EDITORIAL

Sulfonylureas and Cardiovascular Safety
The Final Verdict?

Deborah J. Wexler, MD, MSc

As the options for glucose-lowering medications for patients with type 2 diabetes have expanded, the choices for physicians and patients have become more difficult. Owing to a 2008 US Food and Drug Administration mandate, more than 20 randomized, mostly placebo-controlled, cardiovascular outcomes trials (CVOTs) of new glucose-lowering medications have been published in the last 5 years,[1] prompting a shift in prescribing recommendations for medication management in patients with type 2 diabetes and established atherosclerotic cardiovascular disease.[2] One of the most important findings to emerge from this set of trials—regarding the cardiovascular safety of sulfonylureas—is published in this issue of *JAMA*. A second article, a retrospective cohort study also published in this issue, expands current understanding of the cardiovascular safety of metformin and sulfonylurea use in early chronic kidney disease.

Related articles pages 1155 and 1167

While pharmaceutical companies have been compelled to test the safety of new classes of glucose-lowering medications, no CVOTs have been mandated for older medications, such as metformin and sulfonylureas, the least expensive and most commonly used oral glucose-lowering medications. Metformin has been the first-line recommended glucose-lowering medication for decades based on efficacy, favorable effects on weight, safety, very low cost, and evidence of cardiovascular safety and potentially benefit.[3] Metformin has been the background therapy to which new agents have been added in most patients studied in recent CVOTs.

Sulfonylureas, including glyburide, glipizide, and glimepiride, have demonstrated glycemic efficacy, microvascular benefit, and even potential long-term mortality benefit.[3] While these medications are still recommended in World Health Organization guidelines ahead of newer glucose-lowering medications,[4] the American Diabetes Association-European Association for the Study of Diabetes consensus report recommends sulfonylureas when cost is the primary consideration in medication selection.[2] Despite their long clinical experience and very low cost, the less-favored status of sulfonylureas is due mainly to adverse effects of weight gain and risk for hypoglycemia, as well as long-standing uncertainty regarding their cardiovascular safety. The putative cardiovascular risk associated with sulfonylureas stems from excess cardiovascular mortality observed in a small number of patients treated with a first-generation sulfonylurea, tolbutamide, compared with placebo in the University Group Diabetes Program.[5] This controversial finding has been debated, including in *JAMA*,[6] since the 1970s. A possible mechanism of cardiotoxicity of the sulfonylureas, which act at beta-cell K_{ATP} channels to increase insulin secretion, is cross-reaction with cardiac K_{ATP} channels.[7]

Observational studies and meta-analyses of randomized clinical trials that attempted to evaluate the cardiovascular safety of sulfonylureas compared with metformin have sometimes,[8,9] but not always,[10] supported this concern. Even the most rigorous observational studies of the comparison between metformin and sulfonylureas, however, may be limited by several significant biases. The first, allocation bias (sometimes called confounding by indication), is usually addressed by propensity matching, in which the often substantial differences in baseline characteristics between metformin and sulfonylurea users are balanced for the purposes of the analysis. The second, time-lag bias, in which patients who initiate glucose-lowering medications other than metformin are at a later stage of disease, is much more difficult to address without random assignment of glucose-lowering therapy.[11] Observational studies of sulfonylureas in which metformin is not the comparator tend not to show increased cardiovascular risk.[9]

The perennial concern regarding the cardiovascular safety of sulfonylureas raised by the University Group Diabetes Program more than 40 years ago may finally have been assuaged by the CAROLINA randomized clinical trial published in this issue of *JAMA*.[12] Rosenstock et al for the CAROLINA Investigators included 6033 adults with type 2 diabetes, with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors, aged 70 years and older, or with evidence of microvascular complications. Participants were randomly assigned to linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, 5 mg daily (n = 3023), or the sulfonylurea glimepiride, 1-4 mg daily (n = 3010). The maximum glimepiride dose of 8 mg daily was not part of the protocol. As in the other CVOTs, nonstudy diabetes medications could be intensified or added to maintain glycemic control in both groups. The enrolled population had a mean age of 64 years, with median diabetes duration of 6.3 years and mean glycated hemoglobin level of 7.2%. At baseline, 59% were treated with metformin monotherapy and 42% had established vascular disease.

