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***Review Article***

# Expert Opinion on the Positioning of Sulfonylureas in the Management of Type 2 Diabetes Mellitus: Emphasis on Gliclazide Use Across Diverse Patient Profiles

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## Abstract

Diabetes Mellitus, a prevalent metabolic disorder, poses a significant global health challenge. Type 2 Diabetes Mellitus (T2DM), the most common form, arises from pancreatic beta-cell dysfunction and insulin resistance. Effective management of T2DM is critical to prevent complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. Sulfonylureas, as insulin secretagogues, play a vital role in T2DM management. Despite the emergence of newer antidiabetic agents, sulfonylureas remain widely used due to their efficacy, cost-effectiveness, and extensive clinical experience. This article explores the positioning of sulfonylureas in T2DM management, drawing on insights from recent expert discussions and advisory board meetings. The discussions underscored the benefits of intensive glycemic control, particularly in reducing microvascular complications, with sulfonylureas playing a significant role. Newer generation sulfonylureas, such as gliclazide and glimepiride, offer enhanced safety profiles and reduced hypoglycemia risk. Gliclazide, with its antioxidant properties and cardiovascular benefits, is preferred in patients with renal impairment or high hypoglycemia risk. Real-world practices indicate a preference for sustained-release formulations due to better patient adherence and consistent blood

glucose control. The article also highlights the need for personalized treatment approaches, considering patient-specific factors such as age, comorbidities, and lifestyle. Sulfonylureas, particularly gliclazide and glimepiride, remain integral to T2DM management. Their role is reinforced by their efficacy, affordability, and potential benefits beyond glycemic control. Ongoing research and real-world evidence continue to shape their optimal use, emphasizing individualized treatment strategies to achieve the best clinical outcomes.

## 1. Introduction

Diabetes Mellitus stands as one of the most prevalent and significant metabolic condition, escalating into a worldwide health crisis over the past few decades, posing substantial challenges to healthcare systems globally [1]. According to the World Health Organization (WHO), diabetes is a condition characterized by persistent high blood sugar levels, arising due to irregular insulin secretion, insulin function, or both [2]. It's a metabolic disorder which disturbs how the body processes carbohydrates, fats, and proteins [2]. It is differentiated into type 1 (early onset, immune disorder) and type 2 (late onset, lifestyle disease) [3] on the basis of etiology [3]. Type 2 diabetes mellitus (T2DM) is the most prevalent form accounting for approximately 90% of diabetes cases. The remaining 10% of the patients are diagnosed with type 1 diabetes (T1D) [4], although there are also less common types present [5, 6]. T2DM primarily arises from pancreatic beta-cell dysfunction, resulting in reduced insulin production and release, alongside resistance to insulin in peripheral tissues [7, 8].

The predominant theories link the onset of T2DM largely to diets dominated with carbohydrate and processed food, and characterized by excessive nutrient intake with inadequate energy expenditure, accounting for approximately 90% of diagnosed patients being overweight or obese [9]. Most of the T2DM treatments target effectively lowering high blood sugar levels, by either enhancing insulin secretion or reducing insulin resistance in peripheral tissues [10]. However, despite these treatments, chronic diabetic complications are widespread and T2DM continues to be a primary cause of blindness, end-stage kidney disease, lower limb amputations, and cardiovascular problems [2].

Approximately 537 million individuals are currently living with diabetes mellitus, with projections indicating a rise to 643 million by 2030 and 783 million by 2045 [11]. The expected increase in diabetes prevalence by 2045 is primarily attributed to population aging, with a projected growth of 16% [11]. The prevalence of uncontrolled T2DM rises with age, starting at 11.1% in young adults and peaking at 52.7% in older individuals (ages 15-24 and 65-74, respectively) [11]. In India, the number of people with T2D is currently around 77 million, and this figure is projected to climb to over 134 million by 2045 [12]. Around 57% of these cases go undiagnosed [12]. Maintaining optimal blood glucose levels is of utmost importance for minimizing the risk of severe complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy [13]. Various factors, including personal habits, medical conditions, prescribed medications, and behavioural choices, influence how well individuals manage their blood sugar levels [13]. Glycated haemoglobin (HbA1c) serves as the conventional clinical indicator to evaluate glycaemic control, reflecting the average blood glucose levels across approximately three months [14]. Recently, there's growing recognition of glycaemic variability, encompassing fluctuations in glucose levels, as a significant aspect in diabetes care, potentially standing as an independent risk element for diabetes-related complications [14]. According to the American Diabetes Association(ADA), HbA1c levels below 5.7% are considered as normal, 5.7% to 6.4% indicate prediabetic condition, and 6.5% or higher suggest diabetes [15]. Unhealthy lifestyle habits, like diet and exercise patterns, significantly impact glycaemic control [16]. Making poor choices in these areas can result in less-than-ideal HbA1c

levels, which can ultimately worsen outcomes for individuals with diabetes [16]. The quality of one's diet plays a crucial role in controlling blood sugar levels, particularly for individuals with diabetes [17]. Eating foods rich in fibre and avoiding carbohydrates with high glycaemic index seems to be advantageous for managing glucose levels effectively [17]. Early initiation of diabetes pharmacotherapy is crucial for maintaining blood sugar levels, preventing complications, preserving beta cell function, and slowing disease progression. Combined with lifestyle changes, it ensures better glycemic control and overall well-being [18]. By addressing symptoms like excessive thirst, frequent urination, fatigue, and blurred vision, early initiation of treatment can significantly enhance quality of life for individuals with diabetes [19]. Oral antidiabetic drugs (OADs) regulate blood sugar through different mechanisms. Sulfonylureas stimulate insulin release, while biguanides like metformin reduce liver glucose production and improve insulin sensitivity [20]. Alpha-glucosidase inhibitors slow carbohydrate absorption, glinides promote post-meal insulin release, thiazolidinediones enhance tissue insulin sensitivity, and DPP-4 inhibitors boost insulin secretion and reduce glucagon levels [20]. As per the ADA guidelines, metformin, an activator of adenosine 5′-monophosphate-activated protein kinase (AMPK), is the initial treatment choice for T2D [21]. However, the effectiveness and safety of OADs differs among individuals due to genetic variations. Factors such as genetic polymorphisms can influence drug metabolism, efficacy, and adverse effects [22]. Therefore, personalized treatment plans that consider individual genetic profiles can optimize the T2D management while minimizing potential risks [22]. Sulfonylureas lower blood glucose by stimulating insulin secretion from pancreatic β-cells. They bind to receptors, closing ATP-sensitive potassium channels, causing membrane depolarization and opening calcium channels, which triggers insulin release [23]. This effect may continue even after discontinuation, helping to preserve β-cell function [23].

Sulfonylureas are often combined with other antidiabetic medications like metformin to mitigate risks such as weight gain and hypoglycaemia by targeting different aspects of diabetes pathology [24]. Intensive management of blood glucose using sulfonylureas significantly decreases the likelihood of microvascular complications in T2DM, including the requirement for retinal photocoagulation [25]. Sulfonylureas offer distinct advantages over other oral hypoglycaemic agents due to their affordability and extensive clinical use spanning over 60 years [25]. By augmenting insulin secretion, sulfonylureas aid in achieving improved and sustained glycaemic management, with the benefits extending beyond the duration of administration [26, 27].

