Series: Cardiovascular outcome trials for diabetes drugs. Linagliptin, CARMELINA and CAROLINA

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Abstract

Dipeptidyl peptidase-4 (DPP-4) inhibitors were the first class of new antidiabetic drugs to be studied using modern cardiovascular safety trials, as mandated by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Trials with saxagliptin, alogliptin and sitagliptin satisfied the safety criteria with no increase in major cardiovascular adverse events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. No reduction in MACE was demonstrated in these trials, and an unexpected increase in the secondary outcome of hospitalisation for heart failure was observed in the SAVOR-TIMI 53 trial with saxagliptin.

Unusually, linagliptin was studied in two separate safety trials: CARMELINA compared linagliptin with placebo and CAROLINA compared linagliptin with glimepiride. In both trials MACE events were similar in the linagliptin and comparator groups, and no significant differences were observed in rates of hospitalisation for heart failure. These trials provide evidence of cardiovascular safety for linagliptin but show no clear cardiovascular benefits, and indirectly provide evidence of cardiovascular safety for the sulfonylurea glimepiride.

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Key words: diabetes, cardiovascular outcome trial, linagliptin, glimepiride

Introduction

Licencing requirements for new antidiabetic drugs changed in the US and EU following the rosiglitazone controversy, with a greater requirement to demonstrate cardiovascular safety. Between 2013 and 2015 three dedicated cardiovascular outcome trials (CVOTs) with dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes were completed.[1-3] SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) was the first of these, comparing saxagliptin and placebo. It demonstrated no cardiovascular benefit with no difference in major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and an unexpected increase in the secondary outcome of hospitalisation for heart failure.[1]

EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) compared alogliptin with placebo in patients following an acute coronary syndrome: it showed no significant difference in MACE or hospitalisation for heart failure.[2] TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) comparing sitagliptin with placebo showed no significant difference in the primary endpoint which was the composite of MACE plus hospitalisation for unstable angina, or in the secondary outcome of hospitalisation for heart failure.[3] These three trials have been reviewed earlier in this series.[4-6]

This review describes results from the two cardiovascular safety trials performed with linagliptin in patients with type 2 diabetes: CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) comparing linagliptin with placebo,[7] and CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) comparing linagliptin with the sulfonylurea glimepiride.[8] The review describes the primary endpoint and important secondary outcomes from the principal publications and directs attention to important subsequent publications of data from subgroups and/or post hoc analyses.

Background

Linagliptin was licenced by the FDA in 2011 for use in the US and by the EMA in 2012 for use in Europe. A meta-analysis of cardiovascular events in 5,239 subjects from eight trials in the linagliptin phase 3 development programme was published in 2012.[9] The primary endpoint was a composite of death, stroke, myocardial infarction (MI) and hospitalisation for unstable angina. In this cohort study there were significantly fewer cardiovascular events in the linagliptin group than in the comparator group who were treated with placebo, glimepiride or voglibose. A further prespecified meta-analysis of cardiovascular events in 9,459 subjects from 19 phase 2 and phase 3 trials was published in 2016 and showed no significant difference between the linagliptin and comparator groups.[10] The cardiovascular safety of linagliptin was formally examined in two cardiovascular outcome trials (CVOTs). CAROLINA, comparing linagliptin with glimepiride, was started in 2010 and completed in August 2018, and CARMELINA was started

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in 2013 but completed earlier in January 2018.

For both CVOTs the primary endpoint was initially MACE, comprising cardiovascular death, non-fatal MI and non-fatal stroke, plus hospitalisation for unstable angina, sometimes termed 'MACE plus' or'4-point MACE'. This was later changed to MACE alone or '3-point MACE' as it was felt that the inclusion of hospitalisation for unstable angina introduced a degree of clinical subjectivity in assessing that outcome, and that 3-point MACE was diagnostically more precise.[11]

CARMELINA

A paper describing the rationale, design and baseline characteristics of subjects in CARMELINA was published in 2018.[12] The principal results were presented later that year at the meeting of the European Association for the Study of Diabetes (EASD) and published simultaneously in the Journal of the American Medical Association (JAMA). The key features of the trial and baseline characteristics of subjects are described in Box 1. Linagliptin is excreted in bile, whereas sitagliptin, saxagliptin and alogliptin are excreted in urine, so there was a focus in CARMELINA on renal outcomes and the study deliberately recruited subjects with diabetic kidney disease and a high risk of renal outcomes.

