Incretin-Based Therapies

Viewpoints on the way to consensus

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INTRODUCTION (BY M.A.N.)

— Incretin mimetics and inhibitors of the protease dipeptidyl peptidase (DPP)-4 are new classes of antidiabetic agents first introduced in the years 2005 (exenatide) and 2007 (sitagliptin), respectively. Both use the antidiabetic properties of the incretin hormone, glucagon-like peptide (GLP)-1 (1). This gut-derived peptide hormone not only augments glucose-induced insulin secretion (required to fulfill the definition of an incretin hormone), but does so in a highly glucose-dependent manner (2), thus preventing GLP-1 alone from provoking hypoglycemia. Additional beneficial effects of GLP-1 on endocrine pancreatic islets are that it *1*) supports the synthesis of proinsulin to replenish insulin stores in β-cells; *2*) reduces the rate of β-cell apoptosis when islets are incubated in a toxic environment (glucotoxicity, lipotoxicity, cytotoxic cytokines); and *3*) promotes differentiation of precursor cells with the ability to develop into β-cells and proliferation of β-cell lines, and in whole animals (rodent studies), this leads to an increased β-cell mass within a few days or weeks (1,3). Furthermore, GLP-1 can lower glucagon concentrations, i.e., induce α-cells to respond again to the inhibitory action of hyperglycemia, while leaving the counterregulatory glucagon responses undisturbed, as in the case of hypoglycemia (2,4). Additional activities of GLP-1 are the deceleration of gastric emptying (5), which slows the entry of nutrients into the circulation after meals, a reduction in appetite, and earlier induction of satiety (6), leading to weight reduction with chronic exposure (7). Renal effects (promotion of sodium and water excretion (8), as well as neuro- (9) and cardioprotective (10) properties of GLP-1, have also been described. While GLP-1 is perfectly suitable for lowering, or even stabilizing, glucose concentrations in short-term experiments, its short half-life (~1–2 min for the intact, biologically active form) caused by rapid proteolytic degradation and inactivation through the ubiquitous enzyme DPP-4 and renal elimination (Fig. 1*A*) prohibits long-term use for treatment of a chronic condition, such as type 2 diabetes (1).

For this reason, incretin mimetics (e.g., exenatide and liraglutide) with considerably longer half-lives have been developed. Exenatide is a synthetic form of a natural peptide found in the saliva of *Heloderma suspectum* (11). Through its amino acid sequence homology with GLP-1, it is able to interact with GLP-1 receptors and to mimic all aspects of the antidiabetic activity of GLP-1 (12). Exenatide has a half-life of ~3 h and has been approved for administration (twice-daily injections) to type 2 diabetic patients inadequately controlled by oral antidiabetic agents. Recently developed liraglutide, synthesized by attaching a free fatty acid to a slightly modified GLP-1 molecule, is characterized by a half-life of 12–14 h (suitable for once-daily administration) (13,14). In 2008, results of phase 3 studies were presented, thus facilitating assessment of the potential of this novel agent in the treatment of patients with type 2 diabetes. A common feature of all incretin mimetics is that they are peptides and need to be administered by subcutaneous injection. They bind to and activate the GLP-1 receptor and display the full array of biological (antidiabetic) activity known for/characteristic of GLP-1. Within the group of incretin mimetics, differences are seen with respect to amino acid homology in comparison to native human GLP-1, and in pharmacokinetic characteristics, such as elimination of half-lives, and so forth. Novel attempts have aimed at developing compounds, or preparations, with a longer duration of action, and less frequent administration (e.g., once-weekly) (15).

Another method of exploiting the antidiabetic potential of GLP-1 is by inhibiting its proteolytic degradation and inactivation through the action of DPP-4. Several agents have been identified that are able to inhibit DPP-4 activity (in serum) by >85% and preserve GLP-1 secreted from endogenous sources (mainly in response to meal ingestion) in its intact biologically active forms (GLP-1 [7-36 amide] or GLP-1 [7-37]), thus leading to doubled or tripled integrated incremental responses (16,17). This goes along with stimulation of insulin secretion (relative to the glycemic rise accompanying nutrient ingestion), suppression of the meal-related glucagon response, and a reduction in fasting and postprandial glucose concentrations (16), which translate into a lower A1C value in the long term (18,19). Sitagliptin and vildagliptin (not yet in the U.S.) have been approved as novel oral antidiabetic agents. Alogliptin and saxagliptin are additional agents having undergone clinical studies.

