Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? No, It's Time to Move On!

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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 preceding point narrative, 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 counterpoint narrative below, 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.

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Editor in Chief, *Diabetes Care*

In 2012 guidelines for treatment of type 2 diabetes (T2DM) (1), the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly recommended metformin as the initial drug to prescribe after nutritional therapy and exercise had proven inadequate (Fig. 1). Their algorithm specifies five drug classes to choose from when something must subsequently be added to metformin—sulfonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 agonists, and insulin. They state that no priority is intended by the order in which the five classes are listed. Thus, SUs are recommended as a coequal class from which physicians can choose to add to metformin.

SUs have been a mainstay of T2DM treatment since the 1950s (2), though their use by patients has declined from 61% in 1997 to 22% in 2012 as metformin use increased from 24 to 53% (3). The combination was found to lower HbA_{1c} 1% more than either

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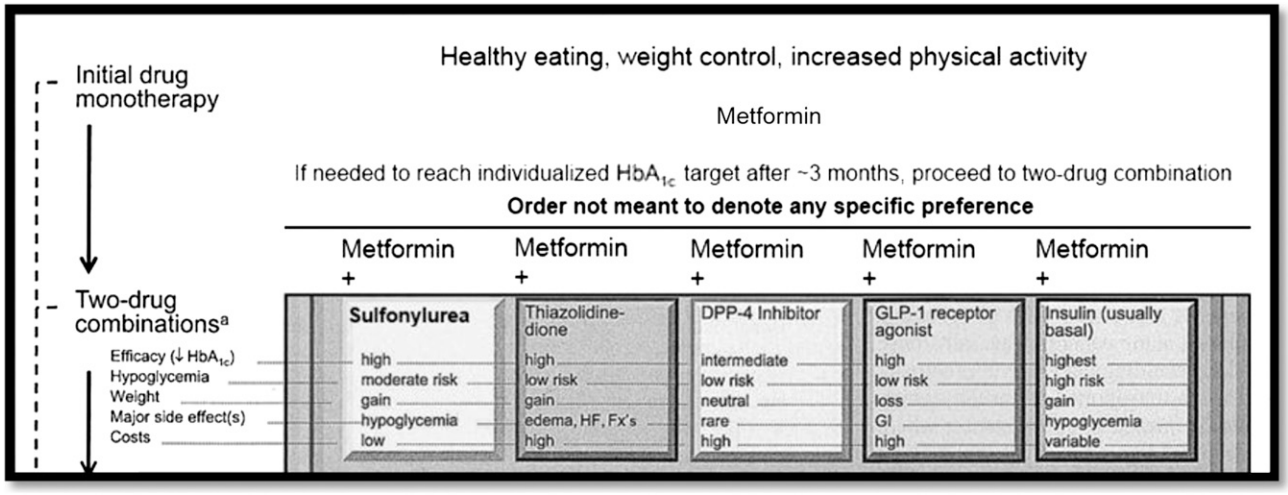

Figure 1—A modified form of the consensus algorithm for treatment of T2DM published by the ADA and the EASD (1). Fx's, bone fractures; GI, gastrointestinal; HF, heart failure. [a]Consider beginning at this stage in patients with very high HbA_{1c} (e.g., ≥9%).

drug alone (4); however, recent data suggest that 6 months after adding an SU to metformin, glycemic control worsens (5). For this and safety reasons, one can question whether SUs still deserve coequal status as an addition to metformin.

To take the counterpoint position, three questions will be addressed:

1. Do we *need* SUs or do newer agents have equal glucose-lowering efficacy as a first addition to metformin?
2. Do other agents have an equal or lesser burden of adverse effects, particularly hypoglycemia, than SUs?
3. Do other agents offer cardiovascular disease (CVD) benefits compared with SUs?

DO WE NEED SUs?

Table 1 shows the results of a retrospective cohort survey of oral drugs added to metformin in 26,278 U.K. patients indicating near-equivalent effectiveness of pioglitazone or DPP-4 inhibitors to SUs (6). Moreover, a number of randomized clinical trials have compared the addition of a TZD with the addition of an SU to metformin, and all have found equivalent glucose-lowering potency of about 1.0% in the absolute HbA_{1c} level (7–10). These comparisons included pioglitazone versus gliclazide and rosiglitazone versus glyburide or gliclazide or glimepiride. Rosiglitazone is now only approved for restricted use and carries a black-box warning in the *Physicians' Desk Reference*.

Two DPP-4 inhibitors, sitagliptin (11) and saxagliptin (12), have been compared with glipizide as additives to metformin, and equivalent reductions of HbA_{1c} in the range of 0.8–1.0% have resulted. Similar results were noted when vildagliptin and linagliptin were compared with glimepiride as add-ons to metformin (13,14).

