



REVIEW

# Role of Gliclazide MR in the Management of Type 2 Diabetes: Report of a Symposium on Real-World Evidence and New Perspectives

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## ABSTRACT

In patients with type 2 diabetes mellitus (T2DM) who require additional glucose-lowering on top of first-line metformin monotherapy, sulfonylureas are the most common choice for second-line therapy followed by dipeptidyl peptidase inhibitors (DPP-4i). This article summarises presentations at a symposium entitled “Real-World Evidence and New Perspectives with Gliclazide MR” held at the International

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Diabetes Federation Congress in Busan, South Korea on 4 December 2019. Although guideline recommendations vary between countries, the guidelines with the highest quality ratings include sulfonylureas as one of the preferred choices as second-line therapy for T2DM. Data from randomised controlled trials (RCTs) have consistently demonstrated that sulfonylureas are effective glucose-lowering agents and that the risk of severe hypoglycaemia with these agents is low. In addition, both RCTs and real-world observational studies have shown no increased risk of mortality or cardiovascular disease with the use of newer-generation sulfonylureas compared with other classes of glucose-lowering treatments. However, differences between sulfonylureas do exist, with gliclazide being associated with a significantly lower risk of mortality or cardiovascular mortality compared with glibenclamide, as well as the lowest incidence of severe hypoglycaemia compared with other agents in this class. Recent real-world studies into the effectiveness and safety of gliclazide appear to confirm these findings, and publication of new data from these studies in patients with T2DM in the UK, and in Muslim patients who are fasting during Ramadan, are awaited with interest. Another study being undertaken with gliclazide is a pan-India study in patients with maturity-onset diabetes of the young (MODY) subtypes 1, 3 and 12. Patients with these MODY subtypes respond particularly well to sulfonylurea treatment, and

sulfonylureas are the first-line agents of choice in these patients. These new and ongoing studies will add to the cumulative data on the efficacy and safety of certain sulfonylureas in patients with diabetes.

**Keywords:** Gliclazide MR; Guidelines; Maturity onset diabetes of the young; Ramadan; Sulfonylureas; Type 2 diabetes

### Key Summary Points

#### Why carry out this study?

Sulfonylureas are consistently the most common choice for second-line therapy in patients with type 2 diabetes mellitus (T2DM) who require additional glucose-lowering during metformin monotherapy.

In this article we describe presentations given at a symposium held at the International Diabetes Federation Congress in Busan, South Korea (December 2019) that examined the place of sulfonylureas generally, and gliclazide modified release (MR) specifically, in the current treatment paradigm for people with T2DM.

#### What was learned from the study?

Newer generation sulfonylureas, such as gliclazide MR, are effective, well-tolerated and accessible treatments for T2DM, and recommended in the early management of people with T2DM.

Among the available sulfonylureas, gliclazide is associated with the greatest beneficial impact on cardiovascular mortality, and the lowest incidence of severe hypoglycaemia.

## INTRODUCTION

Sulfonylureas have been used clinically to treat type 2 diabetes mellitus (T2DM) since the 1960s [1], and are still among the most commonly prescribed oral diabetic treatments [2]. Data on prescription patterns globally show that sulfonylureas are consistently 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 regularly updated to include emerging treatments and evolving evidence, especially from cardiovascular outcomes trials (CVOTs). Yet, there are significant differences between guidelines in the recommendations related to sulfonylureas [4–11].

In this article, we describe presentations at a symposium held at the International Diabetes Federation Congress in Busan, South Korea on 4 December 2019. These presentations examined the place of sulfonylureas generally, and gliclazide modified release (MR) specifically, in the current treatment paradigm for people with T2DM. Guideline recommendations for the use of sulfonylureas are described and the evidence supporting these recommendations is critically evaluated, and recent real-world evidence is reviewed on the efficacy and safety of gliclazide MR, including in special populations of patients, such as T2DM patients who undertake daytime fasting during Ramadan and patients with maturity onset diabetes in the young (MODY).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

## PLACE OF SULFONYLUREAS IN CURRENT TREATMENT 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) [4–6, 8, 10–12]. In patients with established atherosclerotic cardiovascular

