Drug- and Dose-Specific Effects of Sulfonylureas on Cognition and Physical Functioning in Older Nursing Home Residents

By

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Thesis

Submitted in partial fulfillment of the requirements for the
Degree of Master of Science in the Department of Epidemiology at Brown University

PROVIDENCE, RHODE ISLAND

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RESUME

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PREFACE

A dissertation in the Department of Epidemiology takes the form of one publishable paper. This document was re-formatted to comply with the Graduate School requirements at Brown University.

To my daughter, Zeyana and my husband, Jakee.

Thank you for your immense support and encouragement.

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ABSTRACT

Background: Despite data from younger populations suggesting that glipizide is the preferred sulfonylurea due to its lower risk of adverse effects, long-acting sulfonylureas (glimepiride and glyburide) are still prescribed often and at non-geriatric initial doses in the nursing home (NH) setting, which may increase the risk of severe hypoglycemia and subsequently worsen functioning. Since different drugs and doses within the sulfonylurea class are associated with different risks of adverse effects that impacts cognitive and physical functioning, they may also affect cognition and functioning differently among older adults. Therefore, in this study we estimated the drug- and dose-specific effects of sulfonylureas on cognition and physical functioning among older NH residents.

Methods: We conducted a retrospective, new-user cohort study of NH residents in 2007-2010 using national data from the Minimum Data Set (MDS) and Medicare Parts A, B, and D claims (N=6,177). Follow-up began at the initial dispensing of a sulfonylurea and continued until each study outcome (evaluated separately), insurance disenrollment, death, 6-month follow-up, or study end, whichever occurred first. The five outcomes were cognitive decline, cognitive improvement, functional decline, functional improvement, and altered mental status hospitalization/emergency room visit. Cognitive decline and improvement were measured using the MDS Cognitive Performance Scale. Functional decline and improvement were measured using the MDS Activities of Daily Living Scale. Inverse-probability-of-treatment-weighted Cox models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to compare glimepiride versus glipizide and glyburide versus glipizide users. Using the same approach in a separate analysis, we evaluated geriatric versus non-geriatric initial dose.

Results: Glyburide users were less likely to have a functional improvement than glipizide users (HR=0.83, 95%CI 0.67-1.03), though this finding was non-significant. Compared to individuals receiving geriatric doses, those who received non-geriatric initial sulfonylurea doses had fewer functional decline (HR=0.89, 95%CI 0.80-0.99) and cognitive decline (HR=0.89, 95%CI 0.78-1.00) events. No other marked differences were observed by drug or dose.

Conclusions: We observed no difference in cognitive or physical functional events between individual sulfonylurea drug users. Non-geriatric initial sulfonylurea dose was associated with less cognitive and functional decline. Residual confounding remains a plausible explanation for the findings.

CHAPTER 1: INTRODUCTION AND STUDY OBJECTIVES

Diabetes increases the risk of cognitive impairment (1-7) and functional decline (8-11) in older adults, yet very few studies have examined the potential effects of glucose-lowering drugs on these patient-centered outcomes (1, 12-15). Understanding the effects of medications on such outcomes is especially important for frail older adults in the nursing home (NH) setting, where the prevalence of diabetes is over 30% and maximizing quality of life are of central importance to older adults, their families, and their clinicians (16-20).

The exact mechanism responsible for diabetes-related cognitive impairment is unclear. Several congruent factors have been speculated as contributing to cerebrovascular disease and neurodegeneration, including hyperinsulinemia, hyperglycemia, hypoglycemia, microvascular changes, and oxidative stress (21-22). Prior studies have suggested that diabetes-related declines in physical functioning may be attributable to the consequences of diabetes, including vascular disease, neuropathy, and reduced muscle strength. Metabolic pathways plausibly have an important role in the pathogenesis of cognitive and physical dysfunction (23).

By improving glycemic and metabolic control, glucose-lowering medications could mitigate declines in cognitive and physical functioning. Conversely, by causing hypoglycemia and other adverse effects, medications could also worsen these outcomes. Recent epidemiological studies have suggested that oral glucose-lowering drugs like sulfonylureas improve cognition and the ability to perform activities of daily living (12-13, 15).

Since drugs within the sulfonylurea class are associated with different risks of adverse effects (24-29), they may affect cognition differently. Similarly, different doses may also affect functioning differently. There are scarce data about the comparative effects of different sulfonylurea drugs and doses among frail older adults, especially those residing in NHs. Older adults in the NH are particularly susceptible to adverse drug and dose effects due to their frailty and other characteristics (30-32).

Therefore, in this study we estimated the effects of individual sulfonylureas and different doses on cognitive functioning, altered mental status events, and physical functioning among frail, older NH residents.

CHAPTER 2: OVERVIEW OF DATA AND METHODS

2.1 Data Sources and Subjects

We obtained data for this retrospective cohort study from a random 20% sample of Medicare Fee-For-Service beneficiaries with Medicare Parts A (inpatient), B (outpatient), and D (prescription drug) claims. The Medicare claims data included person-level information on demographics, Medicare eligibility, hospitalizations, and dispensing of prescription drugs. The claims data were linked to the Minimum Data Set (MDS) version 2.0, which is a standardized assessment tool that measures nearly all NH residents in the U.S. The comprehensive MDS assessments provide information on several domains including cognitive and physical functional status, psycho-social well-being, health conditions, and active diseases. The assessments occur at a minimum of every 3 months and more often for residents with a major recent change in clinical status (33). The claims and MDS data were additionally linked to the Online Survey Certification and Reporting System (OSCAR) data, which provides facility-level information on NH characteristics, staffing, and quality indicators.

Our study population comprised U.S. NH residents with diabetes who were aged 65 or older, who initiated a sulfonylurea between January 1, 2008 and September 30, 2010, and who had resided in a NH for at least 90 consecutive days (long-stay residents) prior to the initiation (see Supplementary Figure S1 for additional details). Residents with diabetes were identified if a diagnosis was present on any MDS assessment, which has been demonstrated as valid for identifying diabetes in NHs (34). Data from 2007 was available to ascertain prior glucose-lowering treatment use.

Residents were required to be in the NH at the time the sulfonylurea medication was initiated. We excluded prior recipients of sulfonylureas and defined the index date as the date of each resident's first eligible prescription. Residents who were prescribed any other glucose-lowering medication except metformin in the 6 months preceding the index date (prevalent users of any glucose-lowering medication other than metformin or sulfonylureas) were not included in this study to reduce confounding by prior glucose-lowering treatment use. We also excluded patients 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 sulfonylurea (n=644) (35). All patients were required to have 12 months of continuous Medicare enrollment during the study period preceding the index date. The study received ethical review and approval from the Brown University Institutional Review Board.

2.2 Measures

Our exposures of interest were new use of second-generation sulfonylureas (glimepiride, glipizide, glyburide) in the NH setting (36). We defined new use as a dispensing for a sulfonylurea after six months of no glucose-lowering treatment apart from metformin in Part D claims. Metformin was permitted because it is the recommended first-line treatment for type 2 diabetes (37-38). Since residents who had a contraindication to metformin can be managed by second-line agent monotherapy (without metformin) and the prevalence of contraindications is high in the NH setting, as supported by the prior studies (39-40), residents were not required to already be on metformin. We used National Drug Codes (NDCs) to identify sulfonylurea users from

Medicare Part D, which covers at least 81% of all NH residents during the study period and in most cases is the sole source of prescription drug coverage (41).

Another exposure of interest was the use of geriatric and non-geriatric initial sulfonylurea doses in the NH setting. Daily geriatric dosing at sulfonylurea initiation were defined as glipizide 2.5 mg, glimepiride 1 mg, and glyburide 1.25 mg (66). Any doses higher than geriatric dose were regarded as non-geriatric dosing.

Our five outcomes were cognitive decline, cognitive improvement, functional decline, functional improvement, and hospitalizations or emergency department (ED) visits for altered mental status. Cognitive decline or improvement was defined as an increase of 1 point or a reduction of 1 point, respectively, on the validated 6-point MDS Cognitive Performance Scale (CPS) between the pre-initiation baseline and any available MDS assessment following initiation, up to 180 days after initiation. The CPS scale ranges from 0 to 6, with a score of 0 representing intact cognition and a score of 6 representing very severe cognitive impairment (62). A 1-point cognitive change in MDS CPS scale is considered significant (42). We defined functional decline as an increase of 3 points and physical improvement as a decrease of 3 points on the validated Morris 28-point scale of independence in activities of daily living (ADLs), whereby a score of 0 represents no dependence in ADLs (intact physical functioning) and a score of 28 represents total dependence in ADLs (very severe impairment in physical functioning) (43). A 3-point alteration corresponds to a major change in independence in 1 ADL or incremental changes in 2 or more ADLs (44-45). 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

Part A inpatient hospital claim or 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 (46).

We considered each outcome individually to assess changes within 180 days, which is long enough to show clinically meaningful functional changes, but short enough that many of the frail older adults in our sample have not yet died. Death is a highly prevalent competing risk in the NH setting (46). We identified death using the Medicare enrollment file to use it for censoring in the primary analysis and additional stability analyses (described below).

Information on potential confounders including conditions and hospital admissions was obtained from Medicare Part A records, which have been shown to have higher specificity than MDS 2.0 checkboxes for detecting comorbidities and conditions (34, 63). Medicare Part B offered information on ED and healthcare utilization while Medicare Part D claims had data on each resident's prescription drug use including drug name, dosage, route of administration, quantity dispensed, and days supplied. Information on other patient characteristics, including pre-treatment physical functional (43) and cognitive status (50-51); 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 (35, 52), were obtained from MDS 2.0. The MDS 2.0 has demonstrated validity (47-48) and reliability (49) for assessing the health status of NH residents. Finally, we used the OSCAR dataset to evaluate a range of NH characteristics such as size, ownership status, quality of care, and staffing information.

2.3 Statistical Analyses and Modeling

We used propensity score matching methods to adjust for confounding by a range of baseline risk factors. Analogous to an intention-to-treat framework, we defined subjects as new users whereby individuals with an observed dispensing of sulfonylurea were considered exposed throughout the entire duration of the follow-up period (53). Similarly, for the dose analyses, individuals were assumed to be exposed to their initial dose throughout the duration of follow-up.

