



Sulfonylureas in the Current Practice of Type 2 Diabetes Management: Are They All the Same? Consensus from the Gulf Cooperation Council (GCC) Countries Advisory Board on Sulfonylureas

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ABSTRACT

Since their inception in the commercial market in the mid-twentieth century, sulfonylureas (SUs) have remained a therapeutic option in the management of type 2 diabetes (T2D). Despite their established glucose-lowering effects, there is no consensus among global experts and modern guidelines regarding the priority of SUs in relation to other therapeutic options, given

the lack of evidence that SUs are associated with a low risk of macrovascular events and excess mortality. However, findings from recent trials and real-time observations have resolved this contentious issue somewhat, albeit to varying degrees. The present consensus discusses the role of SUs in contemporary diabetes management in the Gulf Cooperation Council (GCC) countries. Regional experts from these countries gathered virtually to formulate a consensus following presentations of topics relevant to SU therapy with an emphasis on gliclazide,

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including long-term efficacy, cost, end-organ benefits, and side effects, based on up-to-date evidence. The present narrative review reflects the conclusions of this assembly and provides a platform upon which future guidelines for the use of SUs in the GCC can be tailored.

Keywords: Type 2 diabetes; Sulfonylurea; Gliclazide; Middle East

Key Summary Points

The role of sulfonylurea (SU) in the management of diabetes within the Gulf Cooperation Council countries is reviewed

Newer-generation SUs, specifically gliclazide MR and glimepiride, are cost-effective options that can provide efficient glycemic control with cardiovascular safety and renal benefits

Despite the provision of universal health care coverage in the GCC, cost is still an issue to consider, and this issue sets SU apart from newer agents for T2D management

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DIGITAL FEATURES

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INTRODUCTION

The last estimates from the International Diabetes Federation (IDF) atlas indicated a sustained and still alarming increase in the global prevalence of diabetes from 9.3% (463 million cases) in 2019 to an expected 10.9% (700 million cases) in 2045 [1]. Consequently, global spending on diabetes is also expected to grow from USD 760 billion in 2019 to USD 845 billion in 2045 [2].

Among all geographical regions, the Middle East and North Africa (MENA) registered the highest age-adjusted prevalence of diabetes in 2019 (12.2%), and this prevalence is predicted to rise by as much as 13.9% by 2045 [1]. Despite having shared customs, culture, and language, there are huge disparities among the MENA nations in terms of their economies and resources, which may also partially explain the unequal distribution of noncommunicable diseases, diabetes in particular [3]. Clustered in the MENA region is a political and economic alliance of six Arab sovereign states known as the Gulf Cooperation Council (GCC), consisting of Bahrain, Kuwait, Oman, Qatar, the Kingdom of Saudi Arabia (KSA), and the United Arab Emirates (UAE). As a bloc, the prevalence of diabetes in the GCC is one of the highest in the world, which has led to one of the biggest healthcare expenditures on diabetes [1, 4]. While many of the GCC states have developed their own national guidelines for diabetes in response, management remains suboptimal [5]. Management limitations have less to do with physicians and more to do with the patients in the GCC. Factors such as health beliefs, cultural and religious factors, and a lack of knowledge about diabetes cumulatively influence a patient's decision to adhere to treatment [6, 7]. Hence, it is clear that while progress is being made, there

is still much to be done given the enormous burden that will be posed by diabetes if the current norm is maintained. As diabetes management around the world is quickly evolving from algorithms to customized therapies, it makes sense to apply this strategy in the GCC region, given the increasing number of glucose-lowering drugs/therapies available on the market and noting that the individual circumstances of the patient undoubtedly affect their outcome [8].

As glucose control is the foundation of diabetes management, most international guidelines recommend the use of metformin together with lifestyle changes as the first line of management in newly diagnosed type 2 diabetes (T2D) patients [9–11]. Discrepancies between the guidelines mostly relate to the recommendations for second-line agents. Among those agents are the oldest non-insulin glucose-lowering drugs, the drug class known as sulfonylureas (SUs). The continuing popularity of SUs as second-line drugs for diabetes can be explained not only by their long-established track record as insulin secretagogues but also by several endpoints, including efficacy, treatment adherence, decline in β -cell function, tolerability over time, and affordability. These characteristics have allowed SUs to retain their prominent position in diabetes management, even with the release of newer, more expensive classes of glucose-lowering drugs with fewer side effects. Even so, given concerns over their cardiovascular safety and their associations with weight gain and hypoglycemia, SUs are mainly included in major international guidelines due to their affordability, and some SUs are more prominent in diabetes management than others [12, 13].

