Commentary on "Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus: International Task Force"

S. K. Singh

Department of Endocrinology and Metabolism, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Sulfonylureas (SUs) have been in use for treatment of type 2 diabetes mellitus (DM) for more than 50 years. The confidence developed with their use in controlling blood glucose to target has been tainted by its untoward effect of hypoglycemia. The newer oral agents have emerged as an alternative to SUs, and the risk of hypoglycemia is no more concern but the efficacy and cost of treatment. Additional benefits such as sustenance of effects and passing the test of cardiac safety are justification for preference of these agents over SUs. Despite a long track record of clinical use of SUs, their cardiac safety has always been a concern due to the paucity of studies designed to address this issue. Cardiac safety of SUs is not feasible to test in randomized controlled trials (RCTs) now, and it is left to resort to analysis of clinical data of the previous studies for safety issues. Efficacy and economical benefit of SUs with unclear cardiac risk continue to place the drug in the choice ladder of oral antidiabetic agents with variable positioning. Known cardiovascular risk factors such as weight gain, fluid retention, and hypoglycemia, are inherent problem with SUs.[1] In contrast, meta-analyses of sulfonylurea randomized controlled trials (RCTs) have produced conflicting findings with respect to cardiovascular events and mortality.[2-4] However, none of these were designed or powered to detect cardiovascular events, and the RCTs used different comparators.

The major reservation of hypoglycemia with SUs has not been unfounded but newer generation SUs have lower chance of causing hypoglycemia. In a study on 14,000 patients with type 2 diabetes, treated with SUs, very few incidences of serious hypoglycemia occurred.[5] The incidence was higher with glibenclamide, and lower with tolbutamide (19.9 vs. 3.5 episodes per 1000 person-years, respectively). Other shorter-acting drugs such as tolazamide and glipizide, had lower incidence than chlorpropamide and glibenclamide.[6] Such observation overemphasizes that to prevent hypoglycemia, the initial dose of SUs can be as low as possible with escalation matching the need of lowering of blood glucose level to the target. Indeed the newer sulfonylureas (glipizide and glimepiride) have lower hypoglycemia risk,[7] and their use is an effective measure to prevent hypoglycemia. Patients with autonomic failure, secondary to aging and to longer duration of diabetes, have high risk of hypoglycemia and SUs may be prescribed to them with utmost care and caution.

Cardiac function may be affected by sulfonylureas. Unfavorable outcomes after myocardial infarction in patients with diabetes on SUs therapy have been previously reported.[8-10] A long-debated outcome study (University Group Diabetes Study) of tolbutamide on cardiac mortality has raised doubt on its cardiac safety.[11]

Subsequently, many studies were designed to clarify the issue of cardiac mortality and treatment with SUs. In the Mayo Clinic, in 185 diabetic patients, death was significant for those treated with a sulfonylurea at the time of the myocardial infarction.[12]

In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction trial, patients on SUs at the time of myocardial infarction had poorest outcome.[13] The Canadian study, based on pharmaceutical data of 5795 patients receiving sulfonylurea or metformin monotherapy reported 67.6 deaths per 1000 person-years for the first-generation sulfonylurea during the follow-up period. These figures were 61.4 for glibenclamide, and 39.6 for metformin.[14] The risk of death or of an acute ischemic event was proportional to amounts of the sulfonylurea used.[14]

The apparent risk association of SUs with cardiac events are explicable simply as there are sulfonylurea receptor isoforms on cardiac myocytes and vascular smooth muscles. SUs have different tissue selectivity characteristics that effect cardiovascular outcomes.[15] Glibenclamide but not Gliclazide prevents cardioprotection by interaction with mitochondrial K+ ATP channels. In the brain, K+ ATP channels mediate counter-regulatory responses to hypoglycemia[16] and reduces membrane excitability during seizure activity. SUs might have effect on these channels. Newer sulfonylureas, such as gliclazide, are selective for the pancreatic sulfonylurea receptors and do not interact with those on cardiac myocytes showing favorable outcome like metformin.[17] In a study of 1310 French patients with diabetes hospitalized for myocardial infarction, in-hospital mortality was significantly lower in patients previously treated with sulfonylureas compared with other oral medications, insulin, or no medication (3.9%, 6.4%, 9.4%, and 8.4%, respectively).[18] Among the SUs-treated patients, mortality was significantly lower in patients receiving gliclazide or glimepiride than glibenclamide.

By blocking ATP-dependent K+ channels on cardiac cells and coronary vessels, sulfonylureas may impair adequate

coronary vasodilatation at time of infarction leading to larger area of myocardial damage. Other proposed theory for the effect of SUs on cardiovascular events and mortality is based on interference with ischemic preconditioning or possible arrhythmogenic effects, and on the inhibitory effect of sulfonylureas on the reverse cholesterol transport mediated by high-density lipoproteins.[19]

Interestingly, the results of clinical trials particularly ADVANCE,[20] using newer sulfonylureas such as gliclazide, are somewhat reassuring. Although the ADVANCE study was not intended to address the issue of cardiac safety lower incidence of hypoglycemia and overall cardiac benefit was good evidence to choose newer generation SUs as an option following metformin.

Many would uphold the view that newer generation SUs should be chosen for second-line oral agent in the treatment of type 2 DM in specific situations given that their use has some concerns but not of serious nature. The truth is that newer oral agents do not have safety record of that long duration as that of SUs. In young patients with short duration of the disease, in symptomatic patients for hyperglycemia, in patients for rapid achievement of glycemic target and patients with economic constraints, SUs can be good option for 6–12 months before initiation of insulin therapy. On an individual basis, the standard of care guidelines can be followed in the other group of patients. The consensus recommendation of choosing SUs after metformin is reasonable for countries with high disease prevalence and resource constraints.

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Conflicts of interest

There are no conflicts of interest.

Address for correspondence: Prof. S. K. Singh, Department of Endocrinology and Metabolism, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
E-mail: sksendocrine@gmail.com

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