



Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus – International Task Force

Sanjay Kalra, Silver Bahendeka¹, Rakesh Sahay², Sujoy Ghosh³, Fariduddin Md⁴, Abbas Orabi⁵, Kaushik Ramaiya⁶, Sameer Al Shammari⁷, Dina Shrestha⁸, Khalid Shaikh⁹, Sachitha Abhayaratna¹⁰, Pradeep K. Shrestha¹¹, Aravinthan Mahalingam¹², Mazen Askheta¹³, Aly Ahmed A. Rahim¹⁴, Fatimah Eliana¹⁵, Hari K. Shrestha¹⁶, Sandeep Chaudhary¹⁷, Nancy Ngugi¹⁸, Jean Claude Mbanya¹⁹, Than Than Aye²⁰, Tint Swe Latt²¹, Zhanay A. Akanov²², Abbas Raza Syed²³, Nikhil Tandon²⁴, A. G. Unnikrishnan²⁵, S. V. Madhu²⁶, Ali Jawa²⁷, Subhankar Chowdhury³, Sarita Bajaj²⁸, Ashok Kumar Das²⁹

Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India, ¹Department of Internal Medicine, Diabetes & Endocrinology, St. Francis Hospital, Nsambya, Kampala, Uganda, ²Department of Endocrinology, Osmania Medical College, Hyderabad, Telangana, ³Department of Endocrinology, IPGIMER and SSKM Hospital, Kolkata, West Bengal, India, ⁴Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, ⁵Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt, ⁶Department of Internal Medicine, Hindu Mandal Hospital, Dar es Salaam, Tanzania, ⁷Department of Endocrinology, Al Jahra Hospital, Al Jahra, Kuwait, ⁸Department of Endocrinology, Norvic International Hospital and Medical College, and Hospital for Advanced Medicine and Surgery, Maharajganj, Kathmandu, Nepal, ⁹Department of Diabetes, Faculty of Internal Medicine, Royal Oman Police Hospital, Muscat, Oman, ¹⁰Department of Pharmacology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka, ¹¹Department of Medicine, Tribhuvan University Teaching Hospital, Maharajganj, Kathmandu, Nepal, ¹²Department of Medicine, Teaching Hospital, Jaffna, Sri Lanka, ¹³Department of Medicine, Tawam Hospital, Al Ain, UAE, ¹⁴Department of Internal Medicine, Diabetes & Metabolism Unit, Faculty of Medicine, Alexandria University, Alexandria, Egypt, ¹⁵Department of Internal Medicine, Faculty of Medicine, YARSI University, Jakarta, Indonesia, ¹⁶Department of Internal Medicine, Kathmandu University Hospital, Dhulikhel, Nepal, ¹⁷Department of Endocrinology, ADK Hospitals, Male, Maldives, ¹⁸Department of Endocrinology, Kenyatta National Hospital, Nairobi, Kenya, ¹⁹Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé, Yaoundé, Cameroon, ²⁰Department of Endocrinology, University of Medicine 2, Yangon, ²¹Department of Medicine, University of Medicine 2, Yangon, Myanmar, ²²Center of Diabetes, Clinic of Internal Diseases, Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan, ²³Department of Endocrinology, Shaikat Khanum Hospital and Research Center, Lahore, Pakistan, ²⁴Department of Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, ²⁵Department of Endocrinology and Diabetes, Chellaram Diabetes Institute, Pune, Maharashtra, ²⁶Department of Medicine, University of Delhi, New Delhi, India, ²⁷Department of Endocrinology, Diabetes and Metabolism, Wilshire Cardiovascular and Endocrine Center of Excellence, Lahore, Pakistan, ²⁸Department of Medicine, MLN Medical College, Allahabad, Uttar Pradesh, ²⁹Department of General Medicine, Pondicherry Institute of Medical Sciences, Puducherry, India

Abstract

For decades, sulfonylureas (SUs) have been important drugs in the antidiabetic therapeutic armamentarium. They have been used as monotherapy as well as combination therapy. Focus on newer drugs and concerns about the risk of severe hypoglycemia and weight gain with some SUs have led to discussion on their safety and utility. It has to be borne in mind that the adverse events associated with SUs should not be ascribed to the whole class, as many modern SUs, such as glimepiride and gliclazide modified release, are associated with better safety profiles. Furthermore, individualization of treatment, using SUs in combination with other drugs, backed with careful monitoring and patient education, ensures maximum benefits with minimal side effects. The current guidelines, developed by experts from Africa, Asia, and the Middle East, promote the safe and smart use of SUs in combination with other glucose-lowering drugs.

Keywords: Gliclazide, glimepiride, sulfonylureas, type 2 diabetes

EXECUTIVE SUMMARY

Sulfonylureas (SUs) in oral combination therapy:

- A1. Modern SUs (glimepiride and gliclazide modified release [MR]) are effective and safe second-line agents in patients who have not achieved predecided glycemic

targets with metformin monotherapy (Grade A; evidence level [EL] 1)

Address for correspondence: Dr. Sanjay Kalra,
Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India.
E-mail: brideknl@gmail.com

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- A2. Modern SUs are effective and safe as initial therapy if used in combination with lifestyle modification and metformin, in patients with a baseline glycated hemoglobin $\geq 7.5\%$ (Grade A; EL 1)
- A3. SUs may be considered for use in combination with all classes of oral antidiabetic drugs except glinides (Grade A, EL1)
- A4. If not used earlier, modern SUs may be preferred as third-line agents for the management of uncontrolled diabetes with dual combination therapy, owing to better safety profile than older SUs (Grade A, EL 1)
- A5. Fixed-dose combinations (FDCs) containing SUs reduce cost, offer convenience, and improve patient adherence (Grade B; EL 1); hence, FDCs with varying strengths of SU + metformin should be made available, while SU + other drugs may be considered (Grade A; EL 4).

Comparative assessment as dual therapy with metformin:

- B1. Compared to metformin uptitration beyond half-maximal dose, the addition of SU to metformin demonstrates better glucose-lowering efficacy, safety, and tolerability (Grade A, EL 1)
- B2. Compared to pioglitazone, SUs demonstrate good glucose-lowering efficacy with significantly lower risk of weight gain (Grade A, EL 1)
- B3. Compared to dipeptidyl peptidase 4 inhibitors, SUs demonstrate better and more durable glucose-lowering efficacy; however, the likelihood of increase in body weight and risk of hypoglycemia should be taken into consideration (Grade A, EL 1)
- B4. Compared to sodium glucose co-transporter 2 inhibitors, SUs show noninferior glycemic control; however, safety criteria need to be considered while preferring either class (Grade A, EL 1)
- B5. Compared to glucagon-like peptide 1 receptor agonists, SUs show similar glycemic efficacy, with acceptable safety at lower cost (Grade A, EL 1).

SU and insulin combination:

- C1. Modern SUs may be continued, with appropriate precaution, when basal insulin is initiated (Grade A; EL1)
- C2. Modern SUs may be continued, in the antipodal meal, if premixed insulin is initiated once daily (Grade A; EL1)
- C3. Short-acting SUs, or glinides, may be continued or added to the third meal, with appropriate glucose monitoring if premixed insulin is initiated twice daily (Grade B; EL 1).

Use in special populations:

- D1. Combinations containing modern SUs can be used in elderly patients as they are associated with low risk of hypoglycemia (Grade A; EL 1)
- D2. SUs (glibenclamide) may be used in the glycemic control of neonatal diabetes (*KCNJ11*, *ABCC8* gene mutations) and Maturity-Onset Diabetes of the Young 3 (MODY 3) (Grade A; EL 3)
- D3. The evidence base for the use of SUs in adolescents with type 2 diabetes is limited (Grade A; EL 4)

Table 1: Classification of sulfonylureas

Classification based on hierarchy of development	
Conventional	TOLB, CHOL, GLIB, GLIP, gliquidone
Modern	GLIM, GLIC, GLIC MR, GLIP MR/XL
Classification based on duration of action	
Short acting	TOLB
Intermediate acting	GLIP, GLIC, gliquidone
Long acting	CHOL, GLIB, GLIM, GLIC MR, GLIP MR

MR: Modified release, XL: Extended release, TOLB: Tolbutamide, CHOL: Chlorpropamide, GLIB: Glibenclamide, GLIP: Glipizide, GLIM: Glimepiride, GLIC: Gliclazide

Table 2: Sulfonylureas listed in the National List of Essential Medicines of different countries in Africa, Middle East and North Africa, and South East Asian region

Countries/drugs	GLIB	GLIC	GLIP	GLIM
Bahrain	Yes	Yes	Yes	Yes
Bangladesh	Yes	Yes	No	No
Egypt	Yes	No	No	No
India	No	No	No	Yes
Indonesia	Yes	No	Yes	No
Kenya	Yes	Yes	No	No
Kuwait	Yes	Yes	No	No
Maldives	Yes	Yes	Yes	Yes
Myanmar	Yes	Yes	Yes	Yes
Nepal	Yes	No	Yes	No
Nigeria	Yes	Yes	No	No
Oman	Yes	Yes	Yes	Yes
Pakistan	Yes	No	No	No
Qatar	Yes	Yes	Yes	Yes
Saudi Arabia	Yes	Yes	Yes	Yes
South Africa	Yes	No	No	Yes
Sri Lanka	Yes	No	No	No
Tanzania	Yes	Yes	Yes	No
The UAE	Yes	Yes	Yes	Yes
Uganda	Yes	No	No	Yes

UAE: United Arab Emirates, GLIB: Glibenclamide, GLIP: Glipizide, GLIM: Glimepiride, GLIC: Gliclazide

- D4. There is insufficient evidence to recommend the use of SUs, as monotherapy or in combination, to be used during pregnancy and lactation (Grade A; EL 2).

Use in comorbid conditions:

- E1. There is insufficient evidence to suggest that modern SUs increase cardiovascular (CV) risk. Modern SUs are preferred over conventional SUs in patients with diabetes and cardiovascular disease (CVD) (Grade A; EL 1)
- E2. Among SUs, short-acting drugs, especially those metabolized in the liver (glipizide), should be preferred in patients with moderate/severe renal impairment. In mild/moderate renal impairment, modern SUs may also be used, preferably at lower doses (Grade A; EL 3)
- E3. Reductions of SU dose and/or longer intervals between

Table 3: A complete list of situational analysis of sulfonylureas and sulfonylurea combinations in participating countries

Countries	Prevalence (%)	Monotherapy available	FDCs (OADs) available
Bangladesh	7.1 million	GLIM, GLIC MR, GLIP, and GLIB	GLIM/MET
Egypt	8.3	GLIM, GLIC MR, GLIP, and GLIB	GLIM/MET GLIB/MET GLIM/PIO
India	10-14	GLIM replaced GLIB in NELM 2015 GLIM, GLIC, GLIC MR, GLIP, and GLIB	GLIM/MET GLIB/MET GLIC MR/MET GLIP/MET GLIM/MET/PIO GLIM/MET/VOGL GLIC/MET/PIO GLIC/MET/VOGL
Indonesia	9.1	SUs are the first priority among other OADs GLIM, GLIC, GLIC MR, GLIP, gliquidone, and GLIB	GLIM/MET GLIB/MET
Kuwait	21	GLIM, GLIC MR, and GLIB	GLIM/MET SU/MET/DPP-4I SU/MET/SGLT-2I
Maldives	8	GLIM, GLIC, GLIP, and GLIB	GLIM/MET
Myanmar	10.5	GLIM, GLIC, GLIP, and GLIB	GLIB/MET GLIM/MET
Nepal	5.6	GLIM, GLIC, GLIC MR, GLIP, and GLIB	GLIM/MET GLIB/MET GLIC MR/MET
Oman	13-14	All SUs except first-generation SUs	No SU FDC
Pakistan	6.9	GLIM, GLIC MR, GLIP, and GLIB	GLIM/MET GLIB/MET SU/PIO
Sri Lanka	10-12	GLIM, GLIC, GLIC MR, GLIP, TOLB, and GLIB	No FDCs for diabetes
Tanzania	9.8	GLIM, GLIC MR, CHOL, and GLIB	GLIM/MET GLIB/MET
The UAE	20	GLIM, GLIC, GLIC MR, and GLIB	GLIB/MET
Uganda	1.4	GLIM and GLIB	GLIM/MET GLIB/MET GLIM/MET/PIO SU/DPP-4I SU/SGLT-2I

CHOL: Chlorpropamide, DPP-4I: Dipeptidyl peptidase 4 inhibitor, FDC: Fixed-dose combinations, GDM: Gestational diabetes mellitus, GLIB: Glibenclamide, GLIC: Gliclazide, GLIP: Glipizide, GLIM: Glimepiride, MENA: Middle East and North Africa, MET: Metformin, MR: Modified release, NELM: National Essential List of Medicines, OADs: Oral antidiabetic agents, PIO: Pioglitazone, SEA: South East Asia, SGLT-2I: Sodium glucose cotransporter-2 inhibitor, SITA: Sitagliptin, SUs: Sulfonylureas, TOLB: Tolbutamide, VOGL: Voglibose, UAE: United Arab Emirates

dosing are recommended in patients with mild/moderate hepatic impairment (Grade B; EL 4).