We estimated the propensity score via multinomial logistic regression models that used 190 covariates to predict use of sulfonylureas (reference group was glipizide use). Binomial logistic regression models with the same covariates were used to predict non-geriatric dose use for the dose analyses (reference group was geriatric dose). Continuous variables were modeled using restricted cubic splines with four knots (64). Variables included in the models were sociodemographic characteristics, chronic medical conditions, baseline medication use, prior hospitalization history, baseline functional and cognitive status, geriatric syndromes, nutrition and fluid status, and NH characteristics (see Supplementary Table S1 for full list of variables). We then constructed stabilized inverse probability of treatment weights (IP-weight). We confirmed that the sample average of the stabilized weights was close to 1, and that the distribution of the probabilities overlapped between the treatment groups (i.e., that the weights were well-behaved) (Supplementary Table S2). Standardized mean differences were used to assess covariate balance across treatment groups before and after IP-weighting.

We used IP-weighted Cox proportional hazards models with robust standard errors to determine the impact of drugs and doses on time to outcomes (54). Study

subjects were censored at the first occurrence of the primary outcomes, end of the six-month follow-up period, death, NH discharge, or disenrollment from Medicare.

Since death can be considered a competing risk for the outcome events, we conducted a stability analysis using inverse probability of censoring by death weights to determine the influence of censoring for death on study results. For that analyses, models were estimated by both the inverse probability of treatment and the inverse probability of remaining alive. We also examined outcomes at 365 days of follow-up to better understand the longer-term effects of prescribing sulfonylureas on cognition and physical function in stability analyses. To help determine whether our definition of sulfonylurea dose at initiation may have influenced our results, we performed separate stability analyses using traditional high and low dose definitions for sulfonylureas rather than geriatric and non-geriatric doses. Traditional low sulfonylurea standardized daily dose, which is higher than the dose of geriatric initial dose (glipizide 2.5 mg, glimepiride 1 mg, and glyburide 1.25 mg), was defined as glipizide 5 mg, glimepiride 2 mg, and glyburide 5 mg. Any doses greater than low dose were regarded as high dose. We also examined the interaction of drug and dose on the outcomes using separate models. All data management and analyses were implemented in SAS version 9.4 (SAS Institute, Cary, N.C.) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria.).

CHAPTER 3: RESULTS

3.1 Characteristics of Cohort Members

Our cohort included 6,177 new sulfonylurea users of which 3,335 (53.99%) received glipizide, 1,593 (25.79%) received glimepiride, and 1,249 (20.22%) received glyburide (Table 3-1). The mean age (SD) of the study population was 81.42 (8.13) years, majority of them were female (70.42%) and of Caucasian race (75.70%). At baseline, most of the residents had stable ADL (64.50%) and CPS (89.52%) scores that had not changed in the prior 3 months. Prominent comorbidities among the participants were hypertension (77.03%), depression (55.84%), non-Alzheimer's dementia (41.71%), and arthritis (33.63%). The majority of residents were using anti-depressants (57.01%). Beta-blockers (44.42%) and proton pump inhibitors (39.92%) were also prevalent.

Before weighting, glyburide users were less likely to have depression, hypertension, stroke, anemia, and renal failure, and more likely to have received anti-depressants, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, beta blockers and proton pump inhibitors medications in the prior 12 months (first three columns in Table 3-1). Glyburide users had a lower median length of NH stay than glipizide and glimepiride users. Additionally, glyburide users were more likely to have Alzheimer's and non-Alzheimer's dementia. IP-weighting resulted in excellent covariate balance between the sulfonylurea treatment groups (right three columns in Table 3-1).

When stratified by dose, 2,600 (42.09%) cohort members received geriatric dose and 3,577 (57.91%) received non-geriatric dose (Table 3-2). Compared to the geriatric dose users, non-geriatric dose users had a shorter median length of NH stay before treatment initiation, were less likely to have Alzheimer's dementia, and were less likely

to have received beta blockers and calcium channel blockers. However, non-geriatric dose users were more likely to have used metformin and to have an anxiety disorder, depression, or stroke before sulfonylurea initiation. Characteristics between the two treatment groups were well-balanced after IP-weighting.

3.2 Glimepiride Users

Glimepiride users appeared as likely as glipizide users to have functional decline (HR=1.00, 95% CI 0.88-1.14) and cognitive improvement (HR=1.01, 95% CI 0.80-1.26) within180 days of treatment initiation (Figure 3-1 and Supplementary Table S3). The risk for cognitive decline (HR=0.94, 95% CI 0.80-1.10), altered consciousness hospitalization (HR=0.87, 95% CI 0.58-1.33) and functional improvement (HR=0.92, 95% CI 0.76-1.12) was lower than the glipizide users, but these results were all highly compatible with chance. The results for the 365 day follow-up outcomes were qualitatively consistent with the main results (Figure 3-2 and Supplementary Table S4).

3.3 Glyburide Users

Within the first 180 days of treatment initiation, glyburide users had a similar rate of functional decline and cognitive improvement compared to the residents who received glipizide. The data also suggested that glyburide use was non-significantly associated with cognitive decline (HR=1.13, 95% CI 0.95-1.33) and altered consciousness (HR=0.74, 95% CI 0.46-1.18) events compared to glipizide users. The risk of functional improvement was 0.83 (95% CI, 0.67-1.03) times lower in glyburide users than those receiving glipizide, though this finding was highly compatible with chance (Figure 3-1

and Supplementary Table S3). Within 365 days post-initiation, results were similar to those of the main analyses (Supplementary Table S4).

3.4 Non-geriatric Dose Users

Compared to geriatric dose users, non-geriatric initial dose use resulted in less functional decline (HR=0.89, 95% CI 0.80-0.99) and cognitive decline (HR=0.89, 95%CI 0.78-1.00) within 180 days of treatment initiation (Figures 3-1 and Supplementary Table S5). This notable difference persisted within 365 days (HR=0.93, 95% CI 0.85-1.02 and HR=0.93, 95% CI 0.84-1.03), but was non-significant (Figure 3-2 and Supplementary Table S5). No other marked differences between dose groups were observed.

3.5 Traditional High Dose Users

Characteristics of traditional high dose and traditional low dose users are shown in Supplementary Table S6. Results were similar to non-geriatric dose use when we classified the dose as traditional high-dose and traditional low-dose (HR=0.82, 95% CI 0.71-0.93 for functional decline and HR=0.85, 95% CI 0.72-0.99 for cognitive decline) (Figures 3-1 and 3-2; Supplementary Table S7). High initial dose users were also less likely to experience altered consciousness hospitalization (HR=0.65, 95% CI 0.41-1.02) compared to the low initial dose users. No significant differences were observed for cognitive improvement, or functional improvement events between residents who initiated sulfonylurea at traditional high versus low doses.

3.6 Drug-Dose Interaction and Competing Risk of Death

We did not find any evidence of notable interaction between sulfonylurea drug and initial dose for cognitive or functional events (Supplementary Table S8) (P values for

interaction not shown). However, given the large number of drug-dose strata examined, the sample size may not have afforded sufficient statistical power to detect differences.

The main results for all outcome events were similar when we applied inverse probability of censoring by death weights in separate analyses (data not shown).

CHAPTER 4: DISCUSSION

In this large national cohort study of NH residents, we observed no significant difference in physical and cognitive functioning events among new users of glyburide compared to the new users of glipizide, since these estimates did not reach statistical significance at traditional significance levels. We did not observe any notable difference in the risk of cognitive and functional changes between the glimepiride and glipizide treatment groups. We found some evidence to suggest that higher initial sulfonylurea doses were associated with less functional decline and cognitive decline. To our knowledge, this is the first study to examine the comparative functional effects of individual sulfonylureas at different doses for frail older adults in the NH setting, where functioning and quality of life are often the most important outcomes to patients and their families.

Very few studies have examined the comparative effects of diabetes medications on cognition, physical functioning, or quality of life [in older adults] (55). Of the studies that have been done, the majority compared the impact of sulfonylurea to metformin (1, 12-13), and none evaluated the effect of individual sulfonylureas. The closest comparable evidence on cognitive and physical functioning is a study by Wu et al. (12), in which their research team evaluated the effect of metformin versus sulfonylurea on changes in cognitive and physical functioning in older Mexican Americans with diabetes mellitus. The study reported a protective role of sulfonylureas in preventing cognitive and functional decline. Their patient population was distinct from our cohort of frail, NH residents, limiting the comparability of the two studies. Likewise, Testa et al. (56) and Gradman et al. (57) reported better cognitive function and perpetual-motor function

among patients with diabetes receiving glipizide versus placebo or no treatment. Participants in Testa et al. were relatively younger while Gradman et al. only included patients with diabetes without any comorbid conditions (mean age: 58.6 years in Testa et al and 67.9 years in Gradman et al). Both of these studies followed patients for a relatively short period of time (15 weeks in Testa et al. and 7 months in Gradman et al.). Our results are not directly comparable to either study since we used only active comparators. However, we did observe less functional improvement among glyburide users compared to glipizide users, though this difference was not significant (HR 0.83, 95% CI 0.67-1.03).

To date, no studies have looked at the influence of different sulfonylurea doses on the cognition and functioning of older patients with diabetes. We found that residents who started sulfonylureas at non-geriatric dose compared to the geriatric dose users had significantly lower risks of cognitive and functional decline. Similar results were observed for traditional high and low dose users. Sulfonylureas are recommended to be initiated at lower doses in patients who are older or have comorbidities like kidney disease (37, 65). In our cohort, it is possible that individuals who started sulfonylureas at low doses were more likely to be sick or frail in ways that were not captured by the data, but that could have influenced prescribing behavior (i.e., confounding by prognosis or indication). This potential residual confounding may have contributed to the higher risk of cognitive and functional decline that we observed among geriatric dose users. Alternatively, it is possible that higher doses of sulfonylureas resulted in better glycemic control and less hyperglycemia, which in turn, resulted in improved cognition and functioning.

