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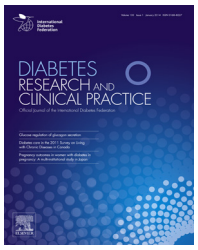

Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus

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ABSTRACT

Aims: Although sulfonylureas increase the risk of hypoglycemia which may lead to fall-associated fractures, studies quantifying the association between sulfonylureas and falls and/or fractures are sparse and existing studies have yielded inconsistent results. Our objective is to evaluate the extent to which sulfonylurea use was associated with fractures and falls among nursing home residents with type 2 diabetes mellitus.
Methods: We performed a propensity-matched retrospective new user cohort study of 12,327 Medicare Parts A/B/D eligible long-stay NH residents. Medicare Part D data provided information on sulfonylurea and biguanide use initiated as monotherapy ($n_{sulfonylurea}$ = 5807 and $n_{biguanide}$ = 6151) after NH entry. Medicare hospitalizations were used to identify hypoglycemic events (ICD-9-CM codes 250.8, 251.1, 251.2) and fall-associated fractures (ICD-9-CM codes 800, 804, 812–817, 820, 823, 824). Minimum Data Set 2.0 (2008–2010) provided information on falls and potential confounders. Cox models conducted on propensity-matched samples provided adjusted hazard ratio (aHR) estimates and 95% confidence intervals (CI).
Results: Falls were common (37.4 per 100 person-years). Fractures were not associated with initiation of sulfonylureas. Sulfonylurea initiation was associated with an excess risk of falls among residents with moderate activities of daily living limitations (aHR: 1.13; 95% CI: 1.00–1.26), but not among those with minimal limitations or dependence in activities of daily living.
Conclusions: Nursing home residents with moderate limitations in activities of daily living are at increased risk of falls upon initiation of sulfonylureas. Initiating sulfonylurea use in NH residents must be done with caution.

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1. Introduction

Falls are a leading cause of injury, disability, and death among older adults [1]. Nursing home residents fall at three times the rate of community dwelling older adults [2], and 50–75% of nursing home residents fall each year. The physical, psychological, and social consequences of falls are considerable [3,4]. Nursing home residents take an average of eight medications per day [5]. Thus, understanding the fall and fracture-related risk of commonly used medications in this setting is important.

Sulfonylureas are often used in diabetes management [6,7], despite the known complication of hypoglycemia which occurs in 11–18% of users [8]. Because of the association between sulfonylurea use and hypoglycemia, a causal link between sulfonylurea use and falls and fractures is reasonable. Our recent systematic review revealed that few studies attempted to estimate the association between sulfonylureas and falls and fall-associated fractures [9]. Those studies conducted to date did not show an increased risk of falls/fractures with sulfonylurea use. These studies may have been biased by the inclusion in the comparator group of use of thiazolidinediones, which are known to increase fracture risk. Furthermore, frail older adults, like nursing homes residents, were often excluded despite their increased risk of hypoglycemia, falls, and fractures.

The purpose of this study was to evaluate the extent to which sulfonylurea use was associated with fractures and falls among nursing homes residents with type 2 diabetes mellitus. The importance of this study is underscored by the increasing prevalence of diabetes [10], with 35% of people with type 2 diabetes using sulfonylureas alone or in combination with biguanide and/or thiazolidinediones [11]. In US nursing homes, one quarter of residents have diabetes and 30% use sulfonylurea alone or in combination with other antidiabetic agents [12].

2. Subjects, materials and methods

This study was approved by the University of Massachusetts Medical School Institutional Review Board.

2.1. Data sources

We obtained the Medicare Beneficiary Summary Files, including the Chronic Condition Summary File, Minimum Data Set (MDS) version 2.0 data, and Medicare Parts A and D data. Medicare Part D is the prescription drug insurance benefit to improve access to essential medications to Medicare beneficiaries. The MDS captures resident-level information on an extensive array of variables including sociodemographics, comorbidities, and physical and cognitive functioning on admission, quarterly, annually, or following a significant change in the resident's status [13]. The MDS has been shown to be a reliable [14], valid [15,16], and comprehensive assessment of residents' medical, cognitive [17], functional [18], and psychological status.

2.2. Study cohort

We conducted a retrospective cohort study. We used a new user study design [19] to improve the validity of the study by allowing adjustment for pre-treatment disease severity [20]. We identified 173,095 residents with a diagnosis of type 2 diabetes mellitus (ICD-9 code: 250) on an annual or quarterly MDS 2.0 assessment, ≥6 months of continuous co-enrollment in Medicare Parts A, B, and D, and ≥1 prescription for a sulfonylurea and/or biguanide between 2008 and 2010. Of these, 48,389 had ≥1 full MDS assessment (admission, quarterly, annual, or significant change in status) preceding the index date of oral antidiabetic therapy initiation. The full assessment is conducted annually. We excluded residents <50 years of age ($n = 876$), comatose/paralyzed ($n = 6566$), receiving hospice care ($n = 717$), had bone cancer/infection ($n = 396$), had a hip fracture before 180 days of initiation of sulfonylurea or biguanide ($n = 2865$), or were missing data on key variables ($n = 223$). Of the remaining 36,746 residents, 12,327 were classified as "new users" if they used Part D ≥90 days before the first observed oral antidiabetic prescription fill, and no evidence of prior antidiabetic use including insulin. The median follow-up time was 683 days (range: 1–1002 days).

2.3. Hypoglycemia, falls, and fractures

We considered three endpoints: (1) severe hypoglycemia; (2) fall; and (3) fractures occurring in parts of the body typically associated with falling. We identified hospitalizations due to hypoglycemia using ICD-9-CM codes (250.8, 251.1, 251.2). Residents were categorized as having a fall (incident or recurrent) prior to hospitalization if there was a discharge diagnosis of an accidental fall (ICD-9-CM E880–E888) or an MDS documentation of a fall in the past 30 days. For fractures, we included hospitalizations coded as: (1) hip fracture (ICD-9-CM 820), (2) radius/ulna fracture (ICD-9-CM 813), (3) humerus fracture (ICD-9-CM 812); (4) hand (ICD-9-CM 814–817), (5) tibia/fibula (ICD-9-CM 823), (6) ankle (ICD-9-CM 824), or (7) skull/face (ICD-9-CM 800, 804). Use of administrative data to identify fracture is valid [21–23].

All outcome measures were calculated as time to event. Using an intention-to-treat approach [24], person time was calculated from initiation of oral antidiabetic medication to the date of the first occurrence of the event of interest, loss of eligibility for Medicare Parts A, B, or D, death, or December 31, 2010, which was the end of the follow-up period.

2.4. Diabetes medication use

We were interested in constructing two primary comparisons. The first compared monotherapy sulfonylurea use and monotherapy biguanide use. Second, we identified residents initiating combination therapy (sulfonylurea and biguanide) compared to biguanide use alone. Using Medicare Part D pharmacy claims, we identified new users as residents initiating one of the target treatments ≥90 days after the first evidence of Part D utilization for any medication, and the absence of any antidiabetic medication use (including insulin)

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