Dose–response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study

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ABSTRACT

Background: Over the past 30 years, the relation between use of sulfonylureas to treat type 2 diabetes and the risk of cardiovascular events has been vigorously debated. The purpose of this study was to determine if the risk of death changes with level of exposure to sulfonylurea drugs.

Methods: This was a retrospective, inception cohort study using administrative data from Saskatchewan Health (1991–1999). The 5795 subjects, identified by their first-ever dispensation for an oral antidiabetic agent, were grouped according to their use of such agents during follow-up. Potential subjects using insulin or combination therapy were excluded. Exposure level was defined by daily dose and degree of adherence. Separate multivariate Cox proportional-hazard models were constructed for each monotherapy group and used to calculate the risk of death associated with higher versus lower exposure category. Disease severity indicators were identified among the administrative data and entered as covariates in each model. The main outcomes were all-cause mortality and death from an acute ischemic event.

Results: The mean age of the cohort members was 66.3 (standard deviation [SD] 13.4) years; 43.4% were female; and their mean duration of follow-up was 4.6 (SD 2.1) years. First-generation sulfonylureas were used exclusively by 120 subjects; glyburide, by 4138; and metformin, by 1537. A greater risk of death was associated with higher daily doses of the first-generation sulfonylureas (adjusted hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.0–4.7) and glyburide (HR 1.3, 95% CI 1.2–1.4), but not metformin (HR 0.8, 95% CI 0.7–1.1). Similar associations were observed for death caused by an acute ischemic event.

Interpretation: Higher exposure to sulfonylureas was associated with increased mortality among patients newly treated for type 2 diabetes. The same relation was not observed with metformin. This implies that the manner in which blood glucose concentration is lowered may be as important as achieving recommended glucose targets.

Diabetes mellitus is a chronic, progressive disease characterized by deteriorating glucose control and increased risk of micro- and macrovascular complications. About 8% of our population have diabetes, among whom the great majority have type 2.[1,2] The 2 most common oral pharmacologic strategies to manage type 2 diabetes include the use of agents that promote insulin release (e.g., sulfonylureas) or improve insulin sensitivity (e.g., metformin and thiazolidinediones).[3] These strategies reduce hyperglycemia to a similar degree; how they affect mortality, however, remains unclear.

Since publication of the results of the University Group Diabetes Project (UGDP),[4] the relation between the use of sulfonylureas and the risk of cardiovascular events has been questioned. Subjects treated with tolbutamide in the UGDP had a significantly higher cardiovascular rate of death than those given placebo.[4]

Despite the UGDP observations, however, sulfonylureas have been the mainstay of therapy for the past 40 years.[5] This treatment choice persists probably because the UGDP study design has had some controversy[6–9] and perhaps because a plausible mechanism remains inevident.[10–13] Moreover, the largest (3867 subjects) and longest (median follow-up 10.0 years) study of glucose control in people with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), showed that intensive therapy with glibenclamide (glyburide) significantly reduced the rate of microvascular events.[14] Contrary to the UGDP results, sulfonylurea therapy was not associated with an increased risk of death.[14]

In 2 large population-based cohort studies,[15,16] we previously observed that the use of metformin by people with newly treated type 2 diabetes was associated with reduced risks of morbidity and death compared with sulfonylurea monotherapy. Questions remain, however, as to whether the observed relation resulted from a protective effect imparted by metformin, or a potentially harmful effect of the sulfonylureas.[12,17,18] The purpose of the study we report here was to determine whether the risk of death changes with the level of exposure to sulfonylureas. We hypothesized that increased exposure to a harmful medication would be associated with an increased risk of death from all causes or from an acute ischemic event.

