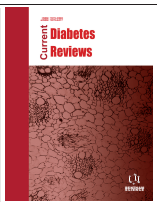
Current Diabetes Reviews, 2016, *12*, 403-413

REVIEW ARTICLE

Glucagon-Like Peptide-1 Receptor Agonists for Type 2 Diabetes: A Clinical Update of Safety and Efficacy



Scott R. Drab*

University of Pittsburgh School of Pharmacy, 719 Salk Hall, Pittsburgh PA 15261, USA

Abstract: ***Introduction*:** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly being used for the treatment of type 2 diabetes mellitus, but consideration of benefits and potential adverse events is required. This review examines the state of glycemic control, weight loss, blood pressure, and tolerability, as well as the current debate about the safety of GLP-1 RAs, including risk of pancreatitis, pancreatic cancer, and thyroid cancer.

***Methods*:** A MEDLINE search (2010-2015) identified publications that discussed longer-acting GLP-1 RAs. Search terms included GLP-1 receptor agonists, liraglutide, exenatide, lixisenatide, semaglutide, dulaglutide, albiglutide, efficacy, safety, pancreatitis, pancreatic cancer, and thyroid cancer. Abstracts from the American Diabetes Association, European Association for the Study of Diabetes, and American Association of Clinical Endocrinologists from 2010 to 2015 were also searched. Efficacy and safety studies, pooled analyses, and meta-analyses were prioritized.

***Results*:** Research has confirmed that GLP-1 RAs provide robust glycemic control, weight loss, and blood pressure re-duction. Current studies do not prove increased risk of pancreatitis, pancreatic cancer, or thyroid cancer but more trials are needed since publications that indicate safety or suggest increased risk have methodological flaws that prevent firm conclusions to be drawn about these rare, long-term events.

***Conclusion*:** GLP-1 RA therapy in the context of individualized, patient-centered care continues to be supported by current literature. GLP-1 RA therapy provides robust glycemic control, blood pressure reduction, and weight loss, but studies are still needed to address concerns about tolerability and safety, including pancreatitis and cancer.

ARTICLE HISTORY

Received: September 22, 2015
Revised: December 04, 2015
Accepted: December 21, 2015

DOI: 10.2174/1573399812666151223093841

Keywords: GLP-1 RAs, liraglutide, exenatide, incretin therapy, efficacy, safety, pancreatitis, treatment.

INTRODUCTION

The health and economic impact of type 2 diabetes mellitus (T2DM) has been well described, and selecting anti-diabetic agents that provide the most favorable balance of glycemic control, weight loss, decrease in blood pressure, and safety remains essential. Due to their efficacy for reducing glycosylated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), body weight, and systolic blood pressure (SBP) while inducing only a low risk for hypoglycemia, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended early and throughout treatment of T2DM patients in guidelines provided by both the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) [1, 2].

As with any treatment, selection of GLP-1 RA therapy for individualized patient care requires weighing benefits and potential adverse events (AEs). This review provides both an update and extension to an earlier examination of the clinical efficacy of GLP-1 RAs in patients with T2DM, [3] adding more information regarding the safety and tolerability of those treatments. In addition, as addressed in this article, when GLP-1 RAs are used in combination with basal insulin therapy, the dose of insulin and potential weight gain can be reduced [4, 5]. However, there have not been sufficient data obtained thus far to make conclusions about any potential cardiovascular (CV) or oncology risks.

GLP-1 RA PHARMACOLOGY

Incretin-based therapies, including GLP-1 RAs and dipeptidyl peptidase (DPP)-4 inhibitors, aim to provide glycemic control and weight loss effects associated with endogenous GLP-1 while extending the duration beyond the rapid degradation of endogenous GLP-1 by DPP-4 and neutral endopeptidase (NEP). Exogenous administration of GLP-1 RAs provides pharmacological levels of GLP-1

*Address correspondence to this author at the University of Pittsburgh School of Pharmacy, 719 Salk Hall, Pittsburgh, PA 15261, USA; E-mail: Drab@pitt.edu

1875-6417/16 $58.00+.00

receptor stimulation and resistance to degradation by DPP-4 and NEP [3]. Importantly, GLP-1-RA effects can be differentiated from the mechanisms of action of DPP-4 inhibitors.

Exenatide Twice Daily and Once Weekly

Exenatide, a synthetic 39-amino acid peptide identical to the exendin-4 molecule isolated from salivary glands of the Gila monster, shares approximately 53% homology with human GLP-1 [6]. Exenatide 10 micrograms (mcg) twice daily is short-acting with a circulating half-life of 60-90 minutes, and is administered using a pen device within 60 minutes of morning and evening meals [7]. Exenatide 2 mg once weekly (long-acting regimen [LAR]) comprises exenatide in a poly (lactide-co-glycolide) polymeric matrix, resulting in biodegradable polymeric microspheres, reaching a plasma concentration steady-state after approximately 6-7 weeks [8]. Exenatide once weekly has received Food and Drug Administration (FDA) approval for the administration of 2 mg subcutaneously at any time of day with or without meals [9]. The full prescribing information for exenatide twice daily contains a warning about fatal and non-fatal hemorrhagic or necrotizing pancreatitis [10]. The prescribing information for exenatide once weekly contains a warning for risk of potential thyroid C-cell tumors, but states that this has been identified only in rats and has not yet been confirmed nor disproven in humans [9]. It should be noted that concern about potential thyroid C-cell tumors was raised after exenatide twice daily was FDA approved.

Liraglutide Once Daily

Liraglutide, an analog of human GLP-1, has 97% homology to native GLP-1, with 1 amino acid substitution (Arg34Lys) and a fatty acid side chain attached through a glutamyl spacer [11]. With a half-life of ~13 hours, concentrations of liraglutide in plasma are seen up to 24 hours after a single dose, allowing once-daily dosing. Liraglutide 1.2 mg and 1.8 mg once-daily dosing using a pen device can be administered at any time regardless of food intake. Similar to exenatide once weekly, prescribing information for liraglutide also contains a warning about potential thyroid C-cell tumors [12]. That document also reports that although the results are not conclusive, in clinical trials 6 cases of thyroid C-cell hyperplasia occurred among patients treated with liraglutide as did 2 among comparator-treated patients (1.3 vs 1.0 cases per 1000 patient-years) [12].