SUs in combination and Ramadan:

- F1. Modern SUs may be used in combination with other drugs during Ramadan, with appropriate counseling and dose modification (Grade A; EL 3)
- F2. Individuals on once-daily SU should take their medication at Iftar (evening meal) (Grade A; EL 3)
- F3. Individuals on twice-daily SU may shift the morning dose to Iftar and half of the evening dose to Suhur (morning meal) (Grade A; EL 4)
- F4. Patients on SU and premixed insulin should consider reducing the dose of either drug or shifting from premix to low-peak basal insulin during Ramadan (Grade A; EL 4)

- F5. Dose titration during Ramadan should be based on twice-weekly or weekly glucose monitoring (Grade A; EL 3).

INTRODUCTION

Epidemiology and burden of diabetes

Type 2 diabetes mellitus (T2DM), a progressive metabolic disorder, is continuously gaining the status of a potential epidemic in the world. According to the 2015 global estimates of International Diabetes Federation (IDF), about 415 million people (1 in 11 adults) have been shown to present with diabetes and is expected to reach 642 million (1 in 10 adults) by 2040.^[1] Moreover, around 318 million adults are associated with impaired glucose tolerance, who

are at a high risk of developing diabetes in the future. The 2015 regional fact sheet of IDF estimates the prevalence to be 10.7%, 8.5%, and 3.2% in the Middle East and North Africa (MENA), South East Asia (SEA), and African regions, respectively.^[1] This increasing burden of the disease may contribute to increased rate of complications, reduction of quality of life, and premature mortality. As per the 2016 World Health Organization (WHO) global report on diabetes, the high blood glucose age-standardized mortality rates are 139.6, 115.3, and 111.3/100,000 in WHO Eastern Mediterranean, South-East Asia, and African regions, respectively.^[2]

Prescription pattern of oral antidiabetic drugs

Tight glycemic control reduces the associated complications and improves the quality of life in patients with T2DM. The United Kingdom Prospective Diabetes Study trial reported that each 1% reduction of glycated hemoglobin (A1C) decreases approximately 12%–43% risk of diabetes-related mortality and morbidity.^[3] Numerous antidiabetic agents are currently available as monotherapy or in combination therapy for the treatment of T2DM. However, oral antidiabetic drugs (OADs) still dominate the prescribing pattern (56.4%) followed by insulin alone (43.6%).^[4,5] Furthermore, sulfonylureas (SUs) alone or in combination with metformin have been the most commonly prescribed OADs in some Afro-Asian countries.^[6–9]

SUs can be classified either according to their hierarchy of development (conventional and modern SUs) or based on the duration of action (short-, intermediate-, and long-acting). The classification has been described in Table 1. This helps to avoid confusion during their use and can be effectively utilized in patients with variable clinical scenario.

Situational analysis of sulfonylureas

The conventional or modern SUs are widely used as second-line agents in the management of T2DM in most countries of Africa, MENA, and SEA region due to low cost and high efficacy. Among all, the combination of glimepiride (GLIM) and metformin is available in most of these countries. The National List of Essential Medicines (NLEM) in different countries containing SUs along with metformin is shown in Table 2. In 2015, the Indian NLEM was updated to align with the current treatment guidelines. Where more drugs were available within a therapeutic class, the core committee considered the best-suited one after due deliberation and careful evaluation of their relative safety, efficacy, and cost.

Accordingly, glibenclamide (GLIB) has been replaced with GLIM in the diabetes section.^[10] Tolbutamide (TOLB) and chlorpropamide (CHOL) are still used in Sri Lanka and Tanzania, respectively; gliquidone is available in Indonesia and Egypt. Fixed-dose combinations (FDCs) containing either conventional or modern SUs are available in most of the countries in Africa, MENA, and SEA regions except Oman and Sri Lanka. Furthermore, basal or premix insulin in combination with SUs is also prescribed for the management of T2DM in different parts of the world. A complete list of situational analysis of SUs in participating countries is summarized in Table 3.

RATIONALE AND METHODOLOGY

Pathophysiological basis

During the course of treatment, progressive nature of T2DM with a gradual decline in the functional β -cells leads to continuing the decrease in the glucose-lowering efficacy of OADs over time.^[11] Evidence suggests that early combination therapy with intensive glycemic control can be an effective approach for better preservation of β -cell function, which may quickly attain the target glycemic level and reduce diabetic-related complications.^[12–17] Early introduction of combination therapy also reduces complications associated with up-titration of monotherapies. The delay in stepping up from monotherapy to combination therapy in the step-wise approach contributes to long periods of hyperglycemia and an increased risk of macro- and microvascular complications.^[18]

Pharmaceutical advances

Metformin produces its antihyperglycemic action without affecting the insulin secretion; hence, it is beneficial in combining metformin with insulin secretagogue, like an SU. Among OADs available as add-on therapies to metformin, modern SUs can be considered as an ideal option owing to their high efficacy, relative cardiovascular (CV) safety, and low cost. The risk of hypoglycemia and weight gain can be minimized using modern SUs such as GLIM and gliclazide (GLIC) modified release (MR) with fewer side effects and better efficacy, which also has contributed to their wider use. Furthermore, combination therapies show a greater blood glucose-lowering effect than that of a single agent, which has been demonstrated in a number of studies and has resulted in the marketing of FDC preparations.^[11,19]

Table 4: Evidence and recommendation grading according to the American Association of Clinical Endocrinologists guideline

Evidence level	Semantic descriptor (reference methodology)	Grades	Recommendation
1	Meta-analysis of RCTs, RCTs	A	Strong
2	Meta-analysis of nonrandomized prospective or case-controlled trials, non-RCT, prospective cohort study, retrospective case-control study	B	Intermediate
3	Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database), consecutive case series, single case reports	C	Weak
4	No evidence (theory, opinion, consensus, review, or preclinical study)	D	No evidence

AACE: American Association of Clinical Endocrinologists, RCTs: Randomized controlled trials

Table 5: Sulfonylureas with respect to their generation, history of development, duration of action, and other pharmacokinetic/pharmacodynamic profile (adapted from)

PK/PD properties	GLIB	GLIC	GLIP	GLIM	GLIP XL	GLIC MR
Generation	Second	Second	Second	Third	Third	Third
History of development	1984	1984	1984	1995	1995	1995
Duration of action (h)	16-24	10-24	12-24	24	>24	>24
V _d (L)	9-10	13-24	10-11	19.8-37.1	10	19
Protein binding (%)	99	85-99	98-99	99	98-99	>90
Metabolism	Hepatic			Hepatic (no active metabolites)		
Bioavailability (%)	99	80	100	100	100	97
Half-life (h)	10	8-12	2-5	5	2-5	16
Time to peak (h)	2-4	2-4	1-3	2-3	6-12	6-7
Excretion	50% renal	80% renal	80% renal	60% renal	80% renal, 10% feces	<60%-70% renal 10%-20% feces
Drug-drug interaction	May interact with CYP2C9 inducers or inhibitors					
PK changes in the elderly	Slow elimination; the high volume of distribution	Half-life likely increase and slower elimination	No significant differences in PK properties			
PK changes in renal and hepatic impairment	May be altered; risk of toxic reactions to the drug increases	May affect the distribution; reduce the capacity for neoglucogenesis	Metabolism and excretion may be slowed	No significant differences in renal impairment; not evaluated in hepatic impairment	May affect the disposition of drug; diminish gluconeogenic capacity	May affect the distribution; reduce the capacity for neoglucogenesis; the risk of hypoglycemia increases

V_d: Volume of distribution, MR: Modified release, XL: Extended release, PK/PD: Pharmacokinetics/pharmacodynamics, GLIB: Glibenclamide, GLIC: Gliclazide, GLIP: Glipizide, GLIM: Glimepiride

Methodology

The current consensus reviews the recent evidence on SUs and presents evidence-based recommendations on the use of SUs and their combination for the management of T2DM. In order to impart the highest possible evidence base for the use of SUs in combination in the management of T2DM, a systematic review of the literature was initiated. Existing guidelines, meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-RCTs, and key cited articles relating to T2DM management were reviewed and recommendations were framed. Recommendations for each section of the consensus statement were discussed by the expert panels and where there was a little or no evidence, the panel relied on logical empiricism and consensus to make their recommendations. The current consensus is developed in accordance with the American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines.^[20] Recommendations are based on clinical importance (graded as A: strong, B: intermediate, C: weak, and D: no evidence based), which were coupled with four intuitive levels of evidence (1 = “at least one RCT or meta-analysis of RCTs,” 2 = “at least one nonrandomized or noncontrolled, prospective epidemiological study,” 3 = “cross-sectional or observational or surveillance or pilot study,” and 4 = “existing guideline or consensus expert opinion on extensive patient experience or review”) [Table 4].

SULFONYLUREAS AND TYPE 2 DIABETES MELLITUS

History

SUs have been a cornerstone in the T2DM management for

the past 60 years. TOLB was the first SU marketed in the 1950s. This was followed by the introduction of the other first-generation agents such as CHOL, acetohexamide, and tolazamide. The next advancement in SU therapy was the development of potent second-generation agents such as GLIB and glipizide (GLIP) in the year 1984 in the United States. Furthermore, GLIM, a third-generation agent with eminent characteristics, was released into the market in the year 1995.^[21-23] SUs with respect to their generation, history of development, duration of action, and other pharmacokinetic/pharmacodynamics profiles are described in Table 5.^[5]

Mechanism of action and differential effects of sulfonylureas

SUs have been categorized as insulin secretagogues. They act by stimulating the pancreatic β -cells to secrete insulin. SUs mainly bind to the SU receptors (SURs), a subunit of potassium ATP-dependent (K_{ATP}) channels located in the β -cell membrane, which eventually blocks the potassium channels and facilitates the influx Ca^{2+} into the cell. This leads to cell depolarization and subsequently accelerates insulin exocytosis [Figure 1a].^[5,23] Furthermore, owing to their cell-mediated and nonglucose-mediated action, all SUs are more effective in the early stages of T2DM when the β -cell function is to its greatest ability.^[11,24] All the SUs are eliminated by liver and kidney and well tolerated by adult patients; however, hypoglycemia and weight gain are the concerns with conventional SUs.^[25,26]

The affinity of SUs varies with different SUR subunits present in K_{ATP} channels.^[5] It is reported that GLIB blocks both

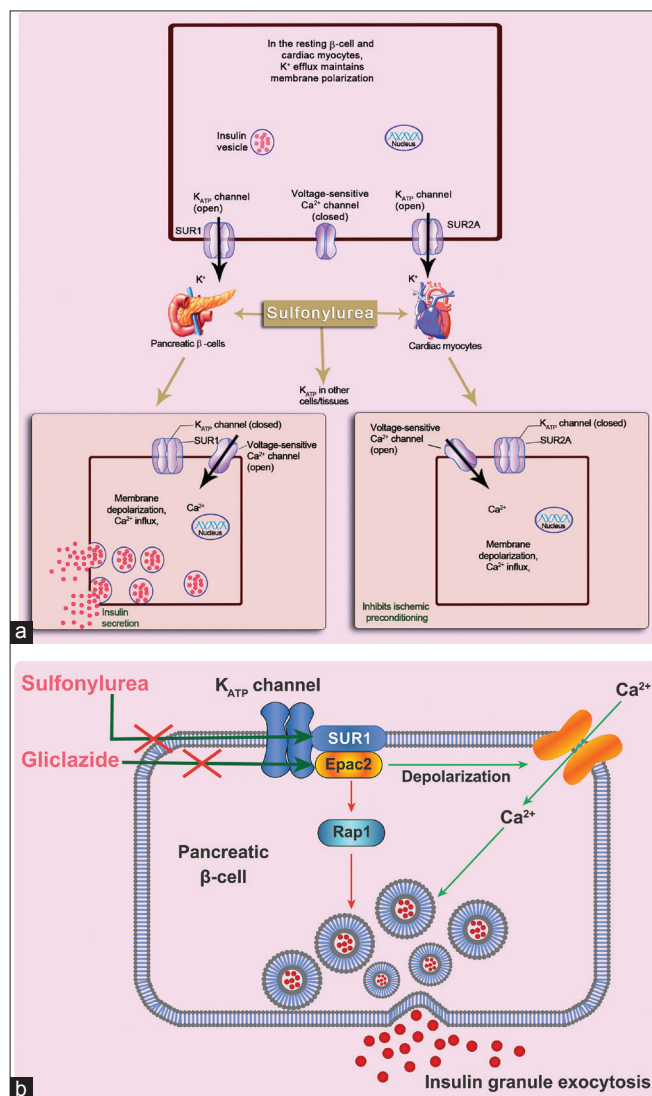


Figure 1: Mechanism of action of sulfonylureas. (a) General mechanism of action of all sulfonylureas. (b) Differential mechanism of action of gliclazide