Our study has several limitations. Because it is an observational study without randomization of treatments, we cannot rule out the possibility of residual confounding. In particular, our study may have benefited from laboratory information on HbA1c 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. Moreover, individual sulfonylureas all have a similar place in therapy for treatment of type 2 diabetes, 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, effect estimates are often imprecise, mandating a more nuanced interpretation of the range of plausible 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) (59-60). 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 to increase the number of new sulfonylurea users available for comparison in the NH setting, and should examine effect modification by baseline duration of diabetes. Moreover, artificial censoring of the study participants for death might have introduced selection bias, though our use of inverse probability of censoring weights did not appreciably alter the results in stability analyses. 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 under-ascertainment is non-differential by treatment group

and the specificity of the MDS-based measures is high (33, 42, 45, 48), relative effect measures are unlikely to be biased (61). Since the MDS requirements do not differ by sulfonylurea use or 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 available to us 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 precise. Our demographically, geographically, and clinically diverse population aids the generalizability of the findings to frail, older adults in long-term care. This strength is particularly important given the systematic exclusion of older NH residents from clinical trials of drug 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, cognitive and physical function did not markedly differ by the use of glimepiride, glipizide or glyburide among older NH residents with diabetes in our large cohort. We also found that higher starting doses might be associated with less decline in cognitive and physical functioning, though confounding by indication could not be ruled out as an explanation. Additional studies are often needed to better understand the comparative safety and effectiveness of treatments in the NH setting, including the comparative effects of individual sulfonylureas on functioning and cognition. 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 selection of treatment for NH residents with type 2 diabetes. 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 patient-centered treatment decisions.

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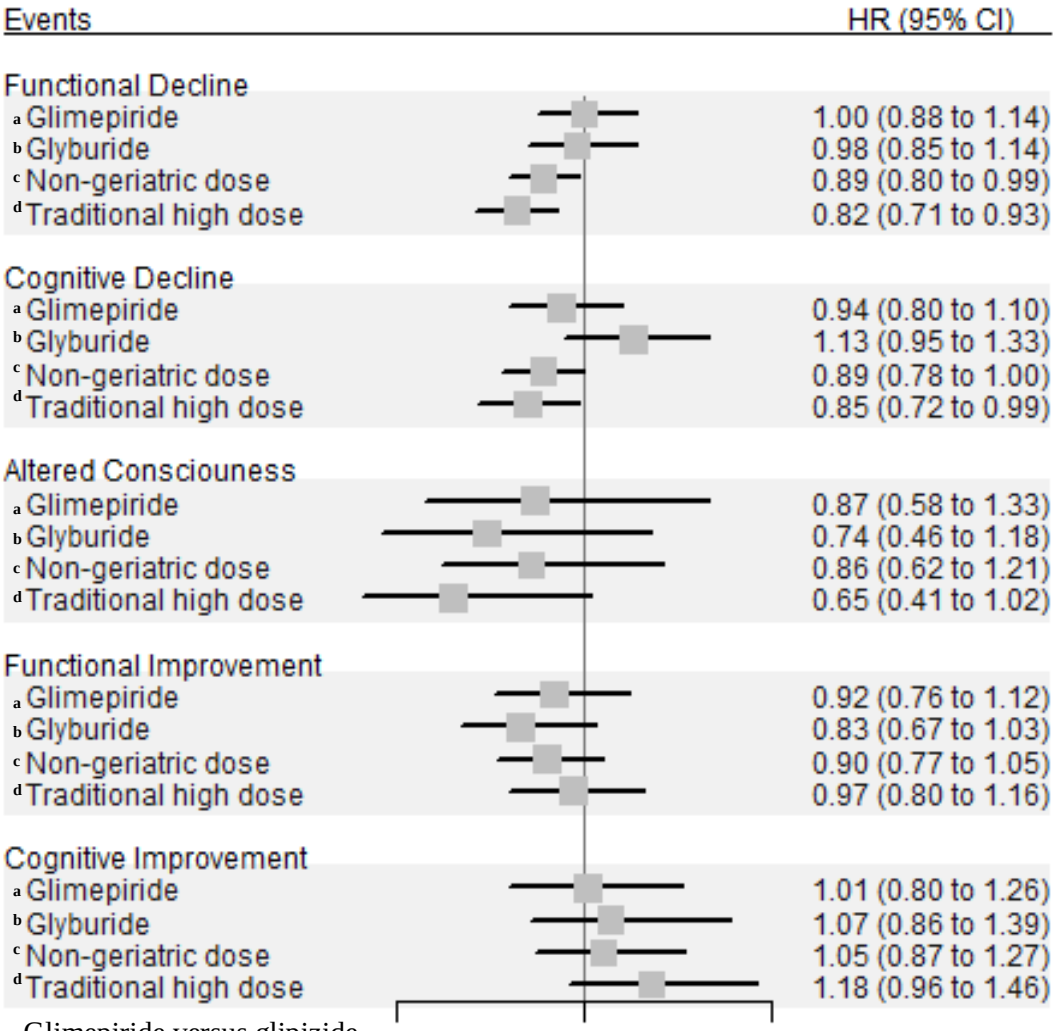
TABLES AND FIGURES

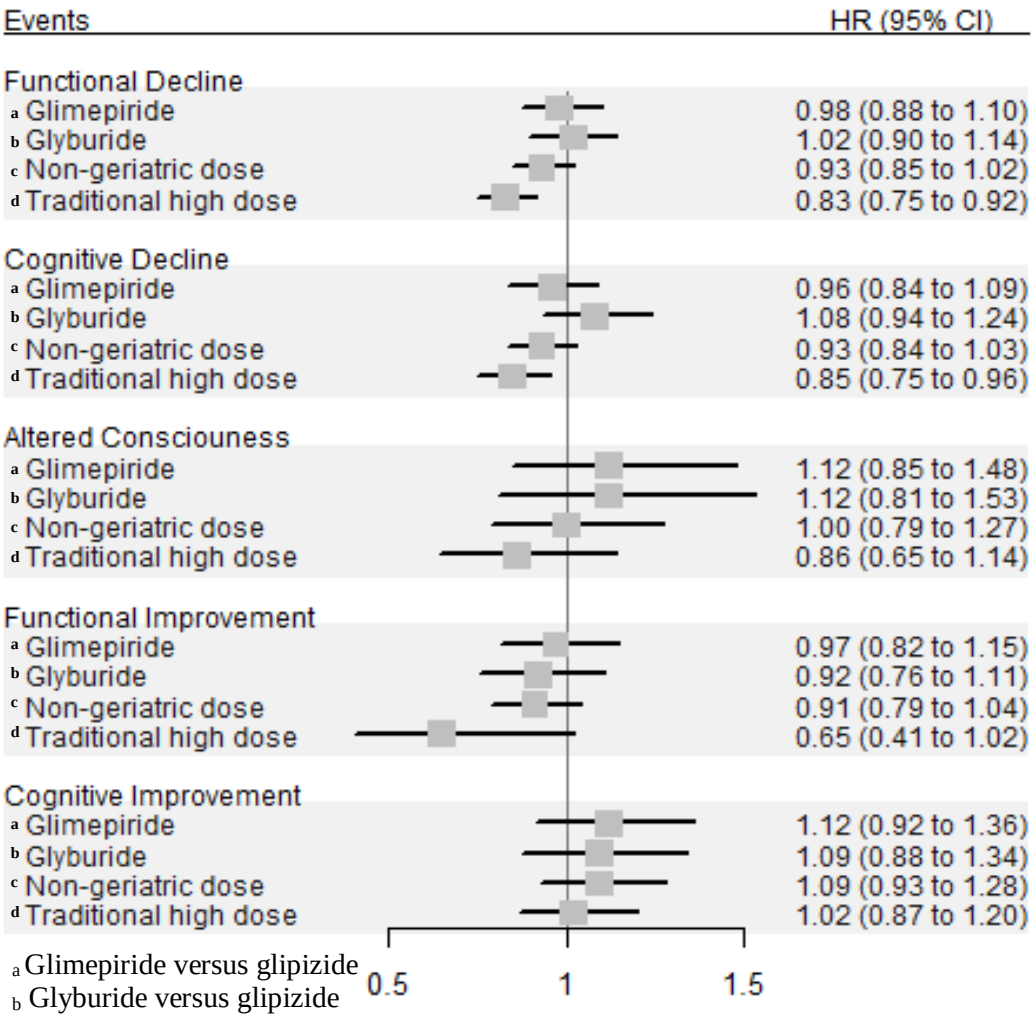
Figure 3-1: Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of outcome events within 180 days after inverse probability of treatment weighting.



[a] Glimepiride versus glipizide
[b] Glyburide versus glipizide
[c] Non-geriatric dose versus geriatric dose
[d] Traditional high dose versus traditional low dose

- Geriatric dose was defined as glipizide standardized daily dose = 2.5 mg, glimepiride standardized daily dose = 1 mg, and glyburide standardized daily dose = 1.25 mg.
- Doses higher than geriatric dose were defined as non-geriatric dose.
- Traditional low dose was defined as glipizide standardized daily dose = 5 mg, glimepiride standardized daily dose = 2 mg, and glyburide standardized daily dose = 5 mg.
- Doses higher than traditional low dose were defined as traditional high dose.

Figure 3-2: Hazard ratios (HRs) with 95% confidence intervals (95% CIs) of outcome events within 365 days after inverse probability of treatment weighting.



a Glimepiride versus glipizide
b Glyburide versus glipizide
c Non-geriatric dose versus geriatric dose
d Traditional high dose versus traditional low dose

- Geriatric dose was defined as glipizide standardized daily dose = 2.5 mg, glimepiride standardized daily dose = 1 mg, and glyburide standardized daily dose = 1.25 mg.
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- Doses higher than traditional low dose were defined as traditional high dose.

Table 3-1: Characteristics of all new sulfonylurea (n=6,177), glipizide (n=3,335), glimepiride (n=1,593), and glyburide (n=1,249) users at baseline and after inverse probability of treatment weighting.

