Safety and efficacy of linagliptin in type 2 diabetes patients with common renal and cardiovascular risk factors

Baptist Gallwitz

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Abstract: Dipeptidyl-peptidase-IV (DPP-4) inhibitors have become an important orally active drug class for the treatment of type 2 diabetes as second-line therapy after metformin failure or as monotherapy or combination therapy with other drugs when metformin is not tolerated or contraindicated. DPP-4 inhibitors act mainly by increasing endogenous incretin hormone concentrations. They stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner with a significantly lower risk for hypoglycaemia than sulfonylureas. Furthermore, DPP-4 inhibitors are weight neutral. Linagliptin is a DPP-4 inhibitor that is eliminated by a hepatobiliary route, whereas the other DPP-4 inhibitors available today show a renal elimination. Therefore, it can be used in normal kidney function as well as in all stages of chronic kidney disease to stage 5 (glomerular filtration rate <15 ml/min/1.73 m²) without dose adjustments. Linagliptin was noninferior to metformin and sulfonylureas in clinical studies. In recent studies, it showed a superior safety profile over sulfonylurea treatment regarding hypoglycaemia and weight gain. More patients reached an HbA1c <7% without hypoglycaemia and weight gain with linagliptin compared with glimepiride. The safety profile with respect to a composite cardiovascular endpoint and stroke was also favourable for linagliptin, most likely due to a higher incidence of hypoglycaemia associated with glimepiride therapy and titration. This review gives an overview on the efficacy and safety of linagliptin in comparison with other antidiabetic drugs in type 2 diabetes patients with renal and cardiovascular risk factors as well as an outlook on the perspective for linagliptin in this patient population in the future.

Keywords: cardiovascular risk, DPP-4 inhibitors, incretin-based therapies, linagliptin, oral antidiabetic drugs, renal impairment, type 2 diabetes

Introduction

Dipeptidyl-peptidase-IV (DPP-4) inhibitors have become important oral antidiabetic agents as second line therapy when patients do not reach their glycaemic targets with metformin alone or as first line therapy when metformin is not tolerated or contraindicated. Sitagliptin was the first substance to be approved in 2006, followed by vildagliptin, saxagliptin, linagliptin and alogliptin [Gallwitz, 2007, 2013]. DPP-4 inhibitors belong to the incretin-based therapies. The incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are secreted from the intestinal L- and K-cells after a meal, respectively. Insulin secretion is stimulated *via* these incretin hormones when hyperglycaemia is

present. The phenomenon that orally ingested glucose leads to a higher insulin response than an isoglycaemic intravenous glucose administration has been termed the incretin effect. GLP-1 and GIP are hormones responsible for this effect [Drucker and Nauck, 2006]. In type 2 diabetes, the incretin effect is diminished [Nauck *et al.* 1993], however supraphysiological concentrations of GLP-1 still exert the typical insulinotropic and glucagonostatic actions in a glucose dependent manner, while GIP has lost its insulinotropic action [Drucker and Nauck, 2006; Nauck *et al.* 1993]. Both incretin hormones possess a biological half-life of only 1–2 minutes due to rapid enzymatic degradation by DPP-4. GLP-1 is the substrate with the highest affinity for DPP-4

Correspondence to:
Prof. Baptist Gallwitz, MD
Department of Medicine
IV, Eberhard-Karls-
University Tübingen,
Otto-Friedrich-Müller-Strasse 10,
72076 Tübingen, Germany
baptist.gallwitz@med.uni-tuebingen.de

[Deacon *et al.* 1998; Mentlein *et al.* 1993; Mentlein, 1999]. DPP-4 inhibition leads to an approximately threefold elevation of endogenous GLP-1 plasma concentrations that contribute significantly to the glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion [Ahren *et al.* 2002; Deacon *et al.* 1998; Drucker and Nauck, 2006]. In recent years, additional, nonglycaemic effects of GLP-1 have been described that may be advantageous with respect to the pathophysiology of type 2 diabetes: GLP-1 has been shown to have cardiovascular effects (e.g. improving left ventricular function, reducing myocardial infarct sizes in artificial ischaemia models and lowering systolic blood pressure in hypertension in clinical studies) and to have neuroprotective effects in animal models [Meier, 2012; Ussher and Drucker, 2012].

