Modern Sulfonylureas: Dangerous or Wrongly Accused?

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Except for insulin, sulfonylureas and biguanides are the best studied and most widely used glucose-lowering agents. However, neither class of drugs has had an easy life because of concern about safety. Phenformin, a biguanide, was associated with lactic acidosis and withdrawn from use (1) after causing increased mortality in the University Group Diabetes Program (UGDP) (2). The UGDP also found a sulfonylurea, tolbutamide, to be associated with increased mortality (3). Since then, a newer biguanide, metformin, has risen to its current place as the leading oral therapy for diabetes based on its relative lack of hazard from lactic acidosis and evidence, especially from a subgroup of participants in the UK Prospective Diabetes Study (UKPDS), that it can reduce cardiovascular risk and mortality (4,5). Even though the main randomized comparison in the UKPDS (sulfonylurea or insulin vs. lifestyle therapy) showed that cholorpropamide, glyburide, or glipizide also can reduce medical risks (5,6), the reputation of all sulfonylureas has remained tarnished. A warning of "increased risk of cardiovascular mortality" remains in their labeling information. Treatment guidelines and publications reporting effects of new drugs in other classes often emphasize the risk of hypoglycemia and weight gain from sulfonylureas. And yet, at least 25% of patients with type 2 diabetes are using sulfonylureas (7,8), presumably because they are very inexpensive, allow once-daily oral dosing, reliably reduce glucose, and rarely cause symptomatic side effects other than hypoglycemia. More than 40 years after the UGDP, their risks versus benefits are still debated (9–11). Statistical assessments of data pooled from randomized studies and clinical databases continue to be published, with conflicting conclusions (12,13).

This issue of *Diabetes Care* includes a thoughtful contribution to this discussion by Azoulay and Suissa (14). These experienced epidemiologists describe the potential pitfalls in designing and interpreting analyses of observational (real world) data on treatment with sulfonylureas or other agents. They identify three difficulties. The first is "exposure misclassification," a failure to identify the time each patient is actually taking the drug in question. A second is "time-lag bias," in which the analysis does not account for the effect of studying patients at earlier versus later stages of diabetes. The third is "selection bias," resulting from exclusion of certain patients because of changes of regimen or clinical events during the period of observation. After assessing 20 observational studies of patients with type 2 diabetes who were using sulfonylureas, they judged that only 6 were free of these kinds of bias. They found cardiovascular risk to be increased during treatment with a sulfonylurea (relative risk 1.53, 95% CI 1.43–1.65) in studies with an identified potential bias, metformin as comparator, and mortality as the outcome. Relative risk was not increased (1.06, 95% CI 0.92–1.23) in studies with no major bias, a comparator other than metformin, and all cardiovascular events as the outcome. Presumably these differences contribute to the inconsistency of the literature.

The authors further commented on difficulties posed by properties of the treatment to which sulfonylureas are compared. All the studies judged free of bias compared use of a sulfonylurea with metformin, except one that compared sulfonylurea plus metformin with metformin alone. The bias-free studies directly comparing sulfonylureas with metformin showed more frequent deaths or cardiovascular events during treatment with a sulfonylurea (relative risk ranged from 1.16 to 1.55, with lower boundaries of the 95% CI above 1.00). A possible interpretation of this finding is that sulfonylureas increase cardiovascular risk. An alternative is that metformin is beneficial, while sulfonylureas have a neutral effect. The cardiovascular benefit of metformin in the UKPDS supports the second interpretation. The bias-free study that included metformin in both arms showed no difference in risk, also suggesting a neutral effect of the sulfonylurea. Because metformin, with its favorable

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Table 1—Arguments for and against the modern sulfonylureas

