REVIEW ARTICLE

Role of Glimepiride in the Evolving Landscape of Type 2 Diabetes Management

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ABSTRACT

Background and aims: The management of type 2 diabetes (T2D) is complex metabolic syndrome owing to the complex etiological factors linked with the disease. The complex etiological factors affect the disease progression, patient's response to the oral hypoglycemic agents, and the development of micro- and macrovascular complications. Glimepiride is a modern sulfonylurea which has demonstrated high efficacy, cost and practicability of use and is therefore placed among one of the most widely prescribed drugs across the world. In this article, the place of glimepiride in the ever evolving management of T2D is evaluated. **Methods:** Authors conducted a review of published literature to evaluate the role of glimepiride in the management landscape of T2DM. Two recent articles were identified, and backward chronological search was conducted to identify all other important articles. **Results and conclusions:** Based on the selection criteria, 46 articles were selected for the review. The themes that emerged after a thorough assessment of the selected articles comprised of the place of glimepiride in T2D management, its glycemic potency, efficacy, durability, cardiovascular (CV) safety concerns, cost-effectiveness and compliance. It has been established that the use of glimepiride as a second-line agent helps in rapid glycemic optimization and prevention and reduction of diabetes-related complications. Authors have concluded that glimepiride is considered to be a good alternative for T2D management because of its high efficacy, relative CV safety and low-cost.

Keywords: Glimepiride, modern sulfonylureas, cardiovascular outcome, T2DM, CAROLINA trial

Introduction

Diabetes is usually diagnosed based on hyperglycemia; however, several complex etiological factors are at work, which may lead to hyperglycemia. These complex etiological processes not only affect the phenotype of the disease, but also have a considerable impact on the disease progression, response to drugs and associated micro- and macrovascular complications. Type 2 diabetes (T2D), thus, is driven by several pathophysiological processes leading to a spread of clinical characteristics which have a profound effect on how the affected individuals are managed.[1] In the management of T2D, an optimal glycemic control, avoiding acute hyperglycemia, hypoglycemia and glycemic variability may considerably improve the outcome.[2]

Numerous oral antidiabetic agents are in use as monotherapy or in combination therapy for the treatment of type 2 diabetes mellitus (T2DM). Currently, oral antidiabetic drugs (OADs) dominate

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the prescribing pattern, of which metformin alone or in combination with sulfonylureas (SUs) are the most frequently prescribed OADs in many countries. Modern SUs like glimepiride is widely used as second-line agent in the management of T2DM. The use of glimepiride as second-line agent helps in quickly achieving the target glycemic level and reduction of diabetes-related complications. Glimepiride is considered to be a good option in T2D management due to their high efficacy, relative cardiovascular (CV) safety and low-cost. It is also associated with fewer side effects and better efficacy.[3]

Considering the widespread use of glimepiride in managing T2DM, in the present article, the role of glimepiride in controlling hyperglycemia and its place in the T2D management landscape is reviewed. The efficacy and safety, adverse effects (hypoglycemia and weight change), and affordability and patient compliance associated with diabetes are also discussed.

Methods

The authors conducted a systematic review of published literature to evaluate the place of glimepiride in the evolving landscape ofT2D management.

Literature Search

The search was primarily conducted on Medline, PubMed and Google Scholar. The aim of the authors was to evaluate all the published literature including randomized clinical trials, clinical trials, retrospective and prospective research, systematic reviews, and meta-analysis for glimepiride in T2D management and its CV safety. A search was conducted on the digital bibliographic database, Medline, PubMed, Google Scholar. The MeSH terms and search phrase used were (((Glimepiride) AND (Type 2 Diabetes Mellitus)). Two important papers were identified on glimepiride and T2DM. In a backward chronological search, all the relevant articles were searched for citations. Titles and abstracts following the electronic search were examined, and full-text articles fulfilling the selection criteria were obtained. Full text of the selected articles was thoroughly screened to extract the study data.

