A Critical Analysis of the Clinical Use of Incretin-Based Therapies

The benefits by far outweigh the potential risks

There is no question that incretin-based glucose-lowering medications have proven to be effective glucose-lowering agents. Glucagon-like peptide 1 (GLP-1) receptor agonists demonstrate an efficacy comparable to insulin treatment and appear to do so with significant effects to promote weight loss with minimal hypoglycemia. In addition, there is significant data with dipeptidyl peptidase 4 (DPP-4) inhibitors showing efficacy comparable to sulfonylureas but with weight neutral effects and reduced risk for hypoglycemia. However, over the recent past there have been concerns regarding the long-term consequences of using such therapies, and the issues raised are in regard to the potential of both classes to promote acute pancreatitis, to initiate histological changes suggesting chronic pancreatitis including associated preneoplastic lesions, and potentially, in the long run, pancreatic cancer. Other issues relate to an increase in thyroid cancer. There is clearly conflicting data that has been presented in preclinical studies and in epidemiologic studies. To provide an understanding of both sides of the argument, we provide a discussion of this topic as part of this two-part point-counterpoint narrative. In the point narrative preceding the counterpoint narrative below, Dr. Butler and colleagues provide their opinion and review of the data to date and that we need to reconsider use of incretin-based therapies because of the growing concern of potential risk and based on a clearer understanding of the mechanism of action. In the counterpoint narrative provided below, Dr. Nauck provides a defense of incretin-based therapies and that benefits clearly outweigh any concern of risk.

—William T. Cefalu, MD
Editor in Chief, *Diabetes Care*

Glucagon-like peptide 1 (GLP-1)–based medications are GLP-1 receptor agonists (incretin mimetics) and inhibitors of the incretin-degrading and incretin-inactivating protease dipeptidyl peptidase-4 (DPP-4), which exclusively (GLP-1 receptor agonists) or predominantly (DPP-4 inhibitors) act by enhancing the stimulation of GLP-1 receptors (1). Their mechanisms of action (1–3) and clinical effects (1,2,4) have been reviewed extensively. With a lot of scientific data relevant to the judgment of these novel medications having accumulated over the past 6 years and the clinical experience of using them in patients with type 2 diabetes, this is a good moment in time to attempt a more general evaluation of the merits and risks associated with incretin-based medications. Such a judgment will have to take into account the core clinical effectiveness (control of glycemia, prevention of diabetes complications), additional effects that are or could be beneficial in type 2 diabetic patients (improvements in cardiovascular risk factors, e.g., weight loss and reductions in blood pressure), aspects of tolerability and safety, and costs. Among the critical issues that have been raised against the use of GLP-1–based medications are their potential role as inducers of acute pancreatitis (5)—perhaps of chronic pancreatitis (6,7)—and in the long run promoting the development of preneoplastic lesions and thus raising the risk for pancreatic cancer (8). Rodent studies with longer-acting GLP-1 receptor agonists have raised the issue of a potential proliferative response of thyroid C-cells (9), giving rise to hyperplasia, adenomas, and, eventually, medullary thyroid carcinomas. Another point of concern is a small rise in pulse rate observed with some GLP-1 receptor agonists (but not with DPP-4 inhibitors) (10,11). In the point article of this point–counterpoint narrative that precedes this article, Butler et al. (12) cite their significant concerns with these adverse events and make a statement that continued human use may be problematic. With those stated concerns, this counterpoint narrative will discuss the current status of the incretin-based therapies and provide an opinion that the clinical benefits are clearly greater than the potential risks based on the evidence to date.

Special issues (rare findings of uncertain clinical importance)

In addition to the influence of GLP-1–based medications on those outcomes that typically determine the morbidity and mortality of patients with type 2 diabetes, i.e., that affect large proportions of such patients, there may be additional safety concerns of special interest. Some signals have suggested an untoward influence of such treatment on the risk for certain rare conditions. For GLP-1 receptor agonists and for DPP-4 inhibitors, these events of special interest are pancreatitis, pancreatic cancer, and thyroid carcinoma (Table 1). In addition, possible consequences of a rise in pulse rate with GLP-1 receptor agonists need to be discussed.

