



## Opinion Paper

# Modern sulphonylureas and cardiovascular adverse effects: Will CAROLINA put an end to the controversy?

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## ABSTRACT

Sulphonylureas (SU) form an important role in management of people with type 2 diabetes. This safety history of SU was tainted for various reasons, the predominant one being lack of demonstration of cardiovascular safety. Since its introduction, SU's have never been subjected to a formal study for its cardiovascular safety. The cardiovascular safety of SUs was derived from small, inadequately powered randomised controlled trials (RCT) and observational studies. CAROLINA (CARDiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) trial planned as a cardiovascular outcome trial randomised people with type 2 diabetes and high cardiovascular risk to Linagliptin and Glimepiride. This opinion paper outlines the salient features of this landmark trial and its implications in general cardiology practice.

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## 1. Introduction

Since the introduction of the first sulphonylurea (SU), Tolbutamide in 1950, they are an important part of hyperglycemia management. Their popularity stems from powerful glycemic efficacy (glycated haemoglobin (HbA1c) reduction by 1–2%), low cost of therapy, gastrointestinal tolerability, and limited adverse effects other than hypoglycemia. However, over the last few years, there is a degrowth of sulphonylurea prescriptions with emergence of newer drugs with proven benefit on the cardiorenal axis; coupled with aggressive marketing of these drugs both to prescribers and consumers.<sup>1</sup> The uncertainty and confusion about the

cardiovascular effects of SU in the absence of properly done trials has contributed to this decline significantly. However, newer oral glucose lowering drugs like DPP4 inhibitors and SGLT2 inhibitors are less potent in glycemic control (average HbA1c reduction 0.5–0.8%), needing addition of drugs like sulphonylureas to achieve good glycemic control in many people. In this article, we review the current knowledge of SU focussing on the cardiovascular outcomes and the safety issues from a cardiology practice perspective.

### 1.1. Why is there controversy about cardiovascular safety of sulphonylureas?

The cardiovascular safety of SU was first called to question by the University Group Diabetes Program (UGDP) trial involving 823 persons. This trial was a randomised controlled trial (RCT), which compared tolbutamide, insulin and diet. Subjects randomized to tolbutamide had excess cardiovascular deaths (26 of 204 people, 12.7%) compared with placebo (10 of 205 people, 4.9%;  $p < 0.01$ ). Although the trial had methodological issues in randomization leading to variable cardiovascular risk at baseline, inclusion of people without confirmed diabetes, and assessment of cardiovascular deaths, the United States Food and Drug Administration (USFDA) required a black box warning on packaging to indicate a possible cardiovascular mortality associated with all sulphonylureas.<sup>2</sup>

**Abbreviations:** SU, Sulphonylurea; RCT, Randomised controlled trials; HbA1c, Glycated haemoglobin; UGDP, University Group Diabetes Program; USFDA, United States Food and Drug Administration; TOSCA.IT, Thiazolidinediones or Sulphonylureas Cardiovascular Accidents Intervention Trial; CAROLINA, CARDiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes; SGLT2 I, Sodium-glucose co-transporter-2 inhibitors; DPP4I, Dipeptidyl peptidase-4 inhibitors; GLP1 RA, Glucagon-Like Peptide 1 Receptor Agonists; WHO, World Health Organisation; IDF, International Diabetes Federation; MACE, Major Adverse Cardiovascular Events; ASCVD, Atherosclerotic Cardiovascular Disease; eGFR, estimated Glomerular.