Effective and safe medications for type 2 diabetes therapy are needed that are easy to use and to distribute because the number of patients affected by this disease is rising dramatically on a global basis [IDF, 2011], especially in countries adopting lifestyles with less physical activity and high caloric intake. Safe medications are needed with respect to a low risk for hypoglycaemias, because additional counselling regarding frequent self control and monitoring may not be feasible. Further than that, the diabetes incidence increases both in a geriatric population, where self-management is difficult and in younger patients that drive vehicles or with occupations with the need for continuously high attentiveness. Furthermore, frequent glucose monitoring necessitated by diabetes therapy with an intrinsic hypoglycaemia risk or mandatory monitoring of organ functions with additional laboratory tests (e.g. for renal or hepatic function) would be associated with additional costs on healthcare systems. DPP-4 inhibitors seem to fulfil most of these requirements since they have shown noninferiority to sulfonylureas regarding efficacy together with a low risk of hypoglycaemia, body weight neutrality and their mostly once daily dosing in a standard dose without a necessary titration. Beyond that, DPP-4 inhibitors have demonstrated a low rate of adverse events and a good tolerability. The translation of the beneficial nonglycaemic cardiovascular effects of GLP-1 is also debated as a potential pharmacological advantage of the DPP-4 inhibitors [Gallwitz, 2013]. Some concerns have been raised connecting incretin-based therapies with an elevated risk for developing acute pancreatitis or even pancreatic cancer [Elashoff *et al.* 2011; Singh *et al.*

2013]. A distinct pathophysiological mechanism explaining these elevated risks for incretin-based therapies has not been identified. However, large controlled retrospective studies that were undertaken to investigate this hypothesis further have not so far shown a difference in the pancreatitis risk or pancreatic cancer risk for the incretin-based therapies [Dore *et al.* 2009; Engel *et al.* 2010; Garg *et al.* 2010; Williams-Herman *et al.* 2010].

For most DPP-4 inhibitors, fixed dose combinations with metformin are already available that have shown a good patient adherence. DPP-4 inhibitors have been perceived as an important addition to the treatment algorithm in type 2 diabetes and have been placed as second and third line therapy among other agents in the recent joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [Inzucchi *et al.* 2012]. In this review article, the efficacy and safety of linagliptin in patients with type 2 diabetes and common renal and cardiovascular risk factors is discussed, since linagliptin is a DPP-4 inhibitor that is eliminated by a hepatobiliary route, whereas the other DPP-4 inhibitors available today show a renal elimination. Furthermore, novel study outcomes have shown better outcomes with linagliptin compared with a conventional treatment with a sulfonylurea. An outlook on the perspective for potential linagliptin use in this patient population in the future is also given.

Chemistry and pharmacology of linagliptin

Linagliptin is a xanthine-based DPP-4 inhibitor and was developed by Boehringer Ingelheim Pharmaceuticals (Ingelheim, Germany). DPP-4 inhibition by linagliptin is competitive and reversible with a slow rate of dissociation from the active center of DPP-4 [Thomas *et al.* 2008]. The selectivity of linagliptin towards DPP-4 is approximately 40,000-fold higher towards DPP-4 compared with other enzymes of this peptidase family. Linagliptin does not inhibit the cytochrome P450 (CYP450) enzymes ($IC_{50} > 50 \mu M$) [Eckhardt *et al.* 2008; Gallwitz, 2011].

Linagliptin is excreted by approximately 90% in unmetabolized form *via* the faeces by a hepatobiliary route, while only 1–6% is eliminated *via* the kidney and urine [Fuchs *et al.* 2009; Heise *et al.* 2009; Huttner *et al.* 2008]. At therapeutic concentrations, linagliptin is almost completely bound to plasma proteins [Fuchs *et al.* 2009].

Steady state concentrations are reached within 2–5 days after once daily administration of linagliptin. In once-daily dosing, linagliptin led to a maximal DPP-4 inhibition of 90% with doses of 5 mg at steady state with approximately 85% inhibition still remaining after 24 hours post dose [Heise *et al.* 2009]. No relevant drug–drug interactions between linagliptin and metformin, other widely used antidiabetic medications or drugs for other indications were detected [Graefe-Mody *et al.* 2010].