## 2. Methods

This article draws from conversations among physicians and experts in endocrinology and diabetology from different regions of India, conducted during multiple advisory board meetings held in late 2023, organized by Dr. Reddy's Laboratories, India. The panel discussed on the various aspects of T2DM management. Before the meeting, a series of topics were distributed to all the experts. They reviewed provided publications comprising meta-analyses, systematic reviews, randomized controlled trials (RCTs), real-world evidence (RWE) studies, as well as national and international diabetes guidelines. The gathered evidence on each topic was compiled and presented at the meeting. The expert panel provided recommendations on the following topics:

- Intensive vs conventional glycemic control of diabetes to managemicro and macrovascular complications.
- Intensive glycemic control and patient profiles that are benefitted with it.
- Unmet need in diabetes management space despite of newer agents.

- Selection of OADs after/along with metformin therapy and reasons to prefer sulfonylureas in T2DM management.
- Opinion on use of new generation sulfonylureas (gliclazide and glimepiride) and choice between the two when sulfonylureas are indicated for glycemic control in patients with T2DM.
- Opinion on use of new generation sulfonylureas (gliclazide and glimepiride) in T2DM patients with chronic kidney disease (CKD).
- Real world prescription practices of glimepiride and gliclazide.
- Drug combinations suggested to use with gliclazide (other than metformin).
- HbA1c reduction observed with sulfonylureas (gliclazide and glimepiride).
- Dose titration of gliclazide in real world practice.
- Sustained release vs quick release gliclazide formulations.

After each presentation, a discussion was conducted which focussed on regional variations in clinical approaches. The recommendations outlined in this article stem from the evidence presented and discussions concluded in the meeting minutes.

## 3. Complications of T2DM

### 3.1 Diabetes-related and cardiovascular complications

Effective diabetes management is crucial as a risk factor for cardiovascular disease (CVD), with vascular complications potentially developing early, even before diagnosis or during pre-diabetes. Research shows that fasting plasma glucose (FPG) levels are significantly linked to CVD risk, even below the diabetes threshold of 7 mmol/l (126 mg/dl). Elevated blood sugar, starting at FPG levels of 5.6 mmol/l (101 mg/dl), adversely affects prognosis [28]. The international EpiDREAM cohort study found a gradual increase in CVD risk across various glycemic statuses, noting that each 1 mmol/l rise in FPG corresponded to a 17% increase in the likelihood of future cardiovascular events or mortality [29].

### 3.2 Macrovascular complications

Arteriosclerotic cardiovascular diseases (ASCVDs), including coronary heart disease (CHD), peripheral artery disease (PAD), and stroke, are prevalent among individuals with diabetes, particularly as glucose status worsens. A recent systematic review involving 4,549,481 individuals diagnosed with T2DM revealed an overall macrovascular complication prevalence of 32.2% [30]. Among these complications, CHD emerged as the most commonly reported form of cardiovascular disease, accounting for 21.2% of cases [30]. Various subsequent studies have consistently concluded that T2DM poses a significant risk equivalent to CHD, specifically evident with the absence of prior CHD indicators, with women being particularly susceptible [31].

Peripheral artery disease (PAD) refers to the obstructive atherosclerosis affecting arteries in the lower extremities and is closely linked with ASCVD. In individuals with diabetes, PAD often affects more distal segments of the leg arteries, particularly in the cruro-pedal region, and may involve calcific medial sclerosis, posing challenges for diagnosis and treatment [32]. While PAD commonly presents with symptoms like claudication, severe cases can lead to lower extremity amputation. A systematic review encompassing over 112,000 participants across various countries noted a significant 23.5% increase in PAD prevalence between 2000 and 2010 [33]. Presently, PAD stands as the most prevalent initial sign of CVD in T2DM [34]. Diabetes-related stroke results from both extracranial carotid artery disease and intracranial large and small vessel diseases triggered by diabetes. Diabetes independently elevates the risk of stroke, with an incidence 2.5-3.5 times greater than that in individuals without diabetes. Stroke stands as the leading cause of mortality among patients with T2DM following CHD [30]. Moreover, stroke related hospitalizations tend to be lengthier and neurological complications are often more

severe in individuals with diabetes. Poor glycemic control exacerbates the risk of stroke-related mortality, with each 1% increase in hemoglobin A1c (HbA1c) levels correlating with a 1.37 times higher likelihood of death from stroke [34]. Diabetes mellitus-induced cardiomyopathy (DMCMP) is primarily attributable to prolonged hyperglycemia and subsequent oxidative stress, presenting with various clinical and echocardiographic phenotypes [35, 36]. Heart failure (HF) stands as a significant cause of hospital admissions among individuals with T2DM. Both hospitalization and mortality rates attributed to HF appear unaffected by strict glycaemic control, particularly when using older medications such as sulfonylureas, metformin, thiazolidinediones, and insulin. This suggests that factors beyond glucose levels likely contribute to the heightened risk of HF in diabetes. A meta-analysis involving 37,229 patients revealed no significant impact of intensive glycaemic control on HF risk in individuals with T2DM, yielding an odds ratio of 1.20 (95% CI: 0.96-1.48) when comparing intensive and standard glycaemic control strategies [37].

### 3.3 Microvascular complications

Microvascular complications stemming from diabetes significantly increase morbidity and profoundly impact the quality of life for affected individuals. These complications primarily include nephropathy, retinopathy, and cardiac autonomic neuropathy (CAN).

- Nephropathy, characterized by elevated urine albumin excretion and CKD marked by reduced glomerular filtration rate (GFR), develops due to prolonged inadequate glycaemic control. Diabetic kidney disease or diabetic nephropathy stands as a prevalent microvascular complication of diabetes mellitus, impacting more than 25% of individuals with diabetes [38]. Presently, diabetes related nephropathy represents the largest subset of end-stage renal disease cases among adults worldwide [39]. A recent meta-analysis, evaluating 16 guidelines and 328 statements concluded that tight glycaemic control (HbA1c < 6.5-7.0%) did not significantly impact these outcomes when compared to less stringent control (HbA1c 7.0-8.5%) [40]. The presence of renal disease substantially contributes to the overall medical burden of T2DM and heightens cardiovascular risk, as lower GFR and albuminuria are closely linked to CVD and increased mortality from all causes [41].
- Diabetic Retinopathy (DR) stands as the most prevalent microvascular complication of diabetes, contributing to roughly 10,000 new cases of blindness annually in the USA and impacting nearly 100 million individuals globally [42]. The burden of DR is steadily increasing, as evidenced by estimates from 1990 to 2010, which revealed a 64% rise in visual impairment and a 27% increase in blindness attributed to DR [42]. Although the chances of DR are significant in T2DM, the occurrence of DR has been found to be greater among individuals with type 1 diabetes compared to those with T2DM (77.3% vs. 25.2%) [43].
- Diabetic neuropathy exhibits a wide range of clinical symptoms it affects both the somatic and autonomic nervous systems [38], with risk increasing with age, hyperglycaemia severity, and duration. Hyperglycaemia drives CAN's pathogenesis by triggering mitochondrial dysfunction and reactive oxygen species production. CAN prevalence ranges from 17-66% in T1DM and 31-73% in T2DM, depending on diagnostic methods, age, and diabetes duration. CAN is associated with higher morbidity, including silent myocardial ischemia, CHD, and stroke [44, 45].