After a median follow-up of 6.3 years, the rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, was 11.8% in the linagliptin group and 12% in the glimepiride group (hazard ratio, 0.98 [95% CI, 0.84-1.14];

$P < .001$ for noninferiority, $P = .76$ for superiority), with the hazard ratio consistent across all subgroups, including participants with established vascular disease and those aged 70 years and older. There was also no difference in all-cause death, cardiovascular death, or hospitalization for heart failure. Unsurprisingly, the incidence of any hypoglycemia was nearly 5-fold higher in the glimepiride group than in the linagliptin group (11.1 vs 2.3 events per 100 participant-years). Rates of severe hypoglycemia were low: 0.45 per 100 patient-years in the glimepiride group and 0.07 per 100 participant-years in the linagliptin group; hospitalization for hypoglycemia was 0.18 vs 0.01 per 100 participant-years ($P < .001$ for all comparisons). At the end of the trial, weight was 1.54 kg higher in the glimepiride group. Over the course of follow-up, 49.3% of participants in the linagliptin group required additional glucose-lowering medication compared with 47.1% of participants in the glimepiride group, with shorter time to intensification required in the linagliptin group. Rates of study drug discontinuation were similar between intervention groups.

Uniquely among CVOTs, CAROLINA has a sister trial, CARMELINA,[13] that compared linagliptin, 5 mg, with placebo and, like the other DPP-4 inhibitor CVOTs, showed that linagliptin was noninferior to placebo, with no increase in MACE. Taken together, CAROLINA and CARMELINA provide a reassuring signal of the safety and efficacy both of linagliptin, the only DPP-4 inhibitor that does not require dose adjustment for low eGFR, and of glimepiride, an inexpensive, widely available, long-acting sulfonylurea. The results of CAROLINA are consistent with the largest meta-analyses of other randomized clinical trials that have not found increased cardiovascular disease risk when sulfonylureas are used as second-line therapy added to metformin.[10] Whether this result may be generalized to the entire class of sulfonylureas is unknown, although observational studies have not noted differences in cardiovascular risk among glyburide, glipizide, or glimepiride.[11,14]

Also in this issue of *JAMA*, Roumie et al[15] evaluated the hypothesis that compared with sulfonylureas, metformin is associated with reduced risk of an expanded MACE end point among patients with type 2 diabetes and reduced kidney function. The authors reported a rigorously conducted retrospective cohort study of US veterans followed up for at least 2 years within the Veterans Administration system with no diabetes medication for 180 days prior to a new prescription for metformin or a sulfonylurea, including glipizide (54%), glyburide (45%), or glimepiride (1%). The subset of these patients who subsequently developed chronic kidney disease, defined as estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 or creatinine level of 1.4 mg/dL or greater in women or 1.5 mg/dL or greater in men, and continued to receive the originally prescribed medication were included in the cohort.

The unmatched cohort included 67 749 persistent metformin users and 28 976 persistent sulfonylurea users. Although similar to sulfonylurea users in many respects, metformin users were younger (67 vs 71 years); had fewer cardiovascular comorbidities, including congestive heart failure, cardiovascular disease, and elevated urinary albumin-to-creatinine ratio; and reached the kidney function threshold in later study years, all possible indicators of time-lag bias. In the propensity-matched analysis of 24 679 metformin and 24 799 sulfonylurea users, these and other baseline differences were minimized. Nonetheless, with median follow-up of 1.2 years for sulfonylurea users and 1.0 year for metformin users, sulfonylurea users had a higher risk of the study outcome, specifically hospitalization for acute myocardial infarction, stroke, transient ischemic attack, or cardiovascular disease death, with rates of 29.2 per 1000 patient-years with sulfonylureas compared with 23.0 per 1000 patient-years with metformin. The relative risk reduction of 0.80 (95% CI, 0.75-0.86) with metformin compared with sulfonylurea is consistent with findings in other well-conducted observational trials,[9] including a prior study by the same group.[16] The study further supports the use of metformin as the first-line treatment to which other diabetes medications are added, even as early chronic kidney disease develops.