SUR₁ (pancreatic β -cells) and SUR₂ (cardiac and skeletal muscles) subunits with similar affinity. The modern SU, GLIM, blocks SUR₁ and preferentially the sarcolemmal SUR₂ while sparing the mitochondrial SUR. A number of studies, however, have demonstrated that GLIM does not have a negative impact on cardiac function and has less effect on the electrical properties of the heart.^[27,28] GLIC and TOLB selectively block only SUR₁ compared to SUR₂.^[29,30] The affinity of SUR₁ protein toward sulfonyl moiety is 100–1000 folds more compared to SUR₂ protein.^[31] Furthermore, GLIC is the only SU which does not bind to the Epac2 receptor [Figure 1b]^[5], a stimulating factor for insulin exocytosis, which may confer a lower risk of hypoglycemia.^[5,32] Similarly, GLIM also confers a low rate of hypoglycemia and weight gain than conventional SUs due to its lower binding affinity (2–3 folds) and quick association and dissociation with SUR proteins.^[33–35] Furthermore, SUs inhibit the mitochondrial K_{ATP} channels in cardiac myocytes, which contributes to impairment of ischemic preconditioning;

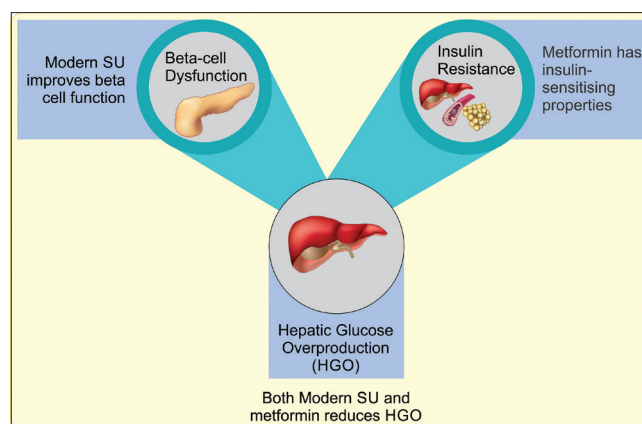


Figure 2: Complementary mechanism of action of sulfonylurea-metformin combination therapy

however, GLIM does not exert this effect and preserves myocardial ischemic preconditioning.^[5] Moreover, a lesser pancreatic overstimulation and resultant low hypoglycemia by GLIC could be due to the restoration of the early insulin peak in response to glucose stimulation and higher reversibility of binding of GLIC to the SUR1 of β -cell.^[36] In addition, modern SUs also exhibit certain pleiotropic effects such as insulin clearance, glucagon secretion, insulin sensitization, anti-oxidative effect, angiogenesis, vascular health, and ischemic preconditioning.^[5]

Summary of guidelines recommending SUs and combinations for the management of type 2 diabetes mellitus

The addition of SUs has been the gold standard combination therapy for decades in patients who fail to achieve target glycemic control with metformin monotherapy.^[37] In addition, pertaining to their low cost and high efficacy, SUs are widely used as a second-line agent in different regions of the world for the management of diabetes. Moreover, modern SUs such as GLIM and GLIC MR are preferred over other SUs in diabetic patients due to low risk of hypoglycemia and CV neutrality.^[36,38–40] A summary of guidelines recommending SUs in combination therapy for the management of T2DM in various countries is depicted in Table 6.

SULFONYLUREAS AND COMBINATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Sulfonylurea + metformin

Mechanism

A combination of two drugs with the complementary mechanism of action may help in addressing multiple etiologies of hyperglycemia in patients with T2DM.^[5] Metformin has insulin-sensitizing properties. It facilitates insulin uptake by the peripheral tissues and enhances the glucose utilization in adipose and intestinal tissues. SUs increase the sensitivity of β -cells to glucose and facilitate endogenous secretion of insulin. Furthermore, both metformin and SUs may reduce hepatic glucose

Table 6: Summary of guidelines recommending sulfonylureas and combination for management of type 2 diabetes mellitus

Guideline	Summary
AACE, 2017 ^[41]	If entry level A1C $\geq 7.5\%$, consider initiation of combination therapy
ADA, 2017 ^[42]	If entry level A1C $\geq 9\%$, consider initiation of combination therapy SUs are recommended as an add-on therapy to metformin If not used in first or second place of the regimen, SUs should be added as a third-line agent
Bahrain guidelines, 2014 ^[43]	SUs are the second-line options for patients with uncontrolled glycemic level with metformin
DAN, 2013 ^[44]	Modern SUs are more effective with fewer side effects than conventional SUs SUs work best with patients >40 years old, who have had diabetes mellitus for <10 years
Dutch guidelines, 2013 ^[45]	As a second-line drug, GLIC is the preferred SU
EMRO, 2006 ^[46]	Combinations of oral agents, in particular, SUs plus metformin, have improved the care of diabetic patients and may be used when monotherapy is ineffective
Kenya guidelines, 2010 ^[47]	Combination therapy should be considered as the initial choice if A1C $>8\%$ SUs are the only second-line option for patients failing monotherapy Fixed-dose combination therapies may prefer over two or three drug combinations
IDF, 2014 ^[48]	SUs are the only usual second-line options for patients with uncontrolled glycemic level with metformin
NICE, 2015 ^[49]	If A1C is still $>7.5\%$ after initiation of first-line therapy, introduce combination therapy SUs are recommended as the second-line agents in patients who are not overweight and those requiring a rapid response due to hyperglycemic symptoms
RSSDI, 2015 ^[50]	It recommends early initiation of combination therapy when monotherapy is unlikely to achieve glycemic goals and SUs should be preferred as dual therapy in patients with long-standing diabetes or from poor financial background
SAFES-I, 2015 ^[5]	SUs are effective second-line agents after metformin, in the management of T2DM. SU monotherapy as first-line agent may be considered in T2DM with metformin intolerance/contraindication and in patients with MODY Modern SUs should be initiated early in the course of T2DM, to achieve maximum glycemic benefits and obtain the benefits of metabolic memory 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
SCAD guidelines ^[51]	All SCAD patients with diabetes should be treated with oral antidiabetics which have shown CV safety/benefits such as metformin and GLIC (Grade A, evidence level 2)
SEMDSA, 2017 ^[52]	GLIC MR is the preferred SU either as monotherapy or add-on therapy in majority of patients with T2DM, due to its equivalent efficacy, lower rates of hypoglycemia, and better CV and renal safety relative to other SUs Other drugs such as pioglitazone and dipeptidyl peptidase 4 inhibitor can be used only when GLIC MR is contraindicated
Tanzania guidelines, 2013 ^[53]	SUs are recommended as the first-line agent for nonobese patients and as add-on to metformin if target is not achieved in 3 months
UAE guidelines, 2009 ^[54]	SUs are recommended as second- and third-line agents in the management of T2DM
Uganda guidelines, 2016 ^[55]	GLIB/GLIM is recommended as add-on to metformin if target is not achieved with both lifestyle therapy and metformin

AACE: American Association of Clinical Endocrinologist, ADA: American Diabetes Association, DAN: Diabetes Association of Nigeria, EMRO: Regional Office for the Eastern Mediterranean, IDF: International Diabetes Federation, MODY: Maturity-Onset Diabetes of the Young, NICE: National Institute for Health and Care Excellence, RSSDI: Research Society for the Study of Diabetes in India, SCAD: Stable coronary artery disease, SEMDSA: Society of Endocrinology, Metabolism, and Diabetes of South Africa, SUs: Sulfonylureas, T2DM: Type 2 diabetes mellitus, UAE: United Arab Emirates, SAFES: South Asian Federation of Endocrine Societies, A1C: Glycated hemoglobin, GLIC: Gliclazide, CV: Cardiovascular, MR: Modified release, DPP-4I: Dipeptidyl peptidase 4 inhibitor, GLIB: Glibenclamide, GLIM: Glimepiride

overproduction by decreasing hepatic gluconeogenesis and glycogenolysis; however, the relative contribution of gluconeogenesis and glycogenolysis by metformin remains controversial.^[56,57] Moreover, SUs may inhibit secretion of glucagon from islet cells^[58] and also stimulates glycogen synthesis in the liver.^[57] Diagrammatic representation of the complementary mechanism is shown in Figure 2.

Glycemic efficacy

The addition of SUs to ongoing metformin monotherapy has shown good glycemic control with acceptable safety and tolerability in numerous meta-analyses and RCTs.

Sulfonylureas add-on to metformin versus metformin monotherapy

A meta-analysis of 15 RCTs each lasting <1 year compared metformin monotherapy with the combination of metformin

and SUs. All included studies favored the combination arm over monotherapy for glycemic efficacy with a pooled between-group difference of 0.9% (95% confidence interval [CI]: $0.7\%–1.2\%$).^[59] In another meta-analysis, when SU was added to oral medication, A1C was reduced by 1.62% (95% CI: $1.00, 2.24$; $P = 94.1\%$) in the SU group than in the comparator group.^[60] A placebo-controlled study by Ahren *et al.* with a duration lasting up to 104 weeks compared metformin (>1500 mg daily) with the combination of metformin (≥ 1500 mg daily) plus GLIM (up to 4 mg daily). The study showed a between-group difference in A1C of 0.63% at the end, favoring the combination arm.^[61] In a randomized, open-label, parallel group, multicenter trial, GLIM/metformin FDC therapy provided significantly greater adjusted mean decreases in A1C (-1.2 vs. -0.8% , $P < 0.0001$) and fasting plasma glucose (FPG) (-35.7 vs. -18.6 mg/dL, $P < 0.0001$) compared

Table 7: Summary of randomized controlled trials evaluating different sulfonylureas in combination with metformin compared to metformin monotherapy

Author	Intervention	Glycemic efficacy	Adverse events	Weight gain	Conclusion
GLIM					
Charpentier <i>et al.</i> , 2001 ^[64]	GLIM + metformin (A) versus metformin (B) with monotherapy failure	↓ A1C (A vs. B): -0.74 ± 0.96 versus $+0.07 \pm 1.20\%$; $P < 0.001$ ↓ FBG (A vs. B): -1.8 ± 2.2 versus $+0.8 \pm 0.4$ mmol/l, $P < 0.001$ ↓ PPBG (A vs. B): -2.6 ± 3.9 versus $+1.1 \pm 5.9$ mmol/l, $P < 0.001$	The incidence of symptomatic hypoglycemia was higher with A than B ($P = 0.039$)	-	Addition of GLIM in T2DM patients uncontrolled by metformin alone resulted in superior glycemic control than metformin monotherapy
González-Ortiz <i>et al.</i> , 2004 ^[65]	GLIM + metformin (A) versus metformin (B)	↓ A1C (A vs. B): -1.3 ± 1.8 versus $-0.7 \pm 2.1\%$ Percentage of patients showed ↓ A1C ($\geq 1\%$) (A vs. B): 47.0% versus 21.2%; $P < 0.001$	The frequency of adverse events was similar for both the groups	-	The combined use of GLIM-metformin in a single presentation was efficacious and safe in patients with T2DM
Kim <i>et al.</i> , 2014 ^[62]	GLIM-metformin FDC (A) versus metformin up titration (B)	↓ A1C (A vs. B): -1.2% versus -0.8% , $P < 0.0001$ ↓ FPG (A vs. B): -35.7 versus -18.6 mg/dL, $P < 0.0001$ Patients achieved A1C $< 7\%$ (A vs. B): 74.7% versus 46.6%, $P < 0.0001$	Hypoglycemia (A vs. B): 41% versus 5.6%, $P < 0.0001$ No serious hypoglycemia in any group	Change in body weight (A vs. B): $+1.0$ versus -0.7 kg	FDC was more effective than metformin up titration
GLIC					
Ristic <i>et al.</i> , 2007 ^[66]	GLIC + metformin versus nateglinide + metformin	Change from baseline to 52 weeks for GLIC combination: A1C, -0.27% ($P = 0.396$); FPG, -0.7 mmol/l; ($P = 0.096$)			Metformin-GLIC combination is effective in uncontrolled T2DM patients
GLIP					
Goldstein <i>et al.</i> , 2003 ^[67]	GLIP/metformin combination (A) versus metformin or GLIP monotherapy (B)	↓ A1C (A vs. B): -1.06% versus -0.98% , $P < 0.001$ Percentage of patients showed ↓ A1C $< 7.0\%$ (A vs. B): 36.3% versus 9.9% or 8.9% FPG and 3 h PPG more effectively ↓ in Group A than B	Both treatments were well tolerated, with a low incidence of symptoms of hypoglycemia	-	Combination was more effective in controlling A1C and FPG in uncontrolled T2DM patients with monotherapies
Feinglos <i>et al.</i> , 2005 ^[68]	GLIP GITS (A) versus placebo (B), both added to metformin ≥ 1000 mg/day for ≥ 3 months	Significantly greater improvements in mean A1C and FPG from baseline to end point in A than B ($P < 0.0002$) Significantly more patients achieved target A1C $< 7.0\%$ ($P < 0.0001$) and A1C $< 6.5\%$ ($P < 0.0033$) in Group A than B	Both treatment regimens were well tolerated	Addition of GLIP GITS did not produce any significant or clinically relevant weight gain or changes in BMI	Addition of GLIP GITS 2.5 mg significantly improved glucose control in patients with T2DM inadequately controlled with metformin monotherapy
GLIB					
Marre <i>et al.</i> , 2002 ^[69]	GLIB/metformin, 2.5 mg/500 mg (A) or 5 mg/500 mg (B) versus metformin 500 mg (C)	↓ A1C (A vs. B vs. C): -1.2% versus -0.91% versus -0.19% ↓ FPG (A vs. B vs. C): -2.62 versus -2.34 versus -0.57 mmol/l Proportion of patients achieved A1C $< 7\%$ (A vs. B vs. C): 75% versus 64% versus 38% $P = 0.001$		Mean changes in body weight were ≤ 1.0 kg	Intensive management with combination therapy improved efficacy at lower doses compared with respective monotherapies, without compromising tolerability

Contd...