**Table 1** Summary of consensus report recommendations on the use of sulfonylureas and gliclazide MR in patients without established atherosclerotic cardiovascular disease

Diabetes guidelines	Second-line treatment recommendation in patients with suboptimal glucose control on metformin	Guideline information specific to gliclazide MR
UK (NICE/SIGN) 2015 <sup>a</sup> [11]	Add DPP-4i, pioglitazone or SU GLP-1RAs not recommended	–
South Asian Federation of Endocrine Societies 2015 [10]	Add SU as second-line agents of choice	Gliclazide MR or glimepiride are preferred over conventional SU
Australia (RACGP and Diabetes Australia) 2016–2018 [5]	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 [4]	Preferred add-on therapies are SU (not glibenclamide/glyburide), DPP-4i or SGLT-2i	–
Global resource-limited settings (WHO) 2018 [23]	Add an SU	Gliclazide is preferred SU if hypoglycaemia is a concern
Canada (Diabetes Canada) 2018 [6]	Add DPP-4i, GLP-1RA, or SGLT-2i	If SU is added to metformin, gliclazide is the first choice
USA/Europe (ADA/EASD) 2018 [8]	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 <sup>b</sup> ) if there is a compelling need to minimise hypoglycaemia or weight gain	Gliclazide not licensed in the US for T2DM
Europe (ESC/EASD) 2019 [12]	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 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

<sup>a</sup> Updated in 2019

<sup>b</sup> TZDs not recommended when there is a compelling need to minimise weight gain

disease, recent guidelines consistently recommend second-line treatment with a sodium-glucose cotransporter 2 inhibitor (SGLT-2i) or a glucagon-like peptide-1 receptor agonist (GLP-1RA) [6, 8, 12], based on data from the large-scale CVOTs showing that these agents reduced the risk of major adverse cardiovascular events (MACE) in patients with diabetes and cardiovascular disease (CVD) [13–22].

For patients without established CVD, the recommendations for add-on glucose-lowering therapy differ between guidelines. Australian, Indian and World Health Organization guidelines specify sulfonylureas as the agents of choice for second-line therapy [5, 10, 23], while guidelines from the National Institute for Health and Care Excellence (NICE) in the UK and the International Diabetes Federation (IDF) include sulfonylureas as one of the preferred options, along with a DPP-4i and either pioglitazone (UK) or a SGLT-2i (IDF) [4, 11]. In contrast, the consensus report from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommends sulfonylureas as second-line therapy only if cost is a compelling issue [8]. These consensus recommendations, as well as joint guidelines from the EASD and the European Society of Cardiology (ESC), place sulfonylureas as a fifth-line treatment after other classes of oral glucose-lowering drugs have been tried [8, 12].

### Why the Differences Between Guidelines?

Some may speculate that the guidelines recommending sulfonylureas as the preferred second-line agents do so because of cost. Certainly, sulfonylureas have a low drug acquisition cost compared with other classes of glucose-lowering agents [24], but to consider that the recommendations are driven by cost alone ignores the well-established efficacy and safety profile of sulfonylureas. As a class, these agents differ in their pharmacokinetic characteristics (Table 2) [10, 25]. The recommendation for sulfonylureas in the Canadian guidelines is based on a thorough assessment of clinical benefits, quality of life, safety concerns, cost and resource use

undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) [26]. This 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 [26]. Another reason for the difference between consensus recommendations may be related to the way in which they are developed. Not all reports are developed using strict rigour in their collection and/or assessment of the evidence. In the ADA/EASD guidelines, for example, the authors themselves write: “...though evidence based, the recommendations presented herein are the opinions of the authors” [8]. Various bodies have developed standards for clinical practice guidelines, including the Institute of Medicine in the USA [27] and the Appraisal of Guidelines for Research and Evaluation (AGREE) consortium in Canada [28]. These standards focus on the process, sources, flexibility, validity, reliability and applicability of the recommendations [27], and have led to the development of the AGREE II instrument that can be used to rate the quality of clinical guidelines [28]. Using this instrument, the IDF ranked the recommendations from a variety of different bodies [4]: the highest ranked guidelines for diabetes were the NICE guidelines from the UK (97%), which recommend sulfonylureas as the first choice for add-on therapy. In contrast, the ADA guidelines and the American Association for Clinical Endocrinology (AACE) guidelines scored a total of 50 and 36%, respectively, with particularly low scores for scientific rigour (28% for ADA and 6% for AACE guidelines) [4]. This suggests that the reputation and popularity of the organisation developing the guidelines may not necessarily reflect the level of the evidence used to make the recommendations.