## 4.Glycaemic control strategies in T2DM management

### 4.1 Intensive vs conventional glycaemic control

There are two strategies for managing blood

glucose: intensive and conventional glycaemic control. Intensive control aims for glycated haemoglobin (HbA1c) below 7%, significantly reducing microvascular and potentially macrovascular complication [46]. However, it increases hypoglycemia risk, especially in older adults, and is associated with weight gain, treatment complexity, and higher costs. Conventional control, targeting HbA1c around 7-8%, poses a lower hypoglycemia risk and is simpler and more tolerable, making it ideal for older patients or those with multiple comorbidities [47, 48].

While conventional control is safer in the short term and easier to manage, it is associated with higher rates of long-term diabetic complications compared to intensive control. As such, it may not be as effective at preventing or delaying the progression of diabetic complications [49]. In a systematic review and meta-analysis of fifty-seven studies conducted to assess intensive glycemic control's risk-benefits in adults with T2D via multi-factorial intervention, intensive control decreased risks of non-fatal myocardial infarction, macroalbuminuria, microalbuminuria, major amputation, retinopathy, and nephropathy. Specifically, the risk reductions ranged from 20% for non-fatal myocardial infarction to as much as 40% for major amputations. However, the risk of hypoglycemia was increased (RR: 2.04, 95% CI: 1.34-3.1). All-cause or cardiovascular mortality showed no reduction overall, but in multi-factorial intervention, all-cause mortality decreased [50].

In the ADVANCE (Action in Diabetes and Vascular Disease - Preterax and Diamicron MR Controlled Evaluation) trial intensive arm, investigating the effects of intensive glucose control on vascular outcomes in T2DM patients (involving 11,140 patients), intensive glucose control aiming for a HbA1c value of ⩽6.5% resulted in a mean glycated hemoglobin level of 6.5%, compared to 7.3% in the standard-control group. After a median follow-up of 5 years, intensive control led to a significant reduction in the combined major macrovascular and microvascular events (18.1% vs. 20.0% with standard control; hazard ratio, 0.90; 95% CI, 0.82 to 0.98; P=0.01), driven primarily by a 21% relative reduction in nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006). However, there were no significant effects on major macrovascular events or mortality [51]. The UKPDS study also demonstrated that rigorous glycemic control led to a decrease in microvascular complications compared to standard treatment. In particular, the intensive glycemic control group experienced a 25% lower risk of requiring retinal photocoagulation [27].

**Expert opinion:** Experts reached a consensus that intensive glycemic control significantly reduces microvascular complications, though opinions on its effect on macrovascular complications varied. They acknowledged the non-significant reduction in cardiovascular mortality in the ADVANCE and ACCORD trials, highlighting the need to explore the relationship between glycemic control and cardiovascular health. Factors such as hypertension, dyslipidemia, and smoking were emphasized as crucial for cardiovascular outcomes. Experts advocated for individualized treatment strategies based on patient characteristics, including age, comorbidities, and life expectancy, suggesting that younger individuals with fewer complications may benefit from more stringent glycemic control while avoiding hypoglycemia. The panel highlighted the role of newer medications, such as DPP-4 inhibitors and GLP-1 receptor agonists, in improving outcomes for both micro and macrovascular complications, emphasizing the need for ongoing research to elucidate their long-term effects. Also, the experts highlighted the importance of sulfonylureas, with reference to the ADVANCE trial demonstrating a 10% risk reduction in both microvascular and macrovascular events emphasizing the intensive glycemic control. Experts asserted the significance of patient education and comprehensive screening for complications to guide treatment decisions effectively.

**Key highlights**

- Intensive glycemic control significantly reduces microvascular complications.
- A stricter approach to glycemic control may be beneficial for younger individuals who have fewer vascular complications and a longer life expectancy, as long as efforts are made to avoid hypoglycemia.
- Sulfonylureas are highly effective for intensive glycemic control and significantly reduce the risk of both microvascular and macrovascular events.

### 4.2 Patient profiles benefiting from intensive glycaemic control

Intensive glycemic control strategies in the management of T2DM are particularly advantageous for certain patient profiles where the long-term benefits outweigh the potential risks. It is especially beneficial for younger patients who have a longer life expectancy and more years to potentially develop diabetes-related complications. These patients can gain significantly because they have 9 more time to benefit from the reduced risk of microvascular complications such as retinopathy, nephropathy, and neuropathy [46].

Additionally, patients with a recent diabetes diagnosis may benefit from intensive glycemic control, as early management can stabilize or slow disease progression through metabolic memory, which yields long-lasting effects. This approach is particularly effective for those without significant cardiovascular disease, preventing new cardiovascular events and microvascular complications better than conventional methods [52]. In a meta-analysis of five RCTs involving 33,040 participants with T2DM, intensive glucose-lowering treatment showed a 17% reduction in non-fatal myocardial infarction and a 15% reduction in coronary heart disease events compared to standard treatment, with no significant effect on stroke or all-cause mortality [52]. Although intensive control led to a 0.9% lower mean HbA(1c) concentration, it did not affect mortality rates [52].

Lastly, intensive glycemic control may also be appropriate for overweight or obese T2DM patients actively managing their weight and lifestyle. Combined with lifestyle modifications, it can improve outcomes by reducing cardiovascular risk factors and enhancing insulin sensitivity [53]. While intensive glycemic control has substantial benefits in reducing the risk of microvascular and potentially macrovascular complications in T2DM, it requires careful selection of patients based on their age, duration of diabetes, absence of significant cardiovascular disease, motivation levels, and lifestyle factors [54].

**Expert opinion:** Healthcare professionals reached a consensus on the benefits of early intensive treatment, acknowledging the risk of hypoglycemia. They emphasized the importance of tailoring treatment to individual profiles, considering factors like age, comorbidities, and hypoglycemia risk. Patients most likely to benefit from intensive control include those with younger onset diabetes, shorter duration, longer life expectancy, fewer comorbidities, and lower hypoglycemia risk. A more aggressive approach is recommended for patients with higher HbA1c levels, using a combination of sulfonylureas and newer drugs like SGLT-2 and DPP-4 inhibitors. While sulfonylureas have a higher hypoglycemia risk, real-world studies did not link newer sulfonylureas to significant hypoglycemia, and in clinical practice, the combination of metformin and sulfonylureas was recommended as effective and sustainable in achieving intensive glycemic 10 control.

**Key highlights**

- Early intensive treatment is important for long term outcomes and stringent glycemic control.
- The patient profiles most likely to benefit from intensive control include: patient with younger onset diabetes, shorter duration of diabetes, longer life expectancy, fewer comorbidities, and reduced chances of hypoglycemia.

- A more aggressive approach to glycemic control is suggested for patients with higher HbA1c levels, often indicative of poor glycemic control.

