"Different diabetes treatment guidelines from several medical societies acknowledge sulfonylureas as part of the current therapeutic arsenal worldwide. Although a member of this drug class, the sulfonylurea gliclazide MR has significant benefits (particularly with regard to the side effect profile) that differentiate it from other sulfonylureas, and such differences between drugs that are available could be exploited with regard to individualization of the treatment for each diabetic patient."

Gliclazide MR as a standard of care in the management of type 2 diabetes

by A. Hohl, *Brazil*

Alexandre HOHL, MD, MSc, PhD
Federal University of
Santa Catarina (UFSC)
Florianópolis, BRAZIL

The treatment of type 2 diabetes mellitus (T2DM) has undergone rapid change in recent years. Drugs available for treatment have gone from few to many and include different therapeutic classes. Meanwhile, the growing body of scientific knowledge about the disease has led to changes in treatment paradigms. Follow-up care in T2DM cannot afford medical inertia (ie, resistance to change in therapy) and failed treatments. Recommended initial therapy for most T2DM patients involves lifestyle changes and the use of metformin. In cases where metformin alone does not control blood glucose, there are several other therapeutic agents available. The choice of drug should take into consideration costs, side effects, and long-term safety, as well as effects on diabetes complications. The most rational way to treat T2DM currently is therapy based on disease pathophysiology and the individualization of goals, taking into account age, disease duration, life expectancy, risk of hypoglycemia, psychosocial factors, and comorbidities. Gliclazide is a modern sulfonylurea, very useful in the pharmacological strategy used for blood glucose control. With a low risk of hypoglycemia, it is the only medication in its therapeutic class with a large cardiovascular outcome study (ADVANCE) guaranteeing its safety and demonstrating real microvascular benefits.

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Introduction

In recent years, the prevalence of diabetes mellitus (DM) has increased progressively and continues to do so, accompanying the sociodemographic, cultural, and behavioral changes of the population. In addition to aging, the population is becoming more and more sedentary and is consuming industrialized foods with high glucose and lipid content, thus increasing the rates of overweight, obesity, and metabolic syndrome. The International Diabetes Federation (IDF) calculates there are 425 million people with DM worldwide and estimates there will be about 629 million patients in 2045.[1]

The pathophysiological defects involved in type 2 DM (T2DM) are numerous and complex. Insulin resistance is an event that precedes and predicts the hyperglycemia characteristic of T2DM, persisting throughout the course of the disease, and is therefore a therapeutic target in the whole evolution process. The liver, muscles, and fat tissue are directly involved in the insulin resistance mechanism.[2] Insulin deficiency is the mechanism that promotes the increase in blood glucose levels; at diagnosis of diabetes, the patient has already lost more than 80% of β-cell function.[2]

Address for correspondence:
Dr Alexandre Hohl, Av. Osmar Cunha, 416 / 605 – Florianópolis / SC – Brazil
(email: alexandrehohl@endocrino.org.br)

www.medicographia.com

The presence of DM is an independent risk factor for the development of a wide spectrum of complications, both microvascular and macrovascular. The absolute risk of elderly patients with DM presenting a cardiovascular event is much higher than that of young adults, which indicates that age is also an important factor associated with chronic hyperglycemia. Diabetic elderly have a high rate of morbidity and mortality compared with nondiabetic individuals of the same age.[3,4]

At high cardiovascular risk, diabetic patients have an increase in functional disabilities, cognitive deficits, depression, and neoplasms and have to learn how to deal with polypharmacy at home.[2,4-6]

The chronic microvascular complications of diabetes (neuropathy, retinopathy, nephropathy) are heterogeneous, with a wide variety of underlying symptoms and mechanisms, neurophysiopathological impairment, evolutionary course, and risk factors involved. Of these, chronic exposure to hyperglycemia is the most commonly associated with development of complications and disease progression. This was shown both in type 1 DM (T1DM) and T2DM, according to the prospective data from the DCCT (Diabetes Control and Complications Trial) and the UKPDS (United Kingdom Prospective Diabetes Study), respectively.[7] In the last decade, the STENO-2 study (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) and the extension of the UKPDS revealed that the early control of hyperglycemia persists over time, characterizing a metabolic memory or legacy, with an impact on reducing the evolution of macrovascular and microvascular complications in diabetic patients.[8,9]

On the other hand, several studies with patients with longstanding DM (ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation[10]; ACCORD, Action to Control Cardiovascular Risk in Diabetes[11]; VADT, Veterans Affair Diabetes Trial[12]) evaluated the microvascular effect of intensive control.[8] Thus, different strategies and metabolic control goals have been proposed for the treatment of T2DM, taking into account the patient's age, life expectancy, risk of hypoglycemia, and duration of illness, among other clinical variables. Psychosocial factors, such as motivation and self-care ability, should also be taken into consideration when choosing a DM treatment.[13-19] This article reviews the place of sulfonylureas, particularly gliclazide, in the management of patients with T2DM.