### Sulfonylureas and Cardiovascular Disease

The EASD/ADA and ESC/EASD consensus guidelines recommend second-line treatment with newer agents (SGLT-2i and GLP-1RA) based on the evidence from CVOTs [8, 12]. These guidelines reserve sulfonylureas for fifth-line therapy after newer agents have been tried,

**Table 2** Features of the different agents in the sulfonylurea drug class

Features of the agents	Agents in the sulfonylurea drug class <sup>a</sup>							
	Tolbutamide	Chlorpropamide	Glibenclamide (glyburide)	Glipizide (regular)	Gliclazide (regular)	Glimepiride	Glipizide GITS	Gliclazide MR
Generation	First	First	Second	Second	Second	Third	Third	Third
Duration of action category	Short	Long	Long	Intermediate	Intermediate	Long	Long	Long
Duration of action (h)	Short	≥ 24	16–24	12–24	10–24	24	> 24	> 24
Time to peak plasma level (h)	3–4	2–4	2–4	1–3	4–6	2–3	6–12	6–7
Excretion	100% renal	80–90% renal	50% renal	80% renal	80% renal	60% renal	80% renal, 10% faecal	< 60–70% renal, 10–20% faecal
Active metabolites	No	Yes	Yes	No	No	Yes	No	No
Use in patients with renal dysfunction	Avoid	Decrease dose by 50% if GFR 50–70 mL/min/1.73 m <sup>2</sup>	Avoid	No dose adjustment needed	No dose adjustment needed	Start at low dose	No dose adjustment needed	No dose adjustment needed
		Avoid if GFR < 50 mL/min/1.73 m <sup>2</sup>						

GITS Gastrointestinal therapeutic system, GFR glomerular filtration rate

<sup>a</sup> References: [10, 25]

and cite results from observational studies which suggest an increased risk of CVD with sulfonylureas compared with other classes of glucose-lowering drugs [29, 30].

However, the compelling benefit of SGLT-2i and GLP-1RAs has only been demonstrated in patients with established CVD—and not in patients with multiple risk factors for CVD [31]. Moreover, most T2DM patients seen in clinical practice (60–92%) would not meet the eligibility criteria for inclusion SGLT-2i or GLP-1RA CVOTs due to their disease characteristics/comorbid conditions [32–37], calling into question the generalisability of these studies to a wider clinical practice population.

The risk of CVD seen with sulfonylureas in some observational studies [38, 39] has not been demonstrated in randomised controlled trials (RCTs), including the TOSCA-IT, CAROLINA, ADVANCE and ADOPT studies [40–43]. TOSCA.IT and CAROLINA showed that a sulfonylurea was noninferior to pioglitazone and linagliptin, respectively, for preventing MACE [41, 42]. In the CAROLINA study, not only was the incidence of the composite endpoint of MACE similar in the sulfonylurea (glimepiride) and DPP-4i arms, but so was the incidence of each individual component of the composite endpoint (cardiovascular death, nonfatal myocardial infarction [MI], and nonfatal stroke) [41]. Importantly, data from a retrospective analysis of real-world outcomes suggest that sulfonylureas and DPP-4i do indeed have a similar impact on cardiovascular outcomes, as seen in the CAROLINA study [44].

