Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? Yes, They Continue to Serve Us Well!

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Diabetes Care 2015;38:166–169 | DOI: 10.2337/dc14-1945

Since their introduction to clinical practice in the 1950s, sulfonylureas have been widely prescribed for use in patients with type 2 diabetes. Of all the other medications currently available for clinical use, only metformin has been used more frequently. However, several new drug classes have emerged that are reported to have equal glucose-lowering efficacy and greater safety when added to treatment of patients in whom metformin monotherapy is no longer sufficient. Moreover, current arguments also suggest that the alternative drugs may be superior to sulfonylureas with regard to the risk of cardiovascular complications. Thus, while there is universal agreement that metformin should remain the first-line pharmacologic therapy for those in whom lifestyle modification is insufficient to control hyperglycemia, there is no consensus as to which drug should be added to metformin. Therefore, given the current controversy, we provide a Point-Counterpoint on this issue. In the point narrative presented below, Dr. Abrahamson provides his argument suggesting that avoiding use of sulfonylureas as a class of medication as an add-on to metformin is not appropriate as there are many patients whose glycemic control would improve with use of these drugs with minimal risk of adverse events. In the following counterpoint narrative, Dr. Genuth suggests there is no longer a need for sulfonylureas to remain a first-line addition to metformin for those patients whose clinical characteristics are appropriate and whose health insurance and/or financial resources make an alternative drug affordable.

—William T. Cefalu
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While the majority of published guidelines for the pharmacologic treatment of type 2 diabetes strongly endorse metformin as first-line therapy for those whose glycemic control is not adequate on lifestyle modification alone, they do not recommend any specific agent to add to metformin when monotherapy fails. Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) identify all the therapeutic options for clinicians and reinforce the "individualization" of choice based on factors that include safety, efficacy, cost, and tolerability (1,2). The AACE guidelines do, however, suggest a hierarchy of use of medications, identify which drugs should be used with caution, and recommend initial combination therapy when the HbA_{1c} exceeds 7.5% (2).

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There remains no clear consensus, however, regarding which drug is the most appropriate to add to metformin to achieve therapeutic goals.

There has been a call to avoid using sulfonylureas (SUs) as an add-on to metformin because of concerns regarding long-term safety of this class of medication, notably cardiac safety and the risk of hypoglycemia. But how valid is this argument? Is use of SUs associated with severe adverse cardiac events? How strongly is hypoglycemia associated with SUs, and do all medications in this class cause hypoglycemia with the same frequency? Should SUs really be relegated to a less acceptable alternative to other drugs, especially at a time when costs of medical care are skyrocketing and these drugs are cheap and very effective? Furthermore, the call to use this class of medication less frequently comes at a time when we as a society have made little headway in increasing the percentage of people who are achieving the desired HbA_{1c} goal of $<7\%$, let alone $\leq 6.5\%$, which is the goal of ADA and AACE (1,2). How "dangerous" are SUs? Should they remain an acceptable add-on to metformin when metformin therapy alone is inadequate to achieve therapeutic goals?

Let us first examine the issue of hypoglycemia. Severe hypoglycemia has been reported in approximately 1 in every 100 people treated with SUs. This contrasts with 1 in 10 people treated with insulin and 1 in 2,000 treated with metformin (3). A number of landmark clinical trials in which SUs have been used also have evaluated the prevalence of hypoglycemia. In the UK Prospective Diabetes Study (UKPDS), the rate of severe hypoglycemia was about 0.5% in the SU-treated group. A total of 11% of subjects taking chlorpropamide and 17.7% of people taking glyburide had more than one episode of hypoglycemia per year (4). Glyburide and chlorpropamide were associated with a severe hypoglycemia rate of 1.4 events and 1.0 events per year, respectively (in the intensively treated group of subjects), as compared with a 1.8 event rate in those taking insulin. In the A Diabetes Outcome Progression Trial (ADOPT), in which glyburide was compared with metformin and rosiglitazone as monotherapy, just under 30% of subjects randomized to SU treatment reported symptoms of minor hypoglycemia during the 5 years of study, yet only 0.6% experienced episodes of severe hypoglycemia (5). Not all SUs are, however, associated with such high rates of hypoglycemia. Glyburide is unequivocally associated with more frequent and severe hypoglycemia than other insulin secretagogues in this class, including glipizide and glimepiride. In a meta-analysis comparing glyburide with other SUs, glyburide was associated with a 1.44 times relative risk increase in overall hypoglycemic events and 4.69 increased risk for severe hypoglycemia (6). Increased risk of hypoglycemia occurs in patients with chronic renal impairment and the elderly. And the most common causal factors were poor nutrition or a missed meal (7). Hence, it is appropriate that glyburide be avoided in these population groups. This becomes even more important as it is well known that hypoglycemia has a negative impact on patients' health status and may result in increased health care utilization and cost (8).