As expected, when two novel classes of antidiabetic agents, both related to the gut endocrine ("incretin") system, are introduced into the market within a short period of time, the properties of the types and agents need to be discussed to determine their clinical value and to define how they should best be used in clinical practice (selection of patients, initiation of treatment, co-medication, and so forth). The present viewpoints focus on several crucial questions that characterize state-

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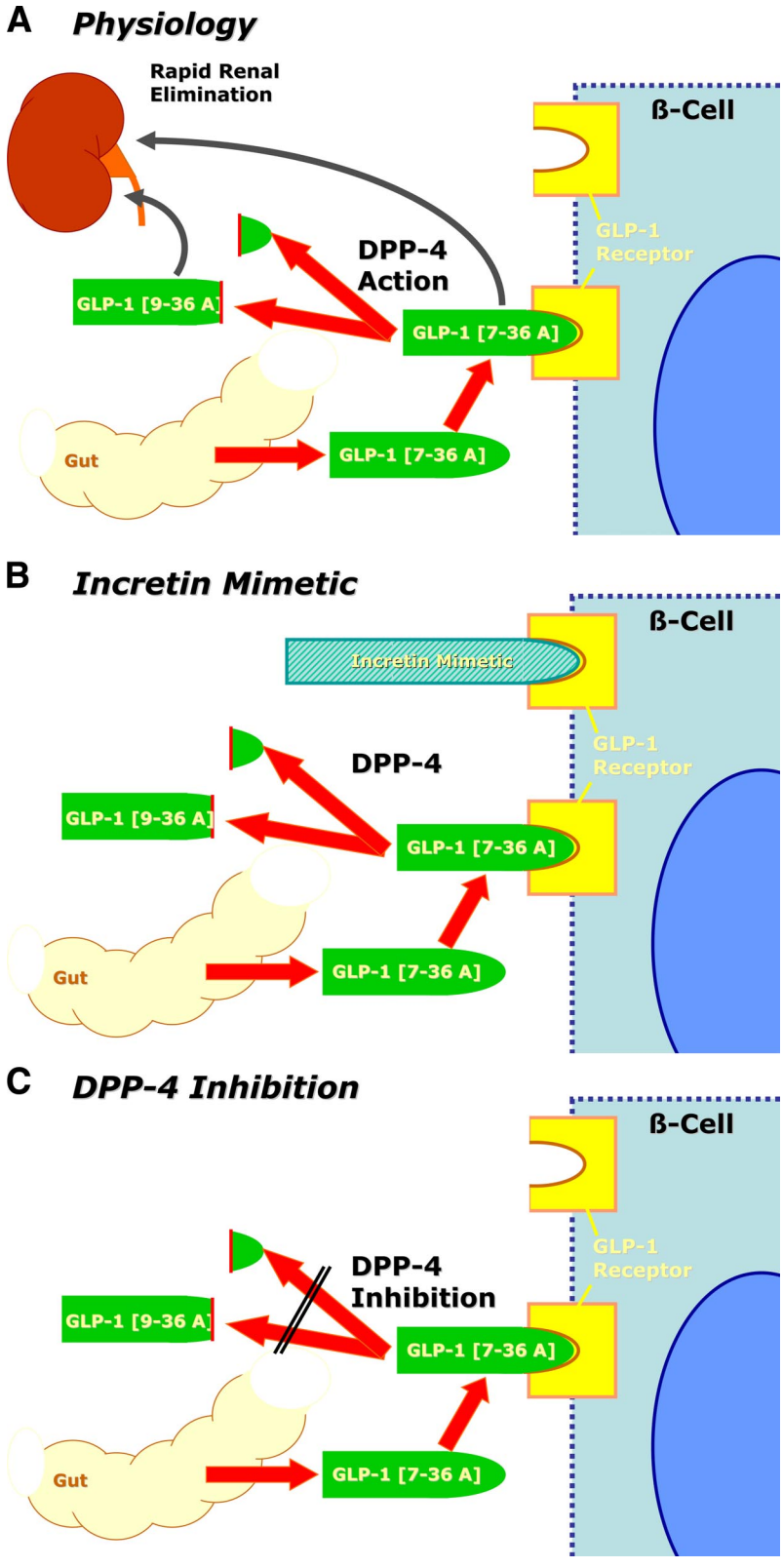

Figure 1—*Schematic diagram explaining the physiological (postprandial) secretion of GLP-1 from the gut, its binding to GLP-1 receptors (e.g., on pancreatic endocrine β-cells), and its degradation by the ubiquitous protease DPP-4 as well as its rapid renal elimination* (A). *Incretin mimetics are peptide GLP-1 receptor agonists more or less structurally similar to GLP-1, which bind and activate the GLP-1 receptor, but are not degraded by DPP-4 and have much slower elimination pharmacokinetics* (B). *DPP-4 inhibitors prevent the degradation/inactivation of the biologically active form of GLP-1 and, thereby, augment the biological activity of GLP-1 released from endogenous sources* (C).

of-the-art incretin-based antidiabetic therapy today.