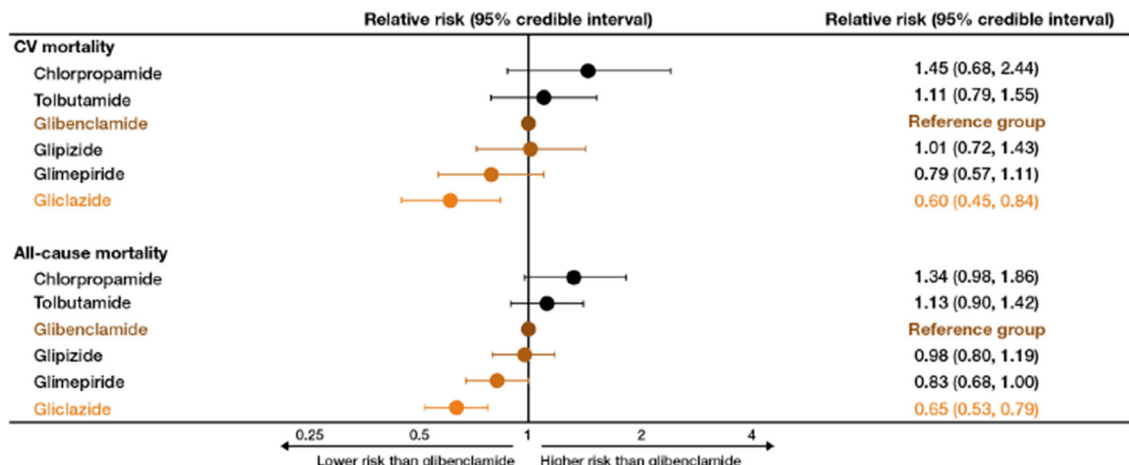
It is also worth noting that sulfonylureas were the major second-line class of glucose-lowering agents used in the large-scale trials that demonstrated the importance of intensive glucose-lowering for delaying the development of macrovascular events in patients with T2DM, such as the UK Prospective Diabetes Study (UKPDS) and ADVANCE [45, 46]. In ADVANCE, intensive glucose-lowering with a combination metformin + sulfonylurea-based regimen also reduced the risk of microvascular events, and the impact of intensive treatment of microvascular and macrovascular outcomes was similar in patients with different levels of baseline renal function [43].

Overall, the weight of the evidence indicates no increased risk of mortality or CVD with the use of sulfonylureas compared with other classes of glucose-lowering treatments [47]. Moreover, examination of the relationship between individual sulfonylureas and CVD outcomes revealed that the lowest risk appears to be associated with gliclazide [48]. A meta-analysis of sulfonylurea studies demonstrated that gliclazide was associated with a significantly lower risk of cardiovascular mortality (relative risk [RR] 0.60; 95% confidence intervals [CI] 0.45–0.84) and all-cause mortality (RR 0.65; 95% CI 0.53–0.79) compared with glibenclamide and others (Fig. 1) [48].

### Sulfonylureas and Severe Hypoglycaemia

Another concern sometimes expressed about the sulfonylureas is the risk of hypoglycaemia. Severe hypoglycaemia is associated with an increased risk of mortality [46, 49, 50], but no causal relationship between hypoglycaemia and mortality has been proven. A more likely explanation is that severe hypoglycaemia is a marker for comorbidity or illness severity. This is borne out by data from RCTs showing a difference in the incidence of severe hypoglycaemia between treatment arms, but no difference in the risk of CVD or mortality [41, 42, 51, 52].

For example, in the CAROLINA study, the risk of MACE was similar in the glimepiride and the linagliptin arms (hazard ratio [HR] 0.95; 95% CI 0.84–1.14;  $p < 0.001$  for non-inferiority), as was the risk of mortality (HR 0.94; 95% CI 0.78–1.06;  $p = 0.23$ ), but the rate of hypoglycaemia was significantly lower in the linagliptin than in the glimepiride arm (HR 0.23; 95% 0.21–0.26;  $p < 0.001$ ) [41]. If hypoglycaemia were causally linked with death, it would be expected that this would be reflected in the mortality outcomes of the CAROLINA study. Another notable element of the CAROLINA study was that it involved a high-risk population for hypoglycaemia, including 35% patients with established CVD, 37% at high cardiovascular risk, 19% aged  $\geq 70$  years and 18% with stage 3 chronic kidney disease [53].