In CARMELINA there was no significant difference in MACE, so non-inferiority was established but not superiority (Figure 1, Box 2). There was no significant difference in the secondary renal outcome which was a composite of death due to renal failure, end-stage renal disease, or a sustained 40% or greater decrease in eGFR from baseline. A similar composite renal outcome was used in SGLT2 inhibitor trials e.g. DAPA-CKD. There was also no significant difference in rates of unstable angina or hospitalisation for heart failure when comparing linagliptin with placebo.

Other results from CARMELINA

The number of further publications from CARMELINA is small compared to the multiple post hoc publications from most cardiovascular outcome trials. The effect on cardiovascular and renal outcomes was examined according to baseline eGFR status (>60, 45 to <60, 30 to <45, and <30 ml/min/1.73m^2).[13] Across the different eGFR categories there was no beneficial effect of linagliptin on MACE or on the secondary renal outcome, but albuminuria progression was reduced with linagliptin regardless of eGFR status (Box 2). A further analysis looked at subjects with nephrotic range proteinuria, defined as a urinary albumin:creatinine ratio of > 2200mg/g at baseline.[14] In this subgroup the cardiovascular event rate was double that of subjects without baseline nephrotic range proteinuria, and kidney events were greatly increased, but again there was no significant difference comparing linagliptin and placebo, and improvement in albuminuria was seen in the linagliptin group.

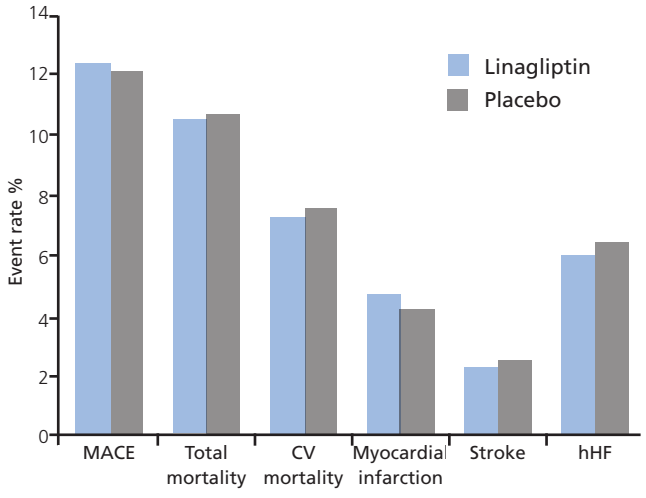
CAROLINA

A paper describing the rationale for the active comparator trial design of CAROLINA was published in 2013,[15] followed by a paper detailing the baseline characteristics of subjects in 2015.[16] The principal results were presented in 2019 at the meeting of the EASD

Box 1 Key features of CARMELINA[7,12]

- CARMELINA compared linagliptin 5mg with placebo for a median follow-up of 2.2 years in 6,979 subjects with type 2 diabetes
- Mean age of subjects was 66 years, with a mean duration of diabetes of 15 years
- Mean baseline HbA_{1c} was 7.9% (63 mmol/mol)
- 57% of subjects had ischaemic heart disease, 27% investigator-reported heart failure, 74% had prevalent kidney disease and 15% had an eGFR < 30 ml/min/1.73m^2
- 54% of subjects were on metformin, 35% sulfonylureas and 58% on insulin

Figure 1. Event rates (%) comparing linagliptin and placebo for major adverse cardiovascular events (MACE), total mortality, cardiovascular mortality (CV mortality), non-fatal myocardial infarction, non-fatal stroke and hospitalisation for heart failure (hHF).



Box 2 Results of the CARMELINA trial[7]

Principal result

- No significant difference in major adverse cardiovascular events (MACE)[7]

