate those of Cox proportional hazards models. The

estimates from logistic and Cox models diverge over long follow-up periods. Since we examined a longer term follow-up period of 180 days, we estimated logistic regression models for comparison to the primary results from Cox proportional hazards regression models.

Table 2.9. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Mortality, Adverse Glycemic, and Adverse Cardiovascular Outcomes Restricting to Prior Metformin Users Only.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Hypoglycemia	90 days	0.76 (0.23-2.56)	0.78 (0.22-2.74)
	180 days	0.52 (0.16-1.70)	0.78 (0.22-2.74)
Hyperglycemia	90 days	1.20 (0.26-5.54)	1.05 (0.15-7.37)
	180 days	0.96 (0.28-3.28)	1.06 (0.22-5.24)
Stroke	90 days	1.79 (0.36-8.85)	1.05 (0.15-7.28)
	180 days	1.67 (0.55-5.12)	1.06 (0.27-4.22)
Acute Myocardial Infarction	90 days	1.60 (0.44-5.81)	1.02 (0.21-5.03)
	180 days	1.44 (0.48-4.33)	1.36 (0.30-6.14)
Heart Failure	90 days	1.34 (0.73-2.47)	1.24 (0.53-2.90)
	180 days	1.41 (0.89-2.32)	1.17 (0.62-2.21)
Major Adverse Cardiovascular Events + Heart Failure	90 days	1.43 (0.83-2.49)	1.11 (0.53-2.33)
	180 days	1.44 (0.95-2.19)	1.14 (0.65-2.03)
Death	90 days	1.53 (1.16-2.02)	1.68 (1.13-2.51)
	180 days	1.27 (1.03-1.58)	1.34 (1.00-1.81)

Footnote: Since metformin is often the preferred first-line medication used to treat type 2 diabetes mellitus, we restricted our study cohort and reanalyzed the data in this subset.

Metformin users had received at least one dispensing of metformin in the 12 months prior to the dipeptidyl peptidase-4 inhibitor or sulfonylurea initiation date. Residents were not required to continue taking metformin after they initiated a dipeptidyl peptidase-4 inhibitor or sulfonylurea.

Chapter 2 Figures

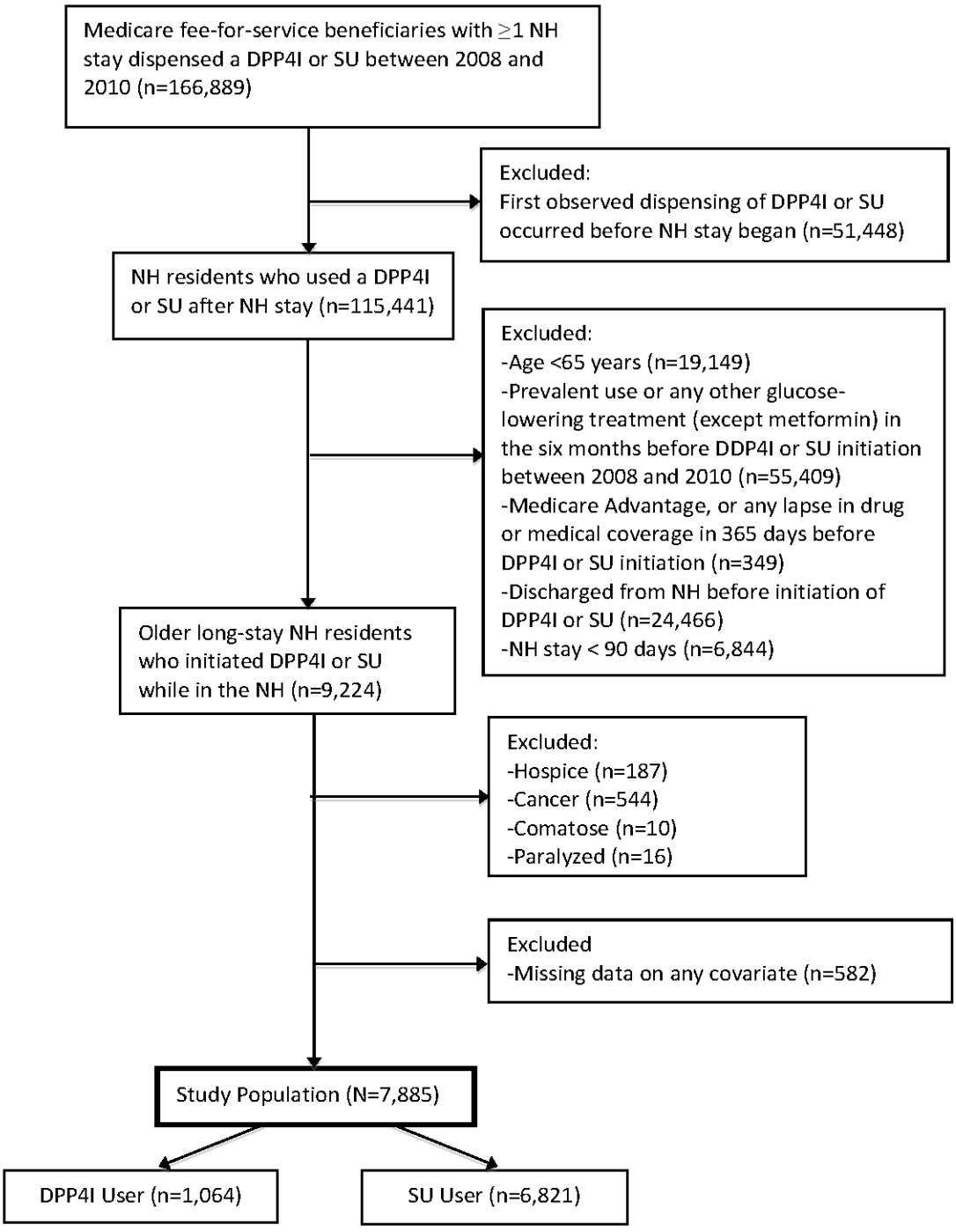

Figure 2.1. Flow diagram of study cohort creation.

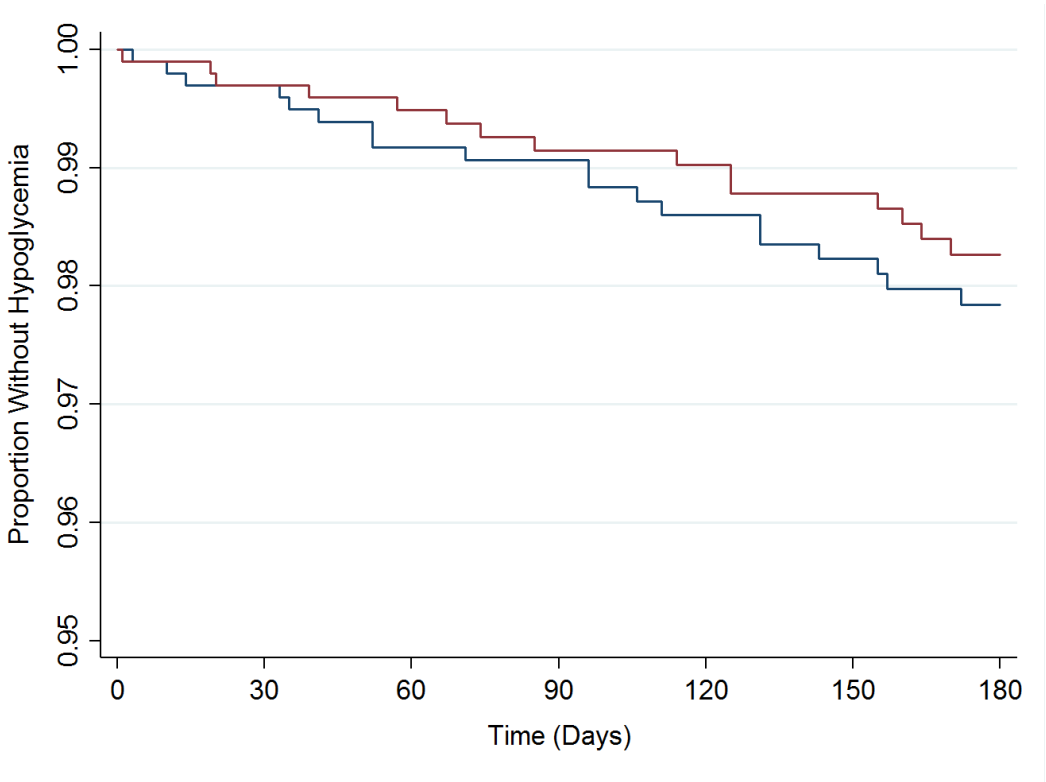

Figure 2.2. Kaplan Meier Plot of Hypoglycemia Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

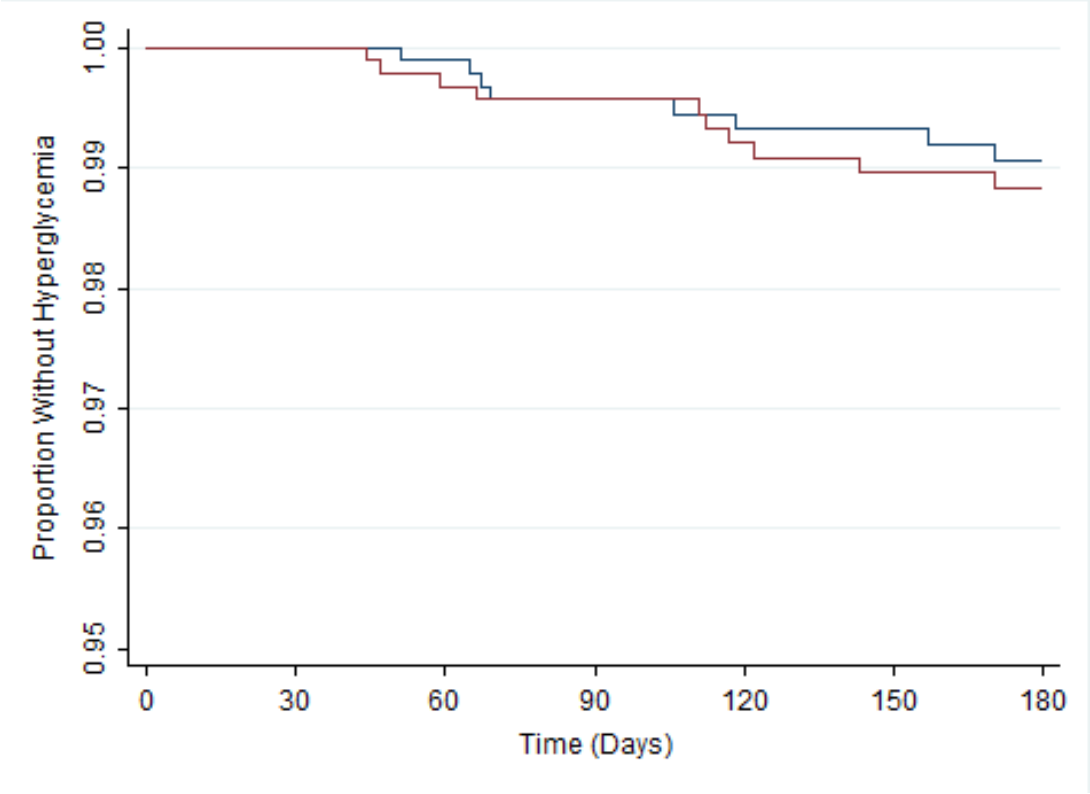

Figure 2.3. Kaplan Meier Plot of Hyperglycemia Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

