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Long-term Sulfonylurea Use Increases Risks among Patients with Type 2 Diabetes

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Abstract

Objective: Sulfonylureas (SU) were the dominant treatment for type 2 diabetes until the mid-1990s and remain widely used today. Evidence on the risks of long-term use of SU is lacking. We measure risks of continued use of SU as diabetes progresses beyond initial stages.

Study Design: Retrospective observational study using instrumental variables models based on provider prescribing patterns with controls for provider-level process quality.

Methods: US veterans were identified who received a prescription for diabetes medication from 2000 to 2005, initiated a 3rd diabetes medication before 2010, and were dually enrolled in Medicare. SU treatment was measured at 7 follow-up dates after initiation of 3rd diabetes medication (either thiazolidinedione (TZD) or insulin). Risks of hospitalization for ambulatory care sensitive conditions (hospitalization) and all-cause mortality were assessed using survival models beginning after each follow-up date.

Results: Among patients who initiated a TZD, SU treatment was associated with significantly elevated hospitalization risk starting at 90 days (HR: 2.79; 95% CI: 1.46-5.35), 1 year (HR: 3.12; CI: 1.73-5.63), 2 years (HR: 3.09; CI: 1.56-6.12), 3 years (HR: 2.63; CI: 1.19-5.78), and 4 years (HR: 2.51; CI: 1.03-6.12). Among patients who initiated insulin, hazard ratios were significantly elevated only at 6 years (HR: 2.22; CI: 1.08-4.54).

Conclusions: Higher exposure to SU was associated with large increases in risk of hospitalization among patients initiating a TZD as their 3rd medication. The amounts of long-term exposure to metformin, TZD or insulin had no significant effects, suggesting that SU was the key factor.

Key Words: Diabetes, comparative effectiveness, medications, instrumental variables

Introduction

Oral medications to treat type 2 diabetes are the mainstay of therapy for most patients. Sulfonylureas (SU) were the only oral agents available for more than 35 years until the introduction of metformin in 1995. Since then the number of oral agents has expanded dramatically¹. Despite the proliferation of alternatives, SU remains widely used. Nearly all current treatment guidelines promote initial therapy with metformin or SU, with metformin as the preferred drug^{2,3}, and a recent analysis of data from Medicare and the US Department of Veterans Affairs (VA) found that metformin and SU continue to be the most commonly prescribed oral hypoglycemics in both systems⁴.

Diabetes is also a progressive disease and oral therapy invariably requires a sequence of medications. Metformin and SU are often combined and other drugs are added as necessary resulting in multi-drug regimens. Patients and providers can choose to start insulin, add a thiazolidinedione (TZD), add a dipeptidyl peptidase-4 inhibitor (e.g. sitagliptin) or other agents. While good evidence exists for long-term efficacy with individual agents, there is a paucity of data on the comparative risks and effectiveness of multi-drug regimens. In particular, despite their favorable effects on glucose control, SU increases the risk of hypoglycemia and concerns about their potential association with cardiovascular disease have been present since the 1970s⁵. The magnitude of these risks relative to the most likely alternatives is not well understood.

This study is the first to use innovative observational comparative effectiveness methods⁶⁻⁸ to address the potential risks of long-term use of SU in patients on multi-drug regimes, specifically those whose diabetes has progressed to the point where a third medication is needed. We conducted a retrospective, observational study using local variations in practice patterns as an instrumental variable to isolate a quasi-experimental component of treatment variation that is independent of patient-level health status differences⁹⁻¹⁵. This technique is

attracting interest recently because of its potential to effectively randomize observational data and the nationally recognized need for comparative effectiveness research using electronic medical records and other forms of administrative data^{6,15-17}.

Methods

Data Sources

We used patient-level national data from the VA to conduct our study because the VA has a national electronic medical record and patients are typically randomly assigned to primary care physicians¹⁸. We supplemented VA data with Medicare claims to ensure completeness in our measures of outcomes because VA patients often use non-VA facilities, particularly for urgent hospitalizations¹⁹. Our study was reviewed and approved by the Institutional Review Board at the VA Boston Healthcare System.

