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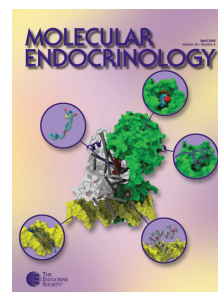
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More Reasons to Say Goodbye to Glyburide

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Sulfonylureas have been used to control hyperglycemia in type 2 diabetes longer than any class of agents except insulins. Their use early in the course of diabetes is supported by evidence of long-term medical benefit (1), and although available in generic form and thus not commercially promoted, they are widely prescribed (2). Given these facts, it is surprising that much remains unknown about these agents, notably how the various members of the class should be deployed in current treatment algorithms.

An article by Zeller *et al.* in this issue of *JCEM* (3) sheds considerable light on this question. The authors report analyses of prospectively collected data from a French registry concerning experience of patients with type 2 diabetes who were hospitalized for myocardial infarction. The question posed was what association, if any, might exist between prior use of sulfonylureas and death and other in-hospital outcomes in these patients. Analyses included comparisons between the individual sulfonylureas used in this population: glyburide (called glibenclamide in Europe), glimepiride, and gliclazide (in most cases given as an extended-acting formulation). The rationale for the study came from the known adverse effect of glyburide on cardiac ischemic preconditioning, the clinical relevance of which has been uncertain. One key finding of the French study was that, among the 1310 acutely ill patients studied, unadjusted mortality rates were lower for those whose treatment on admission included a sulfonylurea (3.9%) than for those taking insulin (9.4%), those on no antihyperglycemic drugs (8.4%), and those on oral therapies other than sulfonylureas (6.4%). Another was that when patients taking glyburide were compared with those taking gliclazide or glimepiride, two sulfonylureas that appear to lack cardiac effects, early mortality was almost 3-fold higher (7.5 *vs.* 2.7%) with glyburide. It is well

known that epidemiological analyses of “real-world” experiences with prescribed pharmacotherapy may be confounded by incomplete collection of information on actual drug usage, concomitant therapies, and medical outcomes, in addition to biases introduced by physicians’ tendencies to assign different treatments to different kinds of patients. Many of these problems were reduced or eliminated by the prospective design of this study, which included systematic recording of detailed clinical information on all patients in a narrow window of time by a structured team of investigators. The problem of allocation bias in assignment of treatments, however, remains in this study as in others. Hence, the authors used several statistical methods to adjust for this kind of confounding, including an extensive multivariable model, further adjustment using a propensity score for assignment to glyburide treatment, and analysis of findings with glyburide *vs.* the other sulfonylureas by subgroups. These statistical adjustments did not alter the associations of sulfonylurea use with lower mortality than other forms of therapy, and of glyburide use with higher mortality than seen with the other sulfonylureas. The excess of mortality with glyburide *vs.* other sulfonylureas showed no tendency toward heterogeneity between subgroups. Thus, several approaches to testing the validity of the observations were supportive, and the magnitude of the effects was substantial. After multivariable adjustment, the risk of death accompanying use of a sulfonylurea was half that when a sulfonylurea was not used (odds ratio, 0.50; 95% confidence interval, 0.27–0.94; $P = 0.03$). After similar adjustment for covariates, the risk of early mortality was 85% lower with glimepiride or gliclazide than with glyburide (odds ratio, 0.15; 95% confidence interval, 0.04–0.56; $P < 0.005$), and with the propensity score included in the model, the risk was 87% lower (odds ratio, 0.13; 95% confidence interval, 0.21–

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0.72; $P = 0.003$). Similar patterns were apparent for nonfatal cardiovascular complications.

Among many epidemiological studies, why is this one important? First, it asks a tightly focused question: do sulfonylureas in general and glyburide in particular alter the risk of death or other complication associated with an ischemic cardiac event? Second, it includes a relatively large number of patients quite representative of the whole population of a single country. Third, data collection was prospectively designed and therefore more complete and accurate than is possible in a retrospective analysis of a database. Fourth, the analytic scheme was appropriate and detailed. Although the possibility of residual allocation bias cannot be ignored, it is a very good study. It is the latest in a series of reports showing that glyburide differs from other widely used sulfonylureas. The story goes back to the University Group Diabetes Program (UGDP) study, in which the sulfonylurea tolbutamide appeared to increase mortality in type 2 diabetes (4). Since then, tolbutamide has rarely been used. Later studies showed that some secretagogues can interact with K_{ATP} channels not only in the β -cell but also in the heart and thereby interfere with ischemic preconditioning, a normally protective adaptation to prior ischemia, providing a plausible mechanism for the UGDP results. This unwanted effect is caused by glyburide (5–8), but not by glimepiride (5, 6), gliclazide (7), or glipizide (8). The present study brings the story all the way to clinical practice, providing strong, although not conclusive, evidence of clinical risk from glyburide relative to other sulfonylureas. In this it is consistent with the results of a similar epidemiological study that used a less reliable retrospective design (9).