Pooled study data investigated the peak and trough concentrations in patients with varying degrees of chronic kidney disease (CKD). Data were obtained from phase III studies from 969 patients who were determined by estimated glomerular filtration rate (eGFR) to have normal renal function ($n = 438$), CKD stage 2 renal impairment (RI) ($n = 429$), CKD stage 3 RI ($n = 44$), or stage 4 RI ($n = 58$). In patients with normal renal function, the geometric mean linagliptin trough concentration (coefficient of variation) was 5.93 nmol/l (56.3%); in patients with stage 2, 3, or 4 of CKD, geometric mean concentrations were 6.07 nmol/l (62.9%), 7.34 nmol/l (58.6%) and 8.13 nmol/l (49.8%), respectively. In patients with type 2 diabetes, CKD had a minor effect on linagliptin exposure. Therefore, neither dose-adjustment nor drug-related monitoring of eGFR is necessary for patients with RI [Friedrich *et al.* 2013].

Linagliptin, cardiovascular safety and risk factors

GLP-1 receptors are not only expressed on pancreatic β -cells, but also on cardiomyocytes and in the vasculature [Ban *et al.* 2008; Ussher and Drucker, 2012]. In patients with myocardial infarction, an intravenous infusion of human GLP-1 significantly improved parameters of left ventricular function [Nikolaidis *et al.* 2004; Sokos *et al.* 2006]. An artificial myocardial ischemia in rats was used to investigate potential cardiovascular effects of linagliptin. A significant reduction of infarcted tissue and infarction size was observed with linagliptin administration that was followed by a significant elevation of endogenous GLP-1 plasma concentrations [Hoche *et al.* 2012].

In a comparative clinical phase III study, patients with type 2 diabetes not optimally controlled on metformin alone received either linagliptin or glimepiride as add on therapy. The rationale and hypothesis in this 2-year trial was that, due to an

increased risk of hypoglycaemia and weight gain, glimepiride treatment might be associated with a higher risk for negative cardiovascular outcomes compared with linagliptin [Gallwitz *et al.* 2012]. Besides being an important study for the phase III programme of linagliptin, this study prospectively assessed cardiovascular safety. A masked independent clinical event committee evaluated the prespecified criteria for adjudication endpoints (cardiovascular death, stroke, myocardial infarction and admission to hospital for unstable angina). In this head-to-head study, the addition of linagliptin achieved basically similar glycaemic reductions compared with glimepiride in patients inadequately controlled by metformin monotherapy, but was associated with much less hypoglycaemia and weight reduction. Prospectively captured and adjudicated major cardiovascular events occurred in 12 (2%) of 776 patients treated with linagliptin and 26 (3%) of 775 patients treated with glimepiride, resulting in a relative risk (RR) reduction of 0.46 [95% confidence interval (CI) 0.23–0.91; $p = 0.0213$] compared with glimepiride, corresponding to a number needed to treat (NNT) of 55.3 patients. This finding was mainly attributable to a significantly lower number of nonfatal strokes in patients on linagliptin compared with glimepiride (RR 0.27, 95% CI 0.08–0.97; $p = 0.0315$) without any relation to a hypoglycaemic event. Whether these findings are explained by a lower cardiovascular risk related to the mode of action of the DPP-4 inhibitor linagliptin and GLP-1 related effects [Frederich *et al.* 2010; Schweizer *et al.* 2010; Williams-Herman *et al.* 2010] or by an increased cardiovascular risk associated with the use of sulfonylureas that has also been shown in some (but not all retrospective analyses of sulfonylurea safety studies [Tzoulaki *et al.* 2009] is not clear. In the context of the overall clinical benefit of glucose-lowering medications for type 2 diabetes, hypoglycaemia may worsen patients' morbidity and mortality, and clearly affects their adherence to therapy and quality of life [Amiel *et al.* 2008]. Weight gain is another undesirable effect that may potentially increase patients' already elevated risk for cardiovascular disease [Eeg-Olofsson *et al.* 2009]. Achieving glycaemic control without hypoglycaemia or weight gain, therefore, is increasingly considered important for individualising therapies and may improve long-term clinical outcomes [Gallwitz *et al.* 2013; Inzucchi *et al.* 2012].