The GLP-1 agonist liraglutide has lowered HbA_{1c} approximately 0.3% more than glimepiride when added to metformin over a 2-year period (15). Adding liraglutide to metformin decreased HbA_{1c} an additional 1.0% compared with metformin treatment alone.

In a comparison of insulin glargine to the SU glimepiride added to metformin, the HbA_{1c} and fasting plasma glucose achieved were similar (16). The addition of glyburide to metformin lowered HbA_{1c} 1.6% in a pivotal trial (4), and the addition of insulin to metformin lowered HbA_{1c} 2.5% in another trial (17). However, the results with insulin can be superior, given no limitation on its doses.

Although sodium–glucose cotransporter 2 (SGLT2) inhibitors are not in the first tier of the algorithm for addition to metformin, canagliflozin was slightly superior to glimepiride by 0.12% (18), and dapagliflozin and glipizide each lowered HbA_{1c} 0.5% (19) in recent trials. On grounds of efficacy and greater safety, SGLT2 inhibitors are reasonable candidates to replace SUs.

There is now abundant evidence that SUs are not essential as first-line additives to metformin as the alternative drugs are basically equal in glucose-lowering effectiveness.

WHAT ARE THE COMPARATIVE RISKS OF SUs AND THEIR COMPETITORS?

From the beginning, SUs were associated with hypoglycemia as a major adverse event because they stimulate insulin secretion virtually independent of plasma glucose levels (2). A recent workgroup of the ADA and the Endocrine Society noted that "for patients with type 2 diabetes, sulfonylureas are the oral agents that pose the greatest risk for iatrogenic hypoglycemia and substitution with other classes of oral agents or even glucagon-like peptide 1 analogs should be considered in the event of troublesome hypoglycemia" (20).

The incidence of hypoglycemia varies with the particular SU, the population, the definition, and the means of

Table 1—Effect of various oral drug additions to metformin on HbA_{1c}

	HbA_{1c}, % (IQR)			
	Baseline	1 year	Difference, %	*P*
SU	8.3 (7.7–9.3)	7.3 (6.7–8.2)	1.0	<0.001
Pioglitazone	8.2 (7.7–9.1)	7.2 (6.7–7.9)	1.0	<0.001
Rosiglitazone	8.2 (7.7–9.1)	7.2 (6.7–7.9)	1.0	<0.001
DPP-4 inhibitor	8.0 (7.5–8.9)	7.3 (6.7–7.9)	0.7	<0.001

Data are from ref. 6, a retrospective study. IQR, interquartile range.

ascertainment (21); old age, long duration of diabetes, and cognitive dysfunction are well-recognized risk factors (21,22). In a meta-analysis of 22 studies of hypoglycemia in T2DM, blood glucose <50–55 mg/dL occurred in 10.1% of SU users and 0.8% experienced severe episodes (23). In a Scottish study of emergency care, an incidence of 8 per 100 person-years was recorded in SU users and 28% of these events required hospital admission (24). In a Swiss study, long-acting agents (e.g., chlorpropamide) were three times as likely as short-acting agents to result in hospital admissions for hypoglycemia with a mean blood glucose of 40 mg/dL (25). Glyburide was associated with almost twice as many episodes of hypoglycemia as other SUs (26) and five times as many as glimepiride (27). In a Tennessee Medicaid study of SU users over 65 years of age, an incidence of 12.3 per 1,000 person-years was reported, with 49% resulting in loss of consciousness, 5% in seizures, and 5% in catastrophic events including stroke, myocardial infarction (MI), injury, and death (22). In the years 2007–2009, there were an estimated 10,656 U.S. hospitalizations annually in older adults aged >65 years for adverse effects of oral hypoglycemic agents and an approximately equal number of emergency room visits without hospitalization (28). Two-thirds involved neurologic sequelae. Though not specified, virtually all these hypoglycemia-initiated events likely involved SUs, alone or in combination. Furthermore, there were 404,467 admissions for hypoglycemia compared with 279,937 for hyperglycemia from 1999 to 2011, according to a recent report (29). No drug data were available, but comorbidity rates ranged from 3.7 to 2.7% for MI and stroke in 2009–2010. Moreover, patients' feelings of burden and quality of life are worsened and health care costs are increased by hypoglycemia (30).

As seen in Table 2, SUs are up to six times as likely as other oral agents to cause hypoglycemia when added to metformin (31). SUs plus metformin are five times as likely as TZDs plus metformin to cause mild to moderate hypoglycemia (32). In a similar comparison, glimepiride was six times more likely to cause hypoglycemia than the GLP-1 agonist liraglutide (15). In a comparative study of adding insulin glargine or exenatide to metformin, no episodes of severe hypoglycemia were noted; however, blood glucose <60 mg/dL occurred in 24.2% of those treated with insulin and in 8.3% of those treated with exenatide (33).

