

## Review Article

# Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement

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### ABSTRACT

Since their introduction in clinical practice in the 1950's, Sulfonylureas (SUs) have remained the main-stay of pharmacotherapy in the management of type 2 diabetes. Despite their well-established benefits, their place in therapy is inappropriately being overshadowed by newer therapies. Many of the clinical issues associated with the use of SUs are agent-specific, and do not pertain to the class as such. Modern SUs (glimepiride, gliclazide MR) are backed by a large body of evidence, experience, and most importantly, outcome data, which supports their role in managing patients with diabetes. Person-centred care, i.e., careful choice of SU, appropriate dosage, timing of administration, and adequate patient counseling, will ensure that deserving patients are not deprived of the advantages of this well-established class of anti-diabetic agents. Considering their efficacy, safety, pleiotropic benefits, and low cost of therapy, SUs should be considered as recommended therapy for the treatment of diabetes in South Asia. This initiative by SAFES aims to encourage rational, safe and smart prescription of SUs, and includes appropriate medication counseling.

**Key words:** Anti-hyperglycaemic agent, gliclazide, glimepiride, glipizide, safety, sulfonylurea, type 2 diabetes mellitus, vascular complications

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## EXECUTIVE SUMMARY

### Sulfonylureas in the management of type 2 diabetes mellitus in South Asia – A consensus statement

An initiative of South Asian Federation of Endocrine Societies (SAFES)

Since their introduction in clinical practice in 1950's, Sulfonylureas (SUs) have remained the mainstay of pharmacotherapy in the management of type 2 diabetes mellitus (T2DM). Despite their well-established efficacy, safety and proven benefits, their clinical utility and place in therapy are inappropriately being overshadowed by newer therapies. Many of the clinical issues associated with the use of SUs are agent-specific and do not pertain to the class as such. A careful choice of SU, appropriate dosage, timing of administration, and adequate patient counseling, that is, person-centered care, will ensure that deserving patients are not deprived of the advantages of this well-established class of anti-diabetic agents. In addition, the modern SUs are backed by a large body of evidence experience and most importantly outcome data, which supports their role in managing patients with diabetes. Considering their efficacy, safety, pleiotropic benefits, and low cost of therapy, SUs should be considered as drugs/agents of choice for the treatment of diabetes in South Asia. This initiative by SAFES aims to encourage the rational, safe, and smart prescription of SUs and includes appropriate medication counseling by diabetes care professionals in South Asia.

#### A. Indications of Sulfonylureas

A1. SUs are an effective, safe, well tolerated, affordable, and convenient therapeutic option in the management of T2DM (Grade A; EL 1).

A2. SUs are effective second-line agents after metformin, in the management of T2DM. SU monotherapy as first-line may be considered in type 2 diabetes with metformin intolerance/contraindication and in patients with MODY (Grade A; EL 2).

A3. Modern SUs (Glimepiride and Gliclazide MR) should be initiated early in the course of T2DM, to achieve maximum glycemic benefits and obtain the benefits of metabolic memory (Grade A; EL 1).

A4. SU-containing dual or triple fixed dose combinations, if available, (with drugs that have complementary modes of action) reduce cost, offer convenience, and improve patient adherence (Grade B; EL 1).

#### B. Preferred Sulfonylureas

B1. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in view of the reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction, stroke, and CV mortality), and renal protection (Grade A; EL 1).

B2. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in T2DM patients at increased risk of hypoglycemia (Grade A; EL 1).

B3. Modern SUs (Glimepiride and Gliclazide MR) should be the preferred choice of SU in overweight/obese T2DM patients (Grade A; EL 1).

B4. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in patients at increased risk of cardiovascular disease (CVD) or with CVD (Grade A; EL 2).

#### C. Sulfonylureas in co-morbid conditions

C1. Shorter acting drugs, especially those metabolized in the liver (glipizide), should be the preferred SU in patients with moderate/severe renal impairment. In mild/moderate renal impairment, gliclazide and glimepiride may also be used, preferably at lower doses (Grade A; EL 3).

C2. Reduction of dose and longer intervals between dose adjustments for SUs are recommended in patients with mild/moderate hepatic impairment (Grade B; EL 4).

C3. SUs with a lower risk of hypoglycemia such as gliclazide MR and glimepiride are recommended in elderly patients. Alternately, short-acting SUs, or SUs in low dose can be used (Grade B; EL 4).

C4. SUs are not indicated for use in children and adolescents, and should be avoided during pregnancy and lactation (Glibenclamide may be prescribed in pregnancy and lactation, if the person absolutely refuses to accept insulin, and if metformin is not tolerated/contraindicated) (Grade A; EL 1).

#### D. Sulfonylureas in Ramadan/Religious fasting

D1. SUs may be used during Ramadan, with appropriate counseling and dose modification. Modern SUs (Glimepiride and Gliclazide MR) are preferred as they confer a lower risk of hypoglycemia (Grade A; EL 3).

D2. Individuals on once daily SU should take their medications at Iftar (During Ramadan, Suhur is the meal taken before sunrise and Iftar is the one taken when the fast

is broken after sunset). The dose may remain unchanged or reduced depending upon their pre-Ramadan glycemic status (Grade A; EL 4).

D3. Individuals on twice daily SUs, with higher doses in the morning and a smaller dose in the evening, may shift the higher morning dose to Iftar and the smaller evening dose, or its half, to Suhur (During Ramadan, Suhur is the meal taken before sunrise and Iftar is the one taken when the fast is broken after sunset). The Suhur dose may be reduced further if the control is adequate (Grade A; EL 4).

D4. Individuals with good control on conventional SUs do not require major changes in drug regimen, except for dose titration (Grade A; EL 4).

### E. Practical tips for using Sulfonylureas

E1. Practice a “start low, step-up slow” approach, up-titrating gradually (Grade A; EL 4).

E2. SU titration should be based on glucose monitoring: (Grade A; EL 4).

- Once in two weeks – for responders with no hypoglycemia
- Once a week – for nonresponders with or without hypoglycemia.

E3. The timing of administration of SUs before the first and subsequent major meals of the day is important. The importance of adherence must be explained (Grade A; EL 4).

E4. Patients/family members should be educated on the need to carry diabetes identity cards, sick day management, and recognition and management of hypoglycemia, including de-escalation of SU doses, if required (Grade A; EL 4).

## INTRODUCTION

The type 2 diabetes mellitus (T2DM) pandemic<sup>[1]</sup> is characterized by increasing complexity of management, raising concerns over safety and cost of therapy. Data from the National Disease and Therapeutic Index (NDTI) indicate that in USA, the number of diabetes medications per treated patient increased from 1.14 (95% CI, 1.06–1.22) in 1994 to 1.63 (1.54–1.72) in 2007, and the aggregate drug expenditure doubled from \$6.7 billion in 2001 to \$12.5 billion in 2007.<sup>[2]</sup> In India, the average number of antidiabetic drugs per prescription is 1.4, and the mean cost per 1 month prescription is INR 354.60 ± 305.72.<sup>[3,4]</sup> Globally, prescription patterns have changed in recent years with the introduction of newer

classes of medications.<sup>[5–7]</sup> While, sulfonylureas (SUs) and human insulins were the mainstay of diabetes pharmacotherapy before 1995,<sup>[6]</sup> several new therapeutics are now available. Oral hypoglycaemic agents (OHAs) still dominate the prescribing pattern (57.0%) followed by insulin alone (14.0%) and insulin + OHAs (13.0%) in USA.<sup>[8]</sup> Similar trends are observed in South Asia, where majority of the population is treated with OHAs, either as monotherapy or in combination.<sup>[3,4,9]</sup> Uncertainty exists regarding the most commonly prescribed OHAs, with some studies reporting it to be SUs<sup>[9,10]</sup> and others, metformin.<sup>[4]</sup> Evidence from literature suggests that SUs account for up to 20% of newly initiated OHAs, either as monotherapy or in combination, for treatment of T2DM.<sup>[11]</sup>

In order to avoid confusion with numerical generations of SUs, an attempt was made to classify them as conventional and modern SUs based on hierarchy of development. Another classification, based on duration of action (short, intermediate and long-acting) helped to define use in patients with specific clinical scenarios [Table 1]. The classifications in Table 1 will be used throughout the article to provide a clear picture of their place in diabetes management.

## SITUATIONAL ASSESSMENT OF SULFONYLUREAS USED IN SOUTH ASIA

Both conventional and modern SUs remain the choice of OHA prescription in South Asia. Conventional SUs are listed alongside metformin, in the National List of Essential Medicines (NLEM) of these nations [Table 2].

