Sulfonylurea Use and Incident Cardiovascular Disease Among Patients With Type 2 Diabetes: Prospective Cohort Study Among Women

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OBJECTIVE

Evidence is inconsistent for the association between sulfonylurea use and risk of cardiovascular disease among patients with diabetes. We aimed to prospectively evaluate this association using the Nurses' Health Study (NHS), a well-established cohort of U.S. women with long-term follow-up.

RESEARCH DESIGN AND METHODS

We followed 4,902 women (mean age 68 years) with diabetes (mean duration 11 years), but without cardiovascular disease at baseline. The use of sulfonylureas and other medications was self-reported at baseline and during the follow-up period of up to 10 years. Cox proportional hazard regression models were used to estimate the relative risk (RR) and 95% CI for the association between the sulfonylurea use and incident cardiovascular disease while accounting for potential confounders, including age, diabetes duration, diabetes-related complications, other antihyperglycemic medications, BMI, lifestyle factors, family history of cardiovascular diseases, and present chronic conditions. We also applied the propensity score stratification method to address the possibility of residual confounding.

RESULTS

We identified 339 incident cases of cardiovascular disease, including 191 cases of coronary heart disease (CHD) and 148 cases of stroke. A longer duration of sulfonylurea use was significantly associated with a higher risk of CHD (*P* for trend = 0.002); the RRs for CHD were 1.24 (95% CI 0.85–1.81) for patients who used sulfonylurea therapy for 1–5 years, 1.51 (0.94–2.42) for 6–10 years, and 2.15 (1.31–3.54) for >10 years, compared with nonusers. Compared with users of metformin monotherapy, the RR for CHD was 3.27 (1.31–8.17) for those who were treated with the combination of metformin and sulfonylurea. The analysis using propensity score stratification yielded similar results. We did not observe a significant association between sulfonylurea therapy and stroke risk.

CONCLUSIONS

Long-term use of sulfonylureas was associated with a significantly higher risk of developing CHD among women with diabetes.

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Cardiovascular disease is a highly prevalent complication of type 2 diabetes that accounts for 50–80% of the deaths among patients with diabetes (1). Therefore, prevention of cardiovascular morbidity and mortality is an important goal for diabetes treatment. Sulfonylureas are one of the effective antihyperglycemic agents recommended by the American Diabetes Association (2). Although sulfonylureas have been a mainstay of type 2 diabetes pharmacotherapy for many years, the potential adverse effects of sulfonylureas have been raised by previous studies (3–5). Currently approved package labels for all sulfonylureas bear a warning for increased cardiovascular risk (6,7). Concerns about the cardiovascular safety of sulfonylureas date back to the 1970s, when the University Group Diabetes Program (UGDP) clinical trial (4) was terminated prematurely because of the excess cardiovascular mortality in the group prescribed tolbutamide, a first generation sulfonylurea.

The UGDP results have been debated concerning the study's nonrandomized design and low statistical power to test the hypothesis of inferior cardiovascular safety for sulfonylureas versus placebo. However, the lack of beneficial effects of sulfonylureas on the incidence of cardiovascular events was observed in the UK Prospective Diabetes Study (UKPDS) (8). A meta-analysis of clinical trials demonstrated a lack of evidence for cardiovascular benefit and an increased mortality risk in patients with diabetes using sulfonylureas (5). In addition, the combination treatment with metformin and sulfonylurea, which are the two most commonly used drugs for glycemic control, has been associated with a higher risk of total mortality in several (9–13), but not all, studies (14). Recently, an increased risk of cardiovascular events or death was documented in several observational studies; however, those studies were mainly retrospective studies (15,16), lacked adjustment for important confounding factors (17,18), had a short period of follow-up (19) or based on the health administrative data without confirmation of cardiovascular outcomes (15,18,19). Thus, the purpose of the current study was to prospectively evaluate the association between long-term use of sulfonylureas and incident cardiovascular disease among patients with diabetes but without a medical history of cardiovascular disease at baseline within an ongoing well-established cohort, the Nurses' Health Study (NHS) (20).

RESEARCH DESIGN AND METHODS

Study Population

The NHS cohort was established in 1976 when 121,700 female registered nurses aged 30 to 55 years and residing in 11 U.S. states completed a mailed questionnaire on their medical history and lifestyle characteristics (20). Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of type 2 diabetes and cardiovascular and other medical events.