Pancreatitis

Cases of pancreatitis have been observed in animals (6,7,13) and patients (14) treated with incretin mimetics and DPP-4 inhibitors (5). The questions are whether pancreatitis occurs more often in association with treatment using GLP-1–based medications, and whether it is causally related to such treatment.

Pancreatitis in animal studies

Animal studies describe histological changes compatible with damage to the exocrine pancreas with exenatide (6,7) and sitagliptin (5). A similar study examining liraglutide did not confirm such damages induced by an incretin mimetic (13). Other studies find an amelioration of the course of experimentally induced acute pancreatitis in mice with exenatide (15) or an anti-inflammatory pattern of cytokines induced by liraglutide treatment (16). Another open question is whether these findings are representative of human acute or chronic pancreatitis.

Clinical acute pancreatitis with incretin-based glucose-lowering medications

Attempts to quantify the number of pancreatitis events while patients are

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Table 1—*Contrasting clinical benefits and improved outcomes with adverse outcomes/risks associated with the use of incretin-based glucose-lowering medications (a, GLP-1 receptor agonists; b, inhibitors of DPP-4)*

Clinical benefits/improved outcomes from using incretin-based glucose-lowering medications	Adverse outcomes/risks from using incretin-based glucose-lowering medications
1. Effective lowering of fasting and postprandial glucose	1. a) Nausea, vomiting, diarrhea, and other "gastrointestinal" adverse events
a) Similar in magnitude to insulin treatment	• Leading to withdrawal of treatment in 3–8%
b) Similar in magnitude to sulfonylurea treatment	• Often improves with prolonged exposure
2. No stimulation of insulin secretion at low glucose = avoidance of hypoglycemia	2. b) DPP-4 = CD26, a marker of activated T cells; enzyme inhibition does not appear to affect immune function
3. No risk of body weight gain	3. Pancreatitis associated with the use of GLP-1 receptor agonists and DPP-4 inhibitors
a) Robust weight loss (2–4 kg) in most patients	• Animal studies controversial (both pro- and anti-inflammatory effects described)
b) No change in body weight or minor weight loss	• Epidemiology controversial (both increased and unchanged numbers reported)
4. Reduction systolic blood pressure	4. Pancreatic cancer hypothesized to be a long-term consequence of using incretin-based glucose-lowering drugs
a) By 2–5 mmHg	• No case reports reported
b) Only in patients with prior arterial hypertension	• Animal studies on potential to induce preneoplastic lesions highly controversial
	• Epidemiological data likely to be influenced by reporting bias
5. Durability better than with sulfonylureas (however, intrinsic improvement in durability due to lasting improvements in β-cell mass or function not proven)	5. C-cell proliferation (hyperplasia, adenomas, medullary thyroid cancer) induced by GLP-1 receptor agonists in rodents
	• No case reports of medullary thyroid carcinoma reported
	• In human subjects, no rise in calcitonin with exposure to GLP-1 receptor agonists
	• Epidemiological data likely to be influenced by reporting bias
	• Presence of GLP-1 receptors on non–C-cells (e.g., follicular cells) and in other thyroid tumors (e.g., papillary carcinoma) controversial
6. Prevention of microvascular diabetes complications based on glucose-lowering effects (supported by preclinical models and preliminary data from clinical trials)	6. Heart rate increased by 2–5 bpm with long-acting GLP-1 receptor agonists (mechanism unclear)
7. Potential to prevent cardiovascular events and mortality; see Fig. 1	

For appropriate literature citations, see text.

treated with GLP-1 receptor agonists or DPP-4 inhibitors have found odds ratios (ORs) around 1, however with relatively wide CIs (Fig. 1*A* and *C*) (17–21). Such data have been taken from claims databases and correlating the prescription of drugs used to treat diabetes with a diagnosis of acute pancreatitis. These analyses have made it clear that obese, type 2 diabetic subjects are more prone to developing acute pancreatitis than the nondiabetic population. On the other hand, one single study reports a more than tenfold excess of pancreatitis in patients using exenatide or sitagliptin (22). This notable exception is a study based on an analysis of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS [formerly known as AERS]). This study, thus, is in obvious contradiction to other epidemiological data. It summarizes reports to the FAERS from a period when publications and changes to drug labels had alerted the medical community to the fact that cases of acute pancreatitis had occurred in patients treated with exenatide and sitagliptin. This probably has prompted some reporting bias. The quality of the individual reports to the FAERS may also be questioned. The standards for the diagnosis of acute pancreatitis (at least two out of three criteria: *1*) typical severe abdominal pain, *2*) elevations in pancreas-specific enzymes such as amylase and lipase, and *3*) typical findings using appropriate imaging procedures [23]) may not always have been applied.