**Table 1: Classification of SUs**

Classification based on	
Hierarchy of development	
Conventional	Tolbutamide, glibenclamide, glipizide
Modern	Glimepiride, gliclazide MR, glipizide MR, gliclazide
Duration of action	
Short-acting	Tolbutamide
Intermediate-acting	Glipizide, gliclazide
Long-acting	Glibenclamide, glimepiride, gliclazide MR, glipizide MR

MR: Modified release, SUs: Sulfonylureas

**Table 2: SUs listed under the NLEM for South Asian countries**

Country	Glibenclamide	Gliclazide	Glipizide	Glimepiride
Bangladesh	Yes	Yes	No	No
India	Yes	No	No	No
Nepal	Yes	No	Yes	No
Pakistan	Yes	No	No	No
Sri Lanka	Yes	No	No	No

NLEM: National List of Essential Medicines, SUs: Sulfonylureas

According to NLEMs, glibenclamide (2.5 and 5.0 mg) is an essential SU in all the five countries (India, Pakistan, Nepal, Sri Lanka and Bangladesh).<sup>[12-16]</sup> Surprisingly none of the countries in the South Asian region have included glimepiride as an option for diabetes treatment in their NLEMs.<sup>[17]</sup> Bangladesh and Nepal are the only countries to have included newer generation SUs (gliclazide [80.0 mg] and glipizide [2.5, 5.0 mg], respectively), in their NLEMs. During 2014, general practitioners (GPs) from Pakistan had prescribed SUs more often than any other OHAs (including DPP-4 inhibitors).<sup>[18]</sup> Similarly in Sri Lanka, glibenclamide is the most commonly prescribed SU by GPs, while gliclazide prescription dominates the public sector. Interestingly, tolbutamide, one of the oldest SU, is still being prescribed in public hospitals of Sri Lanka as it is cheaper compared to other OHAs.<sup>[18]</sup> During 2014, SUs (as combination therapy) constituted the majority of OHAs market in India, with glimepiride combinations posting a growth higher than the market volume in drug class.<sup>[19]</sup> Recent studies from India and Pakistan report that SU/metformin are more efficacious than DPP-4inhibitors/metformin combinations.<sup>[20,21]</sup>

## SULFONYLUREAS IN DIABETES MANAGEMENT

An ideal anti-diabetic should confer glycaemic control, with lower risk of side effects, while providing inexpensive ease of use.<sup>[22]</sup> SUs are well-established glucose-lowering drugs, with insulinotropic action on pancreatic  $\beta$ -cells. Since the introduction of tolbutamide in 1956,<sup>[23]</sup> newer SUs have been developed, broadly classified based on their affinity to bind with sulfonylurea receptor (SUR) proteins.<sup>[24]</sup> The availability of modern SUs (glimepiride, glipizide, gliclazide MR and gliclazide modified release [MR]) with fewer side-effects and better efficacy<sup>[25]</sup> have contributed to their popularity.<sup>[26-29]</sup> Although the mechanism of action of SUs is well understood, their safety has been a matter of debate. Recent reviews and retrospective analyses suggest that SUs may cause hypoglycaemia and weight gain.<sup>[30,31]</sup> In addition, certain SUs are believed to accelerate  $\beta$ -cell apoptosis,<sup>[32]</sup> increase the risk of ischemic complications, and contribute to non-fatal cardiovascular (CV) outcomes and all-cause mortality.<sup>[33]</sup> The present consensus attempts to address their safety issues.

Systematic review of literature was conducted to provide the best possible evidence base for the use of SUs in the management of T2DM. Existing guidelines, meta-analyses, key morbidity-mortality trials, systematic reviews and most cited articles were reviewed, and recommendations relevant to South Asian scenario were framed. Where inadequate evidence was available, the panel relied on experience, judgment and consensus to

make their recommendations. The current consensus is developed in accordance with the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) protocol for standardized production of clinical practice guidelines.<sup>[34]</sup> Recommendations were graded based on clinical importance and levels of evidence as described in Tables 3 and 4, respectively. The recommendations incorporate the objectivity of evidence-based medicine with the subjectivity of a complex clinical challenge. As individual patient circumstances and environments differ, management should be based on the best interest of the individual patient, in a manner appropriate for the local scenario, involving shared decision making by patient and clinician.

## MECHANISM OF ACTION

SUs are insulin secretagogues that stimulate endogenous insulin secretion by blocking adenosine triphosphate-sensitive potassium channels ( $K_{ATP}$ ) on pancreatic  $\beta$ -cells, by binding to the SUR subunit present on the  $\beta$ -cell plasma membrane.<sup>[35]</sup> SUs bind to a common SUR unit on  $\beta$ -cells causing closure of the  $K_{ATP}$  channels and inhibition of  $K^+$  efflux, consequently depolarising the membrane and facilitating influx of  $Ca^{+2}$  ions. This in turn stimulates the exocytosis of insulin

**Table 3: Evidence rating according to AACE protocol 2010**

Evidence level*	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials
1	Multiple randomized controlled trials
2	Meta-analysis of nonrandomized prospective or case-controlled trials, systemic literature review
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study
2	Single randomized controlled trial
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database)
3	Consecutive case series
3	Single case reports, observational study, pilot study
4	No evidence (theory, opinion, consensus, review, or preclinical study)

\* 1: Strong evidence, 2: Intermediate evidence, 3: Weak evidence, 4: No evidence.  
AACE: American Association of Clinical Endocrinologists

**Table 4: Recommendation grading according to the AACE protocol 2010**

Grade	Strength of recommendation
A	Strong
B	Intermediate
C	Weak
D	Not evidence-based

AACE: American Association of Clinical Endocrinologists



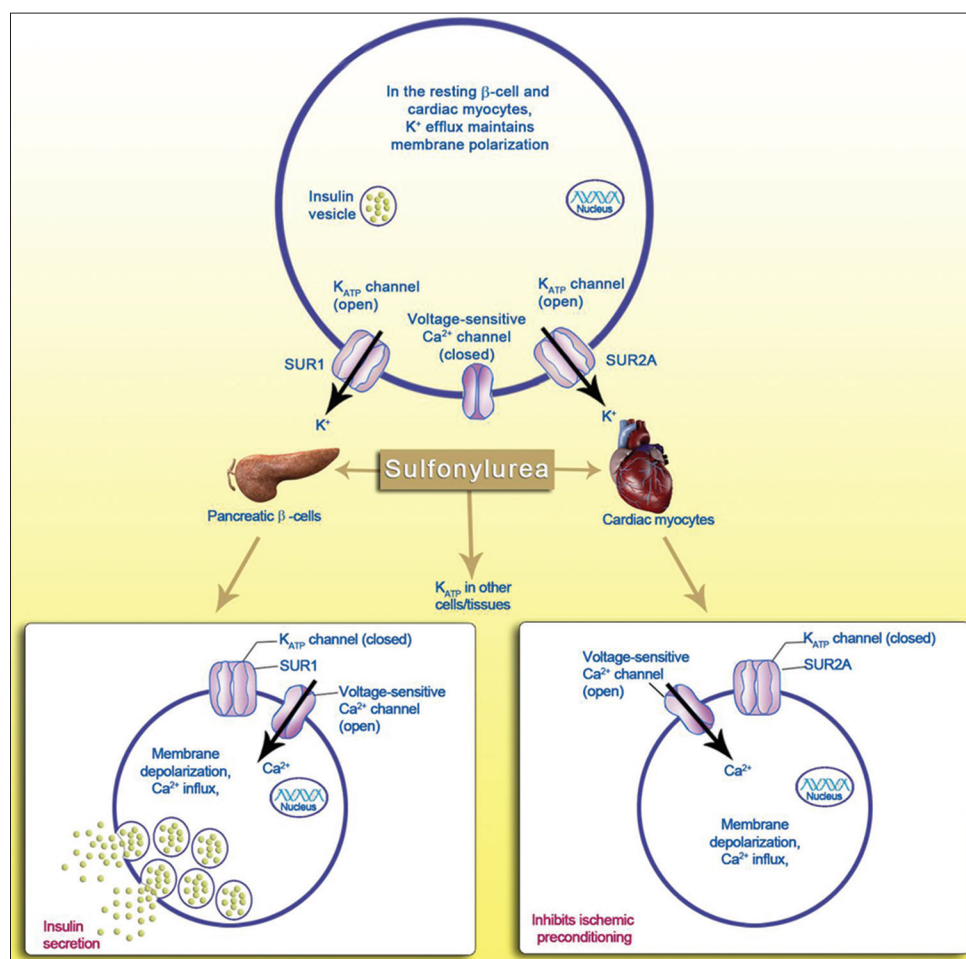
secretory vesicles [Figure 1].<sup>[35]</sup> Because insulin secretion is non-glucose-mediated, conventional SUs have been associated with a higher risk of hypoglycaemia.<sup>[36,37]</sup>