Table 7: Contd...

Author	Intervention	Glycemic efficacy	Adverse events	Weight gain	Conclusion
Chien <i>et al.</i> , 2007 ^[70]	GLIB/metformin 2.5/500 mg BID (A) or 5/500 mg BID (B) metformin 500 mg BID (C)	↓ A1C (A vs. C): -1.77% versus -1.34% ↓ A1C (B versus C): -1.73% vs. -1.30% Both A and B had greater reductions in FPG (all $P < 0.001$)	Both Groups A and B experienced fewer GI adverse events compared to C	-	Both combinations (A and B) were efficacious and well tolerated
Ray <i>et al.</i> , 2008 ^[71]	Metformin - GLIB combination 2.5 mg/500 mg BID (A) or 5 mg/500 mg BID (B) versus metformin 500 mg BID (C)	↓ A1C (A vs. B vs. C): -1.2% versus -0.9% versus -0.2%	Treatment with B was associated with reductions in diabetes-related complications relative to C	-	Compared with metformin, combination therapy was associated with increased quality-adjusted life expectancy, and QALY; reduced direct medical costs and fewer diabetes-related complications

BID: Twice daily, GITS: Gastrointestinal therapeutic system, FDC: Fixed-dose combination, FBG: Fasting blood glucose, FPG: Fasting plasma glucose, PPG: Postprandial glucose, QALY: Quality-adjusted life in years, T2DM: Type 2 diabetes mellitus, GLIM: Glimepiride, GLIC: Gliclazide, GLIP: Glipizide, GLIB: Glibenclamide, A1C: Glycated hemoglobin, PPBG: Postprandial blood glucose, BMI: Body mass index, GI: Gastrointestinal, ↓: Decrease

with metformin uptitration. Furthermore, a significantly greater proportion of patients with GLIM/metformin FDC therapy achieved A1C $< 7\%$ (74.7 vs. 46.6%, $P < 0.0001$) at the end of the study.^[62] In a multicentric epidemiologic surveillance protocol of 60 days, patients ($n = 759$) with T2DM were prospectively prescribed 1–2 tablets of GLIC 60 mg + metformin 500 mg during the course of daily practice. The study reported that 62.5% of patients had achieved the primary outcome (FPG of 90–130 mg/dL) at the end of the study. Mean (95% CI) FPG (mg/dL) decreased from baseline by 48.7 (45.0–51.4) with 1 tablet, by 71.3 (66.0–76.6) with 1½ tablets, and by 86.3 (75.7–96.9) with 2 tablets. Furthermore, the frequency of hypoglycemia was reported as 0.7%.^[63]

A summary of published RCTs comparing the combinations of different SUs and metformin with metformin monotherapy in the management of T2DM is summarized in Table 7.

Sulfonylureas versus thiazolidinedione as add-on to metformin

Compared to add-on therapies with other OADs, SUs as an add-on to metformin have shown a favorable glycemic control in terms of significant A1C reduction. A meta-analysis comparing the outcomes of thiazolidinedione (TZD) and SUs, both add-ons to metformin, reported a pooled between-group difference in A1C of -0.06% (95% CI: -0.19% – 0.06%).^[59] Furthermore, a multicentric randomized, parallel group, open-label, forced titration study reported that GLIM therapy resulted in a more rapid decline in A1C levels at weeks 6, 12, and 20 in comparison to pioglitazone ($P < 0.05$) in patients with uncontrolled glycemic level with metformin. A target A1C $\leq 7\%$ was reached faster in the GLIM group (median, 80–90 days vs. 140–150 days [$P = 0.024$]).^[72] Evidence reported no significant difference in glycemic parameters between GLIC and pioglitazone when added in patients with uncontrolled glycemic level with metformin monotherapy.^[73,74]

Sulfonylureas versus dipeptidyl peptidase 4inhibitor as add-on to metformin

SUs compared to dipeptidyl peptidase 4 (DPP-4) inhibitors (DPP-4I) when added to metformin are associated with a significantly greater reduction in A1C from baseline to 12 weeks (mean difference [MD]: 0.21; 95% CI: 0.06, 0.35) but no significant difference at 52 and 104 weeks (MD: 0.06 and 0.02, respectively, 95% CI: -0.03 , 0.15 and -0.13 , 0.18 respectively).^[75] Furthermore, accumulated evidence from 14 RCTs ($n > 10,000$) reported that SUs were associated with a larger decline in A1C compared to DPP-4I (weighted mean difference [WMD]: 0.08, 95% CI: 0.03, 0.14, $P = 0.001$).^[76] Moreover, a systematic review and meta-analysis reported that GLIM was associated with a 12% greater reduction in A1C compared to DPP-4I (WMD: -0.12 ; 95% CI: -0.16 , -0.07), with a clinically irrelevant weight difference between the treatment (2.1 kg).^[77] A 52-week RCT comparing GLIC and vildagliptin as a second-line agent reported a noninferiority of vildagliptin, with a mean change from A1C ($-0.85\% \pm 0.06$ vs. $-0.81\% \pm 0.06$).^[78] Another 52-week RCT also demonstrated noninferiority of saxagliptin versus GLIP; adjusted mean changes from baseline A1C were 0.74% versus 0.80%; the between-group difference was 0.06% (95% CI: -0.05 , 0.16).^[79] However, in a population-based cohort study in Denmark (4734 patients), A1C reduction with SUs as a second-line agent was better compared to that of DPP-4I (1.2% vs. 0.8%).^[80]

Sulfonylureas versus sodium glucose co-transporter 2 inhibitor as add-on to metformin

In a meta-analysis, the combination of metformin plus an SU with the combination of metformin plus a sodium-glucose co-transporter 2 inhibitor (SGLT-2I) was compared. The results supported the combination of metformin plus an SGLT-2I for A1C reduction (pooled between-group difference in A1C of 0.17%; 95% CI: 0.14%–0.20%).^[59] In EMPA-REG-H2HSU-trial,

a noninferiority trend in terms of change of A1C has been reported with empagliflozin when compared to GLIM at 104 weeks.^[81] Furthermore, in CANTATA-SU trial, no difference in glycemic control was observed with less dose of canagliflozin and GLIM (canagliflozin 100 mg vs. GLIM 6–8 mg [MD – 0.01%]).^[82] Similarly a 52-week, double-blind, active-controlled, noninferiority RCT reported a statistically noninferiority in adjusted mean A1C reduction with dapagliflozin (–0.52%) and GLIP (–0.52%) in T2DM patients with inadequate glycemic control with metformin.^[83]

Sulfonylureas versus glucagon-like peptide 1 analogs as add-on to metformin

The dose-dependent variability has been observed in terms of glycemic control between glucagon-like peptide-1 (GLP-1) analogs and SUs when added to metformin. A meta-analysis of several RCTs has found favorable outcomes with the combination of metformin plus SU despite submaximal doses of SUs being compared with maximal doses of daily exenatide (pooled between-group difference in A1C, –0.26%; 95% CI: –0.48%–0.03%).^[59] In the LEAD-2 trial, liraglutide reported noninferiority in reduction of A1C compared to GLIM, both added on to metformin.^[84] Similarly a 16-week RCT including patients from China, India, and South Korea reported that liraglutide 1.2 and 1.8 mg was noninferior to GLIM (mean A1C reduction: 1.36%, 1.45%, and 1.39%, respectively).^[85] However, combination of metformin plus maximum dose of albiglutide (titrated to 50 mg weekly) compared to metformin plus submaximal dose of GLIM (titrated to 4 mg daily) favored the metformin plus albiglutide arm (A1C reduction, –0.9% vs. –0.3%) in HARMONY 3 trial.^[61]

Sulfonylureas versus insulin as add-on to metformin

In DiaRegis registry ($n = 3810$), the addition of insulin reduced the A1C level more as compared to SU after the failure of metformin monotherapy in a duration of 2 years ($-0.9 \pm 2.0\%$ vs. $-0.6 \pm 1.4\%$).^[86]

Body weight

SU use is associated with weight gain, a secondary effect that also occurs with insulin, TZD, and glinides. Modern SUs such as GLIM and GLIC MR are associated with weight neutralizing/reducing effect compared to conventional SUs.^[5] Furthermore, evidence suggests that GLIM may be the least in the class to endorse weight gain.^[87,88] Nonetheless, weight gain associated with SUs may be due to improved utilization of consumed glucose and a subsequent reduction in glycosuria, thereby indicating reduction in glucotoxicity.^[88]

An extra increment in body weight has been observed when SUs were added to ongoing metformin therapy.^[59] When compared to TZD, a pooled mean between-group difference of 0.9 kg (95% CI: 0.4–1.3 kg) favored the combination of metformin plus SU.^[59] Similarly, the addition of pioglitazone was associated with more weight gain (2.5 kg) than GLIC (1.2 kg) in patients with metformin.^[89] Several meta-analyses and RCTs reported that metformin-SU

combination was associated with more weight gain compared to metformin-DPP-4I combinations and metformin-SGLT-2I combinations; however, the difference was nonsignificant.^[59,77] Zhang *et al.* reported that DPP-4I was associated with a reduction in body weight (WMD, –1.652 kg; 95% CI values here as –1.658, –1.646) compared to SUs.^[90] Furthermore, in a 16-week prospective study, a variation of weight change has been observed between vildagliptin and GLIC (–0.3 kg vs. +1.4 kg, $P = 0.048$) after adding to metformin.^[91] Similarly, in another trial, canagliflozin 100 and 300 mg and GLIM 6–8 mg/day were associated with –4.1%, –4.2%, and 0.9% reductions in body weight, respectively.^[92] Furthermore, several RCTs reported a weight loss in patients with the combination of metformin and GLP-1 receptor agonists and weight gain in patients with the combination of metformin and SUs.^[61,85,93,94] Compared to insulin, in BETA trial, addition of GLIM to metformin produced a less weight gain (mean between-group difference in weight of –1.7 kg, $P = 0.02$) in patients with T2DM.^[95] In DiaRegis registry ($n = 3810$), the addition of insulin also reported increment of body weight from baseline as compared to SU after the failure of metformin monotherapy in a duration of 2 years ($+0.8 \pm 9.0$ vs. -0.4 ± 4.8 kg).^[86]

Safety and tolerability

Hypoglycemia is a primary clinical concern during the intensification of the antidiabetic regimen in patients with T2DM. The hypoglycemic potentials of SUs are different pertaining to their variable mode of action and pharmacokinetic and pharmacodynamic properties. Evidence suggests that modern SUs are associated with less risk of hypoglycemia compared to conventional SUs.^[39,40,96,97] Furthermore, the European GUIDE (GIUcose control in type 2 diabetes: Diamicron MR vs. GLIM) study ($n = 845$) was the first double-blind, 27-week, parallel-group, large-scale, head-to-head study compared once-daily GLIC MR (maximum dose up to 120 mg) to once-daily GLIM (maximum dose up to 6 mg) either as monotherapy or in combination. Hypoglycemia occurred significantly lesser with GLIC MR compared to GLIM (3.7% vs. 8.9%, respectively, $P = 0.003$), though a higher number of patients reached A1C <6.5% with GLIM (17% vs. 2%) which may influence the hypoglycemic episodes. Moreover, no episodes of severe hypoglycemia were reported during the study in patients, reiterating the safety of both these modern SUs.^[98] Kim *et al.* in their randomized, open-label, parallel group, multicentric study reported that patients with GLIM/metformin combination therapy experienced more hypoglycemia compared with metformin uptitration therapy (41% vs. 5.6%, $P < 0.0001$), but there was no serious hypoglycemia reported in any group.^[62] In a 52-week RCT, patients taking GLIC or vildagliptin experienced similar incidence of any adverse events (~61%); however, GLIC patients had more serious adverse events (8.7% vs. 6.7%) and more vildagliptin patients discontinued as a result of an unsatisfactory effect ($n = 22$ vs. 13).^[78]

Evidence shows an increase in hypoglycemia risk with SUs compared to other OADs when added to metformin monotherapy. The hypoglycemic risk, when compared with

SUs, for TZD was as follows: pooled odds ratio (OR): 7.5; 95% CI: 4.0–13.8;^[59] DPP-4I, risk ratio: 0.24, 95% CI: 0.21–0.27, $P < 0.001$;^[76] and SGLT-2I, OR: 0.08 (95% CI: 0.03–0.17).^[59] Furthermore, DPP-4I was associated with lower risk of total adverse events (Mantel–Haenszel odds ratio [MHOR]: 0.79; 95% CI: 0.72–0.87) and CV events (MHOR: 0.53; 95% CI: 0.32–0.87) compared with SUs.^[90]

Several RCTs reported that the rate of genital and urinary tract infections was more common with SGLT-2I compared to SUs.^[92,99] Furthermore, there were increased odds of genital infections for metformin plus SGLT-2I and differences in relative odds by gender were as follows: pooled OR: 5.2 (95% CI: 3.4–7.8) for women and pooled OR: 7.6 (95% CI: 4.0–14.4) for men.^[59] Moreover, volume depletion was observed frequently with canagliflozin than GLIM.^[92] Similarly, gastrointestinal events with liraglutide and exenatide^[84,100] and diarrhea with albiglutide^[61] were more commonly reported.

