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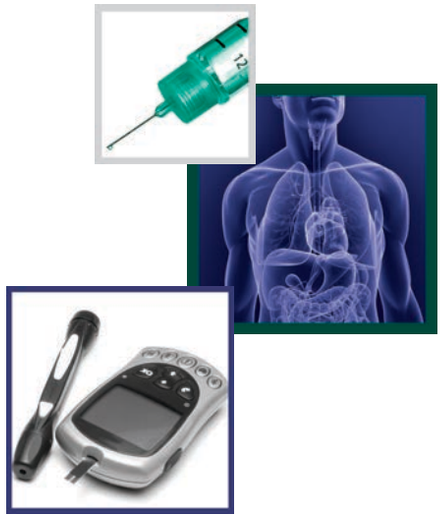

Incretin for the continuing treatment of secondary failure to metformin in Type 2 diabetes

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Practice Points

- The incretin hormone GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner.
- Apart from its effects on glucose metabolism, GLP-1 affects satiety and has cardioprotective and possibly neuroprotective effects.
- Incretin-based therapies utilize the physiological actions of GLP-1.
- GLP-1 receptor agonists (RAs) are peptide molecules with a longer action compared with native GLP-1 that are designed for an injection therapy.
- DPP-4 inhibitors act on the enzyme DPP-4, which cleaves and inactivates endogenous GLP-1 and other substrates. GLP-1 concentrations are raised two- to three-fold by DPP-4 inhibitors that are orally active.
- The main indication for treatment with DPP-4 inhibitors is as a combination therapy with metformin in patients failing on metformin monotherapy.
- GLP-1 RA can be used as a combination therapy with metformin in patients failing on metformin monotherapy, especially when additional body weight loss is desired to reduce the cardiovascular risk.
- With the combination of metformin with incretin-based therapies, the hypoglycemia risk is very low.
- The different pharmacokinetic profiles of GLP-1 RA can be used for individualized therapy.
- Cardiovascular end point studies for incretin-based therapies will be available soon.

SUMMARY For the treatment of Type 2 diabetes, incretin-based therapies have been an established treatment since their introduction in 2006. GLP-1 receptor agonists as an injectable therapy and DPP-4 inhibitors as oral antidiabetic agents have a strictly glucose-dependent action on insulin and glucagon secretion, resulting in a negligible intrinsic hypoglycemia risk. The GLP-1 receptor agonists only act by stimulating the GLP-1 receptor directly at receptor ligand concentrations in the pharmacological concentration range. They decelerate gastric

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emptying dependent on their duration of action and also act directly by stimulating satiety signals in the CNS. These effects lead to a loss of body weight. DPP-4 inhibitors primarily elevate endogenous active GLP-1 plasma concentrations by two- to three-fold. They are body weight neutral since only higher concentrations of GLP-1 than those elicited by DPP-4 inhibitors have direct effects on the CNS or on the retardation of gastrointestinal motility. Novel studies suggest beneficial cardiovascular effects of incretin-based therapies. This article gives an overview of developments in this therapeutic area.

Mode of action of incretin-based therapies

GLP-1 is a peptide hormone secreted from the L cells of the intestinal mucosa in the postprandial state. It is, together with GIP, a so-called incretin hormone. These hormones are responsible for the so-called incretin effect, which describes the phenomenon that orally ingested glucose leads to a much higher stimulation of insulin secretion than an isoglycemic intravenous glucose infusion [1–3]. In Type 2 diabetes mellitus (T2DM), the incretin effect is diminished, mainly because GIP has lost its insulinotropic action as a result of chronic hyperglycemia [4]. Supraphysiological concentrations of GLP-1, however, are able to stimulate insulin secretion in T2DM. In addition to this insulinotropic activity, GLP-1 also inhibits excessive glucagon secretion in T2DM. Both effects contribute significantly to the normalization of glucose concentrations. Beyond that, both effects are strictly glucose dependent, so GLP-1 on its own does not possess an intrinsic hypoglycemia risk [5,6]. There are further physiological actions of GLP-1 that are favorable in T2DM: GLP-1 is also produced in the CNS, and receptors in the brainstem, hypothalamus and vagus are believed to contribute to satiety. In the GI tract, GLP-1 slows gastric emptying and also signals via afferent autonomic neurons from the GI tract to the hypothalamic nuclei in the brain [5]. Other studies, mostly in rodents, have shown an inhibition of apoptosis of pancreatic β-cells and an improvement in β-cell function, as well as an increase in insulin biosynthesis. More recent data also point out a possible beneficial role in cardioprotective mechanisms and even in neuroprotection [7–9]. *In vivo*, GLP-1 is enzymatically cleaved and biologically inactivated within a few minutes by the ubiquitous enzyme DPP-4 [10,11]. Therefore, native GLP-1 cannot be used for therapeutic purposes. The above-described physiological actions of GLP-1 can be utilized by either GLP1 receptor agonists (RAs) or DPP-4 inhibitors [3,5].