## ALL SULFONYLUREAS ARE NOT THE SAME

SUs stimulate insulin secretion by blocking  $K_{ATP}$  channels in the pancreatic  $\beta$ -cell membrane, by binding to the SUR subunit of the channel.<sup>[38]</sup>  $K_{ATP}$  channels are also present in extrapancreatic tissues, but often contain different types of SUR subunit [Table 5]. Evidence suggests that the effect of SUs on these  $K_{ATP}$  channels in different tissues varies.<sup>[39]</sup> For instance, gliclazide and tolbutamide block SUR<sub>1</sub> with higher affinity compared to SUR<sub>2</sub> while glibenclamide and glimepiride block both receptors with similar affinity.<sup>[39,40]</sup> Reversibility also varies, with tolbutamide and gliclazide producing a reversible inhibition of Kir6.2/SUR<sub>1</sub> and Kir6.2/SUR<sub>2</sub> channels, whereas glibenclamide has a reversible effect on cardiac, but not  $\beta$ -cell,  $K_{ATP}$  channels.<sup>[40]</sup> Notably, SUs that inhibit SUR<sub>1</sub> reversibly (tolbutamide and gliclazide) are smaller and possess fewer hydrophobic

groups than SUs that are slowly reversible (glibenclamide and glimepiride).<sup>[38]</sup> These variations may be explained by considering the hetero-octameric complex of SUR<sub>1</sub>  $K_{ATP}$  channels that contains two high-affinity binding sites, one for sulfonyl moiety and other for benzamido moiety.<sup>[41]</sup> The selectivity of SUR<sub>1</sub> for the sulfonyl moiety is 100 to 1000 fold higher than SUR<sub>2</sub>.<sup>[42]</sup> While most SUs possess both sulfonyl and benzamido moieties [Figure 2] and interact with SUR<sub>1</sub> and SUR<sub>2</sub>, short-chain molecules (gliclazide), with no benzamido moiety, bind only to the sulfonyl site. This in part explains the pancreas-selectivity of short chain SUs like gliclazide.<sup>[43]</sup>

Glimepiride stimulates insulin secretion by binding to a specific 65-kDa protein site on the  $K_{ATP}$  channel of pancreatic  $\beta$ -cell and exerts allosteric inhibition of the SUR complex.<sup>[36,44]</sup> Further, compared to glibenclamide, glimepiride exhibits lower binding affinity (2- to 3-fold) for SUR as well as higher rate of association (2.5- to 3-fold) and dissociation (8- to 9-fold) from the receptor.<sup>[36,45]</sup> The distinct binding site and receptor interactions of glimepiride are believed to result in lower inhibition of  $K_{ATP}$  channel and hence, there is reduced



**Figure 1:** Mechanism of action of sulfonylureas on pancreatic  $\beta$ -cells and cardiomyocytes (SUR: Sulfonylurea receptor; Adapted and modified from source: Gore MO, McGuire DK. Resolving drug effects from class effects among drugs for type 2 diabetes mellitus: More support for cardiovascular outcomes assessment. *Euro Heart J* 2011;32(15):1832-4)

risk of hypoglycaemia as compared to conventional SUs.<sup>[37,46]</sup> Moreover the ability of glimepiride to augment first and second phase insulin secretion in T2DM patients, indicate a possible relationship between good glycaemic control and acute improvement of regularity of the *in vivo* insulin release process.<sup>[47]</sup> Gliclazide is the only SU reported not bind to Epac2, a stimulating factor for insulin exocytosis. Consequently, gliclazide confers lower risk of hypoglycaemia [Figure 3].<sup>[30]</sup>

Variations in the pharmacodynamic/pharmacokinetic (PK/PD) profiles [Table 6] of individual SUs also explain the differences in anti-diabetic activity, hypoglycaemic risk, specificities to different tissue-specific SURs, effects on myocardial ischemic preconditioning, and insulin secretory effects.<sup>[48]</sup> In light of this, it may be wise to choose modern SUs that pose lower risk of hypoglycaemia and are cardiac friendly. However, lack of comparable data from clinical trials requires careful assessment of SUs with respect to patient-relevant endpoints.<sup>[49]</sup>

GLYCEMIC EFFICACY

SUs have a robust evidence base for glycaemia lowering, both as monotherapy and in combination with other OHAs. In a recent systemic review and meta-analysis, SU monotherapy

was found to lower glycated haemoglobin (HbA1c) by 1.51% more than placebo (95% CI, 1.25, 1.78).<sup>[25]</sup> Overall, in placebo comparator studies, treatment with SUs was found to reduce the fasting plasma glucose by 20–40 mg/dL and HbA1c by 1.0%–2.0%.<sup>[50,51]</sup> Several landmark trials including UKPDS, ADVANCE, ADOPT and VADT-FS showed that intensive glycaemic control with SU-based therapy (chlorpropamide, glibenclamide, glipizide in UKPDS; gliclazide MR in ADVANCE glibenclamide in ADOPT and glimepiride in VADT-FS) was associated with HbA1c reduction and improved long-term outcomes.<sup>[26,52,53,62]</sup> A meta-analysis of randomised clinical trials (RCTs) comparing the efficacy of metformin and glimepiride monotherapy, reported that glimepiride was as effective as metformin in achieving glycaemic control.<sup>[54]</sup>

In combination therapy with metformin,<sup>[55]</sup> rosiglitazone,<sup>[56]</sup> insulins<sup>[57]</sup> or DPP-4 inhibitor,<sup>[58]</sup> SUs provided better glycaemic control with relatively favourable safety profiles. A systemic review reported HbA1c reduction of 1.62% (95% CI: 1.0, 2.24) with SU + OHAs, and 0.46% (95% CI: 0.24, 0.69) with SU + insulin (with lowered insulin dose).<sup>[25]</sup> The DiaRegis registry that examined the impact of different treatment intensification options in T2DM patients following metformin failure, suggested that adding SU to metformin provides greater reductions in HbA1c than incretin therapy (–0.6% vs. –0.5%, *P* = 0.039) with no difference in the hypoglycaemic event rates.<sup>[59]</sup>

**Table 5: SUR type present in different extrapancreatic tissues**

Tissue	SUR type	Blocked by
Pancreatic beta-cell	SUR <sub>1</sub> /Kir6.2	Tolbutamide and gliclazide
Cardiac and skeletal muscle	SUR <sub>2A</sub> /Kir6.2	Glibenclamide, glimepiride
Vascular smooth muscle	SUR <sub>2B</sub> /Kir6.1	Glibenclamide, glimepiride
Nonvascular smooth muscle	SUR <sub>2B</sub> /Kir6.2	Glibenclamide
Brain	SUR <sub>1-2B</sub> /Kir6.2	-

SUR: Sulfonylurea receptor

Efficacy in lowering micro-vascular and microvascular complications

Metformin, SUs and acarbose are the only OHAs with long term outcome data. An improved long-term outcome with SU based intensive therapy was evident from UKPDS and ADVANCE.<sup>[26,52]</sup> A 10 year follow-up of UKPDS suggested that intensive control with either insulin or SU was associated with relative reductions in risk for any diabetes-related end point (9%, *P* = 0.04) and microvascular disease (24%,

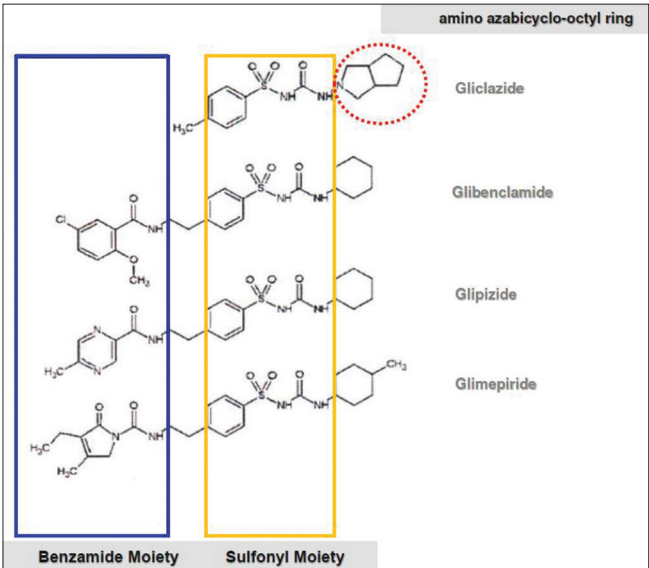


Figure 2: Molecular structure of sulfonylureas

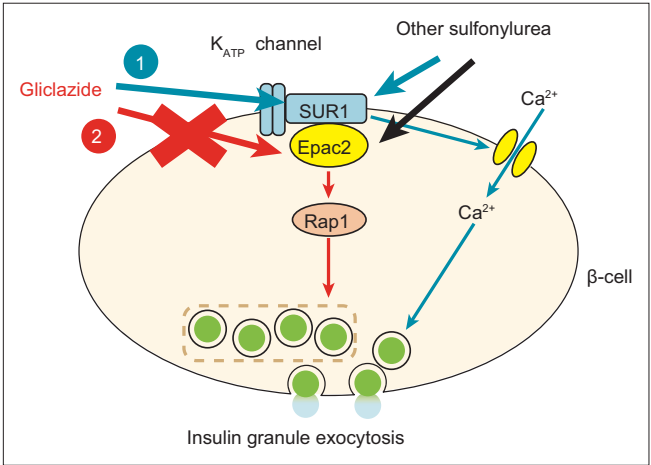


Figure 3: Mechanism of action of gliclazide on pancreatic β-cells (SUR: Sulfonylurea receptor)