DIFFERENT APPROACHES TO DIABETES THERAPY — Although GLP-1 receptor agonists ("incretin mimetics") and DPP-4 inhibitors ("incretin enhancers") are based on antidiabetic properties of insulinotropic gut hormones ("incretins"), they represent different approaches to the therapy of type 2 diabetes.

What are the similarities? (by T.V.)

Treatment with GLP-1 receptor agonists ("incretin mimetics") and DPP-4 inhibitors ("incretin enhancers") are based on antidiabetic properties of insulinotropic gut hormones ("incretins"). Although they represent different approaches to therapy in patients with type 2 diabetes, there are notable similarities (Table 1).

First, both therapy approaches engender significant and clinically relevant improvement in glycemic control regarding fasting plasma glucose, postprandial glucose, and A1C (1,20).

Both treatment modalities benefit from the glucose-dependent effect of GLP-1 on insulin secretion and glucagon inhibition, whereby improvements in glucose control can be achieved with minimal risk of hypoglycemia when combined with metformin or thiazolidinedione (TZD) (1). However, when GLP-1 is combined with sulfonylureas, the risk of hypoglycemia appears to be similar to that of sulfonylureas alone (21).

Studies indicate that both incretin mimetics and enhancers target the most exciting aspects of the incretin-based therapies. It is possible that because of the protective and perhaps tropic effect of mimetics and enhancers on the pancreatic β-cells, the progression of disease that inevitably seems to accompany conventional treatment may change. To date, this has not been established in clinical trials, but animal studies with mimetics and enhancers have shown that β-cell proliferation and cytoprotection is seen with both (1,3).

What are the differences? (by B.G.)

Incretin mimetics as peptides have to be injected subcutaneously. They raise the concentrations of GLP-1 receptor agonists to pharmacologically high levels, leading to concentrations 6- to 10-fold that of the physiological ones found in the postprandial state (14,15,22). The exogenous administration of GLP-1 receptor

Table 1—*Similarities of incretin-based therapies*

Properties/action	Incretin mimetics	DPP-4 inhibitors
Glucose-dependent insulin secretion	Yes	Yes
Glucose-dependent glucagonostatic effect	Yes	Yes
Effect on fasting plasma glucose (reduction)	By 1.4–3.4 mmol/l	By 1.0–1.4 mmol/l
Effect on postprandial glucose	Yes	Yes (but weaker)
Effect on A1C (reduction)	By 0.8–1.8%	By 0.5–1.1%
Effect on (pro)insulin biosynthesis	Yes	Yes (weaker?)
Improved in vivo β-cell function (in humans)	Yes*	Yes*
Beneficial cardiovascular effects	Probable	Not proven

*As determined while patients received treatment (lasting effects need to be proven after washing out treatment).

agonists with a long biological half-life results in constantly high plasma concentrations and consecutively in a continuous and exclusive stimulation of the GLP-1 receptor. This stimulatory route with high GLP-1 agonist plasma concentration is thought to mediate the predominantly endocrine and systemic effects of GLP-1 (1,23). Apart from the insulinotropic and glucagonostatic actions, the actions of incretin mimetics include the slowing of gastric emptying that may result in sensations of fullness, or nausea at initiation of therapy, as well as a stimulation of satiety in the central nervous system (5,6). Currently, it is not known to what exact extent both effects contribute to weight loss and reduced appetite. In clinical studies, patients receiving incretin mimetics had body weight loss irrespective of nausea as an adverse event, favoring a regulatory action on the central nervous system (24,25), whereas patients treated with DPP-4 inhibitors did not substantially change their weight (1).

The formation of anti-exentide antibodies has been observed in ~45% of patients on exenatide therapy (20). High antibody titers may be associated with some loss of efficacy of exenatide (15). With liraglutide, the incidence of antibody formation is lower (5–8%) (26).