**Fig. 1** Comparison of all-cause mortality between different sulfonylureas based on direct and indirect evidence [48]. Data are pooled and analysed by network meta-

analysis. Reference agent is glibenclamide. *CV* Cardiovascular. (Reprinted from Lancet Diabetes Endocrinol., [48] Copyright (2015), with permission from Elsevier)

In fact, the absolute risk of severe hypoglycaemia with the sulfonylureas in RCTs is low, particularly with the later-generation agents, such as gliclazide (Table 3) [41, 42, 54–56]. Gliclazide is available in a regular, intermediate-acting formulation and a long-acting MR formulation (Table 2). The MR formulation uses a hydrophilic polymer base to release gliclazide

progressively over 24 h, allowing once-daily dosing [57]. Based on the data from randomised trials, at least 232 patients would need to be treated with a sulfonylurea to cause one severe hypoglycaemic event (number needed to harm [NNH]), and the NNH for gliclazide MR specifically is 333 [41, 42, 54–56]. The low risk of symptomatic hypoglycaemia is supported by

**Table 3** Absolute risk of severe hypoglycaemia in randomised controlled trials with sulfonylureas

Randomised controlled trials	Duration (years)	Treatments	N	Rate of severe hypoglycaemia
GUIDE 2004 [56]	0.52	Gliclazide MR	405	0
		Glimepiride	440	0
ADVANCE 2008 [55]	5.0	Gliclazide MR-based intensive control	5571	2.7
		Standard control	5569	1.5
Foley et al. 2009 [54]	2.0	Gliclazide	546	0
		Vildagliptin	546	0
TOSCA.IT 2017 [42]	4.8	Sulfonylurea <sup>a</sup>	1493	1.61
		Pioglitazone	1535	0.06
CAROLINA 2019 [41]	6.3	Glimepiride	3010	2.2
		Linagliptin	3023	0.1

<sup>a</sup> Gliclazide (n = 745), glimepiride (n = 723) or glibenclamide (n = 24) in accordance with local practice

data from a prospective observational study of primary care T2DM patients in the UK [58]. This study showed a risk of hypoglycaemia (blood glucose < 3.0 mmol/L) of 0.12 per person-year with sulfonylureas, similar to the rate with incretin-based therapy (0.04 per person-year) and much lower than the rate with insulin (1.03 per person-year) [58].

Moreover, the risk of hypoglycaemia varies between sulfonylureas. A recent meta-analysis demonstrated that the relative risk of hypoglycaemia with gliclazide versus placebo (3.9) is more similar to the risk with metformin (2.0) than it is to the risk with other sulfonylureas such as glimepiride (8.9), glyburide (10.2) or glipizide (13.9) [59]. The risk of hypoglycaemia can be mitigated by avoiding sulfonylureas in high-risk patients, such as elderly or frail patients, those with advanced organ dysfunction or those with a previous history of severe hypoglycaemia.

### Sulfonylureas and Weight Gain

Another reason why some guidelines may recommend newer agents ahead of sulfonylureas is that SGLT-2i and GLP-1RA are associated with weight loss, while sulfonylureas and thiazolidinediones are associated with modest weight gains [59]. In clinical trials, the average weight loss was 1.5–2.4 kg with maximal doses of SGLT2i [59–63] and between 0.9 and 1.8 kg with maximal doses of GLP-1RA [59]. For many patients, weight loss is a desirable side effect of treatment, but there are no data to indicate that the modest loss achieved with SGLT-2i or GLP-1RA contributes to improvements in glycaemic response or clinically measurable outcomes. There was no weight gain with gliclazide MR in the ADVANCE study over a 5-year period.

## ROLE OF SULFONYLUREAS IN A REAL-WORLD POPULATION

As described earlier, the effectiveness and safety of sulfonylureas has been demonstrated in some real-world studies, including data showing that the sulfonylureas and DPP-4i have similar

effects on outcomes [44]. However, data from observational studies performed in the USA using glimepiride may not be applicable in the UK where gliclazide is the most commonly prescribed sulfonylurea.

