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Original Study

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

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A B S T R A C T

Objective: Diabetes mellitus is common in US nursing homes (NHs), and the mainstay treatment, metformin, has US 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 US 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 = 7295).
Measurements: Measures of patient characteristics were obtained from linked national Minimum Data Set assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare claims. Odds ratios (ORs) comparing patient characteristics and treatment initiation were estimated using univariable and multivariable multilevel logistic regression models with NH random intercepts.
Results: Of the 7295 residents in the study population, 3066 (42%) initiated metformin and 4229 (58%) initiated a sulfonylurea. In multivariable analysis, several factors were associated with sulfonylurea initiation over metformin initiation, including heart failure (odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.4) and renal disease (OR 2.1, 95% CI 1.7–2.5). Compared with 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 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).

Approximately 1 million older US 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 (eg, low hypoglycemia risk), and potential cardiovascular benefits.[4–6] Because metformin is cleared unchanged by the kidneys, its product label has included a US Food and Drug Administration (FDA) boxed warning since its approval that cautions

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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/min/1.73 m^2.[8] However, the level of concern about lactic acidosis diminished over time because 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 to 60 mL/min/1.73 m^2.[9,10]

Initiation of metformin or sulfonylurea monotherapy is common in the US NH setting.[11,12] Sulfonylureas have been used for more than 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 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 dispensing 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 3-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 patient's 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 in Medicare Part D claims. We defined long-stay residents as those with 90 or more consecutive days in an NH. Residents lived in all 50 US 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 6 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 12 months preceding the index date and could not have Medicare Advantage coverage. To preserve real-world prescribing patterns and avoid exclusion of participants due to imperfect documentation of diabetes (a known challenge from prior pharmacoepidemiology studies[20]), residents were not required to have a specified diagnosis of diabetes to be in our study sample. However, 6631 (91%) of those in our study sample had a diagnosis of diabetes on at least 1 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 1 year before 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 $\geq$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. Because liver disease was not assessed by the MDS, we used ICD-9 codes from Medicare Part B claims in the 1 year before 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 7 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 7 items forms a 28-point scale, whereby 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 3-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 3 to 5 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 before the index date was assessed.