DPP-4 inhibitors (alogliptin – approved in Japan – Takeda, Osaka, Japan; linagliptin, Boehringer Ingelheim, Ingelheim, Germany; saxagliptin, AstraZeneca, London, UK, and Bristol Myers Squibb, NY, USA; sitagliptin, Merck, NJ, USA; and vildagliptin, Novartis, Basel, Switzerland) are orally active, well tolerated and body weight neutral [12–16]. They are approved in oral combination therapy with metformin or a sulfonylurea or pioglitazone. For triple therapy, they are approved in a combination with metformin and sulfonylurea. With the exception of saxagliptin, all DPP-4 inhibitors are also approved as monotherapies for patients with metformin contraindications or metformin intolerance. Additionally, the DPP-4 inhibitors linagliptin, saxagliptin, sitagliptin and vildagliptin (not approved in the USA) are approved for combination therapy with insulin. They have recently also received indications for the treatment of T2DM in patients with chronic kidney disease (CKD) and can be used with substance-specific dose reductions in the various stages of CKD [17–20].

GLP-1 RAs (exenatide – twice daily and once weekly formulation – Amylin, CA, USA, AstraZeneca and Bristol Myers Squibb; liraglutide, Novo Nordisk, Bagsværd, Denmark; and lixisenatide, Sanofi, Paris, France) are injectable agents that can also be used as second-line therapy when metformin monotherapy fails. Their advantages are their almost negligible intrinsic risk of hypoglycemia, and that they allow significant weight loss and improve metabolic parameters. GLP-1 RAs are approved in dual combination therapy with either metformin or a sulfonylurea, or in a triple combination with metformin and a sulfonylurea. In combination therapies with sulfonylureas and GLP-1 RA, an increased incidence of hypoglycemia is observed, which is mediated by the sulfonylurea and due to the increased efficacy of the combination therapy in lowering glucose. Therefore, it is recommended to reduce the sulfonylurea dose or stop sulfonylurea treatment when GLP-1 RA therapy is started. GLP-1 RAs have demonstrated a higher efficacy in reducing HbA1c

compared with DPP-4 inhibitors [21–23]. Combination therapies with long-acting insulins have also been approved for the GLP-1 RAs exenatide (the twice-daily formulation), liraglutide and lixisenatide. The combinations of a shorter acting GLP-1 RA and a long-acting insulin have gained more importance due to their efficacy, the associated body weight loss and the significantly lower risk of hypoglycemia. Within the GLP-1 RA class, distinctions have to be made between the short- and long-acting once-weekly agents. The short-acting GLP-1 RAs have a more pronounced effect on slowing gastric emptying and, therefore, show a superior postprandial blood glucose reduction in comparison to the long-acting GLP-1 RAs. The long-acting GLP-1 RAs hardly influence the gastric emptying rate and are significantly more potent in normalizing fasting glucose concentrations [24–27]. The gastrointestinal side effects regarding fullness and/or nausea are more pronounced with the short-acting GLP-1 RAs compared with the long-acting ones. Besides their comparable effect on reducing body weight, GLP-1 RAs also lower systolic blood pressure by a body weight-independent mechanism [22].

