REVIEW
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Place of New Generation Sulfonylurea: Gliclazide in the Evolving Landscape of Type 2 Diabetes Management

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Abstract: The management of Type 2 diabetes mellitus (T2DM) has evolved significantly, with a shift towards simplified dosing regimens and novel therapeutic agents. However, traditional medications like sulfonylureas, particularly the modern variant gliclazide, remain essential in managing T2DM, especially in resource-constrained settings. Gliclazide, a second-generation sulfonylurea, and its modified version Gliclazide MR is notable for its long-acting, once-daily formulation, better safety profile, and efficacy in lowering HbA1c levels, making it a preferred choice among sulfonylureas. It is effective in a broad patient population, including elderly individuals and those with chronic kidney disease, due to its minimal risk of hypoglycaemia and compatibility with renal impairment. Comparative studies also indicate that gliclazide has a lower risk of cardiovascular side effects relative to other sulfonylureas, as it selectively targets pancreatic SUR1 receptors without affecting cardiac receptors. Furthermore, its integration into fixed-dose combinations (FDCs) with other antidiabetic agents, such as metformin, supports adherence and helps achieve optimal glycemic control. As diabetes guidelines continue to emphasize individualized treatment, gliclazide is positioned as a promising, effective, and cost-efficient option, especially in countries like India where it addresses affordability and accessibility challenges. The findings underscore the importance of informing healthcare providers about gliclazide's clinical utility, fostering its integration within T2DM treatment frameworks that balance efficacy, safety, and patient needs.

Keywords: Gliclazide; Gliclazide (MR); Sulfonylurea; Hypoglycaemia.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive condition characterized by insulin resistance and relative insulin deficiency, leading to elevated blood glucose levels and increased risk of complications such as cardiovascular disease, kidney failure, and neuropathy. Managing T2DM effectively is critical, as global prevalence continues to rise, especially in low- and middle-income countries where healthcare resources may be limited. The goal of T2DM management is to achieve optimal glycemic control to prevent or delay complications, and this typically involves a combination of lifestyle modifications and pharmacotherapy[1,2].

While recent years have seen the development of new classes of antidiabetic agents—such as Sodium-glucose cotransporter 2 (SGLT2) inhibitors and Glucagon-like peptide 1(GLP-1) receptor agonists—the cost and complexity associated with these drugs limit their accessibility in many parts of the world[3,4].

Traditional medications like sulfonylureas continue to play an important role, especially in resource-constrained settings. Among sulfonylureas, Gliclazide, a second-generation sulfonylurea, and its modified-release formulation, often considered a third-generation option, provide an effective and promising, solution for enhancing glycemic control, making it a cost-effective choice for patients[5].

Gliclazide MR once-daily dosing and minimal risk of hypoglycaemia make it an attractive option, particularly for elderly patients and those with comorbid conditions such as chronic kidney disease. Additionally, gliclazide has been shown to have a lower risk of cardiovascular side effects compared to other sulfonylureas due to its selective action on pancreatic beta-cell receptors without affecting cardiac receptors. This therapeutic profile has led to gliclazide inclusion in numerous diabetes treatment guidelines, where it is recommended as a foundational therapy for patients who are not adequately controlled on metformin alone[6,7].

The current review aims to explore gliclazide pharmacological profile, clinical efficacy, and safety, particularly in the context of T2DM management in resource-limited settings. By understanding the unique advantages of gliclazide, healthcare providers can make informed decisions to tailor treatment plans that prioritize both patient outcomes and accessibility.

Place of sulfonylureas in the evolving T2DM landscape

Sulfonylureas (SUs) have maintained a significant place in the management of Type 2 Diabetes Mellitus (T2DM) over the decades, beginning with their accidental discovery linked to sulfonamides in the 1940s[8]. Early-generation sulfonylureas, such as chlorpropamide and glibenclamide, were once widely used but

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have gradually fallen out of favor due to safety and efficacy concerns. Despite the introduction of newer diabetes treatments, modern sulfonylureas like gliclazide and glimepiride continue to be highly effective in reducing Hemoglobin A1C (HbA1c) levels and offer a favorable gastrointestinal safety profile, making them suitable for patients who need rapid glycemic control[9].