In this narrative review, the present and future role of newer-generation SUs, gliclazide in particular, in the management of diabetes within GCC settings is reviewed. It is important to consider that while there is already a plethora of published international guidelines on SU use, which most GCC physicians follow, the region where the burden of diabetes is striking, lacks its own guidelines. The present consensus on SU use aims to partially fill this gap. This article is based on previously conducted studies and does not

contain any new studies with human participants or animals performed by any of the authors.

GCC TASK FORCE

Twelve regional therapeutic experts across the GCC region (five from Saudi Arabia, one from Kuwait, one from Bahrain, three from the United Arab Emirates, one from Oman, and one from Qatar) convened twice (on October 31, 2020 and November 24, 2020) to discuss SU use in current practice within GCC settings. Both meetings were hosted virtually. Objectives and specific topics relating to SU were assigned to each expert on the first meeting, and they were given 3 weeks to conduct a literature review that took into consideration the most robust and up-to-date literature, including select but relevant systematic reviews and meta-analyses of the assigned topics. In the second meeting, each expert presented their review, which led to group discussion and deliberation. An online survey was also distributed amongst other experts and colleagues within the GCC region to determine the extent of SU use in the GCC in real time, their preferred SU drugs, and the guidelines they adhered to for diabetes management. The present paper is a reflection of what was presented and discussed in the group's assemblies. This consensus was endorsed by the Gulf Association of Endocrinology and Diabetes, the Bahrain Diabetes Society, the Emirates Diabetes Society, and the Saudi Diabetes Society.

SUMMARY OF SU HISTORY

The landmark discovery of sulfonylureas (SUs) followed on from the observation of glucose-lowering effects of synthetic sulfur compounds by Ruiz and colleagues in 1937 [14]. This observation was confirmed clinically years later by Janbon and his group, who, by chance, noted incidental hypoglycemia among individuals infected with typhoid fever and treated with *p*-amino-sulfonamide-isopropyl-thiodiazole [14]. In 1946, these compounds were acknowledged to trigger insulin release via the

stimulation of pancreatic β cells, and within a decade they had become the first widely distributed oral hypoglycemic drugs [14, 15]. More than 60 years have passed since the first generation of SUs (tolbutamide, tolazamide, chlorpropamide, and acetohexamide) were successfully launched into mainstream clinical practice as oral glucose-lowering agents for the management of type 2 diabetes (T2D) [14]. It did not take long, however, for the first major controversy regarding SUs to emerge, when tolbutamide was deemed to have caused an excess of cardiac deaths by the University Group Diabetes Program (UGDP), leading to the premature termination of this limb of its multicenter, placebo-controlled clinical trial [16]. While the UGDP study itself faced a backlash and intense scrutiny, it was not until the emergence of newer generations of safer and more potent SUs that the controversy started to fade, albeit with lingering skepticism until the cardiac safety of the new SUs has been fully established [17].

MECHANISM OF ACTION

Figure 1 shows a schematic of the general mechanism of action of SUs. In brief, SUs stimulate the release of insulin from the β cells of the pancreatic islets via closure of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel [18]. The same channel can be closed by a buildup of ATP, the end-product of mitochondrial glycolysis. Once the K_{ATP} channel is blocked, intracellular K^+ ions start to accumulate, which depolarizes the inner membrane of the cell, leading to an influx of extracellular Ca^{2+} . These calcium ions bind to insulin vesicles and promote insulin release into the circulation [19]. Once insulin latches onto its cell receptor, it activates the glucose transporter GLUT2, which transports glucose molecules into the cell, initiating mitochondrial glycolysis. It should be mentioned that K_{ATP} channels are also abundant in several tissues other than pancreatic β cells, including muscles (skeletal, cardiac, and smooth) as well as some neurons [18]. These extrapancreatic K_{ATP} channels respond to different SU classes based on their sulfonylurea receptor (SUR) affinities [19]. Tolbutamide (a first-generation SU),

