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Commentary

CARMELINA: An important piece of the DPP-4 inhibitor CVOT puzzle

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of glucose-lowering agent for type 2 diabetes (T2D) that are commonly used in clinical practice. With the recent disclosure of data from the CARMELINA cardiovascular outcomes trial (CVOT), which investigated linagliptin, CV and renal outcomes data are now available for four agents in the DPP-4 inhibitor class that are approved in most markets. To consider how the CARMELINA study may be interpreted, and the relevance for our clinical practice, we convened as an expert group of diabetes specialists from the Central and Eastern Europe region to discuss the new disclosures. Our discussions revealed a general confidence in safety across the class that is further supported by CARMELINA. However, we also concluded that there are important differences in the available evidence level between agents in the setting of heart failure and data on renal outcomes. Here, we noted the clinical relevance to our practice of the study population in CARMELINA, which is unique among CVOTs in including a majority of patients with chronic kidney disease (CKD). Given the risk for future development of

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renal impairment that is associated with T2D even in patients without current overt CKD, we believe that the CARMELINA study provides important new insights that are clinically relevant for a broad range of patients. Finally, we discuss how these insights can be integrated into the approach to the pharmacotherapeutic management of hyperglycaemia that is recommended in newly updated guidelines.

1. Introduction

The prevalence of comorbidities in patients with type 2 diabetes (T2D) is a consideration when designing, and interpreting, clinical studies that investigate antidiabetic agents [1]. Cardiovascular disease (CVD) and chronic kidney disease (CKD) are comorbidities that are not only highly prevalent in patients with T2D but also largely responsible for the continued excess mortality in these patients [2]. By including patients with CVD at baseline, cardiovascular outcomes trials (CVOTs) have enabled clinicians to make evidence-based treatment decisions regarding the morbidity and mortality burden posed by CVD in patients with T2D [3]. However, until now, patients with CKD and renal outcomes had not been well represented in CVOTs [1].

At the 2018 European Association for the Study of Diabetes (EASD) annual meeting, study results were disclosed for the CARMELINA CVOT, which investigated the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin in a patient cohort that included both a high proportion of patients with CVD and an unprecedented, major representation of patients with CKD [4]. CARMELINA was also designed, and powered, to assess renal outcomes, in addition to the primary CV outcome [1]. To consider how clinicians can use the CARMELINA study to better inform evidence-based treatment in routine clinical care, where CKD is one of the most prevalent comorbidities of T2D [5], we convened as a group of expert endocrinologists, nephrologists and internists from the Central and Eastern Europe region shortly following the disclosures.

In this article, we will summarise our discussions, in the hope that by sharing our insights we can guide other clinicians in the region as they implement the findings of CARMELINA into their clinical practice, using recently updated guidelines. Our perspectives on CARMELINA should stimulate a useful debate on how linagliptin may be able to simplify treatment by offering an efficacious therapeutic option with a robust safety profile for a broad range of patients with T2D.

2. Why include renal patients in a CVOT?

2.1. *Burden of CKD*

The global burden of CKD has been increasing in recent decades [5,6], with diabetes as the most important contributing factor [5,6]. Impaired renal function in patients with T2D is a major predictor of excess mortality and adverse outcomes [2,7-9], including CV death and other CV events [2,10] (Fig. 1).

As renal function naturally declines with age, and diabetes is a life-long disease, even patients without overt CKD are at risk of future development of the comorbidity, and screening for the presence of CKD in patients with T2D is widely recommended [5]. An analysis of 4,006 patients with T2D from the observational UK Prospective Diabetes Study (UKPDS) found that 53% of patients developed CKD over a median of 15 years' follow-up subsequent to diagnosis, including 28% who developed reduced renal function, with or without albuminuria [11]. Similarly, disease progression in patients with existing CKD can be expected, and T2D is the most common cause of end-stage renal disease [5].

Although renal function and albuminuria endpoints have been included as secondary outcomes in several CVOTs [12], these studies were primarily designed to assess CV, and not renal, outcomes [1]. Furthermore, renal analyses are often underpowered and study populations have been designed to include patients with CV risk burden, whereas renal risk has been underrepresented [1]. Indeed, although an estimated ~50% of patients with T2D are affected by CKD [5], no previous CVOT has been designed to specifically include this population [1], and in some cases patients with reduced renal function have been actively excluded [13]. Consequently, CVOTs have included no more than between one-quarter and one-third of patients with reduced renal function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2), and even fewer patients with severely reduced renal function (eGFR < 30 ml/min/1.73 m^2) have been included in these studies [1].

2.2. *DPP-4 inhibitor CVOTs — What do we know so far?*

DPP-4 inhibitors are a class of glucose-lowering agents for patients with T2D. They achieve a therapeutic effect by inhibiting cleavage of glucagon-like peptide-1 (GLP-1), which is an incretin hormone that is produced in the gut to stimulate insulin secretion when glucose levels rise following a meal [14]. In addition to stabilising the GLP-1 hormone, DPP-4 inhibitors may reduce degradation of other targets of the DPP-4 enzyme, including stromal cell-derived factor 1 (SDF-1), brain natriuretic peptidase (BNP), neuropeptide Y (NPY) and peptide YY (PYY) [14]. It has been suggested that inhibiting these additional pathways may lead to beneficial outcomes, such as improved diabetic wound healing via SDF-1 inhibition [14].