**Table 6: PK/PD profile of frequently prescribed SUs**

PK/PD properties	Glibenclamide	Gliclazide	Glipizide	Glimepiride	Glipizide XL	Gliclazide MR
Duration of action	16-24 h	10-24 h	12-24 h	24 h	>24 h	>24 h
Volume of distribution	9-10 L	13-24 L	10-11 L	19.8-37.1 L	10 L	19 L
Protein binding (%)	99	85-99	98-99	99	98-99	>90
Metabolism	Hepatic	Hepatic (no active metabolites)	Hepatic (no active metabolites)	Hepatic (active metabolites)	Hepatic (no active metabolites)	Hepatic, (no active metabolites)
Bioavailability (%)	99	80	100	100	100	97
Half-life	10 h	8-12 h	2-5 h	5±4.1 h	2-5 h	16 h
Time to peak	2-4 h	2-4 h	1-3 h	2-3 h	6-12 h	6-7 h
Excretion	50% renal	80% renal	80% renal	60% renal	80% renal, 10% feces	<60-70% renal 10-20% in feces
Drug-drug interaction	May interact with CYP2C9 inducers or inhibitors					
PK changes in elderly	Slow elimination; higher volume of distribution	Likely increase half-life and slower elimination	No significant differences in PK properties			
PK changes in renal and hepatic impairment	May be altered increasing the risk of toxic reactions to drug	May affect the distribution and may also reduce the capacity for neoglucogenesis	Metabolism and excretion may be slowed	No significant differences in PK properties in renal impairment while it is not evaluated in hepatic impairment	May affect the disposition of drug and also diminish gluconeogenic capacity	May affect the distribution and may also reduce the capacity for neoglucogenesis increasing the risk of hypoglycemia

MR: Modified release, XL: Extended release, PK/PD: Pharmacodynamic/pharmacokinetic, SUs: Sulfonylureas

$P = 0.001$ ), and risk reductions for myocardial infarction (15%,  $P = 0.01$ ) and death from any cause (13%,  $P = 0.007$ ).<sup>[60]</sup> In ADVANCE, a strategy of intensive glucose control ( $\leq$ HbA1c 6.5%) with gliclazide MR yielded significant reductions in combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% CI, 0.82 to 0.98;  $P = 0.01$ ), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97;  $P = 0.01$ ) with no unfavourable cardiovascular outcomes.<sup>[52]</sup> In addition, a reduction of 10% in risk of serious diabetes complications, 21% in kidney disease, and 30% in macroalbuminuria development was observed in patients treated with intensive regimen.<sup>[52]</sup> Similar trends were observed in the ADVANCE ON Study where intensive target-driven, multifactorial approach with SU therapy, reduced the risk of microvascular complications (specifically end stage renal disease).<sup>[61]</sup> VADT-FS is the long term follow-up of the VADT (high risk diabetic patients treated with a multi-drug regimen using metformin, glimepiride, rosiglitazone and insulin; standard care vs intensive treatment). The 10 year results demonstrate that, compared to standard care, an intensive treatment results in a significant 17% relative reduction in major cardiovascular events, with no difference in mortality. This data provides evidence that a current multidrug glycemic treatment regimen (which includes glimepiride) can be associated with a significant reduction in major macrovascular events even among older patients who have had diabetes for many years.<sup>[62]</sup> The major outcomes of treatment with SUs in landmark trials have been presented in Table 7.

### Adverse effects

Adverse effects, other than hypoglycaemia and weight gain, with the use of SUs include symptomatic hyponatremia,

alcohol-induced flushing or disulfiram-like effect, cholestatic jaundice, macular erythema, rash and, blood dyscrasias.<sup>[63,64]</sup> Conventional SUs may be associated with dizziness and headache,<sup>[65]</sup> hyponatremia, anaemia, leukopenia, and thrombocytopenia.<sup>[66]</sup>

## EXTRA-PANCREATIC EFFECTS

SUs (particularly glipizide) are known to reduce the hepatic uptake and metabolic clearance rate of insulin.<sup>[67]</sup> This effect is complemented by a decreased glucagon secretion from pancreatic  $\alpha$ -cells.<sup>[68]</sup> In addition, modern SUs act as insulin-sensitizers, by increasing the expression of GLUT-4 (Glucose Transporter type-4) transporters and decreasing the insulin resistance in peripheral tissues.<sup>[69]</sup> Adding glimepiride to insulin therapy in patients with T2DM leads to a significant increase in high molecular weight adiponectin ( $P < 0.01$ ), which in turn is inversely correlated to changes in HbA1c, contributing to improved glycaemic control, and lower insulin requirement.<sup>[70]</sup>

The cardiovascular effects of SUs are mediated through the inhibition of sarcolemmal and mitochondrial  $K_{ATP}$  channels on cardiac myocytes, and  $K_{ATP}$  channels on vascular smooth muscle cell.<sup>[71]</sup> This inhibition may lead to impairment of ischaemic pre-conditioning (IPC), a cardio-protective phenomenon. Glimepiride, however, was found not to impair IPC<sup>[72]</sup> while demonstrating anti-inflammatory and angiogenic activity in patients with T2DM.<sup>[73]</sup> Further, the ability of glimepiride to decrease toxic advanced glycation end products (AGEs) and soluble receptor for AGE (sRAGE), and increase colony-stimulating factors, suggests an anti-oxidative,

**Table 7: Outcomes of treatment with SUs in landmark trials**

Study	Interventions	Glycemic efficacy		Safety (rate of major hypos episode/year)	Weight gain (kg)	Outcomes
		6 months	Long-term			
UKPDS33	Intensive (chlorpropamide/glibenclamide or insulin) versus conventional (diet alone)	HbA1c reduced to 7.0% HbA1c reduced to 7.9%		Chlorpropamide 1.0% Glibenclamide 1.2% Diet 0.7%	Chlorpropamide +2.6 Glibenclamide +1.7	12% lower risk of any diabetes-related endpoint
ADVANCE	Intensive (gliclazide MR + combination) versus standard-control therapy	6.5% 7.3%		Gliclazide MR 2.7% Control 1.5%	Gliclazide MR +0.0	Incidence of complications decreased (18% vs. 20%, HR: 0.9, $P=0.01$ )
ADOPT	Glyburide versus metformin versus rosiglitazone	Reduction in FPG and HbA1c, greatest with glyburide	Increase in FPG and HbA1c, greatest with glyburide	Serious hypos, percentage of patients Glyburide 0.6% Metformin 0.1% Rosiglitazone 0.1%	Glyburide +1.6 Metformin -2.9 Rosiglitazone +4.8	Treatment failure (FPG >180 mg/dL) at 5 years Glyburide 34% Metformin 21% Rosiglitazone 15%
ADVANCE ON	Post observational follow-up study from ADVANCE Intensive (gliclazide MR + combination) versus standard-control therapy	HbA1c levels maintained over 10 years		Overall low	The mean body weight was similar in the intensive and standard glucose-control groups	Persistent benefit of intensive glucose control with respect to end-stage renal disease (HR: 0.54; 95% CI: 0.34-0.85; $P=0.007$ ) observed
VADT/ VADT-FS	Intensive versus standard care (SU used was glimepiride)	6.9% versus 8.4% (different 1.5%)	0.2-0.3% different at end of follow-up	Higher in the intensive-therapy group than standard-therapy ( $P<0.001$ )	4 kg gain in intensive group	At 10 years, significantly lower risk of major CV events with intensive therapy (HR, 0.83; 95% CI: 0.70-0.99; $P=0.04$ )

FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, MR: Modified release, CI: Confidence interval, OR: Odds ratio, SUs: Sulfonylureas, HR: Hazard ratio

pro-vascular effect.<sup>[73]</sup> Gliclazide exerts its extra-pancreatic effects by potentiating insulin mediated glucose uptake in muscles (+35%) to increase insulin sensitivity. These effects are consistent with a post-transcriptional action of gliclazide on GLUT-4 transporters. Gliclazide has also been shown to decrease hepatic glucose production, improving fasting glycaemia. Gliclazide exerts haemo-vascular and anti-oxidant effects, decreasing micro-thrombosis by partial inhibition of platelet aggregation/adhesion, increasing vascular endothelium fibrinolytic activity, and reducing plasma lipid peroxide and increases erythrocyte superoxide dismutase.<sup>[74]</sup> Glibenclamide is associated with worsening of blood pressure, due to insulin resistance and activation of the sympathetic system.<sup>[75]</sup> Table 8 summarizes these pleiotropic effects and their mechanisms.