In order to further determine the cardiovascular safety of linagliptin, a meta-analysis of the

cardiovascular risk associated with linagliptin *versus* placebo or active comparators in patients with type 2 diabetes participating in the linagliptin phase III study programme was performed. This was a prespecified meta-analysis in which suspected cardiovascular events were prospectively captured and adjudicated in a blinded fashion by an independent cardiovascular expert committee [Johansen *et al.* 2012]. In total, 8 studies with >12 weeks' duration were included in this meta-analysis. A prespecified list of trigger events (the Standard MedDRA Queries for ischaemic heart disease and cerebrovascular disorders) and all fatal events were identified for adjudication and collected for the full or interim analyses. The primary endpoint was a composite of cardiovascular death (including fatal stroke and fatal myocardial infarction), nonfatal stroke, nonfatal myocardial infarction and hospitalization for unstable angina pectoris. The three secondary endpoints were different cardiovascular composites of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, unstable angina with or without hospitalization, stable angina pectoris and transient ischaemic attacks (TIAs). Risk estimates were calculated using several statistical methods including Cox regression analysis. The main results show that of 5239 treated patients [mean $\pm$ standard deviation (SD) HbA1c $8.0 \pm 0.9\%$, age 58 ± 10 years, body mass index (BMI) 29 ± 5 kg/m²], 3319 received linagliptin once daily (5 mg 3159 patients; 10 mg 160 patients) and 1920 received comparators (placebo 977 patients; glimepiride 1–4 mg 781 patients; voglibose 0.6 mg 162 patients). The cumulative exposure (patient-years) was 2060 for linagliptin and 1372 for comparator drugs. Primary cardiovascular events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving the comparator therapies. The hazard ratio (HR) for the primary endpoint showed significantly lower risk with linagliptin than comparators (HR 0.34, 95% CI 0.16–0.70) as did estimates for all secondary endpoints (HR ranging from 0.34 to 0.55, all upper 95% CIs <1.0) [Johansen *et al.* 2012].

This cardiovascular meta-analysis also indicates that linagliptin may have a beneficial or neutral impact on cardiovascular outcomes in a large population of type 2 diabetes patients compared to therapy with a sulfonylurea or a α -glucosidase inhibitor. The incidence rates of previous myocardial infarction, previous strokes and RI [based

on the Modification of Diet in Renal Disease (MDRD) equation] in this study was comparable with that from previous studies including the National Health And Nutrition Examination Survey (NHANES) population from the United States in 2009 [US Renal Data System (USRDS), 2009; Williams *et al.* 2002]. In general, the study population characteristics were comparable with those of previous studies. The incidence rates (per 1000 patient-years) for the primary cardiovascular endpoint were 5.3 for linagliptin *versus* 16.8 for total comparators [Johansen *et al.* 2012].

Other cardiovascular meta-analyses reported incidence rates for custom MACE ranging from 5.8 to 14.6 with sitagliptin, saxagliptin or vildagliptin, and 9.0 to 14.1 with comparators [Frederich *et al.* 2010; Schweizer *et al.* 2010; Williams-Herman *et al.* 2010]. All these meta-analyses reported relative risks for cardiovascular outcomes with DPP-4 inhibitors *versus* comparators that were below 1.0, but not statistically relevant throughout all studies. The reductions in risk were significant in the meta-analysis of linagliptin (HR 0.34, 95% CI 0.16–0.70) and in the analysis of saxagliptin 2.5–10 mg (HR 0.43, 95% CI 0.23–0.80) [Frederich *et al.* 2010; Johansen *et al.* 2012].

