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ORIGINAL RESEARCH

The Position of Gliclazide in the Evolving Landscapes and Disease Continuum of T2DM: A Collaborative Delphi Survey-Based Consensus from India

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ABSTRACT

Introduction: This Delphi study aims to provide evidence-based expert opinion on the usage and current position of gliclazide in type 2 diabetes mellitus (T2DM) management in India.

Methods: The single interaction modified Delphi-based methodology was used to collect opinions on gliclazide usage and its position in diabetes management from 338 endocrinologists/diabetologists who have had clinical experience with gliclazide. Participants, using a 9-point scale, were asked to rate eight statements comprising a total of 52 items on the related topics.

Results: The Delphi consensus suggests that in drug-naïve patients with T2DM, intolerant to metformin or in whom metformin is contraindicated, dual therapy of gliclazide/gliclazide-modified release (MR) should be considered along with a dipeptidyl peptidase 4 (DPP4) inhibitor if glycated hemoglobin A1c level is greater than 7.5% and with insulin if the A1c level is greater than 9%. If the patients are inadequately controlled with metformin (A1c greater than 6.5% after 3 months of therapy), gliclazide/gliclazide-MR shall be added on to the treatment regimen to achieve greater and sustained reductions in A1c levels. However, it was not preferred over other antidiabetic classes in such clinical settings except alpha-glucosidase inhibitors (AGI). Early addition of gliclazide/gliclazide-MR shall be preferred over the up-titration of metformin beyond half-maximal dose for effective management of T2DM. Gliclazide/gliclazide-MR can be used safely in patients with diabetes and cardiovascular and chronic kidney disease. It can be used in older patients with T2DM as it does not have active metabolites and has a low risk of hypoglycemia.

Conclusion: The expert panel proposed consideration of monotherapy or dual therapy of gliclazide as an ideal choice in patients with T2DM because of its efficacy, long-term

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glycemic control, favorable renal outcomes, cardiovascular safety, and an optimal safety profile.

Keywords: Delphi questionnaire; Endocrinology; Gliclazide; Gliclazide-MR; Single interaction modified Delphi process; Type 2 diabetes

Key Summary Points
Limited information is available about current use of gliclazide in Indian routine clinical practice.
The study aims to provide expert opinion on the usage and current position of gliclazide in India.
This is a single interaction modified Delphi-based study including 338 endocrinologists/diabetologists.
The expert panel preferred gliclazide as monotherapy or dual therapy in patients with diabetes.
The expert consensus-based opinion justified the role of gliclazide in different clinical situations associated with diabetes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13507329

INTRODUCTION

Nearly 80% of the world's diabetes population lives in low- to middle-income countries [1]. In 2019, 77 million Indians aged 20–79 years had diabetes, and this number is projected to rise to 134.2 million by 2045 [2]. More than ever, safe and cost-effective therapies to treat diabetes are needed. Although new antidiabetic drugs offer certain benefits over their predecessors, they are available at higher costs and are not without safety concerns. Sulfonylureas (SUs) are widely used in India because of their glucose-lowering efficacy and affordability, with glimepiride and gliclazide being the most commonly prescribed SUs. A retrospective cross-sectional study from India found an increase in the use of SUs from 23.12% in patients with diabetes for 0–5 years to 70.77% in patients with diabetes for 10–-15 years [3].

Multiple guidelines, such as the American Diabetes Association (ADA) 2020 guidelines, the International Diabetes Federation (IDF) clinical practice recommendations for managing type 2 diabetes mellitus (T2DM) in primary care 2017, Indian Council of Medical Research (ICMR) 2005 and Research Society for the Study of Diabetes in India (RSSDI), and Endocrine Society of India (ESI) clinical practice recommendations for the management of T2DM 2020, recommend oral antihyperglycemic drugs such as SUs to be used as monotherapy (if metformin is not tolerated) or as combination therapy [4–7].

Interestingly, few guidelines on diabetes management specifically suggest gliclazide as the second-line treatment, instead of SUs as a class [8]. The low risk of hypoglycemia, weight neutrality, cardiovascular (CV) safety, and favorable renal outcomes especially in patients with chronic kidney disease (CKD) appear to be the reasons for preference of gliclazide over other SUs [9]. Also, gliclazide protects β-cells by acting specifically on the pancreatic sulfonylurea receptor 1 (SUR1) and thereby delays the development of secondary treatment failure [9]. Further, gliclazide has been included along with metformin and insulin in the World Health Organization (WHO) model list of essential medicines 2019 under medicine for diabetes [10].

Although results from large studies have shown high diabetes burden, and high SUs prescription rate in India, limited information is available about their current use in diabetes management in routine clinical practice in India. Therefore, a collaborative Delphi methodology was considered appropriate to

explore a set of questions drafted by a panel of experts in the field of diabetes and endocrinology. The current consensus is intended to provide opinion on the usage and current position of gliclazide across the diabetes continuum in India.