Screening

Titles and abstracts from the electronic search were checked, and articles meeting the selection criteria were obtained. Relevant information from all the selected articles was extracted. Two investigators independently extracted data from selected literature, and any difference of opinion was resolved through deliberations and consensus between the authors. Where an agreement was not reached, a third author acted as the referee. Qualitative analysis of the selected articles was then conducted by the investigators.

Data Items, Extraction and Synthesis

The study data were extracted by reading the complete article. Selected articles were reported in a table comprising of the following fields: record number, the name of the author(s), publication year, article title and journal. Relevant data for eligible articles were extracted by two authors using pre-structured data extraction grids. These grids were used to extract author name, year of reporting, geographic area, use of glimepiride, benefits, clinical trials, CV safety and adverse events associated with using glimepiride. The disagreements were resolved as detailed above.

Data Synthesis and Analysis

The authors have presented the results in narrative summaries. The themes that emerged after a thorough assessment of the selected articles comprised of the place of glimepiride in T2D management, its glycemic potency, efficacy, durability, CV safety concerns, cost-effectiveness and compliance.

The Changing Landscape of T2DM Management

The management of T2DM is marked with the increasing complexity of management, raising concerns over safety and cost of therapy. In India, the average number of antidiabetic drugs per prescription is 1.4, and the mean cost per 1-month prescription is INR 354.60 ± 305.72.[4,5] The introduction of newer antidiabetic drugs has transformed the prescription pattern across the globe. While oral hypoglycemic agents (OHAs) constitute 57% of the prescribing patterns, insulin alone makes up 14% and OHA + insulin combination about 13% of the prescription pattern. Similar trends are seen in South Asia, where a majority of the treatment pattern is constituted by OHA, either as monotherapy or in combinations. An ideal antidiabetic drug should offer glycemic control, with reduced risk of side effects, while providing economic ease of use.[6]

In the course of T2D management, a gradual reduction in the functional β-cells leads to continuing the decrease in the glucose-lowering efficacy of OADs over time. In consideration of this early combination therapy with intensive glycemic control may be an effective approach for better preservation of β-cell function,

which may rapidly achieve the goal of glycemic level and reduce the diabetes-related complications. An early initiation of combination therapy also brings down complications, which may occur due to up-titration of monotherapies. It has been now established that if the initiation of combination therapy is delayed in stepping up from monotherapy, an increased risk of long terms of hyperglycemia and micro- and macrovascular complications may occur.[3]

Place of Glimepiride in T2D Management Therapy

The antihyperglycemic action of metformin occurs independently without affecting the insulin secretion. Hence, it is beneficial when metformin is combined with an insulin secretagog, like an SU. Modern SUs like glimepiride are considered an ideal choice due to their high efficacy, relative CV safety and low-cost. The risk of hypoglycemia and weight gain can be reduced using modern SUs such as glimepiride and gliclazide with lesser side effects and better efficacy. These effects can be attributed to the wider use of modern SUs. In addition, combination therapies also lead to a higher reduction in blood glucose-lowering effect compared with monotherapy.[3] In addition to lowering the glucose by increasing insulin release from the pancreatic β-cells, glimepiride lowers the risk of hypoglycemia among SUs. Glimepiride can be safely used in patients with CV risk, cardiovascular disease (CVD) and in younger patients with diabetes.[7]

The availability of modern SUs like glimepiride with lesser side effects and improved efficacy has made them a popular antidiabetic option. Owing to its efficacy, cost and feasibility, glimepiride is one of the drugs which are most widely prescribed across the globe.[8] However, there are concerns about CV safety, hypoglycemia and weight gain associated with its use.

Since glimepiride is CV neutral as compared to other SUs, the degree of inhibition of K_{ATP} channels in T2DM patients is less severe during treatment with glimepiride. Hence, it can be safely used in T2DM patients with concurrent coronary artery disease.[9,10]

The low frequency of hypoglycemia and weight gain offered by modern SUs as compared with conventional SUs may be attributed to its reduced binding affinity (2- to 3-fold) and rapid association and dissociation with SU receptors. According to an International Task Force, glimepiride like modern SUs should be preferably used in individuals who are overweight/obese withT2DM, at high risk of hypoglycemia or high risk of CVDs. The main objective of using modern SUs, especially glimepiride and gliclazide is to reduce mortality, achieve better outcomes and preserve renal functions.[11] Along with glycemic control, glimepiride also causes many extra-pancreatic effects which contribute to a better outcome with glimepiride in T2DM patients.[12] Table 1 shows the available strengths of glimepiride as monotherapy and as fixed-dose combinations.