DPP-4 inhibitors can be ingested orally and produce a longer biological half-life of peptides that are substrates for this enzyme, like GLP-1 (1,16,17).

Since DPP-4 is found in the endothelium of the submucosal capillaries in the small intestine, effects of DPP-4 inhibitors are also thought to be mediated locally, through GLP-1 receptors on vagal afferent fibers, in addition to being a true endocrine signal (27) (Table 2).

Differences between incretin mimetics and DPP-4 inhibitors also concern the respective profile of adverse events (20): gastrointestinal side effects are most typical for incretin mimetics (1). Some cases of pancreatitis have been reported, but it is not clear, whether they have occurred at a higher rate than expected for an obese type 2 diabetic population. A somewhat higher rate of nasopharyngitis was reported in patients treated with DPP-4 inhibitors, but this no longer is supported by a recent report on sitagliptin adverse events (28). Occasional elevations in liver enzymes have been reported with vildagliptin, and skin lesions were described with sitagliptin treatment in rare cases.

Table 2 summarizes the differences between incretin mimetics and DPP-4 inhibitors.

ADVANTAGES OF INCRETIN MIMETICS AND DPP-4 INHIBITORS

— Based on currently available information (phase 3 studies designed for drug approval), incretin mimetics and DPP-4 inhibitors have advantages over other antidiabetic drugs.

What are the obvious benefits for the patients? (by A.G.)

Novel effects have been found with incretin-based therapies, such as GLP-1 receptor agonists (exenatide; liraglutide in phase 3 trials) and DPP-4 inhibitors (sitagliptin; vildagliptin), which are beneficial to patients and are not found with other antidiabetic treatments. Perhaps the most significant of these is the glucose-dependent nature of their insulinotropic effects, which means that incretin-based therapies mimic closely the physiologic insulin profile and are associated with very low rates of hypoglycemia. In addition to this key property, and also of major significance, incretin-based therapies do not cause weight gain. In fact, GLP-1 receptor agonists provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, TZDs, and insulin (29–32). DPP-4 inhibitors at least are weight neutral (1,20).

Additional novel features include the positive effect of some incretin-based therapies on the β-cell. GLP-1 receptor agonists improve some parameters of β-cell function during treatment (33,34), while a lasting effect after an appropriate washout period has not been demonstrated after 1 year of treatment with exenatide (35). Finally, one may expect a

Table 2—*Differences of incretin-based therapies*

Properties/action	Incretin mimetics	DPP-4 inhibitors
Administration	Subcutaneous	Oral
GLP-1 levels (or equivalent)	Pharmacological (six- to tenfold)	Physiological (two- to threefold)
Main mechanism of GLP-1 receptor stimulation	Interaction with receptors on target organs/cells	Interaction with receptors on afferent nerves (autonomous nervous system)
Other mediators	No	GIP, PACAP, others (questionable)
Effects on gastric emptying	Yes	No (hardly)
Effects on appetite	Reduced	Hardly influenced
Effects on body weight	Weight loss	Weight neutrality
Adverse events	Nausea, vomiting, antibodies (exenatide, relevance?), pancreatitis (causal relation?)	Upper respiratory tract infections, elevations in liver enzymes (vildagliptin), skin reactions (sitagliptin)

potential halt in progression, driven by a continuing loss in β-cell function (36), from such treatment. This, however, needs to be demonstrated. A hint in this direction may be read from the absolutely constant fasting plasma glucose and A1C concentration during liraglutide treatment in previously drug-naïve type 2 diabetic patients for a full year (26). Most likely, longer treatment will be required to support firm conclusions on this issue. Regarding DPP-4 inhibitors, only preliminary data regarding β-cell function and nonprogression is available (37,38).

Mechanistic studies have suggested cardio-protective activity of GLP-1 (39). Similar effects may be present with GLP-1 receptor agonists. Clinical trials have shown effects of exenatide and liraglutide on surrogate cardiovascular parameters such as systolic blood pressure (31,33), triglycerides, and brain natriuretic peptide (24). Long-term studies proving cardiovascular benefit are necessary for both incretin mimetics and DPP-4 inhibitors.

Besides their positive therapeutic effects, incretin-based therapies offer advantages over traditional oral agents and insulin, in terms of both convenience and reduced side effects, especially with regard to the expected frequency of hypoglycemia and weight gain. Based on these important properties, GLP-1 receptor agonists have been mentioned in recent treatment algorithms for the treatment of type 2 diabetes, however, as less validated therapy (40,41).