Albiglutide Once Weekly

Albiglutide is also a GLP-1 RA with 97% amino acid sequence homology to endogenous human GLP-1 composed of a DPP-4–resistant GLP-1 dimer fused to recombinant human albumin, and it is generated through genetic fusion of 2 tandem copies of modified human GLP-1 [13]. The recombinant fusion protein of the drug, along with human albumin moiety and DPP-4 resistance, extend the half-life of albiglutide to >5 days, enabling once-weekly dosing [14-16]. Albiglutide is administered subcutaneously once weekly, initially at 30 mg, but it can be increased to 50 mg. The prescribing information for albiglutide also contains a warning label, but it simply states that it is unknown whether the drug causes thyroid C-cell tumors, including medullary carcinoma [17].

Dulaglutide Once Weekly

Dulaglutide, another long-acting GLP-1 RA, was approved by FDA in September 2014. It is composed of 2 GLP-1 analogs that are covalently linked by a small peptide to a human immunoglobulin G4 region-specific heavy chain [18]. The GLP-1 analog portion of that drug is 90% homologous to native human GLP-1 (7-37 sequence), and it contains amino acid substitutions specifically designed to optimize the clinical profile by protecting it from inactivation by DPP-4, increasing solubility and reducing immunogenicity while maintaining its potency [18-20]. Dulaglutide is administered subcutaneously once weekly at any time of day, initially at 0.75 mg but the dose can be increased to 1.5 mg for additional glycemic control [21]. Although it is unknown if dulaglutide actually causes thyroid C-cell tumors in humans, it does in rats and it was observed in a single human in one clinical trial and therefore a warning label is included in the prescribing information [21].

METHODS

A MEDLINE search of English publications from 2010 to 2015 was conducted using the terms GLP-1 receptor agonists, liraglutide, exenatide, lixisenatide, semaglutide, albiglutide, dulaglutide, efficacy, safety, pancreatitis, pancreatic cancer, and thyroid cancer. Abstracts presented at ADA, AACE, and EASD from 2010 to 2015 were also searched. This clinical update prioritizes efficacy and safety studies, pooled analyses, and meta-analysis studies involving FDA-approved GLP-1 RAs liraglutide once daily, exenatide twice daily, exenatide once weekly, albiglutide once weekly, and dulaglutide once weekly. The updated evaluation of GLP-1 RA tolerability and safety focuses on current debate about the risk of pancreatitis, pancreatic cancer, and thyroid cancer with GLP-1 RA treatment.

RESULTS AND DISCUSSION

Glycemic Control

Early studies through phase 3 clinical trials examining liraglutide, exenatide twice daily, exenatide once weekly, albiglutide, and dulaglutide compared with placebo or comparator antidiabetes agents have demonstrated efficacy in HbA1c reductions, significant weight loss, and SBP reductions [3, 22-24]. Large-scale pooled analyses and meta-analyses of available studies have confirmed reductions in glycemic levels, blood pressure, and body weight associated with GLP-1 RA therapy [25-28]. A meta-analysis of 33 studies showed GLP-1 RA therapy, including liraglutide, exenatide twice daily, or exenatide once weekly, produced significant HbA1c and FPG reductions from baseline [29].

A prospective, open-label, single-arm, single-center, 24-week observational study was conducted in a real-world setting in India [30]. Participants had T2DM and were not able to achieve or maintain glucose control while receiving antidiabetic therapy (195 subjects were included, 58 were receiving insulin prior to and during the study, 137 were treated with oral antidiabetic drugs prior to and during the study). The doses of liraglutide were 0.6 mg/day for 7 days, 1.2 mg/day for the next 7 days, and 1.8 mg/day for the

remaining 22 weeks. From baseline to week 24 mean FPG decreased from 163.81 mg/dL to 111.6 mg/dL (P<0.001) and HbA1c declined from 8.14% to 6.96% (P=0.006). At week 24, 49.23% of subjects achieved an HbA1c <7.0% and 41.03% reached ≤6.5%. There was also a statistically significant decrease in mean body weight (86.41 kg to 82.37 kg, P<0.001) as well as in diastolic blood pressure (76.18 mm Hg to 70.88 mm Hg, P<0.001) but not systolic blood pressure (129.31 mm Hg to 119.59 mm Hg, P=0.90). Only 22 (11.28%) of the participants reported AEs, all of which were mild to moderate; the most frequently occurring were vomiting, tiredness, diarrhea, and nausea [30].

A retrospective observational study that included individuals receiving exenatide twice daily utilized HbA1c, weight, and body mass index (BMI) as the outcomes measures [31]. Although there were statistically significant improvements in all measures at months 3 and 6 for the responders, the subjects who had no significant decreases in HbA1c showed improvement in weight and BMI, only. Greater baseline HbA1c had a negative linear relationship that correlated with larger reductions at 6 months (P<0.0001), and it was the only factor that predicted exenatide response (greater baseline HbA1c was associated with 5% greater odds of positive response, P=0.004) [31].

A 104-week trial of T2DM patients receiving metformin randomly assigned to 1 of 4 groups revealed that albiglutide significantly reduced HbA1c (-0.63% [-124.2 mg/dL]) compared with sitagliptin (-0.28% [-55.8 mg/dL]), glimepiride (-0.36% [-70.2 mg/dL]), and placebo (+0.27% [54.0 mg/dL]) [22]. Compared with the other groups, the decrease in FPG was significantly greater in the albiglutide group (vs placebo: -28.0 mg/dL, P<0.0001; sitagliptin: -16.0 mg/dL, P=0.0002; and glimepiride: -10.0 mg/dL, P=0.0133). There were significant differences in weight change from baseline between the albiglutide (-1.21 kg) and glimepiride (+1.17 kg) groups (P<0.0001), as well as the rescue rates of hyperglycemia at week 104 (25.8% for albiglutide compared with 59.2% for placebo (P<0.0001), 36.4% for sitagliptin (P=0.0118), and 32.7% for glimepiride (P=0.1504). Rates of serious AEs were similar between albiglutide and comparison groups [22].