### 4.3 Unmet needs despite newer agents.

Despite advances in pharmacological treatments for T2DM, several unmet needs persist even after the introduction of newer agents. One of the primary unmet needs in T2DM management is the continued high risk of CVD. Intensive glycemic control has been shown to have little impact on all-cause mortality and cardiovascular mortality, suggesting that hyperglycemia management alone may not be enough to mitigate these risks significantly [52]. Another significant unmet need is the prevention and management of hypoglycemia, particularly with intensive glycemic control strategies. It is a common, serious side effect, particularly in the elderly and those with renal impairment, impacting both immediate safety and long-term glycemic control [37]. Treating T2DM in populations like the elderly and those with multiple comorbidities remains an unmet need. These groups are often underrepresented in clinical trials, leaving the efficacy and safety of newer treatments poorly documented. This highlights the evidence gaps regarding the benefits of intensive versus conventional glycemic control across various patient demographics and health conditions [55]. Furthermore, despite the range of medications available, the management of T2DM still requires significant lifestyle changes that many patients find challenging to implement and sustain [56]. There is an unmet need for personalized medicine approaches in T2DM. Current treatments are often based on a one-size-fits-all approach, which does not account for the genetic, environmental, and lifestyle factors that vary widely among individuals [57].

**Expert opinion:** The experts also unanimously agreed that the primary challenge lies not in the scarcity of available treatments but rather in their appropriate application and patient adherence. They emphasized on the necessity of patient education, doctor sincerity, and active patient involvement. Additionally, there was a consensus on the importance of using the right doses of medications at the right time, tailoring treatment regimens based on individual HbA1c levels. This approach involves prescribing stronger drugs like sulfonylureas for higher HbA1c levels above 11, while opting for milder agents when HbA1c levels are lower. Furthermore, experts cautioned against overstimulating beta cells with sulfonylureas, especially in patients with severely elevated HbA1c levels. Instead, they recommend initiating basal insulin therapy in such cases to prevent further beta cell exhaustion. Despite the efficacy of newer agents like SGLT2 inhibitors and DPP4 inhibitors, particularly in combination, it was noted that sulfonylureas play a significant role in the Indian population, where patients often present to physicians with very high HbA1c levels exceeding 9. The discussion further underscored the importance of considering additional benefits beyond glucose control, such as lowering blood pressure and preventing target organ damage, when selecting antidiabetic medications. The experts highlighted the need for individualized treatment approaches that consider patients' comorbidities, financial constraints, and lifestyle factors.

### Key highlights

- Patient education, doctor sincerity, and active patient involvement in treatment are crucial factors in addressing these unmet needs.
- Sulfonylureas are recommended for higher HbA1c levels, while milder agents should be opted when HbA1c levels are lower.
- In patients with severely elevated HbA1c levels, initiating basal insulin therapy is recommended to prevent further beta cell exhaustion.

## 5. Role of sulfonylureas in T2DM management

Sulfonylureas enhances insulin secretion from pancreatic β-cells, by binding to ATP-sensitive

potassium channels on the β-cells, triggering a cascade that results in increased insulin release [58]. Over time, their effectiveness may slow down, necessitating the use of additional therapies or combination treatments to maintain glycemic control [24]. Despite concerns regarding their cardiovascular safety, recent studies such as the CAROLINA trial have shown that sulfonylureas 12 do not adversely affect cardiovascular outcomes, reinforcing their safety profile [59]. Several studies indicate that sulfonylureas exhibit anti-inflammatory characteristics, potentially resulting in enduring advantages for glycaemic regulation and vascular well-being [60]. Sulfonylureas also have the potential to regulate epigenetic modifications that impact gene expression associated with glucose metabolism and insulin sensitivity, result in prolonged effects on glycaemic regulation [61].

A cross-sectional analysis study, conducted to investigate the utilization of oral glucose-lowering drugs (OGLDs) among Asian patients with T2D, analysed data from the Joint Asia Diabetes Evaluation (JADE) register. Out of 62,512 patients examined, 87.6% were found to be using OGLDs, with the majority employing one or two types. Sulfonylurea-based therapies were common (59.4%), primarily in combination with metformin (79.5%) or dipeptidyl peptidase-4 inhibitors (22.1%). Gliclazide was the most frequently used sulfonylurea, followed by glimepiride and glibenclamide. Patients on gliclazide generally showed better glycaemic control and fewer incidents of hypoglycaemia [25].

In a retrospective study of 47,895 patients from the JADE Register, 42,813 used oral glucose lowering drugs (OGLDs) with lifestyle modifications (LSM), while 5,082 relied solely on LSM. Patients on OGLDs reported lower health-related quality of life (HRQoL) than those on LSM,ith increased pain/discomfort and anxiety/depression. Among OGLD users, gliclazide showed better HRQoL and lower HbA1c than other sulfonylureas, indicating its advantages for T2DM in real world settings [62].

Sulfonylureas are categorized into two groups: first- and second-generation sulfonylureas. The first group includes the long-acting agents chlorpropamide, tolbutamide, tolazamide, and acetohexamide. The differing pharmacological and pharmacokinetic properties of sulfonylureas stem from variations at specific points in their molecular structure. The second-generation sulfonylureas comprise agents like glyburide (also known as glibenclamide), glipizide, gliquidone, glimepiride, and gliclazide each with a distinct action duration. Glimepiride and glyburide have a prolonged effect compared to glipizide. Glimepiride, the most recent second-generation sulfonylurea, is occasionally regarded as a third-generation agent due to its larger molecular substitutions relative to its counterparts [63-65].

Sulfonylureas also present several drawbacks including an increased risk of hypoglycemia, particularly concerning for elderly or those with irregular eating habits, and associated weight gain, 13 which is disadvantageous for patients dealing with obesity [27]. Also, there are also mixed concerns about their cardiovascular safety [66, 67], and prolonged effectiveness due to secondary failure [24]. Despite these issues, they remain a cost-effective option in many settings like for intensive glycemic control, requiring careful management to balance benefits and risks.

For patients intolerant to metformin, sulfonylureas are a first-line therapy with a 1.5% expected HbA1c reduction. If HbA1c is at least 1.5% above target, sulfonylureas can achieve an average reduction of 1.6%. Adding low-dose gliclazide as second-line therapy to metformin can further lower HbA1c by 0.80% [68]. Lastly, when patients show inadequate glycemic control with the current antidiabetic drugs, employing sulfonylureas as a third-line add-on therapy can reduce HbA1c by 1%. Table 1 highlight the uses of sulfonylurea in different patient profiles [68, 69].

**Table 1. Suggested use of sulfonylurea usage in various patient profiles with T2DM**

| Parameters | Conditions | Sulfonylurea usage |
|---|---|---|
| General diabetic patients | Newly diagnosed T2DM, life expectancy >15 years | Early treatment for favorable long-term outcomes |
| | Patients needing low dose sulfonylurea | Initiate with low dose and escalate to submaximal doses |
| High baseline HbA1c | Patients requiring glycemic targets ⩾1.5% | Intensive control with sulfonylureas to reduce HbA1c up to 1.5% |
| Elderly | -Elderly patients who are considered "strong" for whom life expectancy is considered satisfactory.<br>-Patients on insulin with poor control | When other drugs do not work, use modern sulfonylurea with the least risk of hypoglycemia like Glimepiride, gliclazide modified release (MR) |