Prior to CARMELINA, CVOTs had been reported for three DPP-4 inhibitors approved for clinical use in the European Union: saxagliptin [15], alogliptin [16,17] and sitagliptin [18-20]. Safety was uniformly demonstrated across the class for atherosclerotic CV outcomes, with a neutral effect on major adverse CV event (MACE) outcomes for all three agents [1] (Table 1). However, the safety of the class for hospitalistion for heart failure (HHF) risk was uncertain, with a significant

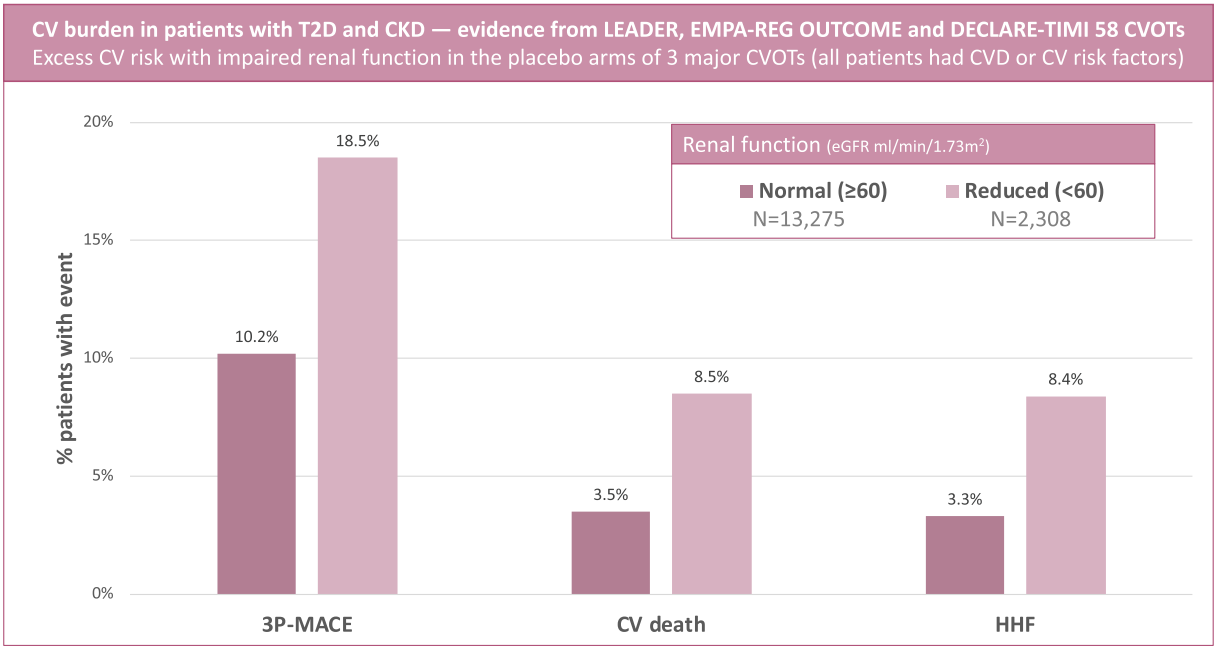

Fig. 1 – Excess CV risk with impaired renal function in patients with T2D. CV event rates in the placebo arms of CVOTs show the excess CV morbidity burden associated with reduced renal function in patients with T2D and CV risk. Shown here are pooled events for 3P-MACE, CV death and HHF from the placebo arms of three major CVOTs: EMPA-REG OUTCOME [36] (empagliflozin), LEADER [37] (liraglutide) and DECLARE-TIMI 58 [13] (dapagliflozin). Events are shown stratified according to renal function at baseline. 3P-MACE is a composite of CV death, stroke or myocardial infarction. All patients in the three CVOTs either had established CVD or multiple CV risk factors. 3P-MACE, 3-point major adverse CV event. CV, cardiovascular. CVD, CV disease. CVOT, CV outcomes trial. eGFR, estimated glomerular filtration rate. HHF, hospitalisation for heart failure. T2D, type 2 diabetes.

increase of 27% with saxagliptin [15] (Table 1), which has added to concerns that some antidiabetic agents that stimulate insulin signalling might increase heart failure risk [21,22]. Non-insulin-related mechanisms have been proposed to additionally contribute to heart failure risk with some DPP-4 inhibitors [21].

Long-term renal function is of particular clinical relevance for treatment with DPP-4 inhibitors, which are with the exception of linagliptin renally excreted (Fig. 2A), necessitating dose adjustment with declining renal function [1]; however, the emerging renal evidence from DPP-4 inhibitor CVOTs to date is incomplete and not consistent across the class (Fig. 2B). A limitation of these CVOTs has been that only a minority of patients in the study cohorts had reduced renal function at baseline [1,19] (Fig. 3A), while renal outcomes were usually only assessed as exploratory or post hoc analyses [15-20]. Analyses of safety outcomes stratified by baseline renal risk have underscored the increased morbidity experienced by patients with CKD in addition to T2D [16,19,20,23] (Fig. 3B). Heart failure risk may be of particular concern in these patients, owing to coincident morbidity between heart failure and CKD that is driven by diverse cardio-renal interactions — including haemodynamic and neurohormonal mechanisms, such as activation of the renin–angiotensin–aldosterone system, in addition to processes such as inflammation that are common to CKD, CVD and diabetes [24].

3. CARMELINA: A first among CVOTs

CARMELINA is a newly reported CVOT investigating the DPP-4 inhibitor linagliptin [1]. Unique among DPP-4 inhibitors in clinical use, linagliptin has a mainly non-renal elimination profile (Fig. 2A), which enables clinicians to prescribe the drug without dose adjustment when renal function declines [1]. As such, during the design of CARMELINA, the opportunity was recognised to include a substantial number of patients with CKD (Fig. 3A) in addition to patients with CVD, as these patients will remain suitable for linagliptin at a single dose regardless of renal function decline [1]. Thus, the CARMELINA cohort comprised patients with T2D and CVD and/or CKD, in contrast to the limited renal risk population of other CVOTs [1].