The results obtained at week 52 of a 156-week, randomized, double-blind, parallel-group, multicenter albiglutide study were published in 2015 [32]. During that trial, subjects received either albiglutide, pioglitazone, or placebo along with metformin and glimepiride. The primary endpoint was the difference in HbA1c between the albiglutide and placebo groups (-0.87 [95% CI -1.07, -0.68]%-unit, [P<0.001]), and there was also a non-inferior difference between albiglutide and pioglitazone (0.25 [95% CI 0.10, 0.40]%-unit P=0.0012). The changes from baseline in HbA1c were -0.55 (±0.06)%-units among the albiglutide group, -0.80 (±0.06)%-units for pioglitazone, and +0.33 (±0.08)% units for placebo. FPG decreased rapidly only in the albiglutide group during the first 2 weeks. The mean (±SEM) change in weight among the albiglutide, pioglitazone, and placebo groups, respectively, was -0.42 (±0.2) kg, +4.4 (±0.2) kg (vs albiglutide P<0.001), and -0.40 (±0.4) kg. There was confirmed hypoglycemia among 25% in the pioglitazone group compared with 14% of both the albiglutide and placebo groups. Serious AEs occurred in 6.3% of the albiglutide, 9.0% of the pioglitazone, and 6.1% of the placebo groups [32].

A phase 3, 52-week, randomized, open-label, non-inferiority trial compared the efficacy and safety of dulaglutide to bedtime insulin glargine, both in combination with prandial insulin lispro, at 105 study sites in 15 countries among patients who were inadequately controlled with conventional insulin [33]. At the end of the study, which was published in 2015, the results included a greater adjusted mean change from baseline in HbA1c with dulaglutide 1.5 mg (-1.48% [95% CI -1.64 to -1.32] and dulaglutide 0.75 mg (-1.42% [-1.58 to -1.26] than glargine (-1.23% [-1.39 to -1.07]. The adjusted mean differences compared with glargine at week 52 were -0.25% (-0.42 to -0.07, P=0.005) for dulaglutide 1.5 mg and -0.19% (-0.37 to -0.02, P=0.014). Fewer than 1% (n=5) of subjects died following randomization, with mortality causes being septicemia (dulaglutide 1.5 mg group, n=1), pneumonia (dulaglutide 0.75 mg group, n=1), and cardiogenic shock, ventricular fibrillation, and an unknown cause (glargine group, n=3). Serious AEs occurred in 27 (9%) of individuals in the dulaglutide 1.5 mg group, 44 (15%) in the dulaglutide 0.75 mg group, and 54 (18%) in the glargine group [33].

Although no published clinical trials have compared dulaglutide to other GLP-1 RAs, several have included at least 2 of the other 3. A meta-analysis of GLP-1 RA therapy as add-on to metformin therapy compared 7 studies with exenatide twice daily to 7 with either liraglutide or exenatide once weekly. Significantly greater HbA1c and FPG reductions were found with longer-acting GLP-1 RAs liraglutide and exenatide once weekly compared with shorter-acting exenatide twice daily, whereas reduction in body weight was similar between longer-acting GLP-1 RAs and shorter-acting exenatide twice daily [34]. A pooled analysis of head-to-head GLP-1 RA studies included 5 trials and found greater HbA1c reductions (P<0.001) with longer-acting GLP-1 RAs compared with exenatide twice daily and similar weight and SBP reductions between longer-acting GLP-1 RAs compared with exenatide twice daily (weighted mean difference HbA1c reduction: -0.47% [95% CI -0.69 to -0.25] for exenatide; -0.60% [95% CI -0.75 to -0.45] for sitagliptin) [35].

Two recent head-to-head studies of liraglutide compared with exenatide once weekly and albiglutide once weekly found greater decreases in glycemia and weight with liraglutide, but no significant differences in blood pressure [36, 37]. In a head-to-head comparison of liraglutide and exenatide once weekly, greater HbA1c (-1.48% vs -1.28%, P=0.02), fasting serum glucose (-38.16 vs -31.68 mg/dL, P<0.0001) and weight (-3.57 vs -2.68 kg, P=0.02) reductions were found with liraglutide over the 26-week study period [36]. The 32-week head-to-head comparison of liraglutide and albiglutide once weekly also found greater HbA1c (-0.99% vs -0.78%), FPG (-30.24 vs -21.96 mg/dL, P=0.0048) and weight (-2.19 vs -0.64 kg, P<0.0001) reductions with liraglutide [37]. A recently published comparison of twice-daily exenatide to dulaglutide 1.5 mg and 0.75 mg reported that both the dulaglutide doses were superior at 26 and 52 weeks (both adjusted one-sided P<0.001), and that greater percen-

Table 1. Number of abstracts reporting adverse events at the ADA, AACE, and EASD, 2010-2014.

	Exenatide BID and LAR			Liraglutide			Albiglutide			Dulaglutide		
	ADA	AACE	EASD	ADA	AACE	EASD	ADA	AACE	EASD	ADA	AACE	EASD
Nausea	30	1	30	24	1	22	16	0	8	5	0	5
Constipation	1	0	1	1	0	0	0	0	0	0	0	0
Vomiting	15	2	15	15	0	15	16	0	8	2	0	4
Diarrhea	11	0	13	6	1	9	11	0	8	4	0	5
Dyspepsia	0	0	0	2	0	1	0	0	0	1	0	1
Injection-site reaction	6	1	10	2	1	3	16	0	9	0	0	1
Headache	2	0	4	1	0	0	0	0	0	0	0	0
Respiratory	4	0	3	2	0	2	1	0	0	0	0	0
Asthenia	0	0	0	0	0	0	0	0	0	0	0	1

[a]The adverse events selected for these searches are the ones listed in the prescribing information documents for each of drugs.

tages of patients in both dosing groups achieved HbA1c <7.0% (P<0.001) [38]. A 26-week non-inferiority comparison revealed the least-squares mean reduction in HbA1c for the dulaglutide group was -1.42% (SEM 0.05) and for the liraglutide group was -1.36% (SEM 0.05), and therefore the mean difference between the 2 groups was -0.06% (95% CI -0.19 to 0.07, non-inferiority P<0.0001) [39].

Although there have been very few comparisons of albiglutide to other GLP-1 RAs and currently no results are published, a few trials have evaluated albiglutide vs insulin. A contrast of the 2 treatment options in patients inadequately controlled on metformin with or without sulfonylurea demonstrated that albiglutide was non-inferior to insulin glargine [40]. At week 52, HbA1c declined from 8.28±0.90% at baseline to 7.62±1.12% in the albiglutide group compared with 8.36±0.95% to 7.55±1.04% in the insulin glargine group, indicating non-inferiority. However, body weight increased in the insulin glargine group while it decreased in the albiglutide group, resulting in a mean between-group difference of -2.61 kg (95% CI -3.20 to -2.02; P<0.0001), and symptomatic hypoglycemia events occurred in a greater proportion of the insulin glargine group (27.4% vs 17.5%, P=0.0377).

