Review Article

Reassuring the CV safety of Sulfonylureas : A Review article to readdress the CV safety of Modern Sulfonylureas post CAROLINA trial

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For decades, sulfonylureas (SUs) have been important drugs in the antidiabetic therapeutic armamentarium. They have been used as monotherapy as well as combination therapy. Focus on newer drugs and concerns about the risk of severe hypoglycemia and weight gain with some SUs have led to discussion on their safety and utility. It has to be borne in mind that the adverse events associated with SUs should not be ascribed to the whole class, as many modern SUs, such as glimepiride and gliclazide modified release, are associated with better safety profiles. One such trial is the CAROLINA trial where the trial finally put concerns about sulfonylureas' cardiovascular safety to rest. Considering their efficacy, safety, pleiotropic benefits, and low cost of therapy, SUs should be considered as recommended therapy for the treatment of diabetes.

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The type 2 diabetes mellitus (T2 DM) pandemic[1] is characterized by increasing complexity of management, raising concerns over safety and cost of therapy. Most guidelines state that metformin should be first-line therapy followed by various options for second-line treatment if sufficient glycemic control is not achieved after metforminmono therapy. Both dipeptidyl peptidase-4 (DPP-4) inhibitor and sulfonylureas are widely used second-line glucose-lowering agents. Sulfonylureas are used mainly based on their low cost, well-established glucose-lowering action, and a longstanding experience in clinical practice. However, sulfonylureas are associated with increased risk of hypoglycemia and modest weight gain[2].

Today, new diabetes agents face increased regulatory scrutiny and are required to demonstrate CV safety before, or after, approval. Indeed, the US Food and Drug Administration (FDA) key post-approval criterion to exclude unacceptable CVD risk for new diabetes drugs is an upper bound of the 95% confidence interval (CI) of <1.3 for the hazard ratio (HR) of CV events[3]. On the other hand, the regulatory requirements provided the opportunity for some of the drugs in CV outcome trials tested for CV benefits. This review covers the current evidence on the long-term risk of CV events with sulphonylureas (SUs), which remains one of the most widely used drug classes in T2 DM.

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Since SUs are still being advocated as second-line therapy added-on to metformin, as one of several classes, and in certain circumstances first-line therapy in T2 DM management, definitive data from a dedicated RCT addressing the CV safety question with SUs would be informative. Cardiovascular Outcome Study of Linagliptin *versus* Glimepiride in Patients with Type 2 Diabetes (CAROLINA) is such a trial, ongoing since November 2010, and is currently the largest head-to-head CV outcome trial that involves a comparison of a SU (glimepiride) with a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin) and provided a unique perspective with respect to CV outcomes with these two commonly used agents[2].

SUs are well-established glucose-lowering drugs, with insulinotropic action on pancreatic ß-cells. Since the introduction of tolbutamide in 1956[4], newer SUs have been developed, broadly classified based on their affinity to bind with sulfonylurea receptor (SUR) proteins[5]. The availability of modern SUs (glimepiride, glipizide, gliclazide MR and gliclazide modified release [MR]) with fewer side-effects and better efficacy[6] have contributed to their popularity.

SUs are insulin secretagogues that stimulate endogenous insulin secretion by blocking adenosine triphosphate-sensitive potassium channels (K_{ATP}) on pancreatic ß-cells, by binding to the SUR subunit present on the ß-cell plasma membrane[7]. SUs bind to a common SUR unit on ß-cells causing closure of the K_{ATP} channels and inhibition of K^+ efflux, consequently depolarising the membrane and facilitating influx of Ca^{+2} ions. This in turn

stimulates the exocytosis of insulin secretory vesicles[7]. Because insulin secretion is non-glucose-mediated, conventional SUs have been associated with a higher risk of hypoglycaemia.

All Sulfonylureas Are Not the Same :

SUs stimulate insulin secretion by blocking K_{ATP} channels in the pancreatic ß-cell membrane, by binding to the SUR subunit of the channel[8]. K_{ATP} channels are also present in extrapancreatic tissues, but often contain different types of SUR subunit. Evidence suggests that the effect of SUs on these K_{ATP} channels in different tissues varies[9]. For instance, gliclazide and tolbutamide block SUR_1 with higher affinity compared to SUR_2 while glibenclamide and glimepiride block both receptors with similar affinity.

Glimepiride stimulates insulin secretion by binding to a specific 65-kDa protein site on the K_{ATP} channel of pancreatic ß-cell and exerts allosteric inhibition of the SUR complex[10,11]. Further, compared to glibenclamide, glimepiride exhibits lower binding affinity (2- to 3-fold) for SUR as well as higher rate of association (2.5- to 3-fold) and dissociation (8- to 9-fold) from the receptor[10,12]. The distinct binding site and receptor interactions of glimepiride are believed to result in lower inhibition of K_{ATP} channel and hence, there is reduced risk of hypoglycaemia as compared to conventional SUs.