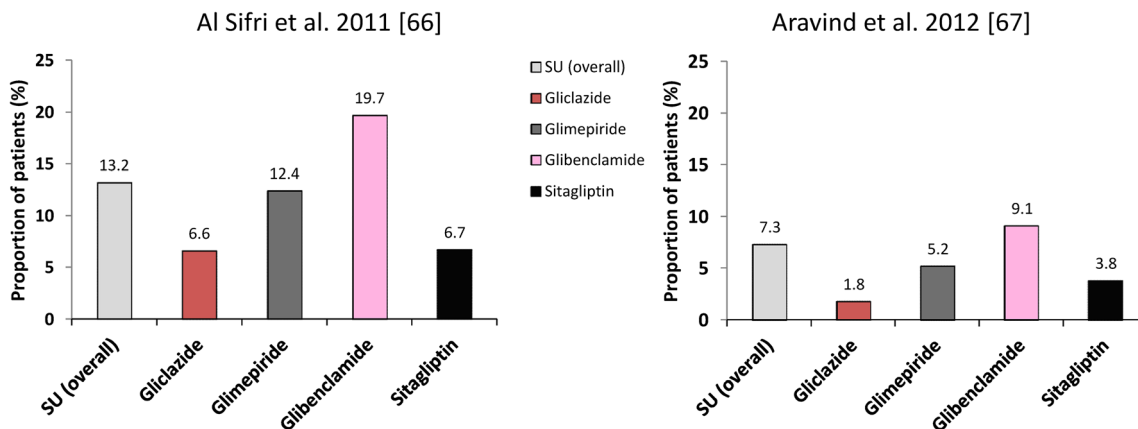
## USE OF SULFONYLUREAS DURING RAMADAN

Approximately 1.8 billion people in the world are Muslim. For many of these individuals, fasting during the holy month of Ramadan is an important tenet of their faith, but the requirements of Ramadan (no food or drink during daylight hours) can pose a health risk for Muslim patients with diabetes [64]. Because the risk of hypoglycaemia is high during fasting, and many Muslim individuals are reluctant to break their fast if they develop hypoglycaemia, optimal care to reduce risks is important. Physicians can minimise the risk by careful treatment choice, risk stratification and patient education, and by encouraging frequent or continuous glucose monitoring during Ramadan [64].

Patients receiving treatment for T2DM show a higher incidence of hypoglycaemia during Ramadan, and this is true for treatment regimens with or without sulfonylureas [65]. Randomised studies have shown that the risk of symptomatic hypoglycaemia during Ramadan is low in patients receiving stable doses of a sulfonylurea for at least 3 months, and is lower with gliclazide than with glimepiride or glibenclamide (Fig. 2) [66, 67]. In the randomised STEADFAST study, combination therapy with gliclazide + metformin was associated with a similar rate of hypoglycaemia during Ramadan as combination therapy with vildagliptin + metformin [68]. However, these studies were conducted with short-acting gliclazide, so the effect of a newer formulation of gliclazide, gliclazide MR, on hypoglycaemia during Ramadan is unknown. The DIA-RAMADAN study was the first international real-world study to investigate the effects of gliclazide MR [69].

The DIA-RAMADAN study was conducted at 64 centres in nine countries (Bangladesh, Egypt, India, Indonesia, Kuwait, Malaysia, Pakistan,





**Fig. 2** The incidence of symptomatic hypoglycaemia during Ramadan in patients receiving a SU or sitagliptin in randomised controlled trials. (Data from Al Shifri et al. [66] and Aravind et al [67])

Saudi Arabia and the United Arab Emirates) and enrolled 1214 patients with T2DM who had been receiving gliclazide MR 60 mg/day for at least 90 days before enrolment and who planned to fast during Ramadan. Patients completed diaries during the 6–8 weeks before Ramadan, the 4.5 weeks of Ramadan and then for 4–6 weeks afterwards. Only patients with glycated haemoglobin (HbA1c) < 9% were to be included in the study; mean HbA1c was 7.5% [69]. Approximately 59% of patients were receiving gliclazide MR in combination with at least one other oral glucose-lowering drug (most commonly metformin or a DPP-4i), but 41% received gliclazide MR as monotherapy. The primary endpoint was the development of symptomatic hypoglycaemia (confirmed or unconfirmed), but patients were asked to check their blood glucose during a hypoglycaemic episode to confirm that the symptoms were caused by hypoglycaemia.