The belief that SU use may be associated with adverse cardiac events dates back to the 1970s when it was reported that tolbutamide use in the University Group Diabetes Program (UGDP) was associated with a greater risk of adverse cardiac events (9). It turns out that subjects randomized to tolbutamide use had experienced more cardiac events at the time the study was initiated and that subsequent review of the data did not support the initial claims. The rationale for associating SU use with adverse cardiac outcomes is based on the mechanism of action of these drugs—by binding to the SUR1 receptor on pancreatic β-cells, closure of the K_{ATP} channels occurs. This leads to a rise in intracellular calcium, which in turn results in insulin exocytosis. K_{ATP} channels are present in a number of other cells including cardiac myocytes, neurons, and smooth muscle cells. In theory, binding of SU to K_{ATP} channels in cardiomyocytes results in inhibition of the protective impact of ischemic preconditioning, a phenomenon that causes worse cardiac outcomes following myocardial ischemia or infarction (10). Glyburide has been shown to inhibit ischemic preconditioning in vitro, but neither glimepiride nor glipizide has been shown to do this in vitro (11). Indeed, these latter two agents bind to the K_{ATP} channels on cardiac myocytes with less affinity than glyburide and have a higher selectivity for binding the K_{ATP} channel on the pancreatic β-cell. In clinical studies, use of SUs has not been associated with adverse cardiovascular outcomes. In the UKPDS, there was a nonsignificant 16% decrease in myocardial infarction rates in patients treated intensively with SUs at the end of the study but a significant 15% decrease in events in these subjects when evaluated 10 years after the end of the original study, despite the fact that they continued to take SUs and their metabolic control had been the same as the conventionally treated group within a year of completion of the original study (12). The ADOPT study failed to show any significant increase in cardiovascular events in the glyburide-treated cohort. In the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study, there was no difference in mortality or cardiovascular events in subjects randomized to treatment of diabetes with either insulin-sparing or insulin-providing therapies (insulin and/or SUs) (13). Retrospective studies of patients admitted to hospital with myocardial infarctions have failed to show greater mortality rates in those who were taking SU at the time of admission (14). In a comparative effectiveness study, metformin use was associated with fewer cardiac events than SU use, but this may be because metformin therapy reduces cardiac events rather than because SU use increases cardiac events (15). Finally, there is no evidence that use of SUs is associated with increased rates of congestive heart failure (CHF).

SUs are certainly effective glucose-lowering agents. In a recent meta-analysis of studies in which SUs were used as monotherapy or in combination with other medications, there was an average 1.5% reduction in HbA_{1c} in nine studies lasting up to 36 months (SU monotherapy vs. placebo) and a 1.6% decrease in HbA_{1c} in four large studies in which SUs were added to patients taking either metformin or thiazolidinediones (TZDs) (16). In the ADOPT study, in which SU use was compared with metformin and the TZD rosiglitazone, there was a greater reduction in HbA_{1c} at 6 months in the group taking glyburide compared with both metformin and rosiglitazone. By the end of the study, a significantly

higher percent of subjects taking glyburide had failed monotherapy compared with both metformin and rosiglitazone, but a detailed analysis of this study revealed that for the first 3 years of the study the glucose-lowering efficacy of all three drugs studied was similar (17). As glyburide use led to a more rapid decrease in glucose initially and as there is compelling evidence to treat patients with newly diagnosed type 2 diabetes more aggressively during the first years after diagnosis (because of the so-called legacy effect), use of SUs may well be appropriate, indeed preferred, to other drugs at this stage of the disease. There are no head-to-head long-term studies comparing SU therapy to other medications as an add-on to metformin to determine which medications are more effective or "durable," but some short-term studies have demonstrated equivalent efficacy to the glucose-lowering effects of SUs. No studies have exceeded 2 years' duration, which provides inadequate time to evaluate newer drugs for long-term side effects or durability of glucose-lowering effects. In the Liraglutide Effect and Action in Diabetes 2 (LEAD 2) trial, 4 mg of glimepiride daily was as effective as liraglutide 1.2 or 1.8 mg daily in lowering HbA_{1c} in subjects taking metformin (18). Glimepiride also has been shown to be as effective as the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin when added to metformin in patients suboptimally controlled on metformin alone (19). Longer-term studies would, of course, be welcomed to determine whether or not newer drugs are as safe and effective as SUs. The results of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), currently under way, should help elucidate the comparative effectiveness of SUs, DPP-4 inhibitors, GLP-1 receptor agonists, and basal insulin as add-ons to metformin in subjects not achieving therapeutic goals with metformin alone (20). It should be noted, however, that sodium–glucose cotransporter 2 (SGLT2) inhibitors were not included in the study as they had not been approved for clinical use when the study was initiated.

If cost of medications needs to be considered when determining what drug to add to metformin, SU would be the preferred class of medication. In the U.S., medications to treat diabetes cost approximately $18 billion annually (21). The cost–benefit evaluation of medications needs to take into account the relative risk of hypoglycemia and its consequences. SUs, when added to metformin, have been shown to be the most cost-effective medication, taking into account cost of drug, improvement in glycemic control associated with the drug, and low absolute risk of severe hypoglycemic episodes requiring medical intervention but more frequent episodes of mild hypoglycemia (22).