In a retrospective cohort study, 20,070 patients were newly treated with an SU, DPP-4I, or a TZD following metformin therapy failure. It was reported that the therapy failure at 1 year was 15% with SU, 23% with DPP-4I, and 8% with TZD.^[101] Furthermore, multivariate analysis of the data showed that addition of a DPP-4I was associated with an increased risk of treatment failure (adjusted hazard ratio (aHR): 1.58; 95% CI: 1.48–1.68) compared to the SU group, while adding a TZD was associated with a adjusted hazard ratio (aHR: 0.45; 95% CI: 0.41–0.50).

Moreover, choice of drugs should be based on the risk of hypoglycemia in an individual patient; further details regarding this are provided in patient and dose selection sections in this article.

All-cause mortality and macrovascular complications

A meta-analysis including several RCTs demonstrated that SUs (GLIB, GLIP, GLIC, and GLIM) as an add-on to metformin were not associated with all-cause mortality (OR: 1.26; 95% CI: 0.94–1.68; $P = 0\%$) and CV mortality (OR: 1.40; 95% CI: 0.61–3.22; $P = 6\%$). Furthermore, among all SUs, GLIP was associated with increased all-cause and CV mortality, while the risk was least with GLIM (numerically, though did not achieve statistical significance).^[38] Modern SUs show less CV mortality than conventional SUs due to more pancreatic selectivity action. A randomized, double-blind, crossover study of GLIC 80 mg twice daily and GLIM 2 mg once daily, each for 4 weeks as add-on therapy to metformin, found no evidence between SUR1-specific (GLIC) and nonspecific SU (GLIM) in differential effects on arterial distensibility, endothelial function, or vasodilator mechanisms.^[102]

Metformin remains an ideal first-line agent and among the SUs, the relative safety of a GLIC makes it a preferred SU. In a population-based study on 107,806 patients from the Danish registry with a median follow-up of 3.3 years, Schramm *et al.* evaluated several mortality end points with different insulin secretagogues compared with metformin in

patients with or without a previous history of myocardial infarction (MI).^[103] The all-cause mortality was significantly higher with all SUs (GLIM: HR: 1.32, 95% CI: 1.24–1.40; GLIP: HR: 1.27, 95% CI: 1.17–1.38; and GLIB: HR: 1.19, 95% CI: 1.11–1.28) except GLIC (HR: 1.05, 95% CI: 0.94–1.16) in patients with a previous history of MI. Similar significant increase in all-cause mortality was observed with all SUs except GLIC in those with a previous history of MI. Furthermore, this was a retrospective study and therefore there is a likelihood of selection bias (patients on GLIM had a higher baseline risk and likely contributed to more morbidity and mortality). In another nationwide study on 202,272 Danish patients, GLIP, GLIB, GLIM, and TOLB appeared to be associated with an increased risk compared with GLIC when used in combination with metformin.^[104]

When added to metformin, pioglitazone found to produce potential benefits in terms of improvements in specific lipid abnormalities compared to GLIC or GLIM.^[74,89,105] Nonetheless, a single retrospective cohort study from a Veterans Affairs population with Medicare ($n = 80,936$) found a nonsignificant increase in the risk of stroke or MI (composite outcome) for SU-based versus TZD-based therapy: aHR: 1.15 (95% CI: 0.8–1.66; $P = 0.46$).^[106]

The pooled OR from five RCTs on mortality between DPP-4I and SUs, when added on to metformin, was 0.64 (95% CI: 0.27–1.51).^[59] In the Danish National Registry, combination therapies with incretin-based drugs and metformin were compared with a combination of metformin and SU in T2DM for all-cause mortality, CV mortality, and combined end point of MI, stroke, and CV mortality. By keeping metformin + SU as a reference, the study demonstrated a significantly decreased risk of death among metformin plus DPP-4I users ($n = 11,138$) with a relative risk (RR) of 0.65 (0.54–0.80) for mortality, 0.57 (0.40–0.80) for CV mortality, and 0.70 (0.57–0.85) for the combined end point. For metformin + GLP-1 receptor agonist, the RR for mortality was 0.77 (0.51–1.17), for CV mortality was 0.89 (0.47–1.68), and for the combined end point was 0.82 (0.55–1.21).^[104] However, a meta-analysis suggested that long-term all-cause mortality (which was low [$<1\%$] across studies) was similar for metformin plus SGLT-2I and metformin plus SU (pooled OR: 0.86; 95% CI: 0.29–2.55).^[59] Moreover, a significant reduction in urine albumin was observed in the metformin plus exenatide arm (37.97%) compared to the metformin plus GLIM arm (5.76%).^[107]

Nonetheless, in a meta-analysis of 301 clinical trials which utilized the glucose-lowering drugs including metformin, SUs, TZD, DPP-4I, alpha-glucosidase inhibitor (AGI), SGLT-2I, GLP-1 receptor agonists, meglitinides, and insulin either alone or in combination suggested no significant difference in the risk of CV mortality between the antidiabetic drugs.^[108]

A summary of landmark trials comparing outcomes of SUs with other antidiabetic drugs as add-on therapy is summarized in Table 8.

Table 8: Summary of landmark trials comparing outcomes of sulfonylureas in combination with other antidiabetic drugs

Study	Interventions	Glycemic efficacy	Adverse events	Weight gain	Conclusion
COM06 ^[109]	Pioglitazone + metformin/SU (A) versus FDC of metformin and GLIB (B)	↓ A1C (A vs. B): 1.11% versus 1.29% ($P=0.192$) ↓ FPG (A vs. B): 2.13 versus 1.81 mmol/L ($P=0.370$)			Co administration of pioglitazone with metformin or an SU is an effective alternative for patients with T2DM
GENERATION ^[110]	Saxagliptin (A) or GLIM (B) added to metformin	Achievement of A1C <7% (A vs. B): 37.9% versus 38.2% ($P=0.9415$)	Confirmed/severe hypoglycemia (A vs. B): 1.1% versus 15.3%; $P<0.0001$		Saxagliptin was numerically (not significantly) superior to GLIM for patients aged <75 years numerically inferior for patients aged ≥75 years
CANTATA-SU ^[82]	Metformin + GLIM versus metformin + canagliflozin 100 mg and 300 mg	Canagliflozin 100 mg was noninferior to GLIM (0.01% [95% CI: 0.11-0.09]), and canagliflozin 300 mg was superior to GLIM (0.12% [0.22-0.02])	More genital mycotic infections, urinary tract infections, and osmotic diuresis-related events observed with canagliflozin		Canagliflozin provides greater A1C reduction than does GLIM and is well tolerated in patients with T2DM receiving metformin
EMPA-REG-H2HSU ^[81]	Metformin + GLIM (A) versus metformin + empagliflozin (B)	Change in A1C from baseline with empagliflozin versus GLIM was 0.11% (95% CI: 0.19-0.02; $P=0.0153$ for superiority)	Serious adverse events A: 11%; B: 16% Confirmed hypoglycemic events A: 24%; B: 2%		Empagliflozin might serve as an effective and a well-tolerated second-line treatment option for patients with T2DM who have not achieved good glycemic control on metformin
LEAD-2 ^[84]	Metformin + GLIM (A) versus metformin + liraglutide (B) and metformin (C)	↓ A1C: A, 0.5%; B, 0.6%; C, 0.3%	Minor hypoglycemia (A vs. B): 24% versus <5% ($P<0.0001$)	Significant weight loss with liraglutide compared with GLIM ($P<0.0001$)	Liraglutide provided sustained glycemic control over 2 years comparable to that provided by GLIM
BETA ^[95]	Metformin + GLIM (A) versus metformin + glargine (B)	A1C and FPG significantly in each group but not different between two groups	No severe hypoglycemia: symptomatic hypoglycemia more frequent with GLIM ($P=0.01$)	Less weight gain was observed in the GLIM group	Glargine and GLIM can be considered after failure of metformin monotherapy
EUREXA ^[100]	Metformin + GLIM (A) versus metformin + exenatide + (B)	Attainment of HbA1c <7% (A vs. B): 31% versus 44% ($P<0.0001$), Attainment of HbA1c ≤6.5% (A vs. B): 18% versus 29% ($P<0.0001$)	Hypoglycemia ($P<0.0001$) higher in GLIM and GI adverse events was significantly higher ($P=0.0005$) in the exenatide group	Significantly greater decrease in body weight in patients given exenatide than in those given GLIM ($P<0.0001$)	These findings provide evidence for the benefits of exenatide versus GLIM for control of glycemic deterioration in patients with type-2 diabetes inadequately controlled by metformin alone

BMI: Body mass index, FDC: Fixed-dose combination, FPG: Fasting plasma glucose, SU: Sulfonylurea, T2DM: Type 2 diabetes mellitus, GLIB: Glibenclamide, GLIM: Glimepiride, CI: Confidence interval, A1C: Glycated hemoglobin, GI: Gastrointestinal, HbA1c: Hemoglobin A1c, ↓: decrease

Sulfonylurea + other oral antidiabetic drugs

Mechanism

In patients with inadequate glycemic control on SUs, there are a number of OADs available which can be used in combination with an SU. However, the choice of therapy should be individualized based on patient characteristics, preferences, and cost. TZDs decrease insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Thus, the combination of SUs

and TZD may be beneficial for supporting each other in T2DM.

DPP-4 inhibitors elevate cellular cyclic adenosine monophosphate (cAMP) levels in pancreatic β -cells, leading to potentiated insulin secretion. SUs mimic the glucose-induced K_{ATP} channel-dependent pathway. Therefore, an increase in cAMP induced by incretin therapy potentiates K_{ATP} channel-independent insulinotropic action by glucose.^[111-113] Therefore, SUs and DPP-4I may be an effective combination for supporting inappropriate insulin secretion in T2DM;

however, careful consideration is required when initiated in the elderly and/or patients with renal insufficiency.^[113]

Glycemic efficacy

A combination therapy with SU and TZD resulted in remarkable glycemic control when compared to each monotherapy. A randomized, double-blind, placebo-controlled, multicentric study comparing the efficacy of add-on of GLIM to on-going rosiglitazone reported that combination therapy with GLIM produced greater reductions in A1C (mean [standard error (SE)]: -1.2% [0.1%] vs. -0.3% [0.2%]; $P < 0.001$) and FPG (mean [SE]: -24.4 [6.0] mg/dL vs. 5.9 [8.0] mg/dL; $P < 0.006$).^[114] Similarly a 28-week, double-blind, parallel-group RCT revealed that GLIM/rosiglitazone FDC significantly reduced A1C ($2.5 \pm 1.4\%$) than rosiglitazone ($1.8 \pm 1.5\%$) or GLIM ($1.7 \pm 1.4\%$) monotherapy (model-adjusted mean treatment difference, $P < 0.0001$ vs. both rosiglitazone and GLIM).^[115] Evidence suggests that treatment with a combination of pioglitazone and SUs provided extensive glycemic control as compared to baseline glycemic level; however, no significant difference was found when compared to metformin and SU-based combinations.^[89,109,116]

In a multicentric, prospective, randomized, open-label study, patients who had an uncontrolled glycemic level with sitagliptin and low-dose GLIM were randomized to receive uptitration with either sitagliptin or GLIM. There was no significant difference in the A1C-lowering effects between the two groups. However, a significant A1C-lowering effect from baseline of GLIM uptitration was found ($P < 0.01$ vs. baseline).^[117] Furthermore in a 52-week, prospective, single-arm study, sitagliptin and low dose GLIC or GLIM also reduced A1C by -0.80% (95% CI: -0.90 to -0.68) ($P < 0.001$) from baseline.^[118]

