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Metformin Safety Warnings and Diabetes Drug Prescribing Patterns for Older Nursing Home Residents

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Abstract

Objective—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 treatment selection in this setting, especially for metformin. We quantified the determinants of initiating sulfonylureas over metformin with the aim of understanding the impact of FDA-labeled boxed warnings in older NH residents.

Design and Setting—National retrospective cohort in 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;

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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.

Conclusions—In response to FDA warnings, providers initiated NH residents on a drug class with a known, common adverse event (hypoglycemia with sulfonylureas) over one with tenuous evidence of a rare adverse event (lactic acidosis with metformin).

Keywords

Nursing home; diabetes; United States Food and Drug Administration; treatment choice variation; contraindications

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.¹ Between 25% and 35% of elderly NH residents have diabetes mellitus; mainly type 2 diabetes (T2D).^{2–4} 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.^{4–6} 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.^{7,8} 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.⁹ Initial guidelines stated that metformin was contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/minute/1.73 m².⁸ 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 m².^{9,10}

Initiation of metformin or sulfonylurea monotherapy is common in the U.S. NH setting.^{11,12} Sulfonylureas have been used for over 60 years and commonly cause hypoglycemia, which is particularly detrimental in frail older adults.^{13–15} 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).^{9,15} 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 2006.¹⁶

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.¹⁷ We used the MDS 2.0, which has been found generally reliable and valid for measuring domains when used by trained staff.¹⁸ 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.¹⁸

The OSCAR database consists of facility-level information collected at NHs for the purpose of certification for Medicare and Medicaid programs.¹⁹ 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.⁴⁻⁶

All patients were required to have maintained continuous Medicare insurance eligibility for the twelve 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 studies²⁰), 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.^{7,8} 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.²¹

Geriatric conditions and the NH resident functional status were also of interest as predictors because they could affect diabetes management decisions.⁵ 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).²² The sum of the seven items forms a 28-point scale, where higher scores indicate greater physical impairment.²² Cognitive function was measured using the MDS Cognitive Performance Scale (MDS-CPS) score, which ranges from 0 (intact) to 6 (severe impairment).²³ 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).²³ 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.^{24,25} Values of three to five on the CHESS scale were collapsed into a single category representing moderate to very high health instability.^{24,25} 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 $[(\text{tablet strength} \times \text{quantity}) \div \text{days supply}]$ 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.²⁶ Because residents are clustered within NHs, we included NH random intercept to obtain more accurate standard errors and CIs.²⁷

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.^{13,28} 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; Table A1). 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 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 3; Table 4; Table A2), 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 3; Table 4; Table A2), 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 A3; Table A4).

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.^{8–10} 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.²⁹ 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.³⁰ 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.³¹ 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.⁶ 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.⁶ 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.^{32–34} 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.^{6,35,36} Third, while DPP-4 inhibitors and thiazolidinediones represented an alternative to metformin between 2007 and 2010, they were used less often than sulfonylureas.^{11,12} 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.^{37–39} 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.

Conclusion

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 m², 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.

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Appendix

Table A1

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 *	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)

Characteristic	n (%)
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.

* Other race/ethnicity includes American Indian/Alaskan Native/Asian Pacific Islander.

Table A2

Univariable and Multivariable Multilevel Logistic Regression Analysis 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) ^{a, †}
	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				

Characteristic	Metformin Initiation (n/N, %)	Sulfonylurea Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) ^{a,†}
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)

Characteristic	Metformin Initiation (n/N, %)	Sulfonylurea Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) [†]
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	3,047/7,245 (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: CHES, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

* Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tachyarrhythmias, 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.

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

Table A3

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

Characteristic	Metformin Initiation (n/N, %)	DPP-4i Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) ^{a, †}
	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				

Characteristic	Metformin Initiation (n/N, %)	DPP-4i Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) ^{a,†}
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)

Characteristic	Metformin Initiation (n/N, %)	DPP-4i Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) ^{*†}
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: CHES, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

^{*} Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tachyarrhythmias, 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.

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

Table A4

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) ^{a,†}
	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				

Characteristic	Metformin Initiation (n/N, %)	Thiazolidinedione Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) ^{a,†}
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)

Characteristic	Metformin Initiation (n/N, %)	Thiazolidinedione Initiation (n/N, %)	Univariable Association (OR, 95% CI)	Multivariable Association (OR, 95% CI) [†]
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: CHES, Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; MDS, Minimum Data Set; ED, Emergency Department.

* Adjusted for all other variables in the table as well as race/ethnicity, hypertension, tachyarrhythmias, 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.

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

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Table 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	2,611 (36)
85 to <95	2,864 (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 *	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	2,575 (35)
Moderate impairment	2,647 (36)
Moderate-severe to very severe impairment	2,073 (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)

Characteristic	n (%)
History of hypoglycemia	788 (11)

SD, standard deviation.

* Other race/ethnicity includes American Indian/Alaskan Native/Asian Pacific Islander.

See Table A1 for a complete list of characteristics.

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Table 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 (%) *	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 (%) *	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 (%) *	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 (%) *	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.

* Percentages are row percentages.

Table 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) ^{*†}
	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)

* 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 A2 for complete list.

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

[‡] Measured using the Changes in Health, End-Stage Disease, Signs, and Symptoms Scale score

Table 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) ^{*†}
	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)

* 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 A2 for complete list.

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

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