A systematic review of the safety of incretin-based therapies in type 2 diabetes

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ABSTRACT

Introduction: Large randomized clinical trials have demonstrated that incretin-based therapies provide effective glycemic control in type 2 diabetes. Long-term safety assessments are ongoing.

Methods: This systematic review of incretin-based therapy safety is based on 112 randomized clinical trials of duration ≥26 weeks published between January 2000 and February 2015 in patients with type 2 diabetes.

Results: As expected, hypoglycemia rates were lower with dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) versus other oral antidiabetic drugs and insulin. The most common adverse events were infection and infestation (DPP-4is) and gastrointestinal (GLP-1 RAs). Pancreatitis cases were rare across all studies and, in the SAVOR-TIMI and EXAMINE trials, pancreatitis rates were similar in DPP-4i- and placebo-treated patients. No thyroid tumors were reported, and increased risk of cardiovascular events was not associated with DPP-4is in SAVOR-TIMI and EXAMINE, albeit over a short follow-up period.

Conclusions: Overall, incretin-based therapies were well tolerated; however, their long-term safety profile should continue to be periodically assessed.

Introduction

Incretin therapies now have a well-recognized place in type 2 diabetes (T2D) clinical practice guidelines and add to the range of diabetic therapies available to target high glycosylated hemoglobin (A1c) levels following failure of lifestyle modifications and metformin use. Along with causing efficacious lowering of A1c with an inherently low risk of hypoglycemia, incretin therapies may provide distinct advantages over conventional T2D medications, such as glucose-dependent inhibition of glucagon secretion and absence of weight gain. The development of incretin-based therapies has focused on two areas: glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which enhance the physiological effects of GLP-1 receptor activation, and dipeptidyl peptidase-4 inhibitors (DPP-4is), which antagonize DPP-4, and hence, lessen native GLP-1 degradation.

In April 2005, exenatide became the first GLP-1 RA to be approved by the US FDA for use in T2D [1]. Since then, exenatide once-weekly [2], liraglutide [3], albiglutide [4] and dulaglutide [5] have been approved by the FDA and the European Medicines Agency (EMA), while lixisenatide has been approved in the European Union (EU) (Table 1) [6]. The DPP-4is sitagliptin, saxagliptin, linagliptin and alogliptin are FDA- and EMA-approved [7–10], while vildagliptin has been approved in the EU since 2007 [11]. The GLP-1 RAs and DPP-4is in phase I–III development are shown in Table 2. Clinical trials show that exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide typically reduce A1c by 0.8–1.9% [12–16], 0.8–1.5% [17–24], 0.6–0.9% [25–29], 0.5–0.9% [30–35] and 0.8–1.5% [36–39], respectively, while sitagliptin, saxagliptin, linaglipitin, alogliptin and vildagliptin have been shown to reduce A1c by 0.4–1.2% [21,40–42], 0.5–1.1% [43–45], 0.4–0.8% [46–48], 0.4–0.7% [49–51] and 0.5–1.0% [52–54], respectively.

Long-term safety assessments of incretin therapies are of ongoing importance. Since the effect of GLP-1 RAs is glucose dependent, the incidence of hypoglycemia is generally low with these therapies [55]; however, rates may differ, depending on whether the GLP-1 RA is used as monotherapy or in combination with other oral antidiabetic drugs (OADs). Slowed gastric emptying appears to be a direct effect of GLP-1 [56], hence gastrointestinal (GI)-related adverse events (AEs) are common with GLP-1-based therapies, though not directly correlated with the degree of retardation of gastric emptying, and are more frequent than with DPP-4is. Side effects most frequently reported for DPP-4is are infections and infestations, which may be due to the fact that DPP-4 (also known as CD26) is also involved in regulating the immune system.

A postmarketing report that an increased risk of pancreatitis and pancreatic cancer may be associated with incretin-based therapies in patients with T2D has sparked much debate regarding their safety profile [57]. A small number of studies in patients with T2D have indicated an association between specific incretin therapies and pancreatitis [58,59]. However, these reports have been controversial due to the methodologies employed and the patient numbers used. Although the proposed mechanism for this risk is based on the fact that native GLP-1 may induce proliferation and differentiation of pancreatic ductal...
preclinical studies have failed to reveal a mechanism linking incretin therapies and pancreatitis. In addition, the long-term trials of saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis In Myocardial Infarction [SAVOR-TIMI 53]) and alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]) report no increased pancreatitis risk with either of these therapies compared with placebo. Furthermore, an EMA/FDA assessment has concluded that a causal association between incretin-based drugs and pancreatitis or pancreatic cancer is inconsistent with currently published data.

Another safety concern with incretin-based therapies is the increased risk of thyroid C-cell tumors. Because some preclinical studies suggest a relationship between GLP-1 RA treatment and thyroid C-cell proliferation, this area continues to be monitored closely in ongoing and future clinical trials using incretin-based therapies.