In conditions where dual therapy failed to obtain optimal glycemic control, the addition of a third agent (SUs) could be helpful in achieving glycemic targets. GLIM as an add-on to metformin and TZD resulted in significant improvement in A1C level (mean [SE]: -1.31% [0.08] vs. -0.33% [0.08], respectively; $P < 0.001$) from baseline with more patients achieving target A1C $\leq 7\%$ compared with metformin and TZD combination (62.2% vs. 26.0% , $P < 0.001$).^[119] Evidence suggests that GLIM strongly enhances the glucose-lowering effect in triple oral antidiabetic therapy with sitagliptin and metformin for patients with T2DM.^[120]

A systematic review and network meta-analysis evaluated the efficacy of triple therapy regimen for T2DM. The study included SUs in all combinations except one (MET + TZD + DPP-4I). For A1C reduction, all triple therapies were statistically superior to MET + SU dual therapy. However, none of the triple therapy combinations demonstrated differences in A1C compared with other triple therapies.^[121]

Body weight

In a randomized, double-blind, placebo-controlled, multicentric study at the end of the 1st year, GLIM with pioglitazone (4.9%) and GLIM with rosiglitazone (6.2%) treatment groups

had significant increases from baseline in body mass index (BMI) ($P < 0.05$).^[122] Furthermore, when added to GLIC, pioglitazone resulted in an increment of body weight in comparison to metformin (3.7 vs. -1.7 kg).^[89] However, in a 52-week, prospective, single-arm study, sitagliptin and low-dose GLIC or GLIM reduced BMI by -0.38 kg/m² (95% CI: -0.72 , -0.04) ($P < 0.05$) from baseline.^[118]

In a prospective observational study, no change in body weight (69.6 ± 3.0 – 69.1 ± 2.9 kg in the low-dose group and 62.1 ± 2.6 – 61.9 ± 3.0 kg in the high-dose group; $P > 0.05$ for both groups) was observed in patients taking combination of 50 mg/day sitagliptin and low-dose GLIM (2 or 3 mg decreased to 1 mg; $n = 15$) compared to high-dose GLIM (4 or 6 mg decreased to 1 mg).^[111]

Safety and tolerability

Evidence suggests that the combination regimens of SU and TZD were well tolerated by the patients with no significant difference in adverse effects with the comparators.^[114,115,122,123]

Furthermore, no hypoglycemic episodes were reported by various studies assessing the efficacy of sitagliptin and SU combinations.^[111,124] Moreover, several studies reported that the combination treatments with sitagliptin and SU were safe and well tolerated in patients with T2DM.^[111,117,118]

In a 30-week, randomized, double-blind, placebo-controlled, parallel-group study, the risk of hypoglycemia (51.2% vs. 8.3% , $P < 0.001$) was greater with GLIM add-on to metformin-TZD than placebo.^[119] Similarly, in EUREXA trial, the ratio of documented symptomatic (blood glucose ≤ 70 mg/dl [3.9 mmol/L]) hypoglycemic rates for add-on GLIM to add-on TZD was 8.48 ($P < 0.0001$).^[125]

All-cause mortality and macrovascular complications

The increase of lipid risk factors for CV diseases (CVDs) from baseline was more significant in GLIM-rosiglitazone patients compared to GLIM-pioglitazone patients.^[122,126] In an Indian RCT, FDC containing GLIM (2 mg), pioglitazone (15 mg), and metformin sustained release (500 mg) significantly reduced the levels of triglyceride, low-density lipoprotein cholesterol, and total cholesterol.^[127]

A summary of published RCTs comparing combinations of SUs and other OADs in the management of T2DM is shown in Table 9.

Sulfonylurea + insulin

Mechanism

SUs when added to insulin increase endogenous insulin secretion and possibly exert some extra pancreatic actions on muscle and liver, thereby improving glycemic control and decreasing daily insulin requirements.^[128] A subset of T2DM patients who are mild to moderately obese, have adequate endogenous insulin secretory reserve, and are in poor glycemic regulation (A1C $> 10\%$), despite twice-daily insulin administration, may show significant improvement in glycemic regulation and/or decrease in insulin daily dose of

Table 9: A summary of published randomized controlled trials comparing sulfonylureas and other oral antidiabetic drugs in the management of type 2 diabetes mellitus

Author	Interventions	Glycemic efficacy	Adverse events	Weight change	Conclusion
Dual therapy combinations					
Derosa <i>et al.</i> , 2004 ^[126]	Pioglitazone + GLIM (A) versus rosiglitazone + GLIM (B)	No significant differences were found between treatment groups after 1 year	-	Both groups experienced significant ↑ BMI ($P<0.05$)	Both combinations of significantly improved glycemic control in the study patients
Shimoda <i>et al.</i> , 2014 ^[117]	Dose up with sitagliptin (50 mg/day) and GLIM (<2 mg/day): 50 mg/day sitagliptin (A) or 0.5 mg/day GLIM (B)	Changes in A1C between the two groups were not significant ($P=0.13$) A1C ↓ significantly by Group B ($P<0.01$ vs. baseline), but not by Group A ($P=0.74$)	No clinically significant adverse events, except for hypoglycemia	-	A significant A1C-lowering effect from baseline of GLIM dose-up was found
Umayahara <i>et al.</i> , 2014 ^[124]	Three treatment groups: Reduced doses of GLIM (0.5 mg/day, 1 mg/day, or 2 mg/day) in addition to sitagliptin for 24 weeks	Despite dose reduction of GLIM, combination therapy with sitagliptin induced significant improvements in A1C levels (0.8%, $P<0.001$)	No symptomatic hypoglycemia was documented	No changes in body weight	Sitagliptin and low-dose GLIM (0.5 mg/day) combination is effective and safe in Japanese patients with uncontrolled T2DM
Comaschi <i>et al.</i> , 2007 ^[109]	Pioglitazone + metformin/SU versus FDC of metformin and GLIB (B) for 6 months	Pioglitazone and FDC resulted in similar ↓ A1C (1.11% vs. 1.29%, respectively; $P=0.192$) and FPG (2.13 vs. 1.81 mmol/L, respectively; $P=0.370$)	-	-	Co-administration of pioglitazone with metformin or an SU is an effective alternative for patients with T2DM
Charbonnel <i>et al.</i> , 2005 ^[89]	Pioglitazone + GLIC (A) or pioglitazone + metformin (B) for 2 years	No significant differences in changes from baseline in glycemic parameters A versus B	Pioglitazone caused greater ↓ in triglycerides and ↑ in HDL than comparators ($P<0.001$)	↑ body weight (A vs. B): 3.7 versus 1.7 kg	As add-on therapy to existing SU/metformin, pioglitazone improved glycemic control and this improvement was sustained over 2 years
Hanefeld <i>et al.</i> , 2004 ^[116]	Pioglitazone + SU (A) or metformin + SU (B) for 1 year	No significant between treatment differences in A1C, FPG, fasting insulin level	Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group	-	SU plus pioglitazone is an effective and well-tolerated combination regimen that may provide additional beneficial effects for patients with T2DM
Triple-therapy combinations					
Roberts <i>et al.</i> , 2005 ^[119]	GLIM + metformin + rosiglitazone or pioglitazone (A) versus placebo (B)	Significantly improved at end point with Group A versus B (mean [SE], 1.31% [0.08] vs. 0.33% [0.08]; $P<0.001$) Attainment of A1C $\leq 7\%$ (A vs. B): 62.2 versus 26.0%; $P<0.001$ between groups	Hypoglycemia (A vs. B): 51.2 versus 8.3%; $P<0.001$	Mean change in weight (A vs. B): (3.76 [0.54] versus 0.45 [0.52] kg; $P<0.001$)	Uncontrolled T2DM patients with dual therapy (metformin and a thiazolidinedione), the addition of GLIM ↑ glycemic control with an acceptable tolerability profile
Arai <i>et al.</i> , 2013 ^[120]	GLIM + metformin + sitagliptin (A) versus metformin + sitagliptin (B)	Significantly greater changes were observed in A1C and glycated albumin levels in both groups during the 2-3 months' period than in the 1-3 months' period	-	-	GLIM is important for good glycemic control in triple therapy with sitagliptin and metformin
Scherthaner <i>et al.</i> , 2015 ^[125]	Metformin + exenatide + GLIM (A) versus metformin + exenatide + thiazolidinedione (B)	A1C: Significantly better with B versus A: 130-week difference 0.48% (95% CI: 0.19, 0.77)	Ratio of documented symptomatic hypoglycemia rates (A to B): 8.48 ($P<0.0001$)	Significantly BMI and systolic blood pressure in Group B	Thiazolidinedione was an effective and well-tolerated third-line therapy in patients with uncontrolled hyperglycemia after long-term therapy of metformin and exenatide BID

GLIM: Glimepiride, SUs: Sulfonylureas, A1C: Glycated hemoglobin, BMI: Body mass index, FDC: Fixed-dose combinations, FPG: Fasting plasma glucose, HDL: High-density lipoprotein, SE: Standard error, SU: Sulfonylurea, T2DM: Type 2 diabetes mellitus, BID: Twice daily, ↓: decreased/decrease in/decrease, ↑: increase in/increase

Table 10: A summary of published randomized controlled trials comparing sulfonylureas and insulin in the management of type 2 diabetes mellitus

Author	Interventions	Glycemic efficacy	Adverse events	Weight gain	Conclusion
Basal insulin + sulphonylureas					
Zhou <i>et al.</i> , 2015 ^[131]	Glargine + GLIC MR versus premix insulin monotherapy	Combination therapy showed a significantly more robust A1C ↓ ($P=0.0308$)	Rates of hypoglycemic episodes were similar -	-	Patients with uncontrolled T2DM with OADs attained greater benefit from OD insulin glargine plus GLIC MR regimen than from a BID premixed insulin
Schiell <i>et al.</i> , 2008 ^[132]	Group A: OD morning glargine+GLIM; Group B: Glargine + GLIM and metformin Group C: premixed insulin	A1C ↓ significantly from baseline in Groups A and B, but not in Group C; (A: -0.35% , $P=0.013$; B: -0.69% , $P=0.0057$; C: -0.0057 ; $P=0.32$)	Symptomatic hypoglycemia (mean events/patient: Group A, 2.2; Group B, 2.3; Group C, 2.0)	-	Switching from premixed insulin to insulin glargine plus OAD treatment resulted in similar glycemic control and treatment satisfaction
Janka <i>et al.</i> , 2007 ^[133]	OD morning glargine with continued OADs (GLIM + metformin) (A) or BID premix insulin 70/30 alone (B)	FBG ↓ significantly more with Group A (-57 mg/dL) than Group B (-40 mg/dL) ($P=0.002$) Adjusted mean ↓ A1C for Groups A and B was -1.9% and -1.4% , respectively ($P=0.003$)	Episodes of any hypoglycemia (A vs. B): 3.68/patient-year versus 9.09/patient-year ($P=0.008$)	Mean weight gain (A vs. B): 1.3 ± 3.0 versus 2.2 ± 3.9 kg ($P=0.17$)	In elderly patients, addition of OD morning glargine + OAD is a simple regimen to initiate insulin therapy, restoring glycemic control more effectively and with less hypoglycemia than BID 70/30 alone
Standl <i>et al.</i> , 2005 ^[134]	Morning glargine + GLIM (A) versus bedtime glargine (B) for 24 weeks titrated to target FBG ≤ 100 mg/dL	No significant difference in change in glycemic parameter, insulin dose, and attainment of A1C $< 7\%$ between groups	No clinically relevant between-treatment differences	-	Flexible dosing with simple GLIM/ glargine regimens achieved significant and practically meaningful improvements in glycemic control
Olsson and Lindström, 2002 ^[135]	Bedtime NPH insulin + daytime SU (A) versus insulin BID group (BID premixed combination of regular human and NPH insulin [B])	No significant difference in change in A1C from baseline between groups ($P<0.03$; NS between treatment groups) Dose of insulin at 24 weeks (A vs. B): 29.4 ± 5.4 U versus 45.8 ± 4.2 U ($P=0.03$)	-	No significant difference in change in body weight between groups (NS; $P<0.02$ between groups)	Combination therapy is an attractive alternative when starting insulin treatment in T2DM patients
Park <i>et al.</i> , 2014 ^[136]	Glargine + metformin (A) versus glargine + GLIM (B) versus glargine + metformin + GLIM (C)	The ↓ in A1C was more pronounced with group C than Groups A and B (overall $P=0.02$)	Hypoglycemia risk of any type did not significantly differ between groups	Weight gain did not significantly differ among the groups	The combination of metformin and GLIM+glargine resulted in a significant improvement in overall glycemic control as compared with the other combinations
Premix insulin + sulphonylureas					
Li <i>et al.</i> , 2014 ^[137]	GLIM-added Group (A) or the insulin-increasing Group (B) while continuing current insulin-based therapy	Insulin doses were significantly ↓, and the mean A1C, FBG, and P2BG were improved greater in the Group A compared with Group B	-	Body weight ↑ significantly in Group B ($P<0.05$); no significant change in Group A ($P>0.05$)	Adding GLIM to current insulin treatment led to ↑ in glycemic control with a significant smaller daily insulin dose

FBG: Fasting blood glucose, MR: Modified release, NPH: Neutral Protamine Hagedorn, NS: Nonsignificant, OD: Once daily, OAD: Oral antidiabetic drugs, P2BG: 2 h postprandial blood glucose, SU: Sulfonylurea, T2DM: Type 2 diabetes mellitus, GLIC: Gliclazide, A1C: Glycated hemoglobin, BID: Twice daily, ↑: increase, ↓: decrease/decreased/decrease in

insulin-SU therapy.^[129] Evidence suggests that addition of SUs to insulin in patients with uncontrolled glycemic levels reduces the insulin dose by 20%–30% and avoids hypoglycemia.^[130] Therefore, studies have compared the treatments with a

smaller insulin dose with SU and a larger insulin dose without SU. A summary of published RCTs comparing combinations of SUs and insulin in the management of T2DM is shown in Table 10.