In 2000 and 2005, 5,536 patients with type 2 diabetes responded to the supplemental questionnaires regarding their diabetes treatment and diabetes-related complications. Participants with prevalent cardiovascular disease ($n = 634$) at the time of supplemental questionnaire collections were excluded from the analysis. Thus, 4,902 participants were included in the current study investigating incident cardiovascular disease. The end of the follow-up period was 30 June 2010.

The institutional review boards at the Harvard School of Public Health and Brigham and Women's Hospital approved the study protocol.

Ascertainment of Type 2 Diabetes

Type 2 diabetes was ascertained by self-reported cases confirmed using a validated supplementary questionnaire (21). We used the National Diabetes Data Group criteria to define type 2 diabetes for the cases before 1998 and the American Diabetes Association diagnostic criteria from 1998 onward.

The validation of self-reported type 2 diabetes diagnosis in the NHS has been documented previously. In a random sample of 62 cases in NHS that were confirmed by the supplementary questionnaire, 61 cases (98%) were reconfirmed after medical record review by an endocrinologist blinded to the supplementary questionnaire (21). In a random sample of participants ($n = 200$) who reported no diabetes, only one participant (0.5%) had an elevated fasting plasma glucose in the diabetic range, and with levels that were barely above the diagnostic cutoffs.

Assessment of Cardiovascular Events and Mortality

We included nonfatal myocardial infarction, coronary heart disease (CHD) death, and stroke in our end point of cardiovascular disease, which was identified primarily through a review of medical records, as previously described (22). We requested permission to review medical records when a woman reported a nonfatal CHD or stroke. We also sought medical records for deceased participants, whose deaths were identified by families and postal officials and through the National Death Index. Physicians blinded to the participant questionnaire reports reviewed all medical records.

Nonfatal myocardial infarction was confirmed if the criteria of the World Health Organization were met, specifically, on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations. Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke, requiring evidence of a neurologic deficit with sudden or rapid onset that persisted for $>$24 h or until death. All strokes since 1976 were reviewed by a neurologist and classified according to the criteria used in the Perth Community Stroke Study by stroke subtype and/or etiology: subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (thrombotic or embolic), or stroke of unknown causes.

Deaths were reported by next of kin and the postal system and through records of the National Death Index. Using all sources combined, we estimated that follow-up for death was over 98% complete. Fatal CHD was defined as fatal myocardial infarction if this was confirmed by hospital records or autopsy, or if CHD was listed as the cause of death on the certificate and this was the underlying and only plausible cause, and evidence of previous CHD was available (22). Fatal strokes were coded using the same criteria as for nonfatal cases, but autopsy evidence was also accepted as was a death certificate listing the cause of death as stroke.

Assessment of Diabetes Treatments and Complications

A supplementary questionnaire on diabetes therapy and complications was administered in the NHS in years 2000

and 2005. This questionnaire was based on the one used in the National Health Interview Survey designed by Dr. Maureen Harris and colleagues (23,24). It asked about diagnosis of the disease, general medical care, frequency of clinical visits, symptoms of diabetes-related complications, glucose monitoring, and diabetes treatment. Diabetes-related complications included diabetic retinal diseases, diabetic kidney diseases, and diabetic brain damage. In the supplemental questionnaires, we asked patients with diabetes about their medication use, including metformin, troglitazone, acarbose, insulin, and other diabetic medications, as well as sulfonylureas (e.g., Micronase, Glucotrol, Tolinase, or Diabinese). We inquired about the total duration of each medication use

Information on microvascular complications, including retinopathy and nephropathy, was collected. Duration of diabetes was assessed by asking participants when they were first diagnosed with diabetes in both the biennial and supplementary questionnaires..

Assessment of Covariates

Information on potential confounders, including age, body weight, smoking status, physical activity, use of aspirin, multiple vitamin supplements, cholesterol-lowering medications, antidepressants, and antihypertensive medications, and a history of major chronic conditions, including hypertension, hypercholesterolemia, cancer, and coronary artery bypass graft, was collected via the regular biennial questionnaires throughout the follow-up of NHS (information of confounders for current analysis was repeatedly collected at 2000, 2002, 2004, 2006, and 2008 cycles). BMI was calculated as weight in kilograms divided by height in meters squared from self-reported weight and height. Starting in 1980, on a 2–4-year cycle, dietary information has been updated using validated semiquantitative food frequency questionnaires. We generated an alternative healthy eating index score to evaluate the diet quality, which has been significantly associated with cardiovascular disease in our cohort (25). Alcohol use was assessed by the food frequency questionnaires, which included questions about average daily consumption of beer, wine, and spirits during the previous year.