In diabetes management, these medications are versatile and should be used flexibly, tailored to individual patient needs and clinical circumstances. For optimal results, combining sulfonylureas with other antidiabetic agents is often necessary to achieve target HbA1c levels. Not all sulfonylureas are the same; newer variants demonstrate improved efficacy and safety profiles, aligning well with contemporary clinical practices, especially in resource-limited settings like India, where they address hyperglycemia affordably and effectively. Educating healthcare providers about the unique characteristics and benefits of modern sulfonylureas is essential to enhance understanding and optimize their use in diabetes care[10].

Gliclazide: An Effective Sulfonylurea

Gliclazide modified release is a third-generation, long-acting sulfonylurea with a duration of action that exceeds 24 hours, reaching peak effectiveness around six hours post-administration. Primarily excreted via the kidneys, it is well-suited for once-daily dosing without the need for adjustments in cases of renal impairment. The exceptional pharmacological profile of gliclazide has solidified its reputation among clinicians, largely due to its consistent and reliable efficacy, which sets it apart from other sulfonylureas like glimepiride. While in India, the older and less expensive Glibenclamide remains commonly prescribed due to financial limitations, Gliclazide is gaining favor due to its superior safety profile and effectiveness. With the advent of newer diabetes medications, like Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors, Gliclazide is increasingly being viewed as a viable second-line option, especially for patients whose glycemic control remains insufficient with these newer agents[6]. Refer Table 1 for understanding clinical studies on the efficacy and safety of Gliclazide/Gliclazide MR in Type 2 Diabetes Management[6,11,12].

Hypoglycemia and weight gain with Gliclazide

Modern sulfonylureas like Gliclazide present a minimal risk of hypoglycemia, making them a promising option for many patients. Studies indicate that even during Ramadan, when Gliclazide is administered at Iftar, it does not lead to significant hypoglycemia, allowing safe glucose management for fasting patients. Furthermore, Gliclazide is not typically associated with weight gain, adding to its suitability for long-term use in diabetes management[6].

Gliclazide in managing diabetes in elderly patients

Gliclazide has emerged as a valuable therapeutic option in managing type 2 diabetes in elderly patients, offering both efficacy and safety. Elderly individuals often require a careful balance between glycemic control and minimizing the risk of hypoglycemia. Gliclazide effectively controls HbA1c levels around 7.5% to 8%, a range considered safe for older patients, to reduce the risk of severe hypoglycaemic events. This feature makes Gliclazide particularly beneficial for elderly patients who may be hesitant to initiate insulin therapy due to the complexity and invasiveness of insulin regimens[6]. Clinical evidence supports its efficacy in this population. For example, Polavarapu et al. demonstrated that Gliclazide, in combination with Metformin, effectively reduces HbA1c levels in Indian patients, including those over 60 years of age[13]. Similarly, the GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride (GUIDE) study highlighted the significant improvement in glycemic control among patients aged over 65 years, with HbA1c levels decreasing from 8.4% to 7.2% within 27 weeks of treatment with Gliclazide MR. Gliclazide MR, typically administered once daily, offers dosing flexibility, particularly for elderly patients with more severe hyperglycemia. In some cases, clinicians may prescribe it twice

Table 1. Clinical Studies on the Efficacy and Safety of Gliclazide/Gliclazide MR in Type 2 Diabetes Management [6,11,12].