Glycemic efficacy

In a Cochrane systematic review including nine trials (316 patients), insulin-SU combination therapy compared with insulin monotherapy was associated with a reduction of A1C; MD of -1% (95% CI: -1.6 to -0.5 ; $P < 0.01$). However, insulin-metformin (-0.9%), insulin-AGIs (-0.4%), and insulin-DPP4I (-0.4%) combinations had revealed a less significant change in A1C compared to insulin-SU combination therapy.^[138] Furthermore, a meta-analysis comprising 17 RCTs reported a significantly lower A1C in SU groups (in combination with insulin) compared with placebo (0.46% lower; 95% CI: 0.24 , 0.69 , $P = 43.6\%$).^[60] Moreover, another meta-analysis also found favorable outcomes with insulin-SU combination therapy in terms of glycemic control compared to insulin monotherapy ($P < 0.0001$).^[139]

Past studies show that approximately half of the patients attain A1C $< 7\%$ with dual insulin therapy whereas patients taking insulin alone met goals only one-third of the time.^[133,134,140-142] Yki-Järvinen *et al.* determined that a basal insulin regimen containing GLIM decreased total daily insulin requirements by approximately one-third.^[143] A combination of once-daily basal insulin with an SU versus monotherapy with premixed insulin has proven to decrease total insulin dose by the same factor.^[133,143]

A Korean RCT after 24 weeks of observation period reported a pronounced reduction of A1C with the addition of GLIM to insulin glargine and metformin than insulin glargine plus metformin (0.49% [95% CI: 0.16% – 0.82%], $P = 0.005$).^[136]

In “4-T” trial, patients with uncontrolled glycemic level with SUs and metformin were randomized to receive twice-daily biphasic insulin aspart 30 or thrice-daily prandial insulin aspart, or once-daily (twice if required) basal insulin detemir. After 1-year follow-up, the mean reduction in A1C was significantly greater in the biphasic (1.3%) and prandial groups (1.4%) than in the basal group (0.8%).^[144] However, after 3 years, basal or prandial insulin-based regimen had better A1C control than biphasic insulin-based regimen.^[145]

Safety tolerability and body weight

The combination of insulin and SU results in a reduction of necessary insulin dose per day.^[60,138] However, most studies adding SUs to insulin reported milder hypoglycemic episodes versus insulin monotherapy (range: 2.2 – 6.1 vs. 2.0 – 2.6 episodes per participant).^[138] The addition of SUs into insulin monotherapy resulted in an additional weight gain of 0.4 to 1.9 kg versus -0.8 to 2.1 kg in the insulin monotherapy group.^[138] However, no change in body weight was observed by addition of SUs to insulin in several older RCTs.^[146,147]

ROLE OF SULFONYLUREAS IN COMBINATION

Cost

Medication cost always plays a significant role in the management of any disease in underdeveloped and developing

countries, as it directly affects the drug utilization and patient compliance. Patients without any medical insurance and below the poverty line encounter numerous challenges for the use of expensive medicines in the management of T2DM. A study revealed that the medication cost for diabetes was USD 138 per patient per year which is equivalent to 8.1% of the total budgeted health expenditure for that financial year in sub-Saharan Africa.^[148] However, SUs are associated with a significantly lower cost per quality-adjusted-life-years (QALYs) and result in the longest time to insulin dependence.^[149] Sensitivity analysis on the medication cost reported the difference in the expected medication cost per QALY from the base-case cost; metformin costs 81.75 USD/month, SU costs 54.85 USD/month, DPP-4I costs 232.84 USD/month, GLP-1 receptor agonist costs 325.97 USD/month, and insulin therapy costs 245.70 USD/month.^[149] This cost comparison indicates that SUs should be preferred as an add-on to metformin if the choice of drug is based on cost.^[19] Furthermore, FDC users on an average had higher out-of-pocket costs for their prescriptions and had a less restricted health plan.^[150] In summary, lower cost without compromising the glycemic efficacy and tolerability could make SUs the prime choice of treatment of T2DM.

Adherence

Medication compliance is directly related to the cost, availability, dosage regimen, and complications associated with the treatment.^[151,152] In the current scenario, FDCs increase the patient compliance by reducing the frequency of drug administration and cost of the medication. Pan F *et al.* reported that the FDC of metformin-glyburide resulted in 13% increase in patient adherence ($P < 0.001$) compared to the 2-pill regimen.^[150] Similarly, a meta-analysis also reported that FDC decreases the risk of medication noncompliance, improves clinical outcomes, and should be considered in patients with chronic conditions.^[153]

Fixed-dose combinations

Combining two or three antihyperglycemic agents with complementary mechanisms of action is a cornerstone of T2DM management.^[154] Apart from that, low-dose combination therapy compared to high-dose monotherapy might exhibit lesser side effects and can achieve similar or better glycemic control.^[155] Furthermore, FDCs reduce number, frequency, and flexibility of dosage administration and minimize the treatment complexity, thereby improving patient adherence.^[156] In a meta-analysis, use of FDCs with antihyperglycemic agents was associated with lower A1C and higher mean possession ratio values compared to dual therapies in patients with T2DM.^[157] Furthermore, a systematic review suggested that T2DM patients treated with FDC therapy may have better adherence, improved satisfaction, and lower direct medical costs, compared to those treated with loose pill combination therapy.^[158] A list of available SUs either individually or in FDCs with their strength, dose, and required dose titration is summarized in Table 11.

Table 11: A list of sulfonylurea monotherapy and fixed-dose combinations of sulfonylureas with available strength, recommended dose, and dose titration

SUs	Strengths available (mg)	Recommended dose	Dose titration
Monotherapy			
GLIB	Tablet: 1.25, 2.5, 5 Micronized tablet: 1.25, 2.5, 5, 6	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 >2.5 mg/day at weekly intervals Adult micro: No >1.5 mg/day at weekly intervals Geriatric: 1.25-2.5 mg, 1-3 weeks
GLIC	Tablet: 40, 80	Adults: 40-80 mg daily in the morning	Increased if necessary up to 320 mg (4 tablets) daily
GLIC MR/XR	Tablet: 30, 60	30-120 mg at breakfast	Daily dose of MR not to exceed 120 mg
GLIP	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
GLIM	0.5, 1, 2, 3, 4, 6	With breakfast or the 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
TOLB	500, 1000	Initial dose: 1-2 g daily Maintenance dose: 0.25-3 g orally Total daily dose may be taken either in the morning or in divided doses through the day	The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions in elderly, debilitated, or malnourished patients, and patients with impaired renal or hepatic function
Gliquidone	30	Initial dose: 15 mg/day taken before breakfast; may increase slowly Usual: 45-60 mg/day in divided doses	It is contraindicated in renal failure, liver diseases, diabetic coma, and type 1 diabetes
FDC			
GLIB + metformin	1.25/250, 2.5/500, 5/500, 2.5/400	With meals Adults: Starting dose: 1.25/250 mg or 5/500 mg orally once or twice a day Maximum initial dose: 10 mg-2000 mg/day	Maximum dose: 20 mg-2000 mg/day
GLIB + metformin + pioglitazone	5/500/7.5, 5/500/15	Both strengths can be prescribed once or twice a day as per physician's recommendation	As with individual agents
GLIC + metformin	30/500, 60/500, 80/500 30 (MR)/500 (ER), 60 (MR)/500 (ER)	With meals As with individual agents	Maximum dose: 20 mg/2000 mg/day Contraindicated in pediatrics
GLIC + metformin + pioglitazone	60/500/7.5, 60/500/15	With meals As with individual agents	As with individual agents
GLIP + metformin	2.5/500, 5/500	With meals Starting dose: 2.5-5/250 mg orally once or twice a day Maximum initial dose: 10 mg-1000 mg or 10 mg-2000 mg/day in divided doses	Maximum dose: 20 mg-2000 mg/day
GLIM + metformin	0.5/500, 1/500, 2/500, 1/850, 2/850, 3/850, 1/1000, 2/1000, 4/1000	With meals	As with individual agents
GLIM + pioglitazone	1/15, 2/15, 2/30, 4/30, 4/45	With the first main meal Initial dose: 2-4/30 mg OD	As with individual agents
GLIM + metformin + pioglitazone	1/500/15, 2/500/15	Both strengths can be prescribed once or twice a day as per physicians recommendation	As with individual agents
GLIM + metformin + voglibose	1/500/0.2, 2/500/0.2, 1/500/0.3, 2/500/0.3	1/500/0.2 mg is recommended OD; 2/500/0.2 mg is recommended once or twice a day 2/500/0.3 is recommended BID All are as per physician's recommendation	As with individual agents

MR: Modified release, IR: Immediate release, ER/XR: Extended release, GLIB: Glibenclamide, GLIC: Gliclazide, GLIP: Glipizide, GLIM: Glimepiride, TOLB: Tolbutamide, SU: Sulfonylurea, BID: Twice daily, OD: Once daily

SPECIAL SITUATIONS

Elderly

SUs are usually well tolerated; however, mild hypoglycemia has been reported with long-acting SUs (e.g., CHOL, glyburide).^[128] For older patients who have persistent hyperglycemia with lifestyle intervention and metformin, the addition of a short-acting SU such as GLIP is a preferred option. A double-blind randomized and open-label comparative study after 2 years of treatment concluded that GLIC MR in combination with other OADs significantly improved glycemic control in the elderly and renal-impaired T2DM patients with a very good safety profile.^[159] A recent review evaluated the comparative safety and efficacy of commonly available SUs (GLIB, GLIC, GLIM, and GLIP) for the management of T2DM in older patients.^[160] The study reported that GLIC can be used in older patients due to its low risk of hypoglycemia; however, it is suggested to restrict the use of GLIB in such populations. Furthermore, several guidelines including IDF and Canadian guidelines also recommend modern SUs (GLIC MR and GLIM) as a drug of choice for elder T2DM patients.^[161,162] In GENERATION trial, a similar proportion of patients achieved the primary end point of A1C <7.0% at week 52 without confirmed/severe hypoglycemia with saxagliptin compared to GLIM when added to metformin (37.9% vs. 38.2%; OR: 0.99, 95% CI: 0.73, 1.34; $P = 0.9415$). However, it is noteworthy that saxagliptin was numerically (but not significantly) inferior for patients aged ≥ 75 years (35.9% vs. 45.5%).^[110]

Children and adolescents

The evidence on the use of SUs in children is limited.^[163] A 26-week, single-blind, active-controlled study, conducted in 285 pediatric patients with T2DM, found that GLIM was as effective as metformin in A1C reduction (-0.54% , $P = 0.001$ and -0.71% , $P = 0.0002$, respectively) with similar rates of hypoglycemia (4.9% vs. 4.2%, respectively).^[164] Furthermore, a prospective trial evaluated the effect of SUs (mainly CHOL) in patients with Maturity-Onset Diabetes of the Young (MODY) patients with 9–29 years of age and found that long-term administration of SUs significantly enhanced glucose-induced insulin concentrations by approximately 68%.^[165] Evidence and guidelines suggested that SUs are the drug of choice for the treatment of MODY.^[166-168] Neonatal diabetes mellitus (NDM) is generally caused by several genetic abnormalities and might be either permanent or transient. In patients with NDM, SUs facilitate insulin secretion through the hormone GLP-1 pathway in response to food present in the gut. Evidence suggests that patients with permanent or transient NDM due to mutations in *KCNJ11* or *ABCC8* gene were successfully treated with SU (GLIB) therapy rather than insulin.^[169-172] An observational case study reported that young children with neonatal diabetes even with blood glucose level of 350 mg/dL also responded to a usual dose of SU.^[173]

Pregnancy and lactation

Second-generation SUs such as GLIB despite low molecular weight do not cross the placenta in significant amounts.^[174] This

phenomenon may be attributed either to its high protein-binding capacity (99.8%) or reverting the total GLIB content into the maternal system by an unidentified placental transport system. Furthermore, the absence of fetal adverse effects such as malformations and hypoglycemia makes GLIB an acceptable treatment option for patients with T2DM during pregnancy.^[174,175] In a meta-analysis including one RCT from India, the outcomes of GLIB, metformin, and insulin were assessed. The study reported similar rate of cesarean delivery (range: 23%–52%) and infant birth weights (MD: -93 g, 95% CI: -191 to 5 g), with no significant difference in maternal glycemic control between the treatments.^[176] Furthermore, a systemic review and meta-analysis reported no significant difference in terms of glycemic control or pregnancy outcomes between GLIB and insulin when used during pregnancy.^[177] Moreover, in a meta-analysis, no significant difference was observed in the rate of neonatal major abnormality or neonatal death among women treated with GLIB-metformin compared with nonexposed women during first trimester; however, the study was limited by heterogeneity.^[178] Nonetheless, long-term efficacy studies of GLIB during pregnancy and lactation are limited.^[175] GLIB compared to metformin was more effective in lowering blood glucose in women with gestational diabetes with a lower treatment failure rate.^[175] Moreover, there are some contradicting results from other studies and the paucity of data regarding the usage of SU combination therapy available during pregnancy and lactation.

