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COMMENTARY

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Is it time to ban sulfonylureas?

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Sulfonylureas (SUs) are a class of agents that lower blood sugar through increasing release of insulin from the pancreas. The SUs are routinely prescribed for type 2 diabetes mellitus (T2DM) as monotherapy or in combination with insulin or other oral hypoglycemic agents. However, the probable associations of SUs in various adverse effects hold a cause of serious concern. With the introduction of more and more new drugs, we would like to discuss whether it is time to ban SUs.

1 | THE SIDE EFFECTS OF SULFONYLUREAS

Hypoglycemia remains the most common side effect reported with the administration of SUs, though it occurs more frequently with long-acting medications. When added to maximal metformin therapy, SUs were associated with similar glycosylated hemoglobin (HbA1c) reductions to other noninsulin antidiabetic drugs but higher rates of hypoglycemia.[1] The relationship between severe hypoglycemia and the subsequent risks of vascular complications and death was examined in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study with 11 140 T2DM patients, which suggested that hypoglycemia was strongly associated with increased risks of a range of adverse clinical outcomes, including macrovascular events, microvascular events, and death from both cardiovascular and noncardiovascular causes.[2] In a survey of Thai patients with T2DM who were treated with SU alone or SU + metformin, approximately one third reported experiencing hypoglycemic symptoms, which subsequently had an impact on health-related quality of life.[3] Therefore, therapies, patient monitoring rationales, or patient education programs that minimize the frequency and severity of hypoglycemia and worry about hypoglycemia would likely increase the diabetic patients' quality of life. In the Hong Kong's primary care settings, several associated risk factors, including smoking status, lowerbody mass index, higher low-density lipoprotein levels, and use of SUs, were all significantly associated with all-cause mortality among the elderly diabetic patients,[4] suggesting that SUs might not be the best choice for diabetes management in the elderly population. A previous meta-analysis of observational studies investigating the association between combination therapy of SUs and metformin and the risk of cardiovascular diseases and all-cause mortality showed that combination therapy of metformin and SUs significantly increased the relative risk of cardiovascular hospitalization or mortality (fatal and nonfatal events) irrespective of the reference group (diet therapy, metformin monotherapy, or SUs monotherapy) used.[5]

Some worrisome evidence suggested the adverse effects of SUs. In a retrospective cohort study in China, SUs monotherapy was significantly associated with a higher risk of heart failure compared with acarbose monotherapy for initial treatment of T2DM.[6] More evidence was seen in the Korean adults with T2DM, SU as an add-on therapy to metformin may increase the risks of heart failure compared with dipeptidyl peptidase-4 (DPP-4) inhibitors.[7]

The safety of different SUs is worthy of our attention. An observational cohort study showed that SUs with greater selectivity for beta-cell receptors, such as glimepiride and gliclazide, were associated with a much lower mortality when used in combination with

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metformin in comparison with glibenclamide, whereas repaglinide showed an intermediate result.[8] The contribution of SU therapy to mortality was recently confirmed in a real-world study, which showed that SU monotherapy was associated with higher all-cause mortality when compared to metformin monotherapy after adjusting for potential confounders.[9]

2 | THE EFFICACY OF SULFONYLUREAS

What about the effectiveness of SUs in glycemic control? A meta-analysis studying the second-line treatment option for T2DM indicated that the three drug classes, SUs, DPP-4 inhibitors, and thiazolidinediones, did not differ in lowering HbA1c in patients with T2D treated with metformin as a first-line therapy; however, SUs had higher risk of myocardial infarction and eye disorders compared with DPP-4 inhibitors.[10] In another study among insured adult patients with T2DM initiating second-line antidiabetic medications therapy, higher cardiovascular risk was associated with use of SUs or basal insulin compared with newer antidiabetic medications, whereas the short-term cardiovascular outcomes of glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and DPP-4 inhibitors were similar, suggesting that clinicians may consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors more routinely after metformin rather than SUs or basal insulin.[11] Particularly, for patients with T2DM by chronic kidney disease stage, SU monotherapy was associated with higher risk for all-cause mortality, major hypoglycemic episodes, and cardiovascular events compared with metformin.[12]

Monitoring glucose fluctuations is of great importance in diabetes treatment.[13] A randomized study showed that both glimepiride and dulaglutide could effectively lower blood glucose and decrease oxidation stress and inflammation; however, glimepiride was less effective on controlling glucose fluctuation as compared with dulaglutide.[14]

Interestingly, in a recent study assessing the comparative effects of SGLT2 inhibitors, Sus, and DPP-4 inhibitors on cardiometabolic risk factors in routine care, the data showed that the profile of cardiometabolic risk was significantly improved in patients using SGLT2 inhibitors than SUs.[15] Moreover, the meta-analysis comparing the efficacy and safety of SGLT2 inhibitors with SUs as second-line therapy in patients with T2DM inadequately controlled on metformin found that despite similar glycemic efficacy in a relatively short term, SGLT2 inhibitors were more effective in the longer term than SUs as add-on to metformin. In addition, SGLT2 inhibitors produced less hypoglycemic events and lead to greater reductions in weight and blood pressure compared with SUs.[16] Therefore, SUs showed less benefit compared with other drugs, even not considering the risk of hypoglycemia.