Statistical Analysis

Among those 4,902 participants for current analysis, 1,367 (28%) only responded to the 2000 supplemental questionnaire and 2,578 (52%) responded to both 2000 and 2005 supplemental questionnaires (2000 cycle was treated as their baseline survey). Another 957 (20%) participants only enrolled in the 2005 cycle, which was treated as their baseline survey. Individuals contributed to person-time from the return of the baseline questionnaire until the date of diagnosis of cardiovascular disease, death, loss to follow-up, or the end of the follow-up period (30 June 2010), whichever came first.

We examined the risk of cardiovascular disease according to the duration of sulfonylurea use (1–5, 6–10, and >10 years) versus a nonuser of sulfonylureas. Participants reporting having used sulfonylureas before baseline but not reporting use of sulfonylureas at baseline or during the follow-up period were classified into the category of nonusers. In a secondary analysis, participants were classified into mutually exclusive categories according to their medication use: metformin alone (reference group), sulfonylurea alone, combination of sulfonylurea and metformin, nonuse of antihyperglycemic medications, insulin only, and other combinations of diabetic medications.

We used multivariable Cox proportional hazards models to estimate hazard ratios as estimates of the relative risk (RR) and 95% CI comparing sulfonylurea users with nonusers. To quantify a linear trend of duration of sulfonylurea use, we conducted a Wald test for linear trend by assigning the median value to each category of duration of sulfonylurea use and modeling this variable as a continuous variable.

Model 1 was an age-adjusted model (age in months). Multivariable model 2 further adjusted BMI (kg/m^2); physical activity (quintiles); smoking status (never smoker, former smoker, or current smoker: 1–14 or ≥15 cigarettes/day); alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥30 g/day); alternative healthy eating index as a marker of overall diet quality (quintile); ethnicity (Caucasian, yes/no); family history of myocardial infarction (yes/no); family history of stroke (yes/no); use of aspirin, multiple vitamin supplements, cholesterol-lowering medications, antidepressants, and antihypertensive medications; and a history of major chronic conditions, including hypertension, hypercholesterolemia, cancer, and coronary artery bypass graft (each yes/no). All covariates, except for family history of myocardial infarction, were updated during follow-up and included as time-varying covariates in the models.

Multivariable model 3 further adjusted for diabetes-related complications and other diabetic medications, e.g., plasma HbA_{1c} (missing and <7, 7–7.9, 8–9.9, 10–11.9, and ≥12); duration of diabetes affecting the back of eyes (retina: not affected and <2, 2–5, and >6 years); duration of diabetes-related kidney disease (not affected and <2, 2–5, and >6 years); duration of diabetes-related neuropathy (nerve damage: not affected and <2, 2–5, 6–9, 10–14, and ≥15 years); and use of other diabetic medications, including insulin, rosiglitazone, pioglitazone, acarbose, and other diabetic medications (past, never, and current users for each). In multivariable model 4, we further adjusted for the duration of diabetes.

To address the possibility of residual confounding, we also applied the propensity score stratification method. The propensity score was the estimated probability of treatment selection conditional on observed covariates (26), which was calculated for each treatment method as dependent variable respectively and all the covariates listed above (from model 1 to 3) as independent variables. Quintiles of the propensity scores of different treatments and untreated subjects were included in the analysis. The effect of treatment on outcomes was estimated within each stratum of the propensity score. Stratum-specific treatment effects were then pooled to obtain an overall treatment effect (26,27).

We examined potential interactions of the sulfonylurea use with presence of hypertension, hypercholesterolemia, or diabetic kidney disease on risk of cardiovascular disease as well as CHD and stroke by including a multiplicative term in the Cox model with adjustment for other potential confounders.

To test the robustness of our findings between sulfonylureas and cardiovascular disease, we conducted two sensitivity analyses. In the first sensitivity analysis, we excluded the participants reporting having used sulfonylureas before baseline but not reporting use of sulfonylureas at baseline or during the

follow-up period from the category of nonusers. In the second sensitivity analysis, we limited our analysis to the participants who responded to the diabetes supplemental questionnaire in both 2000 and 2005 and classified the participants as nonusers, no-consistent users, and consistent users who reported using of sulfonylureas in both 2000 and 2005 cycles.