Patients with comorbidity

Patients with diabetes are always at an increased risk of developing CVD. The risk of stroke, heart disease, and death due to heart disease is 2 folds high in patients with diabetes than in those without diabetes. Newer-generation SUs such as GLIM and GLIC MR reduce CV risk and may prevent protective ischemic cardiac preconditioning after MI.^[179] In the ADVANCE trial, intensive glucose control with a GLIC-containing regimen has been shown to reduce the incidence of combined major macro- and microvascular events (18.1% vs. 20.0% with standard control; HR: 0.90; 95% CI: 0.82–0.98; $P = 0.01$), as well as that of major microvascular events (9.4% vs. 10.9%; HR: 0.86; 95% CI: 0.77–0.97; $P = 0.01$).^[17] Similarly, the Veterans Affairs Diabetes Trial including 1791 military veterans (median follow-up: 5.6 years) reported that GLIM-based intensive regimen was associated with a 17% relative risk reduction in the rate of CV events compared to standard therapy.^[13] Moreover, a recent meta-analysis demonstrates that SUs are not associated with increased risk for all-cause mortality, CV mortality, MI, or stroke.^[38]

SUs such as GLIP and GLIC are mainly excreted as unchanged drug or inactive metabolite. Therefore, they may produce less hypoglycemia in patients with renal impairment. GLIM has been reported to be safe and effective in diabetic patients with renal impairment.^[180,181] However, GLIB may aggravate the risk of hypoglycemia in such populations.^[182] Short-acting SUs such

Table 12: Summary of randomized controlled trials comparing sulfonylureas versus other drugs as add on to metformin during Ramadan

Author	Interventions	Glycemic efficacy	Adverse events	Weight gain	Conclusion
Hassanein <i>et al.</i> , 2014 ^[188]	Vildagliptin (A) versus GLIC (B)	Adjusted mean change in A1C (A vs. B): 0.05%±0.04% versus -0.03%±0.04% ($P=0.165$)	Confirmed hypoglycemia (A vs. B): 3.0% versus 7.0% ($P=0.039$) No significant change in any parameter found in either group	Adjusted mean difference in ↓ weight: -1.1±0.2 kg ($P=0.987$) for both groups	GLIC showed a lower incidence of hypoglycemia in the present study than previous studies
Brady <i>et al.</i> , 2014 ^[189]	Liraglutide (A) versus SUs (B) (GLIC, GLIP or GLIB)	Change in A1C, 12 weeks post-Ramadan: A > B -0.3% versus +0.02% ($P=0.05$)	No episodes of severe hypoglycemia, however, self-recorded episodes of blood glucose ≤3.9 mmol/L: A < B ($P<0.0001$)	Significant reductions in weight and diastolic BP in the A compared with B	Liraglutide compared with SU is well tolerated and maybe an effective therapy in combination with metformin
Azar <i>et al.</i> , 2016 ^[190]	Liraglutide versus SUs (GLIC, GLIM, GLIP, GLIB)	Similar ↓ fructosamine levels were observed for both groups: (liraglutide, -12.8 μmol/L; SU, -16.4 μmol/L; $P=0.43$)	No severe hypoglycemic episodes were reported by either group	↓ Body weight more with liraglutide than SUs (ETD: -0.54 kg; $P=0.0091$)	Liraglutide showed similarly glycemic improvements, fewer hypoglycemic episodes than SU
Malha <i>et al.</i> , 2014 ^[191]	Vildagliptin versus (GLIM/ GLIC)	Change in A1C from baseline to the last visit was similar for both groups	Hypoglycemic events was not statistically significant ($P=0.334$) between the groups	Weight control was improved after the fasting period for both groups	Vildagliptin may be a better agent than SU during Ramadan
Al Sifri <i>et al.</i> , 2011 ^[192]	Sitagliptin versus (GLIM/ GLIC/GLIB)	-	Symptomatic hypoglycemia: Sitagliptin, 6.7%; GLIC, 6.6%; GLIM, 12.4%; GLIB, 19.7%	-	Incidence of hypoglycemia was lower with GLIC than other SUs and similar to sitagliptin

ETD: Estimated treatment difference, SU: Sulfonylureas, T2DM: Type 2 diabetes mellitus, GLIC: Gliclazide, GLIM: Glimepiride, GLIP: Glipizide, GLIB: Glibenclamide, A1C: Glycated hemoglobin, BP: Blood pressure, ↓: decrease in

as GLIC and GLIP can be used with proper dose adjustment and monitoring in patients with renal insufficiency.^[5] An RCT reported that in patients with chronic renal insufficiency, sitagliptin and GLIP provided similar A1C-lowering efficacy, and GLIP produced more hypoglycemia and weight gain than sitagliptin.^[183] Furthermore, SUs should be cautiously used in patients with liver diseases, as most of the SUs are inactivated in the liver, they might accumulate in the body during liver dysfunction, and ultimately cause hypoglycemia. Moreover, in hypoalbuminemia, the concentration of free drug will increase and may produce hypoglycemia.^[5,184] SUs with a short half-life such as GLIP or GLIB are preferred in liver disease patients. Patients with decompensated cirrhosis, i.e., encephalopathy, ascites, or coagulopathy, may have a reduced ability to counteract hypoglycemia, and thus, the response to therapy should be monitored closely.^[185]

Diabetes and Ramadan

Patients who are continuing antidiabetic medications and undergoing fasting during Ramadan may encounter several difficulties such as hypoglycemia and other health-related complications.^[5] Due to the increased risk of hypoglycemia, individuals with SUs should be careful during fasting period; however, some modern SUs (GLIC, GLIM, and GLIP) are associated with lower risk of hypoglycemia compared to GLIB.^[96] The recent IDF-DAR practical guideline advocates that patients continuing second-generation SUs can fast safely during Ramadan.^[186] The Glimepiride in Ramadan study reported that the efficacy and safety of GLIM have remained unchanged during the period of Ramadan in

patients with T2DM.^[187] In the STEADFAST study, there was no significant difference reported in hypoglycemic episodes between vildagliptin and GLIC (both add-ons to metformin) ($P = 0.039$).^[188] Similarly, in Treat 4 Ramadan Trial, liraglutide compared to SUs (both add-ons to metformin) did not reveal any episodes of severe hypoglycemia in either group.^[189] Table 12 summarizes the efficacy and safety of SU combination therapy during Ramadan. Incretin-based therapies such as DPP-4I and GLP-1 receptor agonist work by increasing insulin secretion in a glucose-dependent manner; therefore, they may not produce any risk of hypoglycemia. However, they may amplify the hypoglycemic effect of SUs when used in combination.^[193] Studies conducted during Ramadan found higher hypoglycemic episodes with SUs compared to DPP-4I; however, subgroup analysis found GLIC having least hypoglycemic episodes among all SUs, almost similar to DPP-4I.^[36,192]

Diabetes and other fasting

Fasting is a universal religiocultural tradition observed in varying forms, in different religions across the world. Hindus observe fasting during Navaratri, Karva Chauth, and Guru Purnima; Buddhists observe during Lent; Jains observe in the occasion of Paryushana.^[194-196] In the diabeto-centric viewpoint, patients taking antidiabetic agents should be monitored regularly for the event of hypoglycemia and other associated complications. Furthermore, the antidiabetic dose should be modified or omitted during the fasting period in order to prevent future complications. The dose modification or omission should be tailored according to the type of

medication, food plan, and patient characteristics. Long-acting SUs such as GLIB should not be used; however, modern SUs with low tendency of hypoglycemia such as GLIM and GLIC MR can be considered with dose reduction.^[194-196] In addition, patients with diabetes and who are undergoing fasting should be educated properly for the daily blood glucose monitoring and about hypoglycemic symptoms in order to maintain a safe fasting during rituals.

TRANSFORMING EVIDENCE INTO CLINICAL PRACTICE

Patient selection

Selection of patient plays a vital role in optimizing the SU combination therapy. Combination therapies should be introduced early in all patients with T2DM for preserving β -cell functions. The initiation of combination therapy depends on the individual patients' A1C at entry level. Modern SUs can be used in both obese and lean patients owing to the low risk of weight gain.^[5] SUs should be cautiously used in the elderly patients and in patients at high risk of hypoglycemia.^[32,34] In addition, patients with T2DM using SU combination therapy who wish to go for fasting should be closely monitored during this period to avoid further complications.^[5]

Drug selection

All SUs are not similar in terms of their efficacies, adverse effects, and tolerability. Clinical factors such as levels of fasting, postprandial hyperglycemia, comorbid hypertension or other CVDs, and hepatic or renal dysfunction determine the selection of SU combination therapy.^[5] Shortacting SUs should be preferred in the case of postprandial hyperglycemia; however, twice-daily SU in combination with metformin should be preferred in fasting hyperglycemia.^[197-199] Combining two different SUs is not logical as they have a similar mechanism of action but SUs may be combined with other OADs such as metformin and TZD (with the complementary mechanism of actions), and even with insulin.^[5] Patients taking a combination of SUs with incretin-based therapy should be under vigilant monitoring due to the risk of hypoglycemia.^[193] FDCs containing SUs should be preferred over combination regimens.

Dose selection

Dose adjustment or modification is inevitable in T2DM patients with the comorbid conditions. Dose selection for FDCs containing SUs should be done as per individual patient characteristics and properties of SUs.^[5] The South Asian Federation of Endocrine Societies consensus recommends initiation of SUs at low doses and uptitrating them gradually based on the glycemic responses to prevent hypoglycemia, but when hypoglycemic episodes are confirmed, reduction of dose should be considered.^[113] The consensus also recommends educating the patients and family members about the signs and symptoms of hypoglycemia.^[5] When using combination therapy containing SUs and incretin-based therapies, the dose of SUs should be reduced in the elderly and/or patients with renal insufficiency.

Diabetes education and patient and physician empowerment

Due to chronic nature of the disease, diabetes necessitates self-management plan in day-to-day basis.^[200] Diabetic education enables the patients to make informed decisions and effectively manage the disease without any complications. Diabetic education, which gives information on physical activity, glucose monitoring, diet, hypoglycemia, dosage and timing of medications, and identification of the symptoms of complications, should be provided to patients and their families. Patients should be encouraged and supported to become active partners in the decision-making process, to set realistic goals, select appropriate management strategies, enhance adherence, and improve treatment outcomes.^[5] Self-monitoring of blood glucose (SMBG) at home and self-down titration of doses in case of hypoglycemia by patients are recommended. The patient should be trained for the safe use of FDC containing SUs and should be able to detect the hypoglycemic complications. Furthermore, patients along with their family members should be educated about the usage of SMBG system. When FDCs containing SUs are prescribed, physicians should consider the clinical profile of the patient and implement strategies that will not only help to minimize patient's concerns over SUs treatment but also empower them for self-management. At each visit, physicians should look into symptoms suggestive of hypoglycemia and adjust doses accordingly when risks outweigh glycemic benefits.

CONCLUSION

Intensification of diabetic therapy with a proactive approach is crucial to achieve target glycemic levels. SUs are an important component of pharmacological armamentarium in the treatment of T2DM. Owing to their well-established efficacy and safety profile, they are the most commonly recommended class of agents when glycemic targets are not achieved with metformin alone. Owing to their disparity in pharmacokinetic and pharmacodynamic profile, which results in variability in safety and tolerability, the selection of SUs should be highly individualized with careful monitoring in high-risk patients. Due to their unique characteristics such as increased efficacy, CV safety, fewer episodes of hypoglycemia, and weight-neutralizing effects, modern SUs should be used over conventional SUs in the management of T2DM. Lower treatment cost without compromising the glycemic efficacy and tolerability together with good compliance rate positions SUs as the front-line agent in the management of T2DM. In addition, the complementary mechanisms of action of GLIM and metformin contribute to their enhanced glycemic effects. Appropriate patient selection, suitable drug and dose, along with proper patient and physician education may help in the effective and vigilant use of SUs in the management of T2DM.

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Conflicts of interest

There are no conflicts of interest.

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