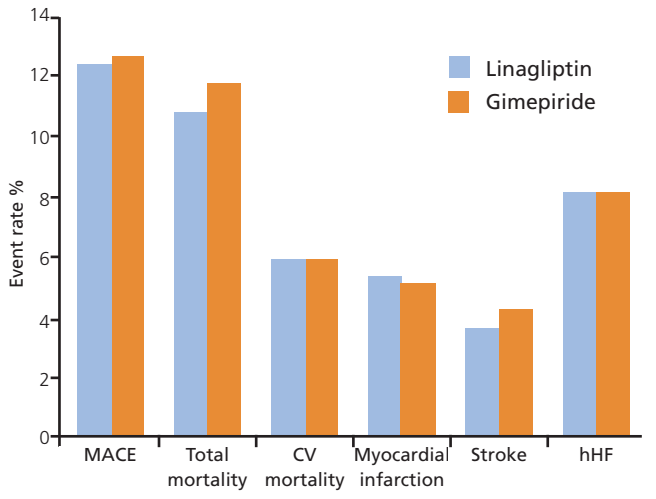
Other results from CARMELINA

- Albuminuria progression was reduced with linagliptin regardless of eGFR, as was HbA_{1c}, without increasing the risk of hypoglycaemia[13]
- In patients with nephrotic range proteinuria linagliptin improved albuminuria and HbA_{1c} but had no effect on cardiovascular or renal events[14]
- Linagliptin did not affect the risk for hospitalisation for heart failure or other selected heart failure outcomes among participants with or without heart failure and independent of previous left ventricular ejection fraction[23]
- 1,545 subjects of the 6,979 participants were included in the CARMELINA-COG substudy, and linagliptin did not modulate cognitive decline over 2.5 years[24]

Box 3 Key features of CAROLINA[8,15,16]

- CAROLINA compared linagliptin 5mg with glimepiride 1 to 4 mg for a median follow-up of 6.3 years in 6,033 subjects with type 2 diabetes
- Mean age of subjects was 64 years, with a mean duration of diabetes of 6 years
- Mean baseline HbA_{1c} was 7.2% (55 mmol/mol)
- 42% of subjects had established atherosclerotic cardiovascular disease, 32% had coronary artery disease, 12% cerebrovascular disease, 7% peripheral artery disease and 4% investigator-reported heart failure
- 83% of subjects were on metformin, 28% sulfonylureas and 3% on an alpha glucosidase inhibitor

Figure 2. Event rates (%) comparing linagliptin and glimepiride for major adverse cardiovascular events (MACE), total mortality, cardiovascular mortality (CV mortality), non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure (hHF).



Box 4 Results of the CAROLINA trial[8]

Principal result

- No significant difference in MACE[8]

Other results from CAROLINA

- Accelerated cognitive decline, measured by the Mini-Mental State Examination and a composite measure of attention and executive function, declined equally in the linagliptin and glimepiride groups[18]
- Cardiovascular outcomes were comparable with linagliptin and glimepiride, but linagliptin had a significantly lower risk of hypoglycaemia and falls or fractures[25]
- In Asian patients, linagliptin demonstrated similar cardiovascular safety to glimepiride with a markedly lower rate of hypoglycaemia and modestly lower weight[26]

and published simultaneously in JAMA. Key features of the trial and baseline characteristics of subjects are described in Box 3. There was no significant difference in MACE in CAROLINA, so non-inferiority was established but not superiority (Figure 2, Box 4). There was also no significant difference in rates of unstable angina or hospitalisation for heart failure when comparing linagliptin with glimepiride.

Other results from CAROLINA

Again, the number of further publications from CAROLINA is small. An important substudy in CAROLINA was the CAROLINA-COGNITION study comparing the effects of linagliptin and glimepiride on accelerated cognitive decline (ACD), as diabetes is associated with an increased risk of cognitive impairment, particularly in patients with concomitant cardiovascular disease. This included 3,163 of the 6,033 subjects in CAROLINA. A paper describing the rationale and design of this substudy was published in 2018,[17] with results published in 2021.[18] No difference was observed in ACD, measured by the Mini-Mental State Examination (MMSE) and a more sensitive compositive measure of attention and executive functioning. Worryingly, ACD occurred in 27.8% of the linagliptin group and 27.6% of the glimepiride group, and the authors concluded that preventing cognitive impairment remains an unmet need in people with type 2 diabetes.

Discussion

Cardiovascular outcome trials with the DPP-4 inhibitors saxagliptin, alogliptin, sitagliptin and linagliptin are now completed, and it is unlikely that any other CVOTs will be performed with this class of drugs. Vildagliptin was approved for use in Europe before the EMA introduced detailed cardiovascular safety requirements. Vildagliptin has not been approved for use in the US, and no CVOT has been performed. A meta-analysis of events in 17,446 patients in 40 double-blind phase 3 and phase 4 studies showed no difference in the rate of adjudicated MACE or hospitalisation for heart failure between vildagliptin and comparators.[19]

