VOLUME - 11, ISSUE - 04, APRIL - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

EFFECTIVENESS OF GLICLAZIDE MR COMPARED TO DPP 4I IN PEOPLE WITH TYPE 2 DIABETES

Dr. Shanthilal AdhiKarla	MD (General Medicine), Drs. Mohans Diabetes Center Domalguda, Hyderabad
Dr A Venkatamuni	MD (General Medicine), Vishnu Sree Multi Speciality Hospital, Sriram Nagar, Karakambadi Road, Andhra Bank Street, Tirupati 517501 Andhra Pradesh
Dr. Subodh Jain	MD(General Medicine),George Town , Prayagraj, ,211002.
Dr. Sumesh T Krishnan	MD(Diabetologist) Olarikkara Clinic , Thrissur 680012.
Dr. Dhananjay Mishra	MD (General Medicine), Diabetes Centre, Morar, Gwalior-474004.

KEYWORDS :

INTRODUCTION

Sulfonylureas have been used since 1960s clinically to treat type 2 diabetes mellitus (T2DM) [1] and are still among the most commonly prescribed oral diabetic treatments[2]. Data on prescription patterns globally show that sulfonylureas are constantly the most common choice for second-line therapy in patients who require additional glucose-lowering during metformin monotherapy, followed by dipeptidyl peptidase 4 inhibitors (DPP-4i). [2,3]

Treatment guidelines for T2DM are frequently updated to include emerging treatments and evolving evidence, especially from cardiovascular outcomes trials (CVOTs). Yet, there are considerable differences between guidelines in the recommendations related to sulfonylureas. [4,5,6,7,8,9,10,11]

Place of Gliclazide MR in Current Guidelines

Diabetes guidelines worldwide almost universally recommend metformin as the first-line glucose-lowering drug in newly diagnosed patients with T2DM, but they vary in terms of the recommendations about which agents should be used as add-on therapies if metformin alone cannot achieve glycaemic targets (Table 1)[4,5,6,8,10,11,12]

Table 1 Summary Of Consensus Report Recommendations On The Use Of Sulfonylureas And Gliclazide MR In Patients Without Established Atherosclerotic Cardiovascular Disease [13]

Diabetes guidelines	Second-line treatment recommendation in patients with suboptimal glucose control on metformin	Guideline information specific to gliclazide MR
UK (NICE/SIGN) 2015[a]	Add DPP-4i, pioglitazone or SU GLP-1RAs not recommended	–
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 less likely to cause hypoglycaemia compared with glibenclamide or glimepiride
Global (International Diabetes Federation) 2017	Preferred add-on therapies are SU (not glibenclamide/glyburide), DPP-4i or SLGT-2i	–
Global resource-limited settings (WHO) 2018	Add an SU	Gliclazide is preferred SU if hypoglycaemia is a concern
Canada (Diabetes Canada) 2018	Add DDP-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 not licensed in the US for T2DM
Europe (ESC/EASD) 2019	Add DDP-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 minimise risk of hypoglycaemia

ADA American Diabetes Association, DPP-4i dipeptidyl peptidase 4 inhibitors, EASD European Association for the

Study of Diabetes, ESC European Society of Cardiology, GLP-1RA glucagon-like peptide 1 receptor agonists, MR modified release, NICE National Institute for Health and Care Excellence, RACGP Royal Australian College of General Practitioners, SGLT-2i sodium-glucose transport protein 2 inhibitors, SU sulfonylurea, T2DM type 2 diabetes mellitus, TZD thiazolidinedione, WHO World Health Organization

a Updated in 2019

b TZDs not recommended when there is a compelling need to minimise weight gain

Further, the analysis found that the sulfonylurea gliclazide ranked number one in all comparisons because it worked as well as other classes of glucose-lowering drugs but cost the least as summarized.