How should clinicians managing hyperglycemia in patients with type 2 diabetes interpret these findings? It is important to keep in mind that all medications have adverse effects. In practice, the risk of hypoglycemia and weight gain with sulfonylureas may be mitigated with individualized glycemic targets[2] and flexible dose adjustment for changes in meal size and physical activity, although these strategies have not been rigorously evaluated. Further evidence on the comparative effectiveness of glimepiride and a DPP-4 inhibitor, a GLP-1 receptor agonist, and basal insulin, each added to metformin, is expected with the publication of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study in 2022.[17] In the meantime, clinicians can continue to use low-cost sulfonylureas added to metformin for management of hyperglycemia in type 2 diabetes with confidence in their effectiveness for reduction of microvascular complications as well as their cardiovascular safety. The adverse effect profile of sulfonylureas and their very low cost must be balanced against characteristics of other glucose-lowering medications as clinicians consider the best approach for an individual patient.

ARTICLE INFORMATION

Author Affiliation: Diabetes Center, Massachusetts General Hospital, Harvard Medical School, Boston.

Corresponding Author: Deborah J. Wexler, MD, MSc, Diabetes Center, Massachusetts General Hospital, Harvard Medical School, 50 Staniford St, Ste 301, Boston, MA 02114 (dwexler@mgh.harvard.edu).

Published Online: September 19, 2019. doi:10.1001/jama.2019.14533

Conflict of Interest Disclosures: Dr Wexler reported serving as a member of a data monitoring committee for Novo Nordisk.

Additional Contributions: I thank David M. Nathan, MD, Massachusetts General Hospital Diabetes Center and Harvard Medical School, for comments on an earlier draft of this article, for which he did not receive compensation.

REFERENCES

1. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? reflections from a

Diabetes Care editors' Expert Forum. *Diabetes Care*. 2018;41(1):14-31. doi:10.2337/dci17-0057

2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018; 41(12):2669-2701. doi:10.2337/dci18-0033

3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359 (15):1577-1589. doi:10.1056/NEJMoa0806470

4. World Health Organization. Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus. https://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf. Published 2018. Accessed August 26, 2019.

5. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes, II: mortality results. *Diabetes*. 1970;19 (suppl):789-830.

6. Bradley RF, Dolger H, Forsham PH, Seltzer H. "Settling the UGDP controversy"? *JAMA*. 1975;232 (8):813-817. doi:10.1001/jama.1975.03250080015008

7. Leonard CE, Hennessy S, Han X, Siscovick DS, Flory JH, Deo R. Pro- and antiarrhythmic actions of sulfonylureas: mechanistic and clinical evidence. *Trends Endocrinol Metab*. 2017;28(8):561-586. doi:10.1016/j.tem.2017.04.003

8. Bain S, Druyts E, Balijepalli C, et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: a Bayesian meta-analysis of survival data. *Diabetes Obes Metab*. 2017;19(3):329-335. doi:10.1111/dom.12821

9. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care*. 2017;40(5): 706-714. doi:10.2337/dc16-1943

10. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA*. 2016;316(3):313-324. doi:10.1001/jama.2016.9400

11. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. *Diabetes Care*. 2017;40 (11):1506-1513. doi:10.2337/dc17-0595

12. Rosenstock J, Kahn SE, Johansen OE, et al; CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial [published September 19, 2019]. *JAMA*. doi:10.1001/jama.2019.13772

13. Rosenstock J, Perkovic V, Johansen OE, et al; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69-79. doi:10.1001/jama.2018.18269

14. 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(2):389-394. doi:10.2337/dc06-1789

15. Roumie CL, Chipman J, Min JY, et al. Association of treatment with metformin vs sulfonylurea with major adverse cardiovascular events among patients with diabetes and reduced kidney function [published September 19, 2019]. *JAMA*. doi:10.1001/jama.2019.13206

16. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2012;157(9):601-610. doi:10.7326/0003-4819-157-9-201211060-00003

17. Wexler DJ, Krause-Steinrauf H, Crandall JP, et al; GRADE Research Group. Baseline characteristics of randomized participants in the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE) [published August 7, 2019]. *Diabetes Care*. doi:10.2337/dc19-0901