Data were analyzed using a commercially available software program (SAS, version 9.3; SAS Institute, Inc.), and statistical significance was set at a two-tailed <0.05.

RESULTS

We collected the sulfonylurea therapy information from 4,902 diabetic nurses without diagnosis of cardiovascular disease at baseline, including 2,467 nonusers and 2,435 users during the follow-up period of 2000–2010. At baseline, the mean age of the nurses was 68 years with an average duration of diabetes of 11 years. As shown in Table 1, sulfonylurea therapy was associated with longer duration of diabetes, diabetes-related complications, and use of other antihyperglycemic medications. The prevalence of smoking, multivitamin use, aspirin use, use of antidepressant medications, family history of cardiovascular diseases, and presence of hypertension at baseline were similar across categories of sulfonylurea therapy (Table 1).

During 5–10 years of follow-up, we identified 339 incident cases of cardiovascular disease, including 191 cases of CHD (145 nonfatal myocardial infarction and 46 CHD deaths) and 148 cases of stroke. Compared with nonusers of sulfonylurea, the multivariable-adjusted RRs of total cardiovascular diseases for patients with diabetes who had been using sulfonylurea therapy for 1–5, 6–10, and >10 years were 1.20 (95% CI 0.91–1.58), 1.40 (0.98–1.99) and 1.65 (1.12–2.43), respectively (Table 2). However, when we examined the association of sulfonylureas with CHD and stroke separately, increasing the duration of sulfonylurea use was only significantly associated with CHD risk (*P* for trends = 0.005) (Table 2). The multivariable-adjusted RRs for CHD were 1.24 (0.85–1.81) for patients who had used sulfonylurea therapy for 1–5 years, 1.51 (0.94–2.42) for 6–10 years, and 2.15 (1.31–3.54) for >10 years compared with nonusers. We did not find a significant association between the duration of sulfonylurea use and risk of stroke (Table 2). As compared with metformin monotherapy, the multivariable RR of combination therapy with metformin and sulfonylurea for total cardiovascular disease was 1.99 (1.07–3.70), which was 3.27 (1.31–8.17) for CHD and 1.10 (0.45–2.69) for stroke (Table 3).

The analysis using propensity score stratification yielded similar results. The multivariable-adjusted RRs for CHD were 1.15 (95% CI 0.79–1.68) for patients who had used sulfonylurea therapy for 1–5 years, 1.39 (0.87–2.23) for 6–10 years, and 1.99 (1.22–3.25) for >10 years compared with nonusers by the stratification of propensity score method (*P* for trend = 0.005). As compared with metformin monotherapy, the multivariable RR of combination therapy with metformin and sulfonylurea for CHD was 3.10 (1.21–7.94).

The interactions between sulfonylurea use and presence of chronic conditions (hypertension, hypercholesterolemia, and diabetic kidney disease) were not significant on risk of cardiovascular disease, CHD, or stroke (*P* for interaction >0.1 for all). After we excluded past users (i.e., the participants reporting having used sulfonylureas before but not reporting use of sulfonylurea during the follow-up period) from the category of nonusers, the multivariable-adjusted RR for CHD was 2.17 (95% CI 1.27–3.71; *P* for trends = 0.004) for participants who had used sulfonylureas for 10 more years as compared with never users. In the second sensitivity analysis among participants who responded to the diabetes supplementary questionnaire in both 2000

Table 1—Basic characteristics of subjects at baseline according to current use of sulfonylurea