The average dose of gliclazide MR during the study was 74 mg; approximately two-thirds of patients (66%) took 60 mg, 7% took 90 mg and 22% took 120 mg. Patients fasted for an average of 15 h a day for 28.7 days. Only 62 patients (5%) broke their fast for more than 3 consecutive days, but this was mostly for non-medical reasons ( $n = 45$ ) or medical reasons other than hypoglycaemia ( $n = 15$ ); three patients broke their fast due to hypoglycaemia. While hypoglycaemia was more common during Ramadan than in the weeks before or after the fast, the

overall rate of symptomatic hypoglycaemia during Ramadan was low (2.2% compared with 0.2% before and 0.3% after Ramadan), as was the rate of confirmed hypoglycaemia (1.6% vs. 0.2% before and < 0.1% after Ramadan). Confirmed hypoglycaemia during Ramadan was much more common among patients who ate  $\leq 2$  meals per day compared with patients who ate > 2 meals per day during Ramadan. No severe hypoglycaemic events occurred [69].

Other outcomes supported the efficacy and safety of gliclazide MR during Ramadan: both HbA1c and bodyweight showed small but significant reductions, no drug-related adverse events occurred and no patient required a dose modification [69]. The DIA-RAMADAN study suggests that gliclazide MR is a safe and effective treatment option for T2DM patients who wish to fast during Ramadan.

## USE OF SULFONYLUREAS IN PATIENTS WITH MODY

Maturity-onset diabetes of the young (MODY) was first described in the 1960s and 1970s as a form of diabetes that developed in young people (generally at an age < 25 years) but which was distinct from type 1 diabetes because there was clear evidence of genetic inheritance and patients did not require insulin [70, 71]. It was subsequently determined that MODY is a form of monogenic diabetes with autosomal

dominant inheritance in which the major phenotypic trait is impaired insulin secretion [70, 71]. More than one subtype of MODY exists, depending on the affected gene, but the most common forms are MODY2 and MODY3, which together account for about 70% of cases, followed by MODY1, MODY5 and MODY10 (Table 4) [70, 72, 73].

It is important for clinicians to be alert to the possibility of MODY in a young person with diabetes. The principal pathogenic defect in MODY is impaired insulin secretion, so (unlike patients with type 1 diabetes) 99% of patients with MODY will not have islet cell autoantibodies, and most will show endogenous insulin secretion for some years after diagnosis [73]. As a result, these patients do not require insulin therapy, and those with MODY1 or MODY3 will respond very well to sulfonylureas, which are the agents of choice in these forms of MODY

[73]. A summary of the clinical features of MODY that can assist with differential diagnosis is shown in Table 5. If MODY is suspected, genetic testing should be undertaken to confirm the diagnosis and to help guide treatment decisions [72, 74].

MODY caused by *HFN* mutations (MODY1, MODY3 and MODY5) responds extremely well to sulfonylureas [73]. These agents should be used as first-line treatment before metformin in patients with MODY because these patients do not have insulin resistance; metformin, as an insulin sensitizer, is better suited for patients with T2DM. This was clearly demonstrated in a crossover trial in which patients with T2DM or MODY3 were randomised to metformin or gliclazide for 6 weeks, and then crossed over to the alternative treatment following a 1-week wash-out period between treatments [75]. Gliclazide was significantly more effective in lowering

**Table 4** Genetics and clinical features of selected subtypes of maturity onset diabetes of the young

Subtype <sup>a</sup>	Affected gene	Locus	Clinical features
MODY1	<i>HNF4A</i>	20q12-q13.1	Represents approx. 10% of MODY cases Near-normal FPG but abnormal PPG, although FPG worsens over time Responds well to sulfonylurea agents
MODY2	<i>GCK</i>	7p15-p13	Represents approx. 32% of MODY cases Mild fasting hyperglycaemia often detected incidentally < 50% of carriers have overt diabetes mellitus and microvascular complications are rare
MODY3	<i>HNF1A</i>	12q24.2	Most common form (approx. 52% of cases) Presents clinically like MODY1
MODY5	<i>HNF1B</i>	17cen-q21.3	Represents approx. 6% of MODY cases Overt diabetes mellitus in association with renal and genitourinary abnormalities
MODY10	<i>INS</i>	11p15.5	Rare (< 1% of cases) Usually associated with neonatal diabetes
MODY12	<i>ABCC8</i>	11p15.1	Rare (< 1% of cases) Usually associated with neonatal diabetes

