

Dipeptidyl peptidase-4 inhibitors and cardiovascular and renal disease in type 2 diabetes: What have we learned from the CARMELINA trial?

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Abstract

Dipeptidyl peptidase-4 inhibitors are a relatively new class of oral anti-hyperglycaemic drugs to treat type 2 diabetes through prevention of degradation of incretins by the dipeptidyl peptidase-4 enzyme. The large trials evaluating the dipeptidyl peptidase-4 inhibitors sitagliptin, alogliptin and saxagliptin demonstrated safety for cardiovascular disease. Post hoc analyses on renal endpoints yielded similar findings. Linagliptin is the latest dipeptidyl peptidase-4 inhibitor evaluated in the CARMELINA trial. CARMELINA included individuals with type 2 diabetes and high cardiovascular and renal risk. Even in this setting, linagliptin displayed cardiovascular safety. CARMELINA also removed initial concerns for heart failure as a class-specific side-effect of dipeptidyl peptidase-4 inhibitors, as no signal for heart failure was found. Although numerically low, CARMELINA did confirm increased rates of pancreatitis in the linagliptin group, suggesting that pancreatitis is a class-specific side-effect of dipeptidyl peptidase-4 inhibitors. Linagliptin reduced progression of albuminuria, but had no effect on other hard renal endpoints. Overall, dipeptidyl peptidase-4 inhibitors are safe but do not confer significant reductions in complications observed for some of the other new glucose-lowering drugs. However, linagliptin is a safe alternative in renal impairment, without dose adjustment. Furthermore, dipeptidyl peptidase-4 inhibitors may hold value as alternatives to sulfonyl-urea derivatives or as an add-on therapy to delay insulin prescription given their favourable safety profile.

Keywords

Dipeptidyl peptidase-4 inhibitors, cardiovascular disease, type 2 diabetes, chronic kidney disease, clinical trials

Introduction

Dipeptidyl peptidase-4 inhibitors (DPP4i) are a relatively new class of oral anti-hyperglycaemic drugs for the treatment of type 2 diabetes. Their anti-hyperglycaemic effect is achieved through prevention of degradation of incretin hormones [mainly glucagon-like peptide 1 (GLP1)] by dipeptidyl peptidase-4 (DPP4). GLP1 improves meal-stimulated insulin secretion by pancreatic β cells, reducing hyperglycaemia. DPP4i are not associated with weight gain or an excess risk of hypoglycaemia¹ and may therefore serve as an alternative to sulfonyl-urea derivatives and may delay insulin use in type 2 diabetes as an add-on therapy, especially for people who have contraindications for other glucose-lowering drugs, such as metformin, sodium glucose reuptake inhibitors (SGLT2i) or GLP1 analogues.

Although initial smaller studies suggested that DPP4i may confer cardiovascular protection,² the large trials evaluating the DPP4i alogliptin [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial],³ sitagliptin [Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial]⁴

and saxagliptin [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial]⁵ showed no obvious benefits with regard to cardiovascular protection compared to the control arm of these studies, and in fact concerns for an elevated risk of heart failure were raised for saxagliptin. These findings underline the importance of large clinical trials by showing

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that a weighted sum of smaller trials may sometimes yield a different result than a large multi-centre trial.⁶

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) trial is the latest of these large multi-centre trials, comparing the addition of linagliptin or placebo to usual care, with a prespecified primary cardiovascular and secondary renal endpoint.^{7,8} By design, participants were at a high risk of cardiovascular disease (CVD) and chronic kidney disease (CKD). Several pre-clinical studies heightened expectations for linagliptin to reduce diabetic complications. First, linagliptin reduced atherosclerosis in non-diabetic apolipoprotein E (ApoE)-deficient mice.⁹ In addition, linagliptin reduced brain atrophy in a rodent model of ischaemic stroke.¹⁰ Furthermore, linagliptin reduced renal fibrosis in diabetic mice,¹¹ independently of glucose control but rather due to normalization of endothelial-to-mesenchymal transition. Based on these potential beneficial effects in rodents and its favourable pharmacokinetic profile in renal failure,¹² linagliptin remained of special interest as a glucose-lowering agent of the DPP4i class, for people with CKD in particular.

In this review, we summarize and critically evaluate the key findings (including adverse events) of the pivotal trials evaluating cardiovascular and renal endpoints and how the recently published CARMELINA trial may influence our insight into the role of DPP4i in managing type 2 diabetes.

