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REVIEW

The Place of Sulfonylureas in the Evolving Landscape of Combination Therapy

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ABSTRACT

This article summarizes a presentation from a recent symposium entitled "SUs in the treatment of T2DM: a fresh look and new insights" held on 18 September 2019 during the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona, Spain, and discusses whether sulfonylureas (SUs) are a good 'team player.' It examines the likely impact of using SUs early in the course of type 2 diabetes mellitus (T2DM), either alone or in combination with other agents, on glycemic outcomes and net side effects. The management of patients with T2DM and cardiovascular disease or chronic kidney disease is discussed, highlighting how glycemic control and cardio-renal effects are equally important in these patients and chronic exposure to hyperglycemia should be minimized. The role of SU-based combination therapy in this patient group is explored, demonstrating how later-generation SUs, either as monotherapy or combined with other antidiabetic drugs, help to ensure maximum benefits with minimal side effects. Evidence regarding the combination of SUs with a sodium-glucose transport protein 2 inhibitor shows that this might prove to be a good clinical option, especially in patients with renal impairment.

Keywords: Cardiovascular disease; Chronic kidney disease; Hyperglycemia; Sulfonylureas; Type 2 diabetes mellitus

Key Summary Points

Early glycemic control can help minimize the risk of chronic exposure to hyperglycemia and thus the cardio-renal effects of type 2 diabetes mellitus (T2DM)

Evidence suggests that monotherapy or combination therapy with sulfonylureas (SUs) is an option for T2DM patients with cardiovascular disease or chronic kidney disease and in some countries (e.g., China) is the backbone of T2DM treatment in clinical practice

Combining a later-generation SU with a sodium-glucose transport protein 2 inhibitor may ultimately prove to be a good clinical option, especially in those with renal impairment

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THE WORLDWIDE CHALLENGE OF GLYCEMIC CONTROL

Average glycated hemoglobin (HbA1c) levels among patients with type 2 diabetes mellitus (T2DM) vary geographically worldwide between 7.5% in Germany and 8.6% in Mexico, Norway and India [1–3]. The National Health and Nutrition Examination Survey (NHANES) study in 1326 US adults with diabetes has demonstrated that the proportion of patients achieving glycemic targets has not improved over the last 20 years, despite the introduction of newer agents [4]. In 1999–2002, 44% and 59% of patients achieved individualized HbA1c targets and HbA1c $< 7.0\%$, respectively, and the most recent estimates show that, in 2011–2014, respective values were 51% and 64%, indicating numerically worse rates of glycemic control [4].

Our goal as diabetologists should be to increase the life expectancy of patients with T2DM. Compared with the general population, life expectancy is reduced by 6 years in patients with diabetes and by 12 years in those with diabetes and cardiovascular disease (CVD, defined as myocardial infarction or stroke) [5]. Therefore, it should be our aim to reduce macro- and microvascular complications of T2DM. As the disease progresses, treatment intensifies, starting with monotherapy and then progressing through combination therapy, triple therapy and insulin [6], and physicians need to assess treatment priorities when managing each patient. Recently announced results of the large VERIFY trial may be useful in determining the best early combinations to use to eliminate the effects of glucotoxicity as early as possible [7].

The current article describes the need for combination therapy to achieve and maintain glycemic control in patients with T2DM and describes the role of combination therapy containing sulfonylureas (SUs), which may be particularly valuable in resource-limited settings. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

MANAGEMENT OF T2DM PATIENTS WITH CVD OR CHRONIC KIDNEY DISEASE

CVD is the largest cause of mortality in patients with T2DM [8]; thus, management of CVD is a priority in these patients. Foundational pharmacologic pillars of cardiovascular (CV) protection in patients with T2DM include the use of statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for reducing low-density lipoprotein-cholesterol levels; angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) for reducing blood pressure; eicosapentenoic acid (EPA) for triglyceride lowering; and glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose co-transporter 2 (SGLT2) inhibitors for glycemic control [9].

Prioritization of the management of CVD is also reflected in the 2018 update of the European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) treatment algorithm, which stratifies treatment options after initial metformin according to whether or not patients have established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD) [6]. Use of GLP-1RAs and SGLT2 inhibitors features prominently in patients with ASCVD or CKD, being recommended as first-choice therapy in both those for whom ASCVD predominates and those for whom heart failure (HF) or CKD predominates, with the choice between the two types of agents dependent on the estimated glomerular filtration rate (eGFR) of the patient [6]. As noted in the presentation by Dr. Amod, sulfonylureas (SUs) are placed at the bottom of the list in this setting, with recommendations to preferentially use the later generations of SUs [6]. However, while the EASD/ADA guidelines suggest that most patients with T2DM should receive GLP-1RAs and SGLT2 inhibitors since a large proportion of patients have CVD or CKD, the reality is that cost and accessibility are also major considerations, especially in China.