## PLACE OF SULFONYLUREAS IN DIABETES MANAGEMENT RECOMMENDATIONS

SUs are the oldest class of OHAs recommended by current guidelines for treatment of T2DM.<sup>[76-80]</sup> The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement recommends use of SU as first line if metformin intolerant, as second-line after metformin, or as third-line when glycaemic goals are not achieved.<sup>[51]</sup> The Scottish Intercollegiate Guidelines Network (SIGN), the International Diabetes Federation (IDF) and National Institute for Health and Clinical Excellence (NICE) guidelines also recommend SUs as first- or second-line agents in patients who are

**Table 8: Pleiotropic effects of different SUs**

Pleiotropic effect	Mechanism
Insulin clearance	Inhibits metabolic clearance rate of insulin
Glucagon secretion	Inhibit glucagon secretion from pancreatic $\alpha$ -cells
Insulin sensitization	Improves insulin sensitization and decreases insulin resistance in peripheral tissues
Ischemic preconditioning	Impairs ischemic preconditioning in cardiac myocytes by binding to SUR2A SUs differ in tissue selectivity for binding to SURs and display different levels of CV risk Gliclazide does not interfere with nicorandil activity and does not interfere with ischemic preconditioning Glimepiride induces ischemic preconditioning, suppresses ventricular tachycardia and lowers BP
Anti-oxidative	Decrease toxic AGEs and sRAGE
Angiogenesis	Glimepiride reduces plasma VEGF and FGF-2 levels
Vascular health	Induces G-CSF and GM-CSF levels

SUs: Sulfonylureas, SUR: Sulfonylurea receptor, CV: Cardiovascular, AGEs: Advanced glycation end-products, sRAGE: Soluble receptor of advanced glycation end-products, VEGF: Vascular endothelial growth factor, FGF-2: Fibroblast growth factor-2, G-CSF: Granulocyte-colony stimulating factor, GM-CSF: Granulocyte-macrophage colony-stimulating factor, BP: Blood pressure

not overweight, with intolerance or contraindications to metformin, and those requiring a rapid response due to hyperglycaemic symptoms.<sup>[76,79,80]</sup>

In addition, national guidelines from South Africa, China, Japan and Korea recommend the use of SUs as first- or second-line agents for the management of T2DM.<sup>[81-84]</sup> According to Japan Diabetes Society, SUs are to be considered early in the course of diabetes where patients present with considerable  $\beta$ -cell number and function.<sup>[82]</sup>



The Indian Council of Medical Research (ICMR) guidelines for management of T2DM advocates the use of SU, either alone, or in combination with metformin,<sup>[85]</sup> and suggests not combining an SU with other SUs or meglitinide, as both have similar mechanism of action.

## ISSUES WITH SULFONYLUREA TREATMENT

Although SUs have been the mainstay of pharmacologic management of T2DM, concern has been raised over their potential role in  $\beta$ -cell failure, blunting of IPC, weight gain, hypoglycaemia, and mortality risk. This section will focus on the concerns related to SUs usage. A thorough search of the literature pertaining to each of these issues was performed to frame evidence based recommendations.

### $\beta$ -cell apoptosis

As SUs act by stimulating insulin release from  $\beta$ -cells, there is concern regarding SU induced “ $\beta$ -cell exhaustion”. In UKPDS and ADOPT, majority of patients treated with glibenclamide experienced a loss of effective antidiabetic response after an initial excellent response (secondary failure).<sup>[26,30,53]</sup> In contrast, data from a systemic review of three RCTs reported lowest rates of secondary failure with gliclazide (7.0%) compared with glibenclamide (17.9%:  $P < 0.1$ ) and glipizide (25.6%:  $P < 0.005$ ) respectively.<sup>[86]</sup> In ADVANCE, compared to standard treatment group, greater proportion of patients in the intensive treatment group (gliclazide based regimen) achieved HbA1c  $< 7.0\%$  with reduced incidence of combined major macro- and microvascular events (HR, 0.90; 95% CI, 0.82 to 0.98;  $P = 0.01$ ).<sup>[52]</sup> Gliclazide is therefore less likely to induce  $\beta$ -cell failure or secondary SU failure as compared to conventional SUs.<sup>[87]</sup>

### $\beta$ -cell de-differentiation

Evidence suggests that  $\beta$ -cell de-differentiation, rather than cell death, is responsible for  $\beta$ -cell failure in T2DM.<sup>[88]</sup> According to Talchai *et al.*, stressed  $\beta$ -cells undergo de-differentiation, where the expression of  $\beta$ -cell specific genes and enzymes that process pro-insulin to insulin is reduced [Figure 4]. De-differentiated  $\beta$ -cells reverted to progenitor-like cells expressing neurogenin<sub>3</sub>, Oct<sub>4</sub>, Nanog, and L-Myc, consequently expressing non  $\beta$ -cell hormones such as somatostatin and glucagon.<sup>[89,90]</sup> Thus  $\beta$ -cell de-differentiation may account for reduced  $\beta$ -cell mass and insulin secretion in patients with T2DM.

In addition, results of a 10 year observational study that investigated the effect of SUs on  $\beta$ -cell function (assessed by postprandial C-peptide) suggested that it was not long-term treatment with SUs ( $P = 0.894$ ), but poor glycaemic control was associated with a decrease in  $\beta$ -cell

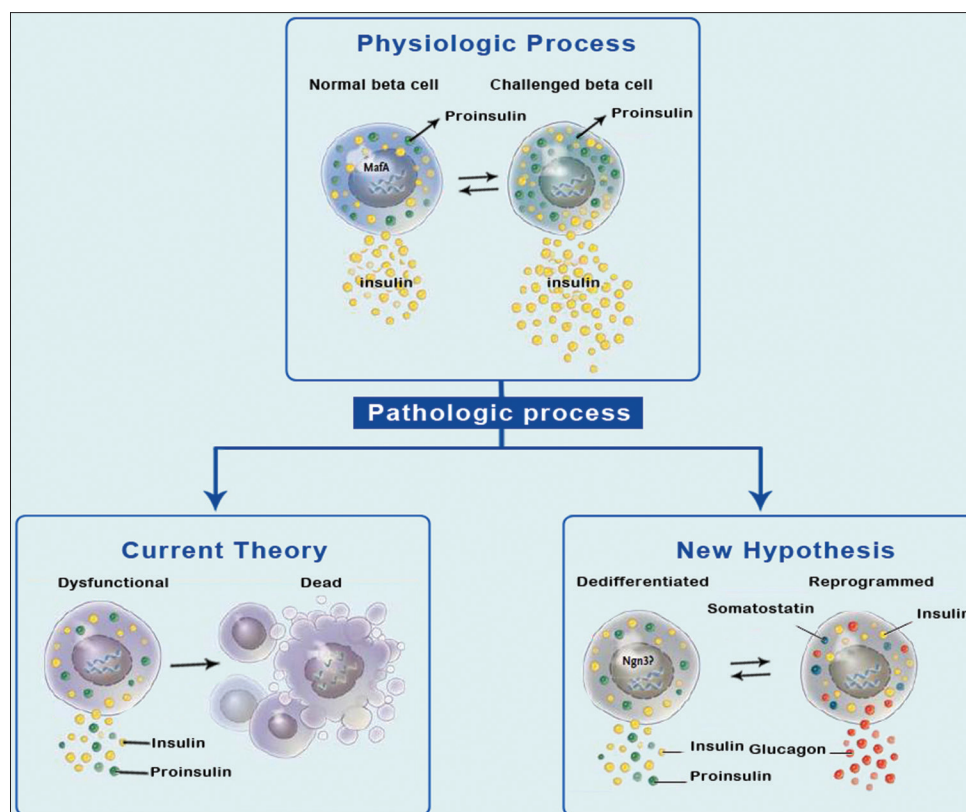
function ( $P < 0.001$ ).<sup>[91]</sup> Further, a study that evaluated the effects of exenatide, sitagliptin, and glimepiride on  $\beta$ -cell secretory capacity in early T2DM, indicated that it was glimepiride but not exenatide or sitagliptin, that enhanced  $\beta$ -cell secretory capacity (functional  $\beta$ -cell mass).<sup>[92]</sup> Current literature does not support the notion that SUs are harmful to  $\beta$ -cell mass or function; on the contrary, SUs appear to improve  $\beta$ -cell secretory capacity when used early in the course of T2DM.

### Weight gain

SUs are linked to significant weight gain, a secondary effect also known to occur with insulin, thiazolidinediones, and glinides. The weight gain observed with SUs may be explained by their insulinotropic actions,<sup>[93,94]</sup> reduction of glycosuria and increased caloric intake to prevent/treat hypoglycaemia.<sup>[31]</sup> In UKPDS, patients on SU monotherapy gained more weight compared to dietary intervention (chlorpropamide: +2.6 kg, glibenclamide: +1.7 kg).<sup>[95]</sup> SU-induced weight gain stabilized after first 3 or 4 years while insulin treatment resulted in a progressive gain.<sup>[96]</sup> However, where SUs were used in combination with insulin, weight gain was minimal compared to insulin monotherapy (1.9 vs. 5.9 kg).<sup>[97]</sup> Glimepiride,<sup>[98]</sup> extended release (ER) glipizide<sup>[99]</sup> and gliclazide MR,<sup>[100]</sup> have reported weight neutrality at least for the first year. Once daily administration of glimepiride was associated with weight neutralizing/reducing effect over a period of 1.5 years.<sup>[101]</sup> Initial treatment of T2DM with glimepiride was associated with a significantly greater decrease in body weight/body mass index than with glibenclamide, ( $-2.04 \pm 3.99$  kg vs.  $-0.58 \pm 3.65$  kg,  $P < 0.001$ ;  $-0.71 \pm 1.38$  kg/m<sup>2</sup> vs.  $-0.20 \pm 1.28$  kg/m<sup>2</sup>,  $P < 0.001$ , respectively) while providing equivalent glycaemic control.<sup>[102]</sup> Five years follow-up of ADVANCE trial showed no weight gain in T2DM patients whose treatment included gliclazide MR.<sup>[61]</sup> Furthermore, in a recent double blind trial, gliclazide MR provided a weight reduction benefit similar to that of vildagliptin ( $-1.1$  kg, in both groups).<sup>[103]</sup>