Several other DPP-4 inhibitors are approved for use in Asian and South American countries, but these have not been studied in large CVOTs.[20] The once weekly DPP-4 inhibitor omarigliptin is approved in Japan and was under development in Europe and the US, including a CVOT. The trial was halted early for commercial reasons when the sponsor decided that approval would not be pursued in the US or Europe. This was an event-driven study and only 228 of the 632 required events were recorded when the trial was halted, so no conclusions can be drawn from the results.[21]

The results of the completed trials of DPP-4 inhibitors demonstrate safety for atherosclerotic cardiovascular events, with no increase compared to comparators, but no reduction in atherosclerotic events. For people with type 2 diabetes and existing atherosclerotic cardiovascular disease GLP-1 receptor agonists and SGLT2 inhibitors are a better treatment choice to further reduce events, as recommended in the consensus report by the

Key messages

- Two cardiovascular outcome trials were performed with linagliptin: CARMELINA comparing linagliptin and placebo, and CAROLINA comparing linagliptin with glimepiride
- In both trials linagliptin had no effect on cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure
- SGLT2 inhibitors and GLP-1 receptor agonists are better treatment options to reduce the risk of cardiovascular events in people with type 2 diabetes

American Diabetes Association and the EASD, with the additional benefit for patients that they are associated with weight loss.

Uncertainty remains about the effects of DPP-4 inhibitors on heart failure. No reduction in hospitalisation for heart failure was observed, and in SAVOR-TIMI 53 an increase in heart failure events was observed with saxagliptin. For the patient with heart failure, or with an increased risk of developing cardiovascular disease, SGLT2 inhibitors are a better choice to reduce further heart failure events.

The updated NICE guideline on the management of type 2 diabetes in adults retains DPP-4 inhibitors as first in a list of possible treatment options to be considered after metformin for patients who do not have chronic heart failure, established atherosclerotic cardiovascular disease or a high risk of cardiovascular disease.[22] If a DPP-4 inhibitor is being used, no dose adjustment is required for linagliptin for patients with renal impairment. Pioglitazone is second in the list, sulfonylureas third, and then SGLT2 inhibitors which can be considered "for some people". If the prescriber truly takes account of patient preferences, as recommended by NICE, then most patients will choose SGLT2 inhibitors for their associated weight loss rather than DPP-4 inhibitors which are weight-neutral or pioglitazone/sulfonylureas which clearly increase body weight.

Based on the results of CAROLINA if a sulfonylurea is to be prescribed then glimepiride has the greatest amount of cardiovascular safety data and should be the sulfonylurea of choice.

