Current Trends in Internal Medicine
Das S, et al. Curr Trends Intern Med 9: 243.
www.doi.org/10.29011/2638-003X.100243
www.gavinpublishers.com

Review Article

The Role of Gliclazide as a Preferred Modern Sulfonylurea

Sambit Das[1], Amogh S Chappalagavi[1], Sanjay Kalra[2], Arun Kumar Choudhury[1], Dayanidhi Meher[1], Sandeep Kumar Sahu[1], Devadarshini Sahoo[1], Sheenam Gupta[1], Ameet Mohan Rathod[3*], Kunal Khobragade[4]

[1]Department of Endocrinology, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India

[2]Department of Endocrinology, Bharati Hospital , Karnal, Haryana, India

[3]Medical Affairs I Assistant General Manager, Mankind Pharma, Mumbai, India

[4]Medical Affairs, Mankind Pharma, Mumbai, India

***Corresponding author:** Ameet Rathod, Medical Affairs I Assistant General Manager, Mankind Pharma, Mumbai, India.

Citation: Das S, Chappalagavi AS, Kalra S, Choudhury AK, Meher D, et al. (2025) The Role of Gliclazide as a Preferred Modern Sulfonylurea. Curr Trends Intern Med 9: 243. DOI: https://doi.org/10.29011/2638-003X.100243

Received Date: 14 May, 2025; **Accepted Date:** 21 May, 2025; **Published Date:** 23 May, 2025

Abstract

Sulfonylureas (SUs) are a cornerstone in the management of type 2 diabetes mellitus (T2DM), with gliclazide emerging as a preferred agent among modern SUs due to its favorable pharmacological profile. This review explores gliclazide's pharmacology, efficacy, safety, and unique advantages in comparison to other SUs, such as glimepiride, emphasizing its role in managing T2DM, especially in complex clinical scenarios. Gliclazide is highlighted for its lower risk of hypoglycemia, cardiovascular benefits, antioxidant properties, renal safety, and potential for weight neutrality. The review also discusses its therapeutic implications and clinical evidence supporting its use as a first-line therapy in certain patient populations, particularly in regions with high accessibility to SUs.

Keywords: Gliclazide, Sulfonylureas, Type 2 diabetes mellitus, Hypoglycemia, Cardiovascular safety, Antioxidant properties, Renal protection, Weight neutrality, Glycemic control

Introduction

Sulfonylureas (SUs) are among the oldest and most widely prescribed drugs for managing type 2 diabetes mellitus (T2DM). They work by binding to specific receptors on pancreatic β-cells, which leads to the closure of ATP-sensitive potassium channels (K+-ATP), depolarization of the cell membrane, and insulin release. SUs are classified as conventional agents (e.g., tolbutamide, glibenclamide, glipizide) and modern agents (e.g., glimepiride, gliclazide). The latter offers improved potency, fewer side effects, and better safety profiles. While SUs can reduce HbA1c by 1-1.5%, they are often combined with other antidiabetic medications, such as metformin, for enhanced glycemic control [1]. Despite the availability of newer drugs like GLP-1 analogs, DPP-4 inhibitors, and SGLT2 inhibitors, which are preferred in most clinical guidelines, SUs remain widely prescribed in countries like India due to their proven efficacy, affordability, better gastrointestinal tolerance, and availability. Modern SUs offers better efficacy and fewer adverse effects compared to conventional ones and are recommended in several clinical guidelines. Although gliclazide and glimepiride both have favorable profiles, gliclazide holds distinct advantages, making it particularly valuable in T2DM management.

Though effective, SUs have limitations, including the risk of hypoglycemia, especially in elderly or renal-impaired patients, and potential for weight gain. However, modern SUs, such as gliclazide modified release and glimepiride, address these concerns by reducing hypoglycemia risk, providing cardiovascular benefits, and simplifying dosing with once-daily formulations [2]. They also offer pleiotropic benefits, such as improved insulin sensitivity

and anti-inflammatory effects, further enhancing their therapeutic potential. This review highlights the distinct advantages of gliclazide over glimepiride, emphasizing its unique benefits and reinforcing its role as a preferred modern SU in the management of T2DM.