<table>
<tr><td>Uncontrolled T2DM</td><td>Patients with uncontrolled T2DM on met/met+DPP4/met+SGLT2i</td><td>Robust efficacy of sulfonylurea in providing glycemic control</td></tr>
<tr><td rowspan="2">OAD Failure</td><td>Before shifting the patient to insulin</td><td>Sulfonylurea as one of the components of triple therapy (OAD Failure)</td></tr>
<tr><td>Initiating insulin</td><td>Small dose sulfonylurea is beneficial</td></tr>
<tr><td rowspan="3">Based on obesity and weight</td><td>Normal TG with high HDL</td><td rowspan="3">Sulfonylurea can be prescribed in those patients who are likely to respond to sulfonylurea.<br>Use *TyG Index to find out insulin resistance and identify those who are suitable for treatment with sulfonylurea.<br>TyG index formula: Ln (fasting triglycerides (mg/dL) x fasting glucose (mg/dL)).<br>This will help to differentiate patients with insulin deficiency from those with insulin resistance.</td></tr>
<tr><td>Normal weight</td></tr>
<tr><td>Lean patient</td></tr>
<tr><td colspan="3">*TyG index may be a reliable biomarker of insulin resistance; Lipid profile can determine if the patient can respond to sulfonylurea or insulin resistant (IR)<br>HDL: high density lipoprotein: OAD, oral anti-diabetic, TG: Triglyceride.</td></tr>
</table>

### 5.1 Overviewof new generation sulfonylureas

Newer sulfonylureas like glibenclamide, gliclazide, and glimepiride offer improved efficacy and safety. Glibenclamide stimulates insulin secretion from pancreatic beta cells with prolonged action, typically dosed once or twice daily. While effective in reducing HbA1c, it poses a higher hypoglycemia risk, especially in the elderly or those with renal impairment, warranting caution. It's contraindicated in severe renal or hepatic impairment due to its long duration of action. Glimepiride, with more selective binding to beta cells, enhances insulin secretion with less hypoglycemia risk, once-daily dosing, and shorter action. It effectively lowers HbA1c and has a more favorable side effect profile, with less hypoglycemia and weight gain, and may offer cardiovascular benefits [70].

Gliclazide, also a second-generation sulfonylurea, offers a shorter half-life compared to glibenclamide, providing more dosing flexibility. It effectively lowers fasting and postprandial blood glucose levels without inducing excessive hypoglycemia. Beyond glycemic control, gliclazide also exhibits antioxidant properties and potential cardiovascular protective effects, making it a preferred option in patients at higher hypoglycemic risk or with comorbidities like renal dysfunction [71].

### 5.2 Selection of OADs after/along with metformin therapy

The selection of OADs alone or in combination therapy requires a thorough understanding of the different drug classes, their effects, and how they match the patient's specific health profile and treatment goals.

- ***Efficacy and Safety:*** After metformin, oral antidiabetic agents such as sulfonylureas, thiazolidinediones, DPP-4 inhibitors, meglitinides, SGLT2 inhibitors, α-glucosidase inhibitors, GLP-1 agonists, bile-acid sequestrants, and bromocriptine are considered. Among these, DPP-4 inhibitors are noted for their moderate efficacy and low side-effect profile, making them a preferred choice in cases where metformin's gastrointestinal side effects limit its use, or where sulfonylurea treatment leads to significant hypoglycaemia or weight gain [72].
- **Pharmacological Profiles:** Various classes of oral antidiabetic drugs offer distinct mechanisms and therapeutic benefits, tailored to individual patient needs. Sulfonylureas and meglitinides stimulate insulin secretion but are associated with potential drawbacks like weight gain and frequent hypoglycemia, necessitating careful patient selection and monitoring [73]. Thiazolidinediones enhance insulin sensitivity, yet they carry risks related to weight gain and cardiovascular complications [74]. DPP-4 inhibitors and GLP-1 agonists improve glycemic control by increasing incretin levels, which boost insulin release and reduce glucagon without causing weight gain [75]. SGLT2 inhibitors uniquely promote glucose excretion through urine, offering additional benefits in weight control and potentially reducing cardiovascular and renal risks, suitable for patients with comorbid conditions [76].

A systematic review of glucose-lowering drugs for T2D patients unable to use metformin, involving 185 trials and 38,376 patients, assessed various OADs, including sulfonylureas, TZDs, glinides, AGIs, DPP-4 inhibitors, SGLT2 inhibitors, insulins, and GLP-1 receptor agonists. Sulfonylureas effectively reduced HbA1c and fasting glucose but increased hypoglycemia risk. GLP-1 receptor agonists lowered BMI and cholesterol, TZDs raised HDL-Cholesterol, and SGLT2 inhibitors reduced systolic blood pressure. AGIs led to more adverse events. Only GLP-1 receptor agonists showed overall benefits, with no significant differences in long-term outcomes like mortality or major vascular events among the drugs [77]. In another network meta-analysis study, a comprehensive analysis of 453 trials involving 21 antidiabetic treatments, no significant difference was observed in mortality, glycemic control, and vascular outcomes in drug-naive T2D patients at low cardiovascular risk. However, in those at

increased risk and on metformin, insulin regimens, and certain GLP-1 agonists significantly reduced HbA1c levels [78].

### 5.3 Reasons for preference of sulfonylureas

Sulfonylureas are preferred in managing T2DM due to their proven efficacy in stimulating insulin secretion, especially for patients who cannot control blood sugar through lifestyle changes [69]. They are among the most cost-effective oral antidiabetics, making them ideal in resource-limited settings [66]. Studies show they reduce microvascular complications without raising all-cause mortality, while certain types, like gliclazide, offer additional haemobiological and antioxidant benefits that help manage vascular risks and retinopathy [27, 67]. Early use can effectively manage hyperglycemia and delay diabetes progression [79]. They also work well in combination with other antidiabetic drugs, providing treatment flexibility.

**Expert opinion:** The discussion among experts made it evident that metformin is the first-line OAD and the selection of OADs after metformin is a nuanced process that involves careful consideration of various factors. The experts unanimously agreed that individualization of treatment is crucial, taking into account patient-specific characteristics and comorbidities. The importance of minimizing costs and ensuring affordability for patients was highlighted. Experts asserted that factors such as CVD, CKD, congestive heart failure (CHF), obesity, and non-alcoholic fatty liver disease (NAFLD) guides the choice of OADs. GLP-1 agonists are suggested in patients with heart failure or renal dysfunction, while sulfonylureas remain a viable option for those unable to afford newer medications or experiencing side effects with newer molecules. For patients with long-standing diabetes and HbA1c levels around 8 to 9, initiating basal insulin therapy is crucial. Insulin use was particularly advocated in patients experiencing weight loss or a catabolic state. Furthermore, the experts stressed the importance of considering weight criteria depending on comorbidity and highlighted the potency of sulfonylureas as oral hypoglycemic agents. Emphasizing the need for minimizing glucose variability and avoiding hypoglycemia in drug selection, a triple-drug combination was recommended in patients with HbA1c levels of 9 or higher.

Experts noted that patients with high HbA1c levels on sulfonylurea treatment typically achieve better glycemic control. They highlighted the potency, affordability, and minimal drug interactions of sulfonylureas, consistent with published literature. The rapid reduction of blood glucose and HbA1c was emphasized as vital, especially in patients needing urgent control, such as those undergoing surgery or facing hyperglycemic emergencies. While acknowledging the preference for newer agents like GLP-1 agonists or SGLT-2 inhibitors in some cases, experts stressed the benefits of sulfonylureas for those with poor control despite metformin or other oral agents, and in genetic forms of diabetes (MODY).