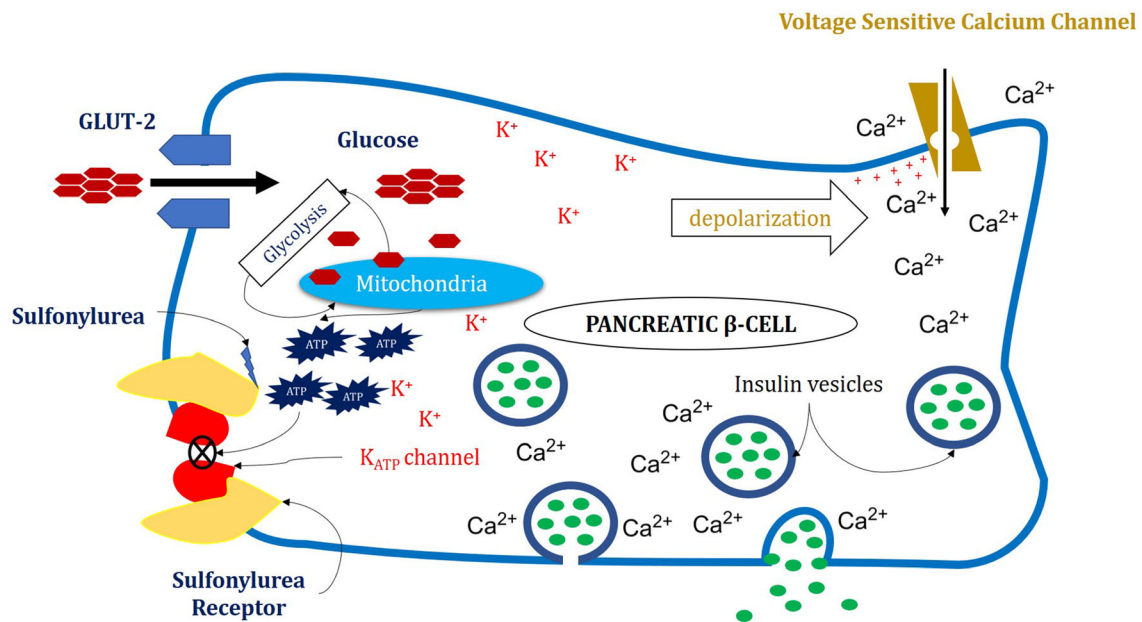


Fig. 1 Mechanism of action of SUs. The SU blocks the K_{ATP} channel once it binds to a SUR, leading to an alteration in internal membrane polarity and causing an influx of Ca^{2+} , which then promotes exocytosis of insulin vesicles

glibenclamide (a second-generation SU), and glimepiride (sometimes classified as a third-generation SU), for instance, target the SUR-1 found in β cells and, to a certain extent, the SURs 2A and 2B found in cardiac tissue and smooth muscle, respectively, while gliclazide MR (a third-generation SU) only has a high affinity for SUR-1 [19–21]. The restoration of the early insulin peak secondary to glucose and the stronger reversible binding of gliclazide MR to the β cell's SUR1 receptor compared to other SUs could be responsible for reduced pancreatic stimulation, which translates into a reduced incidence of hypoglycemia [22]. Furthermore, this affinity for extrapancreatic SURs has been hypothesized to inhibit ischemic preconditioning and to translate into varying degrees of adverse hypoglycemia and cardiovascular outcomes with some SUs [23–26]. These are also the same pharmacodynamics that made SUs the drugs of choice for neonatal diabetes secondary to genetic mutations in K_{ATP} channels [27].

LONG-TERM EFFICACY AND SAFETY

ADVANCE and CAROLINA Studies

Achieving glycemic control is the cornerstone of T2D management, and while metformin remains superior to other oral medications as a first-line monotherapy for T2D [28], physicians always consider add-on medications when needed, and factors such as long-term efficacy and safety are paramount in the decision-making process. Given the long history of SUs in the market, their risks and benefits are much more extensively documented compared to their successors [29–34]. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial was a clinical trial with a long-term follow-up (> 5 years) that aimed to ascertain the vascular benefits of intensified glucose control (glycated hemoglobin, HbA1c < 6.5%) [35]. This landmark study was the largest of its kind, involving 215 collaborating international institutions, and was designed to randomize more than 11,000 T2D patients 55 years and older across regions to either intensive glucose

control (including gliclazide modified release, MR) or standard glucose control [35, 36]. The ADVANCE trial proved that, compared to standard therapy, tighter glycemic control in T2D patients (HbA1c < 6.5) can be achieved [HbA1c reduction 0.67 (95% confidence interval, CI 0.64–0.40; $p < 0.0001$)] and maintained for a longer duration (5 years) using a SU-based regimen, which translated into a 14% reduction in microvascular events (95% CI 3.0–23%; $p = 0.015$). Furthermore, while the regimen did not yield a significant reduction in macrovascular events [hazard ratio, HR 0.94 (95% CI 0.84–1.06); $p = 0.32$] or mortality from any cause [HR 0.93 (95% CI 0.83–1.06); $p = 0.28$], it was considered safe and practical [35–37]. Long-term (> 5 years post-trial) observational follow-up studies also indicated a significant cumulative benefit (as much as 46%) in relation to end-stage kidney disease (ESKD), suggesting that renal protection persisted long after the surviving participants returned to their usual care [38, 39].

