

Cardiovascular Profile of Modern Sulfonylureas: Focus on Glimepiride

SR Aravind¹, Sachin Mittal², S Venkatraman³, Nilakshi Deka⁴, Girish Parmar⁵, S Amarnath⁶, V Mohan⁷

Abstract

Cardiovascular risk has been found to be frequently associated with people with diabetes. The presence of such a condition necessitates the use of caution while prescribing antidiabetic medications to these patients. This is because there has been some concern of antidiabetic drugs and their associated with increase in cardiovascular risk. In this context, glimepiride is a well-studied, efficacious, cost effective option for people with diabetes including those at increased cardiovascular risk. Several clinical studies have validated the 'cardio-safe' profile of glimepiride, thereby, rendering it suitable for use in a wide range of people with diabetes. Here we will discuss about the cardiovascular profile of glimepiride and its cardiovascular safety from the cardiovascular outcome trials.

In contrast, glimepiride preserves ischemic preconditioning since it does not have such inhibitory effects. This is the reason why glimepiride is preferred over conventional SUs, especially in patients at high risk for cardiovascular diseases.⁴

The cardiovascular profile of glimepiride is depicted in Figure 1.

Glimepiride and Cardiovascular Safety: Lessons from Clinical Studies

A nationwide registry involving 1310 people with diabetes mellitus and acute myocardial infarction demonstrated that participants treated previously with modern SUs like glimepiride had

Introduction

People with diabetes are two to three times more likely to have cardiovascular disease.¹ Cardiovascular morbidity and mortality remain higher in people with diabetes than nondiabetic ones, despite several efforts made to control blood glucose and associated risk factors. Therefore, right selection of antidiabetic medications is one of the important tools for managing cardiovascular disease in people with diabetes.²

Glimepiride has been found to maintain myocardial ischemic preconditioning as compared to conventional SUs. Further, glimepiride is not associated with increased cardiovascular or all-cause mortality or with an increased risk of myocardial infarction or stroke. In other words, glimepiride can be considered as a cardio-safe glucose-lowering drug.³ In this article, we will discuss about the cardiovascular effects and cardiovascular safety of glimepiride, in the management of people with type 2 diabetes mellitus.

Cardiovascular Effects of Glimepiride

Compared to other conventional SUs, glimepiride is cardio-safe. Glimepiride has been found to have an insignificant effect in reducing coronary blood flow and in enhancing coronary resistance. The mitochondrial K_{ATP} channels (adenosine triphosphate-

sensitive potassium channels) in cardiac myocytes are inhibited by conventional SUs. This, in turn, leads to impairment of cardiac preconditioning.