### Hypoglycemia

Hypoglycaemia is the foremost clinical concern when intensifying anti-diabetic treatment. Individual SUs differ in their hypoglycaemic potential, mainly due to the duration and time of action, dose equivalence and affinity to SUR on  $\beta$ -cells.<sup>[48]</sup> SU-induced hypoglycaemia with or without the need of external assistance occurs in about 1 in every 100 persons per year.<sup>[104]</sup> In 10-year follow-up analysis of UKPDS, the annual incidence of at least one hypoglycaemic event was found to be less than half with SUs (17.7%) than those occurring with insulin (36.5%).<sup>[26,105]</sup> A recent review and meta-analysis



**Figure 4:** De-differentiation of  $\beta$ -cell under stress

showed that gliclazide-treated patients experienced lower rates of severe hypoglycaemia.<sup>[106]</sup> Glibenclamide has been reported to cause more hypoglycaemic episodes than glimepiride (150 vs. 105 episodes).<sup>[107]</sup> The GUIDE study demonstrated significantly lower rates of confirmed hypoglycaemia (BG <3 mmol/L) with gliclazide MR as compared to glimepiride (3.7% vs. 8.9%,  $P = 0.003$ ). However, there were no episodes of severe hypoglycaemia/hypoglycaemia requiring external assistance in either arm.<sup>[100]</sup> A prospective, population-based, 4-year study reported that glimepiride was associated with fewer episodes of severe hypoglycaemia than glibenclamide in routine clinical use (0.86/1000 person-years vs. 5.6/1000 person-years, respectively).<sup>[46]</sup>

### Cardiovascular safety

Concerns about the CV safety of SUs were raised initially in 1970s when the University Group Diabetes Program (UGDP) study found an increased association between tolbutamide use and risks of coronary artery events.<sup>[108]</sup> However, the UGDP suffers numerous flaws in the design, execution, analysis and interpretation of findings.<sup>[109,110]</sup> Further, the applicability of outcomes of the trial to our current multifactorial approach to reduce CV events is uncertain.<sup>[111]</sup> In fact, the UGDP findings prompted initiation of UKPDS, which found no detrimental effect of SUs on macrovascular complications or mortality in

patients with T2DM.<sup>[26]</sup> This benefit persisted for up to 10 years in patients who had attained better glycaemic control.<sup>[60]</sup> Similar results were observed from 15 well designed long term ( $\geq 72$ -weeks) RCTs, including ADOPT, ADVANCE<sup>[52]</sup> and ADVANCE-ON,<sup>[61]</sup> where treatment with SUs was not found to be associated with an increase in CVD risk or mortality.<sup>[112]</sup>

Modern SUs (gliclazide MR and glimepiride) are associated with a lower risk of all-cause and CV-related mortality compared to conventional SUs in T2DM patients.<sup>[113-115]</sup> A recent case control study showed that the hazard of developing coronary artery disease (CAD) increased by 2.4-fold ( $P = 0.004$ ) with glibenclamide; 2-fold ( $P = 0.099$ ) with glipizide, while it decreased by 0.3-fold ( $P = 0.385$ ) with glimepiride, and 0.4-fold ( $P = 0.192$ ) with gliclazide.<sup>[116]</sup> A large cohort study ( $N = 11,141$ ) demonstrated a trend towards an increased overall mortality risk with glibenclamide (hazard ratio [HR] 1.36 [95% CI 0.96–1.91]) or glipizide (1.39 [0.99–1.96]) vs. glimepiride.<sup>[71]</sup> Gliclazide MR, evaluated in a long duration trial (4.3 years follow-up), in diabetic patients co-treated with perindopril-indapamide combination, was associated with 15% reduction in major macro- and micro-vascular events ( $P = 0.002$ ), 28% reduction in risk of all renal events ( $P = 0.0001$ ) and 18% reduction in all-cause death ( $P = 0.04$ ).<sup>[117]</sup>

## ISCHEMIC PRECONDITIONING

Mocanu *et al.*, using a murine model, demonstrated that glibenclamide inhibited mitochondrial  $K_{ATP}$  channels, impaired IPC and increased experimental infarct size, whereas glimepiride did not inhibit beneficial effects of mitochondrial  $K_{ATP}$  channel opening and showed no adverse effect on IPC or infarct size.<sup>[72]</sup> Moreover glimepiride was found to maintain myocardial preconditioning with fewer CV side effects as compared to glibenclamide ( $P = 0.01$  vs.  $P = 0.34$ , respectively).<sup>[118]</sup> Similar results were observed in a recent nation-wide registry, where the risk of acute MI was significantly lower with modern SUs (gliclazide MR, glimepiride) compared to glibenclamide (2.7% vs. 7.5%;  $P = 0.019$ ).<sup>[119]</sup> This finding further seems to confirm the beneficial effects of modern SUs in maintaining myocardial IPC. Although both glibenclamide and glimepiride have affinity for the  $SUR_2$  receptor, glimepiride appears to preserve myocardial preconditioning, a property not shared by glibenclamide.<sup>[27,72]</sup> Glimepiride was also reported to have a more rapid as well as longer duration of action; despite less stimulation of insulin secretion in comparison with glibenclamide.<sup>[120,121]</sup> Therefore, the effect of SUs on cardiac events depends on the molecule being used and the individual clinical setting of the individual case.<sup>[122]</sup>

### All-cause mortality

Varying risk of non-fatal CV outcomes and all-cause mortality have been reported by recent retrospective SU studies,<sup>[123-125]</sup> indicating the lack of class effect. For instance, a meta-analysis evaluating all-cause mortality risk among SUs, reported the relative risk of death of each SU versus glibenclamide to be: 0.65 (95% credible interval: 0.53–0.79) for gliclazide, 0.83 (0.68–1.00) for glimepiride, 0.98 (0.80–1.19) for glipizide, 1.13 (0.90–1.42) for tolbutamide, and 1.34 (0.98–1.86) for chlorpropamide.<sup>[114]</sup> However, a retrospective study found no difference in overall mortality risk with glipizide versus glibenclamide (hazard ratio 1.04 [0.94–1.15]), versus glimepiride (1.05 [0.92–1.19]), or with glibenclamide versus glimepiride (1.00 [0.89–1.14]) in patients with T2DM.<sup>[71]</sup>

Meta-analysis (14 trials) examining the patient-important outcomes of SUs versus metformin monotherapy found no significant difference in all-cause mortality (relative risk [RR] 0.98, 95% CI: 0.61 to 1.58) or CV mortality (RR 1.47, 95% CI: 0.54 to 4.01) in T2DM patients, but decreased risk of non-fatal macrovascular outcomes (RR: 0.67, 95% CI: 0.48 to 0.93).<sup>[29]</sup> Similar results were observed in a nation-wide study which demonstrated no significant difference between gliclazide and metformin for all-cause mortality in both patients without and with previous MI, [HR: 1.05; 95% CI:(0.94-1.16 and 0.90 (0.68-1.20)

respectively].<sup>[126]</sup> Moreover, studies evaluating the risk of all-cause mortality in combinations of metformin with SUs was lower (OR 0.66, 95% CI: 0.58-0.75)<sup>[127]</sup> compared to combinations of metformin with insulin (33.7 vs. 22.7 per 1000 person years; adjusted hazard ratio (aHR), 1.44; 95% CI, 1.15-1.79;  $P = 0.001$ ).<sup>[133]</sup>

## ROLE OF SULFONYLUREAS IN DIABETES MANAGEMENT IN SOUTH ASIA

### Affordability

Cost of medication is an important consideration, particularly in South Asia where a majority of patients are not covered under medical insurance.<sup>[128]</sup> Documented efficacy/long term outcome improvement, extensive experience, and low cost have positioned SUs as the choice of OHA for the management of T2DM, particularly in resource limited countries.<sup>[129]</sup> SUs offer similar to superior glycaemic efficacy, and remain a reasonable and cost effective alternative<sup>[130]</sup> to newer agents.<sup>[131]</sup> Treatment with modern SUs is associated with a lower economic burden,<sup>[132,133]</sup> and fares better than other regimens in the cost for average glycaemic lowering.<sup>[128]</sup>

### Adherence

Irrespective of the treatment regimen, poor adherence to medication is a common problem in T2DM. Adherence, defined as the extent to which patients take medications as prescribed,<sup>[134]</sup> depends on complexity of regimen, dose timing, need for self-monitoring, frequency of medication, associated side effects and cost of treatment.<sup>[135,136]</sup> Complexity of a regimen may be evaluated by considering the number of doses needed to lower glycaemic targets each day, and route of administration.<sup>[136]</sup> SUs have an oral route of administration (vs. injectable insulins and GLP-1 analogues) and once daily dosing schedule (vs. 1–2 daily for metformin and 3 times daily for alpha-glucosidase inhibitors and glinides).<sup>[128]</sup>

