

---

## Choice within sulfonylurea drugs in ischemic heart disease patients

Dear Sir,

Sulfonylurea drugs (SUDs) continue to be the mainstay of treatment for type 2 diabetes mellitus (T2DM). Studies have highlighted differences between SUDs in terms of their potential to produce hypoglycemia and their impact on ischemic preconditioning (IPC) of myocardium.<sup>[1,2]</sup> We wanted to investigate if our medical practitioners had any preference among SUDs while considering treatment for T2DM patients with ischemic heart disease (IHD), as specific treatment guidelines were not available at the time of this survey. After obtaining approval from Institutional Ethics Committee, a structured questionnaire was administered to 89 practicing physicians of the town who verbally consented to participate in the study.

Forty-four percent of respondents opted for “no

choice” among SUDs. Remaining 56% expressed preference for one or more of the four SUDs mentioned in the questionnaire. Glimepiride and gliclazide were preferred by 39 and 15%, respectively. Glibenclamide and glipizide were opted by 5% each. The major adverse effect of SUDs is hypoglycemia. Glibenclamide is more likely to give rise to severe hypoglycemic episodes than glimepiride.<sup>[2]</sup> Concern was raised about an increase in the cardiovascular mortality due to direct cardiotoxic potential of glibenclamide. *In vitro* and *in vivo* evidences suggest that acute or chronic administration of glibenclamide induces potentially harmful cardiovascular effects in both diabetic and nondiabetic patients with IHD, by blocking ATP sensitive potassium ( $K_{ATP}$ ) channels in cardiomyocytes that are involved in IPC, whereas the pancreas-specific glimepiride may actually preserve the beneficial effects of IPC.<sup>[1-4]</sup> An editorial article even suggests to consider retiring

glibenclamide in favor of other anti-hyperglycemic agents that lack the potential to compromise with IPC.<sup>[2]</sup> Accordingly, a considerable number of survey respondents were in favor of glimepiride despite this drug being more expensive than other SUDs. As per animal studies, the effects of glipizide are similar to those of glibenclamide on the heart<sup>[3]</sup> and both the drugs shared common position in the survey response. Inclination for use of gliclazide was more than that for latter two SUDs probably because it may not abolish IPC of myocardium and its antiatherogenic, antiplatelet and antioxidant properties may have added advantages in cardio protection.<sup>[5,6]</sup> Despite the existing experimental evidence for an impairment of IPC by glibenclamide, there is still no evidence for a detrimental effect of this action on cardiovascular mortality in patients with T2DM.<sup>[6,7]</sup> To what extent IPC may be a clinically relevant phenomenon is still a matter that is unresolved.<sup>[1]</sup> A meta analyses concludes that glibenclamide caused more hypoglycemia than other SUDs but was not associated with an increased risk of cardiovascular events, weight gain or death.<sup>[8]</sup> A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes (2009) preferred the use of three SUDs over glibenclamide for the treatment of T2DM, owing to the substantially greater risk of hypoglycemia related with the latter SUD. The consensus statement neither considered the increased cardiovascular disease mortality hypothesized with SUD use nor did it refer to the preferential use of any SUD for treating T2DM in IHD patients,<sup>[9]</sup> and this survey was carried out before this statement was published.

The survey instrument, being a structured questionnaire, did not provide space for the physicians to justify their choices. Hence, the preference for glibenclamide (5%) or not having preference for a specific SUD (44%), despite the clear evidence for potential cardiac risk of glibenclamide, cannot be rationalized. In a diabetic patient with IHD, poly-pharmacy prescription is inevitable while aiming at achieving good glycemic control and taking care of cardiovascular risk factors along with treating IHD. Glibenclamide being relatively inexpensive, the differential costs of four SUDs may concern the physician while aspiring for a cost-effective treatment. In the absence of a definitive treatment recommendation<sup>[9]</sup> distinguishing between the four SUDs for their use in IHD diabetic patients, the clinician may tend to practice a flexible approach about the choice of SUDs, while trying to trim the cost of diabetes care.

Cardiovascular disease is the major cause of morbidity

and mortality among patients with T2DM and diabetes itself can impair IPC.<sup>[3]</sup> Glibenclamide is also supposed to abolish IPC and is still prescribed to diabetic patients with IHD. Further SUD treatment outcome studies may be needed to conclude on the safety issue of glibenclamide in IHD patients.

## Acknowledgment

Authors acknowledge ICMR, India for funding this STS Project.

**P. Sabitha, Aakash<sup>1</sup>, Prabha M. Adhikari<sup>2</sup>,  
Asha Kamath<sup>3</sup>**

Departments of Pharmacology, <sup>2</sup>Medicine, <sup>3</sup>Biostatistics,  
<sup>1</sup>Internee in Medicine, Kasturba Medical College,  
Mangalore, India

Correspondence to: **Dr. P. Sabitha**,  
Department of Pharmacology,  
Kasturba Medical College, Mangalore, India.  
E-mail: [sabita\\_rao1@rediffmail.com](mailto:sabita_rao1@rediffmail.com),

DOI: 10.4103/0973-3930.66516

## References

1. Caulfield MT, O'Brien KD. Cardiovascular Safety of Oral Antidiabetic Agents: The Insulin Secretagogues. *Clin Diabetes* 2002;20:81-4.
2. Riddle MC. Editorial: Sulfonylureas differ in effects on ischemic preconditioning--is it time to retire glyburide? *J Clin Endocrinol Metab* 2003;88:528-30.
3. Bell DS. Do sulfonylurea drugs increase the risk of cardiac events? *CMAJ* 2006;174:185-6.
4. Bilinska M, Potocka J, Korzeniowska-Kubacka I, Piotrowicz R. 'Warm-up' phenomenon in diabetic patients with stable angina treated with diet or sulfonylureas. *Coron Artery Dis* 2007;18:455-62.
5. Renaud B. Diamicon MR an anti diabetic that offers effective blood glucose control and cardiovascular benefits. *Medicographia* 2007;29:255-60.
6. Meier JJ, Gallwitz B, Schmidt WE, Mügge A, Nauck MA. Is impairment of ischaemic preconditioning by sulfonylurea drugs clinically important? *Heart* 2004;90:9-12.
7. Arruda-Olson AM, Patch RK 3<sup>rd</sup>, Leibson CL, Vella A, Frye RL, Weston SA, *et al.* Effect of second-generation sulfonylureas on survival in patients with diabetes mellitus after myocardial infarction. *Mayo Clin Proc* 2009;84:28-33.
8. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: A comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007;30:389-94.
9. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al.* Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193-203.