Methods

We carried out a retrospective inception cohort study using the administrative databases of Saskatchewan Health. These databases record health care services used by registered beneficiaries in the province who are elegible for prescription drug benefits, who account for 91% of the provincial population of about 1 000 000 people.[19] Saskatchewan residents 30 years of age and older were eligible for inclusion if they were dispensed an oral antidiabetic agent anytime during 1991–1996 (inclusive). These inclusion criteria were used to reduce the chances of including any people with type 1 diabetes in the cohort. The index date was defined as the first dispensation date for an oral antidiabetic agent during the index period; subjects were considered "new users" if they were not dispensed antidiabetic agents for 1 year before the index date.

Findings from the UKPDS and other investigations, including our previous studies, suggest that strategies that do not use sulfonylureas may be associated with different rates of death and cardiovascular events.[15,16,20,21] This variation may be caused by differences in patient characteristics or the pharmacologic properties of the agents. Therefore, to avoid confounding by pharmacologic effects, we identified individuals who used one oral antidiabetic agent exclusively during the observation period. Subjects were excluded if they were dispensed insulin or oral antidiabetic agents from 2 or more classes. Three groups were established according to exclusive dispensation histories of metformin, glyburide or first-generation sulfonylureas (either chlorpropamide or tolbutamide). Study subjects were monitored from their index date until Dec. 31, 1999, death or termination of Saskatchewan Health coverage.

Two measures of level of exposure — dose and adherence — were considered. To determine the average daily dose, we divided the duration of follow-up in days into the total weight of active drug dispensed therein. We identified a median daily dose for each monotherapy group and assigned subjects to the higher- or lower-dose subgroup if their average daily dose was above or below the median, respectively. An adherence rate was calculated by dividing the total expected duration for all dispensations by the subject's duration of follow-up.[22] We developed an algorithm to estimate the expected duration for each dispensation based on the number of tablets dispensed and the feasible daily regimens taken from each antidiabetic agent's product monograph. Subjects with an adherence rate over 0.8 were considered to have good adherence; this cut-off is a well-accepted threshold.[23,24] In addition, we assumed that subjects had discontinued oral antidiabetic drug therapy if the interval between the last dispensation and the end of follow-up was 6 months or more. Given that diabetes is a chronic, progressive disease and that these subjects stopped all antidiabetic drug therapy, including insulin, we included these subjects in the poor adherence group. To test the sensitivity of our definition for adherence, we applied different thresholds for adherence rate (0.66–0.9) and discontinuance (3–12 mo).

For statistical analysis, the primary outcome was time from the index drug-dispensation date to death from any cause. The secondary outcome was time to death attributable to an acute ischemic event. Cause of death was determined from the vital statistics files of Saskatchewan Health; deaths attributable to myocardial infarction (i.e., recorded with the International Classification of Diseases, 9th revision [ICD-9] code 410) or another ischemic cardiovascular event (ICD-9 codes 411–414) were noted. Multivariate Cox proportional-hazards models were used to estimate the hazard ratio (HR) for death while controlling for potential confounding factors. Separate analysis models for each monotherapy group were constructed. Subjects with the lowest level of exposure (either lower daily dose or poor adherence) served as the reference group for each HR reported.

Potential confounding variables that were entered into the models included age, sex, nitrate use, chronic disease score, number of physician visits and hospital admissions. The use of nitrates has been used previously as a marker for the presence of cardiovascular disease.[25,26] The chronic disease score uses pharmacy dispensation information for selected drugs (e.g., angiotensin-converting-enzyme inhibitors, β-blockers, inhaled bronchodilators, antiparkinsonian medications) to estimate the presence of chronic diseases.[27] A relative weight of disease burden was calculated based on the number of chronic diseases identified by drug therapy during the follow-up period of the subject; all subjects therefore had a minimum chronic disease score of 2 because they were dispensed oral antidiabetic agents. Interaction terms between each variable and level-of-exposure variable were examined; but because none reached statistical significance ($p < 0.05$), they were not considered in the final models.