A consensus statement by an initiative of the South Asian Federation of Endocrine Societies (SAFES) has recommended that:[12]

- Glimepiride should be started early in the management of T2DM so that maximum benefits can be attained, and benefits of metabolic memory can be achieved.
- Combination of glimepiride in dual or triple fixed drug combinations with drugs that may have complementary modes of action is beneficial in reducing the cost, offering convenience and in improving patient adherence.
- Glimepiride or gliclazide are preferred over conventional SUs given their reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction [MI], stroke and CV mortality) and renal protection.
- Also, glimepiride and gliclazide MR are recommended to be preferred over conventional SU in patients at increased risk of hypoglycemia, overweight/obese and an increased risk of CVD.
- Glimepiride and gliclazide MR are also recommended in elderly patients because of their lower risk of hypoglycemia.

Glycemic, Efficacy and Durability

Modern SU such as glimepiride exhibit certain pleiotropic effects such as insulin clearance, glucagon secretion, insulin sensitization and antioxidative effect, which may have better effect glycemic durability compared to conventional SU.[11]

Glimepiride as monotherapy is a very effective antidiabetic agent. It was shown in a trial by Goldberg et al that 4-mg dose provided a nearly maximal antihyperglycemic effect. All glimepiride regimen significantly reduced fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) values ($p < 0.001$) compared to placebo by the end of the study period.[13] Another study showed equal effects on FPG, PPG, HbA1c, C-peptide and insulin levels in a crossover study of 98 patients treated with glimepiride.[14] Glimepiride monotherapy

Table 1. Available Strengths of Glimepiride as Monotherapy and as Fixed-dose with Other OADs.[12]

Available strengths (mg)	Dose recommendation	Dose titration
Monotherapy		
0.5, 1, 2, 3, 4, 6	With breakfast or the first main meal Adult:1-2 mg daily Geriatric:1 mg daily	Adult:1-2 mg every 1-2 weeks as needed Geriatric & renal: Conservative titration
FDC: Glimepiride + metformin		
0.5/500, 1/500, 2/500, 1/850, 2/850, 3/850, 1/1000, 2/1000, 4/1000	With meals	As with individual agents
FDC: Glimepiride + pioglitazone		
1/15, 2/15, 2/30, 4/30, 4/45	With the first main meal Initial dose: 2-4/30 mg OD	As with individual agents
FDC: Glimepiride + metformin + pioglitazone		
1/500/15, 2/500/15	Once or twice a day as per recommendation	As with individual agents
FDC: Glimepiride + metformin + voglibose		
1/500/0.2, 2/500/0.2, 1/500/0.3, 2/500/0.3	1/500/0.2 mg OD 2/500/0.3 mg OD or BID 2/500/0.3 mg BID	As with individual agents

reduced both FPG and PPG levels more than placebo once daily administration is equivalent to twice daily dosing. Studies have suggested that glimepiride controls blood glucose level throughout the day via its effect on stimulating insulin release, which appears to be more than 2 hours after meals than under fasting conditions. The trial findings have shown that glimepiride enhances insulin and C-peptide secretion under physiologic conditions.[15]