### Fixed dose combinations

Over time, the glucose lowering efficacy of OHAs may diminish due to the progressive nature of diabetes. A combination of two or more drugs with complementary mechanism of action can help overcome multiple aetiologies of hyperglycaemia. Further, compared to two-pill therapy, fixed dose combinations (FDCs) are known to increase patient adherence.<sup>[137,138]</sup> The most widely used and recommended combination of OHAs with SUs include metformin<sup>[9]</sup> and thiazolidinediones.<sup>[139]</sup> An FDC of glimepiride/metformin (1/250mg twice daily) was associated with significant reduction in HbA1c (−1.2 vs. −0.8%,  $P < 0.0001$ ), and FPG (−35.7 vs. −18.6 mg/dL,  $P < 0.0001$ ) compared to metformin up-titration treatment.<sup>[140]</sup> Similarly,



the FDC of pioglitazone/glimepiride (30 mg/3 mg and 15 mg/1 mg once daily) is well tolerated and found to significantly improve glycaemic control and lipid profiles in Japanese T2DM patients.<sup>[141]</sup> Therefore, using FDCs early in the course of natural history of disease progression, in optimal combinations and dosage may improve therapeutic outcomes in diabetes management.<sup>[142]</sup> Data from a prospective Indian multicentre study in urban primary care settings reported a significant reduction in HbA1c levels with FDC of gliclazide-metformin, with nearly 85% of patients achieving target FPG or HbA1c.<sup>[143]</sup>

## SPECIAL SITUATIONS

### Elderly

The elderly are at an increased risk of hypoglycaemia, due to declining renal and hepatic function, concurrent illnesses, poor caloric intake and poly-pharmacy.<sup>[30]</sup> Therefore, when prescribing SUs in elderly, one must exercise caution. It is suggested that use of either low dose<sup>[144]</sup> or short acting SUs is safe in this age group.<sup>[30,50]</sup>

### Pregnancy and lactation

All SUs are listed as pregnancy Category C drugs and their use during pregnancy is suggested only if benefits outweigh the potential risk.<sup>[145-147]</sup> Studies using a single-cotyledon placental model have found minimal trans-placental transfer of glibenclamide; an observation that paved the way for further research on its role in the management of gestational diabetes mellitus.<sup>[148,149]</sup> However, contradicting results from other studies, together with lack of adequate data regarding its safety during the first trimester, and reports of increased neonatal morbidity, do not allow us to recommend SU as first line therapy in pregnancy.

Chlorpropamide and tolbutamide are known to enter breast milk while glibenclamide and glipizide are excreted in breast milk in negligible amounts. Because of their potential to cause hypoglycaemia in nursing infants, SUs are generally contraindicated in nursing mothers. If these drugs are required to be used in feeding mothers, monitoring of the breastfed infant for signs of hypoglycaemia is advisable.

### Children and adolescents

There is no data supporting the use of SUs in children and adolescents (<18 years), and therefore SUs are not indicated in them. However, with increasing incidence of T2DM in paediatric and adolescent population, studies may be conducted to address the possible use of these agents in this age group. One 26-week, single-blind, active-controlled study, conducted in 285 paediatric subjects with T2DM, found that glimepiride was as effective as metformin in HbA1c reduction ( $-0.54\%$ ,  $P = 0.001$

and  $-0.71\%$ ,  $P = 0.0002$ , respectively) with similar rates of hypoglycaemia ( $4.9\%$  vs.  $4.2\%$ , respectively).<sup>[150]</sup>

### Use of sulfonylureas during Ramadan

Fasting during the holy month of Ramadan has both spiritual and health benefits. In healthy subjects, fasting improves metabolic control, reduces weight and helps control hypertension. However in patients with diabetes it can induce hypoglycaemia and related complications. Ramadan fasting is acceptable for patients with well-controlled T2DM who are adherent to diet and drug intake.<sup>[151]</sup> In case of hypoglycaemia, Islam allows the patients to perform regular blood glucose monitoring and even break the fast in emergency. During Ramadan, patients should follow a highly individualized management plan<sup>[152]</sup> to avoid diabetes-related complications.

Modern SUs like gliclazide MR and glimepiride are relatively safe and effective for use during Ramadan.<sup>[153,154]</sup> South Asian guidelines recommend modern SUs (gliclazide MR and glimepiride) as effective and economical option during Ramadan fasting.<sup>[155]</sup> A study in well-controlled Asian T2DM patients showed that monotherapy with gliclazide MR in the evening can safely maintain glycaemic control with fewer hypoglycaemic episodes during the Ramadan fast.<sup>[154]</sup> Similar findings were observed with glimepiride.<sup>[153]</sup> Therefore, use of modern SUs such as gliclazide MR and glimepiride, supported by a clinician guided dosing schedule<sup>[103]</sup> is suggested in T2DM patients during Ramadan fast.<sup>[155]</sup> Practical considerations to be followed when observing fasting during Ramadan are summarised in Table 9.

### Renal impairment

Most SUs are metabolized in the liver and are excreted by the kidney.<sup>[156]</sup> Therefore in patients with renal impairment, an increased risk of hypoglycaemia is invariably seen.<sup>[30,155]</sup> The use of SUs in patients with chronic kidney disease (Stage 3)

#### Table 9: Practice points for persons with diabetes observing fast during Ramadan

Consultation with physician is required one to 3 months before Ramadan  
Calorie should be kept same during Ramadan as before. Change schedule, amount, and composition of meals. Suhur should be taken close to Suhur time

Physical activity should be reduced during day time. However, physical exercise can be performed about 1 h after Iftar

Patients should monitor their blood glucose even during the fast to recognize subclinical hypo and hyperglycemia. If blood glucose is noted to be low (<60 mg/dl), the fast must be broken. If blood glucose is noted to be (>300 mg/dl), urine ketones should be checked and medical advice sought

Individualization and frequent monitoring of glycemia can significantly reduce the major risks associated with fasting during Ramadan  
Structured education and motivation regarding use of sulfonylureas and glucose monitoring is necessary throughout the year



is associated with increased risk of hypoglycaemia and requires due consideration to dose adjustment. Use of long acting SUs such as glibenclamide should be contraindicated in renal failure as the active metabolites tend to accumulate, resulting in pronounced hypoglycaemia.<sup>[30,145-147]</sup> On the other hand, short acting SUs like glipizide and tolbutamide with inactive metabolites may be used with appropriate dose adjustments and monitoring, in moderate renal impairment (Stage 2 and 3).<sup>[157]</sup> Additionally, attention to hepatic status and potential drug interactions is particularly important when renal function deteriorates. Table 10 summarizes the usage of different SUs in renal impairment.

### Hepatic impairment

Pharmacokinetic studies regarding the use of SUs in patients with hepatic insufficiency is lacking.<sup>[158]</sup> However, as most of the SUs are metabolized in liver, their use in patients with hepatic failure may pose challenges. In liver disease, inactivation of drugs is reduced, prolonging their half-life and consequently increasing the potential for hypoglycaemia. Moreover the extent of binding of SUs is dependent on the albumin concentration. Therefore in hypoalbuminemia, the amount of free drug available in plasma is enhanced resulting in frequent hypoglycaemia.<sup>[159]</sup> Hypoglycaemia is a major concern in patients with non-alcoholic steatohepatitis (NASH) when treated with SUs.<sup>[160]</sup> Further, alcohol induced enzyme degradation of SUs in patients with alcoholic liver disease may decrease clinical effectiveness of SUs. Moreover, patients with liver dysfunction experience depletion of glycogen storage, and lack of gluconeogenesis, predisposing them to hypoglycaemia.

## TRANSLATING EVIDENCE INTO CLINICAL PRACTICE

### Patient selection

Among many factors that are critical to the success of SU therapy, patient selection is paramount. Given that SUs act by stimulating  $\beta$ -cells, it is unlikely that patients without sufficient number of  $\beta$ -cells will respond to these medications. Therefore these agents may provide

clinically meaningful outcomes in T2DM patients who still retain some  $\beta$ -cell function.<sup>[50,51]</sup> SUs should be preferred as initial therapy in patients with newly or previously diagnosed (<5 years) with functional  $\beta$ -cell mass, contraindication or intolerance to metformin, high HbA1c levels, suspected MODY, and willingness to follow a regular dietary and exercise plan [Table 11].<sup>[31]</sup> Since SUs may influence weight changes, they should be preferred in leaner subjects; however, glimepiride and gliclazide MR can be used in both obese and non-obese subjects. Patients with hepatic and/or renal impairment are not suitable candidates for SU therapy.<sup>[161]</sup> Similarly, SUs should be avoided in elderly, patients with long-standing diabetes and those with poor nutrition or who commonly miss meals, or have concomitant CVD.<sup>[30,50,162]</sup>

### Drug selection

Clinical factors such as levels of fasting and post-prandial hyperglycaemia, comorbid hypertension, CVD, and hepatic or renal dysfunction determine the selection of one SU over the other. In patients with fasting hyperglycaemia twice daily SU in combination with metformin, while in those with post-prandial hyperglycaemia, short-acting SUs should be preferred.<sup>[50,145-147]</sup> For patients at higher risk of hypoglycaemia, gliclazide MR may be considered safe and effective. In the elderly and patients with hypertension or CVD or hepatic or renal dysfunction, glibenclamide is not preferred. If clinically indicated, glipizide can be used in patients with hepatic or renal dysfunction, and glimepiride or gliclazide in those with CVD [Table 11]. Combining two SUs with one other is not logical as they have similar mechanism of action. However, SUs may be combined with other OHAs such as biguanides, thiazolidinediones (with complementary mechanism of actions), and even with insulin.