3.1. *Composition of the renal risk cohort*

CARMELINA is the first DPP-4 inhibitor CVOT to have a sizeable proportion of patients with renal impairment and/or characterised macroalbuminuria at baseline [1] (Table 2). The proportion of patients with reduced renal function at baseline was more than two-fold higher in CARMELINA than other DPP-4 inhibitor CVOTs, five-fold higher for severely reduced renal function (eGFR < 30 ml/min/1.73 m^2), and between four- and eight-fold higher for macroalbuminuria (urinary albumin-to-creatinine ratio > 300 mg/g) [1,15,16,19]

Table 1 – Cardiovascular outcomes in DPP-4 inhibitor CVOTs.

	Study drug			
	Alogliptin [16,17]	Linagliptin [4]	Saxagliptin [15]	Sitagliptin [18,35]
3P-MACE (CV death, non-fatal stroke or non-fatal MI)	HR 0.96 (95% CI upper bound < 1.16)	All CVOTs demonstrated non-inferiority HR 1.02 (95% CI 0.89, 1.17)	HR 1.00 (95% CI 0.89, 1.12)	HR 0.99 (95% CI 0.89, 1.11)
CV death	HR 0.79 (95% CI 0.60, 1.04)	HR 0.96 (95% CI 0.81, 1.14)	HR 1.03 (95% CI 0.87, 1.22)	HR 1.03 (95% CI 0.89, 1.19)
Non-fatal MI	HR 1.08 (95% CI 0.88, 1.33)	HR 1.15 (95% CI 0.91, 1.45)	HR 0.95 (95% CI 0.80, 1.12)	HR 0.95† (95% CI 0.81, 1.11)
Non-fatal stroke	HR 0.91 (95% CI 0.55, 1.50)	HR 0.88 (95% CI 0.63, 1.23)	HR 1.11 (95% CI 0.88, 1.39)	HR 0.97† (95% CI 0.79, 1.19)
Hospitalisation for heart failure*	Neutral effect HR 1.07 (95% CI 0.78, 1.15) *Note: 76% increase in subgroup with no history of heart failure*	There were mixed results between CVOTs Neutral effect HR 0.90 (95% CI 0.74, 1.08) *Note: neutral effect was consistent across renal risk groups*	27% increase HR 1.27 (95% CI 1.07, 1.51)	Neutral effect HR 1.00 (95% CI 0.83, 1.20) *Note: neutral effect was consistent across 21 risk factors*

This table summarises primary CV outcomes and secondary CV outcomes of interest for CVOTs investigating DPP-4 inhibitors approved for clinical use in the European Union. A neutral effect on atherosclerotic CV outcomes was demonstrated in all four CVOTs. However, the safety of the class for heart failure risk was uncertain, as there were mixed results for hospitalisation for heart failure, with a significant increase of 27% with saxagliptin [15]; a non-significant, numerical increase with alogliptin [17], which reached significance when looking only at patients without baseline heart failure [21]; and no effect with sitagliptin [35] or linagliptin [4], including across risk groups. 3P-MACE, 3-point major adverse CV event. CI, confidence interval. CV, cardiovascular. CVOT, CV outcomes trial. DPP-4, dipeptidyl peptidase-4. HR, hazard ratio. MI, myocardial infarction.

* exploratory analysis.

† also includes fatal events.