METHODS

Survey Participants

Design

The Delphi method uses a structured group communication technique to explore novel concepts, answer research questions, and solve differences of opinions by looking at the pros and cons of specific arguments from all angles [11]. The present rank-based expert opinion is compiled adopting a single interaction collaborative Delphi process. This modification uses a combination of surveys and meetings involving a large group of endocrinologists and diabetologists (Fig. 1). The adopted methodology allows for arriving at a group consensus with reliability and help in clinical decision-making.

The questionnaire was drafted by the steering committee (50 experts in the field of diabetes and endocrinology) after a thorough review of the literature on gliclazide and included seven statements comprising 46 items. Selection criteria for steering committee members are shown in Fig. 1 and were based on experience and research orientation so that collectively consensus can be formed on most pertinent research questions. After the expert review of the first draft, the final draft of eight statements comprising a total of 52 items was developed by the panel members to identify areas of agreement, relevance, and disagreement. Specifically, the questionnaire addressed the following issues:

1. Decision to use gliclazide/gliclazide-modified release (MR) as valid option for drug-naïve patients with T2DM
2. Decision to use gliclazide/gliclazide-MR as second-line treatment option for T2DM
3. Decision to switch to gliclazide/gliclazide-MR-based combination therapy from other combination therapies in uncontrolled diabetes
4. Efficacy of gliclazide/ gliclazide-MR in patients with diabetes and cardiovascular disease (CVD)
5. Efficacy of gliclazide/ gliclazide-MR in patients with diabetes and CKD
6. Dosing of the gliclazide-MR
7. Safety and tolerability of gliclazide/gliclazide-MR
8. Gliclazide/gliclazide MR in special populations

These eight statements comprising a total of 52 items were then sent to 338 participants through multiple meetings and emails in different parts of the country. All the participants were clinicians with strong experience in the use of gliclazide/gliclazide-MR as shown in Table 1. The participants were asked to rate each item using a 9-point scale, where the scores of 1, 2, 3, or 4 indicated degrees of disagreement and the scores of 6, 7, 8, or 9 indicated increasing degrees of agreement. A score of 5 was considered a neutral opinion. All the participants had the liberty to modify the statements and respond to them.

The rank was determined by calculating the percentage of participants agreeing or

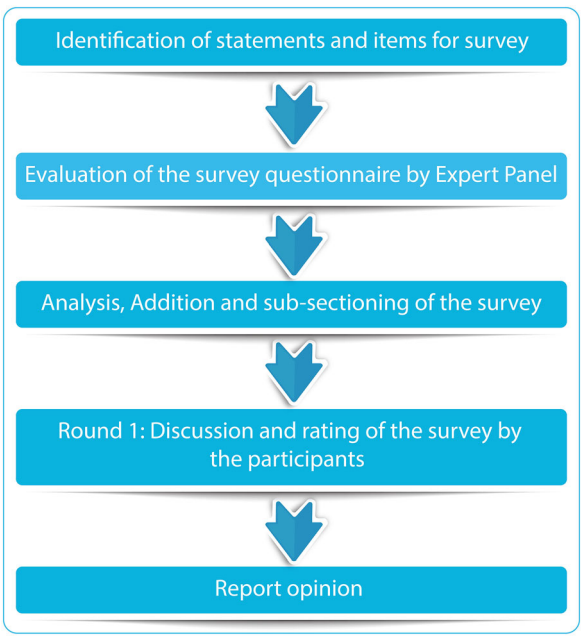

Fig. 1 The Delphi process

Table 1 Qualifications and responsibilities of the Delphi participants

Expert panel
Qualifications
Possess at least 5 years of working experience in the use of or research with gliclazide/gliclazide-MR and
Scientific publication(s) in the field of diabetes and endocrinology or
Have been involved in clinical research initiatives involving gliclazide/gliclazide-MR-based drug therapy
Responsibility
Literature review, draft, review, and finalization of the survey items before release to physicians
Physicians
Qualifications
At least 3 years of working experience in use of gliclazide/gliclazide-MR
Responsibility
Answer the survey based on literature review and their clinical practice to arrive at an agreement

disagreeing (ranking) to each item in the eight statements. Items getting more than 30% responses were included in the final analysis. The items that were agreed upon by more than 50% of respondents were considered to be expert panel opinions.

Compliance with Ethics Guidelines

This study is based on a clinical practice questionnaire that does not involve the participation of human subjects or patient data management and does not aim to modify the current clinical practice of participants. As such, this study was deemed exempt from requiring ethical approval. Consent for publication of survey results was granted from all the experts participating in the program and undertaking the survey.

RESULT

Expert Panel Member Participation

A total of 338 doctors participated in this modified Delphi survey from 19 different cities of India. 39 respondents were from a northern city (Delhi, Jaipur), 88 from western cities (Mumbai, Pune, Nagpur, Indore, and Jabalpur), 54 from eastern cities (Kolkata, Ranchi, and Guwahati), and 157 from southern cities (Bangalore, Hyderabad, Thrissur, Kannur, Vijayawada, Trivandrum, Chennai, and Madurai) of India.