DPP4i and metabolic control

A large meta-analysis mainly including trials with short follow-up times reported that DPP4i on average reduced glycated haemoglobin (HbA1c) by 0.7%. Interestingly, the major trials reported more modest reductions in HbA1c at longer follow-up times, of around 0.3% for alogliptin and sitagliptin.^{3,4} This difference may be explained by the repeated HbA1c measurements in the TECOS trial, showing the largest decrease of HbA1c by sitagliptin in the first 4 months that slightly dispersed over the 4-year follow-up. Similarly, the average glycaemic control improved by 0.36% in the CARMELINA trial, without associated weight gain and no increased risk of hypoglycaemia. CARMELINA, therefore, confirms that DPP4i only achieve modest effects on glucose control compared to usual care, even in the setting of high renal and cardiovascular risk, where clinicians tend to be more careful in achieving a glycaemic target in fear of hypoglycaemia and other adverse events.

In conclusion, DPP4i yield mild reductions in HbA1c without the added benefit of weight loss that is observed with the use of GLP1 analogues. However, DPP4i seem to have a few side-effects, and due to their mechanism of action, the risk of hypoglycaemia attributable to the use of DPP4i is negligible.³⁻⁵

Cardiovascular endpoints

The major cardiovascular safety trials investigated whether the addition of alogliptin, saxagliptin, sitagliptin or linagliptin to usual care was non-inferior to placebo. CVD was defined in these studies as major adverse cardiovascular events (MACE), as either cardiovascular death or ischaemic events. Although the exact definitions of the primary outcomes were not fully consistent across these trials (Table 1), these studies have still yielded similar results.

Although the TECOS study showed that the addition of sitagliptin versus placebo to usual care was non-inferior for MACE after a median follow-up of 3 years, no obvious benefit of sitagliptin use on cardiovascular risk was found. Interestingly, a prior meta-analysis that mainly evaluated smaller phase 2 trials comparing the use of sitagliptin to sulfonyl-urea derivative use suggested that cardiovascular risk was lower in individuals receiving sitagliptin.¹³ Whether this intriguing finding holds true in a large trial will be evaluated in the upcoming Cardiovascular Outcome Study of Linagliptin Versus Glimperide in Patients With Type 2 Diabetes (CAROLINA) study, where linagliptin will be compared to the sulfonyl-urea derivative glimepiride in a large randomized study. This is of importance, as the initial meta-analyses was not powered to address cardiovascular outcomes and in general contained study populations of lower cardiovascular and renal risk.¹³

Non-inferiority for MACE for the addition of saxagliptin versus placebo to usual care was evaluated in the SAVOR-TIMI 53 trial.⁵ This study mainly included participants with a very high burden of prior CVD and cardiovascular risk factors. This study alarmingly reported increased incidence of hospitalization for heart failure, which sparked subsequent analyses for this endpoint in the other major clinical trials evaluating incretin therapies. Alogliptin was evaluated in the setting of even higher cardiovascular risk in the EXAMINE trial. This study included participants that recently suffered an acute coronary syndrome. Even in this setting, alogliptin was non-inferior to usual care, but alogliptin did not demonstrate any obvious benefit with regard to cardiovascular protection either.³ CARMELINA now reveals that linagliptin is also non-inferior for MACE, even when a large portion of the study participants had both CVD and CKD at the time of randomization. This was also the case when cardiovascular death, non-fatal MI and stroke were analysed separately. However, since the event rate for MACE was nearly identical between linagliptin and placebo, no evidence for cardiovascular protection was found.

Although older individuals with diabetes are generally underrepresented in clinical trials, several studies suggest that DPP4i display similar efficacy and safety profiles in older and younger individuals. When older individuals (>75 years) were analysed separately for saxagliptin and sitagliptin,^{14,15} the main findings of the TECOS and

Table 1. The major clinical trials evaluating the cardiovascular safety of DPP4i in type 2 diabetes.

Trial	Compound evaluated	Year published	Participants randomized	Median follow-up time (years)	MACE definition	Main inclusion criteria at baseline
EXAMINE	Alogliptin	2013	5380	1.5	3P: cardiovascular death, non-fatal MI or stroke	Recent myocardial infarction or unstable angina requiring hospitalization HbA1c: 6.5%–11.0% (7%–11.0% when on insulin)
SAVOR-TIMI 53	Saxagliptin	2013	16,492	2.1	3P: cardiovascular death, non-fatal MI or stroke	History of, or high risk for, cardiovascular disease >40 years old HbA1c: 6.5%–12.0%
TECOS	Sitagliptin	2015	14,735	3.0	4P: cardiovascular death, non-fatal MI or stroke, or hosp. unstable angina	Established cardiovascular disease >50 years old HbA1c: 6.5%–8%
CARMELINA	Linagliptin	2018	6991	2.2	3P: cardiovascular death, non-fatal MI or stroke	High cardiovascular (prior CVD or albuminuria) and renal risk HbA1c: 6.5%–10.0%

EXAMINE³: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53⁵: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction; TECOS⁴: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA^{7,8}: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; MACE: major adverse cardiovascular events; MI: myocardial infarction; 3P: 3-point; 4P: 4-point; HbA1c: glycated haemoglobin; CVD: cardiovascular disease.