Various mechanisms could explain the potential cardiovascular benefits for linagliptin. First, linagliptin may confer the beneficial effects of improved glycaemic control, including the lowering of postprandial glucose, without the potentially harmful effects of weight gain or increased hypoglycaemia [Ansar *et al.* 2011; Dicker, 2011; Gallwitz *et al.* 2012, 2013]. Second, the increased endogenous GLP-1 levels attained by linagliptin action may provide beneficial cardioprotection as data from mechanistic-, animal- and clinical studies suggest that increased GLP-1 concentrations can improve lipid metabolism and profiles, reduce infarct size and improve cardiac function [Ansar *et al.* 2011; Ban *et al.* 2009]. Third, DPP-4 acts not only on incretins as substrates but also on vasoactive peptides involved in inflammation, immunity and cardiovascular function. Some studies, mostly in a preclinical setting, show that reduced DPP-4 activity can diminish inflammation, stimulate endothelial repair and decrease ischaemic injury [Fadini and Avogaro, 2011]. Lastly, linagliptin holds inherent anti-oxidative properties, most likely due to its xanthine-based molecular structure with further positive effects

on the vasculature [Brownlee, 2005; Johansen *et al.* 2012; Kroller-Schon *et al.* 2012].

The meta-analysis with linagliptin, however, has a couple of limitations. Despite a large total patient exposure of 3432 years, the duration of individual patient exposure was only 1.7 years. Furthermore, the low incidence of cardiovascular events, low rates of triple oral therapy and lack of insulin treatment all suggest that a large proportion of patients had less progressed type 2 diabetes with a lower cardiovascular risk than those with more advanced type 2 diabetes. However, approximately 30% of patients had a baseline Framingham 10-year cardiovascular risk score of >15% and more than a 50% also had >5 years' known disease duration, which indicates a proportion of the population were at increased cardiovascular risk. Finally, the observed cardiovascular risk reductions for the primary and secondary endpoints were influenced by the differences in cardiovascular events in the head-to-head study with linagliptin *versus* glimepiride as add on to metformin [Gallwitz *et al.* 2012; Johansen *et al.* 2012]. Despite this, it is important to note that glimepiride is an established and recommended second line therapy with a well-characterized safety profile, which has not been directly linked to increased cardiovascular risk either as part of intensive treatment regimens or when compared with other conventional treatments [Johansen *et al.* 2012; Selvin *et al.* 2008]. Moreover, analysis of the pooled placebo studies alone confirmed that linagliptin did not increase cardiovascular risk compared to placebo [Johansen *et al.* 2012].

Linagliptin in patients with type 2 diabetes and CKD

Table 1 summarizes the pivotal trials with linagliptin [Gallwitz, 2013]. Linagliptin is the first DPP-4 inhibitor available that is mainly eliminated *via* a hepatobiliary route and only approximately 5% of linagliptin are excreted with the urine in unmetabolized form [Blech *et al.* 2010; Heise *et al.* 2009]. Therefore, there is no need for a dose adjustment of linagliptin in patients with CKD [Deacon and Holst, 2010; Graefe-Mody *et al.* 2011]. Dose adjustments are recommended for the other DPP-4 inhibitors sitagliptin, saxagliptin and vildagliptin in patients with a creatinine clearance of less than 50 ml/min, including patients with end stage renal disease (ESRD)

requiring dialysis [Eckhardt *et al.* 2008; Kothny *et al.* 2012; National Kidney Foundation, 2012; Nowicki *et al.* 2011a; Taskinen *et al.* 2011].

A recently published study investigated the long-term efficacy, safety and tolerability of linagliptin compared with placebo when administered in combination with existing glucose-lowering background therapy in patients with type 2 diabetes and severe RI over 52 weeks [McGill *et al.* 2013]. In this 1-year, double-blind study, 133 patients with type 2 diabetes and severe RI (eGFR <30 ml/min/1.73 m²) and an HbA1c between 7.0 to 10.0% at screening were randomized to linagliptin 5 mg (*n* = 68) or placebo (*n* = 65) once daily, added to existing background therapy. The primary efficacy endpoint was HbA1c change from baseline to week 12. The efficacy and safety endpoints were assessed after 1 year. At week 12, the adjusted mean HbA1c significantly decreased by −0.76% with linagliptin compared with −0.15% with placebo (treatment difference, −0.60%; 95% CI −0.89 to −0.31; *p* < 0.0001). The HbA1c improvements were sustained with linagliptin (−0.71%) over placebo (−0.01%) at 1 year (treatment difference −0.72%, 95% CI −1.03 to −0.41; *p* < 0.0001). The mean insulin doses decreased by −6.2 units with linagliptin and −0.3 units with placebo. The overall adverse event incidence was similar over 1 year (94.1% *versus* 92.3%) while the incidence of severe hypoglycaemia with linagliptin and placebo was comparably low (3 patients per group). Linagliptin and placebo had little effect on renal function (median change in eGFR, −0.8 *versus* −2.2 ml/min/1.73 m²) and no drug-related renal failure occurred. The incidence of adjudicated cardiovascular events was similar in both groups [McGill *et al.* 2013].