As with any observational study, confounding of the statistical analysis by indication, whereby "sicker" patients would more likely receive higher doses and also be at higher risk of death, was a major concern. We followed the methodology proposed by Sackett and colleagues[28] and used available data to control for this source of confounding. Assuming that sicker patients would visit their physician more frequently and be admitted more often to hospital, we entered the number of physician visits and hospital admissions into the multivariate analysis. We also calculated a propensity score to represent the likelihood of an individual receiving a higher drug dose, given his or her characteristics.[29] As we had also observed in another study with the same database,[16] the addition of a propensity score did not make a substantial change to the observed association; we therefore excluded this score from the final models of analysis.

Results

We identified 12 272 Saskatchewan residents who were new users of oral antidiabetic agents. Of these, 1443 received insulin and 4885 were dispensed oral antidiabetic agents from 2 or more different classes during the observation period. Because their information was insufficient to estimate a level of exposure, we excluded 149 others who were monitored for less than 6 months. Of the remaining 5795 subjects, 120 used a first-generation sulfonylurea exclusively (607 accumulated person-years of follow-up); 4138, glyburide monotherapy (19 298 person-years of follow-up); and 1537, metformin

monotherapy (6995 person-years of follow-up).

The mean duration of follow-up was 4.8 years (standard deviation [SD] 2.1 yr) for subjects taking lower daily doses, compared with 4.5 (SD 2.1) years for those taking higher doses ($p < 0.001$). The mean age of those taking lower daily doses was 65.6 (SD 14.1) years; higher daily doses, 67.0 (SD 12.6; $p < 0.001$). The average burden of chronic diseases, estimated with chronic disease scores, was 8.1 (SD 4.3) among subjects with lower daily doses and 8.2 (SD 4.0) among those with higher doses ($p = 0.36$). Table 1 displays patient characteristics stratified by monotherapy groups.

There were 1503 deaths during the study period, of which 372 (24.8%) were attributable to an acute ischemic event. First-generation sulfonylurea monotherapy users had the highest mortality (67.6 deaths per 1000 person-years), compared with glyburide monotherapy users (61.4 deaths per 1000 person-years) and metformin monotherapy users (39.6 deaths per 1000 person-years).

The high-dose groups using first-generation sulfonylurea monotherapy and glyburide monotherapy had higher rates of death than their counterparts who took lower doses (Fig. 1A). This statistical association was maintained after controlling for age, sex, comorbidities, physician visits and hospital admissions. Higher daily doses of metformin were not associated with an increased risk of death. Similar patterns of association were observed for deaths attributable to an acute ischemic event (Fig. 1B).

To confirm the observed relation between daily dose and increased risk of all-cause risk of mortality, we repeated the analyses using adherence rate to dichotomize the monotherapy groups. Good adherence to prescribed drug treatment was associated with a higher risk of death in the first-generation sulfonylurea and glyburide groups (Fig. 1C), but not in the 2 metformin subgroups. In our sensitivity analyses, these relations did not change substantially with the any of the variations in threshold that we applied to define good versus poor adherence or discontinuance.

Interpretation

This study used information from administrative health databases to further explore the relation between individual antidiabetic drug classes and the risk of death among people with type 2 diabetes. We found that the risk of death was dose-related for chlorpropamide, tolbutamide and glyburide, even after controlling for demographic variables and comorbidities. In contrast, higher doses of metformin were not associated with an increased risk of death.

Our observation of a dose–response relation for sulfonylureas fulfills another element of the Bradford–Hill conditions to establish causality from observational studies.[30] Subjects exposed to higher levels of sulfonylurea monotherapy had a higher mortality. In contrast, the level of exposure to metformin monotherapy had no apparent effect on mortality. The results generated from the UGDP more than 30 years ago suggested that sulfonylurea use may be associated with an increased risk of cardiovascular events and death.[4] Since then, investigations in animal and human models and post-hoc analyses of clinical trial data and observational studies have shown a consistent but perhaps underappreciated association between the use of sulfonylurea drugs and poor cardiac outcomes.[10,12,18,31]