A recent case-control study reported a higher OR for the risk of hospitalization for a diagnosis of pancreatitis in patients taking "incretin-based medications," since a separate analysis for the use of exenatide (GLP-1 receptor agonist) or sitagliptin (DPP-4 inhibitor) did not yield significant findings (Fig. 1*B* and *D*). It cannot be excluded at present that a potential combination of stomach cramps, representing gastrointestinal adverse events of GLP-1 receptor agonists, and spontaneously elevated serum lipase activities were responsible for the hospitalizations and do not represent true pancreatitis episodes. Nevertheless, this small study analyzing only a few patients with pancreatitis is only the second study describing an elevated risk (24), however, only by combining exenatide and sitagliptin treatments as "incretin-based medications" and after adjusting for potential confounders. Figure 1*B* and *D* presents ORs and *P* values (all nonsignificant) calculated without adjustment for potential risk-modifying factors.

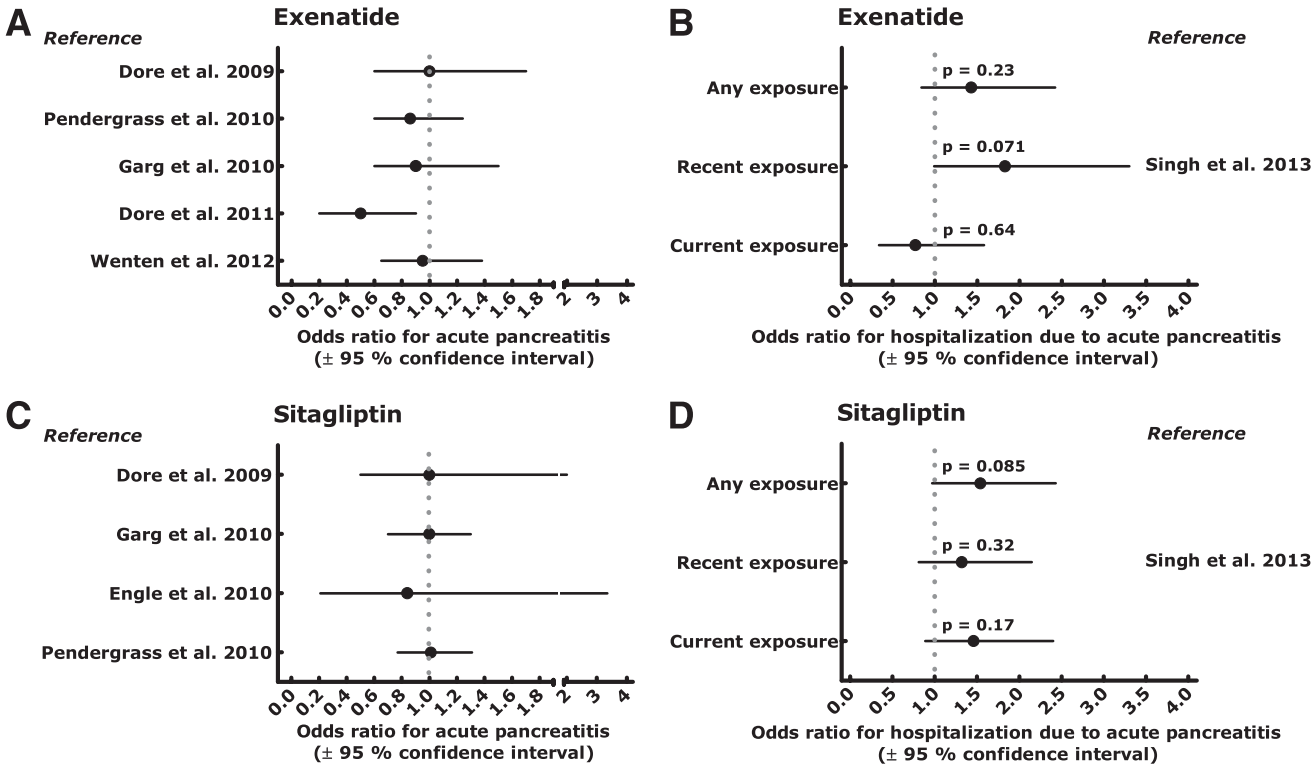

Figure 1—*ORs for the diagnosis of* (A *and* C) *or hospitalization for* (B *and* D) *acute pancreatitis in association with a medication of exenatide (GLP-1 receptor agonist,* upper panels) *or sitagliptin (DPP-4 inhibitor,* lower panels). *ORs and their 95% CIs and related* P *values were obtained directly or calculated (GraphPAD PRISM 5.02) from published analysis of claims databases. Data have been taken from the references quoted in the figure (17–21, 24, 50). Recent exposures: medication prescribed for use between 2 years and 30 days before hospitalization; current exposures: medication prescribed for use <30 days before hospitalization.*

Furthermore, treatment with the GLP-1 receptor agonist liraglutide can lead to elevations in lipase without associated symptoms of pancreatitis (25). Using such enzyme measurements to "screen" for pancreatitis may have resulted in false diagnoses of pancreatitis because elevations in pancreatic enzymes do not have the degree of specificity that would be necessary to make it a helpful screening instrument. Indeed, elevated lipase and amylase activity is found quite frequently in patients with type 2 diabetes with an absence of abdominal pain (26). Under these circumstances, most elevated amylase or lipase levels would be chance findings without any relationship to inflammatory changes within the exocrine pancreas. However, the nature of the elevation in serum lipase induced by liraglutide treatment needs to be explored so that we can understand its mechanism. At least this phenomenon indicates an interaction of GLP-1 receptor agonists with the