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Review

# The place of gliclazide MR in the evolving type 2 diabetes landscape: A comparison with other sulfonylureas and newer oral antihyperglycemic agents

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ABSTRACT

The sulfonylureas are effective oral glucose-lowering agents with a long history of clinical use. While all have the same general mechanism of action, their pharmacokinetic properties are influenced by factors such as dosage, rate of absorption, duration of action, route of elimination, tissue specificity, and binding affinity for pancreatic β-cell receptor. The result is a class of agents with similar HbA1c-lowering efficacy, but well-documented differences in terms of effects on hypoglycemia, and cardiovascular and renal safety. This review examines the differences between currently available sulfonylureas with a focus on how gliclazide modified release (MR) differs from other members of this class and from newer oral antihyperglycemic agents in the form of dipeptidyl peptidase-4 (DPP4) and sodium–glucose cotransporter 2 (SGLT2) inhibitors. The first part focuses on major outcome trials that have been conducted with the sulfonylureas and new oral agents. Consideration is then given to factors important for day-to-day prescribing including efficacy and durability, weight changes, hypoglycemia, renal effects and cost.

Based on current evidence, third-generation sulfonylureas such as gliclazide MR possess many of the properties desired of a type 2 diabetes drug including high glucose-lowering efficacy, once-daily oral administration, few side effects other than mild hypoglycemia, and cardiovascular safety.



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## Contents



## 1. Introduction

Sulfonylureas were the first oral agents to be developed for the treatment of type 2 diabetes in the early 1950s and have a long history of clinical use. Since then our increased understanding of the pathophysiology of type 2 diabetes has led to the development of a number of new drug classes with novel mechanisms of action, yet the sulfonylureas and metformin remain the most widely prescribed antihyperglycemic agents worldwide [1–3].

Safely achieving and maintaining adequate glycemic control remains an important objective and a challenge in many people with type 2 diabetes. Type 2 diabetes is no longer a pandemic only of economically affluent countries, but is also a major problem in the developing world. More than ever, cost-effective and safe therapies to lower blood glucose levels are required. However, while new treatments for diabetes may offer certain advantages over their predecessors, they may also come with new side effects or restrictions for use and at higher costs.

Since the first sulfonylureas became available, drugs in this class have undergone several stages of development and have different pharmacological properties. Emerging evidence indicates that clinical characteristics commonly associated with the use of sulfonylureas are often not a class effect.

This review examines how gliclazide MR differs from other currently available sulfonylureas and newer oral antihyperglycemic agents. The first part focuses on major outcome trials and some observational studies. Consideration is then given to factors important for day-to-day prescribing including efficacy and durability, weight changes, hypoglycemia, renal effects and cost.

## 2. Physiological basis of sulfonylurea action and clinical implications

The sulfonylureas stimulate insulin secretion by binding to specific receptors on the pancreatic β-cells, resulting in closure of ATP-sensitive K-channels ($K_{ATP}$) in the β-cell plasma membrane and opening of voltage-gated calcium channels [4,5]. $K_{ATP}$ channels are a complex of two proteins: a pore-forming subunit (Kir6.2) and a drug-binding subunit (SUR); the latter functioning as the receptor for sulfonylureas (Fig. 1) [6]. Two genes for sulfonylurea receptors have been identified encoding the proteins SUR1 and SUR2 [7]. The predominant type of SUR varies between tissues: SUR1 is predominantly found in pancreatic β-cells, SUR2A in cardiac muscle, and SUR2B in smooth muscle (Fig. 1).

The opening of cardiac $K_{ATP}$ channels is thought to protect the heart during periods of ischemia. Sulfonylureas with affinity for cardiac $K_{ATP}$ channels may inhibit the opening of $K_{ATP}$ channels in the cardiovascular system, whereas those that act selectively on the pancreatic β-cell SUR receptors may pose less of a cardiovascular risk [8] and are preferred especially in individuals at high risk for myocardial ischemia.

While ß-cell oxidative stress is related to chronic hyperglycemia, it has been suggested that certain sulfonylureas may directly increase generation of reactive oxygen species and cause oxidative stress related β-cell apoptosis [9]. Gliclazide is known to be a general free radical scavenger, mediated by the azabicyclooctyl ring on its sulfonylurea core [10], and a number of experimental and clinical studies suggest that gliclazide may protect pancreatic β-cells from apoptosis induced by oxidative stress [11]. Clinically this could manifest as differences amongst sulfonylureas in terms of secondary