One biological mechanism for this relation, as hypothesized by several authors,[10,32,33] may be impairment of ischemic preconditioning. Sulfonylureas promote release of insulin from pancreatic β cells by binding to the sulfonylurea receptor and maintaining closure of the adenosine triphosphate (ATP)-sensitive potassium channel.[32] In cardiac myocytes and smooth muscle cells, the closure of ATP-sensitive potassium channels impairs ischemic preconditioning, a phenomenon that enables myocardial cells to survive brief periods of ischemia.[10,33] The effect on ischemic preconditioning varies substantially among the sulfonylureas, likely because of the wide range of binding affinities for sulfonylurea receptors on cardiac myocytes.[12] For example, glyburide has a high affinity for

Table 1: Demographic and clinical characteristics of patients with type 2 diabetes mellitus prescribed drug monotherapy, by median split of average daily dose*

Characteristic	First-generation sulfonylurea		Glyburide		Metformin	
	Lower dose (n = 46)	Higher dose (n = 74)	Lower dose (n = 2071)	Higher dose (n = 2067)	Lower dose (n = 769)	Higher dose (n = 768)
Age, mean (SD), yr	67.8 (11.8)	68.8 (13.4)	66.4 (14.1)†	67.8 (12.6)	63.2 (14.3)†	64.6 (12.4)
Female, no. (%)	22 (48)	31 (42)	923 (45)‡	828 (40)	350 (46)	359 (47)
Nitrate use, no. (%)	11 (24)	19 (26)	497 (24)‡	557 (27)	164 (21)	157 (20)
Follow-up, mean (SD), yr	5.6 (2.4)†	4.7 (2.3)	4.9 (2.2)†	4.5 (2.2)	4.7 (1.9)†	4.4 (1.9)
Chronic disease score, mean (SD)	9.0 (4.2)	8.0 (3.5)	8.1 (4.2)	8.2 (4.0)	8.1 (4.4)	8.2 (4.0)
Median score	9.0	8.0	8.0	8.0	8.0	8.0
Physician visits, mean (SD)	83.4 (69.5)†	55.7 (37.2)	72.2 (68.2)†	67.1 (57.5)	69.4 (62.5)†	59.3 (44.5)
Median no. of visits (IQR)	60 (40-123)	49 (32-71)	53 (30-94)	53 (31-87)	52 (28-91)	48 (28-78)
Hospital admissions, mean (SD)	3.5 (3.8)†	1.8 (2.1)	2.9 (3.5)†	2.7 (3.4)	2.4 (3.3)†	2.0 (2.6)