exocrine pancreas, perhaps indicating the presence of GLP-1 receptors in this compartment. Effects of GLP-1 receptor stimulation on pancreatic enzyme synthesis, potential leakage into the circulation rather than directional secretion into pancreatic digestive juice, and a potential induction of a chronic inflammatory response need to be studied. To date, it certainly cannot be taken as a fact that chronic stimulation of the GLP-1 receptor (as occurs during the treatment with incretin mimetics and DPP-4 inhibitors) induces acute or chronic inflammatory responses in the pancreas, nor that, based on a well-delineated mechanism and supported by convincing epidemiological data, the clinical use of incretin-based glucose-lowering medications would cause pancreatitis. Clinically, the development of typical chronic pancreatitis diagnosed because of typical morphological findings and exocrine insufficiency leading to maldigestion, nutritional deficiencies, and weight loss over and above what is expected from continued stimulation of brain GLP-1 receptors (1,27) in patients treated with GLP-1–based medications has never been described.

Incretin-based medications and chronic pancreatitis/pancreatic cancer

Regarding the related question of chronic changes in the exocrine pancreas leading to pancreatic duct proliferation and the formation of preneoplastic lesions (like pancreatic intraepithelial neoplasms or pancreatic duct glands [28]), data from animal studies are similarly controversial with studies showing alterations of the exocrine pancreatic histology indicative of chronic pancreatitis with exenatide treatment (5–7), while another recent study using liraglutide did describe occasional pancreatitis as a rare finding—but not at all related to the dose of liraglutide—with similar numbers in placebo-treated rats, mice, and monkeys (13). It appears highly unlikely that there should be a difference intrinsic to the two GLP-1 receptor agonists used (exenatide vs. liraglutide). A recent finding reported that pancreas specimens from organ donors with type 2 diabetes, who had received treatment with the DPP-4 inhibitor sitagliptin ($n = 7$) or exenatide ($n = 1$), relative to patients with type 2 diabetes treated with other agents, had marked β-cell hyperplasia, β-cells coexpressing insulin and glucagon, hyperplasia of α-cells expressing glucagon, increased expression of proliferation markers, and an increased prevalence of preneoplastic lesions (29). This finding needs to be confirmed in a

larger, representative sample of pancreas specimens obtained without preceding long-term critical illness, which alone may be responsible for some proliferative responses (30).