Additionally, the experts agreed upon the concerns regarding beta-cell preservation and insulin resistance associated with the use of sulfonylureas, emphasizing the need for judicious prescribing practices. They advocated for starting with lower doses of sulfonylureas and up-titrating slowly to minimize the risk of hypoglycemia and preserve beta-cell function, also dispelling misconceptions regarding pancreatic damage.

### Key highlights

- Metformin is the first-line OAD. CVD, CHF, CKD, obesity, and NAFLD guides the choice of OADs.
- Insulin use is strongly suggested in patients experiencing weight loss or in a catabolic state.
- Sulfonylureas are a viable option for those unable to afford newer medications or experiencing side effects with newer molecules.
- To minimize the risk of hypoglycemia and preserve beta-cell function, it is advisable to use lower doses of sulfonylureas and up-titrate slowly.

## *6.*Comparative analysis of gliclazide and glimepiride

Both gliclazide and glimepiride effectively lower blood glucose levels by stimulating insulin secretion [65,80]. A study comparing gliclazide and glimepiride found that gliclazide significantly reduced non-severe hypoglycemia. Fifteen of 403 gliclazide users had episodes, compared to 39 of 439 glimepiride users (50% fewer episodes). Both groups saw similar HbA1c reductions (8.4% to 7.2% with gliclazide, 8.2% to 7.2% with glimepiride) [81]. Furthermore, multiple randomized trials have also indicated that among patients receiving consistent doses of a sulfonylurea for a minimum of 3 months, the possibility of experiencing symptomatic hypoglycemia during Ramadan/Navartras is minimal [82, 83]. The incidence of such hypoglycemia appears to be lower with gliclazide (14%) compared to glimepiride (16.8%) [82, 83]. Additionally, gliclazide was found to have a lower risk of cardiovascular events and mortality compared to other sulfonylureas, including glimepiride. Glimepiride exhibited hazard ratio of 1.32 while it was 1.05 for gliclazide. Furthermore, the mortality rate among gliclazide users was 4%, whereas it was 11% among glimepiride users [80, 85]. A study comparing glimepiride and gliclazide in T2DM patients found gliclazide had better safety and efficacy. Gliclazide reduced fasting blood sugar by 52.5%, postprandial blood sugar by 41.3%, and HbA1c by 2.44 while glimepiride showed reductions of 56.9%, 32.3%, and 1.91, respectively [86]. In another study, gliclazide MR caused no adverse drug reactions (ADRs), while glimepiride led to 8 ADRs, including diarrhea, gastric irritation, and weight gain. Severe hypoglycemia occurred more with glimepiride (3.1%) than with gliclazide MR (0.6%) in elderly patients [87]. Gliclazide has also been observed to have a decreased risk of sustained doubling of serum creatinine compared to glimepiride in patients with well-controlled glycemia (A1c < 7%), preserved renal function (GFR $\geqslant$ 60 mL/min/1.73 $m^2$), and older age ($\geqslant$ 62 years) [88]. The study suggested renal protective nature of gliclazide and that it may play a role in preventing renal disease progression.

Studies indicate different sequences in prescribing glimepiride and gliclazide after metformin, with some suggesting glimepiride [89, 90] and others opting for gliclazide [91, 92]. In comparing gliclazide and glimepiride, dosing strategies differ substantially [93, 94]. Gliclazide can vary in dosage, typically up to 320mg daily for standard and 120mg for extended/delayed release [94]. If exceeding 160mg daily, it's divided into two equal doses. Gliclazide immediate release (IR) is available in 80mg tablet, whereas gliclazide MR is available as 30mg and 60mg [95]. Glimepiride tablets come in 1mg to 4mg, with starting doses at 1mg daily for adults, gradually increasing to 4mg and the maximum daily dosage is 6mg [93]. Both glimepiride and gliclazide are eliminated from urine (approx 80%) for glimepiride and 65% for gliclazide) and the duration of action is intermediate for both of these drugs, with 5-8 hours and 10 hours for glimepiride and gliclazide, respectively [96].

**Expert opinion:** Experts favored gliclazide over glimepiride for glycemic control in T2DM patients due to its better safety profile, including a lower incidence of hypoglycemia. Studies also highlighted gliclazide's efficacy in managing postprandial glucose and reducing hyperglycemia risk [80-83,85]. Additionally, the availability of extended-release formulations of gliclazide was noted as advantageous, especially in patients with CKD, with careful dose titration being emphasized.

The use of gliclazide and glimepiride in CKD patients requires caution due to an elevated risk of hypoglycemia that results from potential accumulation of the sulfonylurea and/or its active metabolites, thereby prolonging their duration of action [97]. In patients with mild-moderate renal insufficiency, if the glomerular filtration rate falls below 30 mL/min, it is recommended to decrease the dosage of both gliclazide and glimepiride [98].

Expert discussions favored gliclazide over glimepiride for T2DM patients with CKD.

Despite glimepiride's historical use in India, concerns about hypoglycemia were significant. Clinicians particularly recommended gliclazide for elderly patients and those with CKD, suggesting its use even in stages beyond 3, in cases where sulfonylurea use is mandated. The preference was based on gliclazide's favorable effect on preserving beta cell function, with its distinct mechanism of action being advantageous for patients with remaining beta cell function. Additionally, experts noted that gliclazide's safety profile allows its use at lower eGFRs without dose adjustment, unlike glimepiride. The cardiovascular benefits of gliclazide, including its impact on platelet aggregation and vascular conditions, were noted as additional advantages.

Additionally, gliclazide was favored because it demonstrated a more favorable weight profile than glimepiride. In the ADVANCE trial, patients receiving gliclazide, whether in the intensive or standard therapy arm, did not experience weight gain at the end of follow-up [81]. In contrast, in the ACCORD trial, weight gain of more than 10 kg was observed in 27.8% of participants in the intensive therapy arm and 14.1% of participants in the standard therapy arm who were receiving glimepiride [99].

**Key highlights**

- Gliclazide should be preferred over Glimepiride for glycemic control in patients with T2DM due to its favorable safety profile, including a lower incidence of hypoglycemia and improved postprandial glucose levels.
- In T2DM patients with CKD, Gliclazide is the preferred Sulfonylurea. Gliclazide's safety profile allows for its use even at lower estimated glomerular filtration rates (eGFRs) without the need for dose adjustment, unlike glimepiride
- In patients with mild-moderate renal insufficiency, if the GFR rate falls below 30 mL/min, it is recommended to reduce the dosage of both gliclazide and glimepiride

## *7.* Positioning of sulfonylureas in diabetes management

For patients with diabetes who do not meet glycated HbA1c targets and who do not have atherosclerotic CVD or CKD, the American Diabetes Association (2019) recommends metformin combined with other OADs, including sulfonylureas. However, for those with CVD, SGLT-2 inhibitors or GLP-1 receptor agonists are prescribed [98]. The Research Society for the Study of Diabetes in India (RSSDI) and the World Health Organization (WHO) also align with this recommendation, with sulfonylureas being preferred choice as monotherapy (if metformin is unsuitable) or in a combination therapy [100, 101]. The WHO recommends sulfonylureas for treatment intensification and recognizes them as an important, cost-effective second-line treatment option after metformin for patients with T2D [102, 103]. The preference for gliclazide over other agents in its class is supported by evidence from research and major clinical trials (such as the ADVANCE and GUIDE studies), which demonstrate specific advantages, including a lower risk of hypoglycemia, favorable cardiovascular effects, renal safety, and a generally weight-neutral profile [51, 81, 88, 99, 104-108].