Variations in the pharmacodynamic/pharmacokinetic (PK/PD) profiles of individual SUs also explain the differences in anti-diabetic activity, hypoglycaemic risk, specificities to different tissue-specific SURs, effects on myocardial ischemic preconditioning, and insulin secretory effects[13]. In light of this, it may be wise to choose modern SUs that pose lower risk of hypoglycaemia and are cardiac friendly.

Cardiovascular Safety :

Concerns about the CV safety of SUs were raised initially in 1970s when the University Group Diabetes Program (UGDP) study found an increased association between tolbutamide use and risks of coronary artery events[14]. However, the UGDP suffers numerous flaws in the design, execution, analysis and interpretation of findings[15]. In fact, the UGDP findings prompted initiation of UKPDS, which found no detrimental effect of SUs on macrovascular complications or mortality in patients with T2DM[16]. This benefit persisted for up to 10 years in patients who had attained better glycaemic control. Similar results were observed from 15 well designed long term (≥72-weeks) RCTs, including ADOPT, ADVANCE and ADVANCE-ON, where treatment with SUs was not found to be associated with an increase in CVD risk or mortality[17].

Modern SUs (gliclazide MR and glimepiride) are associated with a lower risk of all-cause and CV-related mortality compared to conventional SUs in T2DM patients[18].

Ischemic Preconditioning :

Glibenclamide inhibited mitochondrial K_{ATP} channels, impaired IPC and increased experimental infarct size, whereas glimepiride did not inhibit beneficial effects of mitochondrial K_{ATP} channel opening and showed no adverse effect on IPC or infarct size[19]. Moreover glimepiride was found to maintain myocardial preconditioning with fewer CV side effects as compared to glibenclamide (P=0.01 *versus* P=0.34, respectively)[20]. Although both glibenclamide and glimepiride have affinity for the SUR2 receptor, glimepiride appears to preserve myocardial preconditioning, a property not shared by glibenclamide. Glimepiride was also reported to have a more rapid as well as longer duration of action; despite less stimulation of insulin secretion in comparison with glibenclamide[21]. Therefore, the effect of SUs on cardiac events depends on the molecule being used and the individual clinical setting of the individual case.

The CAROLINA Study :

In this long-term, multicenter, double-blind, randomized, active comparator trial of individuals with relatively early type2 diabetes at elevated cardiovascular risk, linagliptin was noninferior to glimepiride for the combined 3P-MACE end point. The current study demonstrates noninferior cardiovascular safety effects for linagliptin *versus* glimepiride when used predominantly as a second-line glucose-loweringtreatment option aftermetformin. CAROLINA is the first cardiovascular outcomes trial to include an active comparator and it provides valuable information about both linagliptin and glimepiride. It provides reassurance about the long-debated cardiovascular safety of sulfonylureas.

The new findings don't change current treatment recommendations for use of a type 2 diabetes agent with proven cardiovascular benefit — a sodium-glucose cotransporter type 2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) agonist — after metformin in patients with established cardiovascular disease.But for other patients with type 2 diabetes, SU is the choice of a second-line agent when cost is an issue[22].

CAROLINA involved 6033 individuals with type 2 diabetes from 607 sites in 43 countries[22]. All had relatively recent diabetes onset (median duration 6.3 years) and most had pre-existing cardiovascular disease (42%) or two or more defined cardiovascular risk factors (37%). Most (83%) were already taking metformin, but 9% were treatment naive at baseline. Those taking insulin were excluded. Over a median of 6.3 years — the longest cardiovascular outcomes

trial to date, note the researchers — there were no differences in the overall composite endpoint of cardiovascular death (fatal stroke and fatal myocardial infarction [MI]), nonfatal MI (excluding silent MI), or nonfatal stroke. Overall, the 3-point MACE occurred in 11.8% of the 3023 participants receiving linagliptin compared with 12.0% of the 3010 participants receiving glimepiride (hazard ratio [HR], 0.98; P = 0.7625)[22].

Similarly, nonsignificant differences were seen between linagliptin and glimepiride for each individual component of CV death (HR 1.00; 5.6% *versus* 5.6%; P = 0.9863), nonfatal MI (HR, 1.01; 4.8% *versus* 4.7%; P = 0.9060), and nonfatal stroke (HR, 0.87; 3.0% *versus* 3.5%; P = 0.3352)[22].

The same was true for secondary endpoints including hospitalization for heart failure (HR, 1.21; 3.7% *versus* 3.1%; P = 0.1761), CV death (HR, 1.00), non-CV death (HR, 0.82), and all-cause mortality (HR, 0.91)[22].

No differences were seen in glycemic control. HbA1c levels dropped more quickly with glimepiride, but by the end of the trial both groups had returned to a baseline of around 7.0%. There were no differences in the proportion of patients for whom new glucose-lowering therapies, including insulin, were required (about 40% in both groups).