### Dosage selection

In patients with T2DM who are uncontrolled on metformin, a low initial dose may be started and titrated every 1-2 weeks, based on self-monitoring of blood glucose until maximal benefit is achieved.<sup>[30]</sup> Long-term therapy should be continued as long as the drug maintains

**Table 10: Use of different SUs in renal impairment**

Class	Drug	CKD (stage 3-5)	Dialysis	Complications
Conventional SUs	Chlorpropamide	Reduce dose by 50% if GFR: 50-70 ml/min/1.73 m <sup>2</sup> Avoid if GFR <50 ml/min/1.73 m <sup>2</sup>	Avoid	Hypoglycemia
	Tolbutamide	Avoid	Avoid	Hypoglycemia
	Glibenclamide	Avoid	Avoid	Hypoglycemia
Modern SUs	Glimepiride	Start at low dose: 1 mg/day	Avoid	Hypoglycemia
	Gliclazide	No dose adjustment (ref. NKF 2012 guidelines)	Avoid/low dose and careful monitoring	Hypoglycemia
	Glipizide	No dose adjustment	No dose adjustment	Hypoglycemia
	Gliclazide MR	No dose adjustment (ref. NKF 2012 guidelines)	Avoid/low dose and careful monitoring	Hypoglycemia

GFR: Glomerular filtration rate, CKD: Chronic kidney disease, MR: Modified release, SUs: Sulfonylureas

**Table 11: Place of SUs in diabetes therapy**

Placement	Approach	Indication
Initial therapy	Monotherapy	Contraindication to metformin Intolerance to metformin
	Combination therapy with metformin	High blood glucose levels at presentation
2 <sup>nd</sup> line therapy	Add on therapy	Inadequate glycemic control with metformin
Subsequent add on therapy	Add on to combination	Inadequate glycemic control with existing oral therapy
Special consideration	Biological factors	Age >60  Renal impairment Neonatal diabetes MODY-3
	Psychosocial factors	Ramadan*
	Glucophenotype	Fasting hyperglycemia Postprandial hyperglycemia

\*Preferred SUs include modern SUs like glipizide MR, gliclazide, gliclazide MR, glimepiride. MR: Modified release, SUs: Sulfonylureas, MODY: Maturity-onset diabetes of the young

euglycaemia, without causing hypoglycaemia.<sup>[30]</sup> MR formulations of SUs may be used when further dose reduction is required.<sup>[131]</sup> It is recommended to reduce the dose of SU when DPP-4 inhibitors are initiated, especially in the elderly and/or patients with renal insufficiency. When appropriate glycaemic control is not achieved after initiation of DPP-4 inhibitors, consider increasing the dose of SUs. However when hypoglycaemic episodes are confirmed, reduction of dose should be considered.<sup>[162]</sup> Table 12 summarises strengths, time of administration and recommended dosages of available SUs either individually or in FDCs.

### Patient empowerment

Diabetes being a progressive disease requires constant self-management on day-to-day basis. The need for patient education and participation is more evident with the

**Table 12: Strengths and timing of administration of various SUs**

SUs	Strengths available (mg)	Recommended dose	Dose titration	Dose	
				Renal impairment	Hepatic impairment
Glipizide	IR: 5, 10 ER: 2.5, 5, 10	Before breakfast Adult: 5 mg daily Geriatric: 2.5 mg daily	Adult IR: 2.5-5 mg as frequently as every few days Adult ER: Adjustments no more frequently than every 7 days Geriatric IR: 2.5-5 mg every 1-2 weeks as needed Geriatric ER: Conservative titration	No adjustment	2.5 mg daily
Gliclazide	Tablet: 80 MR: 30,60	Adults: 40-80 mg daily in the morning MR: 30-120 mg at breakfast	increased if necessary up to 320 mg (4 tablets) daily Daily dose of MR not to exceed 120 mg	No dose adjustment (ref. NKF 2012 guidelines)	Tablet and MR: Not indicated in severe cases
Glibenclamide	Tablet: 1.25, 2.5, 5 Micronized tablet: 1.25, 2.5, 5	With breakfast or first main meal Adult: 2.5-5 mg daily Adult micro: 1.5-3 mg daily Geriatric: 1.25-2.5 mg daily	Adult: No more than 2.5 mg/day at weekly intervals Adult micro: No more than 1.5 mg/day at weekly intervals Geriatric: 1.25-2.5 mg, 1-3 weeks	Not recommended in CrCl <50 ml/min	Avoid in severe impairment
Glimepiride	0.5, 1, 2, 3, 4	With breakfast or first main meal Adult: 1-2 mg daily Geriatric: 1 mg daily	Adult: 1-2 mg every 1-2 weeks as needed Geriatric: Conservative titration Renal: Conservative titration	Start at 1 mg daily	No adjustment needed in minor. Contraindicated in severe impairment
Glipizide + metformin	2.5/250 2.5/500 5/500	With meals As with individual agents 2.5-10/250-2000	As with individual agents	As with individual agents	As with individual agents
Glibenclamide + metformin	1.25/250 2.5/500 5/500	With meals As with individual agents 1.25/250-20/2000	As with individual agents	As with individual agents	As with individual agents
Glimepiride + metformin	0.5/500 1/500 2/500 1/850 2/850 3/850 4/1000	Once daily with breakfast or first main meal As with individual agents 1/500-2/500	As with individual agents	As with individual agents	As with individual agents
Gliclazide/gliclazide MR + metformin	80/500 60/500	With meals As with individual agents	As with individual agents	As with individual agents	As with individual agents
Pioglitazone + glimepiride	30/2 30/4 15/1	Once daily with first main meal As with individual agents 30/2-4	As with individual agents	As with individual agents	As with individual agents

SU + voglibose + metformin and SU + pioglitazone + metformin are available in different strengths. IR: Immediate release, ER: Extended release, MR: Modified release, CrCl: Creatinine clearance, SUs: Sulfonylureas

growing complexity of management. Patients should be encouraged and supported to become active partners in decision-making process, to set realistic goals, select appropriate management strategies, enhance adherence and improve treatment outcomes. Patients and their families should be educated on safe use of SUs, while providing information on the signs and symptoms of hypoglycaemia, self-down titration of doses in case of hypoglycaemia, and the importance of regular and healthy lifestyle. Scored tablets may be used to facilitate down titration of doses in case of suspected hypoglycaemia. Training on hypoglycaemia awareness can increase adherence to prescribed SU regimen.<sup>[144]</sup> Self-monitoring of blood glucose (SMBG) is another important tool that aids in improving glycaemic control. Frequent SMBG is recommended in patients at increased risk of hypoglycaemia, particularly elderly and patients with renal or hepatic impairment.

### Physician empowerment

Physicians should adopt a patient-centred approach when prescribing SUs for management of diabetes. Physicians should carefully consider clinical profile of the patient and implement strategies that will not only help to minimize patient's concerns over SU treatment, but also empower them for self-management. Physicians play an important role in selecting the "right drug (SU in this case) in right dose at right time to right patient". It is important that SUs are initiated at low doses and gradually titrated until glycaemic targets are achieved. Clinical judgement is required when titrating SU dose. This is particularly crucial in patients with renal or hepatic impairment. At each visit physicians should enquire about symptoms suggestive of hypoglycaemia and adjust doses accordingly when risks outweigh glycaemic benefits. Pragmatic use of SUs based on various patient-related characteristics has been described in Table 13.<sup>[143]</sup>

## CONCLUSIONS

SUs are the main stream of pharmacotherapy in the management of patients with T2DM. Their well-established glycaemic efficacy, safety and tolerability support their use as an integral part of diabetes treatment. Given the fact that many of the clinical concerns associated with the use of SUs are agent-specific, and do not pertain to the class as such, a careful choice of specific SU should be considered beneficial. Considering better glycaemic efficacy, long-term outcomes and low medication cost, SUs, should be continued to be used as a front-line agent in the treatment algorithm of T2DM, particularly in South Asia. Proper patient selection, choice of drug and dose, patient education and empowerment, and physician training will help ensure effective and safe use of this important class of drugs.

**Table 13: Practical considerations for the use of SUs**

Pragmatic use of SUs
Posology
Begin with low doses and up-titrate slowly, at weekly or fortnightly intervals
Prescription
SUs should ideally be used if one or two other drug classes fail to achieve glycaemic targets
Avoid using SUs in conjunction with another SU and/or premixed or rapid acting insulin and/or meglitinides
SUs can be prescribed as part of BIDS regime
Hypoglycemia
Educate the patient with diabetes, and their family members, about hypoglycemia
Enquire about symptoms suggestive of hypoglycemia at each visit
Lifestyle
Advise a 3+3 meal pattern, especially with longer acting SUs
Avoid physical activity during the time interval between SU administration and meal intake and in the first few hours after SU ingestion
Avoid missing meals
Weight
Measure weight at every clinic visit
Request the patient with diabetes to inform the physician in case of sudden, unexplainable weight gain
Cardiovascular health
Assess cardiovascular health prior to SU prescription
Educate patients with diabetes, and family member, about symptoms of angina
Monitor cardiovascular health regularly
FDCs
Prefer FDCs if available
Prefer scored FDCs if available
Empower the patient with diabetes to self-titrate the dose if hypoglycemia occurs

FDCs: Fixed dose combination, BIDS: Bedtime insulin, day time SU, SUs: Sulfonylureas

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### Conflicts of interest

There are no conflicts of interest.

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