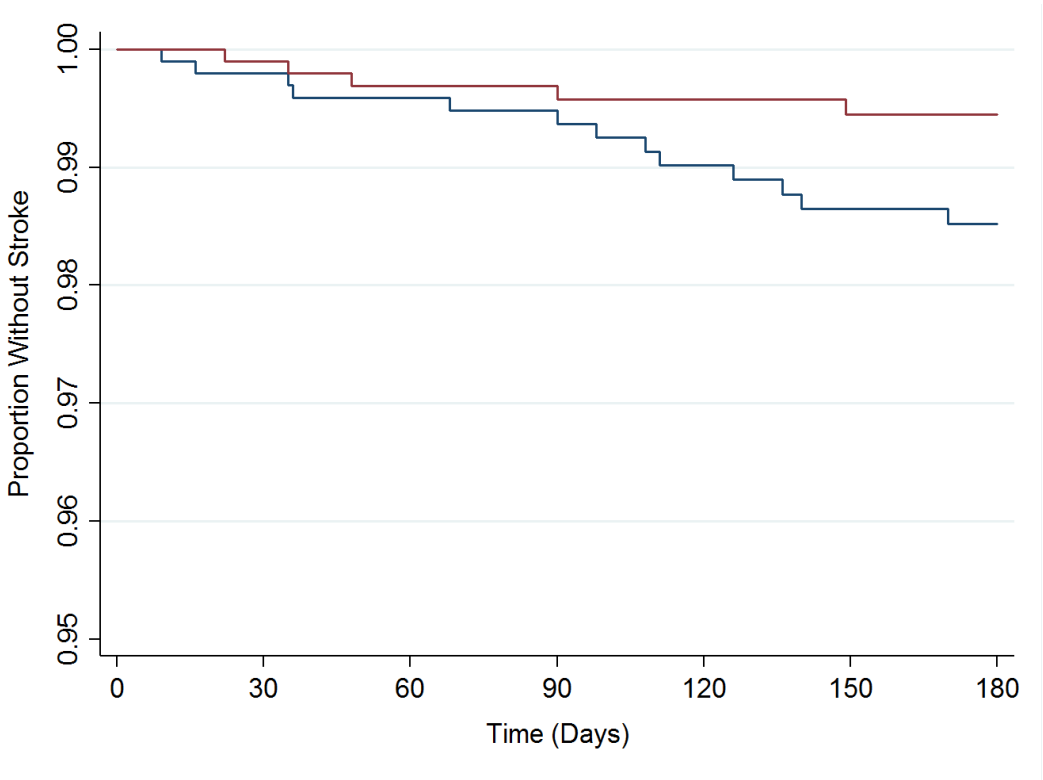

Figure 2.4. Kaplan Meier Plot of Stroke Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

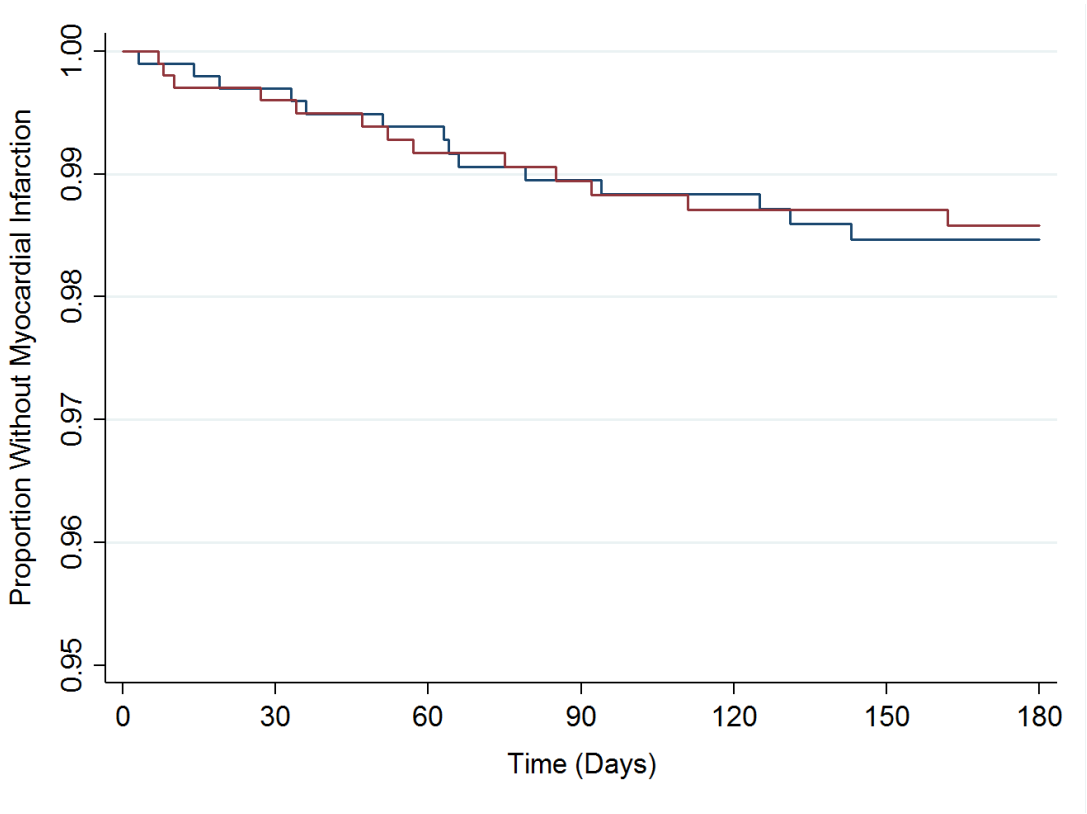

Figure 2.5. Kaplan Meier Plot of Myocardial Infarction Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

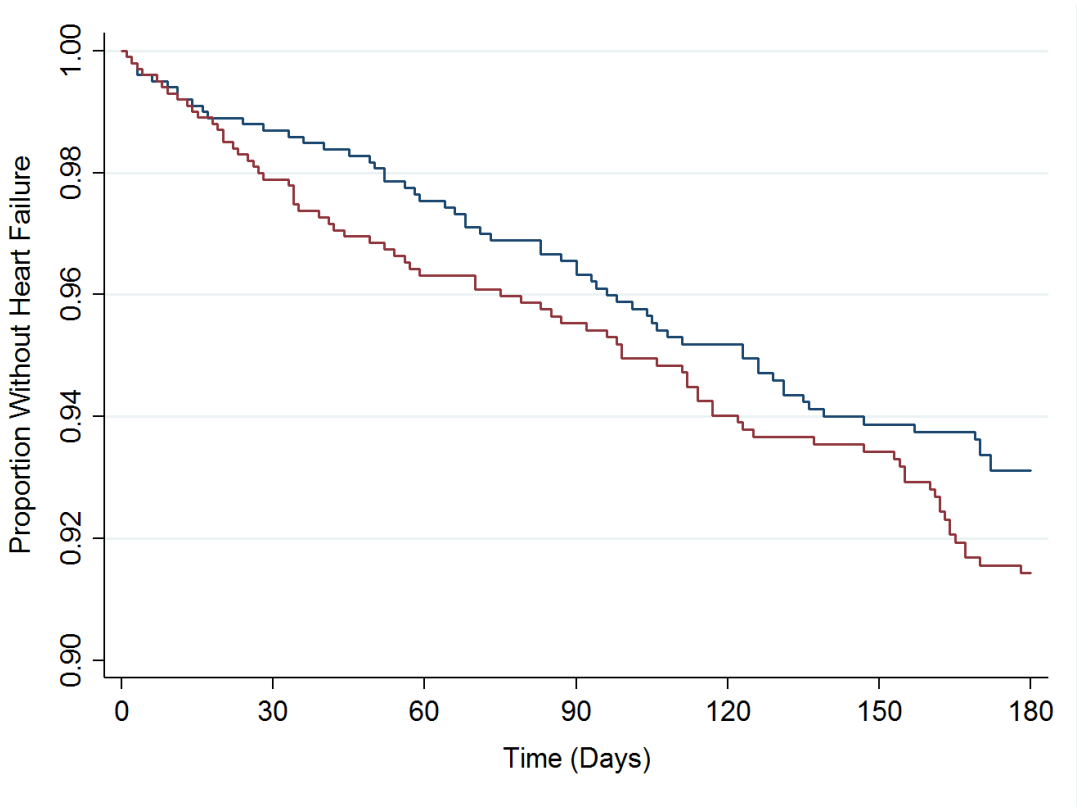

Figure 2.6. Kaplan Meier Plot of Heart Failure Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

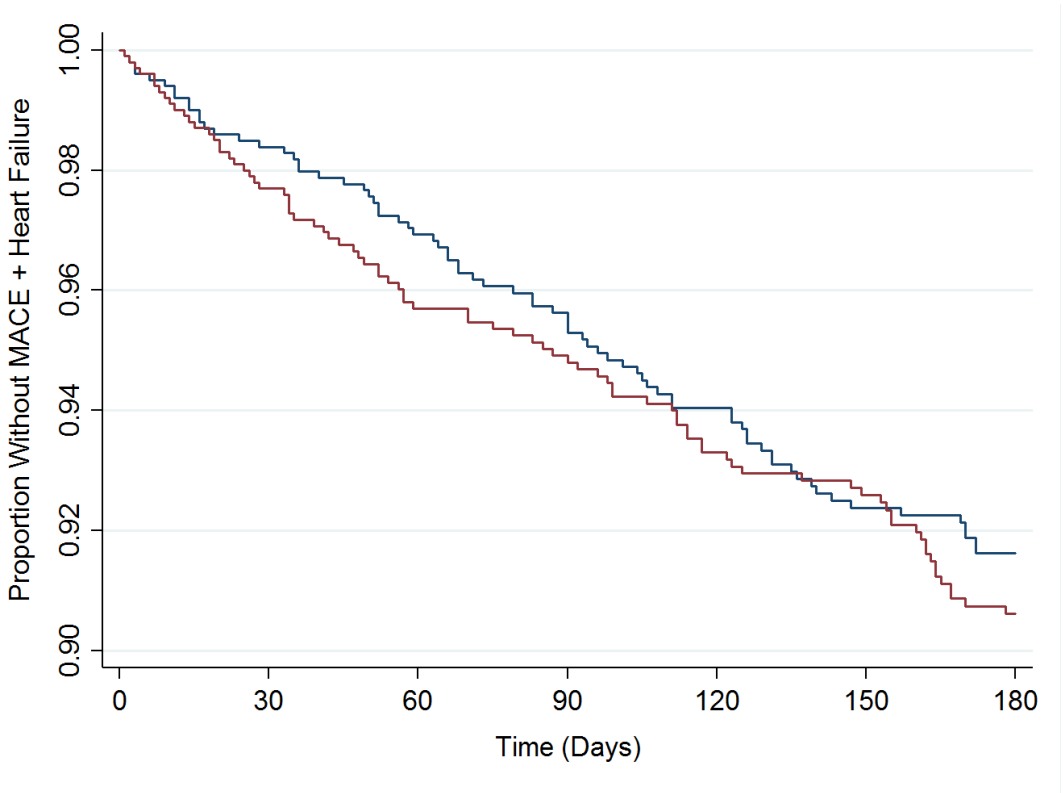

Figure 2.7. Kaplan Meier Plot of Major Adverse Cardiovascular Events (MACE) plus Heart Failure Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

CHAPTER 3: COMPARISON OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS VERSUS SULFONYLUREAS ON COGNITIVE AND PHYSICAL FUNCTIONING IN OLDER NURSING HOME RESIDENTS

Abstract

Background: Dipeptidyl peptidase-4 inhibitors (DPP4Is) provide similar glycemic control to sulfonylureas (SUs), but might reduce the risk of hypoglycemia-mediated declines in cognitive and physical functioning in individuals with type 2 diabetes mellitus (T2DM). Studies of the effects of DPP4Is versus SUs on cognitive and physical functioning are unavailable for older nursing home (NH) residents.