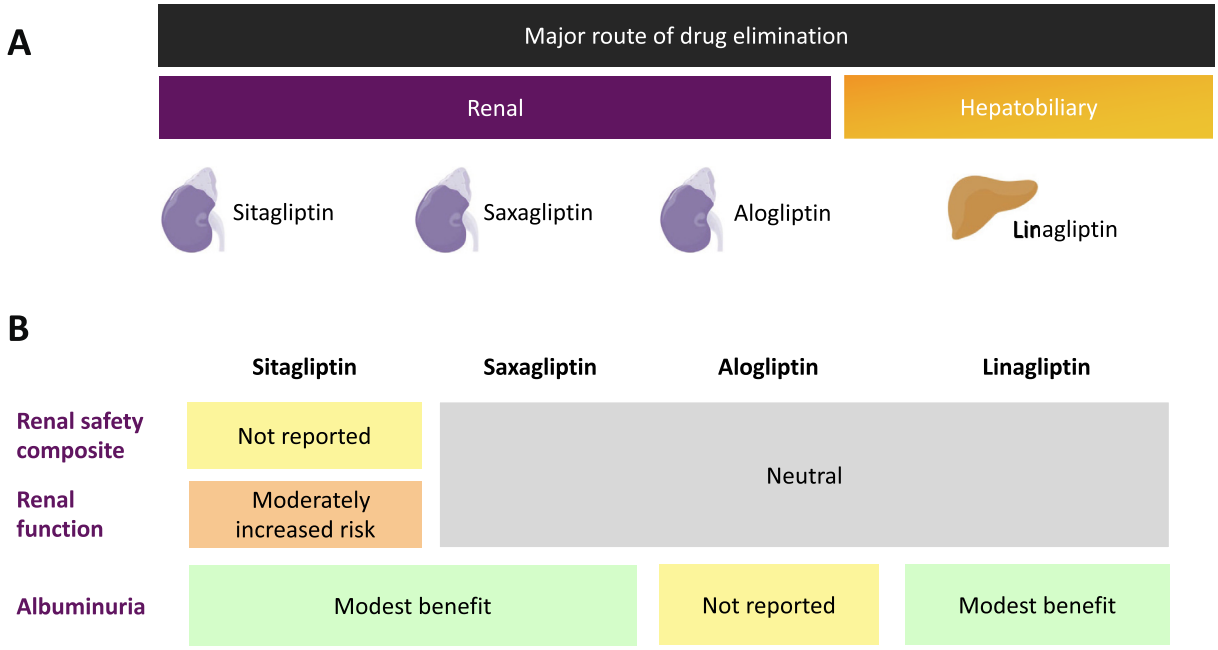

Fig. 2 – Renal safety of DPP-4 inhibitors. (A) Elimination routes of DPP-4 inhibitors. Pharmacokinetic studies of DPP-4 inhibitors show that most of these agents mainly undergo renal excretion, with the exception of linagliptin, which is predominantly eliminated by the hepatobiliary route [38]. (B) Exploratory analyses of renal safety in DPP-4 inhibitor CVOTs. Renal outcomes from DPP-4 inhibitor CVOTs have mostly suggested favourable renal safety. Over the course of the saxagliptin CVOT, patients receiving the study drug had more favourable albuminuria outcomes compared with placebo, but the effect on renal function and other renal safety outcomes was neutral [39]. Albuminuria outcomes have not been reported for the alogliptin CVOT, but renal function and other renal safety outcomes were neutral [16]. In the sitagliptin CVOT, there was a modestly increased risk of eGFR decline with sitagliptin vs placebo, which was not considered to be clinically significant [20]. Albuminuria data were available for about one-third of patients, who showed a modest benefit with sitagliptin vs placebo [20]. All analyses were exploratory. CV, cardiovascular. CVOT, CV outcomes trial. DPP-4, dipeptidyl peptidase-4. eGFR, estimated glomerular filtration rate.

(Fig. 3A). Kidney Disease–Improving Global Outcomes (KDIGO) categorises renal prognosis according to low, moderate, high and very high risk, based on a combination of albuminuria and renal impairment [1]. According to this internationally agreed standard, 93% of patients in CARMELINA had at least moderate renal risk at baseline [1] (Table 2).

3.2. *Renal outcomes*

As with other CVOTs, CARMELINA remains primarily a CV safety study; as such, the primary outcome is 3-point MACE [1]. However, a renal composite was a key secondary outcome, placed joint second in the testing sequence after non-inferiority for 3-point MACE. Thus, CARMELINA was designed and powered to evaluate renal outcomes of linagliptin treatment [1], with a study design that enables a confident assessment of long-term renal safety in patients with T2D and CVD and/or CKD.

4. Interpreting CARMELINA

4.1. *Study outcomes: What we did and didn't learn*

CARMELINA clearly demonstrates a robust long-term safety profile for linagliptin in a high-risk patient population that is highly relevant in our clinical practice, with a strong representation of CKD and CV risk [1]. The demonstration of non-inferiority for the primary outcome of time to first occurrence of 3-point MACE [4] (Table 1) may have been expected from other DPP-4 inhibitor CVOTs, but it is reassuring to confirm the CV safety of linagliptin in this high-risk population.

CARMELINA also suggested a neutral effect on HHF (Fig. 3B), which was an exploratory outcome [4]. As heart failure outcomes have been mixed across the DPP-4 inhibitor class (Table 1), this finding now alleviates a possible concern for clinicians when prescribing linagliptin prior to the availability of CARMELINA data. Given the common co-occurrence of heart failure and CKD, we view this as particularly reassuring in a cohort where the majority of patients had prevalent CKD.

The key secondary renal endpoint was a composite of time to first occurrence of end-stage renal disease, death due to renal failure, or a sustained decrease of at least 40% in eGFR from baseline, which is a commonly used renal composite in CVOTs and was adopted following recommendations from the National Kidney Foundation and the US Food and Drug Administration [1]. CARMELINA convincingly demonstrated a neutral effect with linagliptin for this renal endpoint, including in prespecified sensitivity analyses and subgroup analyses stratified by baseline renal risk [4,24]. The study also