Selected abbreviations and acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation
DCCT	Diabetes Control and Complications Trial
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase 4
IDF	International Diabetes Federation
MI	myocardial infarction
STENO-2	Intensified Multifactorial Intervention in Patients With Type 2 diabetes and Microalbuminuria
SUR	sulfonylurea receptor
T2DM	type 2 diabetes mellitus
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affair Diabetes Trial

Guidelines and recommendations

Drugs available in the therapeutic arsenal have increased in recent years; nevertheless, it is clearly necessary that physicians have a deep understanding of the disease pathophysiology in order to individualize therapy with the appropriate use of these medications, from the most recent to the most classic. In line with this, several diabetes treatment guidelines have been published in recent years in different countries. Common among all of them is the use of sulfonylurea as one of the important early strategies for glycemic control. In 2017, IDF launched the new T2DM treatment guideline, which indicates metformin as a first-line drug. If this medication is not tolerated because of possible gastrointestinal side effects, sulfonylureas, α-glucosidase inhibitors, or dipeptidyl peptidase 4 (DPP-4) inhibitors are alternatives for monotherapy use.[20]

Despite recent changes to the American Diabetes Association (ADA) guidelines recommending use of an agent with proven benefits on cardiovascular events and/or cardiovascular mortality second-line in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD, defined as coronary heart disease, cerebrovascular disease, or peripheral arterial disease), sulfonylureas remain a recommended second-line treatment option. They continue to be noted for their high efficacy and low cost, making them an important treatment option, particularly in view of the continued emphasis on rapid intensification if treatment targets are not met within 3 months.[21]

On a national level, several countries, such as the Netherlands, Italy, Australia, South Africa, and Brazil, have launched diabetes treatment guidelines in recent years. In all of them, sulfonylureas are considered important drugs in the strategy of T2DM treatment, with the use of gliclazide being preferred in most cases.[22-26] In the Brazilian guideline, the authors comment on interference of postischemic cardiac reconditioning, notably with glibenclamide, and they reinforce the cardiovascular safety of gliclazide as demonstrated by the ADVANCE study.[26,27]

In 2017, the World Health Organization (WHO) listed five diabetes-related drugs on its "Model List of Essential Drugs"—including short-acting insulin, intermediate-acting insulin, metformin, gliclazide, and glucagon—with essential medicines

defined by the WHO as those that meet the priority health needs of the population. These same drugs should be included in the National Essential Medicines List (NEML) of countries.[1]

Gliclazide: unlike other sulfonylureas?

Sulfonylureas are one of the most widely documented and lowest costing drug classes among those recommended in combination with metformin.[28] It is known that these drugs are highly effective in reducing blood glucose and glycated hemoglobin.[21,29] However, the drugs available in this class have significant intraclass differences in terms of chemical structure and physiological and clinical properties *(Table I, and Table II page 168).*

Sulfonylureas stimulate endogenous production of insulin by pancreatic β-cells, with an intermediate to long duration of action (8-24 hours). They are useful for the control of fasting blood glucose and 24-hour blood glucose, but they can cause hypoglycemia as well as weight gain. Chlorpropamide and glibenclamide show an increased risk of hypoglycemia. However, studies have demonstrated that the incidence of hypoglycemia with gliclazide may be comparable to that of DPP-4 inhibitors.[30] Mbanya and colleagues conducted a systematic review of the literature to identify randomized clinical trials comparing the efficacy and safety of gliclazide with DPP-4 inhibitors in treating fasting adults with T2DM during Ramadan. They concluded that patients treated with gliclazide or DPP-4 inhibitors during Ramadan have equally low risks of having symptomatic hypoglycemia. Unlike for other sulfonlyureas, this is probably linked to gliclazide's lack of binding to Epac2 (exchange protein directly activated by cyclic adenosine monophosphate 2), a stimulating factor of insulin exocytosis, as well as its highly reversible binding with sulfonylurea receptor 1 (SUR1).[31-33] As a consequence, gliclazide does not overstimulate insulin release, leading to a very low risk of hypoglycemia, as well as a lower risk of weight gain.[4,7,10,12,34]