Another large-scale trial demonstrated that linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, poses a noninferior risk of first three-point major adverse cardiovascular events (3P-MACE) as compared to glimepiride [40]. Prior to that study, SUs and DPP-4 inhibitors were already common second-line therapies for T2D, but the safety profile of SUs appeared to be worse than that of DPP-4 inhibitors, based on observational and intervention studies [41]. Known colloquially as CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes), the trial is the only DPP-4 inhibitor cardiovascular outcome study with an active comparator. A total of 6042 T2D subjects with established cardiovascular risk from 600 international institutions were randomly assigned to receive either glimepiride or linagliptin, and were followed up for an average of 6 years. The composite endpoint, time to 3P MACE, was significant for noninferiority (HR 0.98, 95% CI 0.84–1.14; $p < 0.001$). Modest weight loss was observed in the linagliptin group as compared with the glimepiride group, with a mean difference of 1.54 kg (95% CI – 1.8 to – 1.28) [39]. The incidence of hypoglycemic episodes

was also significantly lower in the linagliptin group across all the subgroups analyzed, and death from any cause was comparable for the groups.

UK Clinical Practice Research Datalink (CPRD) Study

Zaccardi and colleagues retrospectively compared the safety and efficacy of gliclazide MR versus sitagliptin post metformin monotherapy using real-time primary care data for 1986 T2D patients treated for up to 9 years in the UK CPRD study [32]. Outcomes revealed the superiority of gliclazide MR over sitagliptin in terms of rapid achievement of target ($\text{HbA1c} < 7.0\%$), with gliclazide MR giving a 35% higher probability of target attainment within just 3 months [HR 1.35; 95% CI 1.15–1.57; $p < 0.001$]; similar durabilities and persistences were reported for both drugs. The latter and former characteristics of T2D treatment can be indicative of several endpoints, including efficacy, cost, treatment adherence, decline in β -cell function, and tolerability over time. Furthermore, given that the effects of SUs on β -cell exhaustion have always been a major concern, gliclazide's mode of action in reversibly binding to SUR1 receptors was observed to result in a significantly longer duration to treatment failure than observed with other SUs [33, 42]. In this study, gliclazide MR and sitagliptin had comparable durabilities and persistences of more than 2.5 years. Lastly, the incidence rate of symptomatic hypoglycemic events was low for both groups, with 4.7 events per 1000 patient years observed for gliclazide MR versus 2.6 events per 1000 years for sitagliptin [32].

The results of the ADVANCE and CAROLINA trials, as well as the CPRD observational study, largely secured the place of newer-generation SUs—gliclazide and glimepiride in particular—in modern T2D management. While the findings of the CAROLINA trial reinforced the use of both SUs and DPP-4 inhibitors as additional therapies to metformin given their long-term safety profiles, DPP-4 inhibitors were given preference over SUs as second and third lines of therapy in the recent joint guidelines of the

American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [10]. However, global institutions such as the World Health Organization (WHO) continue to categorically recommend SUs as the first-choice second-line therapy for patients whose glucose levels cannot be adequately controlled by metformin [43], as do national guidelines from developing nations such as India [44].

END-ORGAN BENEFITS

Cardiac

Independent of other risk factors, people with diabetes are twice as likely to develop cardiovascular diseases compared to those without diabetes [45], so the issue of the cardiac benefit of any antidiabetes drug is of paramount importance. Despite more than half a century of clinical use, concerns about their cardiac safety continue to haunt SUs. This is partly because the extensive literature available on their association with cardiovascular events is not only inconsistent but also lacks any conclusive evidence of harm associated with their use as second-line agents [46]. While the cardiac safety profile of SU use from the ADVANCE study and the cardiovascular outcome trial data (CVOT) from the CAROLINA trial were, at best, encouraging from the perspective of most practitioners [40], the influx of more promising cardioprotective evidence for newcomers such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-1) receptor agonists will substantially influence future therapeutic choices, especially for T2D patients with established cardiovascular or renal disease [47, 48]. Still, it has been demonstrated that newer-generation SUs, such as glimepiride in the CAROLINA study and gliclazide MR in ADVANCE, are CV safe and are not associated with an increased CV risk. Among elderly (> 75 years) T2D patients, glycemic management with a SU remains an option, but it should be dispensed with great caution given the elevated risk of adverse reactions such as hypoglycemia, its questionable

cardiac safety, and renal impairment [49]. However, in circumstances where affordability and availability are important issues, it is still clinically useful to know which of the widely used and less-expensive medications, including SUs, can achieve glycemic targets with a low risk of adverse outcomes.

The Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT) is the only major trial to have assessed the CVOT from using older diabetes drugs as second-line agents to metformin in T2D individuals with mild-to-moderate cardiovascular risk [50]. This large-scale study with a follow-up period of almost 5 years involved more than 3000 T2D patients who were randomly assigned to receive either pioglitazone or a SU (gliclazide, glimepiride, or glibenclamide). According to the results of TOSCA.IT, the pioglitazone and SU groups did not differ significantly in fatal or nonfatal cardiovascular events, nor in all-cause mortality [51]. Aside from this lack of difference between the treatment groups, the study had a high dropout rate and, as such, the generalizability of the results of the study should be interpreted with caution. It is worth noting, however, that the authors reported that pioglitazone was superior to SUs in providing cardiovascular protection to those who were either free from evident cardiovascular disease or were in the early stages of diabetes [52].

With respect to providing a lower cardiac risk, studies of SU drugs have consistently found in favor of the newer-generation SUs such as gliclazide and glimepiride [53], but not all [54, 55], proving that physicians should still consider differences in cardioprotection when selecting a SU. In fact, several early studies noted poor mortality outcomes when using SUs in combination with metformin [55–57], as well as an increased risk of cancer [58]. Nevertheless, in a systematic review and network meta-analysis of controlled studies reporting the risk of all-cause mortality, CV mortality, or myocardial infarction (MI), later-generation SUs such as glimepiride and gliclazide were associated with a significantly lower risk of all-cause and CV mortality compared to glibenclamide [59], whereas glibenclamide was associated with a

lower risk of sudden cardiac arrest and ventricular arrhythmias, at least when compared to glipizide, and may be associated with a reduced risk of ventricular tachycardia and isolated ventricular premature complexes [60]. Still, among all SUs, gliclazide has been associated with the lowest risk of cardiovascular-related mortality (followed by glimepiride), as well as the lowest risk of severe hypoglycemia [61].

Renal

The benefit of SU use for microvascular outcomes was initially demonstrated by the UK Prospective Diabetes Study (UKPDS 33) trial, which compared the effects of intensive ($N = 2729$) versus conventional ($N = 1138$) glucose control over a 10-year period in newly diagnosed T2D patients. The trial found that intensive treatment with glibenclamide decreased the risk of microvascular complications by 25% ($p = 0.0099$) [62]. Renal safety upon SU use is of particular interest in the Middle East and the GCC region since they have a high prevalence of chronic kidney disease (CKD) risk factors [63], and yet the epidemiology is largely understudied and underestimated [64, 65]. So far, the ADVANCE trial has provided evidence that the long-term intensive use of gliclazide prevents ESKD [35], and real-time observational data [66] indicate that it even confers additional protection from renal complications compared to other SUs (glimepiride in particular) in certain populations. This benefit was still seen after 6 years of follow-up, at which point it showed significant protection against end-stage renal disease (ESRD) (HR 0.54, 95% CI 0.34–0.85; $p = 0.007$) [37–39]. As diabetes is a major risk factor for CKD [67], specialized expert groups such as the Kidney Disease: Improving Global Outcomes (KDIGO) team, with the endorsement of both ADA and EASD, recommend that glycemic management for T2D patients with CKD should involve a combination of metformin and a SGLT-2 inhibitor as first-line therapy, with other drugs such as SUs considered only when additional therapies are needed for optimum glycemic control [68]. It is worth mentioning that SGLT-2

inhibitor use is restricted in patients with renal failure, in which case GLP-1 receptor agonists are considered (down to an eGFR of 15 ml/ml) [68]. Among SUs, KDIGO prefers glipizide for patients under dialysis, since it is largely metabolized in the liver and poses a lower hypoglycemic risk compared to other SUs [69]. Other groups such as the Association of British Clinical Diabetologists (ABCD) only recommend the use of one SU, gliclazide, and only at a low dose with constant monitoring, given that T2D patients with CKD are at higher risk for severe hypoglycemia. Furthermore, they do not recommend SU use in T2D patients with an estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73 m² [70].

Tables 1 and 2 summarize the end-organ benefits (the cardiac and renal benefits in particular) of SU-based therapies, according to the more recent trials.

SIDE EFFECTS

Major Hypoglycemia and Ramadan Studies

Historically, the use of SUs as a monotherapy or in combination has, in general, been perceived to increase the risk for major hypoglycemic events as compared to other diabetes medications [71–73]. The risk is higher for most insulin secretagogues than for other DM drugs, and is in fact a strong indicator of poor prognosis among T2D patients [74]. Accumulating evidence has, however, consistently demonstrated that, among SU drugs, gliclazide poses the lowest risk for episodes of major hypoglycemia [30, 75, 76], and that this risk is comparable to those posed by other commonly used second-line therapeutic drugs [32, 34, 55]. The risk for major hypoglycemia becomes even more important to consider during the holy month of Ramadan, the annual month-long fasting performed religiously by Muslims all over the world, the GCC included. In general, some people with diabetes are not recommended to undertake the fasting component of Ramadan [77, 78]. However, for many who are passionate to observe this season despite the associated

risks, the personal decision to fast should at least be made after a careful risk assessment with their physician, considering the responsibilities, level of discipline, and knowledge needed to prevent adverse events through education as well as the type of diabetes management employed [78, 79]. The clinician's decision regarding the appropriate diabetes medication should therefore be highly individualized, with the previously mentioned factors taken into account to ensure glycemic control with the least possible harm to the fasting diabetic patient. Several multinational studies have provided strong evidence that newer-generation SUs are safe and tolerable in this type of scenario [75, 80–82].