At the end of the Delphi study, the panel agreed on 48 items and disagreed on three items. Approved sentences underlying each statement are summarized in Table 2.

Decision to Use Gliclazide/Gliclazide-MR as Valid Option for Drug-Naïve Patients with T2DM

Current guidelines recommend metformin as the first-line, initial monotherapy, and as part of combination therapy for patients with T2DM [7, 12]. In case metformin is not suitable, the IDF recommends use of SU, dipeptidyl peptidase 4 (DPP4) inhibitor, or alpha-glucosidase inhibitors (AGI) for the treatment and prevention of T2DM [13, 14]. Several clinical trials comparing gliclazide with other antidiabetic agents such as metformin, pioglitazone, vildagliptin, or insulin have reported similar glycemic efficacy [15, 16]. In the EASYDia trial, nearly half of the treatment-naïve patients with diabetes successfully achieved an A1c of 7.0% or less at month 3 with gliclazide-MR therapy [17]. However, initiating therapy with multiple antidiabetes agents in patients with newly diagnosed T2DM, especially those with A1c greater than 8.0% to 8.5%, represents a rational approach to achieve the target A1c level while minimizing side effects. Indeed, the American Association of Clinical Endocrinology (AACE) recommends starting newly diagnosed diabetic subjects with A1c greater than 7.5% on multiple antidiabetes agents [18].

Table 2 The questionnaire to rate each item using a 9-point scale (1–5, disagreement; 5, neutral; 6–9, agreement)

	Disagreement (%)	Neutral (%)	Agreement (%)	Total (%)
Statement 1: Drug-naïve patients with T2DM				
1.1 Gliclazide/gliclazide-MR is a valid first-line treatment option for drug-naïve patients with T2DM intolerant or contraindicated to metformin with A1c levels of 7.5%	5.9	2.7	32.5	41.1
1.2 Gliclazide/gliclazide-MR and metformin dual therapy can be used in drug-naïve patients with T2DM with A1c levels of 7.5–8%	2.4	1.2	39.3	42.9
1.3 Gliclazide/gliclazide-MR and metformin dual therapy can be used in drug-naïve patients with T2DM with A1c levels of 8.0–9.0%	0.9	0.3	34.6	35.8
1.4 Gliclazide/gliclazide-MR and DPP4 inhibitors dual therapy can be used in drug-naïve patients with T2DM intolerant or contraindicated to metformin with A1c levels of 7.5–8.0%	6.2	1.8	51.2	59.2
1.5 Gliclazide/gliclazide-MR and insulin dual therapy can be used in drug-naïve patients with T2DM intolerant or contraindicated to metformin with A1c levels of > 9.0%	13.6	5.3	63.0	81.9
1.6 Gliclazide/gliclazide-MR will be able to achieve of glycemic target of 6.5% in drug-naïve patients, in case required A1c reduction is up to 1.0%	1.8	2.4	40.2	44.4
Statement 2: Gliclazide/gliclazide-MR as second-line treatment in patients with T2DM				
2.1 Gliclazide/gliclazide-MR can be used as second-line treatment for patients with T2DM (add-on to metformin) if A1c level remains > 6.5% after 3 months of therapy	6.8	2.1	52.9	61.8
2.2 Early use (< 3 months) of gliclazide/gliclazide-MR is the preferred second-line treatment option for T2DM, after half maximal dose (1.0 g) of metformin (above target FPG levels)	8.6	3.8	55.0	67.4
2.3 Combination of gliclazide/gliclazide-MR and metformin is always associated with greater reduction in A1c than metformin monotherapy	0.9	0.9	92.0	93.8
2.4 Combination of gliclazide/gliclazide-MR and metformin is always associated with sustained reduction in A1c (over at least 2 years) vs. metformin monotherapy	1.8	2.9	84.9	89.6
2.5 Switch to gliclazide/gliclazide-MR from other SUs as add-on to metformin for T2DM is beneficial if A1c levels remain above the target after 3 months of therapy	36.1	15.1	39.9	91.1
2.6 Gliclazide protects human islet β-cells from apoptosis in T2DM	18.0	13.6	47.9	79.5
2.7 Gliclazide/gliclazide-MR is better alternative to GLP-1 receptor agonist owing to low cost	4.4	4.7	73.4	82.5