In this study, adding linagliptin to glucose-lowering background therapy provided a clinically significant placebo corrected reduction of 0.7% in HbA1c after 52 weeks in patients with type 2 diabetes and severe RI. This finding is in line with previous 24-week studies that reported that linagliptin (5 mg once daily) used either alone or in combination with oral diabetes medications was associated with placebo-corrected HbA1c reductions ranging from 0.5% to 0.9% in patients with uncontrolled type 2 diabetes and normal renal function or mild to moderate RI [Del Prato *et al.* 2011; Gomis *et al.* 2011; Kawamori *et al.* 2012; Taskinen *et al.* 2011].

Table 1. Important clinical studies in the phase III programme with linagliptin (studies with ≥ 24 weeks duration).

Reference	Background therapy	Comparator(s) [n randomized] / treatment arms	Baseline HbA1c [%] ($\pm$ SD)	HbA1c change from baseline [%] ($\pm$ SD or 95% CI)	Placebo/ comparator corrected HbA1c reduction [%]	Duration [weeks]
Del Prato <i>et al.</i> [2011]	Therapy naïve/ washout 1 previous OAD	Placebo [n = 167] Linagliptin 5 mg [n = 333]	8.0 $\pm$ 0.91	-0.46 $\pm$ 0.73 (12 weeks) -0.44 $\pm$ 0.91 (24 weeks)	n.r. (12 weeks) -0.69 $\pm$ 0.08 (24 weeks)	12 24
Kawamori <i>et al.</i> [2012]	Therapy naïve/ washout 1–2 previous OAD	Placebo [n = 80] Linagliptin 5 mg [n = 159] Linagliptin 10 mg [n = 160] Voglibose [0.2 mg tid] Linagliptin 5 mg [n = 159] Linagliptin 10 mg [n = 160]	7.95 $\pm$ 0.67 8.07 $\pm$ 0.66 7.98 $\pm$ 0.68 8.02 $\pm$ 0.71 s.a. s.a.	0.63 [0.08](SE) -0.24 [0.06](SE) <i>versus</i> PBO -0.25 [0.06](SE) <i>versus</i> PBO 0.19 [0.07] -0.13 [0.07](SE) <i>versus</i> VO -0.19 [0.07](SE) <i>versus</i> VO	-0.87 (-1.04, -0.70) -0.88 (-1.05, -0.71) -0.32 (-0.49, -0.15) -0.39 (-0.56, -0.21)	12 <i>versus</i> placebo 26 <i>versus</i> VO
Taskinen <i>et al.</i> [2011]	Add on to metformin	Placebo [n = 177] Linagliptin 5 mg [n = 524]	8.02 $\pm$ 0.07 8.09 $\pm$ 0.04	0.15 $\pm$ 0.06 -0.49 $\pm$ 0.04	-0.64 (-0.78, -0.50)	24
Owens <i>et al.</i> [2011]	Add on to metformin plus sulfonylurea	Placebo [n = 265] Linagliptin 5 mg [n = 793]	8.14 [0.05](SE) 8.15 [0.03](SE)	n.r.	-0.62 (-0.73, -0.50)	24
Gallwitz <i>et al.</i> [2012]	Add on to metformin	Linagliptin 5 mg [n = 776] Glimepiride mean dose 3 mg (week 28–104) [n = 775]	7.17 [0.04](SE) 7.31 [0.04](SE)	-0.56 [0.03](SE) -0.63 [0.03](SE)	0.08 [0.04](SE) (Completers cohort)	104
Haak <i>et al.</i> [2012]	Initial combination with metformin	Placebo [n = 72] Linagliptin 5 mg [n = 142] Metformin 500 mg bid [n = 144] Metformin 1000 mg bid [n = 147] LINA 2.5 mg + MET 500 mg bid [n = 143] LINA 2.5 mg + MET 1000 mg bid [n = 143] Open label LINA + MET [n = 66]	8.7 $\pm$ 1.0 8.7 $\pm$ 1.0 8.7 $\pm$ 0.90 8.5 $\pm$ 0.90 8.7 $\pm$ 1.0 8.7 $\pm$ 1.0 11.8 $\pm$ 1.4	0.1 $\pm$ 0.1 -0.5 $\pm$ 0.1 -0.6 $\pm$ 0.1 -1.1 $\pm$ 0.1 -1.2 $\pm$ 0.1 -1.6 $\pm$ 0.1 -3.7	-0.6 $\pm$ 0.1 -0.8 $\pm$ 0.1 -1.2 $\pm$ 0.1 -1.3 $\pm$ 0.1 -1.7 $\pm$ 0.1 n.r.	24
Gomis <i>et al.</i> [2011]	Initial combination with pioglitazone (30 mg)	Placebo + pioglitazone [n = 130] Linagliptin 5 mg + pioglitazone [n = 259]	8.58 [0.08](SE) 8.60 [0.05](SE)	-0.56 [0.09](SE) -1.06 [0.06]	-0.51 [0.10](SE)	24