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Subsequently UKPDS randomized recently diagnosed people with type 2 diabetes to intensive arm involving sulphonylureas (chlorpropamide, glipizide and glyburide) or insulin or diet alone. After a median follow up of 10 years, there was reduction of mortality and morbidity in intensive arm compared to conventional treatment. There was no increased mortality with the use of glyburide or chlorpropamide.<sup>3</sup>

In the absence of large trials designed to show the cardiovascular safety of SU, clinicians had to rely on meta-analysis data. Meta-analysis of RCTs showed neutral outcomes, whereas observational studies showed variable but increased cardiovascular risk with SU.<sup>4</sup> Individual RCTs were limited by lack of high-risk subjects at baseline, low event rates and short study duration. Observational studies despite their large numbers, suffer from selection bias, information bias, and residual confounding. In RCTs, the protective effect of the comparator vs. the adverse cardiovascular effect of SU is often impossible to make out.<sup>4</sup>

Recently, the Thiazolidinediones or Sulphonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT), a multicentre RCT threw some light on this controversy. Persons aged 50–75 years with type 2 diabetes ( $n = 4956$ ), who were inadequately controlled with metformin monotherapy were randomly assigned to add-on pioglitazone (15–45 mg) or an SU (5–15 mg glibenclamide, 2–6 mg glimepiride, or 30–120 mg gliclazide).<sup>5</sup> 335 (11%) of subjects had cardiovascular disease at baseline. The primary outcome was a composite of first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularisation. When the study was stopped after 57.3 months, there were no significant between-group differences in the composite primary outcome or any of its components. Limitations of the trial include the following: less than anticipated subjects were recruited, the event rates of the primary endpoint were lower than anticipated, early discontinuation of the trial following a futility analysis and imbalance of rate of discontinuation of the study drugs between study groups.<sup>5</sup>

Thus, before the CAROLINA (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) trial, there were no well-done RCTs involving a sulphonylurea compared to other glucose lowering drug with predefined and adjudicated cardiovascular events as outcomes.<sup>6</sup>

### 1.2. What is the current positioning of sulphonylureas in diabetes treatment guidelines?

Most diabetes treatment guidelines have used co-morbidity-based considerations to choose glucose lowering drugs after Metformin.<sup>7</sup> People with type 2 diabetes with cardiovascular or renal morbidity are candidates for SGLT2 inhibitors or GLP-1RA if they do not have any contraindications to their use. DPP 4 inhibitors are the next group of drugs in line due to their proven cardiovascular safety, weight neutrality and low risk of hypoglycemia. Insulin, thiazolidinediones and sulphonylureas have weight gain and/or hypoglycemia and are used later. However, sulphonylureas are used preferentially when cost is a consideration.<sup>7</sup> WHO guidelines and IDF guidelines have used SU in preference to other glucose lowering drugs.<sup>8</sup>

### 1.3. What were the results of the CAROLINA trial?

In CAROLINA trial, people with type 2 diabetes with HbA1c 6.5–8.5% who were at high cardiovascular risk were randomised to Glimepiride at doses of 1–4 mg/day ( $n = 3014$ ) vs. Linagliptin at 5 mg/day ( $n = 3028$ ). After a mean follow up of 6.3 years, the primary outcome of the trial (3-point major adverse cardiovascular events) occurred in 11.8% of Linagliptin vs 12% of people on

Glimepiride (HR, 0.98 [95.47% CI, 0.84–1.14],  $p < 0.001$  for non-inferiority). Various other end points including 4 P MACE (3 P MACE plus hospitalisation for unstable angina), cardiovascular death, all cause death, hospitalisation for heart failure and coronary vascularisation procedures did not differ between Linagliptin and Glimepiride.<sup>6</sup>

### 1.4. Are people randomised to CAROLINA different from those in regular cardiology practice?

Regular cardiology practices would see people with ASCVD (with or without interventions) and those with increased cardiovascular risk in addition to a significant load of patients with heart failure. The baseline characteristics of people in CAROLINA is similar to a regular cardiology practice.<sup>6</sup>(Table 1).