To put the state of this present discussion into perspective, it should be made clear that at most early proliferative or preneoplastic changes have been observed, which as such are not proof that eventually the process described will give rise to pancreatic cancer. Thus we have to discuss a *potential* risk (and certainly want to learn more about the long-term consequences of stimulating GLP-1 receptors for the exocrine pancreas), but not an actual threat to patients treated with incretin-based medications, based on a well-characterized mechanism with a risk clearly elevated based on sound epidemiological analyses. It is reassuring that no case of clinically evident chronic pancreatitis has been described after initiating treatment with incretin-based medications. Certainly, there is also no case report of pancreatic cancer diagnosed after exposing a patient to GLP-1 receptor agonists or DPP-4 inhibitors in a patient in whom there had previously been a morphologically tumor-free pancreas. Since pancreatic carcinomas develop slowly (31), one would probably not expect to see such a case after at most a few years of treatment, considering the recent introduction of the incretin-based medications, even if there were such a long-term risk.

Incretin-based medications and thyroid carcinoma

GLP-1 receptor agonists have the potential to induce proliferative changes in rodent thyroid C cells. Liraglutide increased the number of cases with C-cell hyperplasia, adenomas, and medullary thyroid carcinomas in mice and rats (9). In these species such abnormalities are also found spontaneously, i.e., in the absence of GLP-1 receptor stimulation, especially in male rats, in which medullary thyroid carcinoma developed in some animals treated with placebo (9). Accordingly, rodent C-cell lines in cell culture responded to GLP-1, exenatide, and liraglutide with acutely producing cyclic AMP and secreting calcitonin (9). Similar cell lines of human origin do not show such acute responses when GLP-1 receptors are stimulated (9). Whereas rodent C-cell lines are equipped with GLP-1 receptors at a high level of expression, this is not the case in their human counterparts (9). Along the same lines, long-term treatment in obese human subjects with high liraglutide doses up to 3-mg per day does not lead to elevations in plasma calcitonin (32). Based on these results, the ability of GLP-1 receptor stimulation to induce proliferative responses in human C cells has been judged as probably absent. Medullary thyroid carcinomas are an extremely rare form of thyroid carcinomas in humans (33). No case report has been published describing a medullary thyroid carcinoma in a patient receiving a treatment with a GLP-1 receptor agonist who prior to such treatment had a morphologically normal thyroid gland and low calcitonin concentrations. Given the rare incidence of medullary thyroid carcinoma, *1*) the consequences of a potential elevation in the risk induced by incretin mimetics would still remain small, and 2) to prove or exclude such a relationship, efficient surveillance of extremely large numbers of patients would be needed.

The elevated risk for thyroid carcinoma in more general terms described in the study exploring the FAERS database (22) is difficult to reconcile. Similar reservations apply regarding reporting bias as mentioned for the pancreatitis/pancreatic carcinoma issue raised earlier (vide supra). Certainly, this would not be compatible with an explanation through a higher number of medullary carcinomas alone, which would need to increase by more than 30-fold in order to explain such numbers. However, whether follicular cells express GLP-1 receptors (9) or whether malignant cells from thyroid tumors of different histological varieties (e.g., papillary thyroid carcinomas) express the GLP-1 receptors (34) is controversial and may be related to the specificity of the antibody or the radioligand used for immunohistochemistry (35). The fact alone that some papillary thyroid carcinomas may show evidence of GLP-1 receptor expression (34) does not prove that such receptors and their stimulation by drugs may contribute to the genesis or proliferation of such tumors. Again, even a convincing case report is missing. Regarding the thyroid issues, certainly more investigations are required, but one hardly can conclude that, based on current knowledge, there is a definitely increased risk for medullary (or other types of) thyroid carcinoma with the use of GLP-1 receptor agonists. Nevertheless, patients with an individually elevate genetic risk should not be treated with such agents. An elevated risk when using DPP-4 inhibitors does not have to considered at all since no such findings have been reported (22).

Cardiovascular outcomes

In the absence of large-scale cardiovascular outcome trials, summaries of cardiovascular events reported as adverse events in clinical trials with incretin-based glucose-lowering medications and meta-analyses based thereon (36) are the best available source of information for an overall judgment at present. Phase 3 studies have accrued a number of cardiovascular events sufficient for a preliminary judgment based on trends. These trends observed for the incretin mimetics exenatide (37) and liraglutide (38) as well the DPP-4 inhibitors sitagliptin (39), vildagliptin (40), saxagliptin (41), linagliptin (42), and alogliptin (43) are surprisingly similar. As shown in Fig. 2, in all these analyses the relative risk for a combined end point composed of acute myocardial infarction, stroke, and cardiovascular death is reduced with any of the GLP-1–based medications relative to placebo or comparator treatment to a value below 1 (Fig. 2). However, the 95% CIs ranged to above 1.0 with most compounds, indicating that the number of events available for this analysis was too small to allow the definite conclusion of a significant improvement in cardiovascular prognosis with incretin-based glucose-lowering treatment.