Data were derived from the literature.^{3–5,7,8}

SAVOR-TIMI 53 trials remained similar despite elevated cardiovascular risk in the older subgroups. Although to our knowledge no post hoc analyses of the older participants in the CARMELINA trial have been published yet, a separate smaller phase 3 trial demonstrated safety of linagliptin in older individuals (>70 years) as well.¹⁶

Renal endpoints

The US Food and Drug Administration currently requires demonstration of cardiovascular safety for all new glucose-lowering treatments.¹⁷ Therefore, large trials were designed to primarily evaluate non-inferiority of DPP4i for MACE and evaluated whether DPP4i may confer renal protection or harm in secondary and/or post hoc analyses. Although the exclusion criteria on end-stage renal failure (ESRF) where more or less similar across the four major trials (Table 2), CARMELINA is the first to actively include individuals with established CKD up to an estimated glomerular filtration rate (eGFR) < 15 mL/min per 1.73 m².

Sitagliptin was associated with a slightly greater decline in eGFR when added to usual care, and this was consistent for all post-randomization visits. No effect on albuminuria was reported. The EXAMINE trial reported only that no difference in risk of dialysis was found in the initial publication, at low incidence for this endpoint. Saxagliptin reduced albuminuria, without influencing eGFR in SAVOR-TIMI 53.¹⁸ Interestingly, this effect was independent of HbA1c reduction. A pooled analysis of four smaller trials including participants with CKD showed that

linagliptin reduced albuminuria, heightening expectations for the renal outcomes of the CARMELINA study,¹⁹ after initial promising animal studies suggested renal protection as well.¹¹ CARMELINA included a prespecified renal endpoint as an important secondary outcome and confirmed that linagliptin reduced the progression of albuminuria as reported previously. This finding is interesting given the high proportion of individuals with preexisting CKD at baseline, resulting from CARMELINA's inclusion criteria on either CVD or presence of CKD up to ESRF. However, no obvious protection against the decline of eGFR and/or development of end-stage renal disease was recorded, and thus linagliptin did not display obvious protection on the hard renal endpoints.⁸

Taken together, these four studies suggest that DPP4i may delay the progression of albuminuria, but do not seem to offer any obvious renal protection otherwise. The discrepancy between the effects of saxagliptin and linagliptin on albuminuria but not on hard renal endpoints is of interest and will likely be addressed in long-term follow-up studies of SAVOR-TIMI 53 and CARMELINA. Given the higher prevalence in preexisting CKD, CARMELINA may be most adequately powered to detect any potential renal benefits in long-term analyses.

Use of DPP4i in patients with established CKD

While most DPP4i are predominantly excreted in urine, linagliptin is mainly excreted in faeces without metabolic

Table 2. Dose adjustments according to eGFR in the major clinical trials.

Trial	Compound evaluated	Renal exclusion criteria	Dose adjustments
EXAMINE	Alogliptin	Requiring dialysis 14 days prior to screening	60 mL/min per 1.73 m ² : 25 mg 30–60 mL/min per 1.73 m ² : 12.5 mg <30 mL/min per 1.73 m ² : 6.25 mg
SAVOR-TIMI 53	Saxagliptin	ESRF requiring dialysis, transplantation or serum creatinine > 6.0 mg per decilitre (530 µmol per litre)	>50 mL/min per 1.73 m ² : 5 mg <50 mL/min per 1.73 m ² : 2.5 mg
TECOS	Sitagliptin	eGFR < 30 mL/min per 1.73 m ² or requiring dialysis	>50 mL/min per 1.73 m ² : 100 mg <50 mL/min per 1.73 m ² : 50 mg
CARMELINA	Linagliptin	eGFR < 15 mL/min per 1.73 m ² or requiring dialysis	None

EXAMINE³: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53⁵: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction; TECOS⁴: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA^{7,8}: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; eGFR: estimated glomerular filtration rate; ESRF: end-stage renal failure.

Data were derived from the literature.^{3–5,7,8}

Table 3. Statistical signals for the major safety concerns in the large clinical trials evaluating DPP4i.