Table 2 continued

	Disagreement (%)	Neutral (%)	Agreement (%)	Total (%)
2.8 Combination of gliclazide/gliclazide-MR and basal insulin is more effective approach than basal insulin alone for patients with T2DM having reduced glycemic response with SUs	12.4	6.2	70.4	89.0
Statement 3: Switch to gliclazide/gliclazide-MR-based combination therapy from other combination therapies in uncontrolled diabetes				
3.1 Combination of gliclazide/gliclazide-MR and metformin shows similar glycemic effectiveness to DPP4i plus metformin in uncontrolled T2DM	3.0	3.8	42.9	49.7
3.2 Combination of gliclazide/gliclazide-MR and metformin show better glycemic effectiveness than DPP4i plus metformin in uncontrolled T2DM	0.3	0.6	42.3	43.2
3.3 Combination of gliclazide/gliclazide-MR and metformin show similar glycemic effectiveness to AGI plus metformin in uncontrolled T2DM	1.8	3.3	25.4	30.5
3.4 Combination of gliclazide/gliclazide-MR and metformin show better glycemic effectiveness than AGI plus metformin in uncontrolled T2DM	0.3	1.5	53.8	55.6
3.5 Combination of gliclazide/gliclazide-MR and metformin show similar glycemic effectiveness to TZD (pioglitazone) plus metformin in uncontrolled T2DM	3.8	8.0	37.0	48.8
3.6 Combination of gliclazide/gliclazide-MR and metformin show better glycemic effectiveness than TZD (pioglitazone) plus metformin in uncontrolled T2DM	1.8	2.7	39.0	43.5
3.7 Combination of gliclazide/gliclazide-MR and metformin show similar glycemic effectiveness to SGLT2i plus metformin in uncontrolled T2DM	5.6	7.7	38.2	51.5
3.8 Combination of gliclazide/gliclazide-MR and metformin show better glycemic effectiveness than SGLT2i plus metformin in uncontrolled T2DM	1.2	1.8	29.8	32.8
3.9 Combination of gliclazide/gliclazide-MR and metformin show similar glycemic effectiveness to GLP-1RA plus metformin in uncontrolled T2DM	8.3	7.7	31.9	47.9
3.10 Combination of gliclazide/gliclazide-MR and metformin show similar glycemic effectiveness to basal insulin plus metformin in uncontrolled T2DM	10.9	7.7	25.7	44.4

Table 2 continued

	Disagreement (%)	Neutral (%)	Agreement (%)	Total (%)
3.11 Combination of gliclazide/gliclazide-MR and metformin show poor glycemic effectiveness vs. basal insulin plus metformin in uncontrolled T2DM	4.4	0.6	26.3	31.3
Statement 4: Gliclazide/gliclazide-MR in patients with diabetes and CVD or at high risk of CVD				
4.1 Gliclazide/gliclazide-MR is associated with lower risk of CV-related mortality as compared to old-generation SUs because of more specific action on pancreatic receptors	4.4	7.7	75.1	87.2
4.2 Gliclazide/gliclazide-MR is associated with lower risk of CV-related mortality as compared to GLP-1 receptor agonists	47.6	15.4	24.3	87.3
4.3 Gliclazide/gliclazide-MR is associated with lower blood pressure as compared to GLP-1 receptor agonists	34.6	13.9	21.6	70.1
4.4 Gliclazide/gliclazide-MR could improve endothelial function in diabetes, which may be related to its antioxidant properties	11.2	14.2	65.7	91.1
4.5 Gliclazide/gliclazide-MR is favorable among SUs in reducing left ventricular mass in patients with T2DM	12.4	18.6	57.1	88.1
Statement 5: Gliclazide/gliclazide-MR in patients with diabetes and CKD				
5.1 Gliclazide/gliclazide-MR is associated with a significantly lower risk for the development of sustained doubling of serum creatinine in patients with preserved renal function	6.8	11.8	69.8	88.4
5.2 Gliclazide can be safely use with proper monitoring at eGFR levels > 30 ml/min without titration to a reduced dose	5.6	2.1	46.7	54.4
5.3 Gliclazide can be safely use with proper monitoring at eGFR levels < 30 ml/min with titration to a reduced dose	4.7	5.3	49.7	59.7
5.4 Gliclazide/gliclazide-MR improves glycemic control and prevents diabetic nephropathy in patients with T2DM	8.6	14.2	69.2	92.0
5.5 Gliclazide/gliclazide-MR could improve diabetic nephropathy, which may be related to its antioxidant properties	18.6	20.4	52.1	91.1
5.6 Gliclazide/gliclazide-MR has less risk for prolonged and severe hypoglycemia owing to metabolism to inactive metabolites in patients with CKD	5.9	3.8	79.6	89.3
Statement 6: Safety and tolerability of gliclazide/gliclazide-MR				
6.1 Gliclazide-MR once daily will be more effective and a well-tolerable approach vs. gliclazide twice daily in patients with T2DM	16.0	7.7	68.6	92.3
6.2 Gliclazide-MR once daily is more effective in improving the patients' compliance than twice daily SUs in T2DM	6.2	3.5	81.4	91.1

