

# Controversy about the relationship between sulfonylurea use and cardiovascular events and mortality

Whether or not glucose-lowering therapy decreases the risk of cardiovascular (CV) mortality and morbidity among patients with type 2 diabetes is a crucial issue. Several large-scale clinical trials have shown the importance of glycemic control from an earlier stage, and the term of metabolic memory or legacy effect for lowering the risk of a CV event is widely known. In contrast, strict glycemic control might rather increase the risk of CV death, especially in patients with a long duration of diabetes and a past history of cardiovascular disease (CVD), probably as a result of severe nocturnal hypoglycemia.

Recently, a number of classes of oral antihyperglycemic drug have been in clinical use. Among them, sulfonylurea (SU) drugs showing the potential effect on blood glucose lowering have been used in the majority of patients with type 2 diabetes for many years. Concerns about CV safety of SU, in contrast, have been raised since the 1970s, when the University Group Diabetes Program suggested an increased risk of CV death as a result of tolbutamide, the first generation of SU<sup>1</sup>. Since then, a significant number of studies in which an increased risk of CV events or death associated with treatment with SU have been documented. Almost all of these studies, however, were based on retrospective analysis, and were not based on the data with confirmation of CV outcomes, showing a lack of confident evidence for the relationship

between the incidence of CVD and SU treatment in type 2 diabetes.

A recent report by Li *et al.*<sup>2</sup> has been meaningful in the discussion of the potential adverse effects of SU on CVD. They prospectively evaluated the data of Nurses' Health Study (NHS), a well-established cohort of USA women, to confirm the association between long-term treatment of SU and the incidence of CVD in patients with type 2 diabetes. The NHS cohort was started in 1976, when 121,700 female registered nurses aged 30–55 years sent back a completed mailed questionnaire on their medical history and lifestyle characteristics. The follow-up questionnaires have been sent every 2 years to renew information about potential confounders, including age, bodyweight, smoking status and so on, and potential risk factors and to identify newly diagnosed type 2 diabetes and CVD, and other medical events. A total of 5,536 patients with type 2 diabetes responded to the additional questionnaires regarding their diabetes-related treatment and complications in 2000 and 2005.

Among them, 4,902 participants with the SU therapy information and without diagnosis of CVD at baseline were included in the present study after excluding the participants with prevalent CVD ( $n = 634$ ) at the time of study initiation. They were divided into two groups; 2,467 non-users and 2,435 users, and followed up during the period of 2000–2010. The use of SU was related to longer duration of diabetes, diabetes-associated complications and use of other oral antihyperglycemic drugs.

In order to assess CV events and mortality, non-fatal myocardial infarction,

coronary heart disease (CHD) death and stroke, which was identified primarily by investigating medical records, were included in the end-point of CVD. They requested permission to check medical records when participants reported a non-fatal CHD or stroke, and also confirmed medical records for deceased participants, whose deaths were identified by families and postal officials, and through the National Death Index. Furthermore, physicians blinded to the participant questionnaire reports reviewed all medical records.

Cardiovascular events were confirmed in 339 cases during the follow-up period, including 191 CHD (145 non-fatal myocardial infarction and 46 CHD deaths) and 148 strokes. The multivariable-adjusted relative risks (RRs) of total CVDs were 1.20 (95% confidence interval [CI] 0.91–1.58) for patients whose duration of SU use was 1–5 years at baseline, 1.40 (95% CI 0.98–1.99) for 6–10 years and 1.65 (95% CI 1.12–2.43) for >10 years compared with non-users (Table 1). When the association of SU use with CHD and stroke was assessed separately, the duration of SU use was significantly related only with CHD, but not stroke. Compared with non-users, the multivariable-adjusted RRs for CHD for patients whose duration of SU therapy for 1–5, 6–10, and >10 years were 1.24 (95% CI 0.85–1.81), 1.51 (95% CI 0.94–2.42) and 2.15 (95% CI 1.31–3.54), respectively (Table 1). Furthermore, the multivariable RRs of combination therapy with metformin and SU compared with metformin monotherapy were 3.27 (95% CI 1.31–8.17) for CHD (Table 2).

The current study clearly showed the association of SU therapy with the risk

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**Table 1** | Risk of incident coronary heart disease during 5–10 years of follow up according to current use of sulfonylurea

Coronary heart disease	Duration of sulfonylurea (years)				P for trends
	No	1–5	6–10	>10	
Person-years	14,399	11,996	4,438	2,924	
Number of cases	62	72	30	27	
Incident rate (per 10 <sup>5</sup> person-years)	431	600	676	923	
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
Model 2	Ref	1.37 (0.97–1.94)	1.52 (0.97–2.36)	2.10 (1.32–3.34)	0.002
Model 3	Ref	1.24 (0.85–1.81)	1.50 (0.94–2.42)	2.08 (1.27–3.39)	0.003
Model 4	Ref	1.24 (0.85–1.81)	1.51 (0.94–2.42)	2.15 (1.31–3.54)	0.002

The relative risk (RR) and 95% confidence intervals (CI) were estimated from Cox proportional hazards models. Model 1: adjusted age (months). Model 2: further adjusted body mass index (kg/m<sup>2</sup>); 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 glycated hemoglobin (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: 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). Model 4: further adjusted for duration of diabetes (years). Ref, reference. Reproduced with permission by American Diabetes Association, "Diabetes Care", 2014<sup>2</sup>. Copyright and all right reserved.