Gliclazide: Pharmacology and Mechanism of Action

Pharmacokinetics of Gliclazide

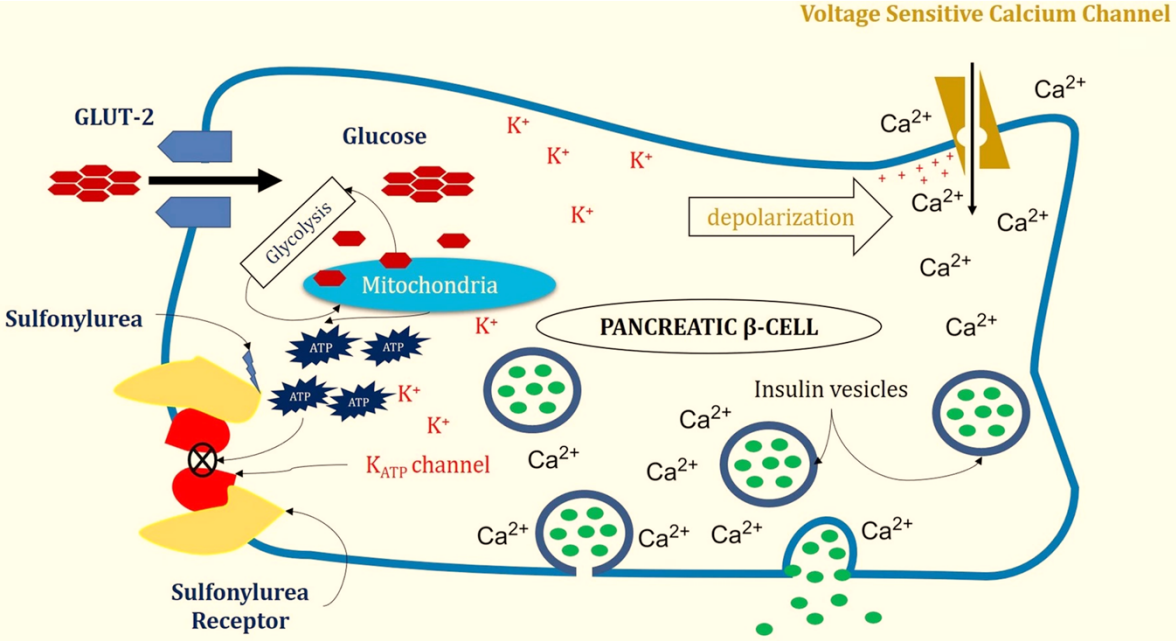
Gliclazide is readily absorbed from the gastrointestinal tract, extensively bound to plasma proteins, and has a half-life of 10–12 hours. It is metabolized in the liver to inactive metabolites, and a small amount of unchanged drug is excreted in the urine [3]. Various studies have explored different formulations and delivery methods to improve its pharmacokinetics and therapeutic efficacy. For instance, Aburuz et al [4]. developed SPE and HPLC methods to measure gliclazide concentrations, while Al-Kassas et al [5]. investigated biodegradable alginate beads to enhance oral delivery through swelling and mucoadhesive properties. Additionally, studies by Al-Salami et al [6-8]. examined the effects of probiotics on gliclazide's pharmacokinetics, showing that probiotics increased gliclazide bioavailability and reduced blood glucose levels in diabetic rats. Aggarwal et al [9]. studied gliclazide's dissolution rate and bioavailability through complexation with β-CD and HPMC. Further research by Arno et al [10]. focused on metformin/gliclazide extended-release tablets, showing sustained drug release over 6–8 hours. Other studies, such as those by Asyarie and Rachmawati [11], found that the dissolution of gliclazide improved in PEG 6000. Brendel et al [12]. evaluated various metrics for assessing gliclazide models in clinical trials, recommending prediction distribution errors for external validation. Studies also reveal that gliclazide undergoes significant first-pass metabolism, limiting its oral bioavailability, with varying profiles depending on formulation types [13]. Modified-release tablets show a two-compartment model with mixed-order absorption, and nanosuspension formulations improve solubility, leading to higher peak plasma concentrations [14]. Gliclazide, particularly in its modified release formulation, offers effective 24-hour glycemic control with a lower risk of hypoglycemia and minimal weight gain compared to other SUs. It is a cost-effective treatment for many patients with T2DM, with cardiovascular outcome studies showing no increased risk of cardiovascular events and evidence of durable glucose-lowering effects [15]. A similar study on modified-release tablets confirmed gliclazide's linear pharmacokinetics and highlighted the potential of minimum drug concentration as a predictor of patient compliance [16].

Sites and Mechanism of Action

Gliclazide exerts its hypoglycemic effect by binding to the sulfonylurea receptor 1 (SUR1) on β-cells in the pancreas. This binding blocks K+-ATP channels, leading to the closure of the channels and a decrease in potassium efflux. The resulting depolarization of the β-cells triggers the opening of voltage-dependent calcium channels, which promotes the activation of calmodulin and the exocytosis of insulin-containing granules, facilitating insulin release. Although K+-ATP channels play a crucial role in insulin secretion, their inhibition also offers potential benefits. Research by Drews and Dufer highlights that blocking K+-ATP channels can protect β-cells from oxidative stress, a key factor in the pathogenesis of T2DM [17]. This protection prevents β-cell apoptosis and preserves insulin secretion, which might offer new avenues for early T2DM intervention. In addition to its effects on insulin release, gliclazide has been studied for its potential cardiovascular benefits [18]. Gliclazide offers a cardiovascular safety advantage over other SUs due to its selective binding to the SUR1 receptor in pancreatic β-cells and its reversible binding, which is absent in other SUs with a benzamide moiety. This selectivity reduces its affinity for SUR2A and SUR2B receptors found in the heart and blood vessels, respectively. The lower affinity for these receptors may protect against ischemic preconditioning, a process that can lead to adverse cardiovascular events and hypoglycemia. Studies have shown that SUs with higher cardiac mitochondrial K+-ATP channel affinity are linked to an increased risk of cardiovascular events [19]. In contrast, gliclazide's pancreas-selective action does not elevate this risk, and its lower incidence of hypoglycemia and weight gain further support its favorable cardiovascular safety profile [20]. Some studies also suggest that gliclazide and other SUs may have ischemic protection effects, particularly in the context of cardiac injury, by influencing the SUR1 receptor and thereby regulating the function of the cardiovascular system. However, the involvement of K+-ATP channels in cardiac and vascular smooth muscle cells has raised concerns about potential adverse effects, such as diminished ischemic response [21, 22].