In a multinational head-to-head clinical trial involving 1066 T2D patients from 6 Middle-Eastern nations, Al Sifri and colleagues compared the incidence during Ramadan of symptomatic hypoglycemia with a DPP-4 inhibitor (sitagliptin) to that with SUs [80]. The study observed a clinically significant reduction in the incidence of symptomatic hypoglycemia with sitagliptin [HR 0.51, 95% CI 0.34–0.75; $p < 0.001$]. Using the intent-to-treat population and with the patients on SUs classified as a single group, the incidence of symptomatic hypoglycemia was 13.2%, compared to only 6.7% in the sitagliptin group. When the SU group was stratified, however, it was observed that those on gliclazide had an incidence comparable to those on sitagliptin (6.6%), and that the higher incidence for the SU group was largely driven by other SU classes (19.7% in the glibenclamide group and 12.4% in the glimepiride group) [79]. These findings were echoed in an analogous trial conducted among 870 Muslim patients with T2D from India and Malaysia by Aravind and colleagues [81]. In their study, the intent-to-treat reported incidence of at least one symptomatic hypoglycemia was significantly lower in the sitagliptin arm than in the SU arm (3.8% versus 7.8%, respectively) [HR 0.52, 95% CI 0.29–0.94; $p = 0.028$] [81]. Similar to the trial in the Middle East [78], among the SUs, the incidence of symptomatic hypoglycemia was again lowest for those on gliclazide (1.8%) [81]. While both trials agreed that a DPP-4 inhibitor was a safer

Table 1 Cardiac and renal benefits of SU-based therapies, as observed in the ADVANCE trials

Study	T2D participants	Cardiac outcomes	Renal outcomes
ADVANCE Patel et al. [35]	<i>N</i> = 11,140 adults \geq 55 years with known major macrovascular or microvascular disease or \geq 1 other risk factor for vascular disease, allocated to either standard therapy (other SUs) or intensive therapy using gliclazide MR for 5 years (<i>N</i> = 5571 intensive control: 42.6% females, 32.2% history of major macrovascular disease, 27% history of microalbuminuria, 90.5% on gliclazide MR at end of follow-up; <i>N</i> = 5569 standard control: 42.3% females, 32.3% history of major macrovascular disease, 26.7% history of microalbuminuria, 1.6% on gliclazide MR at end of follow-up)	No difference between groups in the frequency of macrovascular events during intervention [HR 0.94, 95% CI 0.84–1.06; <i>p</i> = 0.32]	14% decrease in major microvascular events [HR 0.86, 95% CI 0.77–0.97; <i>p</i> = 0.01] and 21% relative reduction in worsening nephropathy [HR 0.79, 95% CI 0.66–0.93; <i>p</i> = 0.0006] with gliclazide MR
ADVANCE ON Zoungas et al. [37]	<i>N</i> = 8494 participants with post-trial follow-up of 5.9 years (<i>N</i> = 4283 intensive control: 43.6% females, 29.7% major macrovascular disease, 9% major microvascular disease; <i>N</i> = 4211 standard control: 42.3% females, 30.9% major macrovascular disease, 9.9% major microvascular disease)	No differences after follow-up in major macrovascular events [HR 1.0, 95% CI 0.92–1.08; <i>p</i> = 0.93]	Cumulative benefit regarding end-stage renal disease (ESRD)* [HR 0.54, 95% CI 0.34–0.85; <i>p</i> = 0.007]
Perkovic et al. [38]	<i>N</i> = 11,140 (<i>N</i> = 5571 intensive control: 42.6% females, 27% history of microalbuminuria, no CKD 54.8%; <i>N</i> = 5569 standard control: 42.3% females, 26.7% history of microalbuminuria, no CKD 55%)		Risk of ESRD was 65% lower (HR 0.35, 95% CI 0.15–0.83; <i>p</i> = 0.02) with gliclazide MR Risk of albuminuria reduced by 9% (95% CI 2–15%; <i>p</i> = 0.01) with intensive treatment

Note: *Few events recorded

option than a SU for T2D patients observing Ramadan, it is worth mentioning that this advantage was apparent only when all patients on any SU drug were clustered into one group, and that its conferred higher protection from symptomatic hypoglycemia became similar to the protection provided by gliclazide in particular when the SU drugs were analyzed separately.