	Duration of sulfonylurea (years)				
	None	1–5	6–10	>10	*P* for trends**
n (total = 4,902)	2,467	1,601	532	302	
Age* (years)	68.8	67.5	67.6	68.6	0.006
BMI (kg/m^2)	30.3	31.3	31.6	31.0	0.0002
Energy intake (kcal/day)	1,613	1,648	1,579	1,649	0.8
Alcohol (g/day)	2.4	1.6	1.5	1.6	0.0008
Physical activity (h/week)	1.0	0.9	0.9	0.6	0.003
Alternative healthy eating index score	52.1	51.0	50.7	50.3	0.0003
Current smoking (%)	7.0	7.3	7.6	5.6	0.7
Multivitamin use (%)	67.9	64.9	67.6	62.6	0.1
Family history of myocardial infarction (%)	27.3	14.0	14.1	12.4	0.98
Family history of stroke (%)	7.1	7.5	6.1	8.9	0.6
Diabetic characteristics and medications					
Diabetes duration (years)	10.5	11.4	12.4	17.2	<0.0001
HbA_{1c} (%)	7.0	7.6	7.7	7.8	<0.0001
Diabetic retina (%)	13.6	19.5	17.6	26.0	<0.0001
Diabetic kidney disease (%)	2.8	3.3	3.7	7.5	0.0004
Diabetic neuropathy (%)	17.6	24.3	25.9	32.1	<0.0001
Insulin (%)	16.4	28.4	22.5	23.7	<0.0001
Rosiglitazone (%)	8.9	12.5	14.7	15.5	<0.0001
Pioglitazone (%)	6.4	10.5	7.4	12.9	0.001
Acarbose (%)	3.1	2.1	2.6	1.3	0.08
Other combinations of medications (%)	15.8	10.0	4.9	6.7	<0.0001
History of other chronic conditions and medications					
Hypertension (%)	57.8	57.8	57.3	58.3	0.7
Hypercholesterolemia (%)	51.3	48.8	47.8	43.8	0.01
Cancer (%)	16.5	19.1	20.8	20.1	0.007
Aspirin (%)	52.6	51.2	51.1	50.2	0.3
Antihypertensive medications (%)	63.0	65.1	68.7	63.1	0.09
Antidepressant medications (%)	13.0	13.9	11.0	12.5	0.4
Cholesterol-lowering medications (%)	43.4	42.9	39.1	35.7	0.006

Values are means or percentages and are standardized to the age distribution of the study population. *Value is not age adjusted. **P for trends was estimated by general linear model for means and logistic model for percentages by assigning the median value to each category of duration of sulfonylurea use and modeling this variable as a continuous variable.

Table 2—Risk of incident cardiovascular diseases during 5–10 years of follow-up according to current use of sulfonylurea

	Duration of sulfonylurea (years)					Yes vs. no
	No	1–5	6–10	>10	*P* for trends	RR (95%CI), *P*
Total cardiovascular disease						
Person-years	14,399	11,996	4,438	2,924		19,358 vs. 14,399
Number of cases	122	126	51	40		217 vs. 122
Incident rate (per 10^5 person-years)	847	1,050	1,149	1,368		1,121 vs. 847
Adjusted RR (95% CI)						
Model 1	Ref	1.25 (0.97–1.61)	1.37 (0.98–1.90)	1.61 (1.12–2.31)	0.006	1.33 (1.07–1.67), *P* = 0.01
Model 2	Ref	1.25 (0.97–1.62)	1.36 (0.98–1.90)	1.60 (1.11–2.30)	0.007	1.33 (1.06–1.67), *P* = 0.01
Model 3	Ref	1.20 (0.91–1.58)	1.39 (0.98–1.98)	1.64 (1.11–2.40)	0.007	1.31 (1.01–1.68), *P* = 0.04
Model 4	Ref	1.20 (0.91–1.58)	1.40 (0.98–1.99)	1.65 (1.12–2.43)	0.007	1.31 (1.01–1.68), *P* = 0.04
CHD						
Number of cases	62	72	30	27		129 vs. 62
Incident rate (per 10^5 person-years)	431	600	676	923		666 vs. 431
Adjusted RR (95% CI)						
Model 1	Ref	1.40 (0.99–1.97)	1.55 (1.00–2.40)	2.15 (1.36–3.39)	0.001	1.55 (1.14–2.10), *P* = 0.005
Model 2	Ref	1.37 (0.97–1.94)	1.52 (0.97–2.36)	2.10 (1.32–3.34)	0.002	1.51 (1.11–2.06), *P* = 0.009
Model 3	Ref	1.24 (0.85–1.81)	1.50 (0.94–2.40)	2.08 (1.27–3.39)	0.003	1.41 (1.01–1.99), *P* = 0.047
Model 4	Ref	1.24 (0.85–1.81)	1.51 (0.94–2.42)	2.15 (1.31–3.54)	0.002	1.42 (1.01–2.00), *P* = 0.04
Stroke						
Number of cases	60	54	21	13		88 vs. 60
Incident rate (per 10^5 person-years)	417	450	473	445		455 vs. 417
Adjusted RR (95% CI)						
Model 1	Ref	1.10 (0.76–1.60)	1.17 (0.70–1.93)	1.05 (0.57–1.93)	0.70	1.11 (0.79–1.55), *P* = 0.54
Model 2	Ref	1.13 (0.78–1.66)	1.17 (0.70–1.95)	1.07 (0.58–1.98)	0.68	1.13 (0.81–1.59), *P* = 0.47
Model 3	Ref	1.19 (0.78–1.80)	1.29 (0.75–2.21)	1.21 (0.63–2.30)	0.43	1.21 (0.83–1.77), *P* = 0.32
Model 4	Ref	1.19 (0.79–1.81)	1.29 (0.75–2.20)	1.19 (0.62–2.27)	0.46	1.21 (0.83–1.77), *P* = 0.32