Objective: To quantify the effect of DPP4Is versus SUs on cognitive and physical functioning among long-stay NH residents age 65 and older.

Design, setting, participants, exposure: New user cohort study of a representative sample of U.S. NH residents in 2008-2010, using national data from the Minimum Data Set and Medicare Parts A, B, and D. We used propensity score matching and Cox regression models to compare outcomes in residents who initiated a DPP4I versus SU.

Main outcomes: Cognitive decline measured using the validated 6-point Cognitive Performance Scale, physical functional decline measured using the validated 28-point MDS Activities of Daily Living scale, and hospitalizations or emergency department (ED) visits for altered mental status in the first 90 and 180 days after DPP4I or SU initiation.

Results: The study cohort included 892 new DPP4I users matched to an equal number of SU users; mean age was 80 years. Overall, 37 (2.1%) residents had a cognitive decline, 46 (2.6%) an altered mental status event, and 49 (2.7%) a functional decline at 180 days. Compared to SU users, DPP4I users had lower 90-day and 180-day risks of cognitive decline (90 days, HR=0.45, 95%CI 0.14-1.45; 180 days, HR=0.61, 95%CI 0.31-1.19) and altered mental status events (90-day, HR=0.69, 95%CI 0.30-1.62; 180-day, HR=0.71,

95%CI 0.39-1.27), but a similar risk of decline in physical functioning (90-day, HR=1.15, 95%CI 0.42-3.17; 180-day, HR=0.89, 95%CI 0.51-1.56).

Conclusions/relevance: Compared with SUs, DPP4Is may result in a lower risk of cognitive decline and altered mental status events, but appear to have little impact on physical functioning in older NH residents. However, biases from differences in loss to follow-up remains a plausible alternative explanation.

Introduction

Dipeptidyl peptidase-4 inhibitors (DPP4Is) and sulfonylureas (SUs) are recommended second-line treatments for type 2 diabetes mellitus (T2DM) in older nursing home (NH) residents, whose prevalence of T2DM is approximately 30%.[35-38,40,68] These recommendations are based primarily on randomized trials in middle-aged and "young-old" adults.[72-74] There are few data about the comparative effects of these medications among frail elders or NH residents, and the preferred second-line agent for this population remains unclear.

Hypoglycemia occurs frequently in the NH population and increases the risk of confusion, delirium, impaired cognition, lightheadedness, fatigue, weakness, and in severe cases, seizures or unconsciousness. [75,76,117-122] Hypoglycemic symptoms have an adverse effect on patients' rating of their health-related quality of life.[123] Hyperglycemia also occurs often in the NH population and is associated with a similar set of symptoms as hypoglycemia.[38,77] The symptoms of hypoglycemia and hyperglycemia may translate into an increased risk of decline in cognitive functioning, physical functioning, and quality of life for frail and vulnerable older adults.[124-127]

It is possible that DPP4Is and SUs differentially impact cognitive and physical functioning through their effects on hypoglycemia and hyperglycemia.[128,129] Evidence suggests that SUs are associated with a greater risk of hypoglycemia than DPP4Is, which may manifest as declines in cognitive and physical functioning.[128-130] Conversely, DPP4Is might produce inadequate lowering of blood glucose (hyperglycemia), which could also manifest as declines in functioning.[128,129] However, studies that directly compare cognitive and physical functioning outcomes for DPP4I and SU users are scarce.[131,132] Vulnerable older adults are particularly susceptible to adverse drug effects.[86,133-137] Furthermore, quality of life, cognitive functioning, and physical functioning are outcomes of central importance to older adults, their families, and their clinicians.[16,138-141]

In this study, we compared the effect of DPP4Is versus SUs on cognitive functioning, altered mental status events, and physical functioning among long-stay NH residents age 65 and older.

Methods

Data Sources and Subjects

Data for this retrospective cohort study came from fee-for-service Medicare Parts A (inpatient), B (outpatient), and Part D (prescription drug) claims; the Online Survey Certification and Reporting System (OSCAR), which provides facility-level information on NH characteristics, staffing, and quality indicators; and the Minimum Data Set (MDS) version 2.0, which comprises assessments made on nearly all nursing home residents in

the U.S. MDS assessments occur a minimum of every 3 months, and more often for residents with a major recent change in clinical status.[87]

The study population comprised U.S. nursing home residents aged 65 and older who initiated a DPP4I or SU between January 1, 2008 and September 15, 2010, who resided in a nursing home for at least the preceding three months (Figure 3.1). Data from January 1, 2007 to December 31, 2007 was available to ascertain prior glucose-lowering treatment use.

We first identified 166,889 Medicare beneficiaries with at least one NH stay and a dispensing of a DPP4I or SU between 2008 and 2010. We excluded prior recipients of a DPP4I or SU (n=51,448) and individuals who were <65 years old (n=19,149). We also excluded recipients of a glucose-lowering treatment other than metformin within six months of initiation (n=55,409) with the aim of reducing confounding by prior glucose-lowering treatment use. Use of prior glucose-lowering treatments is a high-dimensional space consisting of numerous treatment combinations because NH residents are often treated in ways that inexplicably deviate from clinical guidelines.[88] Since the number of subjects with many of the treatment patterns was often too small to allow estimation of the association between initiation of DPP4Is versus SUs within each treatment pattern subgroup, we instead restricted the sample. Other exclusions were persons discharged from the NH before DPP4I or SU initiation (n=24,466), in the NH for <90 days (n=6,844) and not continuously enrolled in Medicare during the study period or had no Part D claims prior to treatment initiation, and residents who were enrolled in a Medicare Advantage (health maintenance organization) plan at any point during this period (n=349). Finally, we also excluded residents with very poor prognosis at baseline (cancer,

n=544; hospice, n=187; comatose, n=10; or fully paralyzed, n=16), with missing covariate information (n=582), and with no cognitive or physical functioning information measured on the last MDS assessment before initiation of a DPP4I or SU (n=907).[57] Analyses of these study data received expedited review from the Brown University Institutional Review Board.

Measures

Our exposures of interest were new use of DPP4Is (saxagliptin, sitagliptin) or SUs (glimepiride, glipizide, glyburide) in the NH setting.[89] We defined this as a Part D claim after six months of no glucose-lowering treatment dispensings with the exception of metformin. Metformin was permitted because it is generally the first-line T2DM treatment.[40,90] Residents were not required to already be on metformin because prior literature has demonstrated that many residents are managed on second-line agent monotherapy (without metformin), perhaps due to a contraindication to metformin.[45,88] Medicare Part D covers at least 81% of nursing home residents and in most cases is the sole source of prescription drug coverage.[49]

Our three outcomes were decline in physical functioning, decline in cognitive functioning, and hospitalizations or emergency department (ED) visit for altered mental status. We defined physical functional decline as an increase of 3 points on a validated 28-point scale of independence in activities of daily living (ADLs) between the pre-initiation baseline and any available MDS assessment following initiation, up to 180 days after initiation.[55] A 3-point increase corresponds to a major loss of independence in 1 ADL or incremental losses in 2 or more ADLs.[142,143] In a sensitivity analysis, we

evaluated the outcome as a 4-point (more substantial) decline in function. Cognitive functional decline was defined as an increase of 1 point on the validated 6-point MDS Cognitive Performance Scale. A 1-point cognitive decline is considered significant.[144] We also tested a 2-point (more substantial) decline in cognitive function in a sensitivity analysis. Lastly, we defined a hospitalization or ED visit for altered mental status using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 780.0, 780.02, 780.09, or 780.97 in any position on a Part A inpatient hospital claim or a Part B ED claim, though inclusion of ED visits contributed only a small number of additional cases. While no validated algorithm or positive predictive value exists for altered mental status events in claims, our definition is consistent with that used in prior literature.[145]

We considered each outcome individually. We also explored two pre-specified composite outcomes: time to substantial functional decline (3-point ADL or 1-point CPS), and time to a very substantial functional decline (4-point ADL or 2-point CPS). We chose a 90-day outcome period because it is long enough to be clinically meaningful, but short enough that many of these highly vulnerable residents have not yet died, a highly prevalent competing outcome which complicates interpretation of longer-term outcomes in the NH setting. We also examined outcomes at 180 days of follow-up to better understand the longer-term effects of prescribing DPP4Is over SUs. We identified death using the Medicare enrollment file to use it for censoring in the primary analysis, and explore how death might act as a competing risk for our outcomes in sensitivity analyses. Study subjects were censored at the first occurrence of the primary outcomes,

end of the study period (September 30, 2010), death, nursing home discharge, or disenrollment from Medicare.

Information on chronic conditions and characteristics of NH residents were obtained from Medicare Part A and MDS 2.0 data, which has demonstrated reliability[96] and validity[97,98] for assessing the clinical status of NH residents. The MDS 2.0 is also provided data on other patient characteristics including pre-treatment physical functional[55] and cognitive status[56,99], geriatric syndromes, nutrition, social characteristics, care preferences, and proxies for frailty like the Changes in Health, End-stage Disease, Signs, and Symptoms Scale (CHESS) score.[57,100]

We used the validated OSCAR dataset to evaluate a variety of nursing home facility characteristics such as staffing, resident mix and quality indicators.[52]

Analyses

We used propensity score matching methods to identify a subset of SU exposed residents who were comparable, on average, with DPP4I initiators on a range of baseline risk factors. Analogous to an intention-to-treat framework, we defined subjects as new users based on an observed dispensing of a DPP4I or SU.[101]

We estimated the propensity score via a logistic regression model that used 190 covariates to predict use of DPP4Is over SUs. Variables included sociodemographic characteristics, chronic medical conditions, baseline medication use, prior hospitalization history, baseline functional and cognitive status, geriatric syndromes, nutrition and fluid status, and nursing home characteristics (Table 3.1). To evaluate whether our logistic propensity score estimation model might be misspecified and result in inaccurate

estimations of the propensity score, we conducted a sensitivity analysis where we estimated the propensity score using generalized boosted regression that attempts to optimize balance on the covariates.[102]

To match DPP4I users with SU users who had similar propensity scores, we first discarded subjects in the top and bottom 1% of the propensity score distribution so as to exclude areas of non-overlap where unmeasured differences in risk are more likely to exist.[103] We then applied a 1:1 greedy (nearest neighbor) 5-to-1 digit matching algorithm without replacement.[104,105] We evaluated the quality of resulting matches by comparing standardized differences between groups for each covariate in our model, and by using t-tests to assess differences in the distribution of propensity scores.[106,107] Our propensity matching yielded good covariate balance, and our primary follow-up period was 90 days, so we did not further adjust for baseline covariates in our models.

We used Cox proportional hazards models with robust standard errors to determine the impact of DPP4I versus SU use on time to outcomes.[108] The robust sandwich estimator was used to account for the clustering within propensity score-matched pairs and forego the need to assume independence of the observations.[108] In sensitivity analyses we used the method of Fine and Gray (similar to Cox regression) to evaluate the impact of DPP4I versus SU use on time to the outcomes while accounting for the competing risk of death.[109] At the end of each follow-up period, subjects were classified as alive without one of the outcomes of interest, having had outcome documented in the MDS or claims in that period, or having died without evidence of an outcome event.

To help determine whether exclusion of individuals with missing data on any covariate may have influenced our results, we assumed the information was missing at random and performed multiple imputation to impute the missing covariate information in a sensitivity analysis.[110] To understand the impact of model misspecification, we also applied logistic regression in a sensitivity analysis. Lastly, since metformin is often the preferred first-line medication used to treat type 2 diabetes mellitus, we restricted our study cohort and reanalyzed the data in this subset.