CI, confidence interval; LINA, linagliptin; MET, metformin; n.r., not reported, OAD, oral antidiabetic drug; PBO, placebo; SD, standard deviation; SE, standard error; tid, three times a day; VO, voglibose; s.a., see above.

These studies have shown the efficacy of linagliptin to improve HbA1c in patients with renal function ranging from normal to severe CKD [McGill *et al.* 2013].

The studies on the efficacy and safety of the other DPP-4 inhibitors (saxagliptin, sitagliptin and vildagliptin) are difficult to compare with this study due to different study designs and patient populations [McGill *et al.* 2013]. The HbA1c reductions in patients with type 2 diabetes and moderate or severe RI with linagliptin were similar, or greater, than those seen with other DPP-4 inhibitors [Kothny *et al.* 2012; Nowicki *et al.* 2011a, 2011b]. In contrast to other DPP-4 inhibitors, linagliptin does not require dose adjustment in patients with severe CKD, whereas a recent study reported that sitagliptin was frequently used at inappropriate doses in patients with type 2 diabetes and RI, and only 15% of patients with moderate to end stage RI received recommended doses [Meyers *et al.* 2011]. The fasting plasma glucose reductions observed with linagliptin over placebo do not seem to fully account for the HbA1c change, suggesting that postprandial glucose reductions, which can occur with incretin-based therapies, must have made more substantial contributions than fasting plasma glucose reductions. This contention is supported by previous observations of linagliptin's positive effects on postprandial glucose [Del Prato *et al.* 2011; Monnier *et al.* 2003; Taskinen *et al.* 2011]. Long-term improvements in glycaemic control with linagliptin were associated with a trend toward decreases in background insulin therapy in the current study [McGill *et al.* 2013]. This may help to improve diabetes management and to lower the hypoglycaemia risk, but warrants further studies to determine the extent of this effect. Along with a previous finding that linagliptin exposure did not vary in patients with normal, mild or moderate CKD, the pharmacokinetic data from this study confirm that linagliptin is not expected to accumulate at any degree of impaired renal function [McGill *et al.* 2013]. In progressive renal failure and advanced cardiovascular disease, glycaemic control is more difficult to achieve without adverse effects because of the increased risk of hypoglycaemia due to reduced renal gluconeogenesis on the one hand and the retarded clearance of insulin as well as of some antihyperglycaemic agents and their metabolites on the other hand [Ritz, 2011]. This study showed that symptomatic hypoglycaemic events and severe hypoglycaemic episodes occurred at similar rates in the linagliptin and placebo groups [McGill *et al.* 2013].