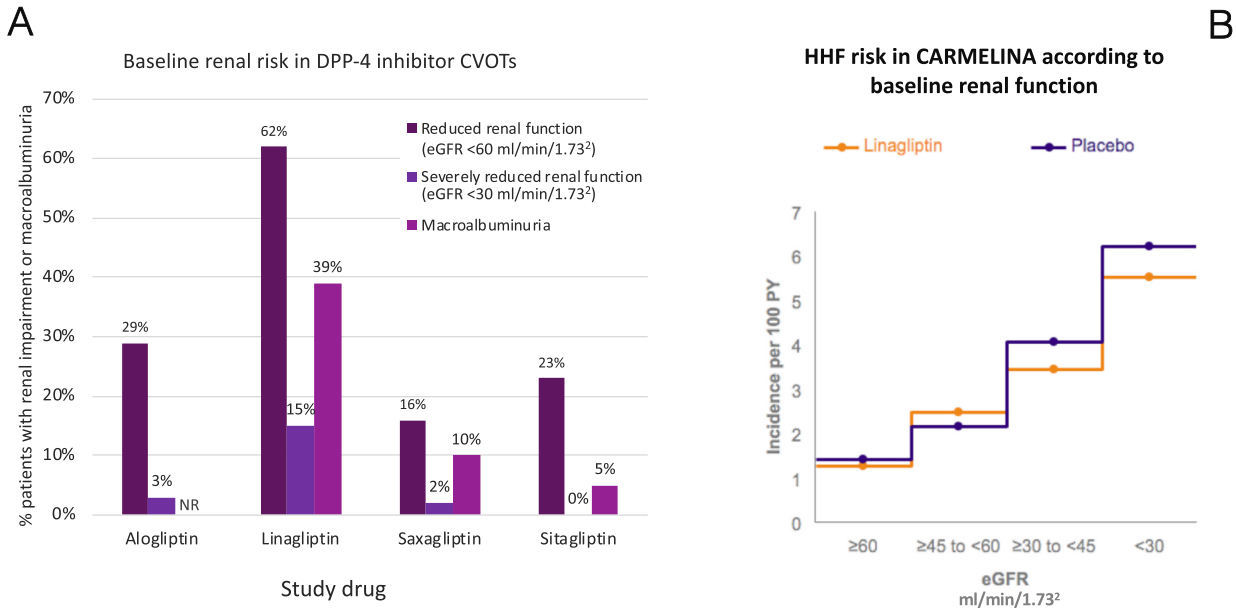

Fig. 3 – Baseline renal risk in CARMELINA and DPP-4 inhibitor CVOTs. (A) Renal impairment and macroalbuminuria at baseline in DPP-4 inhibitor CVOTs. A limitation of DPP-4 inhibitor CVOTs prior to CARMELINA is that only a minority of patients in the study cohorts had reduced renal function at baseline (eGFR < 60 ml/min/1.73 m^2) [1,19]. Even fewer patients had severely reduced renal function (eGFR < 30 ml/min/1.73 m^2) or macroalbuminuria (urinary albumin-to-creatinine ratio > 300 mg/g) [1,16,20,39]. By contrast, 62% and 15% of patients in CARMELINA had reduced or severely reduced renal function at baseline, and the prevalence of macroalbuminuria was 39% [1], which compares with 10% in the saxagliptin CVOT [15]. Macroalbuminuria prevalence for the sitagliptin CVOT was based on a limited number of patients for which data were available [20]; prevalence of macroalbuminuria was not reported for the alogliptin CVOT [16]. (B) HHF risk by baseline renal function in CARMELINA. The heart and kidneys are intricately linked by diverse interactions that drive a coincident morbidity between heart failure and CKD. As expected, HHF risk in CARMELINA was elevated in patients presenting with impaired renal function (as measured by eGFR). However, linagliptin did not seem to affect the risk of HHF, regardless of baseline renal function. CKD, chronic kidney disease. CVOT, cardiovascular outcomes trial. DPP-4, dipeptidyl peptidase-4. eGFR, estimated glomerular filtration rate. HHF, hospitalisation for heart failure.

Table 2 – Renal risk in the CARMELINA cohort.

	CARMELINA primary analysis cohort (N = 6,979)
Prevalent CKD, n (%) [1]	
All patients with CKD	5,148 (74%)
Patients with both CKD and CVD	2,268 (33%)
Renal impairment, n (%) [1]	
Reduced renal function (eGFR < 60 ml/min/1.73^2)	4,349 (62%)
Severely reduced renal function (eGFR < 30 ml/min/1.73^2)	1,063 (15%)
Albuminuria, n (%) [1]	
Microalbuminuria (UACR ≥ 30 and ≤ 300 mg/g)	2,896 (42%)
Macroalbuminuria (UACR > 300 mg/g)	2,691 (39%)
Macroalbuminuria + reduced renal function	1,892 (27%)
KDIGO risk, n (%) [1]	
Moderate	1,561 (22%)
High	1,902 (27%)
Very high	3,033 (44%)

Around three-quarters of patients in CARMELINA had prevalent CKD at baseline, defined as reduced renal function (eGFR < 60 ml/min/1.73 m^2) and/or macroalbuminuria (UACR > 300 mg/g) [1]. KDIGO categorises renal prognosis according to low, moderate, high and very high risk, based on a combination of albuminuria and renal risk [1]. According to this internationally agreed standard, 44% of patients in CARMELINA were at very high risk at baseline, and a further 27% of patients were at high risk, with only 7% at low risk [1]. CKD, chronic kidney disease. CVD, cardiovascular disease. eGFR, estimated glomerular filtration rate. KDIGO, Kidney Disease–Improving Global Outcomes. UACR, urinary albumin-to-creatinine ratio.

included several exploratory analyses for renal and other microvascular outcomes, which suggested a neutral effect of linagliptin, with the exception of progression of albuminuria, where linagliptin had a positive effect [4]. The mechanism underlying the improvement in albuminuria is unknown, and we cannot exclude that it is secondary to the effective glycaemic control achieved with linagliptin in the study. However, for clinicians, the interest is not in the mechanism but in the finding that linagliptin was able to achieve a significant, albeit modest, improvement in albuminuria in a population with prevalent CKD, which is a reassuring observation in a clinically relevant population. Although exploratory, the additional renal analyses provide further confidence in the robust and wide-ranging safety profile of linagliptin. Together, it is our view that the renal outcomes of CARMELINA establish the favourable renal safety of the drug (Fig. 2B), including in patients with reduced renal function.

A final outcome of interest to us was glycaemic control, which was an exploratory analysis. Linagliptin improved glycaemic control versus placebo despite a less frequent initiation or intensification of insulin therapy, due to a study design that aimed for glycaemic equipoise by permitting additional glucose-lowering therapy where required [4]. This was a particularly helpful and relevant observation in a population with renal impairment [4]: when faced with patients with CKD in clinical practice, therapeutic options for glucose-lowering agents can be limited, and this finding now provides clinicians with an evidence-based treatment choice for glycaemic control in patients with reduced renal function.