The place of DPP-4 inhibitors in Type 2 diabetes therapy

The most important indication for DPP-4 inhibitors is combination therapy with metformin in patients who do not reach their therapeutic goal on metformin monotherapy and who should not have an increased hypoglycemia risk or further body weight gain. For this indication, prospective randomized 2-year-long studies comparing each DPP-4 inhibitor as an add-on therapy with metformin and a sulfonylurea as an add-on therapy with metformin have been carried out. In all of these studies, the DPP-4 inhibitors were noninferior to sulfonylurea treatment regarding HbA1c over a time span of 2 years [28–32]. Additional therapy with a DPP-4 inhibitor resulted in a significantly lower incidence of hypoglycemic episodes compared with sulfonylurea, and the risk of hypoglycemia was reduced approximately fivefold in DPP-4 inhibitor-treated patients (hypoglycemia incidence of ~35–40% in sulfonylurea therapy and ~5–8% in DPP-4 inhibitor-treated patients) [28–32]. Regarding body weight, after 2 years, a difference of approximately 2.5 kg was observed between treatment groups, favoring DPP-4 inhibitors with a small body weight loss, while sulfonylureas resulted in a body weight gain [28–32]. A greater proportion of patients reached a combined end point of the target HbA1c without hypoglycemia or body weight gain in the group that received the metformin–DPP-4 inhibitor combination therapy compared with the group that had the metformin–sulfonylurea combination. In addition, the combination of DPP-4 inhibitors with metformin leads to an additive increase in intact GLP-1 plasma concentrations. This is probably due to the stimulatory effect of metformin on proglucagon precursor expression in the large intestine. Therefore, DPP-4 inhibitors and metformin have complementary mechanisms of action and additive effects with respect to increasing the concentrations of active GLP-1 in plasma [33].

The place of GLP-1 RAs in Type 2 diabetes therapy

GLP-1 RAs have their most important indication in patients with metformin failure and especially in those who would gain additional benefit from weight loss and avoidance of hypoglycemia. In patients who require a safe therapy that is not complex, and manageable with standard doses without further dosing algorithms or additional blood glucose monitoring (as in insulin therapy), a treatment with a GLP-1 RA is a feasible alternative compared with insulin therapy. For patients who would not be able or ready to perform daily (q.d.; or twice-daily) injections, a long-acting GLP-1 RA with a once-weekly injection interval would be a practical solution. In comparative studies versus oral antidiabetic agents (sitagliptin and pioglitazone), and exenatide twice daily and a q.d. injection of a long-acting basal insulin analog, exenatide once weekly demonstrated a greater HbA1c reduction [21,34]. Only in the head-to-head study of exenatide once weekly versus liraglutide (DURATION 6 study), was exenatide once weekly found to be inferior to liraglutide in a dose of 1.8 mg q.d. In a recently published meta-analysis comparing the efficacy of GLP-1 RAs and DPP-4 inhibitors, exenatide once weekly led to a greater HbA1c reduction compared with liraglutide [21].

In a comparative long-term study with a mean duration of 4.8 years in patients not optimally controlled on metformin monotherapy, the addition of exenatide twice daily had a more sustained effect compared with glimepiride as an add-on therapy. Sustainability was defined as the necessity to intensify treatment due to predefined

treatment failure when the HbA1c was >7.5% on two consecutive visits after 3 months or >9.0% on any visit. The largest difference in sustainability of treatment with earlier failure in the glimepirirde-treated group was observed in those patients who had the highest HbA1c values at baseline [35]. The reduction of the incidence of hypoglycemia was approximately fivefold in the exenatide arm. Furthermore, exenatide led to a loss of body weight with a difference of 4.5 kg compared with the glimepiride-treated patients [35].

A novel indication for GLP-1 RA is in combination therapy with a long-acting insulin. For this indication, a couple of studies have been published recently. In one study in patients not reaching their therapeutic goal on combination therapy with metformin and the long-acting insulin analog glargine, the addition of exenatide twice daily led to a further reduction of HbA1c of 0.7% compared with patients who stayed on their initial therapy and just increased the insulin glargine dose. The patients treated with the GLP-1 RA–insulin combination therapy were also able to lose body weight, whereas the patients on insulin alone gained weight. At the end of this 30-week study, the mean body weight difference amounted to 2.74 kg. The body weight difference and the lower rate of severe hypoglycemic episodes with the combination therapy can be explained by the reduction of the insulin dose in the combination therapy [36]. Similar data were obtained in the GET GOAL study program with the recently approved GLP-1 RA lixisenatide [37]. In patients who are already treated with a metformin–GLP-1 RA combination, the addition of a basal insulin leads to a comparable improvement of the glycemic parameters. In a study with patients who had an HbA1c >7% on a metformin–liraglutide combination at baseline, the addition of insulin detemir led to a significant improvement in HbA1c levels without weight gain or an increase in the hypoglycemia risk. With this combination, 28% of patients reached the predefined combined therapeutic goal of HbA1c <7%, no weight gain and no hypoglycemic episodes. In the control study arm that continued on the initial metformin liraglutide combination, only 8.3% reached this combined end point [38]. The combination therapy of a GLP-1 RA with a basal insulin is an essential novel widening of the indication for GLP-1 RA and will certainly play an important role in clinical practice in the near future [22,26].