In a randomized, open-label, parallel study including 34 patients with T2DM treated with metformin with an HbA1c of 7.0% to 10.0%, it was seen that similar significant improvements in HbA1c levels were seen in both vildagliptin (-0.8%) and glimepiride (-0.9%). However, the mean amplitude of glycemic excursions (MAGE) and the mean of daily differences (MODD) was significantly reduced by vildagliptin ($p = 0.044$ and $p = 0.031$, respectively) but not by glimepiride. The result of the study has shown that vildagliptin effectively improved glucose level with a considerably higher reduction in glycemic variability and hypoglycemia than glimepiride in patients with T2DM ongoing metformin therapy.[16]A randomized, multicentric, two arms, open study comparing the glycemic efficacy of sitagliptin with glimepiride showed them to be equally effective in controlling HbA1c. The results showed that glimepiride and sitagliptin were equally effective in glycemic control and all other parameters; however, the only difference being the higher and statistically significant frequency of hypoglycemic events in the glimepiride group. Glimepiride and sitagliptin have shown equal efficacy in glycemic control and all other related parameters. The only difference was reported in terms of hypoglycemic events, which was reported to be higher and statistically significant in the glimepiride group.[17]

In an open-label, randomized, comparative, multicenter study, the safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with T2DM was evaluated. The results have shown that in patients with T2DM, glimepiride/metformin combination demonstrated exhibited significant reduction in glycemic parameters compared with sitagliptin/metformin combination. In addition, there was no considerable change in both the groups in terms of alterations in body mass index (BMI) and hypoglycemic incidence. The results showed that after 12 weeks of treatment, there was a statistically

significant difference in the mean HbA1c decrease in glimepiride group (0.42%) compared with sitagliptin group (0.30%) (p = 0.001). Mean decrease in FPG and PPG was also considerably lower in the glimepiride group as compared to the sitagliptin group (p = 0.008).[18]

It was reported that when used in combination with vildagliptin, glimepiride was effective in Chinese patients with T2DM minus raising the risk of hypoglycemia and weight gain. In a 24-week randomized double-blind placebo-controlled study, it was seen after 24 weeks treatment with vildagliptin 50 mg, OD and glimepiride daily dose 3.3 mg; the adjusted mean change in HbA1c was -0.7% (-8 mmol/mol; baseline 8.6%, 70 mmol/mol) in the vildagliptin group and -0.2% (-2 mmol/mol; baseline 8.7%, 72 mmol/mol) in the placebo group, with a treatment difference of -0.5% (-5 mmol/mol; p <0.001). A slight, but not significant, reduction in body weight was seen in both groups.[19]

A study conducted in Japanese subjects showed that the combination therapy with sitagliptin and low-dose glimepiride (0.5 mg/day) is effective as well as safe in individuals who had T2D uncontrolled with high-dose glimepiride. Even though the dose of glimepiride was reduced, combination therapy with sitagliptin induced significant improvements in HbA1c levels (-0.8%, p <0.001).[20] An 18-week randomized parallel-group interventional trial showed that the addition of sitagliptin and glimepiride to metformin monotherapy brought about significant improvement in glycemic control. Benefits were more with glimepiride contrary to sitagliptin. The results showed that at 18 weeks both sitagliptin and glimepiride produced significant (p <0.001) reduction in HbA1c (-0.636% and -1.172%, respectively), with 12% patients in sitagliptin group and36% patients in glimepiride group achieving target HbA1c. The reduction was significant (p <0.001) in both group in FPG (-15.49 mg and -29.84 mg, respectively) and 2-hour PPG (-34.28 mg and -44.83 mg, respectively).[21]

The results of a systematic review conducted by Amate et al showed that a greater effectiveness was observed in the glimepiride/metformin combination, despite slight differences in adverse effects, with absence of severe hypoglycemia in more than 98% of patients being treated. The glimepiride/metformin combination was preferred treatment due to the cost as well as the effectiveness and safety. The study authors concluded that glimepiride offers potential benefit in refractory hyperglycemic populations, tolerant to treatment.[22]

The ability of glimepiride to increase first- and second-phase insulin secretion in T2DM patients are reflective of a possible association between reasonable glycemic control and acute improvement of control of the *in vivo* insulin release process.[23]

