A Verdict for Glimepiride: Effective and Not Guilty of Cardiovascular Harm

Matthew C. Riddle

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Amazingly, whether sulfonylureas pose unacceptable risks compared with other treatments for diabetes has been debated for nearly 50 years. Ever since increased mortality was associated with tolbutamide in the University Group Diabetes Program (UGDP) (1), a warning of potential cardiovascular risk for drugs in this class has been mandated. Their tendency to cause both nonsevere and severe hypoglycemia worries patients and providers alike, who fear that hypoglycemia may precipitate serious cardiovascular events. Despite these concerns, sulfonylureas continue to be widely used for type 2 diabetes because they reliably improve glycemic control, lack symptomatic side effects other than hypoglycemia, and are very inexpensive. A recent commentary in *Diabetes Care* questioned whether the modern drugs in this class—glimepiride and gliclazide—deserve the shadow of guilt cast over them by studies of older sulfonylureas (2). They are conveniently dosed once daily and are less likely to cause hypoglycemia than the older agents, especially glyburide (also called glibenclamide). Unlike glyburide, they do not oppose ischemic preconditioning, a cardioprotective mechanism (3), and meta-analytic evidence suggests they are associated with lower rates of cardiovascular events than glyburide (4).

Up to now, high-quality evidence to resolve the risk-versus-benefit debate has been lacking. Epidemiologic analyses of clinical databases and meta-analyses of short-term clinical studies comparing a sulfonylurea with placebo or an active comparator have shown conflicting results (5–8). Some studies comparing sulfonylureas with metformin suggest higher cardiovascular risk with sulfonylureas (9), but it is unclear whether this is because sulfonylureas are harmful or metformin is protective. Experience in the UK Prospective Diabetes Study (UKPDS) favors the latter interpretation. Over 10 years of randomized comparison with a conventional lifestyle-based regimen in the UKPDS, basal insulin or a sulfonylurea did not alter cardiovascular outcomes, whereas metformin reduced cardiovascular and all-cause mortality (10). But because metformin is preferred as the first glucose-lowering drug, the main question is which of the other classes is best suited for use when a given patient no longer maintains glycemic goals with metformin alone.

Only a few large randomized studies with long-term observation have directly tested a sulfonylurea against an active comparator other than metformin. In ADOPT (A Diabetes Outcome Progression Trial) glyburide was compared with rosiglitazone and metformin (11); in ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) gliclazide was compared with a usual-care policy (12); and in TOSCA.IT (Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial) glimepiride, glipizide, and glyburide were compared with pioglitazone (13). None of these studies provided evidence of either increased or decreased cardiovascular risk in the sulfonylurea arm, but each had significant limitations in addressing this question. The main end point in ADOPT was the time to failure of glycemic control, whereas cardiovascular events were few and assessed only as secondary measures. In ADVANCE, the usual-care arm included use of another sulfonylurea by more than half the participants and resulted in less effective glycemic control. In TOSCA.IT the cardiovascular event rate was low and the study ended early due to futility.

Against this background of uncertainty, two recent randomized controlled trials provide strong evidence (14,15). The CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) compared the effects of glimepiride, a modern sulfonylurea, and linagliptin, a dipeptidyl peptidase 4 inhibitor (14). Its stated goal was to test the hypothesis of a potential cardiovascular benefit of linagliptin over glimepiride (16). The trial enrolled 6,033 participants with a 6.2-year median duration of diabetes, most of them previously treated only with metformin. Other therapies were

Division of Endocrinology, Diabetes & Clinical Nutrition, Oregon Health & Science University, Portland, OR

Correspondence to: Matthew C. Riddle, riddlem@ohsu.edu

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adjusted as needed to achieve desired levels of glycemic control over a median follow-up of 6.3 years. Retention in the study, adherence to the masked study drugs, and ascertainment of outcomes were all excellent. Mean baseline HbA_{1c} was 7.2% (55 mmol/mol), and both treatment arms maintained mean values at that level or lower throughout the trial. A 1.5-kg between-treatment difference in change of weight occurred, favoring linagliptin. Rates of hypoglycemia were higher with glimepiride. The primary outcome—a composite of time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke—revealed no difference between treatments. Specifically, the hazard ratio for linagliptin versus glimepiride was 0.98 (95% CI 0.84, 1.14), with *P* for noninferiority <0.0001 and *P* for superiority of linagliptin 0.76. Similarly, no differences in all-cause death or the frequency of hospitalization for heart failure were found. In short, CAROLINA showed equally excellent adherence to treatment and maintenance of glycemic control and no difference in cardiovascular outcomes between linagliptin and glimepiride. We must congratulate the sponsors and investigators for this well-designed and conclusive trial.

Support for the cardiovascular safety of glimepiride is strengthened by the results of CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin), which compared linagliptin with masked placebo (15). This trial enrolled nearly 7,000 participants with type 2 diabetes accompanied by evidence of renal disease and very high cardiovascular risk. The composite primary cardiovascular end point was the same as in CAROLINA, and the analysis also showed a neutral result—neither an increase nor a decrease of risk with linagliptin versus placebo. With linagliptin's neutral cardiovascular effect in CARMELINA, the lack of excess cardiovascular risk with glimepiride versus linagliptin in CAROLINA strongly suggests a neutral effect overall for glimepiride.