Another study demonstrated non-inferiority of albiglutide to insulin lispro thrice daily as an add-on to insulin glargine [23]. At the end of that 26-week trial, HbA1c had decreased from baseline by -0.82±SEM 0.06% among the albiglutide group and -0.66±0.06% with lispro (treatment difference was -0.16% [95% CI -0.32 to 0.00; P<0.0001]), therefore meeting the pre-determined non-inferiority endpoint margin of 0.4%. Although body weight decreased in the albiglutide group by -0.73±0.19 kg, it increased in the lispro group by +0.81±0.19 kg. The AEs that were more frequent in 1 group than the other included severe hypoglycemia (0 vs 2 events), documented symptomatic hypoglycemia (15.8% vs 29.9%), nausea (11.2% vs 1.4%), vomiting (6.7% vs 1.4%), and injection-site reactions (9.5% vs 5.3%) for the albiglutide and lispro groups, respectively.

Studies have shown glycemic efficacy after intensification of treatment with liraglutide or exenatide twice daily in combination with insulin [4, 5]. Studies on treatment intensification with combined GLP-1 RA and insulin therapy have examined the aim of improvement in glycemic control without increased risk for hypoglycemia or weight gain. Over 30 weeks, exenatide twice daily added to optimized titration of insulin glargine was shown to produce greater HbA1c reduction (-1.74% vs -1.04% [between-group difference: -0.69% (95% CI, -0.93 to -0.46)]; P<0.001) and weight loss (-1.8 kg vs +1.0 kg [between-group difference, -2.7 kg (95% CI, -3.7 to -1.7)]; P<0.001), and smaller increase in insulin dose (between-group difference, -6.5 U/d [-12.3 vs -0.8]; P=0.030), compared with placebo added to insulin glargine [5]. The addition of liraglutide to insulin vs dose increase of insulin also has been examined. No difference in HbA1c reduction was found between liraglutide 1.2 mg/day + insulin vs insulin dose-increase group over the 12-week period; however, the liraglutide add-on group showed significantly greater weight loss, reductions in daily total insulin dose, and lower rates of hypoglycemia [4].

SAFETY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Common Adverse Events

A key safety characteristic of GLP-1 RA therapy is the minimal risk of hypoglycemia, unless combined with sulfonylureas or insulin, due to their glucose-dependent mechanism of action [3]. As has been discussed, the most common AEs associated with GLP-1 RA therapy include mild to moderate gastrointestinal symptoms [3]. Gastrointestinal symptoms are transient and dose-dependent with the initiation of GLP-1 RA and may be less persistent with liraglutide compared with exenatide twice daily and less common with exenatide once weekly compared with exenatide twice daily [3, 35]. The number of specific AEs addressed in abstracts presented at ADA, AACE, and EASD meetings from 2010 to 2014 are presented in Table **1**.

Cardiovascular Safety

Although there are no warnings about CV safety within the prescribing information of any GLP-1 RA therapies, observations made during some phase 3 clinical programs have resulted in such AEs currently being specifically examined in large CV outcomes trials. These trials include The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial for liraglutide; the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial for once-weekly exenatide; the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial for dulaglutide; and the Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with AVE0010 (lixisenatide) (ELIXA) for lixisenatide. Additional safety data will be derived from the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project established by the EMA.

Although the amount of CV safety information pertaining to GLP-1 RAs is extremely limited, data obtained from randomized clinical trials with metabolic outcomes was used to conduct a meta-analysis for major CV events (MACE) among patients treated with exenatide twice daily or once weekly, albiglutide, or liraglutide [41]. A total of 36 trials ≥12 weeks in duration were included, of which 20 reported ≥1 MACE. The authors concluded that none of the randomized trials suggested any increase in CV events among patients treated with GLP-1 RAs; however, the small number of patients included (only 6490 had received GLP-1 RAs and 3995 had not), the relatively short durations of the studies, and the fact that the 36 trials were not designed to assess CV safety clearly indicate that more research is necessary. A study published in 2014 reported that 0.75 mg and 1.5 mg doses of dulaglutide were non-inferior to placebo for changes in 24-hour systolic and diastolic blood pressure and that dulaglutide 1.5 mg significantly reduced the former (least squares mean difference -2.8 mm Hg, 95% CI -4.6 to -1.0; $P \leq 0.001$) [24]. Dulaglutide 0.75 mg was also non-inferior to placebo for 24-hour heart rate (1.6 bpm; 95% CI 0.3 to 2.9; $P \leq 0.02$), but 1.5 mg was not (2.8 bpm, 95% CI 1.5 to 4.2) [24]. Another study reported that after 12 weeks, there was no significant change from baseline in 24-hour heart rate among patients who received either exenatide or placebo (between groups, $P=0.16$) [42].

Several position statements have commented on the ongoing safety debate. The AACE/ADA joint statement, the ADA/EASD/International Diabetes Federation joint statement, and the Endocrine Society statement all have supported continued use of GLP-1 RA therapy in appropriate patients [43-46].

Evidence Suggesting Increased Risk of Pancreatitis, Pancreatic Cancer, and Thyroid Cancer

A significant challenge in determining independent risk for pancreatitis and pancreatic cancer associated with GLP-1 RA therapy is the well-demonstrated increased risk of pancreatitis and pancreatic cancer associated with T2DM and conditions often present among patients with T2DM, including obesity, hypertriglyceridemia, and gallbladder disease. Epidemiological and meta-analysis studies have indicated increased risk of pancreatitis due to T2DM and comorbidities [47, 48]. Recent debate about long-term safety of GLP-1 RA therapy follows conflicting reports from preclinical and epidemiological studies regarding risk for pancreatitis, pancreatic cancer, and thyroid cancer [49]. Expert commentaries in support of continued use of incretin-based therapies while waiting for completion of long-term safety studies argue that the substantial glycemic, body weight, and blood pressure benefits from these therapies outweigh the potential and rare harms and risks that are supported only by controversial data [50]. Alternatively, expert commentary arguing against continued use of incretin-based therapies states that the safety of GLP-1 therapies cannot be assumed given the results of recent studies [51]. It is also important to note that there are not yet any published results that report the incidence of pancreatitis, pancreatic cancer, or thyroid cancer among patients treated with albiglutide or dulaglutide.

The FDA and EMA released an assessment of their independent examinations of pancreatitis and pancreatic cancer risk associated with use of incretin therapies [52]. The agencies note that while they will continue to study the safety of incretin therapies, current data are not consistent with a causal link [52]. Thus, the statements to date have been in agreement that available evidence does not adequately support any new safety concerns for GLP-1 RA therapy, including pancreatic AEs.

