



REVIEW

Latest Evidence on Sulfonylureas: What's New?

Lawrence A. Leiter

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ABSTRACT

This review addresses the question of the cardiovascular (CV) safety of sulfonylureas (SUs) in patients with type 2 diabetes mellitus (T2DM) when directly tested against comparator agents in CV outcome trials. Presented at a recent symposium entitled “SUs in the treatment of T2DM: a fresh look and new insights” held on Wednesday September 18, 2019 during the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona Spain, this review discusses the initial evidence that sparked concerns over the CV safety of SUs as well as more recent findings from large studies of SUs (i.e. ADVANCE, TOSCA.IT and CAROLINA trials), highlighting the differences in CV and hypoglycaemia risks among the various SUs. Finally, the impact of glycaemic control on CV outcomes is also discussed, where the data suggest that the recent positive CV outcomes with some antihyperglycaemic agents may have been driven in part by improved glycaemic control.

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L. A. Leiter (✉)
Division of Endocrinology and Metabolism, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Canada
e-mail: Lawrence.Leiter@unityhealth.to

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Key Summary Points

A review of the available evidence for patients with type 2 diabetes mellitus (T2DM) suggests that good glycaemic control is an important factor in reducing the risk of diabetes-related complications such as cardiovascular (CV) events and hypoglycaemia

There is no difference in CV risk between sulfonylureas (SUs) and agents such as pioglitazone or linagliptin, according to recent large randomised controlled trials (ADVANCE, TOSCA.IT, CAROLINA)

The risk of hypoglycaemia varies between SUs, with the lowest rates reported for gliclazide, although absolute risk of hypoglycaemia is low for the class as a whole

INTRODUCTION

The University Group Diabetes Program (UGDP), a study published 50 years ago,

initially reported increased cardiovascular (CV) mortality in patients with type 2 diabetes mellitus (T2DM) treated with tolbutamide (1.5 g/day) versus standard or variable doses of insulin and placebo [1]. Subsequent studies seemed to suggest that sulfonylureas (SUs) may have a worse impact on CV outcomes than metformin [2, 3], but the data have been inconsistent and often used older SUs than the ones currently in use today [4, 5]. This article critically reviews the initial evidence that sparked concerns over the CV safety of SUs as well as more recent findings from large studies of SUs, and examines the impact of glycaemic control on CV outcomes. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

INITIAL EVIDENCE SPARKING CONCERNS OVER CARDIOVASCULAR SAFETY OF SULFONYLUREAS

The UGDP, which initially reported increased CV mortality in patients with T2DM treated with tolbutamide, was not conducted like a modern cardiovascular outcome trial (CVOT)—the patients did not have similar baseline CV risks, the difference did not reach statistical difference and there were very few events (< 100) [1]. Therefore, this was an underpowered, poorly conducted study. Apparent confirmatory evidence was provided by a real-world study comparing the risk of cardiovascular disease (CVD) or death in patients treated with metformin or SUs [3]. While results suggested that patients treated with metformin did better (hazard ratio [HR] 1.16; 95% confidence interval [CI] 1.08, 1.25), it is unknown whether this was because metformin was better, SUs were worse or, most likely, the patients were different (i.e. as a result of selection bias). The SPREAD-DIM-CAD study, a randomised controlled trial (RCT) that examined the effects of glipizide (15–30 [mean 28.3] mg/day) versus metformin on CV outcomes in Chinese patients with T2DM and coronary artery disease, suggested

that patients treated with metformin had better CV outcomes (43 vs 60 CV events; HR 0.54; 95% CI 0.30, 0.90; $p = 0.026$); however, this was a small study (metformin $n = 156$, glipizide $n = 148$) and the numbers of events were low [2]. It is therefore difficult to put great weight on such a small study.

Among larger studies, the UKPDS33 study ($n = 3041$) showed no deleterious CV effect of SUs (chlorpropamide 100–500 mg/day, glibenclamide 2.5–20.0 mg/day) compared with insulin or conventional therapy [5], although this study tested older SUs that are used less today. Various meta-analyses have also been published evaluating the CV risk with SUs. One such meta-analysis evaluating data from 30 SU CV safety trials of at least 6 months duration ($n = 29,873$) found no consistent association with the risk of major adverse cardiovascular events (MACE; Mantel–Haenszel odds ratio [MH-OR] 1.08; 95% CI 0.86, 1.36; $p = 0.52$) [4] although a small, but statistically significant, increase in mortality was observed with SUs (MH-OR 1.22; 95% CI 1.01, 1.49; $p = 0.047$).