Study	Design	Participants	Duration	Key Findings
ADVANCE Trial	Randomized controlled trial comparing intensive glucose control using gliclazide MR-based regimen vs. standard therapy.	11,140 patients with type 2 diabetes.	Median follow-up of 5 years.	Intensive glucose control achieved a mean HbA1c of 6.5% vs. 7.3% in the standard therapy. Significant reduction in combined microvascular and macrovascular events.
Systematic Review and Meta-Analysis	Analysis of 19 randomized controlled trials comparing gliclazide with other oral glucose-lowering agents.	3,083 patients treated with gliclazide; 3,155 with other agents.	Studies of at least 12 weeks duration.	Gliclazide was slightly more effective in reducing HbA1c compared to other agents (excluding metformin). Extremely low incidence of severe hypoglycemia.
EASYDia Trial	Observational study assessing effectiveness of gliclazide MR 60 mg in type 2 diabetes management.	7,170 participants from eight countries.	6 months.	Significant reduction in HbA1c across all baseline HbA1c strata. Weight loss observed in participants with BMI ≥ 25 kg/m^2. Severe hypoglycemic events were rare (0.06%).
GUIDE Trial	Randomized controlled trial comparing gliclazide MR 30 mg vs. glimepiride for efficacy and safety in type 2 diabetes.	845 patients with type 2 diabetes inadequately controlled on metformin or as monotherapy.	27 weeks.	Gliclazide MR showed similar efficacy to glimepiride in lowering HbA1c, with fewer hypoglycemic events and better safety profile in terms of body weight changes.

daily or at higher doses, such as 80 mg twice daily, to achieve better glycemic control[11]. This flexibility is crucial for optimizing treatment outcomes in older adults, who often present with unique metabolic challenges and comorbidities. Moreover, the introduction of newer diabetes medications has not diminished the relevance of Gliclazide in elderly care. The fear of hypoglycemia, which is a significant concern in geriatric diabetes management, is less pronounced with Gliclazide, even when used at higher doses. This makes it a safer and more patient-friendly option for older individuals with persistently high blood glucose levels and significantly elevated HbA1c[14]. In conclusion, Gliclazide MR provides a reliable, and adaptable solution for managing diabetes in elderly patients. Its ability to effectively control HbA1c levels while maintaining a low risk of hypoglycemia makes it an ideal choice for older individuals, especially those with concerns about starting insulin therapy. With proven efficacy in reducing blood glucose levels, even in patients over 65 years, Gliclazide MR continues to play a vital role in geriatric diabetes management, ensuring better outcomes while addressing the unique needs of this population[14–16].

Safety of sulfonylurea in cardiovascular disease patients

Gliclazide is distinguished by its selective binding to Sulfonylurea receptor 1 (SUR1) receptors on pancreatic beta cells, enhancing its glucose-lowering efficacy without affecting cardiac function. This receptor specificity is a significant advantage in managing diabetes in patients with cardiovascular conditions. Unlike Gliclazide, other sulfonylureas such as Glimepiride bind non-selectively to Sulfonylurea receptor 2 (SUR2) receptors, which are expressed in cardiac tissue, as well as to mitochondrial-related exchange protein directly activated by cAMP 2 (EPAC2) receptors. This non-specific binding can potentially interfere with cardiac function, increasing the risk of adverse cardiovascular events. The targeted action of Gliclazide on SUR1 ensures effective glycemic control while minimizing cardiovascular risks, making it a preferred choice for patients with diabetes and concomitant cardiovascular disease[6], specifically targets pancreatic β-cells to enhance insulin secretion while minimizing cardiac risks. In pancreatic β-cells, Gliclazide binds specifically and reversibly to the SUR1 receptor on potassium (K^+) channels. This binding leads to the closure of K^+ channels, causing cell depolarization and the subsequent opening of calcium (Ca^{2+}) channels. The resulting increase in intracellular calcium triggers insulin secretion. Importantly, Gliclazide does not interact with the SUR2A receptors found in cardiac myocytes, which prevents the closure of cardiac K^+ channels. By avoiding interference with these channels, Gliclazide reduces the risk of impairing ischemic preconditioning and associated cardiac complications. This selective action makes Gliclazide an effective and safer option for diabetic patients, especially those with cardiovascular concerns[6].

Safety of Sulfonylurea in renal failure

For patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, the risk of hypoglycemia is significantly elevated with glyburide and moderately increased with glimepiride. Glyburide should be avoided altogether in this population, while glimepiride should be used with caution and discontinued if eGFR falls below 30 mL/min/1.73 m^2. In contrast, glipizide and gliclazide do not have active metabolites that are cleared by the kidneys, making dose adjustments unnecessary. However, caution is still advised in patients with impaired renal function and Gliclazide should be avoided in sever renal impairment (eGFR < 40 mL/min/1.73 m^2)[17]. Gliclazide MR, in combination with a DPP-4 inhibitor like linagliptin, offers an alternative treatment option to glimepiride for diabetes patients with chronic kidney disease.