Population

We selected all VA patients who received a prescription for diabetes medication from 2000 to 2005 and then followed these patients until death or through 2010. To improve comparability of patients we included only those with a history of prescriptions for metformin, SU, and either TZD or insulin as their 3rd medication (28% of patients). We considered the initiation date for the 3rd medication as the start of our study (“index date”) and treated the prior 12 months as a baseline period. To ensure that all hospitalizations were recorded, we further limited the cohort to include only those enrolled in Medicare as well as VA during the baseline period. The last index date permitted was at the end of 2009 to allow a minimum of 12 months after baseline. The resulting cohort consisted of 134,861 patients, including 78,361 who initiated a TZD on their index date and 56,500 who initiated insulin (see Figures 1A and 1B for details).

SU Treatment

The main objective of the study was to examine the effect of SU treatment after patients start their 3rd drug. SU treatment was defined to be the proportion of days (calculated from “days supplied” in prescription data) for which each patient had an SU prescription between their index date and specific follow-up dates (Figure 1B). This “proportion of days” specification Alternative models used follow-up dates 90 days, 1 year, 2 years, 3 years, 4 years, 5 years and 6 years after the index date. This range of follow-up dates supports investigation of the effects of long-term use of SU while guarding against survivor bias that might be undetected if only the more distant follow-up dates were used^{20,21}. For example, if SU treatment increased mortality risk for patients with heart failure, mortality rates would be associated with SU treatment in models starting at the early follow-up dates, but by the later follow-up dates the number of surviving SU recipients who had heart failure might be very small, making detection of an effect much more difficult.

Provider Prescribing Pattern as Instrumental Variable

As in other observational studies, the principal threat to a simple comparison of outcomes between patients prescribed SU and others is that the selection of treatment by patients and providers could be influenced by unmeasured differences in patient risk (selection bias or confounding by indication). Clinical trials do not suffer from selection bias because patients are randomized to treatment. Instrumental variables models also use randomization by identifying a factor (the instrumental variable or IV) that influences treatment but is effectively random with respect to patient risk and other potential confounders^{22,23}. Unlike randomization in clinical trials, however, the IV does not completely determine treatment status. The statistical model therefore isolates the component of treatment variation attributable to the IV and then measures the relationship between this component and outcomes⁵. The success of the approach depends

critically on the effective randomness of the IV (controlling for all the other variables in the model) as well as the strength of the IV's influence on treatment status^{14,23,24}.

Previous studies have found provider-level prescribing patterns to be effective IVs^{9,12,13,15,25}. In this study the IV was the proportion of all diabetes prescriptions written for SU by each provider in the 12 months prior to each follow-up date. Providers and patients were aligned based on assignments at the index date to minimize confounding that could occur if patients later switched providers in response to changing health status.

Provider Quality Controls

Provider prescribing patterns may not be an effectively random source of treatment variation if they are correlated with other provider characteristics that might also affect outcomes. For example, if providers who frequently prescribe SU are also less likely to aggressively treat high cholesterol, a model of cardiovascular disease outcomes that fails to account for this correlation could erroneously attribute the deleterious effects of less aggressive cholesterol treatment to the SU prescriptions. To address this concern we follow Brookhart and colleagues⁸ and include several measures of provider-level process quality computed for the same providers and time periods as the prescribing rate (see Figure 1B). These variables were percentages of HbA_{1c} values > 9%^{26,27}, blood pressure values >140/90 mm Hg²⁸, and LDL cholesterol levels > 100 mg/dL²⁸.

Outcomes

Outcomes included mortality and hospital admission (VA or Medicare) for any ambulatory care sensitive condition (hereafter "hospitalization"; see Appendix Table 1 for individual conditions and frequencies) as defined by the Agency for Healthcare Research and Quality^{29,30}. The outcome to be modeled was the amount of time between the follow-up date in each model and the date of death, the first date of hospitalization, or the end of the study period

in 2010. We chose this subset of hospitalizations as an outcome because they are widely used in the literature to measure effectiveness of primary care³¹⁻³⁴. They are also particularly relevant to patients with diabetes because they include several admission types related to complications of diabetes³⁵⁻³⁷.

Covariates

Additional control variables computed at baseline included age, sex, race, HbA_{1c}, serum creatinine, urine microalbumin, body mass index (see Table 1 and Supplemental Digital Content for categorizations), and indicator variables for comorbidities³⁸, the components of the Young diabetes severity index³⁹, and calendar years corresponding to index dates.