Results

Our initial cohort included 903 new DPP4I users and 6,075 new SU users. Before matching, new DPP4I users were more likely to have a high medication burden, have used other glucose-lowering treatments, and to have received angiotensin receptor blockers, clopidogrel, fibrates, and omega-3 fatty acid medications in the prior 12 months than new SU users (Tables 3.1 and 3.2). Additionally, DPP4I users were more likely to have abnormal labs, ischemic heart disease, and a prior ED visit for hyperglycemia, but less likely to have a do not resuscitate order.

Propensity score matching yielded a cohort of 892 new DPP4I users and an equal number of SU users (Table 3.2). The mean age (SD) was 80 (8) years. Approximately 73% of the cohort was female and 72% was Caucasian race. Matching balanced covariates closely,[106] with all but 2 variables having an absolute standardized mean differences of 0.06 or less (Appendix 2).

DPP4I users appeared less likely than SU users to experience a cognitive decline or altered mental status event (Tables 3.3 and 3.4; Figures 3.2 and 3.3). In the first 90

days after initiation, the risk of cognitive decline was 0.45 (95%CI, 0.14-1.45) times and the risk of an altered mental status event 0.69 (95%CI 0.30-1.62) times lower in DPP4I users than in those receiving SUs (Table 3.3). Results for cognitive decline (HR=0.61, 95%CI 0.31-1.19) and an altered mental status event (HR=0.71, 95%CI 0.39-1.27) were similar at 180 days post-initiation (Table 3.4).

DPP4I users were as likely as SU users to have a physical functional decline at 90 days after treatment initiation (HR=1.15, 95%CI 0.42-3.17)(Figure 3.4). This absence of any notable difference persisted at 180 days (HR=0.89, 95%CI 0.51-1.56). Results were imprecise with the stringent threshold of a 2-point decline on the CPS scale and a 4-point decline on the Morris ADL scale, but qualitatively consistent with the main results (Table 3.5).

Compared to SU use, DPP4I use was associated with a lower risk of the composite outcome of time to substantial functional decline (90 days, HR=0.86, 95%CI 0.40-1.86; 180 days, HR=0.83, 95%CI 0.53-1.31) or very substantial functional decline (90 days, HR=0.87, 95%CI 0.40-1.88; 180 days, HR=0.84, 95%CI 0.53-1.32), though these results were not statistically significant (Tables 3.4 and 3.5; Figure 3.5).

The main results were generally similar when estimating the propensity score using generalized boosted regression (Table 3.6), implementing multiple imputation of missing baseline covariate information (Table 3.7), employing Fine and Gray models to account for the competing risk of death (Table 3.8), and restricting to metformin users (Table 3.9). Of note, the estimates from the generalized boosted regression propensity score-matched cohort suggested a possible relative reduction in physical functional decline associated with DPP4I use.

Discussion

In this large national cohort study of NH residents, we observed a decreased risk of significant cognitive decline and altered mental status events among new users of DPP4Is compared to new users of sulfonylureas, though these estimates did not reach statistical significance at traditional significance levels. We did not observe any difference in the risk of declines in physical functioning between the two treatment groups. To our knowledge, this is the first study to examine the comparative functional effects of DPP4Is and SUs for frail older adults in the NH setting.

Very few studies have examined the comparative effects of diabetes medications on cognition, physical functioning, or quality of life.[119] Of the studies that have been done, differences in questionnaires and methods of assessment prevent any conclusions from being drawn, and just one of those studies evaluated DPP4Is versus SUs.[119,131] Rizzo et al. evaluated the effect of DPP4Is versus SUs on changes in cognitive function in older Italian patients who already had mild cognitive impairment.[131] The study was not conducted in NH residents and did not appear to account for confounding. Nonetheless, our cognitive decline and altered mental status event results were consistent with their finding that DPP4I use was protective against worsening in cognitive functioning.

The closest comparable evidence on physical functioning is a large Veterans Affairs study of the relationship between glycemic control and functional decline (defined as a 2-point increase) in NH residents.[146] The investigators did not compare treatments, but conducted an analysis stratified by prevalent glucose lowering treatment use—insulin, sulfonylureas, or other glucose-lowering medications. They found that 238

(11.4%) of 2,094 users of glucose-lowering treatments other than sulfonylureas or insulin and 404 (14.1%) of 2,873 sulfonylureas had a functional decline in their unadjusted analysis (risk ratio=0.81, 95%CI 0.69-0.95). This contradicts our own findings of no difference in physical functioning between DPP4I and SU users, but the innumerable differences between the studies likely account for the discrepant findings.

Our study has several limitations. Because it is an observational study without randomization of treatments, we cannot rule out the possibility of residual confounding by indication. In particular, our study may have benefited from laboratory information on hemoglobin A1c and other measures of glycemic control. However, several factors support the robustness of our findings. We obtained good balance on a wide array of baseline covariates across treatment groups. We obtain consistent results using several alternate analytic approaches. Moreover, DPP4Is and SUs have a similar place in therapy for treatment of T2DM, which reduces the likelihood of confounding by indication. Another important consideration is the size of our final study population and precision of our estimates. Since our outcomes were uncommon, DPP4I use not yet very common during the study period, and post-match sample size modest, our estimates are often imprecise. These circumstances mandate a more nuanced interpretation of the range of plausible effect estimates, rather than simply seeking to reject or fail to reject the null hypothesis using p-values (i.e., rather than assessing whether estimates are or are not statistically significant).[114,115] In addition to contributing to the imprecision of our estimates through a reduction in sample size, restriction on glucose-lowering treatment history may have reduced the generalizability of our findings. Future work should seek to confirm the findings by adding more recent data so as to increase the number of new

DPP4I users available for matching and comparison to SU users in the NH setting. Further, the small number of cases for each outcome did not permit subgroup analyses to examine modification of the DPP4I versus SU effect, so addition of more data would also help to address this limitation. Lastly, there may be under-ascertainment of outcomes. It is possible that cases of decline in cognitive or physical functioning are undocumented by the NH staff between MDS assessments. However, provided that the underascertainment is non-differential by treatment group and the specificity of the MDS-based measures is high[55,98,143,144], relative effect measures are unlikely to be biased.[116] Since the MDS requirements do not differ by glucose-lowering treatment status, differential ascertainment of declines in cognitive and physical functioning is unlikely.

Our study has several strengths. We adjusted for many potential confounders, and had many covariates that are not available in administrative and claims-only databases. Our results were robust under several different analytic approaches. Although our estimates were not as precise as desired, they are some of the only estimates of treatment effects for this population and are likely to be some of the most exact. Our demographically, geographically, and clinically diverse population aids the generalizability of the findings to frail, older adults in long-term care—the most widely treated segment of the elderly population. This strength is particularly important given the systematic exclusion of older NH residents from clinical trials of treatments and the resulting paucity of evidence to guide treatment-decisions, despite the continued need and frequent use of medications in the NH. Nonetheless, our findings must be interpreted within the context of the aforementioned study limitations.

In summary, use of DPP4Is for T2DM among older NH residents may result in a lower risk of cognitive decline and altered mental status events compared to use of SUs, but was not associated with a differential risk of decline in physical functioning. Additional studies are often needed to better understand the comparative safety and effectiveness of treatments in the NH setting, including the comparative effects of DPP4Is and SUs on functioning. However, given the absence of prior clinical trials that include NH residents and the lack of any planned future ones, to the best of our knowledge, our study provides new critical evidence to guide patient-centered treatment decisions for NH residents with T2DM. Since many NH residents, their families, their caregivers, and their clinicians value maintaining functioning and quality of life more than extending lifespan or minimizing traditional clinical adverse events, our results should help guide the selection of treatments to achieve those goals.

Chapter 3 Tables

Table 3.1. Standardized differences between dipeptidyl peptidase-4 inhibitor and sulfonylurea users before and after propensity score matching.

			Original Value		Absolute Value	
#	Covariate	Label	Before Matching	After Matching	Before Matching	After Matching
1	comorbidity_burden	Number of comorbidities	0.06	-0.01	0.06	0.01
2	carryadl	Morris activities of daily living scale (0-28 point)	0.02	-0.03	0.02	0.03
3	cna100t	Facility: total nurse aide full time equivalents per 100 beds	-0.02	-0.01	0.02	0.01
4	pt100t	Facility: total physical therapy full time equivalents per 100 beds	-0.02	0.04	0.02	0.04
5	rn100t	Facility: total	0.05	-0.01	0.05	0.01

		registered nurse full time equivalents per 100 beds				
6	prov1090	Facility: pharmacist full time equivalents	-0.02	0.03	0.02	0.03
7	restrain	Facility: Percentage of residents physically restrained	-0.02	0.05	0.02	0.05
8	surv0690	Facility: medication error rate	-0.03	-0.03	0.03	0.03
9	n_qol_def	Facility: count of quality-of-life deficiencies	0.03	-0.02	0.03	0.02
10	restrain	Facility: Percentage of residents physically restrained	0.02	0.01	0.02	0.01
11	paymcaid	Facility: Percentage of residents covered by Medicaid insurance	0.05	0.03	0.05	0.03
12	painmgmt	Facility: Percentage of residents on a	-0.03	-0.02	0.03	0.02

		pharmacy pain management program				
13	antianx	Facility: Percentage of residents receiving antianxiety medications	0.02	0.03	0.02	0.03
14	antidep	Facility: Percentage of residents receiving antidepressants	-0.06	0.05	0.06	0.05
15	bedsores	Facility: Percentage of residents with bedsores	0.05	-0.02	0.05	0.02
16	acuindex2	Facility: acuity of residents (acuity index)	0.05	0.00	0.05	0.00
17	advdir	Facility: Percentage of residents with advance directives	-0.05	-0.01	0.05	0.01
18	carrynummeds	Medication Burden (Number of medications)	0.24	0.03	0.24	0.03

19	durationofpreindexnhstay	Duration of nursing home stay before sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.02	-0.01	0.02	0.01
20	carrymdorderchngs	Number of orders changed by physician	0.11	-0.03	0.11	0.03
21	carrymdvisits	Number of physician visits	0.05	-0.05	0.05	0.05
22	dmsex	Female sex	-0.04	0.04	0.04	0.04
23	dmrace	Race/ethnicity	0.13	0.05	0.13	0.05
24	agecat	Age at index treatment initiation	0.11	0.05	0.11	0.05
25	carrymarried	Marital status	0.06	0.04	0.06	0.04
26	edcat	Highest educational attainment	0.08	0.05	0.08	0.05
27	carrylanguage2	Primary language spoken	0.07	0.05	0.07	0.05
28	carrychurch	Customary routine includes usual attendance at church,	-0.07	-0.04	0.07	0.04

		temple, synagogue, or other place of worship				
29	bmicat	Body mass index at index treatment (DPP4 or SU) initiation	0.15	0.03	0.15	0.03
30	carrydiabetes	Diabetes mellitus	0.10	0.00	0.10	0.00
31	carryhyperthy	Hyperthyroidism	0.04	0.05	0.04	0.05
32	carryhypothy	Hypothyroidism	0.00	0.05	0.00	0.05
33	carryarterhrtdz	Ischemic heart disease	0.07	0.02	0.07	0.02
34	carryarrhythmias	Arrhythmias	-0.03	-0.02	0.03	0.02
35	carrychf	Heart failure	0.06	0.02	0.06	0.02
36	carrydvt	Deep vein thrombosis	0.00	-0.02	0.00	0.02
37	carryhypotn	Hypotension	-0.01	-0.02	0.01	0.02
38	carryhtn	Hypertension	-0.01	-0.06	0.01	0.06
39	carrypvd	Peripheral vascular disease	0.02	-0.02	0.02	0.02
40	carryothercvd	Other (non-ischemic)	-0.01	0.03	0.01	0.03

		cardiovascular disease				
41	carryarthritis	Arthritis	0.02	0.00	0.02	0.00
42	carrymissinglimb	Missing limb	-0.03	-0.04	0.03	0.04
43	carryosteoporosis	Osteoporosis	0.01	-0.04	0.01	0.04
44	carrybonefracture	Bone fracture (other than hip)	-0.02	-0.03	0.02	0.03
45	carryalzheimers	Alzheimer's disease	-0.02	-0.01	0.02	0.01
46	carryaphasia	Aphasia	0.00	0.05	0.00	0.05
47	carrystroke	Stroke	0.01	-0.05	0.01	0.05
48	carrydem	Non-Alzheimer's dementia	-0.03	0.00	0.03	0.00
49	carryresistinfxn	Antibiotic-resistant infection	0.01	0.00	0.01	0.00
50	carryrespinfxn	Respiratory infection	0.01	0.00	0.01	0.00
51	carryepilepsy	Seizure disorder	0.03	0.03	0.03	0.03
52	carryanx	Anxiety disorder	-0.02	-0.01	0.02	0.01
53	carrydepression	Depression	0.01	0.05	0.01	0.05