RR and 95% CIs were estimated from Cox proportional hazards models. Model 1: adjusted age (months). Model 2: further adjusted BMI (kg/m^2); physical activity (quintiles); smoking status (never smoker, former smoker, or current smoker: 1–14 or ≥15 cigarettes/day); alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥30 g/day); alternative healthy eating index (quintile); Caucasian ethnicity (yes/no); multivitamin use (yes/no); family history of myocardial infarction (yes/no); family history of stroke (yes/no); presence of hypertension, hypercholesterolemia, and cancer; self-reported history of coronary artery bypass graft; and regular use of aspirin, antidepressant, antihypertensive, and cholesterol-lowering drugs (yes/no). Model 3: further adjusted plasma levels of HbA_{1c} (missing and <7, 7–7.9, 8–9.9, 10–11.9, and ≥12); duration of retina (not affected and <2, 2–5, and >6 years); duration of kidney disease (not affected and <2, 2–5, and >6 years); duration of neuropathy (nerve damage: no affected and <2, 2–5, 6–9, 10–14, and ≥15 years); and use of other diabetic medications including insulin, rosiglitazone, pioglitazone, acarbose, and other diabetic medications (past, never, and current users for each). Model 4: further adjusted for duration of diabetes (years). Ref, reference.

and 2005, the multivariable-adjusted RRs of CHD were 1.40 (0.76–2.59) for no-consistent users and 1.88 (1.09–3.23) for consistent users of sulfonylureas.

CONCLUSIONS

The primary finding from this prospective follow-up of patients with diabetes was that a longer duration of sulfonylurea therapy was associated with a higher risk of CHD. The continuous sulfonylurea therapy for >10 years was associated with almost two times greater risk of CHD compared with nonusers. Furthermore, we observed that the combination therapy of metformin and sulfonylurea was associated with a three times greater risk of CHD compared with metformin monotherapy.

Compared with people without diabetes, a two- to fourfold increased risk of cardiovascular incidence was observed among patients with type 2 diabetes, even after adjustment for classic risk factors (28,29). Because cardiovascular risk increases with higher HbA_{1c} levels in people without diabetes (30), hypoglycemic treatment may reduce the risk of cardiovascular morbidity and mortality among patients with diabetes. However, the potential cardiovascular benefits through reducing hyperglycemia using sulfonylureas are complicated by their side effects on cardiovascular risk (4,15,16,18). The potential reasons for adverse cardiovascular effects, as previously proposed (3,5,31,32), include its effect on myocardial ischemic preconditioning (32), hypoglycemia (5), weight gain (3), and hypertension (31). Mechanistically, the sulfonylureas bind to ATP-sensitive potassium (KATP) channels on pancreatic β-cells, which results in the subsequent opening of voltage-gated calcium channels that stimulate the movement of insulin-containing secretory granules from the β-cells into the circulation (32). However, sulfonylureas target not only pancreatic but also myocardial KATP channels and therefore may interfere with the cellular pathway that confers myocardial ischemic protection (33). Sulfonylurea-induced hypoglycemia may also contribute to the increased risk of cardiovascular disease events and mortality (34,35). A recent meta-analysis of clinical trials indicated that the likelihood of hypoglycemia associated with sulfonylurea treatment was 14 times greater compared with metformin treatment and 6 times greater compared with placebo or no therapy (5). In addition, compared with the metformin users, sulfonylurea users experienced a 3–5-kg more weight gain (3) and 1.2-mmHg increase in systolic blood pressure (31).