Cardiovascular & pleiotropic effects

Receptors for GLP-1 are found in the myocardium and vasculature. GLP-1 is able to exert favorable cardiovascular effects (e.g., lowering of systolic blood pressure, improvement of left ventricular function and a decrease of the infarct area in ischemia) via this receptor. On the other hand, additional mechanisms may be involved that are transmitted via different pathways including the GLP-1 fragment GLP-$1_{9–36}$, which is not a stimulating or biologically active ligand at the GLP-1 receptor [39]. Recently, an animal study showed cardioprotective properties of the GLP-1 RA lixisenatide in mice that are partly mediated by GLP-1 receptor-independent mechanisms [40]. Therefore, further mechanistic studies have to be performed to fully understand and explain the cardiovascular effects of GLP-1 [39]. Besides lowering the systolic blood pressure in large clinical studies, which is observed with the use of GLP-1 RA, small studies with intravenous native GLP-1 demonstrated an improvement of left ventricular function in patients with myocardial infarct or heart failure [8,9].

In studies with DPP-4 inhibitors, beneficial cardiovascular effects were also observed. A comparative study comparing the effects of linagliptin as an add-on to metformin versus glimepiride as an add-on to metformin demonstrated a significant reduction of a combined cardiovascular end point in the linagliptin-treated patients. The components of this end point were cardiovascular death, myocardial infarct, stroke or hospital admission due to unstable angina. On the other hand, a significant reduction of nonfatal stroke was also apparent in this group [28]. A consecutive retrospective meta-analysis of all studies comparing DPP-4 inhibitors with sulfonylureas confirmed these results [41]. The currently ongoing prospective cardiovascular end point studies for the incretin-based therapies will provide important data in the near future **(Table 1)**.

From animal studies lacking either the GLP-1 receptor, GIP receptor or DPP-4, data are emerging that could have implications for preventing diabetes-related microvascular complications (e.g., retinopathy, nephropathy and neuropathy) and macrovascular complications (e.g., coronary artery disease, peripheral artery disease and cerebrovascular disease), as well as diabetes-related comorbidity (e.g., obesity, nonalcoholic fatty liver disease, bone fracture and cognitive dysfunction) [42].

Table 1. Cardiovascular end point studies with incretin-based therapies.

Drug	Study	Comparator/patients (n)	Projected completion of study	Ref.
Alogliptin (DPP-4 inhibitor)	EXAMINE Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome	Placebo/5400 patients with T2DM and acute coronary syndrome	December 2013	[103]
Linagliptin (DPP-4 inhibitor)	CAROLINA Linaglitpin and Metformin Versus Linagliptin in Newly Diagnosed, Untreated Type 2 Diabetes	Glimepiride/6000 patients with T2DM	2018	[104]
Saxagliptin (DPP-4 inhibitor)	SAVOR-TIMI 53 Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications	Placebo/16,500 patients with T2DM	September 2013	[105]
Sitagliptin (DPP-4 inhibitor)	TECOS Sitagliptin Cardiovascular Outcome Study (0431-082 AM1)	Placebo/14,000 patients with T2DM	2014	[106]
Exenatide once weekly (GLP-1 RA)	EXSCEL Exenatide Study of Cardiovascular Event Lowering Trial: A Trial to Evaluate Cardiovascular Outcomes After Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus	Placebo/9500 patients with T2DM	2017	[107]
Liraglutide (GLP-1 RA)	LEADER Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation	Placebo/9340 patients with T2DM	2016	[108]
Lixisenatide (GLP-1 RA)	ELIXA Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with AVE0010 (Lixisenatide)	Placebo/6000 patients with T2DM	2014	[109]
Dulaglutide (GLP-1 RA)	REWIND Researching Cardiovascular Events with a Weekly Incretin in Diabetes	Placebo/9622 patients with T2DM	2019	[110]

RA: Receptor agonist; T2DM: Type 2 diabetes mellitus.