What information is currently lacking but would be needed for an unequivocal recommendation? (by S.M.)

Choosing antihyperglycemic agents is determined by their efficacy in lowering blood glucose and their extraglycemic effects (including effects on cardiovascular disease and microangiopathy), adverse events, and costs. GLP-1 receptor agonists and DPP-4 inhibitors are relatively novel classes of drugs. To unequivocally recommend these two new drug types, the following information is lacking and should be provided: *1*) Current data on the durability of glycemic control are insufficient, *2*) the durability and magnitude of weight regulation are currently unknown, *3*) neither GLP-1 receptor agonists nor DPP-4 inhibitors have been investigated in trials of sufficient size and duration to evaluate their effects on cardiovascular outcomes, and *4*) long-term trials on safety with prospective collection of adverse events are needed over and above what has been reported so far.

The AMIGO studies showed that after 30 weeks of exenatide treatment, the reduction in A1C was ~0.8–1.0% compared with placebo treatment (1). In the three AMIGO studies, a total of 1,441 type 2 diabetic patients were included, and during a 3-year follow-up of a subgroup of participants (n = 314), the reduction of A1C was stabilized at ~1.1% (33). In a comparison between exenatide and insulin glargine, or premixed aspart insulin, the lowering of A1C did not differ between the groups during 6 and 12 months of treatment. The efficacy of exenatide in lowering A1C compared with other oral antidiabetic agents is unknown.

With the once-daily GLP-1 receptor agonist liraglutide, which offers a 24-h profile of action, the placebo-adjusted reduction in A1C was 1.7% after 14 weeks of treatment (24). In the LEAD program (Liraglutide Effect and Action in Diabetes, including ~6,500 people, of which ~4,440 participants received liraglutide), liraglutide was compared with rosiglitazone as an add-on to glimepiride (LEAD 1), with a reduction in A1C of 1.1 and 0.5% in favor of liraglutide after 26 weeks (32). In LEAD 2 (add on to metformin), the reduction in the liraglutide- and glimepiride-treated groups did not differ after 26 weeks follow-up (−1.0 vs. −1.0%, respectively) (31). Conversely, in a 52-week study of drug-naïve patients, the reduction in A1C was 1.1 and 0.45%, respectively, for the liraglutide and glimepiride groups (LEAD 3), indicating better durability of glycemic control with liraglutide (26). In LEAD 5, liraglutide was compared with insulin glargine in type 2 diabetic patients, who had failed on combination therapy with metformin and sulfonylureas (42). After 26 weeks, A1C levels were reduced to 1.3 and 1.1% in favor of liraglutide. Therefore, the reduction in A1C levels appears to be similar or greater with the GLP-1 receptor agonist liraglutide compared with other antidiabetic drugs.

More than 25 studies have been published on sitagliptin and vildagliptin treatment as add-ons to various antidiabetic regimens. In a few studies, these DPP-4 inhibitors have been compared with metformin, sulfonylurea, rosiglitazone, or pioglitazone (43). Most studies have been of short duration (<30 weeks). The reduction in A1C was ~0.6–0.8% compared with placebo during the first 6 months of treatment (20,43). In comparison with glipizide, metformin, rosiglitazone, or pioglitazone, the reductions in A1C were similar or slightly less (by ~0.2–0.3%) in the DPP-4 inhibitor-treated patients (20,43).

At present, no robust human data indicate that incretin-based therapy may protect or restore β-cell function or even mass. Thus, there was no change in β-cell function before start of treatment, or when tested after 1-year treatment with exenatide followed by a 1-month washout of exenatide (35). Regarding DPP-4 inhibitors, in a 52-week trial looking at the efficacy of sitagliptin versus glipizide added to ongoing metformin therapy, the maximal efficacy in A1C reduction was observed at week 24–30, with a gradual rise in A1C from week 30 to 52, however, at a slower pace with the DPP-4 inhibitor (19). Longer-term studies lasting for up to 2 years with vildagliptin have not resulted in uniform results regarding the "durability" of glucose-lowering effectivity (37,38). Therefore, any potential long-term benefits for incretin-based therapy from preventing deterioration in β-cell function remain to be proven.