Added benefits of Sulfonylurea

Gliclazide has proven to be highly effective in preventing secondary treatment failures and maintaining long-term glycemic control. The modified release (MR) formulation of Gliclazide is particularly advantageous, offering sustained glucose-lowering effects with lower rates of treatment failure compared to other sulfonylureas. This makes Gliclazide a reliable option for long-term diabetes management, ensuring consistent control of HbA1c levels over time.

Early and sustained glycemic control with Gliclazide also plays a critical role in reducing the risk of macrovascular complications. Evidence from The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release (MR) Controlled Evaluation (ADVANCE) trial[12]. highlights its efficacy in mitigating long-term cardiovascular risks, reinforcing its importance in comprehensive diabetes care. By helping patients achieve and maintain glycemic targets, Gliclazide contributes significantly to preventing both microvascular and macrovascular complications, which are common in poorly controlled diabetes.

Numerous clinical studies and registries, such as the ADVANCE trial, the UK Prospective Diabetes Study (UKPDS)[18], and the Joint Asia Diabetes Evaluation (JADE) Register[19], among others, have consistently demonstrated the safety and efficacy of gliclazide in diabetes management. These studies confirm its capability to achieve glycemic targets, even in higher doses up to 320 mg, and its compatibility with insulin for enhanced glucose control in complex cases. Collectively, these findings support Gliclazide as a cornerstone therapy in diabetes management, offering both immediate and long-term benefits for a broad spectrum of patients[6].

Gliclazide Dosing in clinical Practice

Gliclazide offers a flexible dosing regimen that can be tailored to meet the diverse needs of patients with type 2 diabetes. The typical average dose for the extended-release (MR) formulation ranges from 60 to 80 mg daily, with some physicians prescribing up to 120 mg for enhanced glycemic control. In certain cases, doses as high as 240 mg or even 320 mg have been used, particularly in patients with higher glycemic demands. For the immediate-release (IR) formulation, common doses include 80 mg, with reports of up to 320 mg being administered in divided doses across multiple occasions[15].

The frequency of administration also varies based on the for-

mulation and patient requirements. Extended-release Gliclazide is generally prescribed as once daily (OD), providing convenient and sustained glucose control. However, some physicians opt for twice daily (BID) dosing in specific cases to optimize glycemic management. Immediate-release Gliclazide offers even greater flexibility, with typical regimens involving two or thrice daily doses to ensure consistent blood sugar levels throughout the day[20].

A key advantage of Gliclazide is its renal-friendly profile. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines, no dose adjustments are required for Gliclazide, in mild to moderate renal impairment and Gliclazide should be avoided in sever renal impairment (eGFR < 40 mL/min/1.73 m^2). This alleviates concerns regarding dose modifications in patients with compromised renal function, further enhancing its clinical utility.

The wide range of dosing options, combined with its safety and efficacy in CKD patients, makes Gliclazide a highly adaptable and reliable choice for managing type 2 diabetes across various patient populations[13].

Gradual or tapered stoppage of sulfonylurea

When managing long-standing diabetes, particularly in patients with secondary oral antidiabetic (OAD) failure and declining C-peptide levels, caution is essential when altering sulfonylurea prescriptions. These cases often indicate progressive beta-cell failure as the primary cause of declining C-peptide, rather than the sulfonylurea itself. Therefore, discontinuing sulfonylureas abruptly is not advisable.

A gradual tapering of sulfonylurea doses is recommended to prevent sudden spikes in blood glucose levels and to allow for an assessment of the drug's residual efficacy. This approach helps ensure a smoother transition in glycemic management, particularly when introducing alternative therapies or intensifying treatment with insulin. By continuing sulfonylureas during this period, clinicians can better evaluate their impact on glycemic control and determine the optimal timing for discontinuation. Ultimately, careful titration and individualized treatment strategies are key to maintaining stable glycemic levels while mitigating the risks associated with beta-cell decline[15,21].