Characteristics	%						
	All new SU users	Individual drug users					
		Unweighted (n=6,177)			Inverse probability weighted		
		Glipizide (53.99)	Glimepiride (25.79)	Glyburide (20.22)	Glipizide	Glimepiride	Glyburide
Age, mean (SD) years	81.42 (8.13)	81.48 (8.12)	81.13 (8.19)	81. 47 (8.14)	81.44 (8.13)	81.42 (8.04)	81.21 (8.17)
Female sex	70.42	69.74	72.42	69.67	70.57	71.14	70.11
Race/ethnicity							
White	75.70	73.13	78.67	79.03	75.79	76.84	76.44
Black	15.73	17.48	14.84	11.85	15.45	15.32	15.32
Hispanic	5.93	6.57	4.32	6.04	6.03	5.37	5.76
Other	2.72	2.80	2.19	3.13	2.67	2.51	2.57
Body mass index, kilograms/meters^2							
Underweight (<18.5)	2.43	2.54	2.34	2.51	2.43	2.44	2.42
Normal weight (18.5 to 24.9)	28.73	29.49	25.57	30.43	28.49	28.03	28.00
Overweight (25 to 30)	32.51	32.28	32.76	32.82	32.54	32.14	32.75
Obese (>30)	36.42	35.65	39.43	34.39	36.47	37.39	36.83
Number of comorbidities, mean (SD)	5.72 (2.72)	5.71 (2.68)	5.72 (2.69)	5.69 (2.75)	5.70 (2.67)	5.71 (2.65)	5.71 (2.67)
[a]ADL score, mean (SD)	15.83 (7.67)	15.84 (7.66)	15.86 (7.59)	15.63 (7.65)	15.81 (7.68)	15.85 (7.66)	15.64 (7.75)
ADL change past 90 days							
No change	64.50	64.00	65.32	65.29	64.61	64.30	64.79
Improved	6.53	6.69	6.65	6.04	6.49	6.56	5.84
Deteriorated	28.94	29.38	28.09	28.71	29.03	29.03	29.32
[b]CPS score, mean (SD)	2.61 (1.62)	2.60 (1.61)	2.62 (1.62)	2.54 (1.62)	2.61 (1.63)	2.62 (1.62)	2.61 (1.63)

Cognitive status change past 90 days							
No change	89.52	89.58	89.54	89.13	89.22	89.23	88.44
Improved	1.72	1.67	1.76	1.68	1.68	1.58	2.03
Deteriorated	8.93	8.85	8.75	9.19	9.09	9.18	9.58
Conditions							
Anxiety disorder	18.00	17.01	19.54	18.23	17.86	17.65	18.13
Depression	55.84	55.58	58.03	53.55	55.85	56.12	56.58
Bipolar disorder	4.24	4.13	4.31	4.16	4.02	4.06	3.85
Alzheimer's dementia	16.62	15.44	17.89	18.23	16.65	17.16	16.79
Non-Alzheimer's dementia	41.71	42.19	39.32	43.35	41.73	41.35	41.34
Ischemic heart disease	15.21	14.85	15.88	15.32	15.10	14.73	14.76
Congestive heart failure	28.83	29.57	27.67	27.87	28.29	28.28	28.29
Hypertension	77.03	77.52	76.94	76.10	76.76	76.94	77.41
Hypotension	1.11	1.10	1.13	1.23	1.13	1.03	1.10
Arthritis	33.63	33.32	33.87	34.19	33.45	33.87	33.79
Stroke	24.64	25.34	25.13	22.17	24.54	24.65	24.06
Epilepsy	6.23	6.29	6.20	5.79	6.13	5.93	6.54
COPD	20.24	20.58	19.69	19.87	20.13	19.77	20.01
Anemia	28.42	30.01	27.20	25.88	28.23	28.13	27.79
Renal failure	9.42	9.87	9.47	8.21	9.37	9.19	10.03
Medication use							
Anti-depressant	57.01	56.58	59.21	55.45	57.19	58.01	57.48
Anti-convulsant	20.93	20.54	22.21	20.58	20.78	21.04	21.79
Metformin	29.12	28.23	31.08	29.23	28.84	28.21	29.54
Proton pump inhibitor	39.92	39.09	42.76	38.30	39.91	40.45	40.70
ACE inhibitor	37.84	38.68	37.44	36.12	37.37	37.39	37.59
Alpha blocker	3.14	3.31	2.57	3.31	3.21	3.32	3.12
Anti-anxiety	3.03	2.56	3.53	3.45	3.14	3.00	3.23
ARB	11.14	10.54	14.21	9.03	11.09	11.41	11.50
Aspirin	2.12	2.04	2.43	2.04	2.13	2.02	2.21
Beta blocker	44.42	45.21	45.48	41.07	44.24	44.69	44.10

Calcium channel blocker	29.02	28.69	31.01	27.47	29.05	29.03	29.45
Clopidogrel	14.01	14.12	14.76	12.66	13.87	14.48	14.67
Length of nursing home stay before treatment initiation, median (IQR) days	584 (269-1,176)	580 (262-1,147)	610 (297-1,223)	571 (258-1,163)	578 (264-1,132)	576 (286-1,180)	598 (263-1,180)
Number of overnight hospitalizations in prior 90 days, mean (SD)	0.35 (0.55)	0.36 (0.54)	0.27 (0.57)	0.36 (0.56)	0.28 (0.58)	0.29 (0.55)	0.35 (0.58)
Number of ED visits in prior 90 days, mean (SD)	0.12 (0.33)	0.11 (0.32)	0.11 (0.37)	0.12 (0.36)	0.12 (0.33)	0.13 (0.38)	0.12 (0.32)
Number of physician order changes in prior two weeks, mean (SD)	1.77 (1.86)	1.76 (1.75)	1.79 (1.78)	1.75 (1.77)	1.77 (1.86)	1.97 (1.75)	1.86 (1.77)
Nursing Home Facility Characteristics							
Staff hours per resident, mean (SD)	2.87 (1.30)	2.90 (1.32)	2.84 (1.32)	2.87 (1.33)	2.91 (1.32)	2.92 (1.33)	2.89 (1.31)
Ownership							
Profit	70.87	69.43	71.83	73.79	71.21	71.12	71.43
Non-profit	22.22	23.08	22.14	19.93	21.86	22.30	21.79
Government	6.76	7.54	6.00	6.32	6.89	6.57	6.66
Quality indicators							
% of residents with pressure sores, mean (SD)	6.54 (4.20)	6.56 (4.32)	6.54 (3.93)	6.53 (4.02)	6.56 (4.42)	6.54 (3.84)	6.57 (4.00)
% of residents restrained, mean (SD)	3.33 (4.59)	3.34 (4.63)	3.42 (4.55)	3.31 (4.34)	3.32 (4.71)	3.33 (4.45)	3.32 (4.44)
% of residents receiving psychoactive drugs, mean (SD)	65.44 (13.23)	64.68 (13.42)	66.59 (12.21)	65.82 (13.78)	65.44 (13.32)	65.6 (12.53)	65.57 (13.79)

[a]ADL score was measured by the Morris ADL score, which ranges from 0 (totally independent, no impairment) to 28 (totally dependent, total impairment).

[b]Measured by the Cognitive Performance Scale, which ranges from 0 (intact cognition) to 6 (very severe cognitive impairment)

Abbreviations: SU, sulfonylurea; SD, standard deviation; ADL, activities of daily living; CPS, Cognitive Performance Scale; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; IQR, interquartile range.

Table 3-2: Characteristics of residents who received geriatric (n=2,600) versus non-geriatric doses (n=3,577) of sulfonylurea at baseline and after inverse probability of treatment weighting.

Characteristics	%			
	Unweighted (n=6,177)		Inverse probability weighted	
	[a]Geriatric dose (42.09)	[b]Non-geriatric dose (57.91)	[a]Geriatric dose	[b]Non-geriatric dose
Age, mean (SD) years	82.31 (8.00)	80.76 (8.18)	81.48 (8.11)	81.34 (8.14)
Female sex	71.27	69.72	70.46	70.32
Race/ethnicity				
White	74.81	76.40	75.57	75.64
Black	16.54	15.04	15.83	15.72
Hispanic	5.65	6.09	5.84	5.89
Other	3.00	2.46	1.61	2.16
Body mass index, kilograms/meters^2				
Underweight (<18.5)	3.04	1.98	2.50	2.47
Normal weight (18.5 to 24.9)	31.38	26.67	29.27	28.73
Overweight (25 to 30)	33.31	31.95	32.31	32.03
Obese (>30)	32.27	39.39	35.88	39.49
Number of comorbidities, mean (SD)	5.74 (2.70)	5.64 (2.77)	5.65 (2.65)	5.66 (2.76)
[c]ADL score, mean (SD)	16.14 (7.52)	15.52 (7.83)	15.75 (7.70)	15.76 (7.77)
ADL change past 90 days				
No change	64.15	64.91	64.43	64.55
Improved	6.50	6.54	6.53	6.36
Deteriorated	29.35	28.54	29.04	29.09
[d]CPS score, mean (SD)	2.63 (1.56)	2.55 (1.59)	2.59 (1.57)	2.58 (1.57)
Cognitive status change past 90 days				
No change	89.27	89.6	89.32	89.38
Improved	1.69	1.68	1.77	1.71