54	carrybipol	Bipolar disorder	0.03	0.04	0.03	0.04
55	carryemphcopd	Emphysema/chronic obstructive pulmonary disease	0.03	-0.03	0.03	0.03
56	carrycatar	Cataracts	0.02	0.01	0.02	0.01
57	carrydiabretinopathy	Diabetic retinopathy	-0.01	0.06	0.01	0.06
58	carryglaucoma	Glaucoma	0.07	0.02	0.07	0.02
59	carrymacdegen	Macular degeneration	0.00	0.01	0.00	0.01
60	carryanemia	Anemia	0.04	0.00	0.04	0.00
61	carryrenaldx	Renal failure	0.04	0.00	0.04	0.00
62	carryuti	Urinary tract infection	0.07	0.00	0.07	0.00
63	carrywoundinfxn	Wound infection	0.06	0.03	0.06	0.03
64	carrychronicprobflare	Any acute episode or a flare-up of a recurrent or chronic health problem	0.09	-0.01	0.09	0.01
65	accidfallanypartabefore	Accidental fall hospitalization	0.00	0.01	0.00	0.01

66	accidfallanypartbbefore	Accidental fall emergency department visit	0.05	0.00	0.05	0.00
67	ichanypartabefore	Intracranial hemorrhage hospitalization	0.05	0.00	0.05	0.00
68	ichanypartbbefore	Intracranial hemorrhage emergency department visit	-0.01	-0.03	0.01	0.03
69	strokeanypartabefore	Stroke hospitalization	0.03	-0.04	0.03	0.04
70	strokeanypartbbefore	Stroke emergency department visit	0.03	-0.03	0.03	0.03
71	amianypartabefore	Acute myocardial infarction hospitalization	0.00	0.02	0.00	0.02
72	amianypartbbefore	Acute myocardial infarction emergency department visit	0.00	0.03	0.00	0.03
73	hypoglyanypartabefore	Hypoglycemia hospitalization	0.11	-0.06	0.11	0.06

74	hypoglyanypartbbefore	Hypoglycemia emergency department visit	0.12	0.04	0.12	0.04
75	hyperglyanypartabefore	Hyperglycemia hospitalization	0.12	0.02	0.12	0.02
76	hyperglyanypartbbefore	Hyperglycemia emergency department visit	0.11	0.03	0.11	0.03
77	hipfxanypartabefore	Hip fracture hospitalization	0.02	-0.05	0.02	0.05
78	hipfxanypartbbefore	Hip fracture emergency department visit	0.00	-0.03	0.00	0.03
79	alterconsanypartabefore	Altered mental status hospitalization	0.01	0.03	0.01	0.03
80	alterconsanypartbbefore	Altered mental status emergency department visit	0.04	0.00	0.04	0.00
81	hfanypartabefore	Heart failure hospitalization	0.12	-0.01	0.12	0.01
82	hfanypartbbefore	Heart failure	0.09	0.01	0.09	0.01

		emergency department visit				
83	carryweightchange	Weight gain or loss of 3 or more pounds	-0.05	0.02	0.05	0.02
84	carrychessscore	Frailty proxy/overall health stability: Changes in Health, End-stage disease, and Signs and Symptoms (CHESS) Scale (0 to 5) 0=Not at all unstable,5=Highly unstable	0.07	0.05	0.07	0.05
85	carryadlchngninety	Change in ability to perform activities of daily living	0.03	0.05	0.03	0.05
86	carrycps	Cognitive status (Fries and Morris Cognitive Performance Scale score)	0.11	0.04	0.11	0.04
87	carrypain	Highest level of pain	0.07	0.02	0.07	0.02

		present in the prior 7 days (i.e., frequency and severity with which resident complains or shows evidence of pain) on last MDS assessment prior to index treatment (DPP4 or SU) initiation				
88	carryfalloneight	Fell in the past 31 to 180 days on last MDS assessment prior to index treatment (DPP4 or SU) initiation	-0.04	-0.04	0.04	0.04
89	carrycogstatchg	Change in cognitive status, skills, or abilities as compared to status of 90 days ago or since last assessment if less than 90 days	0.08	0.04	0.08	0.04
90	carrycogabilvary	Cognitive ability	0.10	0.03	0.10	0.03

		varies over time				
91	carrybowelcont	Bowel incontinence	0.10	0.05	0.10	0.05
92	carrybladdercont	Bladder incontinence	0.10	0.05	0.10	0.05
93	carrypressulcstage	Pressure ulcers, presence and stage	0.08	0.05	0.08	0.05
94	carrydizziness	Dizziness/vertigo in prior 7 days on last MDS assessment prior to index treatment (DPP4 or SU) initiation	-0.01	-0.03	0.01	0.03
95	carryRP01A	Delirium resident assessment triggered	-0.08	0.02	0.08	0.02
96	carryhallucintns	Hallucinations	-0.02	0.05	0.02	0.05
97	carryhearingaidnotused	Hearing aid present and not used regularly	-0.08	0.01	0.08	0.01
98	carryhearingaidused	Hearing aid present and used	-0.02	0.00	0.02	0.00
99	carrysidevisprob	Side vision problems or decreased	-0.02	-0.03	0.02	0.03

		peripheral vision				
100	carryvisualapp	Glasses, contact lenses, or magnifying glass used	-0.06	-0.02	0.06	0.02
101	carrycutsortears	Skin tears or cuts (other than surgery)	-0.05	-0.01	0.05	0.01
102	carryedema	Edema	0.01	-0.01	0.01	0.01
103	anymetformintwelv	Metformin use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.16	0.04	0.16	0.04
104	anyinsulinintermediatetwelv	Intermediate-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation	0.06	0.04	0.06	0.04
105	anyinsulinlongtwelv	Long-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU)	0.24	0.00	0.24	0.00

		initiation				
106	anyinsulinrapidtwelv	Rapid-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation	0.24	0.01	0.24	0.01
107	anyinsulinshorttwelv	Short-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation	0.16	0.02	0.16	0.02
108	anythiazolstwelv	Thiazolidinedione use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation	0.21	-0.01	0.21	0.01
109	anyaglucosidaseinhibstwelv	Alpha-glucosidase inhibitor use >6 months but ≤12 months prior to index treatment (DPP4 or	0.06	0.02	0.06	0.02

		SU) initiation				
110	otherhtndrugstwelv	Miscellaneous anti-hypertensive use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.07	0.00	0.07	0.00
111	protonpumpitwelv	Proton pump inhibitor use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.14	-0.02	0.14	0.02
112	raloxifenetwelv	Raloxifene use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.02	0.01	0.02	0.01
113	antiarrhythmicstwelv	Antiarrhythmics use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.01	0.05	0.01	0.05
114	anyaceistwelv	Angiotensin-	0.07	-0.03	0.07	0.03

		converting enzyme inhibitor use in the 12 months prior to index treatment (DPP4 or SU) initiation				
115	anyalphablockerstwelv	Alpha blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation	-0.04	0.00	0.04	0.00
116	anybenzostwelv	Benzodiazepine use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.02	0.01	0.02	0.01
117	anyarbstwelv	Angiotensin receptor blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.13	0.00	0.13	0.00
118	anyaspirintwelv	Aspirin use in the 12 months prior to index treatment (DPP4 or	-0.03	0.00	0.03	0.00

		SU) initiation				
119	anybetablockerstwelv	Beta blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.12	-0.02	0.12	0.02
120	anybileacidresinstwelv	Bile acid resin use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.04	0.02	0.04	0.02
121	anycalciumchnlblockerstwelv	Calcium channel blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.05	0.02	0.05	0.02
122	anyclopidogreltwelv	Clopidogrel use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.13	0.00	0.13	0.00
123	anydepressanttwelv	Antidepressant use in the 12 months prior to	0.07	0.05	0.07	0.05

		index treatment (DPP4 or SU) initiation				
124	anyezetimibetwelv	Ezetimibe use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.04	0.03	0.04	0.03
125	anyfibratestwelv	Fibrate use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.12	0.06	0.12	0.06
126	anygabapregabtwelv	Gabapentin or pregabalin use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.08	0.02	0.08	0.02
127	anyglucagontwelv	Glucagon use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.10	0.01	0.10	0.01

128	anyksparingdiureticstwelv	Potassium-sparing diuretic use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.07	0.00	0.07	0.00
129	anylaopioidtwelv	Long-acting opioid use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.02	0.01	0.02	0.01
130	anymoodtwelv	Mood-stabilizing medication use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.08	0.01	0.08	0.01
131	anymuscletwelv	Muscle relaxant medication use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.09	-0.01	0.09	0.01
132	anyniacintwelv	Niacin use in the 12 months prior to index	0.00	0.03	0.00	0.03

		treatment (DPP4 or SU) initiation				
133	anynonbenzohypnotwelv	Nonbenzodiazepine hypnotics in the 12 months prior to index treatment (DPP4 or SU) initiation	0.08	-0.01	0.08	0.01
134	anyomega3fatwelv	Omega-3 fatty acid medication use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.09	0.00	0.09	0.00
135	anypsychotictwelv	Antipsychotics use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.04	0.06	0.04	0.06
136	anystatinstwelv	Statins use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.11	0.01	0.11	0.01
137	anysteroidtwelv	Oral steroids use in	-0.01	-0.04	0.01	0.04

		the 12 months prior to index treatment (DPP4 or SU) initiation				
138	anythiazidediureticstwelv	Thiazide diuretics use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.06	0.00	0.06	0.00
139	anywarfarintwelv	Warfarin use in the 12 months prior to index treatment (DPP4 or SU) initiation	0.02	0.01	0.02	0.01
140	bisphosphonatestwelv	Bisphosphonates use in the 12 months prior to index treatment (DPP4 or SU) initiation	-0.02	-0.03	0.02	0.03
141	carrymedsadlseat	Resisted taking medications, activities of daily living assistance, or eating	0.04	0.03	0.04	0.03
142	carrynewmeds	Number of new	0.05	0.01	0.05	0.01

		medications				
143	carryivmeds	Any intravenous medications	0.07	0.04	0.07	0.04
144	carrytasteproblem	Complains about the taste of many foods	0.08	0.04	0.08	0.04
145	carrytwentfiveuneat	Leaves 25% or more of food uneaten at most meals	-0.02	0.02	0.02	0.02
146	carryplnweightprgm	On a planned weight change program	0.05	0.01	0.05	0.01
147	carryparenteralfeed	Parenteral/intravenous feeding	0.05	-0.01	0.05	0.01
148	carrymechanaltdiet	Mechanically altered diet	-0.01	0.03	0.01	0.03
149	carrytxdiet	Therapeutic diet	-0.03	-0.01	0.03	0.01
150	carrydietsupplement	Dietary supplement between meals	0.02	0.03	0.02	0.03
151	carrychewproblem	Chewing problems	0.00	0.00	0.00	0.00
152	carryRP12B	Nutrition status care	0.09	0.00	0.09	0.00

		plan implemented				
153	carryRP14A	Dehydration/fluid status resident assessment triggered	0.07	-0.02	0.07	0.02
154	carryRP14B	Dehydration/fluid status care plan implemented	0.07	-0.01	0.07	0.01
155	carryfeedrestrict	Feeding restrictions advanced directive documented in the medical record	-0.05	0.02	0.05	0.02
156	carryRP12A	Nutritional status resident assessment triggered	0.07	0.02	0.07	0.02
157	carrytoothloss	Some or all natural teeth were lost	0.04	0.01	0.04	0.01
158	carrytobacco	Customary routine includes use of tobacco at least daily	-0.03	0.04	0.03	0.04
159	carryalcohol	Customary routine includes alcoholic beverages at least	-0.02	0.05	0.02	0.05

		weekly				
160	carryabnormlabs	Abnormal laboratory values	0.11	-0.06	0.11	0.06
161	hypoglyanypartabefore	Hypoglycemia hospitalizations	0.11	-0.05	0.11	0.05
162	hypoglyanypartbbefore	Hypoglycemia emergency department visit	0.12	0.04	0.12	0.04
163	caretransitions	Transitions in care setting	0.12	0.07	0.12	0.07
164	carryostomy	Ostomy (bowel)	-0.06	0.00	0.06	0.00
165	carrydialysis	Dialysis use	0.04	0.02	0.04	0.02
166	carryventilator	Ventilator or respirator use	0.02	0.02	0.02	0.02
167	carryskinutrition	Nutrition or hydration intervention to manage skin problems	0.05	0.01	0.05	0.01
168	carrypreventfootcr	Received preventative or protective foot care	0.01	0.04	0.01	0.04