Table 3—Risk of incident cardiovascular diseases during 5–10 years of follow-up according to baseline combination therapy

	Metformin only	Sulfonylurea only	Metformin and sulfonylurea	No diabetic medications	Insulin	Others*
Total cardiovascular disease						
Person-years	2,955	1,978	3,179	7,006	9,301	9,339
Number of cases	16	13	33	65	131	81
Incident rate (per 10^5 person-years)	541	657	1,038	928	1,408	867
Adjusted RR (95% CI)						
Model 1	Ref	1.14 (0.54–2.40)	1.99 (1.08–3.68)	1.65 (0.94–2.89)	2.63 (1.54–4.51)	1.63 (0.94–2.84)
Model 2	Ref	1.09 (0.52–2.31)	1.97 (1.06–3.64)	1.60 (0.91–2.81)	2.55 (1.48–4.37)	1.61 (0.92–2.80)
Model 3	Ref	1.11 (0.52–2.35)	1.99 (1.07–3.70)	1.55 (0.88–2.74)	2.28 (1.31–3.97)	1.57 (0.90–2.74)
Model 4	Ref	1.11 (0.52–2.35)	1.99 (1.07–3.70)	1.55 (0.88–2.75)	2.28 (1.30–4.00)	1.57 (0.90–2.74)
CHD						
Number of cases	6	7	22	31	77	48
Incident rate (per 10^5 person-years)	203	354	692	443	828	514
Adjusted RR (95% CI)						
Model 1	Ref	1.55 (0.52–4.62)	3.23 (1.30–8.00)	1.94 (0.81–4.67)	3.86 (1.68–8.88)	2.42 (1.03–5.68)
Model 2	Ref	1.48 (0.49–4.46)	3.15 (1.27–7.81)	1.93 (0.80–4.66)	3.78 (1.64–8.74)	2.33 (0.99–5.48)
Model 3	Ref	1.52 (0.51–4.58)	3.23 (1.29–8.06)	1.87 (0.78–4.52)	3.22 (1.37–7.57)	2.32 (0.98–5.46)
Model 4	Ref	1.53 (0.51–4.59)	3.27 (1.31–8.17)	1.90 (0.79–4.60)	3.34 (1.41–7.92)	2.34 (0.99–5.51)
Stroke						
Number of cases	10	6	11	34	54	33
Incident rate (per 10^5 person-years)	338	303	346	485	581	353
Adjusted RR (95% CI)						
Model 1	Ref	0.86 (0.30–2.43)	1.13 (0.47–2.75)	1.45 (0.69–3.03)	1.79 (0.88–3.65)	1.09 (0.52–2.30)
Model 2	Ref	0.82 (0.29–2.35)	1.12 (0.46–2.74)	1.36 (0.64–2.85)	1.67 (0.81–3.42)	1.10 (0.52–2.32)
Model 3	Ref	0.82 (0.29–2.35)	1.11 (0.45–2.72)	1.33 (0.63–2.81)	1.59 (0.76–3.32)	1.05 (0.492–2.22)
Model 4	Ref	0.82 (0.29–2.34)	1.10 (0.45–2.69)	1.31 (0.62–2.78)	1.53 (0.72–3.24)	1.04 (0.49–2.20)

RR and 95% CIs were estimated from Cox proportional hazards models. Model 1: adjusted age (months). Model 2: further adjusted BMI (kg/m^2); physical activity (quintiles); smoking status (never smoker, former smoker, or current smoker: 1–14 or ≥15 cigarettes/day); alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥30 g/day); alternative healthy eating index (quintile); Caucasian ethnicity (yes/no); multivitamin use (yes/no); family history of myocardial infarction (yes/no); family history of stroke (yes/no); presence of hypertension, hypercholesterolemia, and cancer; self-reported history of coronary artery bypass graft; and regular use of aspirin, antidepressant, antihypertensive, and cholesterol-lowering drugs (each yes/no). Model 3: further adjusted plasma levels of HbA_{1c} (missing and <7, 7–7.9, 8–9.9, 10–11.9, and ≥12); duration of diabetes had affected the back of eyes (retina: not affected and <2, 2–5, and >6 years); duration of diabetes-related kidney disease (not affected and <2, 2–5, and >6 years); duration of diabetes-related neuropathy (nerve damage: no affected and <2, 2–5, 6–9, 10–14, and ≥15 years). Model 4: further adjusted for duration of diabetes (years). Ref, reference. *Other combinations of diabetic medications.