Table 2—Risk of hypoglycemia of drugs added to metformin in treatment of T2DM

	Odds ratio (95% CI)
SU	2.1 (1.4–3.0)
TZD	0.5 (0.3–0.9)
DPP-4 inhibitor	0.3 (0.2–0.7)

Data are from ref. 31.

SUs also have exhibited a relative lack of durability. In the A Diabetes Outcome Progression Trial (ADOPT) monotherapy trial, the 5-year failure rate in new-onset patients (fasting plasma glucose >180 mg/dL) was 34% with glyburide, 21% with metformin, and only 15% with rosiglitazone (34). Moreover, 4 years after addition of an SU to metformin, 60–70% of those treated exhibited an HbA_{1c} level of 8–9% (5). Two years after SU addition to metformin, 49% of SU users had discontinued their prescriptions versus 39% of DPP-4 inhibitor users (35).

TZDs are accompanied by edema, aggravated heart failure, and fractures as adverse events (36–40). Pioglitazone added to metformin in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) led to edema in 27%; serious and fatal heart failure in 4.0 and 1.2%, respectively; bone fracture in 1.6%; and serious hypoglycemia in 0.4% (38). Moreover, a hazard ratio (HR) of 1.4 (95% CI 1.03–2.01) for bladder cancer has been reported in patients treated with pioglitazone for more than 2 years (41).

The most prominent adverse effects of GLP-1 agonists are gastrointestinal. Mild to moderate nausea has been reported in up to 50% of exenatide users, along with vomiting and diarrhea in some (33). By comparison, the tolerability of DPP-4 inhibitors has been excellent (42–44). Nausea and vomiting occur much more frequently with a GLP-1 agonist than with a DPP-4 inhibitor (45). A serious concern has been reports of acute pancreatitis in association with GLP-1 agonists and DPP-4 inhibitors. Most, but not all (46), reviews and meta-analyses have not substantiated pancreatitis or pancreatic cancer to be a true risk of such treatment (47–50). However, this remains a controversial issue as illustrated by a recent *Diabetes Care* Point-Counterpoint (51,52). This small risk may be outweighed by the glucose-lowering benefits (47) when these agents are added to metformin.

The various first-tier recommended additions to metformin have diverse effects on body weight, most of which occur within 1 year (53). Compared with metformin alone, SUs increase weight 3.5 kg and when added to metformin the gain is still 2.4 kg (54). TZDs increase weight 1.9–2.6 kg compared with metformin (54,32) and increase weight 2.2 kg when added to metformin (32). Glargine and exenatide added to metformin differ sharply in their effect on body weight, the insulin increasing it 1.0 kg and the GLP-1 agonist decreasing it 3.5 kg after 1 year (33).

The addition of SUs, pioglitazone, and DPP-4 inhibitors to metformin has similar effects on life-years gained (55). However, quality of life was adversely affected by hypoglycemia, greatest with SUs, and weight gain, greatest with SUs and pioglitazone. Quality of life was improved by weight loss induced with liraglutide (56).

Quality of life was greater with liraglutide than with glimepiride when added to metformin (57). It was also greater than that of pioglitazone and similar to that of sitagliptin (58). Estimates of quality-adjusted life-years (QALY) modeled on long-term outcomes show small differences. In the U.S., the difference was 0.28 years for exenatide compared with sitagliptin and 0.24 years for exenatide compared with pioglitazone (59). The difference between exenatide and moderate adherence insulin or pioglitazone was 0.28 and 0.26 QALY gained, respectively (60). TZDs added to metformin yielded approximately 8 QALY gained, modeled over 35 years (61).

Another "adverse effect" of drug use can be their costs. Here, SUs enjoy a major advantage. On a Web site detailing retail prices of the five first-tier drugs at all large national pharmacies (62), the following average prices are quoted for a 30-day supply: $4 for glimepiride, $15 for pioglitazone, $305 for sitagliptin, $330 for 50 units of glargine daily, and $425 for 10 μg of exenatide daily. For patients lacking adequate insurance coverage, all but the SUs and possibly pioglitazone might not be affordable.

The serious sequelae of hypoglycemic events, particularly in older patients, put SUs at a disadvantage when adding a drug to metformin. When the alternatives are tolerable and economically feasible, they are preferred over SUs.

HOW DO SUs STACK UP AGAINST ALTERNATIVE AGENTS WITH REGARD TO CVD?

The University Group Diabetes Program (UGDP) reported in 1970 that the first SU tolbutamide increased CVD deaths and total mortality compared with placebo in a 7-year randomized trial (63,64). This set off a controversy and resulted in an U.S. Food and Drug Administration–ordered black-box warning still present in the *Physicians' Desk Reference* for all subsequent SUs.