Those in the glimepiride group initially gained about 0.6 kg in weight while the linagliptin group lost about 1.0 kg. By the end of the trial, the glimepiride group weighed about 1.5 kg more than the linagliptin participants.

No differences were seen between the groups in systolic or diastolic blood pressure, or in LDL cholesterol, HDL cholesterol, or triglycerides.

Hypoglycemia occurred significantly more often in the glimepiride group, including hypoglycemia overall (37.7% *versus* 10.6%; P<0.0001), moderate to severe hypoglycemia (30.9% *versus* 6.5%; P<0.0001), severe hypoglycemia (2.2% *versus* 0.3%; P<0.0001), and hospitalization due to hypoglycemia (0.9% *versus* 0.1%; P = 0.0004)[22].

Conclusion :

SUs are the main stream of pharmacotherapy in the management of patients with T2DM. Their well-established glycaemic efficacy, safety and tolerability support their use as an integral part of diabetes treatment. The CAROLINA trial addresses the sulfonylurea CV controversy. This reaffirms current clinical recommendations to choose Glimepiride after Metformin based on proven CV benefits and cost factor. CV safety should no longer be a consideration in the decision making process for selecting Glimepiride with other modern SU. Given the fact that many of the clinical concerns associated with the use of SUs are agent-specific, and do not pertain to the class as such, a careful choice of specific SU should be considered beneficial. Considering better glycaemic efficacy, long-term outcomes and low medication cost, SUs, should be continued to be used as a front-line agent in the treatment algorithm of T2DM, particularly in India. Proper patient selection, choice of drug and dose, patient education and empowerment, and physician training will help ensure effective and safe use of this important class of drugs.

References

1 International Diabetes Federation. Key Findings. 2014. [Last accessed on 2015 Mar 25]. Available from: http://www.idf.org/diabetesatlas/update-2014

2 Das SR, Everett BM, Birtcher KK — 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018; **72(24):** 3200-23.

3 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetes therapies to treat type 2 diabetes, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf (2008)

4 Seltzer HS — Efficacy and safety of oral hypoglycemic agents. *Annu Rev Med* 1980; **31:** 261-72.

5 Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JP 4th, Boyd AE 3rd, González G, *et al* — Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science* 1995; **268(5209):** 423-6.

6 Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens R — Diabetologia Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. 2013; **56(5):** 973-84.

7 Kramer W, Müller G, Geisen K — Characterization of the molecular mode of action of the sulfonylurea, glimepiride, at beta-cells. *Horm Metab Res* 1996; **28(9):** 464-8.

8 Gribble FM, Reimann F — Differential selectivity of insulin secretagogues: mechanisms, clinical implications, and drug interactions. *J Diabetes Complications* 2003; **17(2 Suppl):** 11-5.

9 Ashcroft FM, Gribble FM — Tissue-specific effects of sulfonylureas: lessons from studies of cloned K(ATP) channels. *J Diabetes Complications* 2000; **14(4):** 192-6.

10 Briscoe VJ, Griffith ML, Davis SN — The role of glimepiride in the treatment of type 2 diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2010; **6(2):** 225-35.

11 Müller G, Hartz D, Pünter J, Okonomopulos R, Kramer W — Differential interaction of glimepiride and glibenclamide with the beta-cell sulfonylurea receptor. I. Binding characteristics. *Biochim Biophys Acta* 1994; **1191(2):** 267-77.

12 Holstein A, Plaschke A, Egberts EH — Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev* 2001; **17(6):** 467-73.

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13 Proks P, Reimann F, Green N, Gribble F, Ashcroft F — Sulfonylurea stimulation of insulin secretion. *Diabetes* 2002; **51 Suppl 3:** S368-76.

14 Feinglos MN, Bethel MA — Therapy of type 2 diabetes, cardiovascular death, and the UGDP. *Am Heart J* 1999; **138(5 Pt 1):** S346-52.

15 A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). *Seltzer HS Diabetes* 1972; **21(9):** 976-9.

16 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352(9131):** 837-53.

17 Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, *et al* — Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res* 2013; **10(4):** 289-301.

18 Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR — Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3(1):** 43-51.

19 Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM — Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* 2001; **103(25):** 3111-6.

20 Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, *et al* — Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20(6):** 439-46.

21 Raptis SA, Hatziagelaki E, Dimitriadis G, Draeger KE, Pfeiffer C, Raptis AE — Comparative effects of glimepiride and glibenclamide on blood glucose, C-peptide and insulin concentrations in the fasting and postprandial state in normal man. *Exp Clin Endocrinol Diabetes* 1999; **107(6):** 350-5.

22 Rosenstock J, Kahn S, Johansen O, Zinman B, Espeland M, Woerle H, *et al* — Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes. *JAMA* 2019; **322(12):** 1155.