These observations provide important lessons for both clinical research and clinical practice. With regard to research, CAROLINA demonstrates once again the importance of randomized controlled trials. Five decades of uncertainty about the safety of sulfonylureas is too long, and retrospective analyses have been unable to resolve it. We finally have strong evidence that at least one modern sulfonylurea is not guilty of increasing cardiovascular risk. An article in the current issue of *Diabetes Care* puts this evidence into further context. Before the results of CAROLINA were reported, but guided by a baseline paper, Patorno et al. (17) aimed to predict the results of this trial by analyzing data from a clinical database. Using information on the characteristics of the population enrolled in CAROLINA, together with aggregated clinical practice data from the U.S., they estimated Cox proportional hazards ratios comparing linagliptin with glimepiride for the main end points of the trial. This effort proved successful with respect to the main conclusions. With both the values estimated from the clinical database and those from CAROLINA, no significant between-treatment differences were demonstrated for the primary end point and all-cause mortality. For the primary end point, the predicted hazard ratio value was 0.91 (CI 0.79–1.05) and the actual value 0.98 (0.84–1.14). For all-cause mortality, the predicted value was 0.96 (0.79–1.17) and the actual value 0.91 (0.78–1.06). This reasonably accurate prediction of the results of CAROLINA provides further reassurance regarding the safety of glimepiride in clinical use. It also suggests that, with improved quality of data collection and analysis, aggregated data from clinical practice may in the future provide more reliable information about outcomes of therapies than was available in the past.

Additional insight into the relative effects of glucose-lowering therapies early in type 2 diabetes will be provided by Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). A baseline description of GRADE appeared in last month's issue of *Diabetes Care* (18). This trial is an ongoing, 5-year, open-label randomized comparison of glimepiride, sitagliptin, liraglutide, or insulin glargine, each added to prior metformin for type 2 diabetes. The primary end point is the time to requirement of treatment intensification, but other outcomes will be assessed. The 5,047 participants enrolled have a shorter duration of diabetes (median 3.8 versus 6.2 years) and lower cardiovascular risk and frequency of albuminuria than those in CAROLINA, and they may have lower risks of hypoglycemia or cardiovascular events. Results of GRADE should further clarify the roles of modern sulfonylureas and dipeptidyl peptidase 4 inhibitors for patients typically seen in clinical practice.

Most importantly, CAROLINA's findings are already relevant to clinical practice. Both masked study drugs were said to be taken by participants 94% of the potential time of usage in the study, a remarkably high rate of adherence. Discontinuations considered to be possibly due to the drug occurred in only 14% of participants taking either drug during 6 years of observation. Hospitalization due to hypoglycemia occurred in 0.9% of participants taking glimepiride over the same interval. Risk of hospitalization for heart failure with linagliptin was not statistically different from that with glimepiride in CAROLINA or placebo in CARMELINA. Thus, high tolerability and safety were confirmed for both glimepiride and linagliptin, supporting the use of either as a second agent following metformin when maintaining glycemic control to prevent complications of diabetes is the main goal.

Some limitations must also be noted. Whether the conclusions regarding glimepiride and linagliptin can be extended to other drugs in each class is unknown. Observations from this trial cannot be extrapolated confidently to the longer term. Benefits or disadvantages that were not detected within 6 years could become apparent after longer observation. Also, the frequency of hypoglycemia accompanying use of glimepiride in CAROLINA—a fivefold increase of hypoglycemia documented <70 mg/dL (3.9 mmol/L), mostly in the first year—cannot reliably be extrapolated to routine clinical practice. Because the mean HbA_{1c} at baseline was 7.2%, many participants had HbA_{1c} $<7.0\%$ (53 mmol/mol) at entry yet were assigned an aggressive titration regimen. Those randomized to glimepiride started with 1 mg daily, a substantial dose that produces about two-thirds of the effect expected with the 4 mg dose (19), and dosage was to increase at each monthly visit if the fasting glucose that day was higher than 110 mg/dL (6.1 mmol/L). In clinical practice, an additional oral therapy is likely to be added only when HbA_{1c} is at least 7.0%, and dosage is usually increased when HbA_{1c} is not restored to a target level after 3 months, rather than

force-titrated to a fasting glucose target at shorter intervals. With the less aggressive dosing generally used in clinical practice, the frequency of hypoglycemia with glimepiride is likely to be substantially lower than in this trial.

However, the main conclusion from CAROLINA is clear. At least one sulfonylurea—glimepiride—is not guilty of increasing short-term cardiovascular risk. There are other potential reasons to choose linagliptin over glimepiride, especially less hypoglycemia, or glimepiride over linagliptin, especially lower cost, but a difference in cardiovascular risk need no longer be a consideration. This will be good news for many physicians and people with diabetes who can now more confidently use either agent to maintain glucose control with the aim of limiting microvascular complications.

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