Although the amount of safety data currently available are not sufficient for drawing conclusions, several recently published studies have suggested GLP-1 RA therapy may increase the risk for pancreatitis and pancreatic cancer in T2DM patients (Table **2**) [53-66, 67-69]. One study examined post-mortem pancreata from organ donors with T2DM treated with incretin therapy (1 patient had received exenatide; 7 patients the DPP-4 inhibitor sitagliptin) vs other therapy. It was reported that pancreata from patients treated with incretin therapy showed noticeable enlargement of exocrine and endocrine pancreatic compartments, with increased exocrine cell proliferation and dysplasia and α-cell hyperplasia, thus indicating a mechanism linking incretin-based therapy with pancreatic cancer [61]. However, this study has been criticized for serious methodological flaws that negate the conclusions, including differences between the key treatment comparison groups in age, sex, duration of diabetes, use of other antidiabetic drugs, and the possibility of a large percentage of the comparison group having type 1 diabetes, which may have affected the pancreata independent of incretin therapy [70]. Additionally, it is not clear how long the patients were treated or when the treatments occurred relative to the time of death.

Another study with results suggesting an association between GLP-1 RA therapy involving exenatide or sitagliptin and acute pancreatitis examined a large US healthcare claims administrative database, comparing hospitalized cases with acute pancreatitis with control subjects matched on age within 10 years, sex, duration of follow-up or enrollment pattern, and diabetes complications [67]. Analyses were adjusted for available confounders, including hypertriglyceridemia, alcohol and tobacco use, gallstones, obesity, biliary and pancreatic cancer, cystic fibrosis, and any

Table 2. Studies examining GLP-1 RA therapy and risk of pancreatitis in patients with T2DM.

Study Model	Study Methods	Pancreatic Outcomes	Study Critique
Human Tissue			
Butler 2013 [61]	Pancreata from organ donors • 1 exenatide treated, 7 sitagliptin treated vs other therapy	• Enlargement of exocrine and endocrine pancreatic compartments • Exocrine cell proliferation • α-cell hyperplasia	• Uncontrolled differences between comparison groups confound interpretation of study findings
Human Databases			
Dore 2009 [62]	Large US healthcare claims database • Claims for hospitalizations with primary diagnosis of pancreatitis • Comparison of users of exenatide or sitagliptin therapy with users of metformin or glyburide	• No increased risk of pancreatitis	• Methodological flaws associated with claims databases
Dore 2011 [63]	Large US healthcare claims database • Comparison of users of exenatide vs comparators • Rate of pancreatitis confirmed through review of blinded medical records	• No increased risk of pancreatitis with current, recent or past exenatide use	• Methodological flaws associated with claims databases
Elashoff 2011 [64]	FDA AERS database • Comparison of users of exenatide or sitagliptin therapy with users of rosiglitazone, nateglinide, repaglinide, and glipizide	• Increased OR for reported pancreatitis among users of exenatide or sitagliptin	• Significant sources of bias, such as the notoriety bias, associated with the AERS database
Garg 2010 [65]	Large US healthcare claims database • Comparison of exenatide or sitagliptin use with nondiabetic control group and diabetic control group	• Greater risk of pancreatitis in diabetic groups compared with nondiabetic group • Similar risk of pancreatitis between exenatide group and diabetes comparator group	• Methodological flaws associated with claims databases
Romley 2012 [66]	Privately insured US patients • Exenatide use vs other treatment	• No association between exenatide use and hospitalization for acute pancreatitis	• Methodological flaws associated with claims databases
Singh 2013 [67]	Large US healthcare claims database • Comparison of hospitalized acute pancreatitis cases with matched controls	• Increased OR of acute pancreatitis with current or recent use of exenatide or sitagliptin	• Methodological flaws associated with claims databases
Wenten 2012 [68]	Large US healthcare claims database • Current, recent, past use exenatide	• No increased risk pancreatitis	• Methodological flaws associated with claims databases
Human Clinical Trial Meta-Analysis			
Alves 2012 [69]	25 clinical studies involving exenatide or liraglutide therapy vs comparators	• No increased risk of pancreatitis	• Included studies did not have pancreatitis as a predefined primary outcome with predefined diagnostic criteria

neoplasm. Adjusted analyses found significantly increased odds of acute pancreatitis with GLP-1 RA use within 30 days of hospitalization (adjusted odds ratio [OR] 2.24) and with recent use occurring >30 days but <2 years from hospitalization (adjusted OR 2.01) [67]. This study also has been criticized for methodological flaws that are inherent

in studies using a healthcare claims administrative database, including being unable to adjudicate or validate the diagnoses, which is further exacerbated with complex diagnoses like pancreatitis that require confirmation of multiple criteria and may result in misclassification of cases and controls. Misclassification of treatment exposure and inability to adjust for important confounding factors are additional limitations when using such databases. Importantly, findings from this study contrast with several previous healthcare claims database studies that found no increased risk of pancreatitis with GLP-1 RA therapy [62, 63, 65, 66, 68].

A third study examined the FDA Adverse Event Reporting System (FAERS) database and found a 6-fold greater odds ratio for reported pancreatitis among users of exenatide or sitagliptin, as well as increased reporting for pancreatic and thyroid cancer, compared with rosiglitazone, nateglinide, repaglinide, and glipizide [64]. This study also has been criticized for serious methodological flaws that derive from sources of bias within the FAERS database, including lack of diagnosis validation, disproportionate reporting biases, and unreported comorbidities and confounding risk factors [71, 72]. These sources of bias are known and are considered substantial, and as a result, the FDA has taken the position that FAERS cannot be used to calculate the incidence of an AE in the US population [71]. A study on potential bias in the reported outcomes of the Elashoff 2011study used temporal analysis of the FAERS database while examining the association of pancreatitis with antidiabetic drug use. Results from this study showed a strong influence of FDA warnings and publicity on the disproportionate reporting of pancreatitis associated with exenatide use, resulting in the potential overestimation of risk, known as the notoriety bias [72].