Gliclazide's action on platelets has also been explored, with findings indicating it can inhibit platelet aggregation, which is important for reducing vascular complications in diabetic patients [23]. Studies suggest that gliclazide may be more effective than other SUs, such as glibenclamide, in preventing diabetic vascular complications [24]. Moreover, gliclazide has been linked to a potential reduction in cancer risk in diabetic patients. Although the exact mechanisms remain unclear, gliclazide has shown a protective effect against oxidative stress-induced DNA damage in pancreatic cancer cells, enhancing DNA repair mechanisms in these cells [25]. Like other SUs, gliclazide stimulates insulin release from pancreatic β cells by closing KATP channels, which are normally responsive to ATP from mitochondrial glycolysis. This channel blockade leads to intracellular K^+ accumulation, membrane depolarization, and Ca^{2+} influx, triggering insulin secretion. Insulin then activates glucose transporter 2, promoting glucose uptake and further glycolysis. While many SUs acts on β-cell SUR-1 as well as SUR-2A and SUR-2B in cardiac and smooth muscle, gliclazide MR selectively targets SUR-1, which may reduce the risk of hypoglycemia due to

its more reversible binding and limited extrapancreatic action (Figure 1). These pharmacodynamic properties also contribute to more favorable cardiovascular outcomes and justify its use in neonatal diabetes caused by KATP mutations [26]. A study evaluated that low-dose gliclazide enhances β-cell function and incretin action, reducing glucose levels during an oral glucose tolerance test in patients with T2DM. It improves β-cell glucose sensitivity by 50% and late-phase insulin secretion, suggesting effective glucose control with minimal hypoglycemia risk [27]. In the context of Ramadan fasting, gliclazide is considered a safer sulfonylurea for patients with T2DM, as it can be taken in its modified release form (gliclazide MR) in the evening, minimizing the risk of hypoglycemia during fasting. The choice of sulfonylurea for diabetes management during Ramadan is critical, as changes in eating patterns and physical activity can influence the risk of metabolic derangements [28, 29]. Finally, gliclazide is metabolized by the CYP2C9 enzyme, and genetic variations in this enzyme can affect the drug's clearance, influencing its efficacy and safety. Studies show that individuals with certain CYP2C9 variants may experience reduced gliclazide clearance, which could impact its pharmacological effects [30].



GLUT2: Glucose Transporter.

Figure 1: Mechanism of action of Gliclazide [26]. Mechanism of action of SUs. The SU occludes the KATP channel after it binds to a SUR, resulting in a change in internal membrane polarity and inducing an influx of Ca2+, which in turn induces exocytosis of insulin vesicles.

Glycemic Control and Efficacy

There are very few studies directly comparing the different modern SUs. In 2004, a multicentric, double-blind, parallel-group design randomized control trial, the GUIDE study, which included 845 patients, was a head-to-head comparison of glimepiride and gliclazide [31]. Over 27 weeks of treatment, there was an HbA1c reduction of 1.1% with gliclazide and 1% with glimepiride. The fall in FPG was 1.4 mmol/L and 1.3 mmol/L in the gliclazide and glimepiride groups, respectively.

Gliclazide and glimepiride, both second-generation SUs, are widely used in the management of T2DM, with clinical studies comparing their efficacy and safety profiles. Research indicates that gliclazide may offer superior glycemic control, with studies showing a greater reduction in HbA1c compared to glimepiride, including a clinical trial where gliclazide reduced HbA1c by 2.44% versus 1.91% for glimepiride [32]. Real-world data further supports gliclazide's efficacy, with the EASYDia trial reporting HbA1c reductions of up to 1.98% with gliclazide modified release (MR) therapy [1, 33]. Additionally, gliclazide MR has been shown to have a lower risk of hypoglycemia compared to glimepiride, with fewer confirmed hypoglycemic events observed in the GUIDE study [34]. Both medications are considered to have neutral effects on cardiovascular outcomes, although gliclazide's antioxidant properties may provide additional vascular benefits [18]. Overall, while both medications effectively lower blood glucose, gliclazide's safety profile, particularly regarding hypoglycemia, and its potential cardiovascular advantages may make it a preferable choice in certain patient populations.

Risk of Hypoglycemia

Incidence of Hypoglycemia

The GUIDE Study demonstrated that gliclazide MR had a significantly lower incidence of hypoglycemia than glimepiride, with rates of 3.7% and 8.9%, respectively, and this difference was more pronounced in high-risk groups such as the elderly and those with renal impairment [31]. For patients aged >65 years, hypoglycemia occurred in 3.6% with gliclazide versus 9% with glimepiride, while in those with creatinine clearance ≤80 ml/min, it was 2.87% with gliclazide and 12.56% with glimepiride. A systematic review by Schopman JE et al. confirmed that gliclazide was associated with lower rates of both mild (1.4% vs 15.5%) and severe hypoglycemia (0.1% vs 0.9%) compared to glimepiride [35]. Additionally, Siew Pheng Chan et al.'s meta-analysis found that the incidence of mild hypoglycemia was 1.4% with gliclazide versus 10.1% for all SUs, with severe hypoglycemia also less frequent with gliclazide (0.1% vs 0.9%) [1]. Aravind et al. further observed that in patients with T2DM fasting during Ramadan, the incidence of hypoglycemia was only 1.8% with gliclazide compared to 9.1% with glimepiride [36].