The sustained use of sulfonylureas as second-line treatments for diabetes can be attributed to multiple previously discussed factors [109]. Clinical trials comparing gliclazide with other antidiabetic agents, such as metformin, pioglitazone, vildagliptin, or insulin, have also shown similar glycemic efficacy [110, 111]. In using gliclazide-MR as a second-line antidiabetic agent, Schernthaner et al. observed a 1.0% reduction in A1c levels, from 8.4% to 7.4%, in patients with T2DM who were unresponsive to metformin [81]. Compared with other OADs, gliclazide notably reduced HbA1c levels without increasing the risk of hypoglycemia. In contrast, compared to other sulfonylureas, although HbA1c reduction was not significantly different in gliclazide, a substantially lower risk of hypoglycemia was observed [112]. While gliclazide as monotherapy has demonstrated efficacy similar to metformin, combining metformin with gliclazide has shown better glycemic control and lipid profile improvements [113]. Table 2 lists various guidelines recommending the use of sulfonylureas in T2DM.

**Table 2: Various guidelines showing sulfonylureas usage preference**

| Guideline Authority | Recommended Usage | Specific Recommendations |
|---|---|---|
| ADA (American Diabetes Association) [105] | Second-line therapy | Combine with metformin or other agents |
| EASD (European Association for the Study of Diabetes)[106] | Second-line therapy | Use in combination with other agents |
| NICE (National Institute for Health and Care Excellence)[107] | Second-line therapy | Prefer second-generation SUs like gliclazide |
| IDF (International Diabetes Federation)[105] | Second-line therapy | Consider cost-effectiveness in low-income settings |
| AACE (American Association of Clinical Endocrinologists)[108] | Third-line therapy | Reserve for patients who cannot use other medications |
| Japanese Diabetes Society[109] | First-line therapy in some cases | Monotherapy or in combination with metformin |

The panel mentioned that HbA1c reductions can range from 0.6% to 2%, depending on baseline HbA1c, diabetes duration, and patient factors like age and comorbidities. Higher reductions (1.5%-2%) occur in newly diagnosed patients with HbA1c above 8-8.5%, while lower reductions (0.8%-1.2%) are seen in patients with lower baseline levels. Gliclazide, a weight-neutral sulfonylurea, is advantageous when combined with metformin or SGLT2 inhibitors. Sulfonylureas are often used as third-line therapy after DPP4 or SGLT2 inhibitors, though in cases of high HbA1c (11-11.5%), gliclazide may be used first-line with metformin or DPP4 inhibitors.

The efficacy of gliclazide in combination with medications other than metformin has been demonstrated. A combination of DPP-4 inhibitor (linagliptin) and gliclazide has been shown to benefit diabetic patients with CKD who switched from glimepiride. They experienced a notable decrease in overall hypoglycemic events (22.25%). Furthermore, improvements in renal function were observed, including an increase in eGFR levels (+1.77 ml/min/1.73 $m^2$) and a reduction in albuminuria levels (-45.56 mg/g) [110]. The panel stressed on the effectiveness of sulfonylureas as second and third-line therapy for glycemic control,

especially in the Indian population where patients often present with high initial HbA1c levels of 8-9. In elderly patients with uncontrolled T2DM, gliclazide is often preferred over glimepiride by the physicians due to its lower risk of hypoglycemia and potential renal protective effects.

**Expert opinion**: Experts recommended different approaches for lean and obese patients. For lean patients, sulfonylureas may be started as initial therapy, while for obese patients, metformin should be preferred. If control is not achieved after three months, both medications can be combined. For patients with eGFR below 30, experts recommend insulin. However, with eGFR above 40, sulfonylureas like gliclazide can be considered, especially if DPP-4 or SGLT2 inhibitors are ineffective. Gliclazide MR is preferred for eGFR above 50 to effectively lower blood sugar. Experts also support sulfonylureas as a first-line option in cases of metformin intolerance, very high blood glucose, or inadequate control with metformin. Contrary to past beliefs, recent trials show no significant weight gain with gliclazide, making it suitable even for obese patients when metformin or DPP-4 inhibitors fail.

Experts suggested DPP4 inhibitors as a promising option with gliclazide and mentioned combinations like glimepiride with sitagliptin, especially for CKD patients. Gliclazide with linagliptin was also highlighted for CKD benefits, though some members of the panel questioned combining DPP4 inhibitors with sulfonylureas. The discussion explored combinations like gliclazide with SGLT2 inhibitors or insulin, emphasizing the need for individualized treatment. The gliclazide-SGLT2 inhibitor or insulin combination showed promise but required careful dose titration. Concerns over pioglitazone's cardiovascular safety led to recommendations against its use in certain patients.

**Key highlights**

- Higher baseline HbA1c levels in newly diagnosed patients typically result in greater reductions in HbA1c with Sulfonylureas.
- Sulfonylureas should be preferred as third-line therapy after DPP4 inhibitors or SGLT2 inhibitors. For elderly patients with uncontrolled T2DM, Gliclazide can be preferred over Glimepiride due to its lower risk of hypoglycemia and renal protective effects.
- Sulfonylureas may be started as initial therapy for lean patients, while metformin is often preferred for obese patients.
- For patients with eGFR less than 30, experts recommend the use of basal insulin. If eGFR is 40 or above, Gliclazide, can be considered, especially if the patient is not responding well to DPP4 inhibitors or SGLT2 inhibitors.

## 8.Gliclazide titration

The daily dose of immediate-release gliclazide typically ranges from 40 to 80 mg, taken once or twice daily with meals. In some cases, the dose may be increased to 160 mg twice daily, based on patient response [120]. The recommended starting dose of gliclazide MR is 30 mg daily, with a maximum daily dose of 120 mg [121]. If the patient switches from one form to another, one gliclazide 80 mg tablet is equivalent to one MR 30 mg tablet. Consequently, the switch can be performed with careful blood monitoring [121]. Detailed dosage information is provided in Table 3.

**Table 3: The dose titration of gliclazide versus glimepiride**

| Parameter | Gliclazide | Gliclazide MR | Glimepiride |
|---|---|---|---|
| **Initial Dose** | 40 mg once daily | 30 mg once daily | 2 mg once daily |
| **Dose Titration** | Increase to 80 mg if fasting blood sugar levels exceed targets by more than 30 to 40 units | Can be increased to 60, 90 or 120 mg daily; Increase by 30 mg at least after a month | Increase up to 8 mg cautiously |
| **Maximum Daily Dose** | 80 mg once or twice daily, maximum 160 mg twice daily | 120 mg daily | 8 mg once daily |
| **Frequency** | Once daily with a meal or twice daily with breakfast and dinner | Once daily taken orally at breakfast time | Once daily with breakfast |
| **Incremental Increase** | 40 mg increment if fasting glucose slightly above target (7-9), 80 mg if HbA1c is 10 or above | Increase by 30 mg minimum after a month; Can be increased in patients with insufficient response after two weeks | Increase cautiously to avoid hypoglycemia |
| **Monitoring Interval** | Initial review within 4-6 weeks, then every 3 months if target is achieved, followed by every 6 months | Monthly | Initial review within 4-6 weeks, then every 3 months if target is achieved, followed by every 6 months |

**Expert opinion:** Experts strongly recommended careful titration of gliclazide doses, especially in real-world practice, adjusting based on fasting glucose levels and patient response. MR formulations were preferred for easier dosing and lower hypoglycemia risk. The choice of sulfonylurea depends on factors like patient characteristics, tolerability, and hypoglycemia risk. Individualized treatment, considering age, HbA1c, and renal function, was emphasized. Both gliclazide and glimepiride are viable for T2DM, but the decision should focus on safety, efficacy, and personalized treatment strategies. Preferred dosage by the experts included starting gliclazide MR at 30 milligrams, with titration to 60 milligrams if fasting blood sugar levels exceed targets by more than 30 to 40 units. Conversely, glimepiride dosing starts at 2 milligrams and can be titrated up to 8 milligrams, with caution exercised due to the risk of hypoglycemia, especially at higher doses. Expert panel also highlighted the difficulty of titrating doses with certain combinations, particularly those involving glimepiride and SGLT2 inhibitors.