Moreover, a recent retrospective study of 10, 256 patients with T2D initiating second-line treatment in Germany and the UK found that sulfonylureas (SUs) were selected as add-on therapy in 40.9% of patients and dipeptidyl peptidase-4 (DPP-4) inhibitors in 30.7%. SUs has a long history of clinical use and are recognized as a cost-effective method of blood glucose control.8 Currently, many different SUs and DPP-4 inhibitors are available for the treatment of T2D. Gliclazide modified release (MR) – a once-daily SU that allows for a progressive release of medication – reduces glycated haemoglobin (HbA1c) in patients with T2DM with efficacy similar to the once-daily SU glimepiride, but with significantly fewer hypoglycaemic events. A systematic review of randomized controlled trials shows that gliclazide MR has a significantly reduced risk of hypoglycaemia in comparison with other SUs.10 A further study shows that, compared with standard glucose control, an intensive glycaemic control with gliclazide MR as the first-line agent and addition to other agents, if required, can achieve a lower mean HbA1c [6.5% (48 mmol/mol) vs. 7.3% (56 mmol/mol)] and reduces the incidence of combined major macro- and microvascular events. [14]

Gliclazide Modified Release versus Sitagliptin [15]

The retrospective cohort study used records from the UK Clinical Practice Research Datalink. The cohort involved adult patients with T2DM newly treated with either gliclazide MR or sitagliptin as second-line treatment added to metformin and with a glycated haemoglobin (HbA1c) level of ≥7.0% (53 mmol/mol). Patients were 1:1 matched using high-dimensional propensity score matching and then followed to determine the time taken to reach an HbA1c <7.0%. Secondary outcomes consisted of time to HbA1c ≤6.5% (48 mmol/mol), time to ≥1% (11 mmol/mol) HbA1c reduction from baseline, treatment persistence and durability, and hypoglycaemic events.

Overall, patients in gliclazide MR group were 35% more likely to achieve the target of <7.0% (53 mmol/mol) HbA1c more than patients in the sitagliptin group (HR: 1.35; 95% CI: 1.15-1.57). There was a rapid separation of probability curves, with patients in the gliclazide MR group more likely to achieve HbA1c control starting at around 3 months (Figure 1A). Patients treated with gliclazide MR were 51% more likely to achieve the target of HbA1c ≤6.5% (48 mmol/mol) (HR: 1.51; 95% CI: 1.19-1.92); as with the primary outcome, rapid separation of probability curves was observed as well (Figure 1B). Also, patients treated with gliclazide MR were slightly more likely to achieve an HbA1c reduction ≥1% (11 mmol/mol) from baseline (HR: 1.11; 95% CI: 1.00-1.24; Figure 1C).

Hence, in this real-world study, second line gliclazide MR was more effective than sitagliptin in reducing HbA1c, with similar durability and persistence and low rates of hypoglycaemic events, in individuals with T2DM on metformin treatment and HbA1c above the target of 7.0%.