Mechanisms Behind Gliclazide's Lower Hypoglycemia Risk

There are several mechanisms postulated for the lower incidence of hypoglycemia with gliclazide compared to glimepiride evidenced by various studies. The pharmacokinetic and pharmacodynamic properties of gliclazide contribute to its lower incidence of hypoglycemia compared to glimepiride. The binding of gliclazide to SUR1 receptors in the pancreatic β-cells is rapidly reversible, whereas that of glimepiride is largely irreversible [37]. Glimepiride is broken down into active metabolites, which are excreted by the kidney, therefore, the incidence of hypoglycemia is higher in patients with renal compromise in comparison to gliclazide, which is devoid of such metabolites [38]. After oral ingestion, there is a gradual increase in serum levels of gliclazide, whereas an early and sharp rise to maximal levels is seen with glimepiride [31]. In vitro rat pancreatic studies suggest that after being given therapeutic doses of SUs and perfused with 5–8.33 mM of glucose, the prolonged 2nd phase of insulin secretion was seen with glimepiride, whereas an earlier return to basal levels was seen with gliclazide [39].

Cardiovascular Safety and Mortality Outcomes

Cardiovascular risk in T2DM patients is elevated due to multiple factors, including the high prevalence of coronary artery disease and atherosclerosis, with 33.3% of T2DM patients affected [40]. Risk stratification tools like the Systematic Coronary Risk Evaluation (SCORE)2-Diabetes risk score help identify high-risk individuals, but may underestimate actual risk [41, 42]. Poor diabetes control (54% of patients) and hypertension (55% of patients) are strongly correlated with cardiovascular issues [40]. Biomarkers such as elevated 8-isoprostane and decreased sirtuin-1 levels are also predictive of coronary heart disease. Comprehensive risk assessment, incorporating medical history and diagnostic tools, is essential for effective management [43].

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, which compared intensive glucose control (target HbA1c ≤ 6.5) vs standard glucose control against CV outcomes, showed that there were no significant effects of the type of glucose control (intensive vs standard) on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI, 0.84 to 1.06; P=0.32), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI, 0.74 to 1.04; P=0.12), or death from any cause (hazard ratio with intensive control, 0.93; 95% CI, 0.83 to 1.06; P=0.28) [44]. Whereas, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, another landmark trial that compared intensive therapy (targeting a glycated hemoglobin level below 6.0%) and standard therapy (targeting a level from 7.0 to 7.9%) against a primary outcome of a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16) [45]. At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). 90.5% of patients in the intensive therapy group were on gliclazide in the ADVANCE trial, whereas 78.2% of patients in the intensive therapy group and 67.6% of patients in the standard therapy group received glimepiride in the ACCORD trial. Though there is a dedicated CVOT trial for glimepiride showing CV neutrality as compared to linagliptin [The Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) trial], several meta-analyses and RCTs have shown better CV outcomes with gliclazide [46]. A meta-analysis by Simpson et al., which included CV mortality data from 13 studies involving 145,916 patients who used sulfonylurea, showed a 19% additional reduction in CV mortality with gliclazide compared to glimepiride [47]. All-cause mortality data from the same meta-analysis, which included 18 studies and 167,327 sulfonylurea users, showed an 18% additional reduction in all-cause mortality with gliclazide compared to glimepiride.

A Danish nationwide study on mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction, revealed that gliclazide was associated with a significantly lower risk than other SUs [48]. Among the subgroup of patients without a history of previous MI, the hazard ratios for the endpoint of MI, stroke, or cardiovascular death were 1.29 and 1.18 for glimepiride and gliclazide, respectively. The hazard ratios in the other subgroup of patients with a previous myocardial infarction for glimepiride and gliclazide were 1.22

Citation: Das S, Chappalagavi AS, Kalra S, Choudhury AK, Meher D, et al. (2025) The Role of Gliclazide as a Preferred Modern Sulfonylurea. Curr Trends Intern Med 9: 243. DOI: https://doi.org/10.29011/2638-003X.100243

and 0.71, respectively. An umbrella review of the association of glucose-lowering medications with cardiovascular outcomes by Jianhong Zhu et al. showed that the relative risks of MACE (0.83 vs 1.09), MI (0.81 vs 1.01), and Stroke (0.84 vs 2.01) were lower with gliclazide versus glimepiride [49]. The CV safety of gliclazide is mostly attributed to its selectivity to pancreatic β-cell receptors (Kir6.2/SUR1) [37]. Glimepiride at therapeutic concentrations shows significant action on the cardiovascular channels (Kir6.2/SUR2A) [50]. ATP-dependent potassium channels in the heart play an important role in ischemic preconditioning [51]. Blocking of these potassium channels by glibenclamide has been shown to prevent ischemic preconditioning in dogs [52]. This effect is mainly due to the blocking of Cardiac K ATP channels by glibenclamide and glimepiride, whereas gliclazide is highly selective to pancreatic SUR1 receptors and hence is cardiac neutral. Moreover, nicorandil's action on Kir6.2/SUR2A and Kir6.2/SUR2B channels is severely impaired by glimepiride but is unaffected by gliclazide [53]. A systematic review and network meta-analysis by Das et al. comparing linagliptin with gliclazide revealed that gliclazide was an effective and safe glucose-lowering drug in T2DM patients with similar cardiovascular safety to that of linagliptin [54]. A retrospective cohort study analyzed 11,140 adults with T2DM undergoing cardiac catheterization for acute coronary syndrome. Glyburide use (5%) was associated with a higher likelihood of 1-year mortality or rehospitalization compared to gliclazide use (19%), particularly with current (adjusted odds ratio [aOR] 1.37, 95% CI 1.06–1.79) and long-term exposure (aOR 1.37, 95% CI 1.03–1.83). These findings highlight the need to prefer gliclazide over glyburide for diabetes management in such patients [55].