Perspectives for linagliptin concerning cardiovascular outcomes

Although the results of the different meta-analyses of DPP-4 inhibitors are not entirely comparable (due to differences in primary composite endpoints and cardiovascular adjudication methods), all are supportive of the hypothesis that, in general, DPP-4 inhibitor treatment does not have a deleterious impact on the incidence of cardiovascular events. The present analysis shows that linagliptin treatment does not increase cardiovascular risk and may even yield cardiovascular benefits in patients with type 2 diabetes mellitus. Meta-analyses of other DPP-4 inhibitors were frequently retrospective in nature. However, the prespecified design of the present meta-analysis involved prospective and blinded adjudication of cardiovascular events, which should strengthen the validity of the current findings. In addition, this meta-analysis was based on individual patient data from a consistently designed, large clinical development programme; this allows consistent derivation of endpoints and extensive subgroup analyses and minimizes between study heterogeneity that can confound analyses of unrelated studies.

In summary, this pre-specified cardiovascular meta-analysis of a large phase III programme that involved prospective and independent adjudication of cardiovascular events provides valuable new insights on the cardiovascular safety profile of linagliptin. Although a meta-analysis, with distinct limitations, the data indicate that linagliptin does not increase cardiovascular risk and, moreover, support a potential reduction of cardiovascular events with linagliptin compared with pooled comparators. These results suggest that linagliptin may be a valuable new therapeutic option for improving glycaemic control in patients with type 2 diabetes mellitus. The hypothesis that linagliptin may have cardiovascular benefits is currently being tested prospectively in the CAROLINA study (NCT01243424), the first large outcomes study to directly compare a DPP-4 inhibitor *versus* a sulfonylurea (glimepiride), predominantly as second line therapy (i.e. on a background of metformin).

Glycaemic control is fundamental to diabetes management. Several large clinical trials have demonstrated an association between hyperglycaemia and the progression of microvascular complications, such as cardiovascular disease, in patients with type 2 diabetes [UKPDS Group 1998a, 1998b; Ohkubo *et al.* 1995]. However, antihyperglycaemic treatment options are limited

in patients with type 2 diabetes and cardiovascular disease because many oral glucose-lowering agents are cleared by the kidney. Therefore, in patients with severe RI, most of these therapies are either not recommended or contraindicated (e.g. α -glucosidase inhibitors, metformin, GLP-1 receptor agonists and some first-generation sulfonylureas) or may require significant dose reduction (e.g. second generation sulfonylureas, repaglinide and DPP-4 inhibitors) [Bakris, 2011; Shrishrimal *et al.* 2009]. Although advanced cardiovascular disease does not affect the metabolism of thiazolidinediones, these agents must also be used with caution because of the increased risk of fluid retention and heart failure. Furthermore, pioglitazone, the only remaining thiazolidinedione, is no longer available in every country [Chapelsky *et al.* 2003].

The recent study in patients with CKD [McGill *et al.* 2013] supports the use of linagliptin as an effective once-daily treatment option in patients with type 2 diabetes and severe renal impairment, without the inconvenience of dose adjustments or more frequent assessments of renal function specifically for dose calculation. In addition, renal function with linagliptin remained stable over time and overall insulin doses were reduced. Investigations to evaluate these observations further are currently underway [McGill *et al.* 2013].

The US Food and Drug Administration requires evidence that therapies for diabetes do not cause unacceptable increases in cardiovascular risk [Drucker and Goldfine, 2011]. Retrospective analyses of data from DPP-4 inhibitors have not suggested any increased cardiovascular risk for this drug class in the treatment of type 2 diabetes so far [Verge and Lopez, 2010]. The large prospective ongoing CAROLINA trial will be completed in the second half of this decade and will give important answers about the value of DPP-4 inhibitor therapy in type 2 diabetes in general and about linagliptin in particular in patients with type 2 diabetes and a high vascular risk.

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Conflict of interest statement

The author is a member of advisory boards for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim (manufacturer of linagliptin), Eli Lilly, Novartis, Novo Nordisk, Merck, Roche, Sanofi

and Takeda. He has also received honoraria from these companies for giving lectures.

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