	For the prosecution	For the defense	Evidence yet to be presented
Ischemic preconditioning	Tolbutamide and glyburide interfere with ischemic preconditioning	Gliclazide, glipizide, and glimepiride do not alter ischemic preconditioning	
Hypoglycemia	Hypoglycemia and weight gain occur with all sulfonylureas	Gliclazide, glipizide, and glimepiride cause less hypoglycemia than glyburide	
Observational studies	Cardiovascular risk is higher with sulfonylureas vs. comparators in some studies	Cardiovascular risk is mainly higher vs. metformin, which decreases risk	Studies with better design to limit bias
Randomized studies	Short-term mortality was increased with tolbutamide in UGDP	Long-term mortality was decreased with glyburide, chlorpropamide, and glipizide in UKPDS	CAROLINA (glimepiride vs. linagliptin) GRADE (glimepiride vs. other second-line agents)

The modern sulfonylureas—gliclazide, glipizide, and glimepiride—are accused of "increased risk of cardiovascular mortality." The table summarizes the main arguments for prosecution and defense, including evidence from studies of older sulfonylureas.

cardiovascular effects, is the preferred first-line oral agent, a sulfonylurea would most helpfully be compared not with metformin but with alternative second-line therapies.

To summarize, the main findings of Azoulay and Suissa (14) suggest that some of the harm attributed to sulfonylureas may be related to unintended bias in the design or interpretation of studies rather than an effect of this class of agents. Their description of several categories of bias is illuminating and could improve the design of future analyses of observational data. However, some related questions deserve further comment.

One problem lies in the assumption that all sulfonylureas are alike. Sulfonylureas differ in at least two ways that are relevant to cardiovascular risk. One concerns an effect on vascular K_{ATP} channels that interferes with ischemic preconditioning and may increase the risk of cardiac events. This undesired effect occurs with tolbutamide and glyburide but not with gliclazide, glipizide, or glimepiride (15). Whether this difference alters cardiovascular outcomes is not well established, but some evidence suggests it does. A well-conducted, prospective observational study evaluated risks associated with sulfonylureas versus other therapies used by patients admitted to hospitals throughout France for myocardial infarction (16). A multivariable analysis showed that sulfonylureas (as a class) were associated with lower rather than higher mortality from the event (odds ratio 0.50, 95% CI 0.27–0.94, P = 0.03). When individual sulfonylureas were compared, the risk of early mortality was 85% lower for patients who were taking gliclazide or glimepiride than for those taking glyburide (odds ratio 0.15, 95% CI 0.04–0.56, $P < 0.005$). There is also evidence that glyburide causes more hypoglycemia than other currently used agents. A dramatic example is an analysis of emergency department admissions for hypoglycemia in Germany that showed >80% fewer events with glimepiride than glyburide (0.86 vs. 5.6 events per 1,000 patient-years) (17).

Another issue not emphasized by Azoulay and Suissa (14) is selection bias related to the clinician's judgement in choosing a treatment well suited to an individual patient. Treatment allocation bias creates an imbalance that is difficult to neutralize by statistical methods, including calculation of a propensity score, especially in databases lacking detailed information on concurrent illnesses. It is a persistent limitation of observational studies and can be entirely avoided only by random allocation of treatment.

For these reasons, both well-designed observational studies focused on the newer sulfonylureas and randomization comparisons are needed. Notably, it would be good to know whether cardiovascular risk differs when a dipeptidyl peptidase 4 inhibitor is used as second-line therapy instead of a sulfonylurea. This new newer and more expensive class of oral agents is proposed to be safer than sulfonylureas (18) and appears to have little effect on cardiovascular outcomes generally but (at least in the case of saxagliptin) may increase heart failure. The randomized CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) is directly addressing this question (19). Also, in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), treatment with glimepiride or alternative agents is randomly allocated (20).

Meanwhile, metaphorically, the jury is still deliberating as to whether all sulfonylureas are unsafe based on worrisome evidence from studies of tolbutamide and glyburide (Table 1). Gliclazide, glipizide, and glimepiride are reliably effective in lowering glucose, but are they too dangerous to use? As suggested by Azoulay and Suissa (14), more skillful analysis of observational data are possible, and some randomized trial experience is soon to be reported. If new evidence supports a not guilty verdict, the modern sulfonylureas should regain respect and continue to be an important option for controlling glucose.

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