Evidence Not Suggesting Increased Risk of Pancreatitis

Several key studies, including animal model and human healthcare claims database studies, do not support an association between pancreatitis and GLP-1 RA therapy (Table **2**). Investigations involving human subjects have used large health insurance claims databases to examine the association of acute pancreatitis with GLP-1 RA therapy. In contrast to Singh 2013 [67] reviewed above, several large database studies have not supported association of acute pancreatitis with exenatide compared with other antidiabetes drugs such as metformin or glyburide [62, 63, 65]. Additionally, no association was found between exenatide use and hospitalization for acute pancreatitis or pancreatic cancer in privately insured US patients [66]. Another large US health insurance claims database showed no increased risk of pancreatitis with exenatide twice daily, including current, recent, and past exposure to exenatide [68]. Finally, a meta-analysis of 25 published studies did not support an increased risk of acute pancreatitis or cancer from any cause with exenatide or liraglutide therapy vs comparators [69].

The lack of consistency in the evidence either supporting or contradicting the increased risk of pancreatitis was re-cognized by authors of a meta-analysis published in 2014 [73]. That report included the results of 41 studies that enrolled 14,972 patients, and found no increased risk of pancreatitis. However, a nationwide population-based case-control study published in 2015 that compared 12,868 patients after their first-time hospitalization for acute pancreatitis to 128,680 control subjects concluded that there does not appear to be an increased risk of acute pancreatitis associated with the use of incretin-based drugs [74]. However, those types of analyses alone are not enough to draw any conclusions about safety and therefore trials are needed to determine the potential risk of pancreatitis.

Thyroid Cancer Risk

The risk of thyroid cancer associated with liraglutide has been examined in rodent and nonhuman primate animal model studies. Long-term exposure to liraglutide in rodents, but not monkeys, has been associated with thyroid C-cell hyperplasia and tumors through a GLP-1 receptor-mediated mechanism [75]. As an explanation for differences between rodents and nonhuman primates, it has been shown that humans and nonhuman primates have very low thyroid C-cell density and GLP-1 receptor expression compared with rodents; therefore, GLP-1 RA-induced C-cell responses in rodents may not be relevant to primates [75, 76]. As is also true for examining risk of pancreatitis and pancreatic cancer, longer-term studies are needed to further evaluate sustained GLP-1 receptor activation in the human thyroid system. Among the patients in the phase 3 Liraglutide Effect and Action in Diabetes (LEAD) studies, there were no increases of calcitonin levels, and specifically at 2 years the estimated geometric mean values were $\leq$1.0 ng/liter in all groups, which is well below the clinically relevant cutoff of 20 ng/liter that is an indicator of C-cell hyperplasia [77].

For both pancreatic and thyroid AEs, the rarity and long-term timeline of these events require large-scale, long-duration, randomized clinical trials specifically designed to address risk associated with GLP-1 therapy vs T2DM and comorbid conditions [71]. Studies to date have not met these methodological criteria.

Individualized and Patient-centered Treatment Selection

In combination with insulin, GLP-1RA therapy produces greater glycemic control with lower risk of hypoglycemia or weight gain compared with increased insulin dosing [1]. Selection of an agent within GLP-1 RA therapy should consider the patient's primary need for improved FPG (a relatively stronger effect from longer-acting liraglutide and exenatide once weekly) vs postprandial glucose (a relatively stronger effect from shorter-acting exenatide twice daily) control [34].

Certain patient characteristics require caution using GLP-1 RAs. For all patients receiving GLP-1 RA therapy, careful observation for signs/symptoms of pancreatitis is recommended since those treatments should not be used for those patients. Liraglutide, exenatide once weekly, albiglutide, and dulaglutide are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Exenatide is not recommended for patients

with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) or end-stage renal disease (need for dialysis), and caution should be used in patients with moderate (CrCl 30-50 mL/min) renal impairment [10]. As is true with all antidiabetes agents, patient education about the benefits and potential AEs associated with GLP-1 RAs and patient involvement in the treatment selection process are critically important [2].

AACE and ADA/EASD treatment guidelines for T2DM consider GLP-1 RA therapy a first-line option if metformin is contraindicated, and include GLP-1 RA therapy in combination with oral antidiabetes agents and in combination with insulin as a second-line option [1, 2]. Treatment selection for individual patients requires clinical decision making that incorporates knowledge of antidiabetes agents and individual patient characteristics and preferences [2]. Selection of glucose-lowering agents should consider the HbA1c goal, age, medical comorbidities, AEs, and other factors that may limit treatment options for each patient [1]. Minimizing risk of hypoglycemia and weight gain and considering the safety impact of the agent in the context of the individual patient are also treatment selection priorities. Among older patients and patients with comorbid CV, characteristics that support the selection of GLP-1 RA include renal and hepatic disease, a focus on drug safety with emphasis on hypoglycemia, heart failure, renal dysfunction, bone fractures, and drug-drug interactions.

CONCLUSION

The benefits for patients with T2DM of the FDA approved GLP-1 RAs that have been well demonstrated in individual clinical trials, pooled analyses, and meta-analysis studies include glycemic control with low risk of hypoglycemia or weight gain. However, clinical studies completed thus far are insufficient to either confirm or exclude an increased long-term risk of pancreatitis, pancreatic cancer, or thyroid cancer with GLP-1 RA therapy. This is especially true for albiglutide and dulaglutide since they were approved by the FDA recently and there are far fewer safety data currently available for those drugs than for the other GLP-1 RAs currently available in the United States. Studies in support of the safety of GLP-1 RA therapy are therefore necessary. Ongoing studies are currently investigating the incidence of those complications as well as CV disease, and upon completion they will provide more optimal methodological rigor in the examination of the potential for increased risk during treatment with GLP-1 RAs. Currently, continued treatment with GLP-1 RAs in the context of individualized, patient-centered care is supported.

LIST OF ABBREVIATIONS

AACE	=	American Association of Clinical Endocrinologists
ADA	=	American Diabetes Association
AE	=	Adverse Event
AERS	=	Adverse Event Reporting System
BID	=	Twice Daily
CrCl	=	Creatinine Clearance
CRN	=	Caerulein
CV	=	Cardiovascular
DPP-4	=	Dipeptidyl Peptidase 4
EASD	=	European Association for the Study of Diabetes
ELIXA	=	Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with AVE0010 (lixisenatide)
EXSCEL	=	Exenatide Study of Cardiovascular Event Lowering
FAERS	=	FDA Adverse Event Reporting System
FDA	=	Food and Drug Administration
FPG	=	Fasting Plasma Glucose
GLP-1 RA	=	Glucagon-like Peptide-1 Receptor Agonist
LAR	=	Long-acting Release
LEAD	=	Liraglutide Effect and Action in Diabetes
LEADER	=	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	=	Major Cardiovascular Event
NEP	=	Neutral Endopeptidase
OR	=	Odds Ratio
PanIN	=	Pancreatic Intraepithelial Neoplasia
PDGs	=	Pancreatic Duct Glands
REWIND	=	Researching Cardiovascular Events with a Weekly Incretin in Diabetes
SAFEGUARD	=	Safety Evaluation of Adverse Reactions in Diabetes
SBP	=	Systolic Blood Pressure
SP	=	Sprague-Dawley
ST	=	Sodium Taurocholate
T2DM	=	Type 2 Diabetes
US	=	United States
ZDF	=	Zucker Diabetic Fatty

CONFLICT OF INTEREST

Scott R. Drab is an advisory board member for Novo Nordisk Inc.