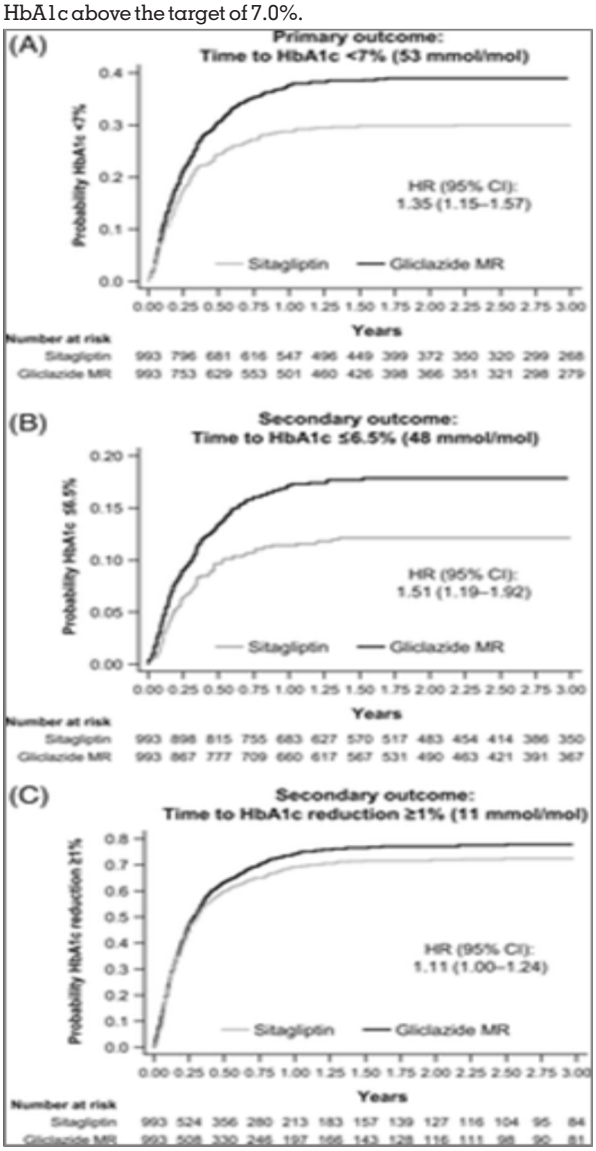


Figure 1: Kaplan-Meier curves for HbA1c control. Probability of achieving a reduction of HbA1c in patients with T2D treated with gliclazide MR or sitagliptin. A, <7% (53 mmol/mol). B, ≤6.5% (48 mmol/mol). C, ≥1% (11 mmol/mol) reduction from baseline. CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; MR, modified release; T2D, type 2 diabetes mellitus

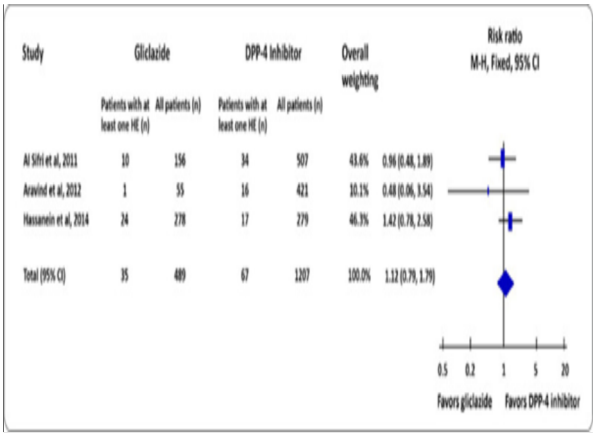


Figure 2 : Risk of hypoglycemic events (HE) during Ramadan;

comparing gliclazide with dipeptidyl peptidase 4 (DPP-4) inhibitors

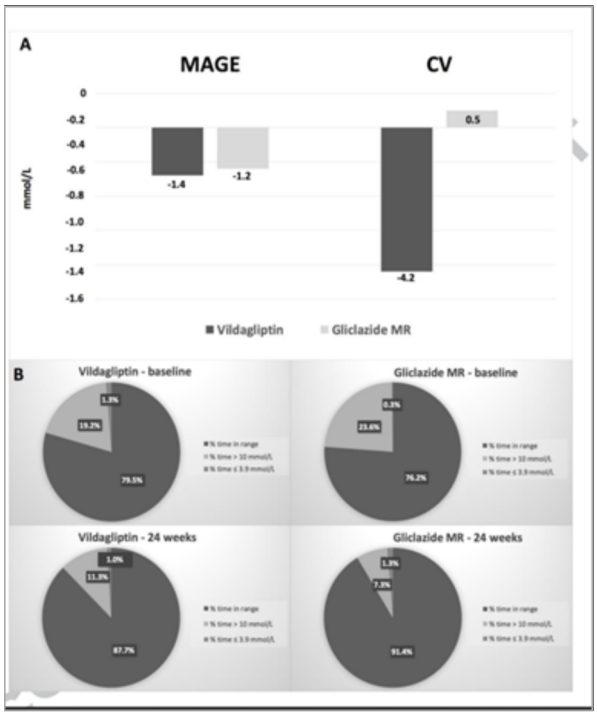


Figure 3 : (A) Reduction in the CGM parameters MAGE and CV and (B) variation in the CGM parameters % of time in range, % of time in hypoglycemia and % of time in hyperglycemia from baseline to week 24 in the vildagliptin and gliclazide MR treatment groups

Gliclazide and risk of hypoglycemia during Ramadan [15]

The use of Gliclazide in the holy month of Ramadan has been shown to be associated with low hypoglycemia risk. A pooled analysis of three Ramadan trials reported similarly low risk hypoglycemic episodes profiles with both gliclazide and DPP-4i in patients with T2DM as shown in figure 2.