Concern	Alogliptin (EXAMINE)	Saxagliptin (SAVOR TIMI 53)	Sitagliptin (TECOS)	Linagliptin (CARMELINA)
Heart failure	No	Yes	No	No
Pancreatitis	No	No	Borderline	Yes
Pancreatic cancer	No	No	No	No

EXAMINE³: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53⁵: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction; TECOS⁴: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA⁸: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus.

Data were derived from the literature.^{3–5,8}

conversion by the liver. Linagliptin has a broad therapeutic window and therefore its use was anticipated to be safe in individuals with CKD without dose adjustment.¹² The CARMELINA trial confirmed that linagliptin can be used safely without dose adjustment across a large spectrum of CKD. Indeed, CARMELINA recruited a high-risk population with a very high event rate, in particular with respect to cardiovascular death, and this trial has nonetheless confirmed safety of linagliptin across a large spectrum of CKD. CARMELINA actively included many individuals with an eGFR below 30 mL/min per 1.73 m². CARMELINA did exclude participants with an eGFR below 15 mL/min per 1.73 m² or requiring dialysis. Therefore, its safety profile in ESRF is not known. Theoretically, linagliptin may be well tolerated in this group as well, based on its pharmacokinetic profile, but this has not been formally addressed in CARMELINA.

Although the other major trials used similar exclusion criteria as CARMELINA (Table 2), none of these trials recruited for CKD. Nonetheless, for the other major DPP4i post hoc analyses have been published to address safety in participants with CKD with appropriate dose adjustments (Table 2). Post hoc analysis of the TECOS study showed that the presence of CKD (defined as an eGFR < 60 mL/min per 1.73 m²) strongly increased the risk of serious adverse events during follow-up, but the use of sitagliptin did not further increase this risk.²⁰

Whether sitagliptin is safe below an eGFR of 30 mL/min per 1.73 m² is unknown, as the TECOS trial excluded these participants. Saxagliptin did not increase renal or cardiovascular events, irrespective of baseline eGFR, and SAVOR-TIMI 53 included individuals with an eGFR below 30 mL/min per 1.73 m², but excluded participants with ESRF as well.²¹ Alogliptin only excluded participants on dialysis at baseline, but its study participants had an average eGFR well above 60 mL/min per 1.73 m².³

Safety concerns

With the introduction of DPP4i, class-specific safety concerns arose regarding elevated risk of heart failure,²² pancreatic cancer and pancreatitis.²³ Although these initially concerning findings could not be consistently replicated across the clinical trials (Table 3), these studies may have lacked statistical power to consistently detect these rare but serious adverse events. Therefore, although most post hoc analyses of the major trials are reassuring, post-marketing studies will further assess the safety of DPP4i.

Heart failure

Because concerns about heart failure associated with saxagliptin use were raised in the SAVOR-TIMI 53 trial in which a large proportion of participants had suffered a

cardiovascular event, a post hoc analysis was performed to address whether alogliptin increased the risk of heart failure as well. No increased risk of heart failure was reported even though all participants had suffered a coronary event at baseline.²⁴ In line, a similar post hoc analysis showed no increased risk of heart failure for sitagliptin either, with all participants having suffered CVD prior to study inclusion.²⁵ Furthermore, a large observational study reassuringly did not find any increased risk of heart failure in DPP4i users in general.²⁶ Indeed, the CARMELINA trial also included an analysis of heart failure risk and reassuringly found once more no signal for an increased risk of heart failure associated with linagliptin use,⁸ even among participants with a history of heart failure, CKD and independently of left ventricular ejection fraction.²⁷ The CARMELINA trial was particularly suitable to address this issue, as 26.8% individuals already had established heart failure at baseline. If anything, point estimates even seemed to point towards slight protection by linagliptin, but this is likely a chance finding as this was not reported for any of the other DPP4i.

Pancreatitis and pancreatic cancer

Although numerically infrequent, sitagliptin use was associated with a slightly higher risk of pancreatitis, and this was borderline significant, while the risk of pancreatic cancer was not significantly increased. For saxagliptin, no such elevated risk of either pancreatitis or pancreatic cancer was reported. A large meta-analysis has found no association between DPP4i and pancreatic cancer, but did detect a small risk of pancreatitis.²⁸ The CARMELINA trial seems to confirm this finding. Linagliptin use was associated with a slightly elevated risk of pancreatitis, while no elevated risk of cancers linked to linagliptin use were reported, although these events were numerically infrequent. Furthermore, pancreatic cancers were rare but numerically higher in the linagliptin group than in the placebo group,⁸ although the oncology committee of that study deemed only one case in each treatment group to be possibly related to study drug treatment.

