CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with T2D trial

The results of the CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with T2D (CAROLINA) study were read out at the 79th Scientific Sessions of the American Diabetes Association annual meeting at the Moscone Center in San Francisco on June 10, 2019. The same was published in JAMA during the European Association for the Study of Diabetes meeting on September 19, 2019.[1]

All cardiovascular outcome trials (CVOTs), mandated by the United States Food and Drug Administration (US FDA) since December 2008 for new anti-diabetic drugs, have to be done with the comparator as placebo as add-on to the standard of care. The reason why the comparator is not an active drug is because if the comparator is an active drug, then there are two ways of interpreting the result. Either that the new drug reduces major adverse CV events (MACE) or that the active comparator increases MACE. It is similar to what happened in the Vioxx Gastrointestinal Outcomes Research trial (rofecoxib vs. naproxen) and the result was interpreted as naproxen reduced MACE rather than rofecoxib increased MACE.[2]

CAROLINA is a CVOT where the comparator is not a placebo but an active drug, glimepiride. Initially, the US FDA did accept this trial as the CVOT for linagliptin, but subsequently, the US FDA informed the sponsor that their mandated CVOT for linagliptin should be designed with placebo as add-on to the standard of care as the comparator and not an active drug such as glimepiride. Hence, the sponsor had to do another study, CV and Renal Microvascular Outcome Study With Linagliptin (CARMELINA),[1] as the CVOT for linagliptin. However, since by then, the CAROLINA study had started recruiting patients (2010), and it was decided to continue CAROLINA in addition to CARMELINA.

So, why did the sponsor decide to do such a study comparing linagliptin with glimepiride? Perhaps, the thinking was that sulfonylureas (SUs) were perceived to be not so CV safe, based on the University Group Diabetes Program study,[3] way back in the 1970s, when older generation SUs such as tolbutamide were found to be associated with an increased incidence of major adverse CV events (impairment of ischemic preconditioning), perhaps because they were not so selective in inhibiting K^+ ATP channels and did so not only in the beta-cells in the Islets of Langerhans (IOL) but also on the heart and blood vessels.

However, the later generation SUs such as gliclazide and glimepiride were designed to be more selective in that they only blocked K^+ ATP channels on the beta-cells in the IOL and not on the heart or the blood vessels.[4] Yet, the historical perception of lack of CV safety persisted and it was included as a class label for all SUs. Perhaps, when sponsor designed the CAROLINA trial,[5] the thinking was that if linagliptin was shown to reduce MACE and glimepiride was demonstrated to increase MACE, then the difference was more likely to be statistically significant. In fact, this study was designed as a superiority trial.

However, the top-line results declared that linagliptin was noninferior to glimepiride. Why did this happen? Is it because glimepiride is truly CV safe as it is very selective in its binding to only the K^+ ATP channels on the beta-cells in the IOL, and not on the heart? Is it because the patient selection for this CVOT was such that fewer than expected MACE occurred, and hence, the difference could not reach statistical significance? Interestingly, the study was designed to include patients at lower CV risk so that the results could be extrapolated to more patients in clinical practice. As compared to CVOTs of empagliflozin and ertugliflozin, where almost all patients had established CVD, in CAROLINA, only 37% had established CVD, and up to 6 years of diabetes duration.

There was a change made to the primary endpoint during the study. Initially, the primary endpoint was 4-P MACE (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, and hospitalization due to unstable angina). Subsequently, hospitalization due to unstable angina was dropped, and 3-P MACE became the primary endpoint. Naturally, this led to some delay in the study completion. The reason why this was done was because it was later realized that 3-P MACE is a more robust endpoint as compared to 4-P MACE. This is because hospitalization due to unstable

angina is not as hard an endpoint as compared to the other three individual component endpoints, namely CV death, nonfatal MI, and nonfatal stroke.

When the primary endpoint is a composite endpoint comprising many individual component endpoints, it is important that all the component endpoints are similarly hard, have similar clinical relevance, and have a similar frequency of accrual. Otherwise what can happen is that one of the individual endpoints accrues disproportionately more than that of the others and this imbalance can reduce the clinical relevance or robustness of the endpoint achievement, especially if the individual endpoint that happened more often during the trial was softer, for example, recurrent angina or hospitalization due to unstable angina. Hence, on the one hand, having more component endpoints in the composite primary endpoint means that the study can get over quickly, as more events accrue faster. This is also why patients at high risk of developing the MACE are selected because such patients are more likely to develop the MACE faster, but then, the generalizability of the study results gets limited to only such high-risk patients in clinical practice. However, on the other hand, if the primary composite endpoint was driven by the more frequent occurrence of the softer individual or component endpoint, then its clinical relevance goes down a notch.