Antioxidant Properties and Cellular Protection

Gliclazide possesses a unique azabicycloctyl ring and acts as a general free radical scavenger in vitro [56]. A study by O'Brien et al. showed that administration of modified-release or standard gliclazide to type 2 diabetes patients resulted in a reduction in lipid oxidation markers and an increase in antioxidant parameters, independent of glycemic control [57]. This effect was exclusive to gliclazide and not observed with other SUs. This is particularly beneficial as people with diabetes may have low Vitamin C levels [58]. In another study, Omi et al. found that gliclazide inhibited glucose-mediated endothelial-neutrophil cell adhesion and increased expression of ICAM-1, P-selectin, and E-selectin on cultured human endothelial cells, an effect not seen with glibenclamide, glimepiride, nateglinide, or metformin [59]. Diabetes is a state of high oxidative stress, increasing the risk of free radical-mediated DNA damage and neoplastic transformation [60]. Gliclazide has been shown to reduce hydrogen peroxide-induced DNA damage in both diabetic and non-diabetic subjects, suggesting a potential role in reducing the risk of oxidative stress-linked chronic diabetes complications, including cancer [61]. In a study by Lee et al., gliclazide was associated with a significantly lower risk of hepatocellular carcinoma compared to glimepiride, offering protective effects, particularly in patients with chronic liver disease [62]. A major drawback of long-term sulfonylurea therapy is β-cell damage and secondary failure, with sulfonylurea-induced ROS being a key factor in β-cell failure. In an in vitro study, gliclazide produced the least ROS and had the lowest rate of β-cell apoptosis compared to glimepiride, glibenclamide, and nateglinide when pancreatic β-cells were exposed to these drugs [63].

Renal Safety and Protection

Gliclazide and glimepiride, both SUs used to manage T2DM, differ in their renal safety profiles and effects on diabetic nephropathy. Gliclazide has demonstrated protective effects against oxidative stress and renal damage, potentially delaying the progression of diabetic nephropathy by reducing oxidative stress markers and inhibiting pathways that lead to renal cell apoptosis [64]. In contrast, while glimepiride is effective in glycemic control, it exhibits less renal protective capability [65]. It is safe for use in patients with renal impairment and can mitigate renal damage in diabetic models, but its effects on oxidative stress and nephropathy are not as pronounced as gliclazide. Gliclazide's antioxidant properties are a key factor in its ability to delay nephropathy, whereas glimepiride shows some renal protection but is less effective in this regard.

The ADVANCE trial demonstrated that intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily because of a 21% relative reduction in nephropathy [44]. A study by YH Lee et al., investigating the effects of glimepiride and gliclazide on kidney outcomes in patients with CKD, showed that compared with glimepiride, gliclazide was associated with a lower risk of doubling creatinine in patients with preserved renal function (glomerular filtration rate ≥ 60 mL/min/1.73 m², HR: 0.21, 95% CI: 0.04–0.99) and good glycemic control (HbA1c < 7%, HR: 0.35, 95% CI: 0.14–0.86), and in older subjects (≥ 62 years, HR: 0.52, 95% CI: 0.27–0.99) [66]. Gliclazide is recommended by the National Kidney Foundation and SAFES guidelines in patients with compromised renal function [67].

Weight Neutrality and Impact on Body Weight

SUs influence body weight through their effects on insulin regulation and adipocyte function. By stimulating insulin release from pancreatic β-cells, SUs enhance glucose uptake in adipose tissue, which can impact weight management. Additionally, SUs receptors present in adipocytes suggest that these medications may modulate lipid metabolism, influencing both lipogenesis and lipolysis, processes crucial for regulating body weight. In the ADVANCE trial, 90.5% of study participants in the intensive therapy arm and 1.8% in the standard therapy arm received

gliclazide, did not have any weight gain at the end of follow-up in either arm. In the ACCORD trial, 78.2% of patients in the intensive therapy group and 67.6% of patients in the standard therapy group received glimepiride. At the end of the follow-up, 27.8% in the intensive therapy arm and 14.1% in the standard therapy arm had a weight gain of more than 10 kg.

Safety During Ramadan Fasting

Hypoglycemia, while a known risk factor for mortality in diabetes, is infrequent as a cause of death in T2DM. Hypoglycemia rates are lower in T2DM compared to type 1, and even lower in patients treated with oral agents [68]. The safety of gliclazide during Ramadan has been demonstrated in several studies. A study by Loke SC et al. found that fasting during Ramadan increased hypoglycemia risk by 1.6 times, with factors like good metabolic control (<8%) and age (>60 years) significantly raising the risk [69]. The Results of the Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study showed that fasting during Ramadan increased the risk of severe hypoglycemia in type 2 diabetes by 7.5-fold, especially when medication doses were adjusted or lifestyle changes occurred [68]. The DIA-RAMADAN study, which included 1214 patients from 9 Asian and Middle Eastern countries on Gliclazide therapy during Ramadan showed that the proportion of patients reporting ≥1 symptomatic hypoglycemic event during Ramadan (confirmed or suggestive) was low (2.2%) and none of the patients reported severe hypoglycemia while having good glycemic control as HbA1c reduction was -0.3% and FBS reduction was -9.7 mg/dL [34]. In a randomized control trial by Al Sifri et al to study the incidence of hypoglycemia in Muslim patients with type 2 diabetes (n=1066) treated with sitagliptin or a SUs during Ramadan, it was found that the proportion of patients who recorded one or more symptomatic hypoglycemic episodes was 6.7% with Sitagliptin, 12.4% with Glimepiride and 6.6% with Gliclazide [70]. In a similar study done by Arvind et al., 870 patients, treated on a stable dose of sulfonylurea ± metformin for ≥3 months, were randomized in a 1:1 ratio to either switch to sitagliptin or to remain on pre-study sulfonylurea during Ramadan. The results revealed that the incidence of hypoglycemia was 9.1 % with Glimepiride, 2.1 % with Sitagliptin, and only 1.8% with Gliclazide in patients with T2DM who fasted during Ramadan [36].