169	carrymentaleval	Evaluation by a licensed mental specialist	0.04	0.03	0.04	0.03
170	carryexercisepref	Prefers exercise or sports	0.01	-0.04	0.01	0.04
171	carrydonothosp	Do not hospitalize advanced directive documented in the medical record	-0.05	0.05	0.05	0.05
172	carrydonotresus	Do not resuscitate advanced directive documented in the medical record	-0.12	0.00	0.12	0.00
173	carryselfsuffchng	Significant change in self-sufficiency as compared to status of 90 days ago or since last assessment if less than 90 days	0.03	0.04	0.03	0.04
174	carryselfinitact	At ease doing self-initiated activities	-0.07	0.03	0.07	0.03
175	carryestabgoals	Established own goals	-0.04	0.05	0.04	0.05

176	carrycommuniscale	Communication scale (communication performance)	0.10	0.05	0.10	0.05
177	carrycommchange	Change in ability to express, understand, or hear information	0.03	0.02	0.03	0.02
178	carrybehaviorsc	Problem behaviors present	-0.02	0.04	0.02	0.04
179	carrybehaviorchng	Change in behavior status as compared to 90 days ago or since last assessment if less than 90 days	0.10	0.03	0.10	0.03
180	carryparticipatefam	Family participation in resident's care	0.05	0.05	0.05	0.05
181	carrysocialcontact	Customary routine includes daily contact with relatives or close friends	-0.05	0.02	0.05	0.02
182	carryresponsibfm	Family member responsible for resident	0.00	-0.03	0.00	0.03

183	hours	Facility: Staff hours per resident	0.09	0.05	0.09	0.05
184	multifac	Facility: part of a nursing home chain	-0.02	0.02	0.02	0.02
185	owner	Facility: Class of ownership (for-profit, non-profit, government)	0.05	0.05	0.05	0.05
186	prov1535	Facility: Organized family group	0.04	0.05	0.04	0.05
187	ppcat	Facility: % of other private pay clients	0.12	0.07	0.12	0.07
188	yearoftx	Year of sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation	0.15	0.04	0.15	0.04
189	carryedvisits	Number of emergency department visits	0.08	0.06	0.08	0.06
190	carryovrnghthosp	Number of overnight hospitalizations	0.08	0.06	0.08	0.06

Table 3.2. Characteristics of dipeptidyl peptidase-4 inhibitor and sulfonylurea users before and after propensity score matching.

Characteristic	n (%)			
	Before matching		After matching	
	DPP4I users (N=903)	SU users (N=6,075)	DPP4I users (N=892)	SU users (N=892)
Age, mean (SD) years	81 (8)	81 (8)	81 (8)	80 (8)
Female sex	652 (72)	4,282 (71)	644 (72)	661 (74)
Race				
Caucasian	651 (72)	4,593 (76)	648 (73)	628 (70)
African-American	145 (16)	963 (16)	142 (16)	155 (17)
Other	107 (12)	519 (8)	102 (11)	109 (13)
Chronic conditions				
Renal disease	97 (11)	572 (9)	96 (11)	96 (11)
Peripheral vascular disease	157 (17)	1,015 (17)	156 (18)	164 (18)
Diabetic retinopathy	16 (2)	116 (2)	16 (2)	9 (1)
Heart failure	284 (32)	1,744 (29)	281 (32)	272 (31)

Ischemic heart disease	162 (18)	927 (15)	159 (18)	153 (17)
Depression	509 (56)	3,399 (56)	504 (57)	483 (54)
COPD	192 (21)	1,223 (20)	191 (21)	202 (23)
Hypertension	692 (77)	4,681 (77)	683 (77)	710 (80)
Hip fracture	15 (2)	108 (2)	15 (2)	25 (3)
Number of comorbidities, median, (IQR)	6 (4-7)	5 (4-7)	6 (4-7)	6 (4-8)
ADL score, mean (SD)*	16 (8)	16 (8)	16 (8)	17 (7)
CPS score, mean (SD)*	3 (2)	3 (2)	3 (2)	3 (2)
CHESS score, mean (SD)	1 (1)	1 (1)	1 (1)	1 (1)
Number of medications prior to treatment initiation, mean (SD)	14 (5)	13 (5)	14 (5)	14 (5)
Medication use*				
Metformin	330 (37)	1,768 (29)	325 (36)	301 (34)
Statins	401 (44)	2,362 (39)	394 (44)	390 (44)
Clopidogrel	168 (19)	849 (14)	163 (18)	164 (18)
Warfarin	141 (16)	899 (15)	139 (16)	137 (15)

Antipsychotics	283 (31)	1,779 (29)	281 (32)	255 (29)
Steroids	110 (12)	751 (12)	109 (12)	122 (14)
Angiotensin-converting enzyme inhibitors	371 (41)	2,297 (38)	368 (41)	379 (43)
Angiotensin receptor blockers	140 (16)	682 (11)	135 (15)	136 (15)
Beta blockers	455 (50)	2,698 (44)	449 (50)	457 (51)
Length of nursing home stay before treatment initiation, median (IQR) days	623 (275-1,260)	586 (270-1,177)	628 (276-1,263)	604 (274-1,248)
Any physician visits in prior two weeks	531 (59)	3,518 (58)	519 (58)	536 (60)
Number of physician order changes in prior two weeks, mean (SD)	2 (2)	2 (2)	2 (2)	2 (2)
Any overnight hospitalizations in prior 90 days	287 (32)	1,792 (29)	282 (32)	295 (33)
Any ED visits in prior 90 days	71 (8)	490 (8)	70 (8)	75 (8)
Nursing Home Facility Characteristics				
Ownership				
For profit	657 (73)	4,317 (71)	648 (73)	626 (70)
Non-profit	193 (21)	1,341 (22)	192 (22)	210 (24)

Government	53 (6)	417 (7)	52 (6)	56 (6)
Quality indicators				
% of residents restrained, median (IQR)	2 (0-5)	2 (0-5)	2 (0-5)	2 (0-5)
No. of quality-of-life deficiencies, mean (SD)	4 (6)	4 (6)	4 (6)	4 (7)
% of residents with pressure sores, mean (SD)	7 (4)	7 (4)	7 (4)	7 (5)
Staffing				
Direct care hours/resident/day, mean (SD)	3 (1)	3 (1)	3 (1)	3 (1)

* ADL status was measured by the Morris 28-point ADL score, where higher values indicate greater dependency in ADLs. Cognitive status was measured by Cognitive Performance Scale (CPS), where higher values indicate greater cognitive impairment.

CHESS stands for Changes in Health, End-Stage Disease, Signs, and Symptoms.

Table 3.3. Outcome Events, Person-Years, and Rates Stratified by Dipeptidyl Peptidase-4 Inhibitors and Sulfonylurea Use.

			Unmatched			Matched		
Follow-up Period	**Outcome**	**Treatment**	**Events**	**Person-Years**	**Rate***	**Events**	**Person-Years**	**Rate***
90 days	Cognitive decline	DPP4I	4	213.4	18.7	4	210.9	19.0
		SU	33	1,433.8	23.0	9	211.4	42.6
	Altered Mental Status	DPP4I	9	213.1	42.2	9	210.6	42.7
		SU	68	1,430.6	47.5	13	211.0	61.6
	Physical Functional Decline	DPP4I	8	213.5	37.5	8	211.0	37.9
		SU	39	1,433.1	27.2	7	211.7	33.1
180 days	Cognitive decline	DPP4I	14	407.1	34.4	14	402.4	34.8
		SU	97	2,746.3	35.3	23	404.0	56.9
	Altered Mental Status	DPP4I	19	406.9	46.7	19	402.2	47.2
		SU	145	2,742.2	52.9	27	403.9	66.8
	Physical Functional Decline	DPP4I	23	407.0	56.5	23	402.4	57.2
		SU	135	2,742.5	49.2	26	404.3	64.3

*Per 1,000 person-years of follow-up

Table 3.4. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Cognitive Decline, Altered Mental Status Events, and Physical Functional Decline.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Cognitive Decline	90 days	0.82 (0.29-2.30)	0.45 (0.14-1.45)
	180 days	0.98 (0.56-1.71)	0.61 (0.31-1.19)
Altered Mental Status	90 days	0.88 (0.44-1.77)	0.69 (0.30-1.62)
	180 days	0.88 (0.55-1.42)	0.71 (0.39-1.27)
Physical Functional Decline	90 days	1.38 (0.65-2.95)	1.15 (0.42-3.17)
	180 days	1.15 (0.74-1.79)	0.89 (0.51-1.56)
Composite	90 days	1.19 (0.64-2.19)	0.86 (0.40-1.86)
	180 days	1.12 (0.78-1.61)	0.83 (0.53-1.31)

Table 3.5. Results from sensitivity analysis using a 2-point threshold for CPS score and a 4-point threshold for ADL score.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Cognitive Decline	90 days	1.50 (0.32-6.92)	1.00 (0.14-7.12)
	180 days	0.97 (0.34-2.75)	0.81 (0.22-3.00)
Physical Functional Decline	90 days	1.50 (0.62-3.62)	1.51 (0.43-5.35)
	180 days	1.19 (0.70-2.02)	0.95 (0.48-1.88)
Composite	90 days	1.19 (0.65-2.20)	0.87 (0.40-1.88)
	180 days	1.13 (0.78-1.62)	0.84 (0.53-1.32)

Table 3.6. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Cognitive Functioning, Altered Mental Status, and Physical Functioning Outcomes Using Generalized Boosted Regression to Estimate the Propensity Score.

Outcome	**Follow-up**	**Hazard Ratio (95% Confidence Interval)**
Cognitive Decline	90 days	0.50 (0.12-2.01)
	180 days	0.71 (0.34-1.45)
Altered Mental Status	90 days	0.99 (0.35-2.82)
	180 days	0.86 (0.43-1.73)
Physical Functional Decline	90 days	0.36 (0.12-1.15)
	180 days	0.68 (0.35-1.32)
Composite	90 days	0.47 (0.19-1.15)
	180 days	0.75 (0.45-1.26)

Footnote: Since misspecification of the propensity score estimation model is a possibility that can influence the results of our study, we employed generalized boosted regression as an alternative propensity score estimation approach. There were 752 new SU users

matched to 752 new DPP4I users. The distribution of propensity scores was nearly identical between the matched groups (P=0.95); the mean (SD) was 0.18 (0.07) in both the SU and DPP4I users.