Table 2 continued

	Disagreement (%)	Neutral (%)	Agreement (%)	Total (%)
6.3 Gliclazide causes weight gain of up to 0.5 kg in patients with T2DM with BMI < 25 kg/m^2 in 3–12 months of therapy	9.7	8.9	45.0	63.6
6.4 Gliclazide/gliclazide-MR may promote weight loss in patients within the higher BMI range (≥ 25 kg/m^2) in 3–12 months of therapy	41.1	21.6	27.2	89.9
6.5 Risk of weight gain is equivalent for gliclazide/gliclazide-MR and GLP-1RAs	15.7	6.8	18.3	40.8
6.6 Risk of weight gain is more with gliclazide/gliclazide-MR compared to GLP-1RAs	1.8	1.2	33.1	36.1
6.7 Risk of weight gain is equivalent for gliclazide/gliclazide-MR and DPP4i	9.2	7.7	34.3	51.2
6.8 Risk of weight gain is equivalent for gliclazide/gliclazide-MR and SGLT2i	14.2	4.4	11.8	30.4
6.9 Risk of weight gain is more with gliclazide/gliclazide-MR than SGLT2i	1.8	1.5	35.2	38.5
6.10 Risk of hypoglycemia is low with gliclazide/gliclazide-MR vs. older SUs	2.0	1.8	79.3	83.1
6.11 Risk of hypoglycemia is low with gliclazide/gliclazide-MR vs. other newer antidiabetic agents	10.9	3.0	32.5	46.4
6.12 Risk of hypoglycemia is more with gliclazide/gliclazide-MR than other newer antidiabetic agents	1.5	0.3	28.4	30.2
Statement 7: Dosing of the gliclazide/gliclazide-MR				
7.1 The usual starting dose of gliclazide-MR is 30–60 mg administered once daily with the morning/evening main meal	0.9	2.1	85.2	88.2
7.2 Consider starting with the higher (60 mg) dose when the A1c target is more than 0.5% from the prevailing A1c level, or if the patient has symptomatic hyperglycemia	7.1	4.1	76.0	87.2
7.3 The dose can be escalated by 30–60 mg every 1–4 weeks, guided by fasting glucose levels	4.4	9.2	73.6	87.2
Statement 8: Gliclazide/gliclazide-MR in special populations				
8.1 Use of gliclazide/gliclazide-MR appears to be safe in older patients with T2DM	5.6	4.1	68.1	77.8

A1c glycated hemoglobin A1c, *AGI* alpha-glucosidase inhibitor, *BMI* body mass index, *DPP4* dipeptidyl peptidase 4, *DPP4i* dipeptidyl peptidase 4 inhibitor, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *GLP-1* glucagon-like peptide 1,*SGLT2i* sodium/glucose cotransporter 2 inhibitor, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinedione

Opinions from experts on gliclazide use as first-line agent in drug-naïve patients with T2DM intolerant or contraindicated to metformin

Gliclazide/gliclazide-MR and insulin dual therapy can be used in patients with A1c levels of > 9.0% (63.0%)

Gliclazide/gliclazide-MR and DPP4 inhibitors dual therapy can be used in patients with A1c levels of 7.5–8.0% (51.2%)

Decision to Use Gliclazide/Gliclazide-MR as Second-Line Treatment Option for T2DM

Several meta-analyses and randomized controlled trials have demonstrated the addition of SUs to metformin providing optimal glycemic control with acceptable safety [19, 20]. With the use of gliclazide-MR as a second-line antidiabetic agent, Schernthaner et al. demonstrated a significant reduction of 1.0% in A1c from 8.4% to 7.4% in patients with T2DM uncontrolled by metformin [21]. Australian and WHO guidelines (global resource-limited setting) recommend gliclazide as one of the preferred options for second-line therapy if hypoglycemia is a concern, while guidelines from the Canada and India specify gliclazide as the agent of choice for second-line therapy [6, 22–24]. In contrast, the 2018 consensus report from ADA and the European Association for the Study of Diabetes (EASD) recommends SU as second-line agents if the cost is a compelling issue. Indian consensus by Kalra et al. has also recommended SUs over glucagon-like peptide 1 (GLP-1) receptor agonists owing to similar glycemic efficacy and acceptable safety at a lower cost [19]. However, several studies have reported weight gain in patients on metformin and SUs and weight loss in patients on metformin and GLP-1 receptor agonists [25–28]. In 2016, a systematic review and network meta-analysis found a non-significant reduction in the incidence of hypoglycemia among patients with T2DM on GLP-1 receptor agonists compared to SUs [29]. It also recommends the addition of SU to metformin rather than metformin up-titration beyond half-maximal dose for better glycemic control [19]. HARMONY-3, a 104-week study, comparing metformin (more than 1500 mg daily) versus metformin (1500 mg or less daily) plus glimepiride also favored the combination therapy over metformin monotherapy with a between-group difference in A1c of 0.63% [30]. Several clinical studies have observed a sustained A1c reduction with gliclazide-based therapy. The action in diabetes and vascular disease: Preterax and Diamicron MR controlled evaluation (ADVANCE) study comparing intensive gliclazide-MR-based therapy with standard therapy reported gradually reduction in A1c levels to 6.5% and then maintained them for a median of 5 years [31]. Another study found that patients with diabetes taking gliclazide can avoid escalation to insulin treatment for a longer period (14.5 years) than those taking glibenclamide (mean of 8 years) [32]. However, patients with diabetes who are inadequately controlled with oral antidiabetic drugs can benefit from the addition of once-daily insulin glargine to the gliclazide-MR regimen. In 2015, Zhou et al. demonstrated that once-daily insulin glargine plus gliclazide-MR also decrease A1c more effectively than the twice-daily premixed insulin regimen [33].