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References

1. Scirica BM, Bhatt DL, Braunwald E *et al*, for the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317–26. https://doi.org/10.1056/NEJMoa1307684
2. White WB, Cannon CP, Heller SR *et al* for the EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;**369**:1327–35. https://doi.org/10.1056/NEJMoa1305889
3. Green JB, Bethel A, Armstrong PW et al for the TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**373**:232–42. https://doi.org/10.1056/NEJMoa1501352
4. Fisher M. Saxagliptin and SAVOR-TIMI 53. *Br J Diabetes* 2019;**19**:34-6. https://doi.org/10.15277/bjd.2019.213
5. Fisher M. Alogliptin and EXAMINE. *Br J Diabetes* 2019;**19**:133-5. https://doi.org/10.15277/bjd.2019.230
6. Fisher M. Sitagliptin and TECOS. *Br J Diabetes* 2020;**20**:55-7. https://doi.org/10.15277/bjd.2020.242
7. Rosenstock J, Perkovic V, Johansen OE *et al* for the CARMELINA Investigators. Effects of linagliptin versus placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and high renal risk. The CARMELINA randomized clinical trial. *JAMA* 2019;**321**:69-79. https://doi.org/10.1001/jama.2018.18269
8. Rosenstock J, Kahn SE, Johansen OE *et al* for the CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA* 2019;**322**:1155-66. https://doi.org/10.1001/jama.2019.13772
9. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle H-J. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. *Cardiovasc Diabetol* 2012;**11**:3. https://doi.org/10.1186/1475-2840-11-3
10. Lehrke M, Leiter LA, Hehnke U *et al*. Safety and efficacy of linagliptin in patients with type 2 diabetes mellitus and coronary artery disease: analysis of pooled events fo 19 clinical trials. *J Diabetes Complications* 2016;**30**:1378-84. https://doi.org/10.1016/j.jdiacomp.2016.06.015
11. Marx N, McGuire DE, Perkovic V *et al*. Composite primary end points in cardiovascular outcome trials involving type 2 diabetes patients: should unstable angina be included in the primary end point? *Diabetes Care* 2017;**40**:1144-51. https://doi.org/10.2337/dc17-0068
12. Rosenstock J, Perkovic V, Alexander JH *et al* on behalf of the CARMELINA® investigators. Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascualr outcomE study with LINAgliptin (CARMELINA®): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. *Cardiovasc Diabetol* 2018;**17**:39. https://doi.org/10.1186/s12933-018-0682-3
13. Perkovic V, Toto R, Cooper ME *et al* on behalf of the CARMELINA investigators. Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: secondary analysis of the CARMELINA randomized trial. *Diabetes Care* 2020;**43**:1803-12. https://doi.org/10.2337/dc20-0279
14. Wanner C, Cooper ME, Johansen OE *et al* on behalf of the CARMELINA investigators. Effect of linagliptin versus placebo on cardiovascular and kidney outcomes in nephrotic-range proteinuria and type 2 diabetes: the CARMELINA randomized controlled trial. *Clinical Kidney Journal* 2021;**14**:226-36. https://doi.org/10.1093/ckj/sfaa225
15. Rosenstock J, Marx N, Kahn SE et al. Cardiovascular outcome trials in type 2 diabetes and the sulponylurea controversy: rationale for the active-comparator CAROLINA trial. *Diabetes & Vascular Disease Research* 2013;**10**:289-301. https://doi.org/10.1177/1479164112475102
16. Marx N, Rosenstock J, Kahn SE *et al*. Design and baseline characteristics of the CARdiovascular Outcome trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA®). *Diabetes & Vascular Disease Research* 2015;**12**:164-74. https://doi.org/10.1177/1479164115570301
17. Biessels GJ, Janssen J, van den Berg E *et al* on behalf of the CAROLINA® investigators. Rationale and design of the CAROLINA®-cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus. *BMC Nuerology* 2018;**18**:7. https://doi.org/10.1186/s12883-018-1014-7
18. Biessels GJ, Verhagen C, Janssen J *et al*. Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study. *Diabetologia* 2021;**64**:1235-45. https://doi.org/10.1007/s00125-021-05393-8
19. McInnes G, Evans M, Del Prato S *et al*. Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients. *Diabetes Obes Metab* 2015;**17**:1085-92. https://doi.org/10.1111/dom.12548
20. Mackin S, Currie G. DPP-4 inhibitors. In: Fisher M, McKay G, Llano A editors. Diabetes Drug Notes 2022, 67-94. John Wiley, Chichester.

21. Gantz I, Chen M, Suryawanshi S *et al*. A randomized, placebo-controlled study of the cardiovascular safety of the once weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes. *Cardiovasc Diabetol* 2017; **16**:112. https://doi.org/10.1186/s12933-017-0593-8
22. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. [NG28]. 02 December 2015, updated 31 March 2022https://www.nice.org.uk/guidance/ng28 (accessed 31 March 2022).
23. McGuire DK, Alexander JH, Johansen OE *et al* on behalf of the CARMELINA investigators. Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes at high cardiovascular risk and renal risk in CARMELINA. *Circulation* 2019;**138**:351-61. https://doi.org/10.1161/CIRCULATIONAHA.118.038352
24. Biessels GJ, Verhagen C, Janssen J *et al* on behalf of the CARMELINA investigators. Effect of linagliptin on cognitive performance in patients with type 2 diabetes and cardiorenal comorbidities: the CARMELINA randomized trial. *Diabetes Care* 2019;**42**:1930-8. https://doi.org/10.2337/dc19-0783
25. Espeland MA, Pratley RE, Rosenstock J *et al*. Cardiovascular outcomes and safety with linagliptin, a dipeptidyl peptidase-4 inhibitor, compared with the sulphonylurea glimepiride in older people with type 2 diabetes: a subgroup analysis of the randomized CAROLINA trial. *Diabetes Obes Metab* 2021; **23**:569-80. https://doi.org/10.1111/dom.14254
26. Kadowaki T, Wang G, Rosenstock J *et al*. Effect of linagliptin, a dipeptidyl peptidase-4 inhibitor, compared with the sulfonylurea glimepiride on cardiovascular outcomes in Asians with type 2 diabetes: subgroup analysis of the randomized CAROLINA® trial. *Diabetol Int* 2021;**12**:87-100. https://doi.org/10.1007/s13340-020-00447-5