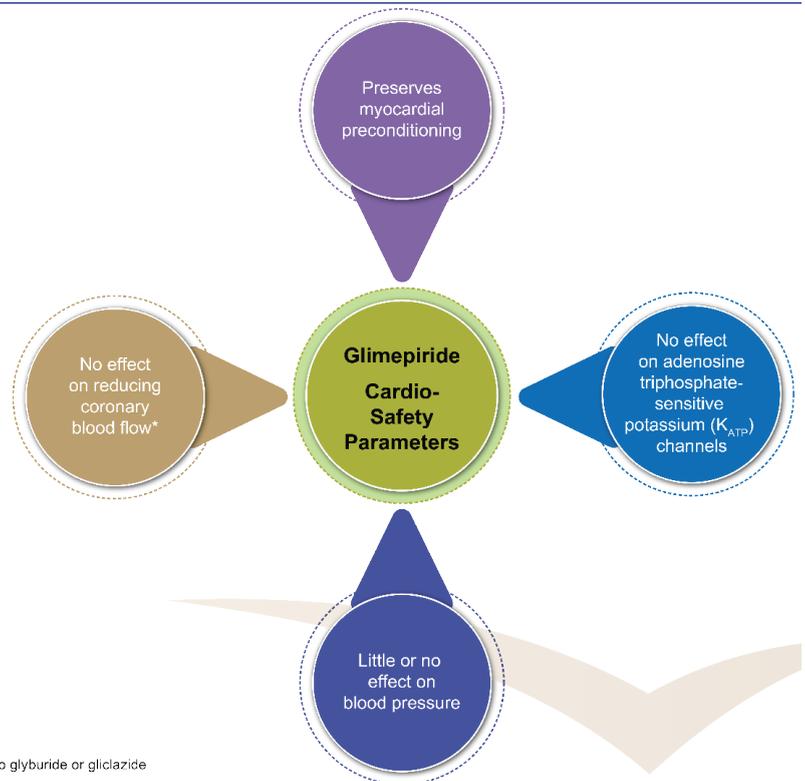


Fig. 1: Effects of glimepiride on cardiovascular health

¹Director, Diacon Hospital, Bangalore, Karnataka; ²Senior Consultant Endocrinologist, Department of Endocrinology, Fortis Hospital, Mohali, Punjab; ³Senior Consultant Diabetologist, Apollo Sugar Clinics, Chennai, Tamil Nadu; ⁴Consultant Endocrinologist, Apollo Hospital, Guwahati, Assam; ⁵Consultant Endocrinologist, Nanavati Hospital, Mumbai, Maharashtra; ⁶Medical Affairs Diabetes and Cardiovascular, Sanofi India Ltd.; ⁷Chairman and Chief Diabetologist, Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu

Table 1: Clinical studies evaluating all-cause and CV-related mortality with use of glimepiride vs. other SUs

Clinical trial	Study findings on mortality risk associated with glimepiride vs. other SUs
Zeller M <i>et al</i> , 2010 ⁵	In-hospital mortality was lower in CAD patients treated with glimepiride (2.7%) vs. glibenclamide (7.5%). Occurrence of ischemic complications and arrhythmias was less frequent with glimepiride vs. glibenclamide.
Pantalone KM <i>et al</i> , 2010 ⁶	Increased overall mortality risk and adverse CV outcomes with glyburide versus glimepiride (1.36 [0.96–1.91]) and glipizide versus glimepiride (1.39 [0.99–1.96]) was noted in patients with documented CAD
Simpson SH <i>et al</i> , 2015 ⁷	Glimepiride and gliclazide were associated with lower risk of all-cause and CV-related mortality and adverse cardiovascular events compared to glibenclamide.

CV:Cardiovascular

lower mortality than those treated with other oral antidiabetic medications or insulin.⁵ In people with diabetes and coronary artery disease, glimepiride was found to be associated with reduced mortality rates. In a retrospective cohort study by Pantalone *et al*, the association of glimepiride with reduced mortality rates in people with diabetes and coronary artery disease was revealed, vs. other antidiabetic drugs, such as glyburide.⁶ In a systematic review and network meta-analysis by Simpson *et al.*, it was revealed that the use of glimepiride was associated with a significantly lower risk of mortality than glibenclamide and glipizide.⁷ A meta-analysis with sequential analysis of randomized clinical trials found that SUs, including glimepiride, are not associated with enhanced risk for cardiovascular mortality, stroke, myocardial infarction or all-cause mortality.⁸ Table 1 summarizes clinical studies evaluating all-cause and CV-related mortality with use of glimepiride compared to other SUs.⁵⁻⁷

Glimepiride and Cardiovascular Safety: Lessons from Cardiovascular Outcome Trials

A randomized, multicenter, pragmatic clinical trial on 3028 people with type 2 diabetes mellitus aged 50-75 years was performed to study the incidence of CV events following the addition of pioglitazone vs. SUs (including glimepiride) to metformin. This trial, called the TOSCA.IT, included people with type 2 diabetes inadequately controlled with metformin. The study showed that the incidence of cardiovascular events was similar with sulfonylureas (mostly glimepiride and gliclazide) and pioglitazone as add-on treatments to metformin, thereby highlighting the CV safety of glimepiride. The study findings suggested that overall incidence serious adverse events;

occurrence of confirmed malignant neoplasms; pathological bone fractures and neoplasms, was similar in SU and pioglitazone groups.⁹

The long-term impact of linagliptin vs. glimepiride on cardiovascular morbidity, mortality, safety (like hypoglycemia and weight gain), and relevant efficacy parameters (like glycemic parameters) on people with type 2 diabetes mellitus was investigated in the cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) trial. According to this study, linagliptin was found to be noninferior to glimepiride in the treatment of adults with type 2 diabetes mellitus at high CV risk, in terms of the time to first major adverse cardiovascular event.¹⁰ The trial results that were presented at the Scientific Sessions of the American Diabetes Association (ADA) 2019 revealed that among the people with early type 2 diabetes mellitus there was no difference between the effects of linagliptin and glimepiride.¹¹