Safety of Glimepiride

Hypoglycemia

Earlier, it has been postulated that glimepiride, which is a long-acting SU, may heighten the risk of hypoglycemia when compared with the short-acting drugs.[24] An observational study has shown that long-acting SUs were associated with an increased risk of severe hypoglycemia compared with the use of specific, short-acting SUs. However, a secondary analysis showed no significant differences in the risks profile.[25] Another Clinical Practice Research Datalink (CPRD)-based study also reported no difference in hypoglycemic risk between long-acting and short-acting SUs.[24,26] It has also been established that the increased risk of hypoglycemia does not apply to every stage of diabetic disease.[24] It has been proven that while longer-acting SUs led to an almost threefold higher incidence of severe hypoglycemia compared with shorter-acting SUs when used as the first-line treatment,[26] but the incidence of severe hypoglycemia in the two groups was similar when the drug was given as a second-line treatment.[27]

Glimepiride has been compared with other SUs, including glibenclamide, glipizide and gliclazide in many clinical trials. The incidence of hypoglycemia was lower with glimepiride (1.7%) than with glibenclamide. Another study showed glimepiride to be associated with fewer hypoglycemic episodes compared to glibenclamide.[15] When compared with gliclazide, the use of glimepiride was associated with a similar incidence of hypoglycemic episodes. The study concluded that glimepiride is as effective as gliclazide either as monotherapy or in combination therapy.[28]

Weight Gain

Sulfonylureas have been linked with considerable weight gain, a secondary side effect which is also known to be associated with the use of insulin, thiazolidinediones and glinides. Glimepiride has reported weight neutrality at least for the first year of use.[29] Glimepiride administered once daily was linked with weight neutralizing or weight-reducing effect over 1.5 years. Another study showed that once-daily

glimepiride provides effective glycemic control and may be beneficial over other SUs as it shows weight neutralizing/reducing effects in patients with T2D. In an open, uncontrolled surveillance study, it was seen that treatment with glimepiride led to significant and stable weight loss relative to baseline except for patients with a BMI of <25 kg/m^2. Mean body weight was lowered from 79.8 kg at baseline to 77.9 kg after 4 months, 77.2 kg after 1year and 76.9 kg after 1.5 years (mean intra-individual change from baseline: -1.9 kg, p <0.0001; -2.9 kg, p <0.05, respectively).[30]

Initial treatment with glimepiride led to a significantly higher reduction in body weight or BMI than with glibenclamide (-2.04 ± 3.99 kg vs. -0.58 ± 3.65 kg, p <0.001; -0.71 ± 1.38 kg/m^2 vs. -0.20 ± 1.28 kg/m^2, p <0.001, respectively), while providing equivalent glycemic control.[31]

Cardiovascular Safety Concerns

Glimepiride is a pancreas nonspecific SU which is also known to bind to cardiac muscle and vascular smooth muscle cells, and hence there have been concerns regarding its raised CV risks.[32,33] However, animal studies have demonstrated that glimepiride upon binding to the myocardium could preserve or even show some ischemic preconditioning, eventually preventing ventricular arrhythmias.[34]

It has been seen that modern SUs are linked with reduced risk of CV mortality, MI and hospitalization for acute coronary syndrome (ACS) when compared with traditional SUs.[35] The major adverse CV event (MACE) outcome safety data for glimepiride is reassuring and preliminary research in the field of personalized medicine as shown that drugs directly targeting β-cell insulin exocytosis may continue playing an essential role in managing T2D.[36] Simpson et al in 2015 showed in a meta-analysis of 18 studies, including 1,67,327 patients that gliclazide and glimepiride were linked with reduced risk of all-cause and CV mortality compared with glibenclamide. Trials have shown that the risk of all-cause and CV mortality was lesser with glimepiride and gliclazide compared with glibenclamide (all-cause mortality for gliclazide 0.65, 955 confidence interval [CI] 0.53-0.79).[37]

In a review by Aravind et al have shown that several clinical studies have validated the 'cardio-safe' profile of glimepiride; hence, making it suitable for use in a wide range of people with diabetes. Compared with other conventional SUs, glimepiride is cardio-safe. It has been reported to have an insignificant effect in reducing coronary blood flow and in increasing coronary resistance. Glimepiride preserves ischemic preconditioning since it does not have such inhibitory effects, hence preferred over conventional SUs, particularly in patients at increased risk for CVD.[38]