Guideline recommendations on use of Sulfonylureas and Gliclazide

Gliclazide is recognized as an effective and well-tolerated option for the management of T2DM, either as a first-line or second-line agent depending on the patient's clinical status. According to the American Diabetes Association (ADA) guidelines, if a patient's HbA1c target is not met after approximately three months of metformin monotherapy and the patient does not have atherosclerotic cardiovascular disease (ASCVD) or CKD, a sulfonylurea like Gliclazide can be added. This combination offers a practical and effective strategy for achieving glycemic control in patients without significant comorbidities[22,23], refer Table 2.

Choice of combination therapy with sulfonylureas

The American Diabetes Association recommends early combination therapy for patients whose initial HbA1c levels are 1.5% to 2.0% above target[24]. In India, clinicians frequently initiate treatment with fixed-dose combinations (FDCs) due to their multiple benefits, particularly in a healthcare system where costs are largely borne by patients[22]. FDCs not only reduce the economic burden but also improve treatment adherence by simplifying medication regimens[24]. Metformin is the cornerstone of most FDCs for T2DM. Triple FDCs, such as metformin, sulfonylurea, and voglibose, target multiple pathophysiological factors, improving fasting plasma glucose, postprandial glucose, and overall glycemic control. This comprehensive approach addresses all

Table 2. Guideline recommendations on use of Sulfonylureas and Gliclazide[24].

Diabetes Guidelines	Second-line Treatment Recommendation in Patients with Suboptimal Glucose Control on Metformin	Guideline Information Specific to Gliclazide MR
South Asian Federation of Endocrine Societies 2015	Add SU as second-line agents of choice	Gliclazide MR or glimepiride are preferred over conventional SU
Australia (RACGP and Diabetes Australia) 2016–2018	Add SU as second-line agents of choice. Another agent may be used if SU are contraindicated or not tolerated.	Gliclazide is less likely to cause hypoglycaemia compared with glibenclamide or glimepiride
International Diabetes Federation 2017	Preferred add-on therapies are SU (not glibenclamide/glyburide), DPP-4i or SGLT-2i	
Global Resource-Limited Settings (WHO) 2018	Add an SU	Gliclazide is preferred SU if hypoglycaemia is a concern
Canada (Diabetes Canada) 2018	Add DPP-4i, GLP-1RA, or SGLT-2i	If SU is added to metformin, gliclazide is the first choice
USA/Europe (ADA/EASD) 2018	Add SU as second-line agents if cost is a compelling issue. Reserve SU for fourth-line treatments (after DPP-4i, GLP-1RA, SGLT-2i and/or TZD b) if there is a compelling need to minimise hypoglycaemia or weight gain.	Gliclazide is not licensed in the US for T2DM
Europe (ESC/EASD) 2019	Add DPP-4i, GLP-1RA, SGLT-2i or TZD. Reserve SU for fourth-line treatments (after DPP-4i, GLP-1RA, SGLT-2i and/or TZD).	If using SU, choose a later generation agent to minimize risk of hypoglycemia

five components of the glycemic pentad while reducing the pill burden, which can enhance patient compliance. However, high-dose regimens necessitate larger pill sizes, potentially decreasing adherence, particularly in patients who experience difficulty swallowing[25]. FDCs combining Gliclazide or Gliclazide MR with metformin offer significant advantages. These combinations have shown notable reductions in HbA1c in Indian patients, providing effective glycemic control with a convenient dosing regimen[26]. By reducing the number of pills and optimizing therapy, these FDCs support better adherence and long-term management outcomes[13]. Nevertheless, the use of FDCs requires a careful distinction between rational and irrational combinations to ensure safety, efficacy, and tolerability. Indian clinicians are encouraged to adopt a multistep approach, assessing individual patient needs and considering the clinical evidence for each combination[15] (Table 3). FDCs remain a vital tool in achieving glycemic targets while improving patient compliance and reducing the overall treatment burden[22].

Table 3. Patient Profile and Rationale for Starting sulfonylureas[15].