Be that as it may, in the CAROLINA trial, eventually there was no difference between linagliptin and glimepiride in the 3-P MACE, 4-P MACE, overall mortality, CV mortality or non-CV mortality, or in the heart failure (HF)-related outcomes. The subgroup analysis of the 3-P MACE also showed that the result was consistent across all predefined subgroups (*P* value for interaction was not significant for any of the predefined subgroups). Interestingly, the hazard ratio for HF-related outcomes, overall, was numerically 21% higher (1.21) in patients on linagliptin, but the 95% confidence interval limits included one, which meant that it was statistically not significant. This was surprising since this was a relatively lower CV risk population, and in CARMELINA, the use of linagliptin was associated with numerically lesser hospitalization due to HF (HHF). The association of HHF with gliptins in their respective CVOTs is inconsistent and equivocal, and it has been seen with saxagliptin (27% statistically significant increase in HHF, though a prespecified secondary endpoint, SAVOR TIMI-53), alogliptin (numerical increase in HHF; EXAMINE), sitagliptin (neutral; TECOS), vildagliptin, and as mentioned above with linagliptin.

In terms of hemoglobin A1c (HbA1c) reduction, as expected, glimepiride was more potent initially, but subsequently, the Nike swoosh effect could be seen for actually both glimepiride and linagliptin, and by the end of the study, there was hardly any difference in HbA1c reduction between the two arms, indicating that glimepiride's effect was also as sustainable as that of linagliptin. There was also no difference between the two active drugs in terms of their effect on the lipid profile or on blood pressure reduction, time to rescue medication, or need for additional anti-hypertensive, anti-diabetic, or lipid-lowering medication. In terms of overall safety profile too, there were no significant differences in incidence or discontinuation of drugs due to adverse events.

However, as expected, there was significantly more hypoglycemia experienced by patients on glimepiride as compared to linagliptin, and perhaps, this also led to more defensive snacking and weight gain. However, this difference in hypoglycemia and weight gain did not make a significant difference to the 3-P MACE, which is the primary endpoint of the study, based on which sample size is calculated. The weight gain with glimepiride (1.54 kg) and the weight loss of 0.5 kg with linagliptin meant a bigger difference between the two as the differences were in opposite directions, but later, this difference narrowed down and plateaued, another surprising finding.

In terms of titration, patients on glimepiride (add on to metformin) were up titrated from 1 to 2 mg, then from 2 to 3 mg, and finally, from 3 to 4 mg, every 4 weeks such that in 16 weeks, most of them (61%) were on 4 mg glimepiride (submaximal dose), considered to be equivalent to the 5 mg dose of linagliptin. When patients are titrated like this, naturally, the chance of hypoglycemia occurring increases. In the real world of clinical practice, patients are individually up or down titrated and at different time points. Hence, in the real world, the incidence of hypoglycemia with glimepiride is much lower than that reported in randomized controlled clinical trials. Furthermore, the mean HbA1c was 7.2%, and the use of a SU in this kind of patient population is fraught with a higher risk of hypoglycemia.

To conclude, for the first time in a dedicated CVOT, it was shown that a SU (glimepiride) was as CV safe as linagliptin, as linagliptin was found to be noninferior to glimepiride. Now, some might want to surmise that an SU is as CV safe as a gliptin. Strictly speaking, one cannot infer like this. The results pertain to only linagliptin and glimepiride (linagliptin was noninferior to glimepiride) and may not be extrapolatable to other SUs (even selective advanced generation SUs such as gliclazide) or other gliptins.

More importantly, the results provide reassurance to doctors that as first add-on to metformin, in patients with early diabetes (up to 6 years duration) and relatively lower CV risk, they can put patients either on glimepiride or linagliptin. The class warning for all SUs in their respective labels may need to exclude glimepiride, while the class warning for HHF and gliptins in their respective labels may also need to be changed.

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Conflicts of interest

There are no conflicts of interest.

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