The promising safety profile of gliclazide as the SU of choice for T2D patients fasting during Ramadan has been confirmed in a recent large-scale, real-time observational study by

Hassanein and colleagues [82]. In this study involving 1244 T2D adults from 9 countries in the Middle East, the Indian subcontinent and Southeast Asia, the incidence of hypoglycemia while on gliclazide MR treatment was recorded for a 14- to 18-week period encompassing Ramadan. The findings revealed that there were no severe hypoglycemia events during the entire observation period and that the incidence of symptomatic hypoglycemic events was low (2.2%). In parallel, the study also showed clinical improvements in the metabolic profile, with marked reductions in HbA1c (– 0.3%) and

Table 2 Cardiac benefits observed in recent glycemic equipoise SU trials

Study	T2D participants	Cardiac outcomes
TOSCA.IT Vacarro et al. [51]	<i>N</i> = 3028 adults 50–75 years old with low cardiovascular risk and with insufficient glycemic control from metformin who were allocated to pioglitazone (<i>N</i> = 1535, 59% men, 12% previous CVD, 7% previous MI) or SU (<i>N</i> = 1493, 58% men, 10% previous CVD, 6% previous MI). Interim futility analysis ended the trial after 57.4 months of follow-up	No difference between groups in primary cardiovascular outcomes in intent-to-treat analysis [HR 0.96, 95% CI 0.74–1.26; <i>p</i> = 0.79] and on-treatment (post-hoc) analysis [0.82, 95% CI 0.60–1.1; <i>p</i> = 0.19]
CAROLINA Rosenstock et al. [40]	<i>N</i> = 6042 adults with elevated cardiovascular risk, HbA1c 6.5–8.5, who were allocated to receive either linagliptin (<i>N</i> = 3023, 60.8% men, 37.4% multiple CVD risk factors, 32.1% history of coronary artery disease) or glimepiride (<i>N</i> = 3010, 59.2% men, 36.9% multiple CVD risk factors, 31.2% history of coronary artery disease). Followed up for 6.3 years	Noninferior risk of major cardiovascular event [HR, 0.98, 95.47% CI 0.84–1.14; <i>p</i> < 001 for noninferiority]. Time to all-cause mortality not significant [HR 0.91, CI 0.78–1.06; <i>p</i> = 0.23]

weight (− 0.5% kg) over time (*p* 0.001) [82]. Table 3 summarizes the findings from the highlighted studies on the safety of SU use during Ramadan.

Weight Gain

Another unsolicited side effect of SU use is weight gain [83]. This is an unwanted consequence, especially in the GCC region, which is already plagued by both diabetes and obesity [3, 62, 84]. In the ADVANCE trial, an overall weight gain of 0.7 kg over a 5-year period was observed among those allocated to receive gliclazide [35]. However, when subpopulations of the same ADVANCE cohort were analyzed based on type of medication and glycemic control at trial entry, participants who were already on a progressive titration model of gliclazide over time—an approach consistent with actual clinical practice—showed no weight gain [34]. This discrepancy in results for the same trial implies that outcomes changed considerably when participants whose diabetes management had been abruptly altered by trial allocation were clustered together with those already receiving

the same treatment. Gliclazide's effect on weight was even more beneficial during short than long treatment periods, as demonstrated by the EASYDia trial, where participants with a baseline body mass index ≥ 25 kg/m² actually lost weight over a 6-month period (− 0.9 kg to − 2.2 kg) [30], and by the DIA-RAMADAN study, where an overall mean weight loss of 0.5 kg was observed over a 14- to 18-week period [78]. Results from the studies mentioned above uniformly imply that there is no evidence of weight gain from SU use, particularly with gliclazide.