Prior to the data disclosures, some of us had hoped to see a benefit with linagliptin in cardiorenal outcomes. Outside of a modest benefit in albuminuria, it is clear from CARMELINA that no significant benefit in reducing CV or renal risk was observed, in common with other CVOTs for the DPP-4 inhibitor class. Unfortunately, the high event rate in the trial across both study arms, which may have been due to the substantial burden of cardiorenal risk at baseline, led to early cessation of the study [4]. Therefore, follow-up was only available for a median of 2.2 years [4], and thus any speculated long-term benefit that may arise with linagliptin would not be apparent [25].

Nevertheless, we feel that this should not detract from the important safety findings from CARMELINA, and here we can summarise the key takeaways for our clinical practice as: evidence for a robust CV and renal safety profile with linagliptin, even in high-risk patients; reassurance that linagliptin does not increase the risk of HHF; and confirmation of effective glycaemic control with linagliptin in patients with renal impairment.

4.2. *CARMELINA in the context of other DPP-4 inhibitor CVOTs*

The availability of data from CARMELINA now allows us to consider CVOT evidence for four DPP-4 inhibitors. Although we cannot draw conclusions as to relative efficacy and safety, as head-to-head studies have not been performed, and each study has marked differences in design, cohort and methodology, we can consider the evidence level available across the class, and the relevance for clinical practice.

A consistent observation has been a neutral effect on atherosclerotic CV outcomes (Table 1), which adds to considerable evidence for DPP-4 inhibitors as antidiabetic agents with a favourable safety profile. However, there were also some important inconsistencies in heart failure outcomes between CVOTs, which we have described (Table 1). It is not known why this outcome has differed between agents; it may be a safety difference that is intrinsic to the molecules themselves, or it may be due to a difference in study design or cohorts, such as differential insulin use [22]. However, as clinicians we believe that treatment decisions should be made with the best available evidence, and in this regard CARMELINA provides clinicians with an additional DPP-4 inhibitor that has demonstrated a neutral effect on HHF [4] (Fig. 3B).

The quality of evidence for renal outcomes has varied between DPP-4 inhibitor CVOTs. In general, there seems to be a pattern of modest benefit in albuminuria outcomes, although this conclusion is derived from exploratory analyses and incomplete reporting (albuminuria was not reported for alogliptin, and measurements were only recorded for around one-third of patients in the sitagliptin CVOT). Due to the modest effect size of this benefit, and neutral effect on renal function (with the exception of a modest but significant decline with sitagliptin), the key takeaway for clinicians across the class is more likely to be the conclusion of renal safety, rather than efficacy [25]. Here, CARMELINA was generally consistent with other DPP-4 inhibitor CVOTs, although the evidence is strongest for linagliptin and saxagliptin, as these agents showed a neutral effect on both renal function and renal safety composites in addition to the benefit in albuminuria (Fig. 2B). Furthermore, CARMELINA was distinct from other CVOTs in providing evidence for renal safety with linagliptin as a key secondary outcome in a population with baseline CKD present in the majority of patients [1] (Fig. 3A). To achieve a significant benefit, however modest, in albuminuria in such a population is in our view a finding of clinical interest.

In summary, according to our interpretation of the available evidence, CARMELINA is consistent with other DPP-4 inhibitor CVOTs in demonstrating atherosclerotic CV and renal safety, and also showed a neutral effect on HHF, which has been an outcome with inconsistent results across the class. The key benefit of CARMELINA, however, is that it has demonstrated this robust safety profile, in addition to efficacious glycaemic control, in the clinically relevant population of patients with impaired renal function, as the agent that is supported by the most evidence for CV and renal safety.

5. Translating CARMELINA to the clinic

5.1. *CARMELINA in the light of guideline recommendations*

CARMELINA confirms that DPP-4 inhibitors are a class that should be used for glycaemic control with reassurance of safety in patients with T2D and comorbidities, but based on currently available evidence these agents are not preferred

as a treatment choice to achieve a reduction in cardiorenal risk. This conclusion is in keeping with the latest update to EASD–American Diabetes Association (ADA) recommendations on the management of hyperglycaemia in patients with T2D, which prefer sodium–glucose transporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists for reducing CV risk, and SGLT2 inhibitors for reducing the risk of heart failure and progression of renal disease [26] (Fig. 4).

The EASD–ADA recommendations take a view that CV and renal risk should be included as early as possible in the treatment pathway [26], but that clinicians may wish to consider adding on a DPP-4 inhibitor where enhanced glycaemic control is required in patients receiving an SGLT2 inhibitor for cardiorenal risk or in clinical situations where an SGLT2 inhibitor is not used [25]. Exceptions are saxagliptin, which should not be used in the setting of heart failure, and agents that require dose adjustment due to renal excretion, which should be dose-adjusted or avoided in the setting of kidney disease [26]. CARMELINA provides evidence supporting the use of linagliptin as an add-on DPP-4 inhibitor for these patients, including those with heart failure or renal risk. Furthermore, the study adds to a picture of inconsistent findings across the class for heart failure (Table 1), supporting the EASD–ADA recommendation to differentiate within the class in this setting.