Overall, these studies suggest that there is a small but real risk of pancreatitis associated with the use of DPP4i. The CARMELINA trial seems to confirm that this is a class effect of DPP4i. Therefore, the use of these agents should be carefully (re)considered for patients at an increased risk of pancreatitis.²³

Discussion

With the completion of the four large trials evaluating the cardiovascular safety of the addition of a DPP4i to usual

care, we can conclude that DPP4i seem to be relatively safe and well tolerated, but do not seem to confer any obvious cardiovascular or renal benefit on the short term. Furthermore, DPP4i have a relatively modest effect on HbA1c, although no increased risks of hypoglycaemia or weight gain have been reported. An additional benefit of linagliptin in particular, is its safe use in patients with renal impairment without dose adjustment. Although DPP4i are linked to some serious adverse events (pancreatitis in particular), their incidence seems low. CARMELINA now removes concerns for the risk of heart failure as a class effect of DPP4i, again demonstrating safety on this endpoint. Post-marketing studies will further address the prevalence of adverse events associated with DPP4i use.

Sitagliptin, alogliptin, saxagliptin and now linagliptin did not show any obvious cardiovascular or renal benefits in the large clinical trials. Although these studies demonstrated non-inferiority for their primary endpoints (MACE), not one of these trials suggested obvious cardiovascular or renal protection by DPP4i. Administration of the GLP1 analogues liraglutide and semaglutide directly increases GLP1 levels, seems superior to DPP4i in terms of glucose-lowering potency and seems to confer cardiovascular protection and weight loss.^{29,30} Using an entirely different mechanism of action, SGLT2i lower glucose through enhancement of glycosuria. The seminal Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose (EMPA-REG) study has put empagliflozin at the forefront of these novel glucose-lowering treatments.³¹ Cardiovascular protection was also shown for canagliflozin, another SGLT2i,³² with a possible renoprotective effect, although an increased risk for amputations was observed. The latest SGLT2i evaluated, dapagliflozin, was associated with a lower risk of hospitalization of heart failure and CKD, but did not reduce MACE.³³ Overall, a recent network meta-analysis showed that the use of SGLT2i and GLP1 analogues is associated with lower all-cause mortality compared to the use of DPP4i.³⁴ Although these large cardiovascular outcome trials have yielded a wealth of data on the efficacy of newer glucose-lowering drugs, it remains unclear whether this gain in knowledge is offset by the tremendous resources needed to perform these studies. Furthermore, the generalizability of these studies is limited to their (high-risk) study populations. Moreover, the short follow-up times of these studies may be insufficient to capture the true benefit or harm of these interventions. Improvement of the design of these large trials is a major challenge in the continued efforts to improve management of type 2 diabetes.³⁵

In conclusion, the new glucose-lowering drugs have opened up a range of treatment options for type 2 diabetes. DPP4i achieve an overall modest reduction of HbA1c,

without obvious protection against diabetic complications. Therefore, DPP4i are unlikely to become the cornerstone treatment of type 2 diabetes, particularly given the results of the trials that evaluated the major SGLT2i and GLP1 analogues. However, DPP4i may remain valuable as an add-on therapy or serve as an alternative to sulfonyl-urea derivatives since DPP4i are not associated with hypoglycaemia or weight gain. We are therefore awaiting results from the CAROLINA study, in which linagliptin will be compared to glimepiride to address this question. CARMELINA was unique in its active inclusion of patients with a very high burden of both CVD and CKD, and still demonstrated safety and tolerability in this population. Therefore, the main advantage of DPP4i is that they can be used with relative safety in individuals with CKD and CVD, for linagliptin even without dose reduction. For specific subpopulations, DPP4i may therefore provide an even greater flexibility to the recently expanded arsenal to reduce hyperglycaemia in type 2 diabetes.

Key messages

- Linagliptin is safe regardless of kidney function without dose reduction up to an eGFR of 15 mL/min per 1.73 m².
- Alogliptin, saxagliptin, sitagliptin and linagliptin did not show any obvious cardiovascular or renal benefits on hard endpoints and have generally a modest effect on HbA1c.
- When compared to SGLT2i or GLP1, DPP4i do not confer similar short-term cardiovascular or renal protection, but may be useful as an add-on therapy to delay insulin use.
- The CARMELINA trial removed concerns for heart failure as a class-specific side-effect of DPP4i, but confirmed a small but consistent increase in risk of pancreatitis associated with DPP4i use.
- DPP4 inhibitors are generally well tolerated and may be preferable to sulfonyl-urea derivatives in some settings. This is still under active investigation.

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