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Cardiovascular safety of Glimepiride: An indirect comparison from CAROLINA and CARMELINA

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Abstract

Background: Despite having unquestionable glucose lowering efficacy, current guidelines no more favour the uses of sulphonylureas for CV safety concern, except when cost is an issue. However, formal cardiovascular outcome trial (CVOT) is not available.

Materials and methods: We performed an indirect treatment comparison to find the hazard ratio for 3-point MACE, all-cause death, CV death and non-CV death between glimepiride and placebo based on two large CVOTs which established the CV safety of linagliptin (CARMELINA and CAROLINA).

Results: Glimepiride was shown to have a non-inferior risk compared to placebo for 3-point MACE (HR 1.04, 95% CI 0.850, 1.274), all-cause mortality (HR 1.08, 95% CI 0.880, 1.317), CV death (HR 0.96, 95% CI 0.732, 1.259), and non-CV death (HR 1.24, 95% CI 0.893, 1.733).

Conclusion: Cardiovascular safety of glimepiride is re-assuring and may help patients with type 2 diabetes world-over to avail the benefit of this affordable efficacious medication.

Keywords

Cardiovascular safety, glimipiride, CAROLINA, CARMELINA

Novelty statement

Q1. 'What is already known'?

A: Sulfonylurea especially Glimepiride is no longer preferred as a glucose lowering agent after metformin except where there is economic constraint. This is primarily because of its putative Cardio Vascular safety concern based on anecdotal studies. Recent meta-analyses are discordant in this issue. Formal CVOT trials are not available for Glimepiride.

Q2. What this work has found?

A: Based on two CVOT trials on CV safety of Linagliptin (CARMELINA and CAROLINA), an indirect comparison (Network Meta analysis) between glimepiride and placebo was done which showed Glimepiride is non inferior to placebo with regards to 3 point MACE and all cause mortality.

Q3. What are the clinical implications of the study?

A: Confirmation of the CV safety of glimepiride is re-assuring and may help patients with type 2 diabetes world-over to avail the benefit of this affordable efficacious medication.

Conventionally sulphonylureas (SUs) were only second to metformin in terms of usage, worldwide as anti-hyperglycaemic agents in type 2 diabetes. The SUs have unquestionable glucose lowering efficacy. However risks of hypoglycaemia and weight gain have been limitations of SUs. Additionally cardiovascular safety of SUs has remained a matter of concern ever since the publication of 'The University Group Diabetes Program (UGDP)' study.[1] Subsequently several meta-analysis and real world data have been published with conflicting and variable results.[2,3]

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Table 1. The treatment effect summary on 3 point MACE.

	Glimepiride	Linagliptin	Placebo
Glimepiride	–	1.02 (0.880, 1.183)	1.04 (0.850, 1.274)
Linagliptin	0.98 (0.845, 1.136)	–	1.02 (0.889, 1.170)
Placebo	0.96 (0.785, 1.176)	0.98 (0.855, 1.125)	–

Expressed as hazard ratio (95% CI).

It needs to be appreciated that all drawbacks of SUs, including risk of hypoglycaemia, weight gain or cardiovascular safety may be different for different SUs. Following the cardiovascular safety concerns of rosiglitazone[4] the US FDA made it mandatory for all newer anti-hyperglycaemic agents to undergo cardiovascular outcome trials (CVOT). The results of CVOTs of SGLT2 inhibitors and GLP-1 analogues have lead to changes in treatment paradigm. The ADA-EASD guideline has downgraded the roles of SUs in the management of type 2 diabetes.[5] In fact they have suggested that SUs are to be used preferentially only when cost of therapy is a major issue.[5] The major reason for looking down upon SUs by these major wise bodies is the cardiovascular uncertainty of SUs including Glimepiride.

As per FDA regulations SU approved for use in the US includes a product labelstating that SU use has been associated with increased CV mortality. The older anti-hyperglycaemic agents including SUs do not need dedicated CVOTs for usage and since these drugs are cheap and off patents it is unlikely that any placebo controlled CVOTs will be conducted in future to refute the CV safety concerns.

Recently, two large robust CVOTs have been published establishing the CV safety of linagliptin. The CARMELINA trial,[6] documented that linagliptin is non-inferior to placebo with regards to a composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke (3-point major adverse CV event [MACE]) in subjects with T2DM and high CV and renal risk. After a median follow-up of 2.2 years (hazard ratio was [HR] 1.02; 95% confidence interval [CI] 0.89, 1.169), which is consistent with that of other DPP-4 inhibitors. The CAROLINA trial[7] documented that linagliptin is non-inferior to the active comparator glimepiride (HR 0.98; 95.47% CI 0.84, 1.14) with regards to 3 point MACE in elderly subjects with high CV risk after a median follow-up of 6.3 years. Never before has a study been done with so many patients on glimepiride.

Utilising the data available from these two big published CVOTs, we performed an indirect treatment comparison (ITC) to determine whether glimepiride was non-inferior to placebo with regards to the time to first occurrence of CV outcomes.

Summary measure was hazard ratio for time to first occurrence of 3-point MACE, all-cause death, CV death, and non-CV death. Indirect treatment comparison was performed using *netmeta* package (version 1.1-0) in R-3.6.1. This package uses the graph-theoretical method for analysis,[8] which has been found to be equivalent to the frequentist approach to network meta-analysis.[9,10] Inverse variance method, using Log HR and their standard error (SE), were used for pooling treatment effects; and both fixed effect and random effects models were applied. Since, at log scale, HR and their CIs are approximated by normal distribution, the following relationship was used to impute SEs from CIs of HRs ($ln(CI) = ln(HR) \pm Z_1 - \alpha/2 * SE_{lnHR}$).[11]

The results of this ITC show that the use of glimepiride has a non-inferior risk as compared to placebo for time to first 3-point MACE (HR 1.04, 95% CI 0.850, 1.274), all-cause mortality (HR 1.08, 95% CI 0.880, 1.317), CV death (HR 0.96, 95% CI 0.732, 1.259), and non-CV death (HR 1.24, 95% CI 0.893, 1.733) (Table 1). As we pooled only two studies, there was obviously no estimable statistical heterogeneity and inconsistency ($Q = 0$, $tau^2 = 0$) hence, results of both fixed and random effects models were identical. In addition, in the included studies, as HRs and their CIs were reported only to two decimal places, SEs estimated from them was only a crude approximation. Lastly, in our model, as no direct comparison studies are available comparing glimepiride against placebo, there was no opportunity to test the results for consistency. Nonetheless, a large data set and homogeneous study population probably outweighs the abovementioned limitation.

These findings also reinforce the results of a meta-analysis by Simpson et al. which clearly suggests lower risk of all-cause and cardiovascular-related mortality.[12] Confirmation of the cardiovascular safety of glimepiride is re-assuring and we hope will help patients with type 2 diabetes world over to avail the benefit of this affordable efficacious medication.

Authors' contribution

S.G.: conceptualised the analysis; P.M.: wrote the first draft; P.P.: performed statistical analysis; K.P. and P.C.: revised the draft.

Declaration of conflicting interests

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Availability of data and materials

Data in public domain.

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