It should be noted, however, that there is evidence of differences among the SUs, suggesting that it may be inappropriate to combine data from trials utilising different SUs. For example, results of a Danish real-world study in 107,806 patients suggested that certain SUs may increase mortality and CV morbidity while others do not [6]. Monotherapy with certain commonly used SUs (i.e. glimepiride, glyburide, glipizide and tolbutamide), but not gliclazide or repaglinide, appeared to be associated with increased mortality and CV risk versus metformin in patients both with and without previous myocardial infarction (MI) [6]. Another study examining all-cause and CV mortality risk among sulfonylureas showed a dramatically reduced risk of mortality with gliclazide relative to glyburide (glibenclamide), in contrast to the other SUs [7].

The ADOPT study examined the glycaemic durability of rosiglitazone, metformin and glyburide (2.5–15.0 mg/day) monotherapy, and showed better glycaemic durability (primary endpoint) with rosiglitazone versus metformin (between-group differences in glycated haemoglobin (HbA1c) -0.13% ; 95% CI

–0.22%, –0.05%; $p = 0.002$) and glyburide (–0.42%; 95% CI –0.50%, –0.33%; $p < 0.001$) [8]. However, surprisingly, rates of investigator-reported vascular serious adverse events were lower with glyburide than with rosiglitazone (CVD 1.8% vs 3.4%; congestive heart failure 0.2% vs 0.8%; both $p < 0.05$) or metformin [8]. At the time, the data were dismissed because of the small number of events despite being similar to the number of events in the aforementioned UGDP [1].

CARDIO-RENAL OUTCOMES IN LARGE STUDIES OF SUS

ADVANCE Study

The ADVANCE study was a landmark study comparing intensive versus standard glucose control, in which more than 90% of the 5571 patients randomised to intensive therapy were receiving gliclazide (30–120 mg/day as modified release) while approximately 57% of 5569 patients in the standard therapy group were receiving other SUs (Table 1) [9]. While this was not a formal CV safety study, it should be noted that the group where all patients were virtually receiving gliclazide had no higher CV risk than the group where only about half were on SUs (cumulative incidence of CV death, MI, stroke: HR 0.94; 95% CI 0.84, 1.06; $p = 0.32$). Additional findings of the ADVANCE study included a significant 10% decrease in the primary endpoint of combined major macrovascular and microvascular events with intensive versus standard therapy ($p = 0.01$); a non-significant 6% decrease in major macrovascular events ($p = 0.32$); a significant 14% decrease in major microvascular events ($p = 0.015$); and a significant 21% reduced risk of nephropathy ($p = 0.006$) [9].

Examination of the renal outcomes in more detail revealed improvements not just in proteinuria, i.e. a 9% reduction in new-onset microalbuminuria and a 30% reduction in macroalbuminuria (both $p \leq 0.012$), but also in harder kidney outcomes. End-stage renal disease (ESRD; defined as renal transplant or dialysis) was also reduced by 65% at the end of the

original study with intensive versus standard therapy ($p = 0.0017$), and by 43% after an additional 5 years of follow-up [10, 11].

TOSCA.IT Trial

The TOSCA.IT study [12] enrolled patients who had been diagnosed with T2DM for at least 2 years, had an HbA1c of at least 7.0% and at most 9.0%, were aged 50–75 years, were on at least 2 g of metformin per day, had a body mass index (BMI) of 20–45 kg/m² and had not experienced any acute CV events in the past 6 months (Table 1). The study used a simple design, with patients randomised to add-on pioglitazone or SUs. Metformin dosage was constant throughout the study (2–3 g/day). The investigators could choose the specific SU (glibenclamide 5–15 mg/day, gliclazide 30–120 mg/day or glimepiride 2–6 mg/day), with most patients receiving gliclazide or glimepiride. The other randomised group received pioglitazone 15–45 mg/day. The dose was titrated at the discretion of the investigators, based on the results of HbA1c and self-monitoring of blood glucose [12].

While it would have been expected that metformin + pioglitazone would have better glycaemic durability, examination of HbA1c levels over 5 years of follow-up showed that reductions in HbA1c with metformin + SUs were similar to those in the metformin + pioglitazone group [12]. Rates of moderate and severe hypoglycaemia (i.e. plasma glucose below 60 mg/dL) were higher with SU-based therapy versus pioglitazone-based therapy (32.4% vs 9.6% and 1.6% vs 0.1%, respectively), but the absolute risk was actually quite small [12]. There was no difference between treatment groups in the primary outcome of the cumulative incidence of all-cause death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation over 60 months of follow-up [12]. Unfortunately, as a result of recruitment challenges, there were fewer participants and events than planned, so the study was underpowered and was therefore terminated for futility after 5 years. While the results can therefore not be

Table 1 Study design and outcomes of the ADVANCE, TOSCA.IT and the CAROLINA trial