3 | THE COST-EFFECTIVENESS OF SULFONYLUREAS

Another key issue is the cost-effectiveness of SUs. SUs are indeed cheaper than the newer drugs in the short term; however, in the long run, the substantial cost of the newer drugs is offset by the benefits attainable on the reduction of complications, especially cardiovascular events and hypoglycemia. In the cost-utility analysis, dulaglutide was shown to be a cost-effective treatment option from the Italian healthcare system perspective as add-on therapy to metformin in patients with inadequately controlled T2DM compared to gliclazide or basal insulin glargine.[17]

In conclusion, although SUs were a good therapeutic option for T2DM in the past, their side effects deserve more caution and investigation. Even reassured about the safety of SUs by the controlled trials, adverse effects have still been reported. There is no convincing evidence showing that SUs should be preferred to other more modern therapies. Moreover, the cost/benefit ratio compared to other less expensive drugs does not justify a possible preferential use of SUs.

DISCLOSURE

Antonio Ceriello disclosed the following conflict of interest: advisory board membership: BD, Eli Lilly, Mundipharma. Lectures: Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly, Mundipharma, Novo Nordisk, Roche Diagnostics. Research Grants: Mitsubishi.

REFERENCES

1. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;303(14):1410-1418.
2. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410-1418.
3. Pratipanawatr T, Satirapoj B, Ongphiphadhanakul B, Suwanwalaikorn S, Nitiyanant W. Impact of hypoglycemia on health-related quality of life among type 2 diabetes: a cross-sectional study in Thailand. *J Diabetes Res*. 2019;2019:5903820.
4. Ying DG, Ko SH, Li YC, Chen CX. Association between intensive glycemic control and mortality in elderly diabetic patients in the primary care: a retrospective cohort study. *Prim Care Diabetes*. 2020 Apr 11;S1751-9918(19)30442-5. https://doi.org/10.1016/j.pcd.2020.02.012

5. Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care*. 2008; 31(8):1672-1678.
6. Xu Y, Wang T, Yang Z, Lin H, Shen P, Zhan S. Sulphonylureas monotherapy and risk of hospitalization for heart failure in patients with type 2 diabetes mellitus: a population-based cohort study in China. *Pharmacoepidemiol Drug Saf*. 2020;29(6):635-643.
7. Lee SJ, Ha KH, Lee JH, Lee H, Kim DJ, Kim HC. Second-line glucose-lowering drugs added to metformin and the risk of hospitalization for heart failure: a nationwide cohort study. *PLoS One*. 2019;14(2):e0211959.
8. Monami M, Luzzi C, Lamanna C, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. *Diabetes Metab Res Rev*. 2006; 22(6):477-482.
9. Reiff S, Fava S. All-cause mortality in patients on sulphonylurea monotherapy compared to metformin monotherapy in a nationwide cohort. *Diabetes Res Clin Pract*. 2019;147:62-66.
10. Vashisht R, Jung K, Schuler A, et al. Association of hemoglobin A1c levels with use of sulfonylureas, dipeptidyl peptidase 4 inhibitors, and Thiazolidinediones in patients with type 2 diabetes treated with metformin: analysis from the observational health data sciences and informatics initiative. *JAMA Netw Open*. 2018;1(4):e181755.
11. O'Brien MJ, Karam SL, Wallia A, et al. Association of second-line antidiabetic medications with cardiovascular events among insured adults with type 2 diabetes. *JAMA Netw Open*. 2018; 1(8):e186125.
12. Whitlock RH, Hougen I, Komenda P, Rigatto C, Clemens KK, Tangri N. A safety comparison of metformin vs sulfonylurea initiation in patients with type 2 diabetes and chronic kidney disease: a retrospective cohort study. *Mayo Clin Proc*. 2020; 95(1):90-100.
13. Ceriello A. Glucose variability and diabetic complications: is it time to treat? *Diabetes Care*. 2020;43(6):1169-1171.
14. Li H, Xu X, Wang J, et al. A randomized study to compare the effects of once-weekly Dulaglutide injection and once-daily glimepiride on glucose fluctuation of type 2 diabetes mellitus patients: a 26-week follow-up. *J Diabetes Res*. 2019;2019: 6423987.
15. Wilkinson S, Williamson E, Pokrajac A, et al. Comparative effects of sulphonylureas, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UKprimary care. *Diabetes Obes Metab*. 2020;22(5):847-856.
16. Chen Z, Li G. Sodium-glucose co-transporter 2 inhibitors compared with sulfonylureas in patients with type 2 diabetes inadequately controlled on metformin: a meta-analysis of randomized controlled trials. *Clin Drug Investig*. 2019;39(6): 521-531.
17. Torre E, Bruno GM, Di Matteo S, et al. Economic evaluation of Dulaglutide vs traditional therapies: implications of the outcomes of the rewind study. *Clinicoecon Outcomes Res*. 2020;12: 177-189.