This additional evidence may be sufficient to call for discontinuing use of glyburide, as has previously been proposed (10, 11). Animal studies and human physiological and epidemiological data are all consistent with increased cardiovascular risk with glyburide relative to other agents in its class. In addition, glyburide differs from other sulfonylureas in another way: it causes more hypoglycemia. In the early years of the United Kingdom Prospective Diabetes Study (UKPDS), participants recently diagnosed with type 2 diabetes were randomized to treatment with diet, metformin, chlorpropamide, glyburide, or insulin. In the first year, the percentages of participants reporting hypoglycemia with these treatments were 0.6, 8, 15, 36, and 34%, respectively (12). Thus, glyburide caused as much hypoglycemia as insulin and twice as much as chlorpropamide, a sulfonylurea now rarely used due to various side effects, among them serious hypoglycemia. This pattern was the same for major hypoglycemia and persisted over the first 3 yr. Higher risk of hypoglycemia with glyburide has been confirmed in other reports. In a review of 33,243 patients

using a sulfonylurea in the United Kingdom, the risk of clinically reported hypoglycemia, after adjustment for covariates, was 40% lower with glipizide and 26% lower with gliclazide than with glyburide (13). A population-based study in a part of Germany where the only sulfonylureas used were glyburide and glimepiride found that severe hypoglycemia leading to care in an emergency room was much less frequent with glimepiride (0.86 vs. 5.6 events per 1000 patient-years) (14). Therefore, glyburide has well-documented differences from other sulfonylureas in causing hypoglycemia and interfering with ischemic preconditioning, and now also good epidemiological evidence for an association with greater mortality in vulnerable populations. Even so, it is still often prescribed.

More evidence distinguishing glyburide from other sulfonylureas is not the only important finding in the report of Zeller *et al.* (3). The further observation that early mortality after myocardial infarction was 50% lower when the patient was taking a sulfonylurea is at odds with widespread beliefs. It must be acknowledged that bias in treatment assignment to metformin, insulin, a sulfonylurea, or other antihyperglycemic agents is more likely to elude efforts to adjust for it in statistical models than is bias in assignment to one or another sulfonylurea. Even so, the highly significant association of lower risk of death after myocardial infarction during sulfonylurea therapy in this study is quite different from what has been reported in earlier studies that compared sulfonylureas with other therapies, especially metformin (15–17). In those studies, which have suggested that sulfonylurea therapy leads to increased cardiovascular risk compared with metformin, glyburide was the most frequently used or only sulfonylurea, yet the results have been assumed to apply to all sulfonylureas. The present study, in which glyburide was used less by less than one third of those taking a sulfonylurea, suggests that this assumption may not be valid. The balance of benefits vs. risks and costs with sulfonylureas relative to other classes of agents is not a trivial concern. Treatment for type 2 diabetes is complex, costly, often unsuccessful, and a topic of current debate. Considerable resources are devoted to promoting newer but less well-tested therapies, such as thiazolidinediones, GLP-1 (glucagon-like peptide-1) agonists, and DPP-4 (dipeptidyl peptidase-4) inhibitors, which are still under patent protection and therefore potentially very profitable. Sulfonylureas are inexpensive, easy to use, and have proven medical benefits. They deserve adequate consideration as well. Well-designed randomized studies are needed.

One large, long-term randomized study including a sulfonylurea was recently completed (18). This study, called ADOPT, examined the effects of glyburide rather than a newer sulfonylurea. The aim of ADOPT was to assess the

persistence of glycemic control with rosiglitazone in comparison with metformin and glyburide, using the time until fasting glucose rose above 180 mg/dl as the primary endpoint. Thus defined, monotherapy failure occurred earliest with glyburide and latest with rosiglitazone. With hemoglobin A1c, a more revealing endpoint, the differences between the treatments were less obvious, and glyburide produced more improvement in the first year. In the UKPDS, similarly, more rapid loss of glycemic control was observed among participants randomized to glyburide relative to metformin, but the greatest persistence of glycemic control was observed not with metformin but with another sulfonylurea, chlorpropamide, which contributed as many participant-years to the study as did glyburide (19). Although ADOPT was not intended to identify medical outcomes, safety findings were reported. Glyburide caused the most hypoglycemia and 1.6-kg weight gain (*vs.* a 4.8-kg gain with rosiglitazone and weight loss with metformin), but serious cardiovascular events were, if different at all, less frequent with glyburide (26 events) than with metformin (46 events) or rosiglitazone (49 events). We must wonder what ADOPT might have shown had glimepiride or extended-release formulations of gliclazide or glipizide been studied instead of glyburide. We should reconsider the balance of benefits *vs.* risks accompanying use of these sulfonylureas. Suppose a new drug were proposed for clinical use with properties including very low cost, once-daily oral administration, glucose-lowering power equal to metformin, few side effects other than hypoglycemia and moderate weight gain, and similar (possibly less) cardiovascular risk than other available drugs? Would we not take it seriously? At present these appear to be the properties of modern sulfonylureas.

In conclusion, the report by Zeller *et al.* (3) draws attention to important questions about the role of sulfonylureas in medical practice. These include whether glyburide should continue to be used despite safety concerns and how other sulfonylureas should be placed in treatment algorithms. To the first question I propose that, just as we said farewell to phenformin (20) and allowed metformin to demonstrate its superior qualities, we say goodbye to glyburide. To answer the second question, we need comparative effectiveness studies that directly compare modern sulfonylureas (gliclazide, glimepiride, or glipizide), not glyburide, with metformin and with newer agents. Why let one bad apple spoil the whole barrel?

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