### 1.5. Was either of the drugs superior in terms of glycemic control?

Being a cardiovascular outcome trial, the investigators tried achieving glycemic equipoise: similar glycemic control in both the arms of the trial.<sup>9</sup> At the end of trial, the HbA1c remained same in people randomised to the Linagliptin arm and Glimepiride arm. Addition of new drugs were also same in both the arms of the trial.<sup>6</sup>

### 1.6. What was the risk of hypoglycemia and weight gain in the trial?

Severe hypoglycemia and hypoglycemia requiring admissions were higher in subjects randomised to the Glimepiride arm. Linagliptin was used in a fixed dose of 5 mg/day whereas Glimepiride was started at 1 mg/day and titrated at 4 weekly intervals to maximum of 4 mg/day over 16 weeks. The protocol followed was to force titrate Glimepiride every 4 weeks if fasting plasma glucose (FPG)  $> 110$  mg/dl (6.1 mmol/L) on the day of the visit although investigator discretion was allowed. This is unlike real world practice of modifying therapy based on HbA1c and glycemic levels. Since baseline HbA1c was only 7.2%, the starting dose of 1 mg and aggressive dose titrations would have increased risk of hypoglycaemia in the glimepiride arm. There was increased risk of hypoglycemia in the glimepiride arm in the first 16 weeks of the trial compared to the latter part of the trial.<sup>6</sup>

In the subgroup analysis of time to first occurrence of investigator defined hypoglycemic adverse events, subgroups with longer duration of diabetes ( $>10$  yrs), prior use of SU or glinide, albumin creatinine ratio (ACR) ( $>0.33$  mg/gm), body mass index (BMI $<30$ ), ethnicity and geographical region achieved significance. Subgroups of baseline HbA1c, eGFR or baseline ASCVD did not achieve significance. However, this imbalance of hypoglycemia between the two arms did not translate to excess cardiovascular harm.<sup>6</sup>

Weight gain was modest in Glimepiride arm in comparison to Linagliptin and mainly occurred during the beginning of the study (weighed mean difference:  $-1.54$  kg (95%CI,  $-1.80$  to  $-1.28$ ). This persisted throughout the course of the trial.<sup>6</sup>

### 1.7. Can this cardiovascular safety of Glimepiride be extrapolated to other sulphonylureas?

Sulphonylureas differ from one another in terms of their affinity and action on the SU receptor and their action on extra pancreatic tissues including the cardiovascular system. In ADVANCE study, Gliclazide MR was used in the intensive arm to target HbA1c  $< 6.5\%$ . However, there was no restriction in adding any other glucose lowering agent including sulphonylureas (other than Gliclazide) in the comparator arm. The mean HbA1c reached in the intensive arm was 6.5% vs. 7.3% in the standard arm. The primary end point of

**Table 1**  
Baseline participant characteristics of CAROLINA trial.<sup>6</sup>

	Linagliptin (n = 3023) N (%)	Glimepiride ((n = 3010) N (%)
Age, mean (SD) years	63.9 (9.5)	64.2 (9.5)
Age > 70 years	566 (37.4)	592 (19.7)
Duration of diabetes (median, Q1, Q3) years	6.3 (3.0,11.1)	6.2 (2.9, 10.9)
HbA1c	7.2 (0.6)	7.2 (0.6)
FPG	140 (31)	140 (30)
ASCVD (any)	1272 (42.2%)	1250 (41.7%)
Heart failure	122 (4.1%)	149 (5.0%)
eGFR (MDRD, ml/min/1.73m <sup>2</sup> )		
Mean (SD)	76.5 (19.7)	77.0 (19.8)
> 90	693 (23.0)	722 (24.1)
60–89	1726 (57.3)	1740 (58.0)
30–59	576 (19.1)	525 (17.5)
15–29	13 (0.4)	13 (0.4)
< 15	3 (0.1)	0

SD: standard deviation, ASCVD: Atherosclerotic Cardiovascular Disease, eGFR: estimated Glomerular Filtration Rate, MDRD: Modification of Diet in Renal Disease, Q1, Q3: interquartile range, HbA1c: glycated hemoglobin

composite of microvascular and macrovascular arm was significantly reduced in the intensive arm (18.1%). There were no significant differences in the number of macrovascular events between the two groups, the primary end point being driven in the intensive treatment group by reduction in diabetic nephropathy.<sup>10</sup>