Patient Profile	Rationale for Starting Sulfonylureas
General case	1. Newly diagnosed T2DM for whom the life expectancy is >15 years and without CV history 2. Patients needing low dose SU 3. Early treatment for favorable long term outcomes 4. Escalation to submaximal doses that are as effective as maximal doses could help achieve therapeutic goals more rapidly
High baseline HbA1c, FPG, and PPG	1. Patients requiring glycemic targets greater than 1.5% 2. High FPG 3. High PPG 4. SU reduces HbA1c up to 1.5% and effectively reduces FPG and PPG
Elderly	1. Considered “strong” for whom life expectancy is considered satisfactory 2. Patients on insulin with poor control 3. When other drugs do not work, probably use modern SU with the least risk of hypoglycemia like gliclazide MR
Uncontrolled T2DM	1. Patients with uncontrolled on met/met + DPP4/met + SGLT2i 2. Robust efficacy of SU in providing glycemic control
Drug-induced hyperglycemia	1. Steroid-induced hyperglycemia (mild, persistent hyperglycemia) 2. SU is preferred due to its immediate blood-glucose-lowering and improved post-prandial hyperglycemia (gliclazide is preferred over glipizide and glimepiride)
OAD failure	1. Before shifting the patient to insulin 2. SU as one of the components of triple oral therapy (OAD failure)
Based on obesity and weight	1. Normal TG with high HDL 2. Normal weight 3. Lean patient 4. Small dose SU is beneficial 5. SU can be prescribed in those patients who are likely to respond to SU 6. Use *TyG index to find out insulin resistance and identify those who are suitable for treatment with SU TyG index formula: Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)] This will help to differentiate patients with insulin deficiency from those with insulin resistance

Conclusion

The landscape of diabetes management continues to evolve, emphasizing more convenient and patient-friendly dosing options. However, traditional therapies like sulfonylureas remain integral, particularly in regions such as India, where accessibility and cost-effectiveness are key considerations. Among modern sulfonylureas, Gliclazide distinguishes itself through its robust efficacy and favorable safety profile, making it an optimal choice for a broad spectrum of patients, including the elderly and those with comorbidities.

Despite the rise of newer antidiabetic agents, Gliclazide maintains its relevance due to its sustained ability to lower HbA1c levels and its minimal risk of hypoglycemia, a critical factor in improving patient adherence and safety. The drug’s flexible dosing options, including modified release formulations, further enhance its utility, allowing tailored treatment strategies that align with individual patient needs. Additionally, Gliclazide / Gliclazide (MR) compatibility with combination therapies, such as fixed-dose combinations with metformin, underscores its adaptability in achieving comprehensive glycemic control.

Educating healthcare providers about Gliclazide / Gliclazide (MR) benefits and appropriate use is essential for optimizing its role in treatment protocols. Informed prescribing practices can ensure that patients receive the most suitable therapy based on their clinical profiles and preferences. As diabetes care shifts towards more personalized approaches, Gliclazide remains a cornerstone of treatment, bridging the gap between historical significance and modern clinical demands. Its enduring efficacy, safety, and adaptability affirm its place in the rapidly advancing field of diabetes management.

Abbreviation

EPAC2, exchange protein directly activated by cAMP 2; FDC, Fixed Dose Combination; FPG, Fasting plasma glucose; HbA1c, glycosylated haemoglobin; OAD, oral antidiabetic drugs; PPG, post prandial glucose; SUR1, Sufonylurea receptor 1; T2DM, Type 2 Diabetes Millitus.

Conflicts of interest

Dr. Abhijit Trailokya, Dr. Shaijesh Wankhede, Dr. Amar Shirsat and Avinash Talware are associated with pharmaceutical industry.

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Authors' contributions

AAT conceptualized and designed the review, critically evaluated the literature, and prepared the manuscript. SW conducted the literature search and drafted specific sections of the manuscript. AS contributed by compiling and organizing data, creating tables and figures, and assisting in refining the manuscript. AT provided overall supervision of the review process, validated the accuracy of the content. All authors have made significant contributions to the work, reviewed the final manuscript, and approved it for submission.

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