In a cohort study using real-world data, the results have shown that for patients with diabetes taking an insulin secretagogue, glimepiride was related with the best clinical outcome, exhibiting the lowest mortality and CV event risk. The results showed that among glimepiride, gliclazide, glipizide, glyburide and repaglinide groups, glimepiride was associated with the best clinical outcome, exhibiting lowest mortality and CV event risk of the five insulin secretagogues. In the study results revealed that the adjusted HR of all-cause mortality and CV event risk were 1.52 (p <0.001) and 1.22 (p = 0.005) for gliclazide, 1.42 (p <0.001) and 1.19 (p = 0.073) for glipizide, 1.43 (p <0.001) and 1.32 (p <0.001) for glyburide, and 1.88 (p <0.001) and 1.69 (p = 0.001) for repaglinide.[39]

In a study by Douros et al, it was seen that when compared with other second-generation SUs, glimepiride was linked with a similar incidence of MI and ischemic stroke, with a nonsignificant trend towards an increased incidence of severe hypoglycemia. On the contrary, glimepiride use was associated with a reduced incidence of all-cause mortality, and a nonsignificant trend of a lower incidence of CV death. During a mean follow-up of 1.1 years, SUs were related with an increased risk of MI (incidence rate 7.8 vs. 6.2 per 1,000 person years, HR 1.26, 95% CI 1.01-1.56), all-cause mortality (27.3 vs. 21.5, 1.28, 1.15-1.44) and severe hypoglycemia (5.5 vs. 0.7, 7.60, 4.64-12.44) compared with continuing metformin monotherapy. A trend towards increased risks of ischemic stroke (6.7 vs. 5.5, 1.24, 0.99-1.56) and CV death (9.4 vs. 8.1, 1.18, 0.98-1.43).[26] The findings from the CAROLINA trial showed that there is no difference in the risk of CV events or all-cause mortality between the dipeptidyl peptidase-4 (DPP-4) inhibitors linagliptin and glimepiride. The findings revealed that the primary outcome occurred in 356 of 3,023 participants (11.8%) in the linagliptin group and 362 of 3,010 (12.0%) in the glimepiride group (hazard ratio [HR], 0.98 [95.47% CI, 0.84-1.14]; p <0.001 for noninferiority), meeting the noninferiority criterion but not superiority (p = 0.76). Adverse events occurred in 2,822 participants (93.4%) in the linagliptin group and 2,856 (94.9%) in the glimepiride group, with 15 participants (0.5%) in the linagliptin group vs. 16 (0.5%) in the glimepiride group with adjudicated-confirmed acute pancreatitis.[40]

The TOSCA.IT, a multicenter, randomized, pragmatic clinical trial, including patients aged 50 to 75 years with T2D with uncontrolled blood glucose with metformin monotherapy. A comparison of glimepiride, gliclazide and pioglitazone showed that the primary outcome (a composite of the first incidence of all-cause death, nonfatal MI, nonfatal stroke or urgent coronary revascularization) occurred in 105 patients (1.5 per 100 person-years) who were given pioglitazone and 108 (1.5 per 100 person-years) who were given SUs (HR 0.96, 95% CI 0.74-1.26, p = 0.79). The trial authors concluded that the incidence of CV events was similar with glimepiride, gliclazide and pioglitazone as add-on treatments to metformin and hence are suitable options in terms of efficacy and adverse events in the management of diabetes.[41]

In an observational study which evaluated the correlation between selectivity for β-cells among several SUs and CV mortality among T2DM patients, the patients treated with a combination of SUs and biguanides at enrollment had considerably higher mortality when compared with the rest of the sample (5.2% vs. 6.4% annually; p <0.05). Compared with glimepiride, mortality was significantly higher in patients treated with repaglinide and gliclazide. The study authors concluded that glimepiride due to its higher selectivity for β-cells was associated with reduced mortality when used in combination with metformin, compared with other SUs like glibenclamide.[42]

In a study evaluating the impact of SUs on in-hospital outcome in MI, patients assessed the difference in outcomes between MI patients vs. diabetic patients who did not receive SUs. The findings showed that the incidence of in-hospital complications, mainly, in-hospital death was more in the insulin group compared with the glimepiride or gliclazide group.