Statistical Models

We used STATA Version 10 and Cox proportional hazards models with random effects for VA Medical Centers to estimate the effects of SU use. The instrumental variables approach estimates a pair of simultaneous equations: one for the amount of treatment and the second for the outcome (see Figure 1B). The treatment equations modeled the proportion of days between index and follow-up dates covered by a prescription for SU as a linear function of the provider-level prescribing rate and control variables. The outcome equations related treatment and control variables to probabilities of hospitalization and death. Because the outcome equations were nonlinear, we used the two-stage residual inclusion technique for IV estimation⁴⁰. These Cox models assume that SU treatment increases or decreases outcome risk by a constant proportion over time. We tested this assumption using scaled Schoenfeld residuals from the mortality and hospitalization equations at 2-years⁴¹.

Two-stage models typically require bootstrapping to calculate unbiased standard errors, but this step is computationally intensive⁴². Given the large number of models estimated in this study, we bootstrapped standard errors for selected models and determined that our large samples

and strong instruments resulted in bootstrapped values that were virtually identical to the asymptotic values generated automatically by the statistical software.

Subgroup and Sensitivity Analyses

We estimated all of our models separately in two groups defined by whether TZD or insulin was chosen as the third medication. One alternative hypothesis is that differences in risk are not due to SU treatment but to delayed use of insulin that is correlated with prolonged SU treatment. To test this hypothesis, we estimated alternative models in the TZD group that simultaneously modeled the proportion of days with an insulin prescription along with the SU treatment variable. Another alternative hypothesis is that SU does not increase risk itself, but interacts unfavorably with another medication. We tested this hypothesis by estimating alternative versions of the models with metformin, rosiglitazone, and pioglitazone substituted for SU as the treatment variable. If interactions with any of these medications were responsible we would expect to see increased risk associated with greater long-term exposure to at least one of them.

Results

Patients in the sample were elderly (mean age = 70), about 85% white, and overwhelmingly male (see Table 1). To demonstrate the quasi-random nature of the instrumental variable, we divided the sample into those linked to providers with above- or below-median SU prescribing. The two columns of Table 1 compare means of the proportion of SU days, selected risk adjustment variables, provider quality variables, and outcomes for these two groups at the 1-year follow-up date (see Supplemental Digital Content for complete results). Treatment differed substantially by design, with the above-median group receiving SU prescriptions on 73% of days compared to 65% for the below-median group. The risk adjustment variables and one provider quality variable (percentage of HbA_{1c} > 9%) were closely balanced. The other two provider

quality variables indicate that the above-median group had 43% of BP and LDL values elevated compared to 38% (BP) and 35% (LDL) for the below-median group (at 1 year). Outcomes were also substantially worse for the above-median group with 36% mortality compared to 21% in the below-median group and 29% hospitalization compared to 15% (across all years).

We selected the model beginning at the 2-year follow-up date for detailed presentation because it is roughly in the middle of the range of follow-up dates and because detailed results from the other models were qualitatively the same. Selected results from the first stage of the model are shown in Table 2, which indicates that provider prescribing history was strongly predictive of SU treatment, with a coefficient of 0.260 (95% CI: 0.228-0.293). This coefficient means that a 10 percentage point increase in past SU prescribing by the provider was associated with a 2.6 percentage point increase in patient days with an SU prescription measured at 2 years. The F-statistic of 245 on provider prescribing history easily exceeds the standard threshold for instrumental variable strength ($F > 10$)²³. The model also shows that most comorbidities and complications were associated with lower SU prescribing, indicating that patients receiving longer courses of SU were typically healthier at baseline.

Selected results from the second stage of the model are shown in Table 3, which presents estimates from the Cox model of hospitalization beginning at 2 years for the TZD group. The estimated hazard ratio for SU treatment is 3.09 (95% CI: 1.56-6.12), indicating that a patient who shifted from zero SU prescriptions to full SU treatment between the index date and 2 years would have faced roughly triple the risk of hospitalization. The percentage of the provider's LDL levels that were elevated also had a significant effect on hospitalization risk (HR: 1.36; CI: 1.15-1.61), demonstrating the importance of controlling for correlated provider quality. Other results from the model make clinical sense in that hospitalization risk was higher for patients with elevated baseline HbA_{1c}, obesity, microalbumin, serum creatinine, and for those with most

comorbidities and complications. This model was used to test the assumption of proportional hazards for the treatment variable⁴¹ and the test supported the assumption ($P = 0.12$).