Table 3.7. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Cognitive Functioning, Altered Mental Status, and Physical Functioning Outcomes Using Multiple Imputation of Missing Pretreatment Covariate Information.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Cognitive Decline	90 days	0.78 (0.28-2.18)	0.55 (0.15-2.04)
	180 days	0.92 (0.53-1.60)	0.69 (0.33-1.45)
Altered Mental Status	90 days	0.83 (0.41-1.66)	0.57 (0.22-1.50)
	180 days	0.81 (0.51-1.31)	0.64 (0.32-1.29)
Physical Functional Decline	90 days	1.45 (0.71-2.98)	1.14 (0.36-3.65)
	180 days	1.21 (0.79-1.85)	0.94 (0.51-1.74)
Composite	90 days	1.21 (0.67-2.18)	0.92 (0.37-2.29)
	180 days	1.13 (0.80-1.61)	0.89 (0.53-1.49)

Footnote: We were concerned about the sample size reduction due to missing pretreatment covariate information. We were also concerned that pretreatment covariate information might be missing for a reason related to the outcomes we studied. Therefore, we used multiple imputation to impute the missing information for covariates that were used to estimate the propensity score. No outcome

information was imputed. We assumed that the covariate information was missing at random. We used the fully conditional specification method (also known as iterative chained equations) with the discriminant function and logistic regression to impute the missing values because many covariates must only take on specific values. We multiply imputed 10 datasets. No auxiliary covariates were included in the imputation model, but all covariates used in the propensity score estimation model were included. To obtain the propensity score-matched estimates, we followed our primary analytic approach and performed the propensity score estimation and matching in each multiply imputed complete dataset. We then estimated the outcome model in each imputed dataset, and pooled the parameter estimates across the datasets using the formulas previously developed by Rubin.

Table 3.8. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Cognitive Functioning, Altered Mental Status, and Physical Functioning Outcomes Using Fine and Gray Models for the Competing Risk of Death.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Cognitive Decline	90 days	0.82 (0.24-2.05)	0.44 (0.12-1.36)
	180 days	0.97 (0.53-1.64)	0.61 (0.30-1.16)
Altered Mental Status	90 days	0.89 (0.41-1.69)	0.69 (0.29-1.60)
	180 days	0.88 (0.53-1.38)	0.88 (0.53-1.38)
Physical Functional Decline	90 days	1.38 (0.60-2.80)	1.14 (0.41-3.26)
	180 days	1.15 (0.72-1.75)	0.88 (0.50-1.55)
Composite	90 days	1.19 (0.61-2.11)	0.85 (0.39-1.85)
	180 days	1.12 (0.76-1.58)	0.83 (0.52-1.30)

Footnote Death is common in the nursing home setting and can preclude the observation of other events like cognitive and physical functioning outcomes. This creates two potential problems when using the Cox proportional hazards regression model. First, the independent censoring assumption that the future risk of those whose follow-up has ended can be represented by nursing home

residents who are followed longer. Such an assumption may be too bold for frail older individuals in the nursing home setting. Second, the Cox proportional hazards regression models attempt to project forward the experience of a censored nursing home resident by representing their experience with those residents who were followed longer. To extrapolate to a setting where death is not possible would be to project to a new population or the ability to extend lives, which alters the underlying conditions of the study. Therefore, we can acknowledge death as another possible outcome and end follow-up for other outcomes rather than attempt to project experience beyond nursing home residents' lifetimes. Since exposure to dipeptidyl peptidase-4 inhibitors versus sulfonylureas might be related to unmeasured confounding covariates that increase the risk of death, we were interested in examining outcomes on the cumulative incidence scale. To do so, we employed Fine and Gray regressions. These regressions adapt the essence of the Cox proportional hazards model to the cumulative incidence formulation by modeling a different kind of rate function. The Fine and Gray counts nursing home residents who die in the denominator of the rate. In doing so, the model acknowledges that individuals who succumb to a competing risk (like death) will not develop the event of interest and more importantly, does not require extrapolation to a setting where death is not possible.

Table 3.9. Impact of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Cognitive Functioning, Altered Mental Status, and Physical Functioning Outcomes Restricting to Prior Metformin Users Only.

		Hazard Ratio (95% Confidence Interval)	
Outcome	**Follow-up**	**Unmatched**	**Matched**
Cognitive Decline	90 days	Undefined	Undefined
	180 days	0.51 (0.16-1.65)	0.33 (0.07-1.66)
Altered Mental Status	90 days	1.19 (0.40-3.51)	0.50 (0.12-1.99)
	180 days	1.19 (0.55-2.57)	0.87 (0.31-2.41)
Physical Functional Decline	90 days	1.35 (0.29-6.37)	2.00 (0.18-22.05)
	180 days	1.36 (0.66-2.83)	1.00 (0.37-2.69)
Composite	90 days	0.60 (0.14-2.59)	0.67 (0.11-4.00)
	180 days	0.81 (0.40-1.64)	0.61 (0.25-1.49)

Footnote: Since metformin is often the preferred first-line medication used to treat type 2 diabetes mellitus, we restricted our study cohort and reanalyzed the data in this subset. Metformin users had received at least one dispensing of metformin in the 12 months

prior to the dipeptidyl peptidase-4 inhibitor or sulfonylurea initiation date. Residents were not required to continue taking metformin after they initiated a dipeptidyl peptidase-4 inhibitor or sulfonylurea.

Chapter 3 Figures

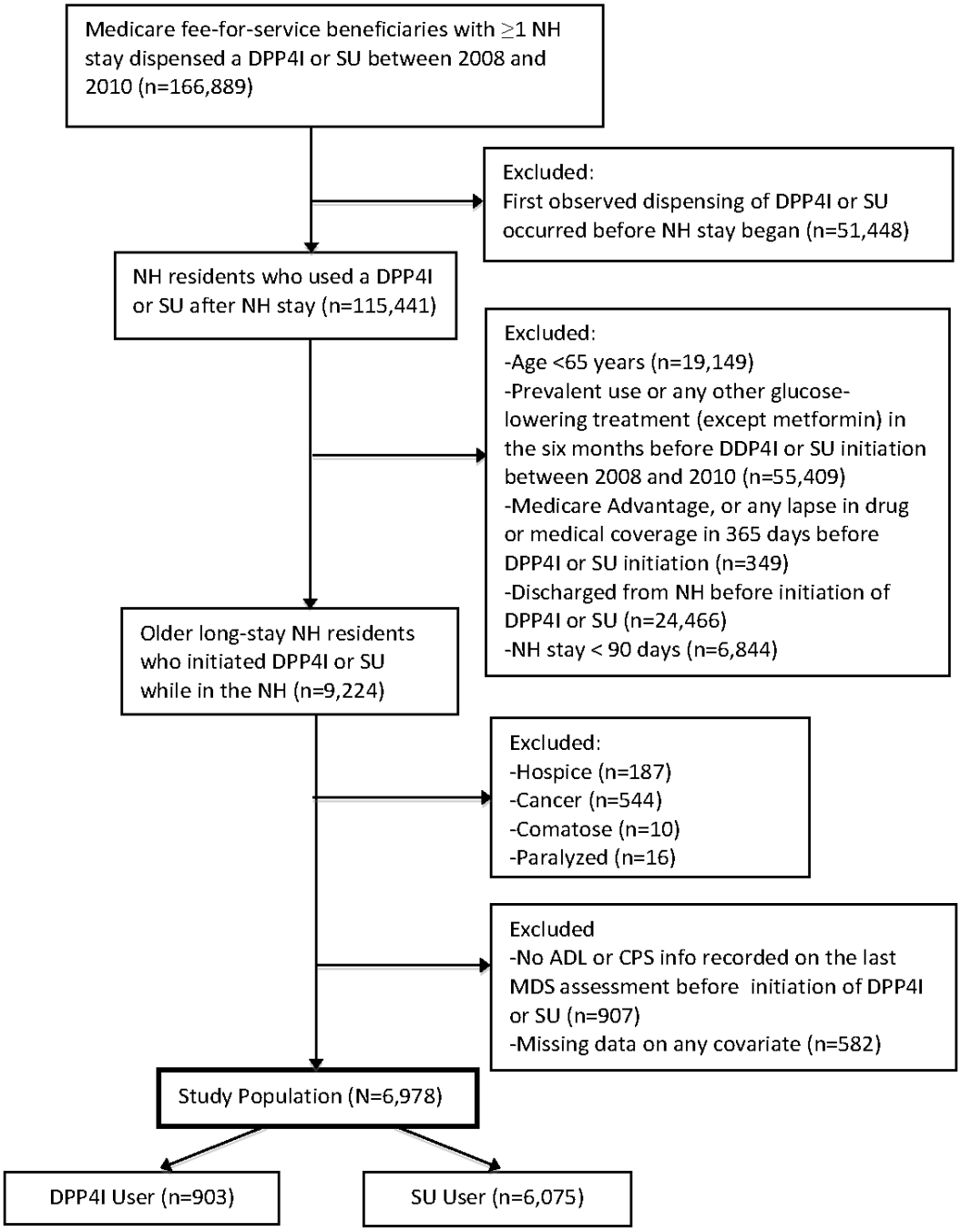

Figure 3.1. Flow diagram of study cohort creation.

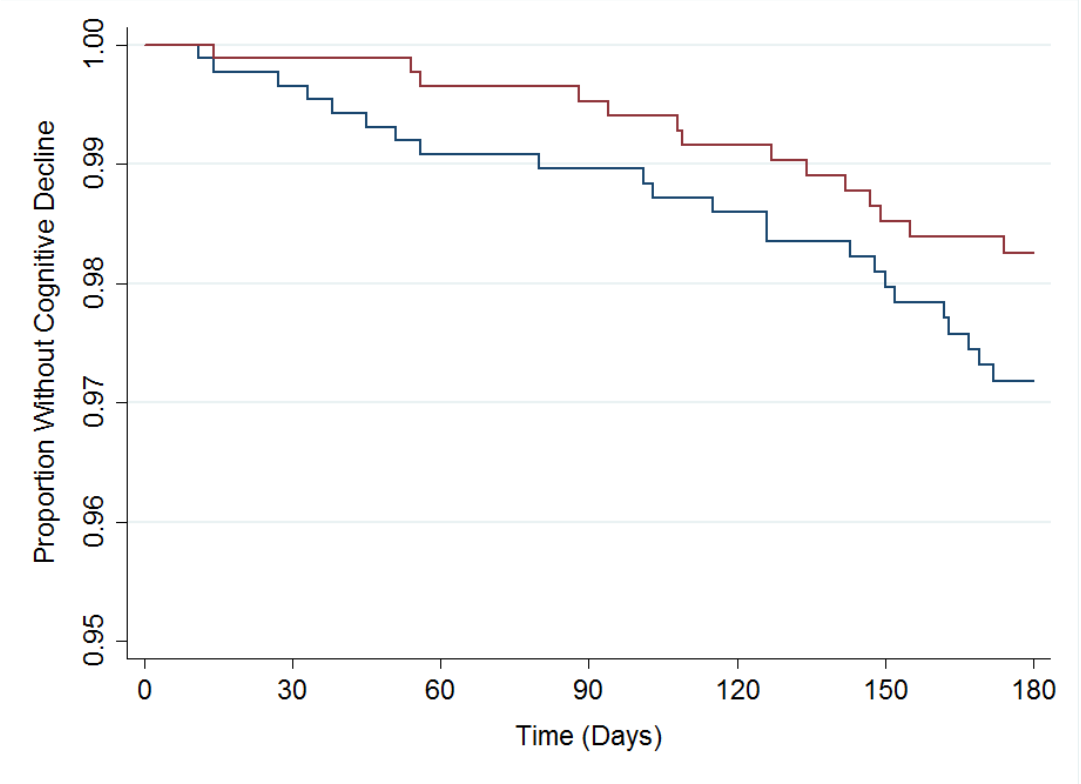

Figure 3.2. Kaplan Meier Plot of Cognitive Decline Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