Opinions from experts on gliclazide use as second-line agent in patients with T2DM

Combination of gliclazide/gliclazide-MR and metformin is always associated with greater reduction in A1c than metformin monotherapy (92.0%)

Combination of gliclazide/gliclazide-MR and metformin is always associated with sustained reduction in A1c (over at least 2 years) vs. metformin monotherapy (84.9%)

Gliclazide or gliclazide-MR preferred over GLP-1 receptor agonist owing to low cost (73.4%)

Table b continued

Combination of gliclazide/gliclazide-MR and basal insulin is effective vs. basal insulin alone for patients with T2DM having reduced glycemic response with SUs (70.4%)
Early use of metformin plus gliclazide/gliclazide-MR combination is preferred over up-titration of metformin beyond half-maximal dose (1.0 g) during the initial treatment duration of 3 months for effective management of T2DM (55.0%)
Gliclazide or gliclazide-MR can be used as second-line treatment for patients with T2DM (add-on to metformin) if A1c level remains > 6.5% after 3 months of therapy (52.9%)
Expert opinion on switch to gliclazide/gliclazide-MR-based combination therapy from other combination therapies
Combination of gliclazide or gliclazide MR and metformin shows better glycemic effectiveness than AGI plus metformin in uncontrolled T2DM (53.8%)

Decision to Switch to Gliclazide/Gliclazide-MR-Based Combination Therapy from Other Combination Therapies in Uncontrolled Diabetes

Rational treatment decisions regarding second-line therapy for T2DM require a comprehensive assessment of the relative merits and disadvantages of the available therapeutic options. Several systematic reviews and meta-analyses have found that the second-line agents are similar in terms of A1c-lowering efficacy but differ concerning the attainment of an A1c goal of less than 7% [34, 35]. In 2018, Colagiuri et al. found that the percentage of patients with diabetes achieving an A1c goal was highest with the SUs (48%), followed by DPP4 inhibitors and glinides (39% for each), TZDs (33%), and AGIs (26%) [9]. Multiple studies investigating the SUs have shown adequate glycemic control with gliclazide regardless of baseline A1c level [36, 37]. A meta-analysis of 12 randomized studies (10,982 patients with T2DM) comparing DPP4 inhibitors with SUs also favored SUs regarding A1c reduction (weighted mean difference 0.105, 95% CI 0.103–0.107) [38]. However, two trials comparing SUs and sodium/glucose cotransporter 2 (SGLT2) inhibitors (added to metformin as dual therapy) reported that the A1c reduction was significantly higher with SGLT2 inhibitors compared with SUs [39, 40].

Efficacy of Gliclazide/Gliclazide-MR in Patients with Diabetes and CVD

CVDs are the leading cause of death among patients with diabetes, though risk was low in those taking pancreatic β-cell-specific SUs like gliclazide and glimepiride [41]. However, the EASD/ADA and ESC/EASD consensus guidelines reserve SUs for fifth-line therapy after newer agents (SGLT2i and GLP-1RA) on the basis of the evidence which suggests an increased risk of CVD with SUs compared with other newer agents [42–45]. In 2004, Katakami et al. showed that gliclazide significantly ($P < 0.05$) and independently reduced the progression of carotid artery intima-media thickness (atherosclerosis) as a result of its antioxidant properties [46]. The ADVANCE study also found that the intensive gliclazide-MR-based glucose control strategy reduced cardiovascular death by 12% ($P = 0.12$) [31]. However, the STENO-2 study reported about a 50% reduction in CVD risk with gliclazide-based intensive therapy after the mean follow-up of 7.8 years [47]. At 13.3 years of follow-up, a significantly lower risk of death from CV causes (HR 0.43, 95% CI 0.19–0.94; $P = 0.04$) and CV events (HR 0.41, 95% CI 0.25–0.67; $P < 0.001$) was observed [48]. Recent data from a 21.2-year follow-up of the STENO-2 study reported an increase of a median of 7.9 years in the patient's lifespan attributed to the intensified multifactorial approach. This life gain was matched by the time free of incident ischemic heart disease of 8.1 years [49].