Conclusion

Gliclazide is a modern SUs that offers several advantages over older agents, including a lower risk of hypoglycemia, favorable cardiovascular and renal outcomes, and potential antioxidant and anti-inflammatory effects. Its unique pharmacokinetic profile, especially in its modified-release form, contributes to its safety and efficacy in managing type 2 diabetes. Gliclazide's multiple therapeutic benefits make it a preferred choice for T2DM management, especially in populations at risk of hypoglycemia or diabetic complications. Further research is warranted to explore its full potential in preventing long-term diabetes-related complications and its role in personalized diabetes care.

References

1. Chan SP Colagiuri S (2015) Systematic review and meta-analysis of the efficacy and hypoglycemic safety of gliclazide versus other insulinotropic agents. Diabetes research and clinical practice. 110:75-81.
2. Riddle MC (2017) Modern sulfonylureas: dangerous or wrongly accused? Diabetes Care. 40: 629-631.
3. Al-Omary FA (2017) Gliclazide. Profiles of Drug Substances, Excipients and Related Methodology. 42: 125-192.
4. AbuRuz S, Millership J, McElnay J (2005) The development and validation of liquid chromatography method for the simultaneous determination of metformin and glipizide, gliclazide, glibenclamide or glimperide in plasma. Journal of Chromatography B. 817:277-286.
5. Al-Kassas RS, Al-Gohary OM, Al-Faadhel MM (2007) Controlling of systemic absorption of gliclazide through incorporation into alginate beads. International journal of pharmaceutics. 341: 230-237.
6. Al-Salami H, Butt G, Tucker I, Golocorbin-Kon S, Mikov M (2012) Probiotics decreased the bioavailability of the bile acid analog, monoketocholic acid, when coadministered with gliclazide, in healthy but not diabetic rats. European journal of drug metabolism and pharmacokinetics. 37:99-108.
7. Al-Salami H, Butt G, Tucker I, Mikov M (2008) Influence of the semisynthetic bile acid MKC on the ileal permeation of gliclazide in vitro in healthy and diabetic rats treated with probiotics. Methods and findings in experimental and clinical pharmacology. 30:107-113.
8. Al-Salami H, Butt G, Fawcett JP, Tucker IG, Golocorbin-Kon S, et al. (2008) Probiotic treatment reduces blood glucose levels and increases systemic absorption of gliclazide in diabetic rats. European journal of drug metabolism and pharmacokinetics. 33:101-106.
9. Aggarwal S, Singh P, Mishra B (2002) Studies on solubility and hypoglycemic activity of gliclazide beta-cyclodextrin-hydroxypropylmethylcellulose complexes. Die Pharmazie. 57:191-193.
10. Arno EA, Anand P, Bhaskar K, Ramachandran S, Saravanan M, et al. (2002) Eudragit NE30D based metformin/gliclazide extended release tablets: formulation, characterisation and in vitro release studies. Chemical and pharmaceutical bulletin. 50:1495-1498.
11. Asyarie S, Rachmawati H (2007) In vivo and in vitro evaluation of a solid dispersion system of gliclazide: PEG 6000. PDA Journal of Pharmaceutical Science and Technology. 61:400-410.
12. Brendel K, Comets E, Laffont C, Laveille C, Mentré F (2006) Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. Pharmaceutical research. 23:2036-2049.
13. Sampathi S, Prajapati S, Junnuthula V, Dyawanapelly S (2022) Pharmacokinetics and anti-diabetic studies of gliclazide nanosuspension. Pharmaceutics. 14:1947.
14. Pop DI, Marcovici A, Oroian M, Gheldiu A-M, Vlase L (2020) Kinetics of gliclazide after single dose oral administration of gliclazide 60 mg modified release tablet. Studia Universitatis Babes-Bolyai, Chemia. 65:187-196.
15. Tomlinson B, Li YH, Chan P (2022) Evaluating gliclazide for the treatment of type 2 diabetes mellitus. Expert Opin Pharmacother. 23:1869-1877.

16. Czyrski A, Resztak M, Hermann T (2018) Determination of gliclazide minimum concentration in type 2 diabetes mellitus patients. Biomedicine & Pharmacotherapy. 106:1267-1270.

17. Drews G, Düfer M (2012) Role of K ATP channels in β□cell resistance to oxidative stress. Diabetes, Obesity and Metabolism. 14:120-128.

18. Sahin I, Bakiner O, Demir T, Sari R, Atmaca A (2024) Current position of gliclazide and sulfonylureas in the contemporary treatment paradigm for type 2 diabetes: a scoping review. Diabetes Therapy. 15:1687-1716.

19. Wang M-T, Huang Y-L, Lai J-H, Lee C-H, Wang P-C, et al. (2022) Association between specificity of sulfonylureas to cardiac mitochondrial KATP channels and the risk of major adverse cardiovascular events in type 2 diabetes. Diabetes Care. 45:1276-1287.

20. Singh AK, Singh R (2016) Is gliclazide a sulfonylurea with difference? A review in 2016. Expert review of clinical pharmacology. 9:839-851.