To determine effects on absolute risks, we calculated predicted probabilities of hospitalization in the 365 days following the 2-year follow-up date for two idealized patients. These patients had average baseline characteristics and had either no prescriptions for SU or had full exposure to SU prescriptions between TZD initiation and 2 years later. The predicted probability of hospitalization for each patient was 2.4% and 7.4%, respectively.

Results from second-stage Cox models predicting hospitalization and mortality starting on each follow-up date for the TZD subsample are summarized in the first two rows of Table 4. Hazard ratios for hospitalization indicate large and statistically significant increases in risk with SU treatment at 90 days (HR: 2.79; 95% CI: 1.46-5.35), 1 year (HR: 3.12; CI: 1.73-5.63), 2 years (HR: 3.09; CI: 1.56-6.12), 3 years (HR: 2.63; CI: 1.19-5.78), and 4 years (HR: 2.51; CI: 1.03-6.12). Estimates for the later dates were less precise due to smaller sample sizes (5-year HR: 2.83; CI: 0.96-8.35 and 6-year HR: 3.14; CI: 0.86-11.4). The fact that large and stable effects were estimated from models starting across the entire range of follow-up dates suggests that survivor bias was not an important factor. Point estimates of hazard ratios for mortality arising from long-term SU use were also elevated for patients initiating a TZD, but were not statistically significant at standard thresholds (second row in Table 4).

Patients initiating insulin therapy as their third medication faced lower risks associated with SU use. Hazard ratios for hospitalization were elevated only in years 4-6, with statistical significance only at the 6-year date (third and fourth rows of Table 4). Again, the assumption of proportional hazards for the treatment variable in the 2-year hospitalization model was supported ($P = 0.42$).

In sensitivity analyses we added a second treatment variable for days with a prescription for insulin to the hospitalization models for the TZD group to test whether observed effects were due to postponing needed insulin prescriptions. The results (fifth row of Table 4) show slightly larger estimated hazard ratios, confirming that the measured effects of SU were not due to unmeasured insulin use (or non-use). To test whether the estimated hospitalization effects were truly attributable to SU, we repeated the hospitalization models for the TZD group, substituting metformin, rosiglitazone, or pioglitazone for SU treatment. The results (bottom of Table 4) indicate that none of these medications were associated with significantly elevated risks of hospitalization, strengthening the inference that SU treatment was responsible.

Discussion

Long-term SU use significantly increases the risk of hospitalization for patients initiating a TZD as a third medication to treat type 2 diabetes. Estimated hazard ratios of approximately 3.0 were obtained from survival models starting at dates ranging from 90 days to 6 years after TZD initiation, indicating that the risk of hospitalization roughly tripled if patients maintained their SU prescriptions after starting a TZD. Point estimates of the effect of SU prescriptions on mortality were also elevated, although not statistically significant. We found these effects by using a large, national VA database and an instrumental variables statistical model featuring extensive patient characteristics, provider-level quality of care controls, and exploiting prescribing patterns as a source of quasi-randomization.

These results complement a recently published study finding that use of SU instead of metformin as first-line treatment is associated with increased risk of cardiovascular events and death⁴³. Our study goes further by addressing the more uncertain question of SU use after initial therapy is established, and our quasi-experimental study design supports more robust causal inferences⁴⁴. Based on these results, clinicians should be aware that patients who continue SU

therapy after initiating a TZD as their 3rd medication may experience an elevated risk of hospitalization that increases with exposure to SU. Providers weighing treatment alternatives for patients at this stage should balance the potential benefits of continued SU prescriptions against this risk.

The lack of IV methods may have prevented detection of this effect in previous research. Patients whose providers were likely to prescribe SU were typically healthier at baseline (Table 2), so a comparison of outcome rates without quasi-experimental techniques would be biased. Provider quality is another potentially confounding factor. Providers who prescribed more SU had higher percentages of elevated BP and elevated LDL among their patients (Table 1). Since elevated LDL was also associated with increased hospitalization risk (Table 3), failure to adjust for provider control of LDL also would have led to biased estimates.

Sensitivity analyses showed that the increased risk of hospitalization for these patients cannot be attributed to late initiation of insulin therapy. In addition, hospitalization risk was not associated with increased use of TZD or metformin. This makes it less likely that interaction with either of these medications was responsible for the SU effect, although the possibility that an adverse effect occurred without a dose response from the interacting medication cannot be ruled out. The remaining explanation is that SU itself was the causal factor.