For patients without CV or renal risk (or without a compelling need to reduce weight), DPP-4 inhibitors may be considered ahead of SGLT2 inhibitors, at the discretion of the prescriber [26]. However, SGLT2 inhibitor add-ons to metformin have been shown to provide better improvement in glycaemic control compared with DPP-4 inhibitors [27]. Furthermore, there has been some suggestion that SGLT2 inhibitor add-ons to DPP-4 inhibitors achieve a greater Hb1Ac reduction than the reverse sequence, but this has not been consistently shown in all studies [28-31].

5.2. *Considering future renal risk*

Our discussions revealed one possible unintended consequence of the unique study population included in

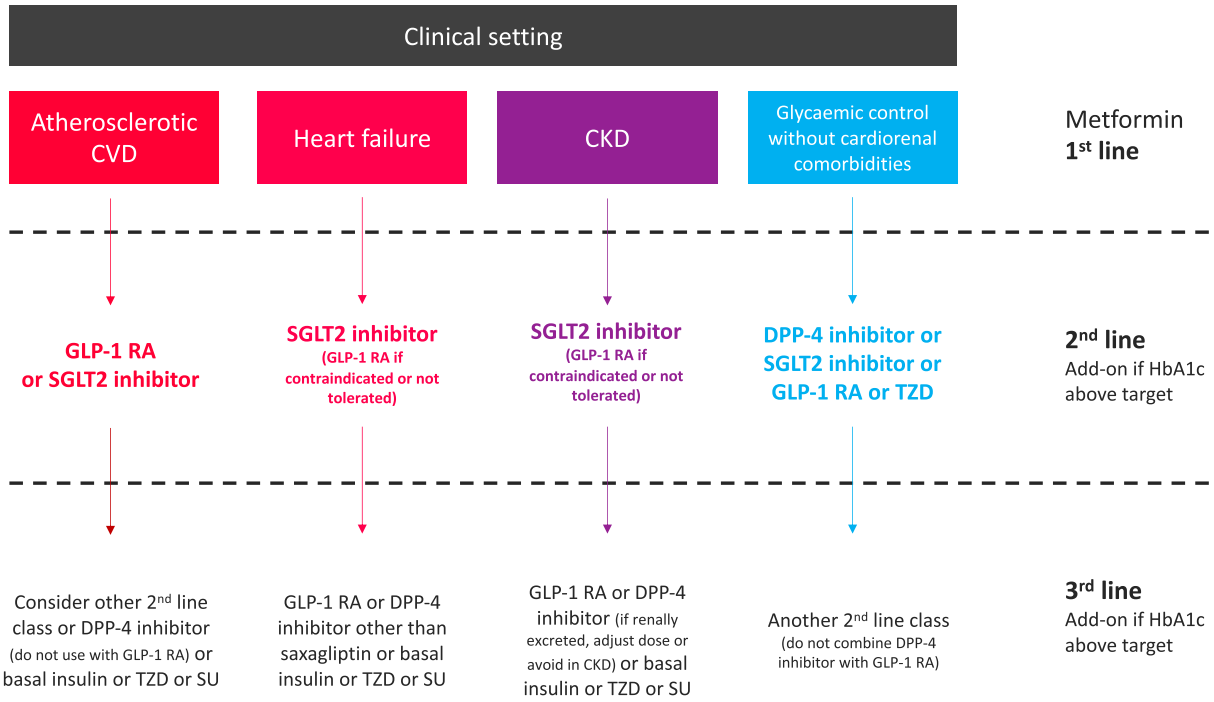

Fig. 4 – Positioning of DPP-4 inhibitors in updated EASD–ADA recommendations for the management of hyperglycaemia in T2D. Newly updated EASD–ADA recommendations provide guidance for the pharmacotherapeutic management of hyperglycaemia in patients with T2D in different clinical settings, in part based on insights from CVOT studies [26]. These settings include atherosclerotic CVD, heart failure and CKD, as well as patients where cardiorenal comorbidities are not a priority (shown here is the treatment pathway based on avoiding hypoglycaemia; recommendations are also provided for patients with obesity and cost considerations, not shown) [26]. For patients with cardiorenal comorbidities, a DPP-4 inhibitor may be considered as an add-on to a SGLT2 inhibitor to enhance glycaemic control, with the exception of saxagliptin, which should not be used in a heart failure setting [26]. The recommendations also advise that renally excreted DPP-4 inhibitors should be dose-adjusted or avoided in patients with renal disease [26]. Note that DPP-4 inhibitors should not be used in combination with a GLP-1 RA, and all agents should be used in accordance with locally approved prescribing information [26]. ADA, American Diabetes Association. CKD, chronic kidney disease. CVD, cardiovascular disease. CVOT, cardiovascular outcomes trial. DPP-4, dipeptidyl peptidase-4. EASD, European Association for the Study of Diabetes. GLP-1 RA, glucagon-like peptide-1 receptor agonist. SGLT2, sodium–glucose transporter 2. SU, sulfonylurea. T2D, type 2 diabetes. TZD, thiazolidinedione.

CARMELINA, which is that clinicians may perceive linagliptin as a specialist drug for patients with CKD. This possibility is concerning, as it overlooks the potential benefits of linagliptin across a broad range of patients.

First, CARMELINA demonstrated the efficacy and safety of linagliptin across CV and renal risk groups, including patients with and without CVD, and with normal, reduced or severely reduced renal function [4]. Rather than a niche population, the study cohort in CARMELINA is a highly relevant population that reflects the diversity of our clinical practice. Thus, the CARMELINA cohort broadens rather than narrows the conclusions that can be drawn regarding patients who can benefit from linagliptin.