Study	Study design and patients	Number of patients and treatment	Median follow-up duration	CV outcomes
ADVANCE [9] NCT00145925	Phase III RCT Patients with T2DM aged ≥ 55 years with a history of major macrovascular or microvascular disease or ≥ 1 other risk factor for vascular disease	Intensive control: gliclazide MR 30–120 mg/day ($n = 5571$) Standard control: other SUs ($n = 5569$)	5 years	Comparative risk with intensive versus standard therapy Cumulative incidence of CV death, MI, stroke: HR 0.94; 95% CI 0.84, 1.06 ($p = 0.32$) Significant decrease in major macrovascular and microvascular events ($p = 0.01$) Non-significant decrease in major macrovascular events ($p = 0.32$)
TOSCA.IT [12] NCT00700856	Randomised phase IV trial Patients with T2DM aged 50–75 years with an HbA1c of 7.0–9.0%, BMI 20–45 kg/m ² , on metformin ≥ 2 g/day, and had not experienced any acute CV events in the past 6 months	Add-on pioglitazone: 15–45 mg/day ($n = 1535$) Add-on SUs: glibenclamide 5–15 mg/day ($n = 24$), glimepiride 2–6 mg/day ($n = 723$) or gliclazide 30–120 mg/day ($n = 745$)	57.3 months	First occurrence of all-cause death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation: HR for add-on pioglitazone vs sulfonylurea 0.96, 95% CI 0.74–1.26 ($p = 0.79$) Incidence of hypoglycaemia: pioglitazone vs SU: 10% vs 34% ($p < 0.0001$)
CAROLINA [13, 14] NCT01243424	Multicenter, double-blind, phase III RCT Patients with early T2DM with an increased CV risk or established complications	Linagliptin 5 mg/day ($n = 3023$) Glimepiride 1–4 mg/day ($n = 3010$)	6.3 years	Non-inferiority for CV death, non-fatal MI, non-fatal stroke for linagliptin versus glimepiride: HR 0.98; 95.47% CI 0.84, 1.14 ($p < 0.0001$) Similar between-group risks of CV mortality (HR 1.00; 95% CI 0.81, 1.24), non-CV mortality (HR 1.00; 95% CI 0.66, 1.03) and all-cause mortality (HR 0.91; 95% CI 0.78, 1.06)

BMI body mass index, *CI* confidence interval, *CV* cardiovascular, *HbA1c* glycated haemoglobin, *HR* hazard ratio, *MI* myocardial infarction, *MR* modified release, *RCT* randomised controlled trial, *T2DM* type 2 diabetes mellitus, *SU* sulfonylurea

considered definitive, there was no suggestion of harm in the patients treated with SUs [12].

CAROLINA Trial

The most recently reported study is the CAROLINA trial, which was designed to assess the CV safety of linagliptin versus glimepiride in patients with early T2DM at increased CV risk (Table 1) [13]. Enrolled patients had T2DM, an HbA1c of 6.5–8.5% (treatment-naïve or treated with metformin and/or α -glucosidase inhibitor) or 6.5–7.5% (on alternative T2DM therapy), and had a high risk of CV events, defined as at least one of the following: previous CV complications; evidence of end-organ damage; age at least 70 years; or at least two CV risk factors [13]. After a 2-week placebo run-in, patients were randomised to linagliptin 5 mg/day or glimepiride 1–4 mg/day, both in combination with standard of care for up to 6 years. The primary endpoint was 4P-MACE (i.e. CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina), while 3P-MACE (i.e. CV death, non-fatal MI or non-fatal stroke) was a key secondary endpoint [13].

Baseline assessment showed that 42% of enrolled patients had established CV disease, 37% displayed at least two defined CV risk factors and 40% had suffered from T2DM for no more than 5 years [14]. In addition, 9% of patients were treatment-naïve, 83% were receiving metformin and none were receiving insulin. Again, there was no overall meaningful difference in HbA1c between linagliptin and glimepiride over 5 years of follow-up: weighted average mean difference up to week 256, 0.00% (95% CI – 0.05, 0.05) [14]. This is contradictory to animal models, which suggested that dipeptidyl peptidase 4 (DPP4) inhibitors have protective effects on beta cells [15–17], and thus may have greater glycaemic durability than existing therapies.

With regard to CV outcomes, non-inferiority for 3P-MACE (CV death, non-fatal MI, non-fatal stroke) was observed for linagliptin versus glimepiride, with virtually superimposable curves (HR 0.98; 95.47% CI 0.84, 1.14; $p < 0.0001$ for non-inferiority, $p = 0.76$ for superiority) [14].

Also, risks of CV mortality (HR 1.00; 95% CI 0.81, 1.24), non-CV mortality (HR 1.00; 95% CI 0.66, 1.03) and all-cause mortality (HR 0.91; 95% CI 0.78, 1.06) were not different between groups. Thus, this was the second recent study showing no increased CV risk with SUs.