The study revealed that similar CV mortality was observed both in case of linagliptin and glimepiride, HbA_{1c} levels dropped more rapidly with glimepiride and by the end of study both the agents had similar effects on lowering HbA_{1c}, time to first occurrence of 3P-MACE (CV death, non-fatal myocardial infarction, non-fatal stroke) were comparable for both. Even in case of 4P-MACE criteria, hospitalization for unstable angina, data were similar for both glimepiride and linagliptin.¹⁰

Less number of cases were reported for hospitalization to heart failure in case of glimepiride, while 20 more cases, numerically higher were observed in case of Linagliptin.¹⁰

The authors of the CAROLINA trial concluded that the use of linagliptin compared with glimepiride over a median of 6.3 years resulted in a

noninferior risk of a composite CV outcome, suggesting that cardiovascular safety should no longer be a concern when choosing sulfonylureas especially glimepiride for people with type 2 diabetes.¹⁰

SUs are amongst the oldest class of oral hypoglycemic agents that are recommended by the current guidelines for use in the therapy of people with type 2 diabetes mellitus. Table 2 summarizes the guidelines of different global bodies regarding the use of SUs including glimepiride in type 2 diabetes mellitus therapy.¹

Conclusion

Glimepiride is a modern SU, which can be used as monotherapy or in combination with other antidiabetic agents, including insulin and metformin. Multiple studies have found glimepiride to be safe for use in people with type 2 diabetes at increased cardiovascular risk. The recently released results from the CAROLINA trial provide resounding answers to any questions regarding the CV safety of glimepiride. To reinforce the study conclusion, cardiovascular safety should no longer be a concern when choosing sulfonylureas, especially glimepiride, for people with type 2 diabetes.

Conflict of Interest

SA is an employee of Sanofi India. All other authors report no conflicts of interest.

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Authorship

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Table 2: Recommendations of different global bodies on the use of SUs like glimepiride in T2DM management

Name of the Global Body	Recommendations
The American Diabetes Association/European Association for the Study of Diabetes (ADA 2019) ¹¹	<ul style="list-style-type: none"> • Recommends use of SU as first-line therapy in case patient is metformin intolerant • Recommends SU as second-line therapy after metformin • If glycemic goals are not reached, SU can be used as third-line therapy
The International Diabetes Federation (IDF) ¹	<p>Recommends the use of SUs both as first- or second-line agents in patients who are:</p> <ul style="list-style-type: none"> • With intolerance or contradictions to metformin • Not over-weight • Requiring a rapid response owing to hyperglycemic response
South Asian Federation of Endocrine Societies (SAFES) ¹²	<ul style="list-style-type: none"> • Recommends use of SUs both as second-line (after metformin) and first line agents (in case of metformin intolerance) in management of T2DM • Recommends early initiation of modern SUs like glimepiride in T2DM for maximum glycemic benefits. • Recommends modern SUs like glimepiride as the preferable choice of therapy in T2DM over conventional SUs, owing to their reduced mortality, renal protection, lower hypoglycemic effects, and better CV outcomes, lower weight-gain risk.
Research Society for Study of Diabetes in India (RSSDI) ¹³	When glucose targets are not achieved with first-line therapy in T2DM patients, a sulfonylurea or thiazolidinedione or SGLT2 inhibitor or DPP-4 inhibitor or AGI can be added, using a patient-centric approach.
World Health Organisation (WHO) ¹⁴	<p>SUs should be used as a second-line treatment if:</p> <ul style="list-style-type: none"> • Metformin alone is insufficient • Metformin is contraindications <p>SUs with a better safety profile are preferred in patients for whom hypoglycemia is a concern:</p> <ul style="list-style-type: none"> • People at risk of falls • People who have impaired awareness of hypoglycemia • People who live alone • People who drive or operate machinery as part of their job

T2DM: Type 2 diabetes mellitus; CV: cardiovascular; SU: Sulfonylurea

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