Expert opinion on gliclazide/gliclazide-MR use in patients with diabetes and CVD

Gliclazide/gliclazide-MR is associated with lower risk of CV-related mortality as compared to old-generation SUs because of more specific action on pancreatic receptors (75.1%)

Gliclazide/gliclazide-MR could improve endothelial function in diabetes, which may be related to its antioxidant properties (65.7%)

Gliclazide/gliclazide-MR is favorable among SUs for reducing the left ventricular mass in patients with T2DM (57.1%)

Efficacy of Gliclazide/Gliclazide-MR in Patients with Diabetes and CKD

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline 2020 recommends lifestyle therapy, first-line treatment with metformin and an SGLT2i, and additional drug therapy including SUs as needed for glycemic management in patients with T2D and CKD [50]. The antihyperglycemic agents should be selected and dosed according to eGFR [51]. In patients with renal diseases, the recommendation is to limit the use or avoid SUs (long-acting or cleared by the kidney) at low eGFR as inadequate clearance of SUs or its active metabolite may increase the risk for symptomatic and severe hypoglycemia [50, 52, 53]. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and CKD recommends no dose adjustment for gliclazide in patients with stage 3–5 CKD, thus alleviating issues regarding dose adjustment [53]. Also, modern SUs like gliclazide and glipizide are not contraindicated by the joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology in patients with renal dysfunction, since these SUs are metabolized by the liver and excreted in the urine as inactive metabolites. However, the position statement recommends dose adjustment and caution with these agents [52]. The ADVANCE study has provided data on gliclazide throughout the clinical course of renal disease. Compared with standard control, intensive glucose-control strategy involving gliclazide-MR in the ADVANCE trial significantly reduced renal events including new-onset microalbuminuria (HR 0.91, 95% CI 0.85–0.98; $P = 0.02$), macroalbuminuria (2.9% vs. 4.1% with standard control; HR 0.70, 95% CI 0.57–0.85; $P < 0.001$), new or worsening nephropathy (HR 0.79, 95% CI 0.66–0.93; $P = 0.006$), and need for renal replacement therapy or death from renal causes (0.4% vs. 0.6%; HR 0.64, 95% CI 0.38–1.08; $P = 0.09$) [54]. In 2015, Lee et al. also revealed a lower risk of sustained doubling of serum creatinine with gliclazide compared with glimepiride in patients with good controlled glycemia (A1c less than 7%, HR 0.35, 95% CI 0.14–0.86), preserved renal function (GFR at least 60 mL/min/1.73 m^2, HR 0.21, 95% CI 0.04–0.99), and older age (62 years or older, HR 0.52, 95% CI 0.27–0.99), suggesting that gliclazide may have a protective role against renal disease progression [55]. This unique clinical benefit of gliclazide-MR in renal protection may be explained in part by its antioxidant properties.

Expert opinion on gliclazide/gliclazide-MR use in patients with diabetes and CKD

Gliclazide/gliclazide-MR has a lower risk for prolonged and severe hypoglycemia owing to its metabolism to inactive metabolites in patients with CKD (79.6%)

Gliclazide/gliclazide-MR is associated with a significantly lower risk for the development of sustained doubling of serum creatinine in patients with preserved renal function (69.8%)

Gliclazide/gliclazide-MR is the preferred treatment option to improve glycemic control and prevent diabetic nephropathy (69.2%)

Gliclazide/gliclazide-MR could improve diabetic nephropathy, which may be related to its antioxidant properties (52.1%)

Safety and Tolerability of Gliclazide/Gliclazide-MR

Once-daily dosing of gliclazide-MR has been associated with higher compliance rate (odds ratio [OR] 3.50, 95% CI 1.73, 7.08; $P < 0.001$) and adherence rate (OR 3.07, 95% CI 1.80, 5.23; $P < 0.001$) compared with more than once-daily dosing [56]. Gliclazide-MR also has a lower risk of hypoglycemia compared to other SUs as it gets metabolized into inactive metabolites and a gradual increase in drug concentrations [9]. This finding was supported by a meta-analysis which found a significantly lower risk of hypoglycemia with gliclazide compared with other SUs (risk ratio [RR] 0.47, 95% CI 0.77–0.70; $P = 0.004$) [57]. However, a meta-analysis comparing DPP4 inhibitors with SUs found a lower risk of hypoglycemia with DPP4 inhibitors (OR 0.13, 95% CI 0.11–0.16) [38]. Similarly, another meta-analysis (13 studies, $n = 5175$) found a lower risk for hypoglycemia with SGLT2 inhibitors when compared with SUs [58].

When considered as a class, SU monotherapy has been reported to cause a weight gain of 1.5–2.5 kg [59]. In the ADVANCE study, there was a gain of 0.1 kg weight and frequent hypoglycemia (12 per 1000 patient-years) in the intensive gliclazide MR-based glucose control group compared to 0.8 kg weight reduction and nine episodes of hypoglycemia per 1000 patient-years in the standard control group over the 5 years of follow-up. However, a mean weight loss of 0.5 kg was observed in people with obesity (BMI 30 kg/m^2 or higher) when analyzed by baseline BMI subgroup [60]. Data from thiazolidinediones or sulfonylureas cardiovascular accidents intervention trial (TOSCA.IT) showed a moderate weight gain (less than 2 kg, on average) in both pioglitazone and SUs groups while the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial showed no increase in the weight of patients allocated to dual therapy with metformin and a SU [61, 62].