A potential reduction in cardiovascular event rates with linagliptin treatment is further supported by a recent study comparing linagliptin with the sulfonylurea glimepiride (44).

There is some plausibility based on the influences of GLP-1–based drugs on cardiovascular risk factors (45). GLP-1 receptor agonists reduce body weight by reducing appetite and food intake. They also reduce systolic blood pressure by 2–5 mmHg, mechanistically explained by improved endothelial function and vasodilation, enhanced natriuresis, and fluid excretion. There is a potential for a reduction in postprandial triglyceride-rich lipoproteins, especially with those agents that have and preserve over time a prominent effect on gastric emptying. Effects on "nonclassical" cardiovascular risk factors point in the same direction. Furthermore, GLP-1 receptor stimulation has reduced the extent of myocardial necroses in animal experiments inducing acute myocardial infarction by coronary artery ligation. The results have been surprisingly uniform using different agents (GLP-1, exenatide, liraglutide, sitagliptin) in various species (45). In addition, in animal models of left ventricular failure,

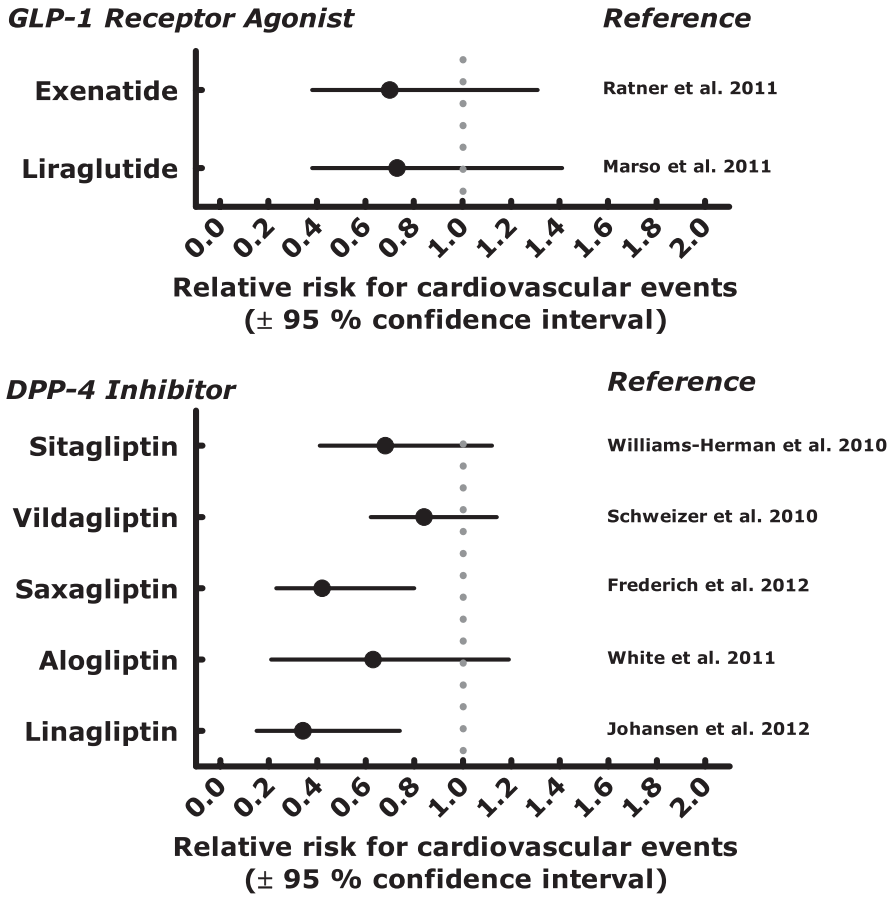

Figure 2—*Relative risk for major cardiovascular events reported as adverse events during phase 3 studies with the GLP-1 receptor agonists exenatide and liraglutide* (upper panel) *and with the DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin* (lower panel) *compared with pooled comparators (placebo or active control medications). The relative risk is displayed together with the 95% CIs (bars). Data have been taken from the references quoted in the figure (37–43).*