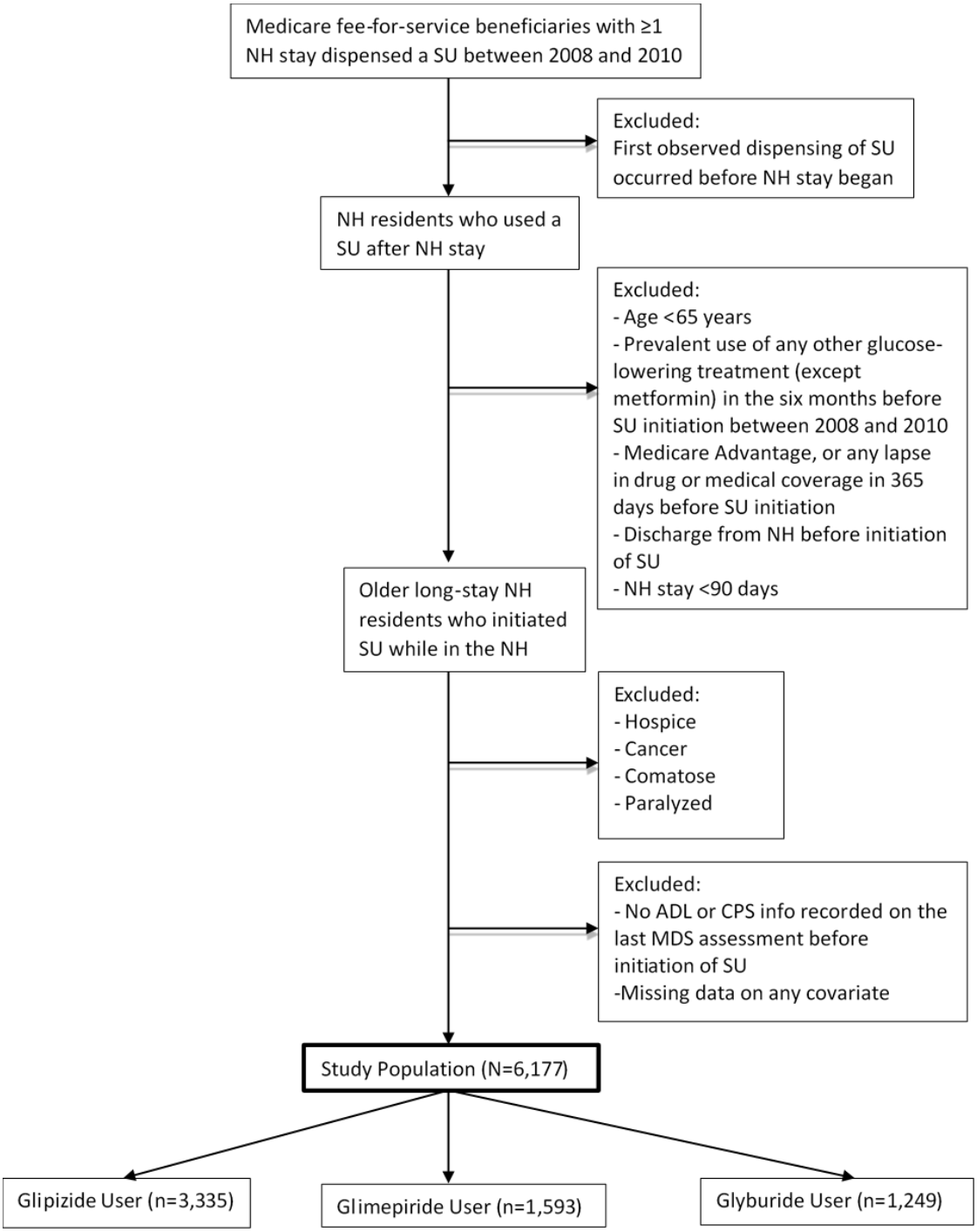
Deteriorated	9.04	8.72	8.91	8.91
Conditions				
Anxiety disorder	16.58	18.95	17.94	15.08
Depression	55.50	56.02	55.51	55.66
Bipolar disorder	3.92	4.33	4.15	4.18
Alzheimer's dementia	17.54	15.94	16.56	16.48
Non-Alzheimer's dementia	42.04	41.40	41.68	41.70
Ischemic heart disease	14.38	15.82	15.02	15.11
Congestive heart failure	29.46	28.24	28.51	28.50
Hypertension	76.69	77.27	77.06	77.02
Hypotension	1.00	1.23	1.11	1.15
Arthritis	33.19	33.94	33.54	33.60
Stroke	23.96	25.05	23.97	24.44
Epilepsy	6.62	5.84	6.19	6.14
COPD	20.12	20.30	19.90	20.15
Anemia	30.50	26.95	28.01	28.25
Renal failure	10.23	8.86	9.22	9.30
Medication use				
Anti-depressant	58.23	56.14	57.09	56.84
Anti-convulsant	20.92	20.94	20.98	20.99
Metformin	27.35	30.42	29.04	29.23
Proton pump inhibitor	40.42	39.50	40.18	39.91
ACE inhibitor	39.12	36.87	37.76	37.86
Alpha blocker	3.88	2.57	3.07	3.11
Anti-anxiety	3.15	2.94	2.96	2.97
ARB	11.00	11.24	10.99	10.99
Aspirin	2.19	1.98	2.00	2.07
Beta blocker	47.42	42.21	44.37	44.23
Calcium channel blocker	30.12	28.26	29.00	28.95
Clopidogrel	13.58	14.26	14.21	14.18
Length of nursing home stay before treatment	601	578	569	583

initiation, median (IQR) days	(276-1,180)	(263-1,170)	(264-1,134)	(266-1173)
Number of overnight hospitalizations in prior 90 days, mean (SD)	0.35 (0.63)	0.35 (0.61)	0.35 (0.63)	0.35 (0.60)
Number of ED visits in prior 90 days, mean (SD)	0.09 (0.33)	0.10 (0.37)	0.09 (0.34)	0.09 (0.35)
Number of physician order changes in prior two weeks, mean (SD)	1.86 (1.84)	1.84 (1.81)	1.85 (1.85)	1.85 (1.82)
Nursing Home Facility Characteristics				
Staff hours per resident, mean (SD)	2.92 (1.24)	2.87 (1.27)	2.89 (1.26)	2.89 (1.26)
Ownership				
Profit	68.65	72.83	71.03	71.19
Non-profit	23.58	20.88	22.01	21.97
Government	11.62	6.29	6.95	6.87
Quality indicators				
% of residents with pressure sores, mean (SD)	6.62 (4.42)	6.56 (4.12)	6.57 (4.89)	6.57 (4.13)
% of residents restrained, mean (SD)	3.26 (4.49)	3.37 (4.73)	3.31 (4.49)	3.33 (4.70)
% of residents receiving psychoactive drugs, mean (SD)	64.75 (13.22)	65.93 (13.17)	65.52 (13.03)	65.48 (13.19)

[a]Geriatric dose is defined as glipizide standardized daily dose = 2.5 mg, glimepiride standardized daily dose =1 mg, and glyburide standardized daily dose = 1.25 mg.
[b]Non-geriatric dose is defined as glipizide standardized daily dose > 2.5 mg, glimepiride standardized daily dose > 1mg, and glyburide standardized daily dose > 1.25 mg.
[c]ADL score was measured by the Morris ADL score, which ranges from 0 (totally independent, no impairment) to 28 (totally dependent, total impairment).
[d]Measured by the Cognitive Performance Scale, which ranges from 0 (intact cognition) to 6 (very severe cognitive impairment).
Abbreviations: SU, sulfonylurea; SD, standard deviation; ADL, activities of daily living; CPS, Cognitive Performance Scale; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; IQR, interquartile range.

APPENDIX 1: SUPPLEMENTARY TABLES AND FIGURES

Supplementary Figure S1: Flow diagram of study cohort creation.



Abbreviations: SU, sulfonylurea; NH, nursing home; ADL, Activities of Daily Living; CPS, Cognitive Performance Scale.

Supplementary Table S1: Covariates included in propensity score estimation model.

#	Covariate	Label
1	comorbidity_burden	Number of comorbidities
2	carryadl	Morris activities of daily living scale (0-28 point)
3	cna100t	Facility: total nurse aide full time equivalents per 100 beds
4	pt100t	Facility: total physical therapy full time equivalents per 100 beds
5	rn100t	Facility: total registered nurse full time equivalents per 100 beds
6	prov1090	Facility: pharmacist full time equivalents
7	restrain	Facility: Percentage of residents physically restrained
8	surv0690	Facility: medication error rate
9	n_qol_def	Facility: count of quality-of-life deficiencies
10	restrain	Facility: Percentage of residents physically restrained
11	paymcaid	Facility: Percentage of residents covered by Medicaid insurance
12	painmgmt	Facility: Percentage of residents on a pharmacy pain management program
13	antianx	Facility: Percentage of residents receiving antianxiety medications
14	antidep	Facility: Percentage of residents receiving antidepressants
15	bedsores	Facility: Percentage of residents with bedsores
16	acuindex2	Facility: acuity of residents (acuity index)
17	advdir	Facility: Percentage of residents with advance directives
18	carrynummeds	Medication Burden (Number of medications)
19	durationofpreindexnhstay	Duration of nursing home stay before sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation
20	carrymdorderchngs	Number of orders changed by physician
21	carrymdvisits	Number of physician visits
22	dmsex	Female sex
23	dmrace	Race/ethnicity
24	agecat	Age at index treatment initiation
25	carrymarried	Marital status
26	edcat	Highest educational attainment
27	carrylanguage2	Primary language spoken
28	carrychurch	Customary routine includes usual attendance at church, temple, synagogue, or other place of worship

29	bmicat	Body mass index at index treatment (DPP4 or SU) initiation
30	carrydiabetes	Diabetes mellitus
31	carryhyperthy	Hyperthyroidism
32	carryhypothy	Hypothyroidism
33	carryarterhrtdz	Ischemic heart disease
34	carryarrhythmias	Arrhythmias
35	carrychf	Heart failure
36	carrydvt	Deep vein thrombosis
37	carryhypotn	Hypotension
38	carryhtn	Hypertension
39	carrypvd	Peripheral vascular disease
40	carryothercvd	Other (non-ischemic) cardiovascular disease
41	carryarthritis	Arthritis
42	carrymissinglimb	Missing limb
43	carryosteoporosis	Osteoporosis
44	carrybonefracture	Bone fracture (other than hip)
45	carryalzheimers	Alzheimer's disease
46	carryaphasia	Aphasia
47	carrystroke	Stroke
48	carrydem	Non-Alzheimer's dementia
49	carryresistinfxn	Antibiotic-resistant infection
50	carryrespinfxn	Respiratory infection
51	carryepilepsy	Seizure disorder
52	carryanx	Anxiety disorder
53	carrydepression	Depression
54	carrybipol	Bipolar disorder
55	carryemphcopd	Emphysema/chronic obstructive pulmonary disease
56	carrycatar	Cataracts
57	carrydiabretinopathy	Diabetic retinopathy
58	carryglaucoma	Glaucoma
59	carrymacdegen	Macular degeneration
60	carryanemia	Anemia
61	carryrenaldx	Renal failure
62	carryuti	Urinary tract infection
63	carrywoundinfxn	Wound infection
64	carrychronicprobflare	Any acute episode or a flare-up of a recurrent or chronic health problem
65	accidfallanypartabefore	Accidental fall hospitalization
66	accidfallanypartbbefore	Accidental fall emergency department visit
67	ichanypartabefore	Intracranial hemorrhage hospitalization