21. Bao Y, Sun X, Yerong Y, Shuyuan L, Yang W (2012) Blockers of sulfonylureas receptor 1 subunits may lead to cardiac protection against isoprenaline-induced injury in obese rats. European journal of pharmacology. 690:142-148.

22. Engbersen R, Masereeuw R, van Gestel MA, Siero HL, Moons MM, et al. (2012) Differential effects of sulfonylurea derivatives on vascular ATP-sensitive potassium channels. European journal of pharmacology. 681:75-79.

23. Konya H, Hasegawa Y, Hamaguchi T, Satani K, Umehara A, et al. (2010) Effects of gliclazide on platelet aggregation and the plasminogen activator inhibitor type 1 level in patients with type 2 diabetes mellitus. Metabolism. 59:1294-1299.

24. Konya H, Hasegawa Y, Hamaguchi T, Satani K, Umehara A, et al. (2010) Effects of gliclazide on platelet aggregation and the plasminogen activator inhibitor type 1 level in patients with type 2 diabetes mellitus. Metabolism. 59:1294-1299.

25. Śliwińska A, Śliwiński T, Kasznicki J, Drzewoski J (2010) Effect of gliclazide on nucleotide excision repair (NER) and NON-homologous DNA and joining (NHEJ) in normal and cancer cells. Journal of Physiology and Pharmacology. 61: 347-353.

26. Al-Saleh Y, Sabico S, Al-Furqani A, Jayyousi A, Alromaihi D, et al. (2021) Sulfonylureas in the current practice of type 2 diabetes management: are they all the same? Consensus from the Gulf Cooperation Council (GCC) countries advisory board on sulfonylureas. Diabetes Therapy. 12:2115-2132.

27. Cordiner RL, Mari A, Tura A, Pearson ER (2021) The impact of low-dose gliclazide on the incretin effect and indices of beta-cell function. The Journal of Clinical Endocrinology & Metabolism. 106:2036-2046.

28. Ahmed MH, Abdu TA (2011) Diabetes and Ramadan: an update on use of glycemic therapies during fasting. Annals of Saudi medicine. 31:402-406.

29. Zargar A, Basit A, Mahtab H (2005) Sulphonylureas in the management of type 2 diabetes during the fasting month of Ramadan. Journal of the Indian Medical Association. 103:444-446.

30. Banu H, Renuka N, Vasanthakumar G (2011) Reduced catalytic activity of human CYP2C9 natural alleles for gliclazide: molecular dynamics simulation and docking studies. Biochimie. 93:1028-1036.

31. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, et al. (2004) GUIDE study: double□blind comparison of once□daily gliclazide MR and glimepiride in type 2 diabetic patients. European journal of clinical investigation. 34:535-542.

32. Chipirishetti R (2015) Comparative study of glimepiride and gliclazide in type 2 diabetes patients on safety, efficacy and tolerability. Journal of Drug Delivery and Therapeutics. 5:10-2.

33. Leiter LA, Shestakova MV, Satman I (2018) Effectiveness of gliclazide MR 60 mg in the management of type 2 diabetes: analyses from the EASYDia trial. Diabetology & metabolic syndrome. 10:30.

34. Hassanein M, Al Sifri S, Shaikh S, Raza SA, Akram J, et al. (2020) A real-world study in patients with type 2 diabetes mellitus treated with gliclazide modified-release during fasting: DIA-RAMADAN. diabetes research and clinical practice. 163:108154.

35. Schopman JE, Simon AC, Hoefnagel SJ, Hoekstra JB, Scholten RJ, et al. (2014) The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta□analysis. Diabetes/metabolism research and reviews. 30:11-22.

36. Aravind S, Ismail SB, Balamurugan R, Gupta JB, Wadhwa T, et al. (2012) Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study. Current medical research and opinion. 28:1289-1296.

37. Gribble F, Ashcroft FM (1999) Differential sensitivity of beta-cell and extrapancreatic KATP channels to gliclazide. Diabetologia. 42:845-848.

38. Rosenkranz B, Profozic V, Metelko Z, Mrzljak V, Lange C, et al. (1996) Pharmacokinetics and safety of glimepiride at clinically effective doses in diabetic patients with renal impairment. Diabetologia. 39:1617-1624.

39. Gregorio F, Ambrosi F, Cristallini S, Filipponi P, Santeusanio F (1996) Effects of glimepiride on insulin and glucagon release from isolated rat pancreas at different glucose concentrations. Acta diabetologica. 33:25-29.

40. Aleemuddin H, Iqbal J, Soomro B, Memon SA, Fatima N, et al. (2024) Evaluating cardiovascular disease risk in type 2 diabetes mellitus patients in a tertiary care hospital in Hyderabad, Sindh, Pakistan. Asian Journal of Science, Engineering and Technology (AJSET). 3:1-9.

41. Cavender M, Sorensen A, Bonaca M, Cannon C, Clemmensen K, et al. (2024) Prediction of cardiovascular risk in patients type 2 diabetes using the SCORE2-Diabetes risk score. European Heart Journal. 45:ehae666. 2716.

42. Arabidze G, Mamedov M, Akhundova H (2024) Ten-year cardiovascular risk estimation in type 2 diabetes in Europe using the novel SCORE2-Diabetes model. Cardiovascular Therapy and Prevention.23:3966.

43. Bshara S, Alkhoubi Q, Hamood T (2024) Assessment of cardiovascular complications in patients with type 2 diabetes.

44. Group AC (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England journal of medicine. 358:2560-2572.

45. Group AtCCRiDS. (2008) Effects of intensive glucose lowering in type 2 diabetes. New England journal of medicine. 358:2545-2559.

46. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, et al. (2019) Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. Jama. 322:1155-1166.

47. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, et al. (2015) Mortality risk among sulfonylureas: a systematic review and network meta-analysis. The lancet Diabetes & endocrinology. 3:43-51.

48. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, et al. (2011) Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes,

Citation: Das S, Chappalagavi AS, Kalra S, Choudhury AK, Meher D, et al. (2025) The Role of Gliclazide as a Preferred Modern Sulfonylurea. Curr Trends Intern Med 9: 243. DOI: https://doi.org/10.29011/2638-003X.100243

with or without a previous myocardial infarction: a nationwide study. European heart journal. 32:1900-1908.

49. Zhu J, Yu X, Zheng Y, Li J, Wang Y, et al. (2020) Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map. The Lancet Diabetes & Endocrinology. 8:192-205.
50. Song DK, Ashcroft FM (2001) Glimepiride block of cloned β□cell, cardiac and smooth muscle KATP channels. British journal of pharmacology. 133:193-199.
51. Gross GJ, Auchampach JA (1992) Role of ATP dependent potassium channels in myocardial ischaemia. Cardiovascular research. 26:1011-1016.
52. Gross GJ, Auchampach JA (1992) Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. Circulation research. 70:223-233.
53. Reimann F, Ashcroft FM, Gribble FM (2001) Structural basis for the interference between nicorandil and sulfonylurea action. Diabetes. 50:2253-2259.
54. Mohan V, Wangnoo S, Das S, Dhediya R, Gaurav K (2022) Comparison of gliclazide vs linagliptin on hypoglycemia and cardiovascular events in type 2 diabetes mellitus: A systematic review. World Journal of Diabetes. 13:1168-1183.
55. Long W, Light PE, Simpson SH (2024) Glyburide use is associated with a greater likelihood of mortality or rehospitalization after acute coronary syndrome compared to gliclazide use in adults with type 2 diabetes: A cohort study. Diabetes Obes Metab. 26:5408-5419.
56. Scott NA, Jennings PE, Brown J, Belch JJ (1991) Gliclazide: a general free radical scavenger. European Journal of Pharmacology: Molecular Pharmacology. 208:175-177.
57. O'Brien RC, Luo M, Balazs N, Mercuri J (2000) In vitro and in vivo antioxidant properties of gliclazide. Journal of Diabetes and its Complications. 14:201-206.
58. Yue D, McLennan S, McGill M, Fisher E, Heffernan S, et al. (1990) Abnormalities of ascorbic acid metabolism and diabetic control: differences between diabetic patients and diabetic rats. Diabetes research and clinical practice. 9:239-244.
59. Omi H, Okayama N, Shimizu M, Okouchi M, Ito S, et al. (2002) Participation of high glucose concentrations in neutrophil adhesion and surface expression of adhesion molecules on cultured human endothelial cells: effect of antidiabetic medicines. Journal of Diabetes and its Complications. 16:201-208.
60. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010) Oxidative stress, inflammation, and cancer: how are they linked? Free radical biology and medicine. 49:1603-1616.
61. Sliwinska A, Blasiak J, Kasznicki J, Drzewoski J (2008) In vitro effect of gliclazide on DNA damage and repair in patients with type 2 diabetes mellitus (T2DM). Chemico-Biological Interactions. 173:159-165.
62. Lee J-Y, Kim G, Lee Y-H, Lee B-W, Cha B-S, et al. (2019) Comparison of hepatocellular carcinoma risk between patients treated with glimepiride and gliclazide. Diabetes & metabolism. 45:83-85.
63. Sawada F, Inoguchi T, Tsubouchi H, Sasaki S, Fujii M, et al. (2008) Differential effect of sulfonylureas on production of reactive oxygen species and apoptosis in cultured pancreatic β-cell line, MIN6. Metabolism. 57:1038-1045.
64. Shehab FA, Jasim AL, Mohammed AG (2024) Impact of Gliclazide Modified Release or Glimepiride as Add-on Therapy to Metformin on Glycemic and Oxidative Stress Parameters in Type 2 Diabetic Patients. Iraqi Journal of Pharmaceutical Sciences. 33:20-30.
65. Hagras MM, Gamal SM, Amin HA (2009) Histological assessment of the possible protective role of glimepiride against progression of experimentally induced diabetic nephropathy in rats. The Egyptian journal of hospital medicine. 36:483-498.
66. Lee Y-H, Lee C, Lee H, Choe E, Lee B-W, et al. (2015) Comparing kidney outcomes in type 2 diabetes treated with different sulphonylureas in real-life clinical practice. Diabetes & Metabolism. 41:208-215.
67. National Kidney Foundation (2012) KDOQI clinical practice guideline for diabetes and CKD: 2012 update. 60:850-886.
68. Ahmad J, Pathan MF, Jaleel MA, Fathima FN, Raza SA, et al. (2012) Diabetic emergencies including hypoglycemia during Ramadan. Indian J Endocrinol Metab. 16:512-515.
69. Loke SC, Rahim KF, Kanesvaran R, Wong TW (2010) A prospective cohort study on the effect of various risk factors on hypoglycaemia in diabetics who fast during Ramadan. The Medical journal of Malaysia. 65:3-6.
70. Al Sifri S, Basiounny A, Echtay A, Al Omari M, Harman□Boehm I, et al. (2011) The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. International journal of clinical practice. 65:1132-1140.