FPG Fasting plasma glucose, MODY maturity onset diabetes of the young, PPG postprandial plasma glucose

<sup>a</sup> References: [70, 73, 79]

**Table 5** Features of maturity onset diabetes of the young that can assist with differential diagnosis

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Young age at onset (usually but not exclusively < 25 years)
Usually non-obese, normotensive and without elevated lipid levels
Clear pattern of inheritance—diabetes present in at least three generations of family, and usually in parents and siblings
Autoantibodies to pancreatic islet cells almost always absent
Insulin reserve evident for some years after diagnosis
Glycosuria at lower than usual blood glucose levels (MODY1, 3 and 5)
Marked sensitivity for sulfonylureas (MODY1, 3 and 5)

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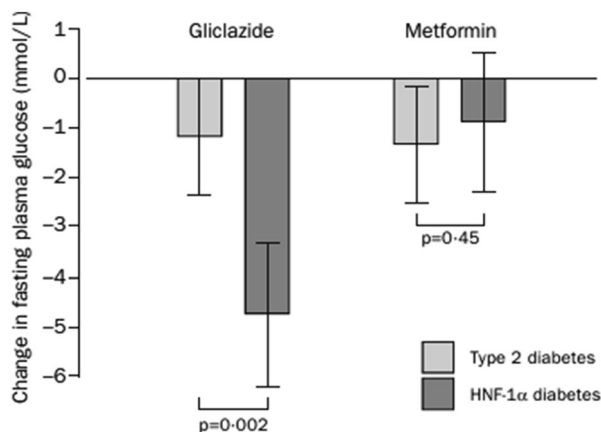
Reference: [73]

fasting plasma glucose in the patients with MODY3 than it was in the patients with T2DM, whereas metformin was slightly (but not significantly better) in the T2DM than the MODY3 group (Fig. 3) [75]. In addition, while gliclazide increased  $\beta$ -cell function by 55% in patients with T2DM, the increase was 310% in patients with MODY3 [75].

The profile of T2DM in South Asia, including India, differs from that in Western populations, with a propensity to develop insulin resistance at a younger age and lower body mass index,

and a high prevalence of several high-risk genetic polymorphisms [76, 77]. There is also evidence that the epidemiology of MODY differs in India compared with European populations [78]. Genomic data from South India show that, while MODY3 was the most common subtype (as it is elsewhere), the next most common was MODY12, which is associated with a mutation in *ABCC8*, which is rare in European populations [78]. Since MODY subtype can impact treatment choice, it is important to understand the prevalence of different subtypes in different populations, so a nationwide study of MODY in India is being undertaken.

This Pan-India MODY study is being conducted throughout India between November 2019 and October 2021. There are two parts to the study. Part 1 is a comprehensive genetic screening program for MODY to identify the prevalence of different subtypes, but there is also a substudy within part 1 aimed at investigating whether it is feasible to conduct genetic testing on saliva samples, since it is easier to collect saliva than blood, especially in children. Part 2 is a trial with gliclazide MR 60 mg in patients with MODY1, MODY3 or MODY12 to investigate the efficacy (primary objective) and safety (secondary objective) of this treatment. Results of this Pan-India MODY study will provide important information about the prevalence of MODY and the effect of treatment with gliclazide MR 60 mg in patients with MODY.



**Fig. 3** Change in fasting plasma glucose level after 6 weeks of treatment with gliclazide or metformin in patients with type 2 diabetes or maturity-onset diabetes of the young subtype 3 (MODY3; HNF-1 $\alpha$  diabetes) [75]. Vertical lines indicate 95% confidence intervals. (Reprinted from Lancet., [75] Copyright (2003), with permission from Elsevier)

## CONCLUSIONS

Sulfonylureas are effective, well-tolerated and inexpensive treatments for T2DM, and are recommended as add-on therapy in evidence-based international consensus reports. These agents are also the first-line treatment of choice in the majority of patients with MODY. Among the available sulfonylureas, gliclazide is associated with the greatest beneficial impact on cardiovascular mortality, and the lowest incidence of severe hypoglycaemia. It is hoped that the results from the DIA-RAMADAN study and other analyses will provide new data on gliclazide MR and other second-line therapies.

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