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, glimepiride, 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. Consecutively several meta-analysis and real world data have been published with conflicting and variable results. ¹ ² ³

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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 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. In fact they have suggested that SUs are to be used preferentially with that of other DPP-4 inhibitors. The CAROLINA trial\(^7\) documented that linagliptin is non-inferior to placebo with regards to a composite endpoint of CV death, 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, 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 ($ln(HR) ± Z_{\alpha/2}*SE_{ln(HR)}$).\(^11\)

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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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

|                  | Glimepiride | Linagliptin       | Placebo            |
|------------------|-------------|-------------------|--------------------|
| **HR (95% CI)**  | 0.96 (0.785, 1.176) | 0.98 (0.845, 1.136) | 1.02 (0.880, 1.183) |

Expressed as hazard ratio (95% CI).
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Availability of data and materials
Data in public domain.

References
1. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult onset diabetes. II. Mortality results. *Diabetes* 1970; 19(suppl.): 789–830.
2. Bain S, Druyts E, Balijepalli C, et al. Cardiovascular events and all-cause mortality associated with sulfonylureas compared with other anti-hyperglycaemic drugs: a Bayesian meta-analysis of survival data. *Diabetes Obes Metab* 2017; 19(3): 329–335.
3. Varvaki Rados D, Catani Pinto L, Reck Remonti L, et al. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. *PLoS Med* 2016; 13(4): e1001992.
4. Nissen SE and Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356: 2457–2471.
5. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020; 43(2): 487–493.
6. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *J Am Med Assoc* 2019; 321(1): 69–79.
7. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *J Am Med Assoc* 2019; 322(12): 1155–1166.
8. Schwarzer G, Carpenter JR and Rücker G. *Meta-analysis with R (use-R!)*. Cham: Springer International Publishing, 2015.
9. Rücker G, Schwarzer G, Krahmer U, et al. Package netmeta: network meta-analysis using frequentist methods. R package version 0.9-8, https://CRAN.R-project.org/package=netmeta (2018, accessed 12 September 2020).
10. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; 3: 312–324.
11. Simpson SH, Lee J, Choi S, et al. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015; 3(1): 43–51.
12. Higgins JPT and Green S (eds). *Cochrane handbook for systematic reviews of interventions version 5.1.0*. London: The Cochrane Collaboration. www.handbook.cochrane.org (2011, accessed March 2011).