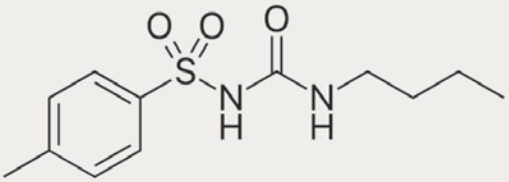
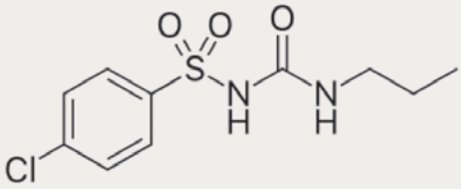
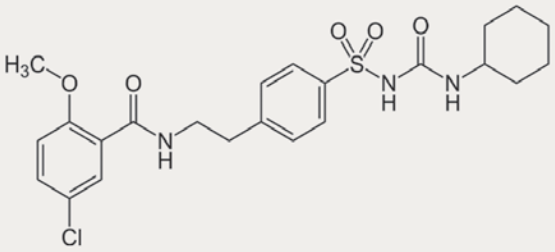
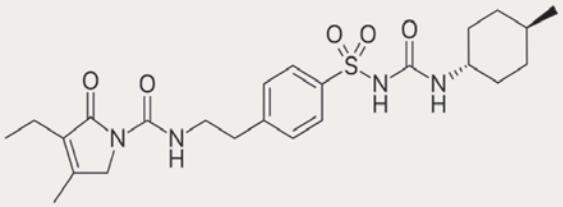
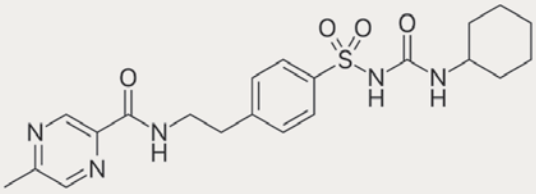
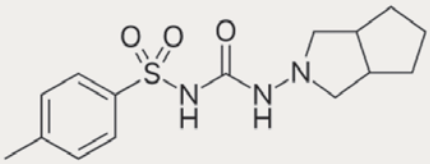
Sulfonylureas	Chemical structure
Tolbutamide MW: 270.347 g/mol MF: $C_{12}H_{18}N_2O_3S$	
Clorpropramide MW: 276.735 g/mol MF: $C_{10}H_{13}ClN_2O_3S$	
Glibenclamide (glyburide) MW: 494.003 g/mol MF: $C_{23}H_{28}ClN_3O_5S$	
Glimepiride MW: 490.619 g/mol MF: $C_{24}H_{34}N_4O_5S$	
Glipizide MW: 445.538 g/mol MF: $C_{21}H_{27}N_5O_4S$	
Gliclazide MW: 323.411 g/mol MF: $C_{15}H_{21}N_3O_3S$	

Table I. *Chemical structure of sulfonylureas.*

Abbreviations: *MF, molecular formula; MW, molecular weight.*

From the molecular point of view, gliclazide MR (modified release) has important differences from glibenclamide and glimepiride with respect to the anterior and posterior part of the molecule. In gliclazide MR, the presence of a nitrogen ring imparts antioxidant properties, and the absence of a benzamide ring determines the selectivity of binding to the SUR1 receptor (pancreatic) and its nonbinding to SUR2a (cardiac) *(Table I).*

Sawada et al demonstrated that gliclazide may be beneficial with regard to pancreatic β-cells in that it does not stimulate production of reactive oxygen species (ROS) the way other sulfonlyureas, such as glibenclamide and glimepiride,

Molecules	Duration of action* (T 1/2)	Activity of metabolites (T 1/2)	Elimination
1st generation			
Tolbutamide	Short	Inactive†	Urine ≈ 100%
Chlorpropamide	Long	Inactive	Urine ≈ 80%-90%
2nd generation			
Glibenclamide	Intermediate to long	Active	Bile ≈ 50%
Glipizide	Short to intermediate	Inactive	Urine ≈ 70%
Gliclazide	Intermediate	Inactive	Urine ≈ 65%
3rd generation			
Glimepiride	Intermediate	Active	Urine ≈ 80%
Gliclazide MR	Long	Inactive	Urine ≈ 65%

*Duration of action: short, <12 h; intermediate, 12-24 h; long, >24 h. †Active metabolites (minimum quantity).

Table II. *Various generations of sulfonylureas.*

Abbreviations: *MR, modified release; T 1/2, half-life.*

Adapted from reference 35: *Colagiuri et al.* Diabetes Res Clin Pract. *2018;143:1-14.*

and nateglinide do through the protein kinase–dependent activation of NAD(P)H oxidase.[36] The researchers demonstrated that such ROS cause β-cell apoptosis in vitro.[36]

Despite questions about cardiovascular safety and long-term efficacy, insulin secretagogue drugs have been widely used in the treatment of T2DM for several decades. In addition to lifestyle intervention, monotherapy with oral antidiabetic agents is the typical strategy for initial treatment in T2DM patients. In the context of the "legacy effect" suggested by glycemic reduction in the UKPDS 10-year follow-up, the impact of initial treatment in patients with T2DM may have a crucial influence on long-term risks.[9]

Mainly on the basis of the metformin results from the UKPDS substudy, this biguanide has become the main drug of choice in the treatment of T2DM. However, the cardiovascular safety and long-term efficacy of metformin compared with secretagogues (and more modern drugs) remains unclear. Despite the extensive use of secretagogues, few randomized trials have evaluated long-term mortality outcomes related to monotherapy with these drugs. In the UGDP (University Group Diabetes Program) study, tolbutamide was associated with increased cardiovascular and total mortality, causing the premature termination of the tolbutamide arm of the study.[37] On the other hand, the UKPDS study (initial phase) did not show any effect of chlorpropamide and glibenclamide on complications of macrovascular diseases or mortality.