68	ichanypartbbefore	Intracranial hemorrhage emergency department visit
69	strokeanypartabefore	Stroke hospitalization
70	strokeanypartbbefore	Stroke emergency department visit
71	amianypartabefore	Acute myocardial infarction hospitalization
72	amianypartbbefore	Acute myocardial infarction emergency department visit
73	hypoglyanypartabefore	Hypoglycemia hospitalization
74	hypoglyanypartbbefore	Hypoglycemia emergency department visit
75	hyperglyanypartabefore	Hyperglycemia hospitalization
76	hyperglyanypartbbefore	Hyperglycemia emergency department visit
77	hipfxanypartabefore	Hip fracture hospitalization
78	hipfxanypartbbefore	Hip fracture emergency department visit
79	alterconsanypartabefore	Altered mental status hospitalization
80	alterconsanypartbbefore	Altered mental status emergency department visit
81	hfanypartabefore	Heart failure hospitalization
82	hfanypartbbefore	Heart failure emergency department visit
83	carryweightchange	Weight gain or loss of 3 or more pounds
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
85	carryadlchngninety	Change in ability to perform activities of daily living
86	carrycps	Cognitive status (Fries and Morris Cognitive Performance Scale score)
87	carrypain	Highest level of pain 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
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
90	carrycogabilvary	Cognitive ability varies over time
91	carrybowelcont	Bowel incontinence
92	carrybladdercont	Bladder incontinence
93	carrypressulcstage	Pressure ulcers, presence and stage
94	carrydizziness	Dizziness/vertigo in prior 7 days on last MDS assessment prior to index treatment (DPP4 or SU) initiation

95	carryRP01A	Delirium resident assessment triggered
96	carryhallucintns	Hallucinations
97	carryhearingaidnotused	Hearing aid present and not used regularly
98	carryhearingaidused	Hearing aid present and used
99	carrysidevisprob	Side vision problems or decreased peripheral vision
100	carryvisualapp	Glasses, contact lenses, or magnifying glass used
101	carrycutsortears	Skin tears or cuts (other than surgery)
102	carryedema	Edema
103	anymetformintwelv	Metformin use in the 12 months prior to index treatment (DPP4 or SU) initiation
104	anyinsulinintermediatetwelv	Intermediate-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
105	anyinsulinlongtwelv	Long-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
106	anyinsulinrapidtwelv	Rapid-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
107	anyinsulinshorttwelv	Short-acting insulin use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
108	anythiazolstwelv	Thiazolidinedione use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
109	anyaglucosidaseinhibstwelv	Alpha-glucosidase inhibitor use >6 months but ≤12 months prior to index treatment (DPP4 or SU) initiation
110	otherhtndrugstwelv	Miscellaneous anti-hypertensive use in the 12 months prior to index treatment (DPP4 or SU) initiation
111	protonpumpitwelv	Proton pump inhibitor use in the 12 months prior to index treatment (DPP4 or SU) initiation
112	raloxifenetwelv	Raloxifene use in the 12 months prior to index treatment (DPP4 or SU) initiation
113	antiarrhythmicstwelv	Antiarrhythmics use in the 12 months prior to index treatment (DPP4 or SU) initiation
114	anyaceistwelv	Angiotensin-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
116	anybenzostwelv	Benzodiazepine use in the 12 months prior to index treatment (DPP4 or SU) initiation
117	anyarbstwelv	Angiotensin receptor blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation

118	anyaspirintwelv	Aspirin use in the 12 months prior to index treatment (DPP4 or SU) initiation
119	anybetablockerstwelv	Beta blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation
120	anybileacidresinstwelv	Bile acid resin use in the 12 months prior to index treatment (DPP4 or SU) initiation
121	anycalciumchnlblockerstwelv	Calcium channel blocker use in the 12 months prior to index treatment (DPP4 or SU) initiation
122	anyclopidogreltwelv	Clopidogrel use in the 12 months prior to index treatment (DPP4 or SU) initiation
123	anydepressanttwelv	Antidepressant use in the 12 months prior to index treatment (DPP4 or SU) initiation
124	anyezetimibetwelv	Ezetimibe use in the 12 months prior to index treatment (DPP4 or SU) initiation
125	anyfibratestwelv	Fibrate use in the 12 months prior to index treatment (DPP4 or SU) initiation
126	anygabapregabtwelv	Gabapentin or pregabalin use in the 12 months prior to index treatment (DPP4 or SU) initiation
127	anyglucagontwelv	Glucagon use in the 12 months prior to index treatment (DPP4 or SU) initiation
128	anyksparingdiureticstwelv	Potassium-sparing diuretic use in the 12 months prior to index treatment (DPP4 or SU) initiation
129	anylaopioidtwelv	Long-acting opioid use in the 12 months prior to index treatment (DPP4 or SU) initiation
130	anymoodtwelv	Mood-stabilizing medication use in the 12 months prior to index treatment (DPP4 or SU) initiation
131	anymuscletwelv	Muscle relaxant medication use in the 12 months prior to index treatment (DPP4 or SU) initiation
132	anyniacintwelv	Niacin use in the 12 months prior to index treatment (DPP4 or SU) initiation
133	anynonbenzohypnotwelv	Nonbenzodiazepine hypnotics in the 12 months prior to index treatment (DPP4 or SU) initiation
134	anyomega3fatwelv	Omega-3 fatty acid medication use in the 12 months prior to index treatment (DPP4 or SU) initiation
135	anypsychotictwelv	Antipsychotics use in the 12 months prior to index treatment (DPP4 or SU) initiation
136	anystatinstwelv	Statins use in the 12 months prior to index treatment (DPP4 or SU) initiation
137	anysteroidtwelv	Oral steroids use in 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
139	anywarfarintwelv	Warfarin use in the 12 months prior to index treatment (DPP4 or SU) initiation
140	bisphosphonatestwelv	Bisphosphonates use in the 12 months prior to

		index treatment (DPP4 or SU) initiation
141	carrymedsadlseat	Resisted taking medications, activities of daily living assistance, or eating
142	carrynewmeds	Number of new medications
143	carryivmeds	Any intravenous medications
144	carrytasteproblem	Complains about the taste of many foods
145	carrytwentfiveuneat	Leaves 25% or more of food uneaten at most meals
146	carryplnweightprgm	On a planned weight change program
147	carryparenteralfeed	Parenteral/intravenous feeding
148	carrymechanaltdiet	Mechanically altered diet
149	carrytxdiet	Therapeutic diet
150	carrydietsupplement	Dietary supplement between meals
151	carrychewproblem	Chewing problems
152	carryRP12B	Nutrition status care plan implemented
153	carryRP14A	Dehydration/fluid status resident assessment triggered
154	carryRP14B	Dehydration/fluid status care plan implemented
155	carryfeedrestrict	Feeding restrictions advanced directive documented in the medical record
156	carryRP12A	Nutritional status resident assessment triggered
157	carrytoothloss	Some or all natural teeth were lost
158	carrytobacco	Customary routine includes use of tobacco at least daily
159	carryalcohol	Customary routine includes alcoholic beverages at least weekly
160	carryabnormlabs	Abnormal laboratory values
161	hypoglyanypartabefore	Hypoglycemia hospitalizations
162	hypoglyanypartbbefore	Hypoglycemia emergency department visit
163	caretransitions	Transitions in care setting
164	carryostomy	Ostomy (bowel)
165	carrydialysis	Dialysis use
166	carryventilator	Ventilator or respirator use
167	carryskinutrition	Nutrition or hydration intervention to manage skin problems
168	carrypreventfootcr	Received preventative or protective foot care
169	carrymentaleval	Evaluation by a licensed mental specialist
170	carryexercisepref	Prefers exercise or sports
171	carrydonothosp	Do not hospitalize advanced directive documented in the medical record
172	carrydonotresus	Do not resuscitate advanced directive documented in the medical record
173	carryselfsuffchng	Significant change in self-sufficiency as compared

		to status of 90 days ago or since last assessment if less than 90 days
174	carryselfinitact	At ease doing self-initiated activities
175	carryestabgoals	Established own goals
176	carrycommuniscale	Communication scale (communication performance)
177	carrycommchange	Change in ability to express, understand, or hear information
178	carrybehaviorsc	Problem behaviors present
179	carrybehaviorchng	Change in behavior status as compared to 90 days ago or since last assessment if less than 90 days
180	carryparticipatefam	Family participation in resident's care
181	carrysocialcontact	Customary routine includes daily contact with relatives or close friends
182	carryresponsibfm	Family member responsible for resident
183	hours	Facility: Staff hours per resident
184	multifac	Facility: part of a nursing home chain
185	owner	Facility: Class of ownership (for-profit, non-profit, government)
186	prov1535	Facility: Organized family group
187	ppcat	Facility: % of other private pay clients
188	yearoftx	Year of sulfonylurea or dipeptidyl peptidase-4 inhibitor initiation
189	carryedvisits	Number of emergency department visits
190	carryovrnghthosp	Number of overnight hospitalizations

Supplementary Table S2: The distribution of the stabilized inverse probability of treatment and censoring by death weights.

Characteristic	**IPTW**	**IPCW[a]**
Mean (SD)	1.00 (0.37)	1.04 (0.54)
Median (IQR)	0.92 (0.78 - 1.13)	0.87 (0.82 - 1.04)
Minimum	0.29	0.27
1st percentile	0.45	0.34
99th percentile	2.29	3.43
Maximum	6.12	8.67

[a]IPCW used only in a stability analysis, not in the primary analyses.
Abbreviations: SD, standard deviation; IQR, interquartile range; IPTW, inverse probability of treatment weights; IPCW, inverse probability of censoring by death weights.

Supplementary Table S3: 180-days cognitive and functional change events, person-years, rates, and hazard ratios associated with glipizide (n=3,335), glimepiride (n=1,593), and glyburide (n=1,249) use.

