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 historical 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 concern of risk.

Incretin-based glucose-lowering medications have proven to be efficacious in type 2 diabetic patients (12) cite their significance with increased 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 therapies 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...
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)

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

For appropriate literature citations, see text.
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 malabsorption and malnutrition—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 pre-neoplastic 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 be 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 sitaglaptin (39), vildaglaptin (40), saxaglaptin (41), linaglaptin (42), and aloglaptin (43) are surprisingly similar. As shown in Fig. 2, in all these analyses the relative risk for a combined endpoint 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 sulfonlurea glimepiride (44).

There is some plausibility based on the differences 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,
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.

**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

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**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).

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

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

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

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