Conclusion & future perspective

The incretin-based therapies are well established due to their efficacy and safety profiles. The DPP-4 inhibitors have demonstrated noninferiority compared with sulfonylureas regarding glycemic parameters. Beyond that, they have the advantages of significantly reducing the hypoglycemia risk, leading to an approximately fivefold reduction of hypoglycemia incidence, and show body weight neutrality or even a small reduction in body weight. The difference in body weight was up to approximately 3 kg compared with patients treated with a sulfonylurea over a time period of 2 years. Additional advantages of DPP-4 inhibitors are their standard dosing without titration that also allows fixed-dose combinations with metformin, as well as their approval for CKD patients with impaired renal function. In impaired kidney function, linagliptin can be given without dose titration in all stages of CKD, saxagliptin could be given in a reduced dose of 2.5 mg q.d. down to a creatinin clearance of 29 ml/min, but has only been approved in combination with metformin, so the use of metformin is the limiting factor. Sitagliptin and vildagliptin have approval in all stages of CKD, sitagliptin with a reduced dose of 50 mg q.d. down to a creatinin clearance of 49 ml/min, and with a dose of 25 mg q.d. at the more advanced stages of CKD; vildagliptin can be used with a dose of 50 mg q.d. The advantages of the GLP-1 RAs are their superior efficacy in lowering HbA1c compared with oral medications, including DPP-4 inhibitors, as well as their ability to reduce the hypoglycemia risk and their effect on body weight, with the potential to reduce weight.

Regarding safety, some concerns have been raised connecting incretin-based therapies with an elevated risk for developing acute pancreatitis or even pancreatic cancer [43,44]. In a recent study investigating pancreatic tissue from a very small number of brain-dead organ donors with diabetes and donors without diabetes, prominent histological differences have been observed between those having received either sitagliptin or exenatide, diabetic controls who had not received those therapies and nondiabetic controls [45]. The number of α- and β-cells was greater in the pancreatic samples of the patients who had received incretin-based therapies, but the number of these cells in replication was equal in all groups. Likewise, pancreatic mass was found to be increased in the patients who had received incretin-based therapies. The increase in pancreatic mass was accompanied by an increase in proliferation of exocrine cells and an increase in dyplastic changes (intraductal intraepithelial neoplasias). In three pancreata from sitagliptin-treated patients, glucagon-producing microadenomas were found and one patient was found to have an endocrine neoplasia [45]. The study has been criticized for the heterogeneity of its three groups. In the control group with diabetes not having received incretin-based therapies, there are patients with Type 1 diabetes. The study was not corrected for confounders such as age, diabetes duration, duration and dosing of incretin-based therapy, comedication, and other lifestyle-related confounders such as smoking, alcohol consumption and other important clinical variables. In addition, the three groups were not well matched. This critique has been summarized in an editorial by Kahn [46] in the same journal as the original study. Furthermore, from a pathophysiological viewpoint, acute pancreatitis, as opposed to long-standing chronic pancreatitis, has been considered to be associated with an increased pancreatic carcinoma risk [47–49]. However, large controlled retrospective studies that were undertaken to investigate this hypothesis further have not shown a difference in the pancreatitis or pancreatic cancer risk for the incretin-based therapies so far [50–53]. The US FDA and the European Medicines Agency are now taking the important step to investigate the available pooled safety data of incretin-based therapies and are also evaluating the histological methods used in the study by the Butler group [101,102]. These agencies, as well as professional diabetes associations such as the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), have not changed their positions towards prescribing recommendations of incretin-based therapies.

GLP-1 RAs have been shown to increase calcitonin plasma concentrations in rodents in toxicology studies. In these studies, a higher prevalence of thyroid C-cell hyperplasia and C-cell carcinoma was observed in the animals in rare cases. In humans, C-cells have a significantly lower expression of GLP-1 receptors than in rodents. In all clinical studies and in the wide use of GLP-1 RAs in the clinic, there has been no sign of an elevation of calcitonin

plasma concentrations or histological changes in C-cells [54].

In clinical practice, DPP-4 inhibitors and GLP-1 RAs have established themselves as important drug classes for second-line treatment of T2DM when metformin fails. Both drug classes stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, resulting in an improvement of the glycemic parameters HbA1c and fasting and postprandial plasma glucose without an intrinsic hypoglycemia risk. GLP-1 RAs are more effective compared with DPP-4 inhibitors, and the short-acting GLP-1 RAs have a more pronounced effect on postprandial glucose compared with the long-acting ones, and lower fasting glucose more effectively. The combination therapy of GLP-1 RA with basal insulin offers a novel option to improve glycemic control very effectively without increasing the hypoglycemia risk and without further body weight gain. The most common adverse events under GLP-1 RA therapy are transient mild-to-moderate fullness and nausea at the beginning of therapy. DPP-4 inhibitors are weight neutral and are widely established as add-on therapy to metformin (also as fixed-dose combination tablets with metformin). In this indication, there are signs of an advantage regarding cardiovascular incidents in comparison to a combination of metformin and a sulfonylurea. For both drug classes, cardiovascular end point studies will reveal data in the near future.

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