### Key highlights

- Experts recommend cautious titration of gliclazide doses based on fasting blood sugar levels and individual patient responses.
- Sustained-release formulations of gliclazide should be favored for their ease of dosing and potentially reduced risk of hypoglycemia.
- The choice between gliclazide and glimepiride should consider patient characteristics, tolerability, and hypoglycemia risk.

## *9.* Real-World practices and clinical implications

### *9.1 Factors influencing gliclazide dosing and prescription*

- **Individual response variability**

Individual response variability significantly affects gliclazide's pharmacokinetics and pharmacodynamics, necessitating personalized dosing based on factors such as age, body weight, and comorbidities [122]. Variations in absorption and metabolism can influence dosing decisions, and higher doses do not always enhance therapeutic outcomes, potentially leading to adverse effects, such as increased postprandial hyperglycemia when escalating from 80 mg to 160 mg daily without additional clinical benefits [123]. Gliclazide enhances insulin secretion sensitivity at lower doses [124], improves cardiovascular risk factors [125], and shows benefits beyond glycemic control, such as improving endothelial function and reducing oxidative stress [126, 127]. Adjustments may be required for specific subgroups, such as the elderly or those with renal impairment [123], and disease duration and severity should be considered for effective therapy [128]. Historically, glimepiride gained prominence due to its widespread availability and affordability, as well as its familiarity among healthcare providers. The advent of multiple brands offering glimepiride at competitive prices further bolstered its utilization. Additionally, evidence from studies such as the GUIDE trial demonstrated comparable efficacy between glimepiride and gliclazide, reinforcing its popularity.

**Expert opinion:** The Majority of experts aligned with the above reasons. Moreover, experts asserted that the availability of fixed-dose combinations with metformin, particularly in varying strengths, streamlined treatment regimens, and reduced pill burden, is a crucial consideration in polypharmacy scenarios. Pharmaceutical companies' vigorous marketing efforts, coupled with the accessibility of multiple glimepiride combinations, significantly influenced prescribing patterns. According to some experts, the absence of gliclazide in the US market limited its exposure and adoption, contributing to the dominance of glimepiride. While acknowledging gliclazide's potential advantages, including lower hypoglycemic risk and prolonged efficacy, experts emphasized the need for enhanced

marketing and promotion to elevate its visibility and usage. Despite the ongoing debate, clinicians' consensus underscores the pivotal roles of market dynamics, physician preferences, and patient-specific considerations in shaping prescribing practices.

### 9.2 Gliclazide usage in various patient profiles

Table 4 highlights various patient profiles in which using gliclazide can be beneficial.

**Table 4: Use of gliclazide in various patient Profiles**

| Parameters | Values | Gliclazide use |
|---|---|---|
| De-novo patients HbA1c Levels | 6.5-7% | Gliclazide is considered only when lifestyle changes fail to achieve target levels |
| | >7% | Gliclazide is suggested at higher HBA1C levels, above 7 (usually 9 and above) in combination with metformin or other newer OADs |
| Renal impaired pts CrCL | 30 mL/min | Gliclazide is not recommended due to the increased risk of hypoglycemia |
| | 30-50 mL/min | Cautious use with dose adjustments and close glucose monitoring is suggested |
| | >50 mL/min | Patients with mild or no renal impairment can use gliclazide more freely |
| BMI | Normal/Lean (<25 kg/m$^2$) | Gliclazide is an effective treatment option |
| | Overweight (25-30 kg/m$^2$) | Gliclazide should be used with caution, monitoring hypoglycemia risk |
| | Obese (>30 kg/m$^2$) | Gliclazide is not recommended |
| Age (at the time of diagnosis of T2DM) | <40 years | Can be prescribed with lifestyle changes for tighter glycemic control |
| | 40-60 years | Can help manage microvascular and macrovascular complication |
| | >60 years | Should be used cautiously in elderly patients, considering comorbidities and other medications |
| Patients on multiple drug therapy with HbA1c level | 6.5-7% | Can be used in younger patients if newer drugs are contraindicated or fail to provide adequate control |
| | >7% | Recommended in combination therapy for better glycemic control |

### 9.3 Modified release (MR)/ Sustained release (SR) vs quick release formulations

MR formulations of gliclazide and glimepiride offer consistent glucose control, fewer doses, and a lower risk of hypoglycemia. They maintain stable drug levels, simplifying treatment, improving adherence, and enhancing quality of life. They also optimize absorption, offering consistent therapeutic effects regardless of meal timing. These benefits make MR formulations ideal for long-term diabetes management and preventing complications [129-131]. SR formulations of glimepiride release 73.11%-98.76% of the drug over 8 hours, compared to 100% within an hour for IR formulations, promoting more stable glucose levels throughout the day [132]. Additionally, studies indicate higher patient adherence to SR formulations, with 91.7% for glimepiride/metformin SR versus 88.6% for the IR formulation. Moreover, SR tablets modify peak plasma times and reduce fluctuations in drug levels, enhancing metabolic control and minimizing side effects associated with peak drug concentrations [133]

## 10. Conclusion

The article discussed the significance of maintaining optimal blood glucose levels to reduce the risk of complications, including cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Lowering HbA1c, minimizing glycemic variability, and initiating treatment early are essential strategies to preserve beta-cell function and prevent disease progression. While metformin remains the first-line treatment for T2DM, sulfonylureas, particularly gliclazide, continue to play a significant role due to their efficacy, affordability, sustained glycemic control, and cardiovascular safety, especially in specific populations such as those with renal insufficiency and older adults. Experts emphasized the careful titration of gliclazide in patients with renal impairment and recommend tailoring drug combinations to manage T2DM effectively. Ultimately, the article underscores the evolving landscape of diabetes management, where early intervention, lifestyle modifications, and carefully tailored pharmacotherapy are paramount in controlling T2DM and improving patient outcomes.

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**Conflicts of Interest**

Bhavesh Kotak, Syed Mujtaba Hussain Naqvi, Deepak Bachani, and Simran Chhatwal are full-time employees of Dr. Reddy's Laboratories Ltd. All other authors declare no conflicts of interest related to this work.

**Author Contribution Details**

Simran Chhatwal was responsible for conceptualizing and interpreting the literature underpinning the expert opinion presented in this article. All authors contributed to the critical review, revision, and approval of the final version of the manuscript.

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