THE ROLE OF SULFONYLUREA-BASED COMBINATION THERAPY IN THIS PATIENT GROUP

Since their introduction in clinical practice in the 1950s, SUs have been a mainstay of pharmacotherapy in the management of T2DM. However, a report by the South Asian Federation of Endocrine Societies (SAFES) stated that, despite their well-established efficacy, safety and proven benefits, the clinical utility of SUs and their place in therapy are being inappropriately overshadowed by newer therapies [10]; however, this is not the case in China. Chinese T2DM guidelines are updated every 3 years, with the latest version published in a Chinese-language journal in 2017 and an English-language journal in 2019 [11]. These guidelines show that SUs form the backbone of T2DM treatment in Chinese clinical practice, recommending SUs as an alternative choice of monotherapy when metformin is not tolerated and combined with other agents as dual and triple therapies [11]. This central place in the treatment algorithm is underpinned by the relatively superior glucose-lowing efficacy of SUs with reported mean HbA1c reductions of 1.0–1.5%, similar to metformin and GLP-1RAs, and better than newer agents such as SGLT2 inhibitors (mean reductions of 0.5–1.0) and dipeptidyl peptidase-4 (DPP-4) inhibitors (mean reductions of 0.4–0.9) (Fig. 1) [11–13].

SUs have demonstrated significant reductions in HbA1c and fasting plasma glucose (FPG) from baseline when administered as monotherapy [14–16], as well as dual therapy in combination with metformin, an alpha-glucosidase inhibitor (AGI), a GLP-1RA or basal insulin [15, 17–19], and as triple therapy in combination with metformin and either a DPP-4 inhibitor or SGLT2 inhibitor [20, 21]. With regard to triple therapy, the STRATEGY study was a unique study of SUs, metformin and a DPP-4 inhibitor conducted in China [21]. During stage 1 of this study, patients were exposed to metformin plus sitagliptin. Patients who did not achieve target were then randomized to one of four treatment arms: gliclazide, glimepiride, repaglinide or the AGI acarbose [21]. Among these combinations, those containing gliclazide, glimepiride or repaglinide showed similar and comparable reductions in HbA1c, while

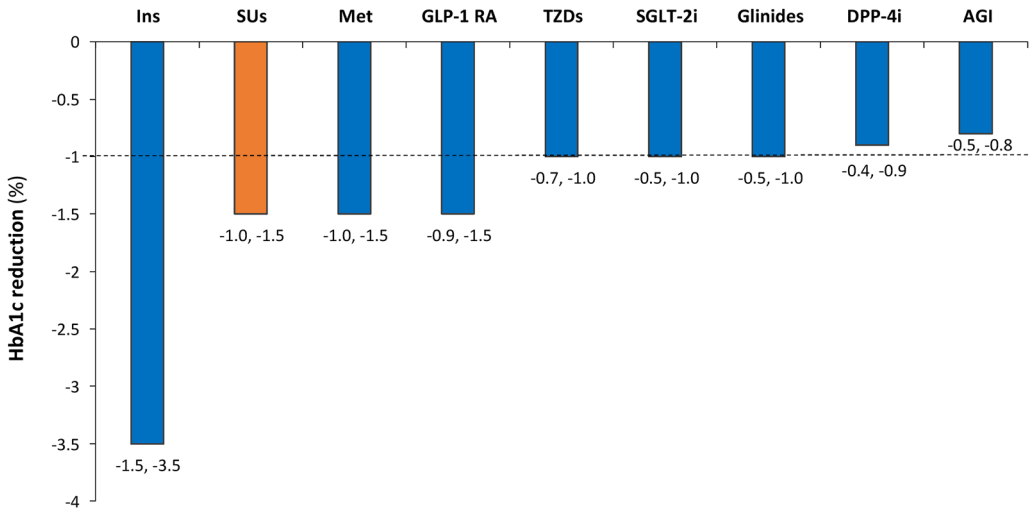

Fig. 1 Glucose-lowing efficacy of therapeutic agents. The maximum value for the range in HbA1c reductions associated with each treatment is indicated by each bar, and the range (minimum; maximum) is specified below each bar. *AGI* alpha-glucosidase inhibitors, *DPP-4i* dipeptidyl peptidase 4 inhibitors, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *HbA1c* glycosylated hemoglobin, *Ins* insulin, *Met* metformin, *SGLT2i* sodium-glucose co-transporter 2 inhibitors, *SUs* sulfonylureas, *TZDs* thiazolidinediones Data are from Jia et al. [11] except for GLP-1RA (from Cavaiola and Pettus [12]) and insulin and AGI (from Campbell et al. [13])