A longer durability of glycemic control may also be expected from persisting weight loss. The DPP-4 inhibitors are weight neutral, whereas the GLP-1 receptor agonists induce weight loss (1,20). The precise durability and magnitude of weight regulation are currently unknown. In the AMIGO and LEAD studies, weight loss after 14–52 weeks of treatment was 1.5–4 kg compared with placebo treatment (1,20,26,31,32,43). However, ~20–25% of patients in the AMIGO studies and the LEAD program did not lose weight during treatment with exenatide or liraglutide, respectively. The reasons are not obvious, but could be explained by lower bioavailability of the drugs in some patients. Relatively high levels of GLP-1 are needed for weight regulation (44), which also explains the absent effect on weight loss during treatment with DPP-4 inhibitors. DPP-4 inhibitors do not have a consistent effect on lipid profiles, and any reduction in blood pressure is minimal (43).

Type 2 diabetes is associated with a high risk of cardiovascular disease. Ideally, diabetic drugs should improve macrovascular outcomes and mortality. Neither GLP-1 receptor agonists nor DPP-4 inhibitors have been investigated in trials of sufficient size to evaluate their effects on cardiovascular end points.

At present, few long-term (>6 months) safety data in human subjects during treatment with GLP-1 receptor agonists and DPP-4 inhibitors are available. Regarding adverse events of GLP-1 receptor agonists, the focus has been on pancreatitis and thyroid C-cell neoplastic changes. More than 150 cases of pancreatitis have been reviewed by the U.S. Food and Drug Administration post-marketing during treatment with exenatide, and five cases have been diagnosed during the LEAD program with liraglutide, although additional cases occurred on, e.g., glimepiride as well. However, it is not clear whether the overall incidence is higher than expected in an obese type 2 diabetic population. Thyroid C-cell adenomas, which have been observed in rodents, have not been seen in humans (24). Recent reports have also linked increased levels of GLP-1 with the development of nesidioblastosis and hypoglycemia in a small number of patients who had undergone gastric bypass (45). A reanalysis of the same pancreatic sections, however, when compared with appropriate control pancreases, did not reveal β-cell hyperplasia as originally suspected (46).

DPP-4, also known as CD26, is found as a membrane protein expressed in many different tissues, including lymphocytes, and in a circulating soluble form (47); DPP-4 inhibitors also prolong the action of a number of growth factors, neuropeptides, cytokines, chemokines, and various hormones other than GLP-1 and gastric inhibitory polypeptide (47). Potential side effects include neurogenic inflammation and allergic reactions (48). In a recent Cochrane review of 25 trials with DPP-4 inhibitors, more infections (i.e., urinary tract infections and nasopharyngitis) were observed in the groups treated with sitagliptin or vildagliptin (43). Additional reported side effects are abdominal pain, nausea, diarrhea, and arthralgias. Postmarketing reports include anaphylaxis, angioedema, and exfoliative skin conditions, including Steven-Johnsons syndrome. Based on a recent meta-analysis of 12 large-phase IIb and III studies with up to 2 years' duration including 6,139 patients receiving either sitagliptin or a comparator agent, the incidence rates of serious adverse events and discontinuations due to adverse events, however, were similar in the two groups, indicating that sitagliptin is well tolerated (28). Only nasopharyngitis occurred more frequently in the sitagliptin group, whereas the incidence of urinary tract infection was similar in the groups.

INCRETIN MIMETICS AND DPP-4 INHIBITORS — Incretin mimetics and DPP-4 inhibitors will be/will not be used in the same patient population, i.e., at the same "stage" of type 2 diabetes.

Profile of incretin mimetics and DPP-4 inhibitors is so similar that there are no differential indications (by S.M.)

Given that the GLP-1 receptor agonists and DPP-4 inhibitors have not yet been compared head-to-head in any long-term clinical trial, it is difficult to identify the patient population most likely to respond optimally to these two groups of drugs.

Both classes of drugs exert a beneficial effect on glycemic control, irrespective of the type of background oral agents, and both complement the action of metformin, TZD, and sulfonylureas. Both display beneficial effects on weight compared with other oral antidiabetic drugs (except DPP-4 inhibitors versus metformin), however, more pronounced for the GLP-1 receptor agonists (1,20,43). Lastly, both are rarely, if ever, associated with severe hypoglycemia if not used in combination with sulfonylurea. The use of DPP-4 inhibitors is simple: once- or twice-daily oral administration. Exenatide has to be injected twice daily and is associated with relatively high rates of nausea and vomiting initially.