This study concluded that the hospital mortality among patients admitted with acute MI and who received glimepiride or gliclazide before admission was comparatively lower than that among patients who did not receive similar treatments.[43] Another study which compared the association between the choice of SU and the risk of overall mortality among a large cohort of patients with T2D with coronary artery disease (CAD) demonstrated a trend towards increased overall mortality risk with glyburide vs. glimepiride (1.36 [0.95-1.91]) and glipizide vs. glimepiride (1.39 [0.99-1.96]). The study suggested that glimepiride may be the preferred choice of SU in individuals with underlying CAD.[44]

Cost-Effectiveness and Compliance

Diabetes is a complex disease; pharmacotherapy for a chronic disease like diabetes has substantial economic implications for patients especially in a developing nation like India. In terms of cost-effectiveness, only efficacy may not justify a drug choice for long-term therapy as the occurrence of adverse events such as β-cell loss, hypoglycemia, negative CV effects. Management of adverse effects such as hypoglycemia poses an additional health and economic burden on the public.[45,46]

As is seen from the ensuing discussion that modern SUs like glimepiride have a lower risk of hypoglycemia and have favorable cost, efficacy and safety profiles. Sulfonylureas as a class of antidiabetic medicines form a reasonable choice for diabetes management, especially when the cost is a crucial consideration. The risk of hypoglycemia linked with glimepiride can be easily tackled with the help of patient education and the use of variable dosing. Glimepiride is one of those modern SUs which have a lower risk of hypoglycemia compared with conventional SUs.[11]

In a review, the authors concluded that metformin, glimepiride and pioglitazone are safe and efficacious oral hypoglycemic medicines. Glimepiride is the preferred SU as it is not associated with the adverse events as others in its class. Glimepiride was not associated with weight gain, hypoglycemia or negative CV events relative to other SUs.[45]

A study conducted to evaluate the cost-effectiveness of commonly practiced combination therapies in the management of T2DM. The cost-effectiveness for per unit reduction in HbA1c and FPG was significant in metformin *plus* glimepiride group as compared to the metformin *plus* teneligliptin group though it was comparable for both the groups for per unit PPG reduction. However, there was no significant change in BMI levels between the groups. The authors concluded that compared to combination of metformin with teneligliptin, the metformin-glimepiride combination is a significantly cost-effective therapy when used as an initial combination therapy in patients of T2DM in reducing HbA1c and FPG.[46]

In the case of Asian diabetic patients, an open, randomized, comparative, multicenter, clinical trial to assess the efficacy and safety glimepiride was conducted. The results showed that the frequency of successful blood glucose control (3.9 < FBG <7.8 mmol/L) was not considerably different from other groups. The authors suggested that glimepiride could be used

effectively and safely for the control of hyperglycemia; however, since glimepiride demonstrated equivalent efficacy with a single dose, it was anticipated that it might improve patients' compliance.[15]

Given this, treatment with modern SUs like glimepiride is associated with reduced economic load and better performance in terms of the outcome when compared with other regimens in the cost for average glycemic-lowering. Also, the once-daily dosing schedule via the oral route of administration is an essential feature of glimepiride, making it an appropriate option for improved adherence to medication regimen.[12]

Conclusion

Optimized glycemic control, reduced risk of side effects, along with economic feasibility, are the main features of oral antidiabetic agents. Glimepiride is a modern SU which is CV neutral as compared to other SUs and hence can be safely employed in managing T2DM. Multiple studies have reported glimepiride to be safe for use in people with T2D at increased CV risk. It is recommended to be initiated early in the management of T2DM for attaining maximum benefits. Patient compliance and affordability associated with glimepiride make it an attractive option in the management of T2DM.

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