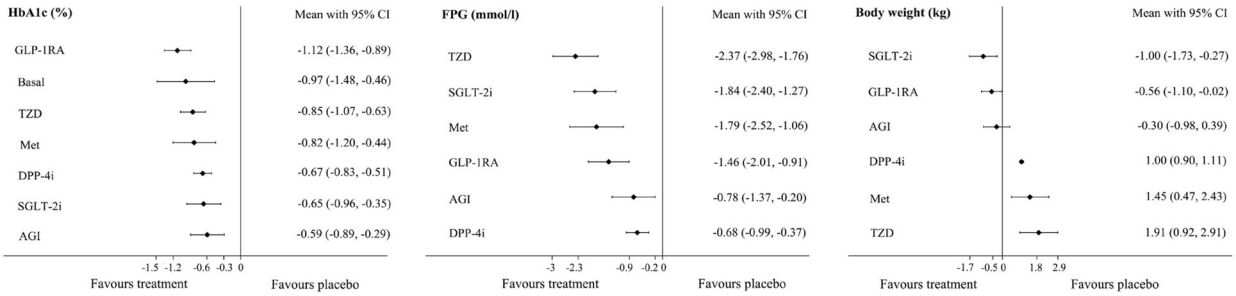

Fig. 2 Effects of different classes of diabetes agents in combination with sulfonylureas on HbA1c, fasting plasma glucose (FPG) and body weight in a network meta-analysis of studies [24]. *AGI* alpha-glucosidase inhibitors, *Basal* basal insulin, *DPP-4i* dipeptidyl peptidase 4 inhibitors, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *HbA1c* glycosylated hemoglobin, *Met* metformin, *SGLT2i* sodium-glucose co-transporter 2 inhibitors, *TZDs* thiazolidinediones. (Reproduced from Qian et al. [24])

the acarbose-containing combination was less effective [21].

The percentage of patients on target (i.e., HbA1c $\leq$ 7%) ranged from 46.7 to 72% with SU monotherapy and approximately 40% with SU-based dual and triple therapies [15, 16, 19–22]. Furthermore, results of the EasyDIA study revealed that uptitration of the SU dosage (between 30 and 120 mg per day) was associated with improved glycemic control, with dose-related significant improvements from baseline (all $p < 0.001$) observed in mean levels of HbA1c and FPG after 6 months of gliclazide modified release (MR) [23]. Results from the study also showed that improvements in glycemic control were irrespective of baseline HbA1c level, with > 40% of patients with a baseline HbA1c of 10% achieving an HbA1c target of $\leq$ 7% after 6 months of SU therapy [23]. Finally, a Chinese network meta-analysis of data from 10,032 patients from 24 trials reported improved glucose control when all drug classes were added to SU, but superior weight loss without an increased risk of hypoglycemia when SGLT2 inhibitors were combined with SUs (Fig. 2) [24]. The baseline HbA1c in the studies ranged from 7.6 to 9.9% (mean 8.5%) [24].

SGLT2 inhibitors have shown cardio-renal protective effects in CREDENCE and other trials [25–27], but what about their efficacy? Taking dapagliflozin as an example, limited efficacy has been observed in patients with stage 3a and stage 3b CKD [28]. Also, 2015 European clinical practice guidelines for the management of patients with diabetes and stage $\geq$ 3b CKD (i.e., eGFR < 45 ml/min) highlight that there is limited experience available and/or reduced efficacy with SGLT2 inhibitors while, with appropriate dose adjustment, SUs can be used even in patients with end-stage renal disease [29].

CONCLUSIONS

In conclusion, HbA1c-lowering and cardio-renal effects of anti-diabetes treatments are equally important in patients with T2DM, and chronic exposure to hyperglycemia should be minimized. Later-generation SUs, either as monotherapy or combined with other antidiabetic drugs, reinforced with careful monitoring and patient education, provide glucose-lowering efficacy with minimal side effects. As a result, these agents provide a valuable treatment option for many patients with type 2 diabetes, particularly in resource-limited settings where access to newer or more expensive agents may be restricted. SUs combined with a SGLT2 inhibitor appear to be a good clinical option, especially in patients with reduced eGFR.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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