**Table 2** | Risk of incident coronary heart disease during 5–10 years of follow up according to baseline combination therapy

Coronary heart disease	Metformin only	Sulfonylurea only	Metformin and sulfonylurea
Person-years	2,955	1,978	3,179
Number of cases	6	7	22
Incident rate (per 10 <sup>5</sup> person-years)	203	354	692
Adjusted RR Model 1 (95% CI)			
Model 1	Ref	1.55 (0.52–4.62)	3.23 (1.30–8.00)
Model 2	Ref	1.48 (0.49–4.46)	3.15 (1.27–7.81)
Model 3	Ref	1.52 (0.51–4.58)	3.23 (1.29–8.06)
Model 4	Ref	1.53 (0.51–4.59)	3.27 (1.31–8.17)

The relative risk (RR) and 95% confidence intervals (CI) were estimated from Cox proportional hazards models. Model 1: adjusted age (months). Model 2: further adjusted body mass index (kg/m<sup>2</sup>); 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 glycated hemoglobin (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: not affected, and <2, 2–5, 6–9, 10–14 and ≥15 years). Model 4: further adjusted for duration of diabetes (years). Ref, reference. Reproduced with permission by American Diabetes Association, "Diabetes Care", 2014<sup>2</sup>. Copyright and all right reserved.

of CVD, and the RR of CHD was positively correlated with the duration of SU therapy. The continuous SU use for >10 years induced an almost twofold higher risk of CHD in comparison with non-users. The overall findings were consistent with the previous reports from retrospective observational studies.

The pathophysiological processes by which SUs adversely induce the risk of

CVD have not been fully clarified. As for a potential mechanism, it should be noted that a kind of SU targets myocardial adenosine triphosphate-sensitive potassium channel (KATP) channels, and might directly interrupt the ischemic preconditioning process, an endogenous protective mechanism on ischemic heart disease. It is well known that SU receptors (SURs) include several subtypes,

such as SUR1, SUR2A and SUR2B. The SUR1 is expressed only in pancreatic β-cells, but SUR2A and SUR2B distribute not only in the pancreatic β-cell, but also cardiomyocytes and vascular smooth muscle. In cardiomyocytes, ischemia results in KATP opening, K<sup>+</sup> efflux, reduced Ca<sup>2+</sup> influx and through these mechanisms reduced contractility and, consequently, a decreased need for oxy-

gen. In vascular smooth muscle cells, KATP opening decreases muscular tone resulting in increased blood flow. Thus, theoretically, SUs, by closing KATP channels, might cause a double hazard for the cardiac muscle during ischemia.

The mode of receptor binding is dependent on the structure of SU. Gliclazide targets mainly SUR1, but glibenclamide, glipizide and glimepiride show a high affinity to SUR2A and SUR2B, thereby these three SUs are more harmful for CVD theoretically than glipizide. In contrast, the maximal inhibitory concentration of glibenclamide for closing the  $K_{ATP}$  channel is fourfold lower than that of glimepiride, probably because of different post-receptor events. Thus, the influence on CHD could vary according to what kind of SU is used, but the difference in clinical outcomes is not always clear. Zeller *et al.*<sup>3</sup> showed that the patients previously receiving gliclazide/glimepiride had improved in-hospital outcomes compared with those taking glibenclamide. Klamann *et al.*<sup>4</sup>, however, reported that in-hospital mortality in patients with type 2 diabetes is higher than in non-diabetic patients suffering acute myocardial infarction regardless of whether or not they had been treated with SUs.

As the other potential reasons for adverse CV effects of SUs, hypoglycemic episodes, weight gain and hypertension have been well documented. The impact of hypoglycemia on incidental CHD is related to several factors, such as endothelial dysfunction, sympathoadrenal response, blood coagulation abnormalities and inflammation. In fact, many trials uncovered a significant relationship between hypoglycemia and CV events and mortality. Furthermore, bodyweight gain might also play a role as a risk factor of CVD. The accumulation of visceral fat has been shown to increase insulin resistance and to deteriorate several CV risk markers (i.e., lipid profiles, blood

pressure and high-sensitivity C-reactive protein).

Conversely, there are a number of reports to show a lack of evidence for the association of SU use and CVD risk. Rosenstock *et al.*<sup>5</sup> suggested that SUs were not related with an increase in CV risk compared with the conventional policy of diet therapy and active comparator (i.e., thiazolidines, metformin, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analogs) based on 15 published randomized controlled trials.

As described so far, the relationship between SU treatment and CV events is still controversial. The studies including the current cohort trial cannot assess the impact of hypoglycemia, even if confounders, such as the duration of diabetes, diabetes-related complications and other diabetic drugs, could be excluded. It is still ambiguous if the significant association would still be positive even in the cases using a low dosage of SU. The present study by Li *et al.* showed that a longer duration of SU therapy was related to a higher risk of CHD, but a significant difference might be lost if it is possible to correct it by the SU dosage.

In conclusion, we cannot deny the relationship between SU use and CVD risk in patients with type 2 diabetes. However, it is not yet clear whether SU directly contributes to the increased risk of CVD. Appropriate use in suitable patients with a comfortable level of attention might reduce the risk of hypoglycemia and the incidence of CVD.

#### DISCLOSURE

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