GLP-1 and incretin mimetics may increase cardiac output by stimulating glucose and oxygen uptake into the myocardium. Clinical pilot trials support the notion that GLP-1 receptor stimulation may be beneficial in patients with acute coronary syndrome and chronic congestive heart failure (45). Therefore, one may be optimistic that cardiovascular outcome trials being performed to date, which will report after the year 2015 (Table 2), will at least confirm cardiovascular safety with a potential to substantiate the beneficial effects in this important respect.

Table 2—*Cardiovascular outcomes studies conducted with incretin-based glucose-lowering drugs*

Incretin-based medication	Name of clinical trial	Number of planned patients	Recruitment started	Trial completion expected	Identification number (ClinicalTrials.gov)
GLP-1R agonists					
Liraglutide	LEADER	8,754	8/2010	1/2016	NCT 01179048
Exenatide*	EXCEL	9,500	6/2010	3/2017	NCT 01144338
DPP-4 inhibitors					
Sitagliptin	TECOS	14,000	12/2008	12/2014	NCT 00790205
Saxagliptin	SAVOR-TIMI 53	16,500	5/2010	5/2015	NCT 01107886
Alogliptin	EXAMINE	5,400	9/2009	12/2014	NCT 00968708
Linagliptin	CAROLINA	6,000	10/2010	9/2018	NCT 01243424

*Once-weekly preparation; all data have been taken from ClinicalTrials.gov. GLP-1R, GLP-1 receptor.

The greater picture—weighing benefits against potential risks and harms regarding the clinical use of incretin-based glucose-lowering medications—Table 1 summarizes the beneficial effects of incretin-based glucose-lowering agents and their advantages over other antidiabetic pharmaceutical agents, but also the open issues discussed earlier in this article in order to define the balance of benefits on the one hand and the risks and harms on the other. Regarding the properties of incretin-based medications as antidiabetic drugs, they are effective in lowering glucose and avoid the problems of some other classes of glucose-lowering medications that are related to the induction of hypoglycemia and weight gain. Surrogate parameters indicate an improvement in the cardiovascular risk profile, and preliminary analyses of cardiovascular outcomes suggest the potential for benefit in this respect. Critical issues exist, but in many respects they are discussed in a controversial manner with only some data in support of an elevated risk (Table 1). Nausea and vomiting may be intolerable and lead to the discontinuation of treatment with GLP-1 receptor agonists. Putative interference of DPP-4 inhibitors with immune function does not lead to increased rates of common infections (39,46). Regarding the issues related to the potential short-term induction of acute and the putative long-term risk for chronic pancreatitis and eventually pancreatic cancer, data at hand today do not convincingly prove such risks. Thyroid issues related to GLP-1 receptors on C cells appear to mainly apply to rodents with a paucity of convincing human data that show a definite risk. This applies even more so to other forms of thyroid cancer. The fact that heart rate may increase with GLP-1 receptor agonists needs to be understood mechanistically. Potential explanations could be a reflex compensating for vasodilation (47) and lower blood pressure (10,11,48), a direct effect on the sinus node, or an increased relationship of sympathetic versus parasympathetic autonomous nervous system tone. Epidemiological findings relating higher heart rates to premature cardiovascular morbidity and mortality probably use pulse rate as a surrogate parameter for physical fitness (49). There is no reason to assume that incretin-based medications would lead to a reduced cardiorespiratory

fitness. A lower body weight speaks against this hypothesis.

Thus, while the benefits—expected or proven—from using incretin-based medications seem to be substantial and address risks central to patients with type 2 diabetes, the potential harms and risks typically refer to rare events and are discussed in a controversial manner, e.g., without certainty regarding a potential role of incretin-based medications to cause substantial harm. Obviously more needs to be learned regarding the open questions, but based on today's available knowledge, incretin-based medications can be considered effective and safe. Safety concerns related to the exocrine pancreas and the thyroid are not substantiated enough. Such considerations should not currently influence our treatment decisions regarding the potential prescription of GLP-1 receptor agonists or DPP-4 inhibitors within a treatment regimen for type 2 diabetes.

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