UGDP study results led to a change in labeling of sulfonylureas commercialized in the United States, so that labels include a warning about the potential for increased cardiovascular mortality. However, there is some evidence of intraclass heterogeneity in terms of cardiovascular safety of different sulfonylureas. In particular, gliclazide and glimepiride have been associated with a lower risk of total and cardiovascular mortality than glibenclamide.[38] In 2010, Pantalone and colleagues conducted a large retrospective study of more than 11 000 patients using sulfonylureas available in the United States (glibenclamide, glimepiride, and glipizide) and did not observe an increased risk of mortality.[39] In 2012, the same Pantalone group analyzed 7320 diabetic patients and evaluated the use of sulfonylureas compared with metformin.[40] The results did not identify an increased risk of mortality between different combinations of sulfonylureas and metformin.

In 2004, a Japanese study evaluated 118 diabetic patients divided into three treatment groups: glibenclamide, gliclazide, and glibenclamide plus metformin. Participants were followed-up for 3 years, and the measurement of the carotid artery intima-media thickness was recorded at baseline and at the end of the study. Findings indicated that metformin or gliclazide, but not glibenclamide, have a potential antiatherogenic effect on T2DM.[41]

Most studies of sulfonylurea monotherapy focus on populations of different cardiovascular risk profiles. Schramm et al conducted a large Danish study with more than 107 000 diabetic patients.[42] The researchers analyzed the mortality and cardiovascular risk of diabetic patients with or without previous acute myocardial infarction (MI), comparing results for treatment with different secretagogues versus metformin.

In diabetic patients without previous MI, the analysis of the outcomes of total mortality and cardiovascular mortality and of the composite end point of cardiovascular mortality, MI, and stroke showed that only gliclazide and repaglinide presented no significant increase in risk over that seen with metformin. Glimepiride had the highest hazard ratio, at 1.32, higher than that of tolbutamide (1.28).

When assessing diabetic patients with previous MI, analysis of the same outcomes as above again showed that only gliclazide and repaglinide had no significant increase in risk over metformin. Glipizide had the highest hazard ratio, at 1.53, also higher than tolbutamide (1.47).

Thus, Schramm et al demonstrated an increase in cardiovascular risk and mortality associated with the use of some insulin secretagogues compared with metformin. However, gliclazide did not present this risk. Therefore, the idea that different sulfonylureas have clinically important differences in their safety profiles is reinforced.[41]

From the cardiovascular point of view, it is notable that in the ADVANCE study, the intensively treated group, which used gliclazide MR, did not have increased cardiovascular mortality.[10] A different result was observed in the ACCORD study, which predominantly used glimepiride in the intensively treated group: total mortality was increased.[11]

Specifically on the use of gliclazide, ADVANCE was a randomized controlled study of blood pressure (indapamide perindopril versus placebo) and glycemic control (intensive control based on the use of gliclazide MR versus standard treatment) on the incidence of microvascular and macrovascular events in 11 140 individuals with T2DM recruited from 215 centers in 20 countries.[10]

An intensive glycemic control strategy involving gliclazide MR and other drugs, which lowered glycated hemoglobin to a value of 6.5%, provided a 10% reduction in the combined outcomes of major macrovascular events and microvascular events, mainly owing to a 21% reduction in nephropathy.

Conclusion

Thus, different diabetes treatment guidelines from several medical societies acknowledge sulfonylureas as part of the current therapeutic arsenal worldwide. Although a member of this drug class, the sulfonylurea gliclazide MR has significant benefits (particularly with regard to the side effect profile) that differentiate it from other sulfonylureas, and such differences between drugs that are available could be exploited with regard to individualization of the treatment for each diabetic patient. Such individualization takes into account important factors such as age, duration of illness, body weight, complications, and the type of diabetes being treated.

Sulfonylureas are very effective at decreasing fasting and postprandial blood glucose and reducing glycated hemoglobin. Despite the heterogeneous risks of hypoglycemia and weight gain carried by this drug class, sulfonylureas are very well studied, widely available, and relatively inexpensive. This guarantees their use as a standard of care in the treatment of T2DM even now, many decades after their discovery. ■

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Keywords: gliclazide MR; glycemic control; individualization of treatment; standard of care; sulfonylurea; type 2 diabetes mellitus