The GLP-1 receptor agonists may be particularly effective in overweight patients who want to lose weight and in overweight patients who are uncontrolled with oral agents, and who do not want to start insulin treatment because of the risk of weight gain and fear, or high risk, of hypoglycemia. The GLP-1 receptor agonists may, in addition, have some indications in patients with type 2 diabetes who are receiving insulin therapy (49), either replacing it or in addition to insulin. Experience, however, is limited. When added to insulin treatment in a 24-week study, vildagliptin reduced A1C by 0.5% compared with 0.2% in the placebo-treated group (50).

In conclusion, incretin-based therapy is a useful addition to the existing antidiabetic drugs. Both classes of drug can, in principle, successfully be used in drug-naïve patients, but the official indications are patients are being treated with one or more oral antidiabetic agent. Whether the patients will choose treatment with a DPP-4 inhibitor or exenatide will depend on the desire for weight loss versus treatment with a tablet to avoid injection therapy. At present, the GLP-1 receptor agonist to be administered once daily, i.e., liraglutide, or once weekly, i.e., exenatide, are in clinical development (15,31).

Incretin mimetics and DPP-4 inhibitors are so different that well-defined patient populations can be identified for whom to use either incretin mimetics or DPP-4 inhibitors (by A.G.)

There are distinct differences between incretin mimetics and DPP-4 inhibitors, ranging from their mode of administration to their effects on body weight. These differences will inevitably lead to a differentiation of patient groups in whom one treatment is favored over the other.

The five key differences are as follows: *1*) GLP-1 receptor agonists are administered via subcutaneous injection, whereas DPP-4 inhibitors are delivered as oral tablets; *2*) GLP-1 receptor agonists are probably more effective than DPP-4 inhibitors at reducing A1C; *3*) GLP-1 receptor agonists show a more prominent β-cell preservation/improvement effect than has been observed with DPP-4 inhibitors; *4*) GLP-1 receptor agonists cause significant weight loss, especially in very obese patients, whereas DPP-4 inhibitors do not induce weight loss; and *5*) GLP-1R agonists have a positive effect on systolic blood pressure, which has not been shown by DPP-4 inhibitors.

It is simple to envisage the effect of the first disparity. Because GLP-1 receptor agonists are administered via subcutaneous injection, and DPP-4 inhibitors are delivered as oral tablets, initiating DPP-4 inhibitor therapy does not represent any major change in practice from metformin/oral antidiabetic agent therapy. As a result, DPP-4 inhibitors will be used earlier in the treatment algorithm than GLP-1 receptor agonists, regardless of any pharmacologic similarities the drugs may have. Indeed, their oral administration indicates that DPP-4 inhibitors are likely to replace existing oral antidiabetic agents, whereas delivery via subcutaneous injection may

classify GLP-1 receptor agonists as competitors for insulin treatment. Thus, patient groups for whom DDP-4 inhibitors are likely to be preferred are those who formerly would have added an oral antidiabetic agent to their regimen and, for GLP-1 receptor agonists, those who formerly would have initiated insulin treatment.

Both the second and third differences (GLP-1 receptor agonists are more effective in reducing A1C and show a β-cell preservation/improvement effect) also suggest that GLP-1 receptor agonists will be used later in the course of the disease, as insulin typically is. This is because it is usually in patients several years after diagnosis, when decline of incretin system function is more advanced, that both larger decreases in A1C are necessary, and non-insulin therapies requiring some residual β-cell function are less effective.

The fourth key variation (i.e., GLP-1 receptor agonists, but not DPP-4 inhibitors, cause significant weight loss) clearly makes them the treatment of choice for a large group of diabetic patients who are prominently obese. When viewed alongside the reduction of systolic blood pressure observed with GLP-1 receptor agonists but not with DPP-4 inhibitors, it is possible to suggest that GLP-1 receptor agonists will be the preferred treatment in type 2 diabetic patients with BMI >30 kg/m^2, and perhaps even replace several drugs (e.g., anti-obesity drugs, anti-hypertensive drugs), despite the requirement for subcutaneous administration. Therefore, whereas very obese patients may significantly benefit from GLP-1 receptor agonist therapy, type 2 diabetic patients with lower BMI may be directed toward DPP-4 inhibitors as an easier/simpler regimen.

These considerations, which suggest that GLP-1 receptor agonists may find themselves classified as a third-line alternative to insulin, should be viewed against evidence that earlier initiation may lead to clinical benefits (51). A drug class that does not carry the risk of hypoglycemic episodes, or the weight gain as associated with insulin, and can be administered once daily independent of meals should not be grouped as something like a "new insulin" based on its mode of administration.