Second, it is important to consider future risk of renal impairment in our patients with T2D. As discussed, T2D is a major risk factor for the development of CKD, renal function declines naturally with age, and CKD is a leading cause of excess mortality in patients with T2D [5]. Therefore, even in patients without overt CKD, the presence of T2D places an expectation of the development of CKD as a likely future morbidity, with significant risk of mortality. CARMELINA gives clinicians confidence that linagliptin will continue to display a favourable efficacy and safety profile in patients subsequent to future development of CKD. Furthermore, the non-renal elimination profile of linagliptin provides reassurance that treatment will not need to be dose-adjusted or ceased in the event of reduced renal function.

6. Future studies — what evidence is still missing?

There is a paucity of data available for renal outcomes with glucose-lowering agents in T2D, as well as for patients with renal comorbidities [25]. Even for SGLT2 inhibitors, which are recommended for use in a renal disease setting in the updated ADA–EASD guidelines [26], renal outcomes had at the time of our discussions only been evaluated as secondary outcomes (although results for the CREDENCE renal study on canagliflozin were reported during the preparation of this manuscript, and dedicated renal studies with other SGLT2 inhibitors are ongoing [32,33]).

While CARMELINA is the first CVOT to provide evidence in a majority population with prevalent renal risk, further studies with DPP-4 inhibitors would be welcome, and results are expected shortly from the CAROLINA CVOT, which will compare linagliptin with a sulfonylurea as an active comparator [34]. Such additional evidence from randomised controlled studies, as well as real-world observational studies, will be helpful in guiding recommendations on considering renal risk early in the treatment pathway, as well as the use of this class as an add-on for enhanced glycaemic control in at-risk patients treated with SGLT2 inhibitors.

7. Conclusions

We hope that summarising our discussions from a meeting convened to respond to the CARMELINA disclosures will be helpful to clinicians by providing the benefit of our experience of clinical practice in T2D. Importantly, our conclusions are generalisable beyond our region, given the international scope of the clinical studies discussed and the broad geographical reach of the EASD–ADA recommendations that we have used to guide our considerations.

As CARMELINA demonstrates cardiorenal safety for a fourth DPP-4 inhibitor, we are pleased that clinicians can now be further reassured of the generally robust safety profile of the class. When selecting a DPP-4 inhibitor in patients with comorbidities, clinicians may wish to consider emerging evidence from the study and other CVOTs on heart failure and renal risk, which have been recognised as important factors in the management of hyperglycaemia in T2D by updated EASD–ADA guidelines.

In the heart failure setting, the guidelines advise against saxagliptin, owing to evidence for significantly increased risk for HHF. In the renal disease setting, the guidelines advise that renally excreted DPP-4 inhibitors should be dose-adjusted or avoided; as the sole agent in the class that does not undergo renal excretion, linagliptin may be a practical choice of DPP-4 inhibitor in these patients. CARMELINA will now reassure clinicians considering such a choice, by demonstrating cardiorenal safety and antihyperglycaemic efficacy with linagliptin in patients with prevalent CKD.

Finally, the guidelines also advise that CV and renal risk are considered early in the treatment pathway. In the context of DPP-4 inhibitors, linagliptin may offer an option to simplify treatment for clinicians concerned about the expected future risk of declining renal function in patients with T2D, as an agent that will not require dose adjustment once CKD manifests.

Authors' contributions

All authors participated in the discussion during the face-to-face meeting, with GS and CW moderating the conversation. All authors contributed to the content and critical review of the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interests

AK has received research support, lecture fees and served as advisory board member for Astra Zeneca, Boehringer Ingelheim and Novo Nordisk.

AT has received lecture fees and served as an advisory board member for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi.

BM has previously received honoraria for advisory boards and speaking from AstraZeneca and Boehringer Ingelheim.

CG participated in scientific advisory boards and received consulting fees from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Zentiva.

CW serves as a steering committee member for Akibia, Boehringer Ingelheim, GlaxoSmithKline, Gilead and Merck, and as an advisory board member for Bayer, Boehringer Ingelheim, Nestle, Sanofi-Genzyme, Reata and Vifor.

DJE has previously received consultancy fees from Astra Zeneca, Boehringer Ingelheim, Eli Lily, Novo Nordisk, Sanofi Aventis and Takeda.

GS has previously received research grants and honoraria for speaking from Abbot, Amgen, Andromeda, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, DeveloGen, Eli Lilly, GSK, Janssen, Merck, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Serono, Servier and Takeda, and has served as principal investigator in more than 40 studies.

IJM has received lecture fees and serves as an advisory board member for Astra Zeneca, Boehringer Ingelheim, Novo Nordisk and Sanofi.

IW has previously participated in advisory boards for Astra Zeneca, Berlin-Chemie/A. Menarinig, Boehringer-Ingelheim, Lilly, MSD, Novartis, Novo Nordisk and Sanofi-Aventis.

JG has previously received honoraria for speaking and advisory board member from AstraZeneca, Bayer, Bioton, Boehringer Ingelheim, Eli Lilly, Merck, MSD, Mundipharma, Novartis, Novo Nordisk, Sanofi-Aventis and Servier.

MP has previously participated in advisory boards, speaker bureaus or received consultancy fees from Abbott, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Dexcom, Medtronic, Novartis, Novo Nordisk, Roche, Sanofi, Takeda and Teva.

NL declares no competing interests.

TT has received lecture fees and serves as an advisory board member for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mylan, Novo Nordisk, Sanofi and Servier.

TW has received honoraria for consulting and lecturing from Astra Zeneca, Boehringer Ingelheim, Eli Lilly Merck Sharp Dohme, Novo Nordisk, Sanofi and Takeda.

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