Outcome	Treatment	Events	PY	Rate / 1000 PY (95% CI)	Unweighted		Inverse probability weighted	
					Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Decline events								
Functional decline	Overall	1,499	2,441.40	613.99 (583.30-645.88)	---	---	---	---
	Glipizide	809	1,321.56	612.16 (570.69-655.83)	Ref	Ref	Ref	Ref
	Glimepiride	395	628.15	628.83 (568.34-694.01)	1.03 (0.91-1.16)	0.66	1.00 (0.88-1.14)	0.96
	Glyburide	295	491.70	599.96 (533.44-672.48)	0.98 (0.86-1.12)	0.77	0.98 (0.85-1.14)	0.79
Cognitive decline	Overall	1,103	2,543.36	433.68 (408.46-460.05)	---	---	---	---
	Glipizide	585	1,378.98	424.23 (390.54-460.04)	Ref	Ref	Ref	Ref
	Glimepiride	281	657.84	427.16 (378.67-480.13)	1.01 (0.87-1.16)	0.93	0.94 (0.80-1.10)	0.43
	Glyburide	237	506.55	467.87 (410.20-531.38)	1.10 (0.95-1.28)	0.20	1.13 (0.95-1.33)	1.16
Altered consciousness hospitalization	Overall	148	2,733.23	54.14 (45.78-63.61)	---	---	---	---
	Glipizide	87	1,478.87	58.83 (47.12-72.56)	Ref	Ref	Ref	Ref

	Glimepiride	35	708.24	49.42 (34.42-68.73)	0.84 (0.57-1.24)	0.38	0.87 (0.58-1.33)	0.53
	Glyburide	26	546.12	47.61 (31.10-69.76)	0.81 (0.52-1.25)	0.34	0.74 (0.46-1.18)	0.21
Improvement events								
Functional improvement	Overall	714	2,604.13	274.18 (254.44-295.05)	---	---	---	---
	Glipizide	410	1,400.18	292.82 (265.16-322.58)	Ref	Ref	Ref	Ref
	Glimepiride	180	677.18	265.81 (228.39-307.60)	0.91 (0.76-1.08)	0.28	0.92 (0.76-1.12)	0.39
	Glyburide	124	526.77	235.40 (195.79-280.66)	0.81 (0.66-0.99)	0.03	0.83 (0.67-1.03)	0.09
Cognitive improvement	Overall	509	2,668.99	190.71 (174.50-208.02)	---	---	---	---
	Glipizide	264	1,445.28	182.66 (161.29-206.08)	Ref	Ref	Ref	Ref
	Glimepiride	133	690.32	192.66 (161.31-228.33)	1.06 (0.86-1.30)	0.62	1.01 (0.80-1.26)	0.96
	Glyburide	112	533.39	209.98 (172.90-252.66)	1.15 (0.92-1.43)	0.22	1.07 (0.86-1.39)	0.47

Abbreviations: PY, person years; Ref, reference category.

Supplementary Table S4: 365-days cognitive and functional change events, person-years, rates, and hazard ratios associated with glipizide (n=3,335), glimepiride (n=1,593), and glyburide (n=1,249) use.

Outcome	Treatment	Events	PY	Rate / 1000 PY (95% CI)	Unweighted		Inverse probability weighted	
					Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Decline events								
Functional decline	Overall	2,205	3,969.63	555.47 (532.52-579.15)	---	---	---	---
	Glipizide	1,191	2,146.80	554.78 (523.72-587.20)	Ref	Ref	Ref	Ref
	Glimepiride	561	1,019.51	550.26 (505.67-597.74)	0.99 (0.90-1.10)	0.87	0.98 (0.88-1.10)	0.77
	Glyburide	453	803.32	563.91 (513.17-618.31)	1.02 (0.91-1.13)	0.75	1.02 (0.90-1.14)	0.80
Cognitive decline	Overall	1,617	4,264.67	379.16 (360.90-398.10)	---	---	---	---
	Glipizide	861	2,313.55	372.16 (347.71-397.87)	Ref	Ref	Ref	Ref
	Glimepiride	412	1,098.58	375.03 (339.67-413.05)	1.01 (0.90-1.13)	0.91	0.96 (0.84-1.09)	0.48
	Glyburide	344	852.53	403.50 (361.99-448.48)	1.09 (0.96-1.23)	0.20	1.08 (0.94-1.24)	0.27
Altered consciousness hospitalization	Overall	310	4,900.72	63.26 (56.41-70.70)	---	---	---	---
	Glipizide	161	2,655.41	60.63 (51.63-70.75)	Ref	Ref	Ref	Ref

	Glimepiride	85	1,262.07	67.35 (53.80-83.28)	1.11 (0.86-1.45)	0.43	1.12 (0.85-1.48)	0.42
	Glyburide	64	983.24	65.09 (50.13-83.12)	1.07 (0.80-1.43)	0.64	1.12 (0.81-1.53)	0.50
Improvement events								
Functional improvement	Overall	931	4,480.46	207.79 (194.66-221.58)	---	---	---	---
	Glipizide	515	2,412.99	213.43 (195.39-232.68)	Ref	Ref	Ref	Ref
	Glimepiride	246	1,155.86	212.83 (187.06-241.15)	0.99 (0.85-1.16)	0.93	0.97 (0.82-1.15)	0.72
	Glyburide	170	911.61	186.48 (159.50-216.72)	0.88 (0.74-1.04)	0.13	0.92 (0.76-1.11)	0.38
Cognitive improvement	Overall	687	4,639.22	148.09 (137.22-159.59)	---	---	---	---
	Glipizide	349	2,525.63	138.18 (124.06-153.47)	Ref	Ref	Ref	Ref
	Glimepiride	189	1,188.95	158.96 (137.11-183.31)	1.14 (0.96-1.36)	0.14	1.12 (0.92-1.36)	0.26
	Glyburide	149	924.64	161.14 (136.31-189.20)	1.16 (0.96-1.41)	0.13	1.09 (0.88-1.34)	0.43

Abbreviations: PY, person years; Ref, reference category.

Supplementary Table S5: 180- and 365-days cognitive and functional change events, person-years, rates and hazard ratios associated with geriatric (n=2,600) versus non-geriatric doses (n=3,577) initial sulfonylurea dose.

Follow-up period	Outcome	Sulfonylurea dose	Events	PY	Rate / 1000 PY (95% CI)	Unweighted		Inverse probability weighted	
						Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Decline events									
180 days	Functional decline	[a]Geriatric	652	1,006.16	648.01 (599.22-699.71)	Ref	---	Ref	---
		[b]Non-geriatric	847	1,435.24	590.15 (551.07-631.26)	0.91 (0.82-1.01)	0.08	0.89 (0.80-0.99)	0.04
	Cognitive decline	Geriatric	481	1,049.75	458.20 (418.17-501.04)	Ref	---	Ref	---
		Non-geriatric	622	1,493.61	416.44 (384.35-450.49)	0.91 (0.81-1.03)	0.12	0.89 (0.78-1.00)	0.06
	Altered consciousness hospitalization	Geriatric	70	1,135.89	61.63 (48.04-77.86)	Ref	---	Ref	---
		Non-geriatric	78	1,597.35	48.83 (38.60-60.94)	0.79 (0.57-1.09)	0.15	0.86 (0.62-1.21)	0.40
365 days	Functional decline	Geriatric	926	1,609.39	575.37 (538.91-613.66)	Ref	---	Ref	---
		Non-geriatric	1,279	2,360.25	541.89 (512.60-572.42)	0.95 (0.87-1.03)	0.22	0.93 (0.85-1.02)	0.11
	Cognitive decline	Geriatric	679	1,731.37	392.17 (363.23-422.82)	Ref	---	Ref	---
		Non-geriatric	938	2,533.30	370.27 (346.95-394.74)	0.95 (0.86-1.05)	0.32	0.93 (0.84-1.03)	0.18

	Altered consciousness hospitalization	Geriatric	133	2005.54	66.32 (55.53-78.59)	Ref	---	Ref	---
		Non-geriatric	177	2,895.18	61.14 (52.46-70.84)	0.92 (0.73-1.15)	0.44	1.00 (0.79-1.27)	0.99
Improvement events									
180 days	Functional improvement	Geriatric	315	1,075.78	292.81 (262.36-327.00)	Ref	---	Ref	---
		Non-geriatric	399	1,528.35	261.07 (236.08-287.98)	0.90 (0.77-1.04)	0.14	0.90 (0.77-1.05)	0.19
	Cognitive improvement	Geriatric	202	1,111.74	181.70 (157.50-208.56)	Ref	---	Ref	---
		Non-geriatric	307	1,557.25	197.14 (175.70-220.47)	1.09 (0.91-1.30)	0.36	1.05 (0.87-1.27)	0.59
365 days	Functional improvement	Geriatric	404	1,818.16	222.2 (201.06-244.96)	Ref	---	Ref	---
		Non-geriatric	527	2,662.30	197.95 (181.41-215.59)	0.91 (0.80-1.03)	0.14	0.91 (0.79-1.04)	0.16
	Cognitive improvement	Geriatric	264	1,907.75	138.38 (122.19-156.12)	Ref	---	Ref	---
		Non-geriatric	423	2,731.47	154.86 (140.45-170.35)	1.13 (0.97-1.32)	0.12	1.09 (0.93-1.28)	0.28

[a]Geriatric dose is defined as glipizide standardized daily dose = 2.5 mg, glimepiride standardized daily dose =1 mg, and glyburide standardized daily dose = 1.25 mg.
[b]Non-geriatric dose is defined as glipizide standardized daily dose > 2.5 mg, glimepiride standardized daily dose > 1mg, and glyburide standardized daily dose > 1.25 mg.
Abbreviations: PY, person years; Ref, reference category.

Supplementary Table S6: Characteristics of residents who received traditional high (n=1,314) versus low doses (n=4,863) of sulfonylurea at baseline and after inverse probability of treatment weighting.