Note: SD = standard deviation, IQR = interquartile range.
*Whether drug exposure was higher or lower than the median for the group of patients taking that drug.
†‡$p < 0.05$ when lower and higher daily dose groups within a treatment cohort are compared †by analysis of variance or ‡by χ^2 test.
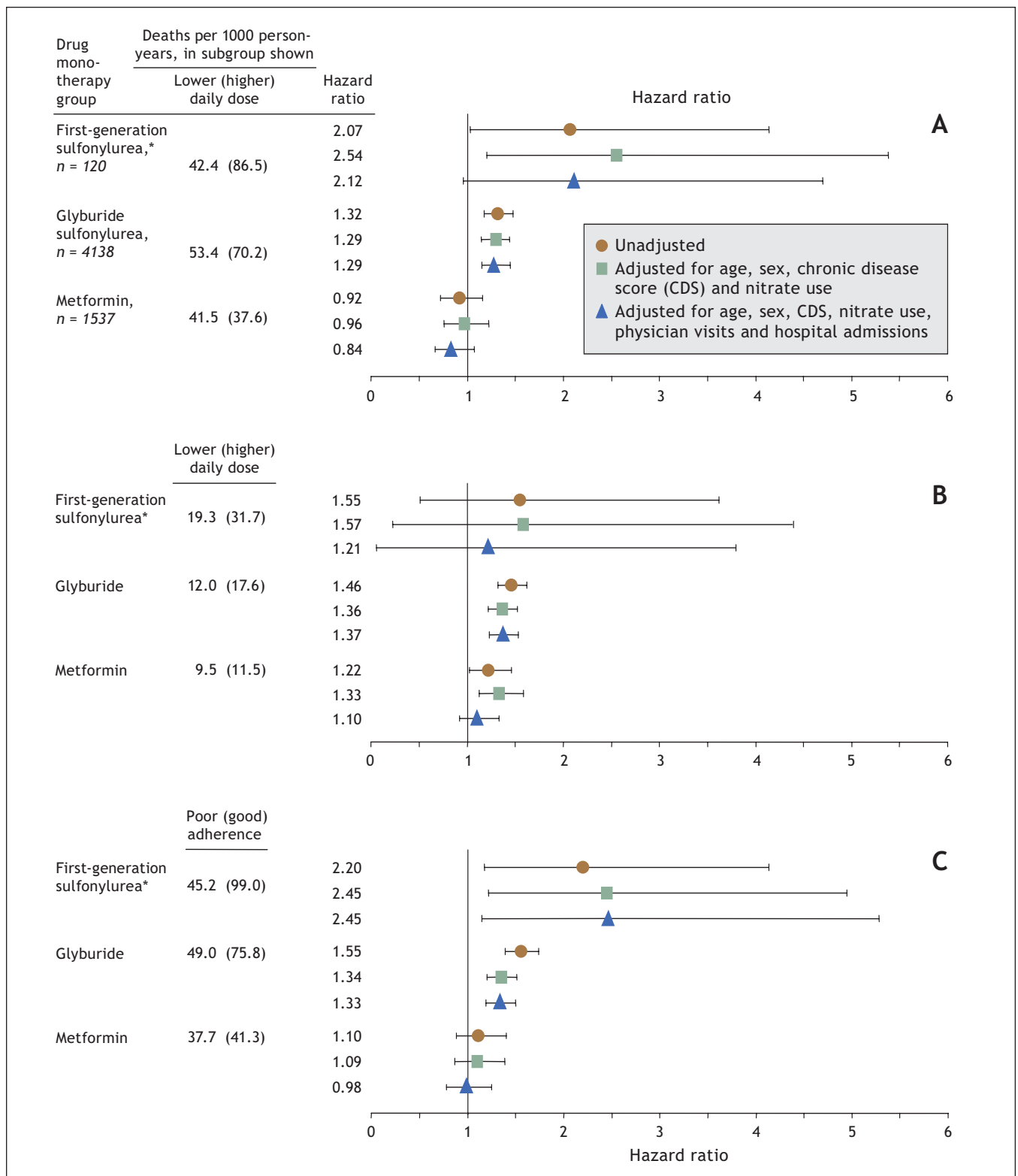
Fig. 1: Hazard ratios among patients with type 2 diabetes mellitus, comparing 2 subgroups within each drug-monotherapy group: **1A**, hazard ratios for deaths from all causes, according to median split for drug exposure (i.e., whether their individual daily dose was more than the group median [higher subgroup] or less [lower subgroup — used as the reference]); **1B**, for deaths attributable to an acute ischemic event, also according to median split for drug exposure; and **1C**, for all-cause mortality, according to drug-treatment adherence (patients were assigned to the poor-adherence [reference] subgroup if their adherence rate was < 0.8 or if they stopped therapy > 6 months before end of follow-up). Error bars indicate 95% confidence intervals. *Either chlorpropamide or tolbutamide.

both pancreatic and cardiac sulfonylurea receptors, whereas gliclazide and nateglinide have high selectivity for pancreatic sulfonylurea receptors.[12] Equally plausible explanations for sulfonylurea toxicity include direct arrhythmogenic effects, associated weight gain, hypoglycemia and the toxicity of elevated insulin levels.[10,33]