ACKNOWLEDGEMENTS

The author thanks Lynanne McGuire, PhD, and Aric Fader, PhD, of MedVal Scientific Information Services, LLC, for providing medical writing and editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines." Funding to support this study and the preparation of this manuscript was provided by Novo Nordisk.

REFERENCES

[1] Garber AJ, Abrahamson MJ, Barzilay JI, *et al*. Mechanick JI, Rosenblit PD, Umpierrez G, Davidson MH. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013; 19: 327-36.

[2] Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-79.

[3] Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. Pharmacotherapy 2010; 30: 609-24.

[4] Li CJ, Li J, Zhang QM, *et al*. Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. Cardiovasc Diabetol 2012; 11: 142.

[5] Buse JB, Bergenstal RM, Glass LC, *et al*. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2011; 154: 103-12.

[6] Gryskiewicz KA, Coleman CI. Exenatide: a novel incretin mimetic hormone for the treatment of type 2 diabetes. Formulary 2005; 40: 86-90.

[7] Kolterman OG, Kim DD, Shen L, *et al*. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm 2005; 62: 173-81.

[8] Fineman M, Flanagan S, Taylor K, *et al*. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. Clin Pharmacokinet 2011; 50: 65-74.

[9] Amylin Pharmaceuticals Inc. Bydureon® (exenatide extended-release for injectable suspension) [prescribing information]. Amylin Pharmaceuticals, Inc., San Diego, CA; January, 2012.

[10] Amylin Pharmaceuticals. Byetta® (exenatide) injection [prescribing information]. Amylin Pharmaceuticals, Inc., San Diego, CA; February, 2013.

[11] Knudsen LB. Glucagon-like peptide-1: the basis of a new class of treatment for type 2 diabetes. J Med Chem 2004; 47: 4128-34.

[12] Novo Nordisk Inc. Victoza® (liraglutide [rDNA origin] injection) [prescribing information]. Novo Nordisk Inc., Princeton, NJ; April, 2013.

[13] Rosenstock J, Stewart MW. Albiglutide: glucagon-like peptide GLP-1 receptor agonist, treatment of type 2 diabetes. Drugs Future 2010; 35: 701-12.

[14] Matthews JE, Stewart MW, De Boever EH, *et al*. Pharmacodynamics, pharmacokinetics, safety and tolerability of albiglutide, a long-acting GLP-1 mimetic, in patients with type 2 diabetes. J Clin Endocrinol Metab 2008; 93: 4810-7.

[15] Bush MA, Matthews JE, De Boever EH, *et al*. Safety, tolerability, pharmacodynamics and pharmacokinetics of albiglutide, a long-acting glucagon-like peptide-1 mimetic, in healthy subjects. Diabetes Obes Metab 2009; 11: 498-505.

[16] Rosenstock J, Reusch J, Bush M, Yang F, Stewart M. The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care 2009; 32: 1880-6.

[17] GlaxoSmithKline. Tanzeum® (albiglutide) for injection [prescribing information]. GlaxoSmithKline LLC, Research Triangle Park, NC; April, 2014.

[18] Terauchi Y, Satoi Y, Takeuchi M, Imaoka T. Monotherapy with the once weekly GLP-1 receptor agonist dulaglutide for 12 weeks in Japanese patients with type 2 diabetes: dose-dependent effects on glycaemic control in a randomised, double-blind, placebo-controlled study. Endocr J 2014; 61: 949-59.

[19] Glaesner W, Vick AM, Millican R, *et al*. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. Diabetes Metab Res Rev 2010; 26: 287-96.

[20] Kuritzky L, Umpierrez G, Ekoe JM, Mancillas-Adame L, Lando LF. Safety and efficacy of dulaglutide, a once weekly GLP-1 receptor agonist, for the management of type 2 diabetes. Postgrad Med 2014; 126: 60-72.

[21] Eli Lilly and Company. Tulicity® (dulaglutide) injection, for subcutaneous use [prescribing information]. Eli Lilly and Company, Indianapolis, IN; 2014.

[22] Ahren B, Johnson SL, Stewart M, *et al*. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014; 37: 2141-8.

[23] Rosenstock J, Fonseca V, Gross JL, *et al*. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist versus thrice daily prandial insulin lispro . Diabetes Care 2014; Jun 4. [Epub ahead of print]

[24] Ferdinand KC, White WB, Calhoun DA, *et al*. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. Hypertension 2014; 64: 731-7.

[25] Wang B, Zhong J, Lin H, *et al*. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. Diabetes Obes Metab 2013; 15: 737-49.

[26] Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res 2012; 2012: 672658.

[27] Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012; 344: d7771.

[28] Bergenstal RM, Li Y, Porter TK, Weaver C, Han J. Exenatide once weekly improved glycaemic control, cardiometabolic risk factors and a composite index of an HbA1c < 7%, without weight gain or hypoglycaemia, over 52 weeks. Diabetes Obes Metab 2012; Oct 18 [Epub ahead of print]

[29] Aroda VR, Henry RR, Han J, *et al*. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. Clin Ther 2012; 34: 1247-58.e22.

[30] Kesavadev J, Shankar A, Gopalakrishnan G, Jothydev S. Efficacy and safety of liraglutide therapy in 195 Indian patients with type 2 diabetes in real world setting. Diabetes Metab Syndr 2015; 9: 30-3.

[31] Khan M, Ouyang J, Perkins K, Nair S, Joseph F. Determining predictors of early response to exenatide in patients with type 2 diabetes mellitus. J Diabetes Res 2015; 2015: 162718.

[32] Home PD, Shamanna P, Stewart M, *et al*. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. Diabetes Obes Metab 2015; 17: 179-87.

[33] Blonde L, Jendle J, Gross J, *et al*. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet 2015; 385: 2057-66.