Our finding on the association between sulfonylurea and CHD is consistent with previous reports from retrospective observational studies (15,16,19,36). A recent meta-analysis of observational studies indicated a 20% higher risk of myocardial infarction among sulfonylurea users compared with sulfonylurea nonusers (36). Using the National Veterans Health Administration data linked to Medicare files, sulfonylurea users experienced a higher risk of composite outcome of hospitalization for acute myocardial infarction or stroke or death compared with metformin users (15). In another study from the U.K. (16), the association between sulfonylurea and incident acute myocardial infarction was not significant (hazard ratio 1.09 [95% CI 0.94–1.27]) (16), but they reported an increased all-cause mortality when comparing sulfonylurea to metformin users (16). Another retrospective study (19) using administrative data from Sakatchewan Health observed a dose-response relationship between sulfonylurea drugs and mortality in type 2 diabetic patients. Although we did not collect the dosage of sulfonylureas, we observed that the risk of CHD increased with the duration of sulfonylurea treatment (i.e., the risk was doubled among those using sulfonylurea for >10 years).

When we classified the participants according to their antihyperglycemic medications, patients being treated with the combination of metformin and sulfonylurea had three times higher likelihood of CHD compared with metformin monotherapy. Although the mechanism for the synergistic effect between metformin and sulfonylurea is unclear, patients on the combination therapy had previously been shown to have a higher risk of total and cardiovascular mortality in a clinical trial and several observational studies (11–13,37).

The strengths of the current study include its prospective study design, long-term follow-up, validated cardiovascular outcome using medical records, relatively large sample size, and data on important potential confounders including obesity, diet, and other cardiovascular risk factors.

Our study also has several limitations. First, as with any observational study, the possibility of confounding by indication could not be excluded because the allocation to a diabetic medication was not randomized. We attempted to limit confounding by adjusting the estimates for many potential risk factors and by accounting for time-varying covariates. We also used the propensity score stratification method to adjust for differences across groups, and the results of sulfonylurea treatment remained largely unchanged, although the results between insulin treatment versus metformin monotherapy was largely attenuated. As demonstrated by Rosenbaum and Rubin (26), stratifying on the quintiles of the estimated propensity score eliminated ~90% of the bias due to the measured confounders. Second, although our multivariable analysis controlled for a wide range of risk factors for diabetes, unmeasured confounding may still exist. However, only a very strong unmeasured risk factor for cardiovascular disease together with a very large prevalence imbalance among exposure groups could explain our findings (38). We estimated that an unmeasured confounder or an underreported confounder with a risk for CHD of 1.5 would need to have a very large prevalence imbalance to explain our findings (39). A stronger confounder with a risk for CHD equal to 2.0 would need to be less imbalanced (but still ~36% more common among sulfonylurea users above 10 years) to explain our results (39). Third, our participants were older women with long-term diabetes. In a 10-year post-interventional follow-up of the UKPDS participants (40), intensive therapy with sulfonylurea-insulin combination in patients with newly diagnosed type 2 diabetes was associated a significant reduction in myocardial infarction and death from any cause. However, participants in the UKPDS study were ~10 years younger than our study population. Therefore, whether the association between sulfonylurea therapy and CHD is only present among patients with increased cardiovascular risk warrants further studies in a younger population with newly diagnosed type 2 diabetes. Fourth, our cohorts included mostly Caucasian women who were relatively healthy; thus, these associations may not be generalizable to other populations such as men and other ethnic groups. However, the relative homogeneity of our study population in terms of educational attainment and socioeconomic status reduces confounding and enhances the internal validity. The lack of information regarding the subtype and dosage of sulfonylurea treatments was also a limitation of our study. Previous studies reported different associations with cardiovascular and all-cause mortality between the first- and second-generation sulfonylureas (3). Further studies of different types of sulfonylureas on incident CHD are warranted.

In conclusion, our study suggests that a longer duration of sulfonylurea therapy was associated with a higher risk of CHD, and the combination therapy of metformin and sulfonylurea was associated with an increased CHD risk compared with metformin monotherapy or sulfonylurea monotherapy. Further prospective cohort studies are warranted to replicate our findings.

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Author Contributions. Y.L. analyzed and interpreted data, provided statistical expertise, drafted the manuscript, critically revised the manuscript for important intellectual content, and provided final approval of the manuscript. Y.H., S.H.L., and S.R. analyzed and interpreted data, critically revised the manuscript for important intellectual content, and provided final approval of the manuscript. F.B.H. conceived and designed the study; obtained funding; obtained study materials or patients; collected, assembled, analyzed, and interpreted data; provided statistical expertise; critically revised the manuscript for important intellectual content; and provided final approval of the manuscript. F.B.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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