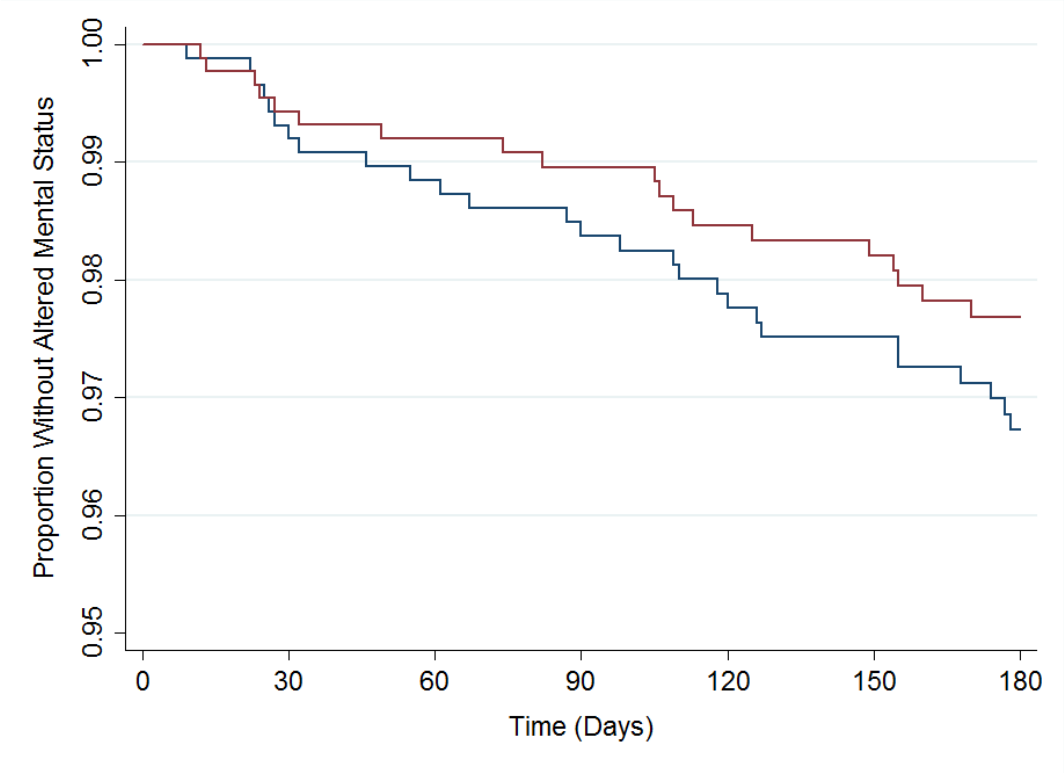

Figure 3.3. Kaplan Meier Plot of Altered Mental Status Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

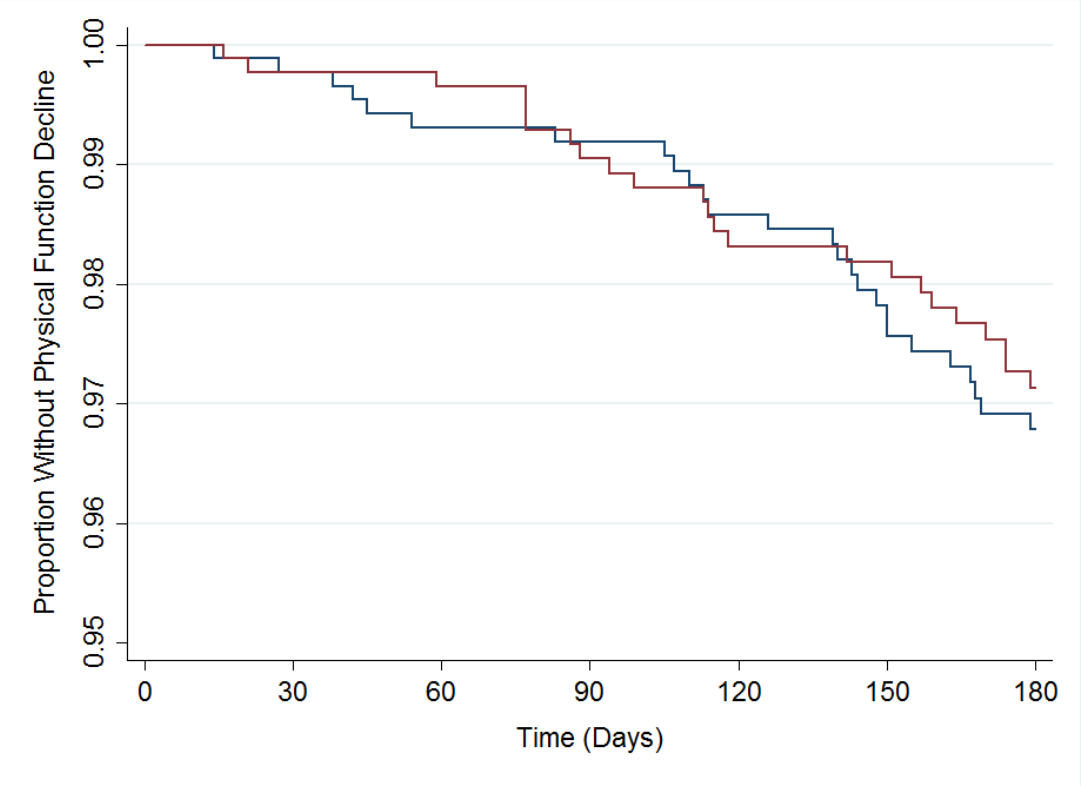

Figure 3.4. Kaplan Meier Plot of Physical Function Decline Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

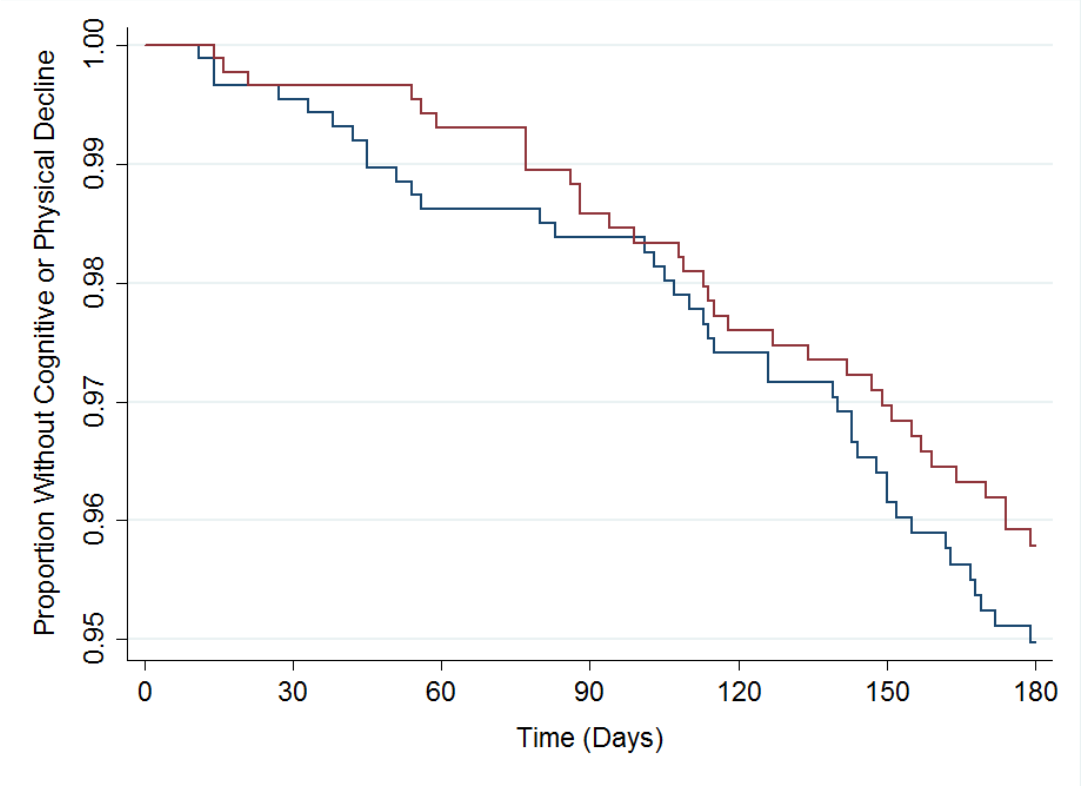

Figure 3.5. Kaplan Meier Plot of Cognitive or Physical Function Decline (Composite) Stratified by Dipeptidyl Peptidase-4 Inhibitor versus Sulfonylurea Use. Red lines are DPP4I users; blue lines are SU users. Lines are survival curves.

General Discussion

In the three chapters of this dissertation, we examined: 1) the frequency and determinants of initiating sulfonylureas over metformin with the aim of understanding the impact of the boxed warnings on metformin use in a nationally representative cohort of NH residents, with a focus on conditions included in the U.S. Food and Drug Administration (FDA)-labeled boxed warning for metformin; 2) the effect of dipeptidyl peptidase-4 inhibitors (DPP4Is) versus sulfonylureas (SUs) on mortality, adverse glycemic events, and cardiovascular events among long-stay NH residents age 65 and older; and 3) the effect of DPP4Is versus SUs on cognitive functioning, altered mental status events, and physical functioning among long-stay NH residents age 65 and older.

In Chapter 1, we found that patient conditions included in the FDA boxed warning were the strongest predictors of initiating monotherapy with SUs over metformin. These conditions included advanced age, heart failure, and renal disease. Few other patient characteristics were strong predictors of initiating sulfonylureas over metformin despite our large sample size.

In Chapter 2, we observed a decreased risk of hospitalization and emergency department visits for hypoglycemic and stroke events among new users of DPP4Is compared to new users of sulfonylureas. We did not observe any difference in the risk of hyperglycemia, acute myocardial infarction, or heart failure between the two treatment groups. To our knowledge, this is the first study to examine the comparative safety of DPP4Is and SUs for frail older adults in the NH setting.

In Chapter 3, we observed a decreased risk of significant cognitive decline and altered mental status events among new users of DPP4Is compared to new users of

sulfonylureas, though these estimates did not reach statistical significance at traditional significance levels. We did not observe any difference in the risk of declines in physical functioning between the two treatment groups. To our knowledge, this is the first study to examine the comparative functional effects of DPP4Is and SUs for frail older adults in the NH setting.

This dissertation has several key implications. First, the FDA should consider how their warnings will influence drug prescribing and health care in the nursing home setting. Second, in the absence of prior clinical trials that include NH residents and the lack of any planned future ones, to the best of our knowledge, our study suggests that DPP4Is may be preferred to optimize glycemic outcomes for older NH residents with diabetes. Finally, our study provides new critical evidence to guide patient-centered treatment decisions for NH residents with T2DM. Since many NH residents, their families, their caregivers, and their clinicians value maintaining functioning and quality of life more than extending lifespan or minimizing traditional clinical adverse events, our results suggest that DPP4Is may be the preferred second line therapy (over SUs) to achieve those goals.

Taken together, the findings from the three chapters of this dissertation can help improve the prescribing of diabetes treatments and subsequent health outcomes for older adults who reside in nursing homes. Future work should continue to fill the many gaps in the medical evidence that are created through the exclusion of older nursing home residents from clinical trials of medications.

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