This study builds on observations from our previous analyses illustrating a difference in the risks of morbidity and death among classes of oral antidiabetic drugs used by patients.[15,16] The reason for this risk difference has been the topic of much recent discussion.[12,17,18] The focus appears to be on differences in pharmacologic effects, whereby sulfonylureas may be cardiotoxic and metformin may provide some degree of cardioprotection.[17] Although the potential cardiotoxic effects of sulfonylureas have been debated over the last 30 years,[4,13] the potential cardioprotective effects of metformin, first shown by the UKPDS,[20] have not been well described. In our current study, stratification by monotherapy group eliminated confounding from pharmacologic differences between drug classes. This allowed us to evaluate the effect of different levels of exposure by comparing the risk of death among users of the same antidiabetic agent. Although our study provides additional evidence to support the theory of a cardiotoxic effect of sulfonylureas, it does not resolve the question of whether the risk difference between antidiabetic drug classes is the result of different pharmacologic effects.

There are several limitations to this observational study. First, our observations are based on administrative data. Such databases do not record clinical information such as the subject's height, weight, blood pressure, cholesterol profiles or glucose control. We believe that information on glucose control would not change our observations substantially, given that the largest randomized controlled study involving people with type 2 diabetes did not demonstrate that good glucose control reduced the risk of all-cause mortality.[14] Nevertheless, residual confounding, such as differences in underlying cardiovascular risk between exposure groups, may partially explain our observed differences in risk of death. We used available prescription drug data (i.e., nitrate use to identify subjects with cardiovascular disease, and the chronic disease score as a measure of chronic disease burden), demographic information (age and sex) and health resource utilization information (i.e., physician visits and hospital admissions) to control for these underlying risks and to adjust for case mix.

Second, our measures for exposure share the same limitations as other pharmacy claims databases.[22] We assumed that drug acquisition is a surrogate marker for consumption and thereby may have overestimated actual exposure.

Third, subjects using higher doses of oral antidiabetic agents may have required this level of drug use to manage higher blood-glucose levels or more advanced diabetes — a form of confounding by indication. If confounding by indication were present, the positive association observed in the unadjusted model could be expected to move toward unity with adjustment for disease severity.[28] The addition of physician visits and hospital admissions to the multivariate models, however, did not have a substantial effect on the observations. Furthermore, enrolment criteria for our inception cohort controlled for duration of disease by identifying subjects filling their first prescription for an oral antidiabetic agent. Intriguingly, subjects in the group taking lower daily doses had a longer follow-up than subjects prescribed higher daily doses.

Fourth, the index period for our data set predated the availability of the thiazolidinediones acarbose and repaglanide. If ischemic preconditioning, rather than the other postulated mechanisms, is responsible for the potential toxicity of the older but commonly used sulfonylureas that we studied, then this may become less of an issue as accepted practice shifts to the newer sulfonylureas.[12,13]

In conclusion, we observed a dose–response relation between sulfonylurea exposure and risk of death. This evidence, taken within the context of observations collected over the last 30 years, suggests that clinicians should carefully assess the need for sulfonylurea therapy in subjects at high risk of cardiovascular events — particularly now, when several other classes of antidiabetic oral medications are available.

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Editor's take

- Existing evidence suggests that in patients with type 2 diabetes, the risk of death is higher among those who are taking sulfonylurea monotherapy than among those taking metformin.

- In this study, the authors used administrative data to confirm previous findings: they found that rates of mortality per 1000 patient-years were 67.6 among users of first-generation sulfonylureas, compared with 39.6 among users of meformin. Additionally, the authors have demonstrated that the risk of death was higher in patients taking high doses of sulfonylureas than taking low doses, suggesting a causal link.

- As is typical in studies that use administrative databases, detailed clinical data were unavailable for analysis. It is therefore possible that important confounding variables were unaccounted for.

Implications for practice: The results of this study should add to existing caution about prescribing sulfonylurea monotherapy for patients with type 2 diabetes. Clinicians should weigh the need for sulfonylurea drugs in light of their possible risks, given the availability of other oral hypoglycemic agents.