Characteristics	%			
	Unweighted		Inverse probability weighted	
	[a]Low dose (78.73)	[b]High dose (21.27)	[a]Low dose	[b]High dose
Age, mean (SD) years	81.81 (8.10)	79.93 (8.13)	81.44 (8.12)	81.35 (8.30)
Female sex	70.33	70.55	70.54	71.59
Race/ethnicity				
White	75.94	74.96	75.68	74.71
Black	15.59	15.98	15.74	16.22
Hispanic	5.76	6.47	5.90	6.40
Other	2.71	2.59	1.15	2.74
Body mass index, kilograms/meters^2				
Underweight (<18.5)	2.71	1.37	2.44	2.59
Normal weight (18.5 to 24.9)	30.31	22.53	28.66	29.32
Overweight (25 to 30)	32.59	32.27	32.48	31.23
Obese (>30)	34.38	43.84	36.42	36.94
Number of comorbidities, mean (SD)	5.69 (2.73)	5.65 (2.78)	5.68 (2.72)	5.68 (2.76)
[c]ADL score, mean (SD)	15.86 (7.67)	15.49 (7.82)	15.77 (7.69)	15.82 (7.78)
ADL change past 90 days				
No change	64.32	65.60	64.48	64.81
Improved	6.64	6.09	6.61	6.47
Deteriorated	29.04	28.31	28.92	28.71
[d]CPS score, mean (SD)	2.60 (1.56)	2.52 (1.61)	2.58(1.57)	2.52 (1.57)
Cognitive status change past 90 days				
No change	89.49	89.35	89.42	89.26
Improved	1.71	1.60	1.71	1.68

Deteriorated	8.80	9.06	8.89	9.06
Conditions				
Anxiety disorder	17.58	19.33	18.00	17.82
Depression	55.52	56.85	55.77	55.60
Bipolar disorder	4.13	4.26	4.19	3.81
Alzheimer's dementia	16.68	16.36	16.60	17.21
Non-Alzheimer's dementia	42.22	39.65	41.64	41.28
Ischemic heart disease	15.20	15.30	15.18	15.16
Congestive heart failure	28.95	28.01	28.64	27.80
Hypertension	76.39	79.38	76.99	77.30
Hypotension	1.15	1.07	1.13	1.14
Arthritis	33.48	34.17	33.48	32.52
Stroke	24.41	25.27	24.61	24.98
Epilepsy	6.37	5.40	6.16	6.25
COPD	20.46	19.33	20.25	20.26
Anemia	29.34	25.11	28.47	27.80
Renal failure	9.54	9.06	9.45	9.44
Medication use				
Anti-depressant	57.74	54.34	57.03	57.35
Anti-convulsant	20.95	20.85	20.97	21.71
Metformin	28.36	31.96	29.21	29.86
Proton pump inhibitor	40.37	38.13	39.77	38.84
ACE inhibitor	37.67	38.36	37.74	36.86
Alpha blocker	3.31	2.44	3.12	3.20
Anti-anxiety	3.08	2.82	3.04	2.89
ARB	11.12	11.19	11.15	11.12
Aspirin	2.06	2.13	2.07	1.98
Beta blocker	45.71	39.57	44.39	43.56
Calcium channel blocker	29.26	27.55	29.03	29.09
Clopidogrel	14.23	13.01	13.95	13.86
Length of nursing home stay before treatment	588	575	586	581

initiation, median (IQR) days	(269-1186)	(269-1132)	(268-1188)	(282-1165)
Number of overnight hospitalizations in prior 90 days, mean (SD)	0.35 (0.62)	0.34 (0.59)	0.35 (0.63)	0.35 (0.61)
Number of ED visits in prior 90 days, mean (SD)	0.09 (0.34)	0.10 (0.41)	0.09 (0.34)	0.09 (0.35)
Number of physician order changes in prior two weeks, mean (SD)	1.86 (1.84)	1.82 (1.76)	1.85 (1.84)	1.86 (1.77)
Nursing Home Facility Characteristics				
Staff hours per resident, mean (SD)	2.90 (1.25)	2.86 (1.28)	2.89 (1.26)	2.88 (1.25)
Ownership				
Profit	70.78	72.15	70.71	72.20
Non-profit	22.02	21.99	22.00	22.01
Government	7.20	5.86	7.19	5.86
Quality indicators				
% of residents with pressure sores, mean (SD)	6.50 (4.22)	6.53 (4.01)	6.58 (4.20)	6.59 (3.99)
% of residents restrained, mean (SD)	3.31 (4.68)	3.37 (4.46)	3.32 (4.66)	3.21 (4.29)
% of residents receiving psychoactive drugs, mean (SD)	65.24 (13.20)	66.16 (13.17)	65.45 (13.19)	65.41 (13.37)

[a]Low dose is defined as glipizide standardized daily dose = 5 mg, glimepiride standardized daily dose = 2 mg, and glyburide standardized daily dose = 5 mg.
[b]High dose is defined as glipizide standardized daily dose > 5 mg, glimepiride standardized daily dose > 2 mg, and glyburide standardized daily dose > 5 mg.
[c]ADL score was measured by the Morris ADL score, which ranges from 0 (totally independent, no impairment) to 28 (totally dependent, total impairment).
[d]Measured by the Cognitive Performance Scale, which ranges from 0 (intact cognition) to 6 (very severe cognitive impairment)
Abbreviations: SU, sulfonylurea; SD, standard deviation; ADL, activities of daily living; CPS, Cognitive Performance Scale; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; IQR, interquartile range.

Supplementary Table S7: 180- and 365-days cognitive and functional change events, person-years, rates and hazard ratios associated with traditional high (n=1,314) versus low doses (n=4,863) initial sulfonylurea dose.

Follow-up period	Outcome	Sulfonylurea Dose	Events	PY	Rate / 1000 PY (95% CI)	Unweighted		Inverse probability weighted	
						Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Decline events									
180 days	Functional decline	[a]Low	1,209	1,897.38	63.72 (60.18-67.42)	Ref	---	Ref	---
		[b]High	290	544.02	53.31 (47.35-59.81)	0.84 (0.74-0.95)	0.01	0.82 (0.71-0.93)	0.00
	Cognitive decline	Low	890	1,981.82	44.91 (42.01-47.96)	Ref	---	Ref	---
		High	213	561.55	37.93 (33.01-43.38)	0.85 (0.73-0.98)	0.03	0.85 (0.72-0.99)	0.04
	Altered consciousness hospitalization	Low	125	2,133.68	5.86 (4.88-6.98)	Ref	---	Ref	---
		High	23	599.55	3.84 (2.43-5.76)	0.66 (0.42-1.02)	0.06	0.65 (0.41-1.02)	0.06
365 days	Functional decline	Low	1,761	3,053.69	5.77 (5.50-6.04)	Ref	---	Ref	---
		High	444	915.94	4.85 (4.41-5.32)	0.85 (0.77-0.94)	0.00	0.83 (0.75-0.92)	0.00
	Cognitive decline	Low	1,294	3,290.16	39.33 (37.22-41.53)	Ref	---	Ref	---
		High	323	974.51	33.14 (29.63-36.96)	0.85 (0.76-0.96)	0.01	0.85 (0.75-0.96)	0.01

	Altered consciousness hospitalization	Low	248	3,794.10	6.54 (5.75-7.40)	Ref	---	Ref	---
		High	62	1,106.62	5.60 (4.30-7.18)	0.85 (0.64-1.12)	0.25	0.86 (0.65-1.14)	0.30
Improvement events									
180 days	Functional improvement	Low	565	2,033.02	27.79 (25.55-30.18)	Ref	---	Ref	---
		High	149	571.10	26.09 (22.07-30.63)	0.94 (0.79-1.13)	0.53	0.97 (0.80-1.16)	0.71
	Cognitive improvement	Low	3,811	2,091.23	182.24 (176.50-188.12)	Ref	---	Ref	---
		High	128	577.76	22.15 (18.48-26.34)	1.22 (1.00-1.49)	0.05	1.18 (0.96-1.46)	0.12
365 days	Functional improvement	Low	125	2,133.68	5.86 (4.88-6.98)	Ref	---	Ref	---
		High	23	599.55	3.84 (2.43-5.76)	0.66 (0.42-1.02)	0.06	0.65 (0.41-1.02)	0.06
	Cognitive improvement	Low	723	3,471.00	20.83 (19.34-22.41)	Ref	---	Ref	---
		High	208	1,009.46	20.61 (17.90 -23.60)	1.01 (0.87-1.18)	0.90	1.02 (0.87-1.20)	0.79

[a]Low dose is defined as glipizide standardized daily dose = 5 mg, glimepiride standardized daily dose = 2 mg, and glyburide standardized daily dose = 5 mg.
[b]High dose is defined as glipizide standardized daily dose > 5 mg, glimepiride standardized daily dose > 2 mg, and glyburide standardized daily dose > 5 mg.
Abbreviations: PY, person years; Ref, reference category.

Supplementary Table S8: Interaction of individual drugs and doses on 180-days cognitive and functional change events.

Type of event	Event	Drug	[a]Geriatric dose		[b]Non-geriatric dose	
			N with event	[c]Hazard ratio (95% CI)	N with event	*Hazard ratio (95% CI)
Decline events	Functional decline	Glipizide	496	Ref	313	0.87 (0.75-1.02)
		Glimepiride	129	0.98 (0.78-1.22)	266	1.05 (0.79-1.40)
		Glyburide	27	1.05 (0.68- 1.62)	268	1.02 (0.64- 1.63)
	Cognitive decline	Glipizide	361	Ref	224	0.82 (0.68-0.98)
		Glimepiride	98	0.98 (0.76-1.26)	183	0.98 (0.70-1.38)
		Glyburide	22	0.98 (0.60-1.58)	215	1.30 (0.77-2.20)
	Altered consciousness Hospitalization	Glipizide	59	Ref	28	0.78 (0.48-1.26)
		Glimepiride	10	0.77 (0.38-1.58)	25	1.62 (0.64-4.10)
		Glyburide	1	0.21 (0.03-1.50)	25	4.77 (0.60-37.82)
Improvement events	Functional improvement	Glipizide	230	Ref	180	1.07 (0.86-1.32)
		Glimepiride	66	1.06 (0.77-1.46)	114	0.76 (0.50-1.15)
		Glyburide	19	1.28 (0.77-2.13)	105	0.58 (0.33-1.04)
	Cognitive improvement	Glipizide	149	Ref	115	1.13 (0.87-1.47)
		Glimepiride	38	1.04 (0.69-1.55)	95	0.89 (0.54-1.48)
		Glyburide	15	1.69 (0.95-3.01)	97	0.58 (0.30-1.11)

[a]Geriatric dose is defined as glipizide standardized daily dose = 2.5 mg, glimepiride standardized daily dose =1 mg, and glyburide standardized daily dose = 1.25 mg.
[b]Non-geriatric dose is defined as glipizide standardized daily dose > 2.5 mg, glimepiride standardized daily dose > 1mg, and glyburide standardized daily dose > 1.25 mg.
[c]Hazard ratios estimated using inverse probability of treatment weighting.
Abbreviations: Ref, reference category.