Essentially ADVANCE was a trial comparing two 2 levels of glycemic control, intensive (HbA1c < 6.5%) vs. standard (managed according to local practice) and not a cardiovascular safety trial of Gliclazide. Although there are no trials focussing on cardiovascular outcomes of other SUs, a network meta-analysis involving 167,327 patients in 18 studies showed that Gliclazide and Glimepiride are associated with lower risk of cardiovascular and all cause mortality in comparison to Glibenclamide.<sup>11</sup>

### 1.8. What were the strengths of CAROLINA trial?

The design of CAROLINA as a randomised trial in subjects with high cardiovascular risk, use of time to event analysis, predefined and centrally adjudicated end points, low rates of loss to follow up, long duration of the trial and achievement of glycemic equipoise gives it credibility. The CAROLINA trial has answered a very pertinent question that has been vexing physicians for decades.<sup>6</sup>

Since the trial has not studied other SUs, we are unable to extrapolate the results of CAROLINA to Gliclazide, Glipizide or Glibenclamide. A sub study of CAROLINA looking at beta cell function was done and the results of the same are eagerly awaited.<sup>12</sup> The addition of glucose lowering therapies including insulin were not significantly different between the arms and the similar glycemic control in both the arms is an indirect proof that there may not be any significant difference between glimepiride and linagliptin on progression of diabetes.<sup>6</sup>

### 1.9. Has the CAROLINA trial proven beyond doubt the cardiovascular safety of Glimepiride?

Within the duration of the CAROLINA trial, Glimepiride has proven cardiovascular safety for the end points considered. The effect on 3 P MACE persisted across various subgroups which include baseline cardiovascular disease, age and renal dysfunction.

CAROLINA did not include people with previous exposure to insulin or thiazolidinediones. Subsequently these drugs were added in small numbers of subjects to achieve glycemic control. The safety of these drug combinations (Glimepiride + Insulin and Glimepiride + Thiazolidinediones) which are commonly used in clinical practice cannot be deduced from this study. In CVOTs, to achieve glycemic equipoise, the investigators can add other glucose

lowering drugs to both arms of the trial. These drugs added in either arm of the trials should have mechanisms different from that of the drug under trial e.g. in CVOTs of DPP4 inhibitors, drugs acting on incretin axis (GLP-1RA and DPP4 inhibitors) are not added to either arms of the trial.<sup>9</sup> However, in CAROLINA trial, sulfonylureas, DPP4 inhibitors and GLP1Ras were added to both the arms of the trials although in small numbers. The influence of these on the final outcomes of the trial cannot be discounted.<sup>6</sup>

Duration of diabetes and low eGFR are independent risk factor for cardiovascular events including heart failure. Baseline heart failure and recent cardiovascular events are independent risk factors for hospitalization for heart failure and CV events. People with low eGFR, baseline heart failure, recent cardiovascular events and longer duration of diabetes were not represented in CAROLINA.<sup>6,12</sup> (Table 1) Extrapolating the CV safety of Glimepiride to these subsets of people with diabetes cannot be considered from this trial.

## 2. Conclusions

Sulphonylureas have been an integral part of glycemic management in developing nations including India. The proof of cardiovascular safety of Glimepiride in CAROLINA trial against DPP4 inhibitors will give the cardiologist confidence to use it in a variety of conditions including stable coronary artery disease, cerebrovascular disease and peripheral arterial disease. Due to lack of adequate representative population in CAROLINA, its use should be limited in those with acute coronary and stroke syndromes, recent coronary events and those with heart failure. Judicious use of Glimepiride in smaller dose at initiation and gradual dose titration will help reduce the risk of hypoglycemia. The CAROLINA study has proven that cardiovascular safety for Glimepiride is at par with Linagliptin. In this context, USFDA should consider revising the black box warning for modern sulfonylurea for risk of cardiovascular mortality. This would give confidence for use of modern sulphonylureas in people with cardiovascular risk.

### 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 any of the authors.

### Disclosure

All authors had full access to the articles reviewed in this manuscript and take complete responsibility for the integrity and

accuracy of this manuscript. The content published herein solely represents the views and opinions of the authors.

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