Cost Comparison

Globally, the health-related expenditure for T2D imposes a huge burden on individuals with T2D and their families, especially in low- to middle-income countries [2, 85]. Medication costs can be a major source of stress for T2D patients, and can contribute to poor adherence to medications [86]. Cost-reducing strategies may improve adherence in some cases [87]. The recent prices listed for non-insulin therapies in the ADA clinical practice guidelines showed

Table 3 Safety of SU use during Ramadan

Study	T2D participants	Outcomes
Al Sifri et al. [80]	<i>N</i> = 1066, \geq 18 years of age, on a stable dose of SU with or without metformin 3 months prior to the clinical trial, and allocated to maintain their SU use or to sitagliptin	Symptomatic hypoglycemia was observed in 4.8% of patients in the sitagliptin arm versus 14.3% in the SU arm in the per-protocol population, driven mostly by glibenclamide and glimepiride users [HR 0.33, 95% CI 0.20–0.57; <i>p</i> < 0.001]. Among the SUs, symptomatic hypoglycemia was lowest with gliclazide (6.6%), followed by glimepiride (12.4%) and glibenclamide (19.7%). No events required medical intervention
Aravind et al. [81]	<i>N</i> = 870, \geq 18 years of age, on a stable dose of SU with or without metformin for at least 3 months, and allocated to maintain their SU use or to sitagliptin	Symptomatic hypoglycemia was lower in the sitagliptin than in the SU group (3.8% versus 7.8%) [HR 0.52, 95% CI 0.29–0.94; <i>p</i> = 0.028]. Among the SUs, symptomatic hypoglycemia was highest with glimepiride (9.1%), followed by glibenclamide (5.2%) and gliclazide (1.8%). Both arms were well tolerated
DIA-RAMADAN Hassanein et al. [82]	<i>N</i> = 1214, \geq 18 years of age, and on gliclazide MR alone or in combination 90 days before first visit; gliclazide maintained for 14–18 weeks (6–8 weeks pre-Ramadan, 4.5 weeks during Ramadan, and 4–6 weeks post-Ramadan)	Overall, 2.2% patients had \geq 1 symptomatic hypoglycemic event (confirmed or suggestive) (0.2% pre-Ramadan, 2.2% during Ramadan, and 0.3% after Ramadan). None of the participants had a severe hypoglycemic event during the entire study period

that the low costs of SU utilization do not account for discounts, rebates, or other price adjustments that are common in prescription sales and affect the actual cost to the patient [88].

Since GCC healthcare services are provided free to residents and expatriates by the government or insurance companies, literature allowing cost comparisons of DM drugs is limited. In Saudi Arabia for instance, the cost of DM drugs is not a major factor when the physician needs to choose or switch therapies; such decisions are driven mostly by efficacy, tolerability, favorable effects on weight gain, and risk reduction for symptomatic hypoglycemia [89]. Despite an underinvestment in healthcare services compared to most developed nations [90], treatment prevalence is relatively high in GCC countries (> 80%) [4], and improvements in

national policies over the years have helped to reduce the economic burden of diabetes [5]. The direct costs of diabetes mostly affect low-skilled expatriate workers, who occupy a huge percentage of the GCC migrant workforce. Under these circumstances, where cost is a major consideration, the lower prices of SUs compared to their counterparts represent a major advantage, and—when coupled with their comparable efficiency in terms of glycemic control and tolerability—make SUs a prime choice for T2D management [10, 43, 55, 91].

SUs as the Standard of Care in the GCC

Modern guidelines and consensus available for diabetes management have expressed mixed opinions regarding SU use, and while they categorize relevance according to different SU

drugs and the patient's preexisting conditions, SUs in general, remained consistently popular throughout the decades, and have secured their place in the contemporary arsenal for the global fight against diabetes for the years to come. The most widely used consensus, that of the ADA/EASD, ranks SUs as the last option for patients with established cardiovascular or renal disease, and suggests that they should only be prioritized when cost is an issue [10]. In contrast, recommendations where evidence has been appraised and rigorously evaluated, such as those from WHO and IDF, include SUs as the best options for second-line management [12, 43, 92].

CONCLUSIONS

With the increase in the DM medications at the clinician's disposal comes an even greater responsibility to carry out more robust scrutiny and customized T2D management. Hence, given our present but still evolving knowledge about SUs, it has become increasingly clear that the newer-generation SUs have the same glucose-lowering potency as their predecessors. These newer-generation SUs are often superior to other drug classes in terms of speed in achieving in glycemic control, offer better protection against adverse cardiac and renal outcomes, and show low incidences of untoward side effects that can rival those of other DM drugs, making them the safer option among SUs. Most endocrinologists in the region, including the experts in this therapeutic area who were involved in the present consensus, are fully aware that not all SU drugs are the same, and continue to prescribe SUs—gliclazide MR specifically—as one of the top options for second-line treatment in patients with no known cardiovascular and renal diseases. Newer-generation SUs, specifically gliclazide MR and glimepiride, have been shown to be a cost-effective option for reducing the disease burden in T2D patients, providing efficient glycemic control, cardiovascular safety, and renal benefits, and are the preferred SUs for diabetes therapy during Ramadan. Lastly, despite the provision of universal health care coverage in

the GCC, cost is always an issue to consider in the selection of medications. This is an additional advantage of SUs that sets them apart from newer agents for T2D management.

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