The UK Prospective Diabetes Study (UKPDS) appeared to exonerate SUs by reporting that participants randomized to either chlorpropamide or glibenclamide had no increase in MI, stroke, or total mortality compared with those randomized to diet treatment over an 11-year follow-up (65). However, in a UKPDS substudy, participants treated with SUs were later randomized either to receive or not to receive metformin. The incidences of total mortality and of diabetes-related death in those receiving the combination compared with those receiving the SUs alone were 30 versus 19 per 1,000 persons ($P = 0.041$) and 17 versus 9 per 1,000 persons ($P = 0.039$), respectively (65). In the context of this debate, metformin alone would be a more appropriate comparator to the combination, and the UKPDS investigators interpreted the substudy result as a type 1 error; this evidence of risk in combining metformin with an SU remains concerning. Other studies also have found evidence of an increase in cardiac events (66), in hospitalization for CVD disease and mortality (67), and in heart failure and mortality (68) with the combination of metformin and SUs, particularly glyburide. Compared with metformin, SUs have been associated with an increased risk of CVD or death (69,70), and a dose–response relationship between glyburide use and mortality was not seen with metformin (71). In a retrospective study of T2DM therapy with metformin as referent monotherapy, the HR for all-cause mortality for metformin plus an SU was 1.10 ($P = 0.011$) (69). Of course, such retrospective results may be influenced by selection bias.

Of the alternative agents, the most information available is for pioglitazone. In a meta-analysis of 19 trials involving over 16,000 patients and lasting 4–42 months (37), for the outcome of death, MI, or stroke the HR of pioglitazone to comparator was 0.82 (95% CI 0.72–0.92, $P = 0.005$). In the PROactive study of pioglitazone versus placebo added to other glucose-lowering drugs (35% on metformin with or without an SU) in patients with prior CVD, there was no significant difference in the primary outcome of major coronary, cerebral, or peripheral arterial events (HR 0.90, 95% CI 0.80–1.02) (72). But the HR for the secondary outcome of death, MI, or stroke was 0.84 (95% CI 0.72–0.98, $P = 0.027$) (72) and the HRs for recurrent MI (0.72), acute coronary syndrome (0.63) (73), and recurrent stroke (0.53) (74) were statistically significant favoring pioglitazone. However, 5.7% of pioglitazone versus 4.1% of patients randomized to placebo developed heart failure leading to hospitalization ($P = 0.007$) (75). Pioglitazone also decreases progression of atherosclerosis, independent of glucose control (76), more than glimepiride (77,78), as well as preventing restenosis in coronary stents (79).

For DPP-4 inhibitors, saxagliptin was compared with placebo added on to other glucose-lowering therapies in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial of 16,492 participants at high risk for CVD. Over 2 years of follow-up there was no difference in the primary outcome of CVD death, MI, or stroke (HR 1.00, 95% CI 0.89–1.12) or in an expanded secondary outcome that included unstable angina and coronary revascularization (80). In preclinical trials involving 4,607 persons, the saxagliptin/control HR for 41 CVD events was 0.45 (95% CI 0.24–0.83) (81). However, some concern has been raised about a small unexpected increase in hospitalization for heart failure when DPP-4 inhibitors were given to patients with previously known heart failure (82).

With regard to insulin, the UGDP found a lower incidence of CVD events than with tolbutamide (63). The UKPDS found a similar incidence of CVD events with insulin as with either glyburide or chlorpropamide (65). An HR of 1.34 (95% CI 1.15–1.58, $P = 0.002$) for insulin plus metformin has been reported versus metformin alone (69).

In a randomized trial of linagliptin versus glimepiride added to metformin (83) over a 2-year follow-up, the GLP-1 agonist/SU HR for major cardiovascular events was 0.46 ($P = 0.0213$). Reviews of the CVD effects of GLP-1 agonists and DPP-4 inhibitors suggest no adverse effects, and a growing body of animal evidence supports an overall beneficial effect (84–86).

CONCLUSIONS

1. There is no need to retain SUs as a first-line addition to metformin because new drugs are available with equal glucose-lowering efficacy, much less risk of hypoglycemia, and possibly greater benefit for protection from CVD.
2. An exception may be made for patients with inadequate health insurance who cannot afford alternate drugs.
3. SUs should not be prescribed to elderly patients who live alone, have unreliable food intake, and lack a family or social support system.
4. Serious consideration should be given to removing the long-acting SU glyburide from our therapeutic armamentarium for safety reasons.

Author's Note

In this issue of *Diabetes Care*, the ADA and EASD have updated their guidelines for treatment of T2DM (Inzucchi et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149). They now include SGLT2 inhibitors in their first tier of drugs to be added to metformin when monotherapy with the latter is inadequate. SGLT2 inhibitors are approximately equally efficacious in lowering HbA_{1c} as the other oral drug classes, are associated with less risk of hypoglycemia than SUs, and are associated with weight loss rather than weight gain. A disadvantage is their high cost.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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