Expert opinion on safety and tolerability of gliclazide/gliclazide-MR

Gliclazide-MR once-daily approach also improves compliance (81.4%)

Risk of hypoglycemia is also low with gliclazide vs. older SUs (79.3%)

Gliclazide-MR once daily is a more effective and well-tolerable approach than gliclazide twice daily in patients with T2DM (68.6%)

Dosing of Gliclazide-MR

The dose of gliclazide-MR may vary from 30 to 120 mg once daily and should be adjusted according to clinical response. The recommended starting dose for gliclazide-MR is 30 mg daily. If blood glucose is not adequately controlled, the dose may be increased to 60, 90, or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not been reduced after 2 weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment. The maximum recommended daily dose is 120 mg. In the observational study to analyze titration of Diamicron MR 60 mg (EASYDia) study, a step-by-step intensification of the gliclazide-MR formulation (up to 120 mg once daily) helped the patients with diabetes and different baseline target values to achieve glycemic control as the difference between those taking gliclazide-MR 30 mg and gliclazide-MR 120 mg at month 6 was 1.1 mmol/L for fasting plasma glucose (FPG) [17]. The Xrise study investigating the once-daily breakable gliclazide extended-release (XR) 60 mg in patients with T2D ($n = 679$), uncontrolled with diet alone or metformin monotherapy, reported effective glycemic control with a low frequency of hypoglycemia. At month 4, FPG was reduced by 66.0 (61.1–70.9, $P < 0.01$) mg/dl with one tablet, by 80.1 (71.2–88.5, $P < 0.01$) mg/dl with

1.5 tablets, and by 106.5 (93.4–119.5, $P < 0.01$) mg/dl with two tablets from baseline in patients with T2DM [63].

Expert opinion on dosing of gliclazide-MR
The usual starting dose for gliclazide-MR is 30–60 mg administered once daily with the morning/evening main meal (85.2%)
Initiating gliclazide/gliclazide-MR with the higher dose when the A1c target is more than 0.5% from the prevailing A1c level increases the likelihood of achieving A1c goals (76.0%)
The dose can be escalated by 30 to 60 mg every 1–4 weeks, guided by fasting glucose levels (73.6%)

Gliclazide/Gliclazide-MR in Special Populations

Careful selection of antidiabetic agents paying particular attention to drug safety and the risk of hypoglycemia is important in optimizing diabetic therapy for older people with T2DM. In 1994, Tessier et al. compared glibenclamide with gliclazide for the frequency of hypoglycemic events and glycemic control in older people (more than 71 years of age) with T2DM. They found comparable glycemic control (A1c glibenclamide $7.4 \pm 0.2\%$ vs. gliclazide $7.9 \pm 0.5\%$; P = not significant)] at 6 months with both drugs, but the incidence of hypoglycemic episodes was significantly greater with glibenclamide when compared with gliclazide [64]. A subgroup analysis comparing gliclazide-MR versus glimepiride in patients with diabetes and more than 75 years of age found that most hypoglycemic episodes occurred at the lowest treatment doses (15 on 30–60 mg gliclazide-MR out of 22 episodes, and 48 on glimepiride 1–2 mg out of 56 episodes) [21].

Expert opinion on gliclazide/gliclazide-MR use in special populations
Gliclazide is a safe option for older patients with T2DM (68.1%)

Limitation of the Survey

Limitation of this Delphi survey is the single round design. Another shortcoming includes a lower response rate for some statements in this survey, though face-to-face contact with participants has been found useful in increasing the response rate. Consideration must be given to the fact that individual time constraints and lack of familiarity with the Delphi technique may have prevented some participants from being able to make responses on time. Nonetheless, the quality of the responses provided made clear that those who did take part were firmly committed to offering us detailed and extremely thoughtful answers to our statements. The findings may offer an overly optimistic picture. This needs to be borne in mind when interpreting the findings.

CONCLUSION

When deciding on a treatment strategy for diabetes it is essential to consider both patient- and drug-specific characteristics. The collaborative Delphi methodology provided expert consensus-based opinion which could help to justify the role of gliclazide in different clinical situations associated with diabetes. Although gliclazide has the risk of mild hypoglycemia, and small weight gain, it is preferred in patients with T2DM because of its sustained glycemic efficacy maintained over the long term, unique end stage kidney disease prevention, and CV safety at lower cost.

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Compliance with Ethics Guidelines. This study is based on a clinical practice questionnaire that does not involve the participation of human subjects nor patient data management and does not aim to modify the current clinical practice of participants. Consequently, as per ethical approval procedures in India, the questionnaires compiled in this study did not require ethical approval. Consent for publication of survey results was granted from all the experts participating in the program and undertaking the survey.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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