Another study comparing the risk of hypoglycemia between second generation SUs and DPP-4 inhibitor (sitagliptin) in 1024 T2DM patients during Ramadan found that rate of ≥1 HEs was lowest in gliclazide MR arm (6.6%) compared to glibenclamide (19.7%), glimepiride (12.4%), and sitagliptin (6.7%) arms.

Gliclazide MR versus DPP-4 inhibitor Vildagliptin on Glycemic Variability and Control Measured By Continuous Glucose Monitoring (CGM) [16]

An open-label, randomized study was carried out in T2DM women on steady-dose metformin monotherapy which were treated with 50 mg vildagliptin twice daily or 60-120 mg of gliclazide MR once daily. CGM and GV indices calculation were performed at baseline and after 24 weeks.

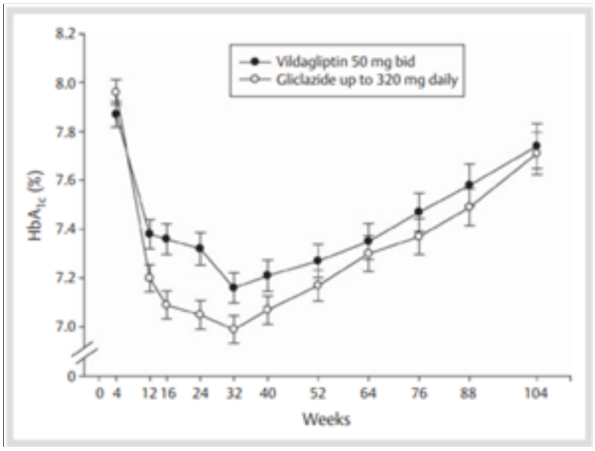
It was reportged that, Vildagliptin and gliclazide MR reduced GV, as measured by the mean amplitude of glycemic excursions (MAGE, p = 0.007 and 0.034, respectively). Vildagliptin also significantly decreased the standard deviation of the mean glucose (SD) and the mean of the daily differences (MODD) (p = 0.007 and 0.030). (Figure 3)

Hence, vildagliptin and gliclazide MR similarly reduced the MAGE in women with T2DM after 24 weeks of treatment.

Gliclazide MR versus Vildagliptin After Two Years of Monotherapy in Drug-Naïve Patients With Type 2 Diabetes [17]

A multi-center, double-blind, randomized, active-controlled study was conducted to compare the efficacy and safety of two years of monotherapy with vildagliptin 50 mg bid and gliclazide up to 320 mg/day in drug-naïve patients with type 2 diabetes.

As shown in figure 4, in the vildagliptin group, HbA1c decreased to ~ 7.3 % from a baseline of 8.6 % within 12 weeks and was more or less maintained for next 52 weeks; by 104 weeks, HbA1c had increased to ~ 7.7 % . In the gliclazide group, HbA 1c decreased to ~ 7.1 % from a baseline of 8.7 % within 16 weeks and was more or less maintained for next 24 weeks; by 104 weeks, HbA 1c had increased to ~ 7.7 % . These changes from baseline to Week 104 were significant for both groups. The diff erences between these ~ 7.7 % HbA1c values at week 104 and the mean reductions in HbA1c to ~ 8.0 % in the vildagliptin group and ~ 8.1 % in the gliclazide group above.



Summary

Gliclazide ranked number one in all comparisons with other SUs because it worked as well as other classes of glucose-lowering drugs but cost the least as summarized. Further, compared to Sitagliptin, gliclazide MR was more effective in reducing HbA1c, with similar durability and persistence and low rates of hypoglycaemic events, in individuals with T2DM on metformin treatment and HbA1c above the target of 7.0%. Also, gliclazide has been shown to be associated with low hypoglycemia risk compared to Sitagliptin. When CGM and GV indices were calculated, vildagliptin and gliclazide MR similarly reduced the MAGE in women with T2DM after 24 weeks of treatment.

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