Hypoglycemia is one mechanism through which SU use could lead to hospitalizations. Although we cannot explicitly link SU use to hypoglycemia in the data due to unrecorded events and inconsistent coding, we found that providers with high SU prescribing rates had 16% of patients over age 70 with at least one recorded HbA_{1c} < 6%, whereas other providers had only 12% (Table 1). This combination of age and low HbA_{1c} has been linked to hypoglycemia risk^{27,45}. Furthermore, long-term SU use by patients initiating insulin as a third medication had proportionally smaller effects. If the hospitalization risk of SU use for TZD patients is due to

hypoglycemia, the substantial hypoglycemia risk of insulin therapy may make these effects more difficult to detect in the insulin sub-population.

Increased risk of cardiovascular events is another possible mechanism. We could not estimate separate models for each type of hospitalization because some occur too infrequently, so we used a simplified test on the 6 most common types (Appendix Table 1). Of these, admissions for CHF were significantly associated ($P = 0.01$) with SU treatment and admissions for COPD were weakly associated ($P = 0.06$). Both of these results would be consistent with elevated risk of cardiovascular events⁴⁶. Hypoglycemia may increase the risk of cardiovascular events⁴⁷, so one mechanism does not preclude the other.

Although this study included several controls for provider quality as well as facility effects, quality has many dimensions and we could not explicitly control for them all. Consequently, it is possible that some uncontrolled provider quality variable was responsible for the results. On the other hand, to account for the measured effect of SU, an omitted quality factor would have to be highly correlated with SU prescribing and uncorrelated with LDL control, BP control, HbA_{1c} control, or facility effects. This seems unlikely. A further limitation of this study is that we did not directly address use of SU as a second-line treatment. Nevertheless, our results may be generalizable because the risks of hypoglycemia and cardiovascular events probably apply to SU whether two or three medications are used. Future research should assess whether the risk of SU usage applies when there are fewer other medications involved, whether different SU agents pose different risks, and whether the same risk relationships apply to populations not well represented in our sample of veterans, particularly women and patients with higher incomes.

As the number of medications approved to treat diabetes has grown in recent years, offering valuable treatment alternatives, the need for evidence on comparative risks and

effectiveness has become more pressing. With this study we contribute to this evidence by measuring a large and previously undetected risk associated with long-term use of a widely prescribed class of medications. We also demonstrate the power of an innovative large database analysis technique that is applicable to many other important comparative effectiveness questions and has the potential to provide specific information to support shared decision making.

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Appendix

Table A1. Specific ACSC Hospitalizations after 1-year follow-up		
	N	%
Diabetes short term complications	496	0.42
Perforated appendix	139	0.12
Diabetes long term complications	5,115	4.38
COPD	2,852	2.44
Hypertension	553	0.47
CHF	8,852	7.57
Dehydration	2,292	1.96
Bacterial pneumonia	5,627	4.81
UTI	2,287	1.96
Angina	821	0.70
Uncontrolled diabetes	697	0.60
Lower extremity amputation	4	0.00
None	87,166	74.6
Total	116,901	100

SU: Sulfonylurea; TZD: Thiazolidinedione; ACSC: Ambulatory care sensitive condition.
 No hospitalizations were observed for asthma.
 Patients with multiple admissions on the same day were dropped.

To explore which hospitalization types are most likely to be affected by SU, we estimated separate linear probability models for the six most common types occurring after the 1 year follow-up date: long-term complications of diabetes, COPD, CHF, dehydration, bacterial pneumonia, and UTI. Other types were too infrequent to be tested separately. These models included all covariates, fixed effects for VA Medical Centers, and an indicator variable for patients whose providers had above-median SU prescribing history. In these models, the coefficients on the high-SU indicator variables are estimates of the change in hospitalization probability associated with high SU prescribing. The results for the TZD subsample were: diabetes long-term complications 0.001 P = 0.59; **COPD 0.003 P = 0.06; CHF 0.006 P = 0.01;** dehydration -0.002 P = 0.11; bacterial pneumonia 0.001 P = 0.54; and UTI 0.002 P = 0.09.

These results imply that patients in the TZD subsample who had providers with above-median SU prescribing histories had risk of admission for CHF elevated by 0.6 percentage points, controlling for differences in baseline patient risk, provider quality and facility effects.