SU use is associated with weight gain, which is recognized as an undesirable effect of treatment. It is recognized that there are other medications that could be used as an alternative to SUs that are either weight-neutral or their use may be associated with weight loss. It is accepted that for the majority of people with type 2 diabetes, weight loss should be encouraged, primarily through changes in lifestyle. Furthermore, there is clear evidence that significant weight loss (achieved through intensive "medical" therapy or with bariatric surgery) improves glycemic control with use of fewer medications and may even result in resolution of diabetes and less need to treat other cardiovascular risk factors (23). There are no data, however, that weight gain associated with use of some glucose-lowering medications (primarily insulin, TZDs, and SUs) is associated with worse outcomes when compared with medications that are associated with no change or loss in weight at equivalent reductions in HbA_{1c}.

SUs are very well tolerated apart from weight gain and the low absolute increased risk of hypoglycemia but moderate risk of mild hypoglycemia. Unfortunately, no medication used to treat diabetes is free of side effects. TZD use is also associated with weight gain, increased risk of CHF, long bone fractures in women, and a possible increased risk of bladder cancer. DPP-4 inhibitors may increase risk of hospitalization for CHF and may increase the risk of pancreatitis. GLP-1 analogs may cause gastrointestinal side effects and may increase risk for pancreatitis. There is an increased risk of urinary tract and mycotic vaginal infections, polyuria, and orthostasis when SGLT2 inhibitors are used. And insulin use is associated with weight gain and a greater risk of hypoglycemia than SUs, which in turn are associated with a greater risk of hypoglycemia than the other medications listed in Table 1 (24). The risk–benefit ratio needs to be considered when determining the most appropriate medication to add to metformin.

In summary, SUs have been in clinical use for approximately 60 years. They are very effective glucose-lowering medications, but their use is unquestionably associated

Table 1—Comparison of medications that could be added to metformin

	SU	TZD	DPP-4	GLP-1	SGLT2	AGI	Colesevelam	Cycloset	Insulin
Efficacy	High	High	Moderate	High	High	Moderate	Moderate	Moderate	High
Major side effects	Well tolerated	Edema, CHF, fractures	Pancreatitis (rare)	Nausea, vomiting, pancreatitis (rare)	UTI, vaginal yeast infection, polyuria, orthostasis	Flatulence, diarrhea	Well tolerated	Nausea, vomiting	Well tolerated
Hypoglycemia risk	Moderate	Low	Low	Low	Low	Low	Low	Low	High
Weight	Gain	Gain	Neutral	Loss	Loss	Neutral	Neutral	Neutral	Gain
Cardiovascular safety	Neutral	Neutral	Neutral	Neutral	Unknown	May lower MACE	Neutral	May lower MACE	Neutral
Cost	Low	Low	High	High	High	Moderate	Moderate	Moderate	Variable

AGI, α-glucosidase inhibitors; MACE, major adverse cardiovascular events; UTI, urinary tract infection.

with an increased risk of hypoglycemia, particularly in certain population groups, such as those with renal impairment and the elderly. Glyburide is associated with far greater rates of severe hypoglycemia than either glipizide or glimepiride. As a class, these drugs have not been associated with deleterious cardiovascular outcomes, and in vitro studies have failed to demonstrate inhibition of ischemic preconditioning with either glimepiride or glipizide. It is reasonable to avoid using glyburide in any patient as an add-on to metformin as both glimepiride and glipizide have better safety profiles. However, avoiding use of SUs as a class of medication as an add-on to metformin is not appropriate as there are many patients whose glycemic control would improve with use of these drugs with minimal risk of adverse events. Understandably, not every person with type 2 diabetes would be an ideal candidate for treatment with an SU when metformin alone provides insufficient glycemic coverage. As noted, such patients include the elderly who are at higher risk of deleterious consequences of hypoglycemic events, even mild ones. Choosing the most appropriate patients to use these medications is something that the practicing clinician needs to do. Furthermore, starting SU at a low dose and escalating the dose to submaximal doses that are as effective as maximal doses in those who warrant such escalations could help more people achieve therapeutic goals more rapidly, especially early after diagnosis, and thus reduce the long-term consequences of this disorder. A similar conclusion was reported in a recent published consensus report from *Diabetes Care* that suggested that "the ideal antihyperglycemic agent would be easy to administer, unlikely to cause symptomatic side effects that pose barriers to adherence, inexpensive, reliably efficacious, and safe. By such standards, it can be argued that the remaining modern SUs do well (although they do leave some clinical needs unmet)" (25).

Duality of Interest. M.J.A. serves on the advisory boards of Novo Nordisk, Janssen Pharmaceuticals, WebMD Health Services, and Halozyme. No other potential conflicts of interest relevant to this article were reported.

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