[34] Deacon CF, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes-a review and meta analysis. Diabetes Obes Metab 2012; 14: 762-7.

[35] Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis (July/August). Ann Pharmacother 2011; 45: 850-60.

[36] Buse JB, Nauck M, Forst T, *et al*. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381: 117-24.

[37] Pratley RE, Nauck MA, Barnett AH, *et al*. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289-97.

[38] Wysham C, Blevins T, Arakaki R, *et al*. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014; 37: 2159-67.

[39] Dungan KM, Povedano ST, Forst T, *et al*. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014; 384: 1349-57.

[40] Weissman PN, Carr MC, Ye J, *et al*. HARMONY 4: randomized clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia 2014; Sep 11. [Epub ahead of print]

[41] Monami M, Cremasco F, Lamanna C, *et al*. Glucagon-like Peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res 2011; 2011: 215764.

[42] Gill A, Hoogwerf BJ, Burger J, *et al*. Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study. Cardiovasc Diabetol 2010; 9: 6.

[43] American Association of Clinical Endocrinologists. Correcting and Replacing American Association of Clinical Endocrinologists, American Diabetes Association issue joint response to published JAMA article. Available at: http://aace.newshq.businesswire.com/press-release/correcting-and-replacing-american-association-clinical-endocrinologists-american-diabe. Accessed October 18, 2013.

[44] American Diabetes Association. ADA/EASD/IDF statement concerning the use of incretin therapy and pancreatic disease. Available at: http://www.diabetes.org/for-media/2013/recommendations-for.html. Accessed October 18, 2013.

[45] The Endocrine Society. Experts raise concerns about JAMA study and pancreatitis risk of diabetes medications. Available at: https://www.endocrine.org/news-room/current-press-releases/experts-raise-concerns-about-jama-study-and-pancreatitis-risk-of-diabetes-medications. Accessed October 18, 2013.

[46] American Diabetes Association. First CVD outcome trial of a GLP-1 agonist finds no cardiac risk or benefit. Available at: http://www.diabetes.org/newsroom/press-releases/2015/elixa.html. Accessed November 17, 2015.

[47] Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care 2009; 32: 834-8.

[48] Girman CJ, Kou TD, Cai B, *et al*. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diabetes Obes Metab 2010; 12: 766-71.

[49] Cefalu WT, Rosenstock J, Henry RR, Riddle M. Signals and noise in drug safety analyses: the incretin therapy debate provides the rationale for revamping epidemiologic pharmacovigilance. Diabetes Care 2013; 36: 1804-6.

[50] Nauck MA. A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. Diabetes Care 2013; 36: 2126-32.

[51] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 2013; 36: 2118-25.

[52] Egan AG, Blind E, Dunder K, *et al*. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. New Engl J Med 2014; 370: 794-7.

[53] Gier B, Matveyenko AV, Kirakossian D, Dawson D, Dry SM, Butler PC. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. Diabetes 2012; 61: 1250-62.

[54] Gotfredsen CF, Molck AM, Thorup I, *et al*. The human GLP-1 analogs liraglutide and semaglutide: absence of histopathological effects on the pancreas in nonhuman primates. Diabetes 2014; Mar 7. [Epub ahead of print]

[55] Koehler JA, Baggio LL, Lamont BJ, Ali S, Drucker DJ. Glucagon-like peptide-1 receptor activation modulates pancreatitis-associated gene expression but does not modify the susceptibility to experimental pancreatitis in mice. Diabetes 2009; 58: 2148-61.

[56] Nachnani JS, Bulchandani DG, Nookala A, *et al*. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. Diabetologia 2010; 53: 153-9.

[57] Nyborg NC, Molck AM, Madsen LW, Knudsen LB. The human GLP-1 analog liraglutide and the pancreas: evidence for the absence of structural pancreatic changes in three species. Diabetes 2012; 61: 1243-9.

[58] Tatarkiewicz K, Smith PA, Sablan EJ, *et al*. Exenatide does not evoke pancreatitis and attenuates chemically induced pancreatitis in normal and diabetic rodents. Am J Physiol Endocrinol Metab 2010; 299: E1076-E1086.

[59] Tatarkiewicz K, Belanger P, Gu G, Parkes D, Roy D. No evidence of drug-induced pancreatitis in rats treated with exenatide for 13 weeks. Diabetes Obes Metab 2013; 15: 417-26.

[60] Vrang N, Jelsing J, Simonsen L, *et al*. The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis. Am J Physiol Endocrinol Metab 2012; 303: E253-E264.

[61] Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013; 62: 2595-604.

[62] Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin 2009; 25: 1019-27.

[63] Dore DD, Bloomgren GL, Wenten M, *et al*. A cohort study of acute pancreatitis in relation to exenatide use. Diabetes Obes Metab 2011; 13: 559-66.

[64] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011; 141: 150-6.

[65] Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care 2010; 33: 2349-54.

[66] Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol Thera 2012; 14: 904-11.

[67] Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med 2013; 173: 534-9.

[68] Wenten M, Gaebler JA, Hussein M, *et al*. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med 2012; 29: 1412-8.

[69] Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. Diabetes Res Clin Pract 2012; 98: 271-84.

[70] Harja E, Lord J, Skyler JS. An analysis of characteristics of subjects examined for incretin effects on pancreatic pathology. Diabetes Technol Ther 2013; 15: 609-18.

[71] Drucker DJ, Sherman SI, Bergenstal RM, Buse JB. The safety of incretin-based therapies--review of the scientific evidence. J Clin Endocrinol Metab 2011; 96: 2027-31.

[72] Raschi E, Piccinni C, Poluzzi E, Marchesini G, De PF. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. Acta Diabetol 2011; 50: 569-77.

[73] Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. Diabetes Res Clin Pract 2014; Jan 14 [Epub ahead of print]:

[74] Thomsen RW, Pedersen L, Moller N, Kahlert J, Beck-Nielsen H, Sorensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care 2015; 38: 1089-98.

[75] Knudsen LB, Madsen LW, Andersen S, *et al*. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing

calcitonin release and C-cell proliferation. Endocrinology 2010; 151: 1473-86.

[76] Boess F, Bertinetti-Lapatki C, Zoffmann S, *et al*. Effect of GLP-1R agonists taspoglutide and liraglutide on primary thyroid C-cells from rodent and man. J Mole Endocrinol 2013; 50: 325-36.

[77] Hegedus L, Moses AC, Zdravkovic M, Thi TL, Daniels GH. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. J Clin Endocrinol Metab 2011; 96: 853-60.