Incretin mimetics and DPP-4 inhibitors should be incorporated in treatment algorithms to be published as guidelines for treatment of type 2 diabetes

Incretin mimetics and DPP-4 inhibitors will be an option aside from first-line treatment recommendations to be used in occasional patients (by B.G.). The American Diabetes Association and the European Association for the Study of Diabetes have published a joint treatment recommendation with an algorithm for the stepwise escalation of therapeutic steps in the course of type 2 diabetes (52). Based on evidence from clinical studies and on available cost-effectiveness data, exenatide, DPP-4 inhibitors, and other novel compounds were not included in this algorithm because of their generally still limited clinical data and/or relative expense. Considering the epidemiological development of type 2 diabetes and the financial burden on the different health care systems, it seems prudent to use cost-effective nonpharmacological and cheap pharmacological interventions in type 2 diabetes. Conversely, the established therapies have their limitations and draw-backs (53). From this perspective, the novel therapeutic options could be used in occasional patients, i.e., DPP-4 inhibitors as oral therapy when hypoglycemia prevention is important (e.g., patients with hypoglycemia unawareness, patients operating motor vehicles or heavy machines, geriatric patients) or when further weight gain is undesirable due to concomitant complications of obesity and a strong wish to lose weight. The latter condition would favor incretin mimetics over DPP-4 inhibitors, because weight loss is associated with this treatment option. As long as more long-term data, studies with hard clinical end points, and cost-effectiveness data from studies with incretin-based therapies are lacking, it is difficult to judge which patient populations comprise the pertinent characteristics that will profit most from such a therapy compared with standard treatment. This is especially valid for patients who failed oral treatment with two agents and are already on multiple oral compounds, or on insulin therapy. Conversely, the still limited study results allow the use of incretin mimetics and DPP-4 inhibitors in occasional patients who, from current knowledge, will most likely benefit from this therapy. These patients should be followed up closely to gain more data on these treatment options in an everyday clinical setting apart from controlled clinical trials. Only in this way and in conjunction with further study data, patient characteristics, and treatment situations will we ascertain better definitions that may finally lead to novel guidelines.

Incretin mimetics and DPP-4 inhibitors will find a place/be included as standard treatment in certain well-characterized patients and/or situations (by T.V.). Despite the range of oral agents targeting different facets of diabetes (metformin, TZD, insulin sensitizers, sulfonylureas), available treatment paradigms are unsatisfactory, with many patients failing to achieve adequate glycemic control, even when multidrug approaches are used. Patients remain inadequately treated, because existing therapies have a number of shortcomings, including inadequate efficacy in glucose lowering, limited durability of glycemic response, inconvenient dosing regimens, and safety and tolerability issues. The latter include hypoglycemia (sulfonylureas, meglitinides, and insulin), body weight gain (sulfonylureas, meglitinides, insulin, and TZDs), and gastrointestinal intolerance (metformin and α-glucosidase inhibitors). There is, therefore, a need for new and more efficacious agents, targeted not only at treatment, but also at prevention of the disease, its progression, and its associated complications.

As the treatment efficacy of mimetics and enhancers have been firmly established in respect to lowering A1C, and improved β-cell function during treatment, these treatment modalities are expected to find a place/be incorporated as standard treatments (40) and to be included in the recommendations for the treatment of type 2 diabetes within coming years. To date, the main part of clinical trials with the new treatment modalities have been conducted in patients with new-onset type 2 diabetes or patients being treated with one or two antidiabetic drugs (1). Therefore, studies including patients with pre-diabetes and patients in the later stages of diabetes, e.g., when treated with insulin/on insulin therapy, are important to evaluate the applicability in different stages of diabetes. In addition, long-term clinical studies with a broader range of clinical end points (including trials with cardiovascular end points) are warranted to reveal the true benefits of enhancing incretin actions and enable a more effective treatment of a broader spectrum of patients.

CONCLUSIONS (BY M.A.N.)

— As may be expected for relatively novel classes of antidiabetic agents, incretin mimetics and DPP-4 inhibitors receive a lot of attention because they display properties that make them attractive antidiabetic agents and, on first sight, present advantages over existing older agents, namely absence of any risk of hypoglycemia and weight loss/weight neutrality, respectively. On the other hand, based on phase 3 clinical trial data and some experience gained after approval, many open questions remain, and the discussion regarding their therapeutic value, and concerning the appropriate place within treatment algorithms for type 2 diabetic patients, will have to continue in the coming years.

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