While rates of hypoglycaemia were higher with glimepiride than with linagliptin (Table 2), it is important to note that the absolute risk of hypoglycaemia was quite small, even in the SU-treated patients [18]. It is also important to highlight that the SU used in the CAROLINA study was glimepiride, and that there are differences among SUs in the risk of hypoglycaemia, as discussed later.

IMPACT OF GLYCAEMIC CONTROL ON SAFETY OUTCOMES

It is also important to consider the glucose-lowering ability of SUs relative to other drug classes. A recently published model-based meta-analysis of T2DM antihyperglycaemic agents examined the impact of 24 T2DM drugs from six drug classes on glycaemic control, weight change and hypoglycaemia risk [19]. The study included data from 229 randomised, controlled trials, 710 individual treatment arms and 121,914 patients. Somewhat greater HbA1c reduction was observed with the glucagon-like peptide 1 receptor agonists (GLP-1RAs), but HbA1c reduction was greater with gliclazide (1.04%) than with DPP4 inhibitors (0.58–0.72%), sodium–glucose transport protein 2 (SGLT2) inhibitors (0.65–1.01%) and thiazolidinediones (0.62–0.98%). While the risk of hypoglycaemia was generally greater with SUs than with the other drug classes, among the SUs the relative hypoglycaemia risk was significantly lower with gliclazide than with glimepiride, glyburide and glipizide (3.6 vs 8.9, 10.2 and 13.9, respectively) [19].

Another study, the GUIDE trial, compared the change in HbA1c and incidence of hypoglycaemia with gliclazide MR30 (30–120 mg/day) versus glimepiride (1–6 mg/day), both as monotherapy and in combination with metformin in 845 patients with T2DM under conditions of everyday clinical practice [20].

Table 2 Risk of hypoglycaemia in the CAROLINA study [18]

	Rates of hypoglycaemia, %		HR (95% CI)	<i>p</i> value
	Linagliptin	Glimepiride		
Any	10.6	37.7	0.23 (0.21, 0.26)	< 0.001
Moderate or severe	6.5	30.9	0.18 (0.15, 0.21)	< 0.001
Severe ^a	0.3	2.2	0.15 (0.08, 0.29)	< 0.001
Hospitalisation due to hypoglycaemia	0.1	0.9	0.07 (0.02, 0.31)	< 0.001

CI confidence interval, *HR* hazard ratio

^a Hypoglycaemic event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

After a follow-up of 27 weeks (6 months), similar reductions from baseline were observed in HbA1c with gliclazide versus glimepiride (1.1% vs 1.0%), but rates of confirmed hypoglycaemia were lower (3.7% vs 8.9%) with no severe hypoglycaemia reported.

Finally the recently published EasyDIA study, which evaluated the real-world efficacy of gliclazide MR60 (30–120 mg/day) as monotherapy, add-on therapy to metformin, or switch from SU/metformin in more than 7000 patients with T2DM, demonstrated a 1.8% reduction in HbA1c, with 46.2% and 65.3% of patients achieving a target of HbA1c no greater than 7% at 3 and 6 months, respectively [21]. Severe hypoglycaemia was reported in only four (0.06%) patients.

The existence of outcome studies showing CV and renal benefits above and beyond glycaemic control does not mean that glycaemic control is not important. This is supported by the results of a Swedish cohort study ($N = 271,174$ T2DM patients vs 1,355,870 controls), which confirmed that glycaemic control remains the most important risk factor for CV disease [22]. The primary aim of the study was to evaluate the association between the excess risks of death and CV outcomes in patients with T2DM. The study showed that an HbA1c level outside the recommended target range was the strongest predictor of stroke and acute MI. Also, recent meta-regression analysis using data from 12 CVOTs of various antihyperglycaemic agents, as well as those comparing intensive with standard therapy, showed that the trials

with the greatest HbA1c reduction had the lowest HR of MACE [23].

CONCLUSIONS

Early glycaemic control in patients with T2DM is associated with a long-lasting 'legacy' effect in reducing later complications. Recent large randomised controlled trials have not shown differences in CV risk of SUs versus pioglitazone or linagliptin. However, the risk of hypoglycaemia varies among the SUs and may be dose dependent. It is therefore important to study the effect on CV outcomes of the doses of SUs currently used in clinical practice. It should also be noted that the glycaemic durability of different SUs may affect their CV risk in patients with T2DM and therefore may be an important parameter that requires further attention in clinical trials. The recent positive CVOTs with some antihyperglycaemic agents may be partly due to differences in glycaemia, indicating that good glycaemic control is an important component of a comprehensive risk-reduction strategy in diabetes.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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