Due to FDA requirements, long-term cardiovascular safety trials with incretin-based therapies are already completed or underway. Results from the SAVOR-TIMI 53 (median duration 2.1 years) and EXAMINE (median duration 18 months) trials do not indicate an increased risk of ischemic events with incretin therapies; results from ongoing long-term cardiovascular safety studies will also be required to support these findings. In the past, physicians and patients would tolerate certain side effects in return for treatment efficacy; however, the increasing number of agents with differing safety profiles means that AEs are becoming increasingly important for drug selection. The goal of this study was to systematically review the studies where safety data for incretin-based therapies have been reported. In addition to addressing any new information available on major safety concerns such as pancreatitis and neoplasia, the authors report on the incidence of more common AEs.

Table 1. Currently available incretin-based therapies.

| Trade name | Proprietary name | Date of approval | Company | Characteristics |
|------------|-----------------|------------------|---------|-----------------|
| DPP-4is    |                 |                  |         |                 |
| Januvia® [7] | Sitagliptin    | October 2006 (FDA) | Merck | Peak: 1–4 h Half-life: 12.4 h Initial dose: 100 mg (OD) |
|            |                 | March 2007 (EMA)  |         |                 |
| Onglyza® [8] | Saxagliptin    | July 2009 (FDA)  | Bristol Myers Squibb /AstraZeneca | Peak: 2 h Half-life: 2.5–3.1 h Initial dose: 2.5–5 mg (OD) |
|            |                 | October 2009 (EMA) |         |                 |
| Trajenta®[9] | Linagliptin    | May 2011 (FDA)   | Boehringer | Peak: 1.5 h Half-life: ~12 h Initial dose: 5 mg (OD) |
|            |                 | August 2011 (EMA) | Ingelheim |                 |
| Nesina® [10] | Alogliptin     | January 2013 (FDA) | Takeda Pharmaceuticals | Peak: 1 h Half-life: 12.5–21.1 h Initial dose: 12.5–25 mg (OD) |
|            |                 | September 2013 (EMA) |         |                 |
| Galvus® [11] | Vildagliptin   | September 2007 (EMA) | Novartis | Peak: 2.5 h Half-life: 2–3 h Initial dose: 50 mg (BID) |
| GLP-1 RAs  |                 |                  |         |                 |
| Byetta® [1] | Exenatide      | April 2005 (FDA) | Amylin, Eli Lilly & Co. | Peak: 2.1 h Half-life: 2.4 h Initial dose: 5 µg (BID) |
|            |                 | November 2006 (EMA) |         | Peak: steady-state levels Median half-life: 2 weeks Initial dose: 2 mg (QW) |
| Bydureon®[2] | Exenatide QW  | January 2012 (FDA) | Amylin, Eli Lilly & Co. | Peak: 8–12 h Half-life: 13 h Initial dose: 0.6 mg (OD) |
|            |                 | June 2011 (EMA)  |         |                 |
| Victoza®[3] | Liraglutide    | January 2010 (FDA) | Novo Nordisk | Peak: 3–5 days Median half-life 6–7 days Initial dose 30 mg (QW) |
|            |                 | June 2009 (EMA)  |         |                 |
| Tanzeum®/Eperzan® [4] | Albiglutide | April 2014 (FDA) | GlaxoSmithKline | Peak: 48 h Median half-life 4 days Initial dose 0.75 mg (QW) |
|            |                 | March 2014 (EMA) |         |                 |
| Trulicity® [5] | Dulaglutide  | September 2014 (FDA) | Eli Lilly | Peak: 1.2 h Median half-life: 3 h Initial dose: 5 µg (OD) |
|            |                 | November 2014 (EU) |         |                 |
| Lyxumia® [6] | Lixisenatide  | February 2013 (EMA) | Sanofi | Peak: 1–2 h Median half-life: 3 h Initial dose: 5 µg (OD) |

Table 2. Emerging incretin-based therapies.

| DPP-4is | GLP-1 RAs | Other incretin-related agents |
|---------|-----------|-----------------------------|
| MP-513 | Teneligliptin | Mitsubishi Tanabe Pharma Phase III |
| GW823093 | Denagliptin | GlaxoSmithKline Phase II/III |
| GLP-1 RAs | Semaglutide | Novo Nordisk Phase II/III |
| Other incretin-related agents | TAK-875 | Fasigliflam Takeda Pharmaceuticals Phase I–II |

BID: twice daily; DPP-4i: dipeptidyl peptidase-4 inhibitor; EMA: European Medicines Agency; EU: European Union; GLP-1 RA: glucagon-like peptide-1 receptor agonist; OD: once daily; QW: once weekly.

DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist.

[60], preclinical studies have failed to reveal a mechanism linking incretin therapies and pancreatitis [61]. In addition, the long-term trials of saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis In Myocardial Infarction [SAVOR-TIMI 53]) and alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]) [62] and albiglutide (Examination of Cardiovascular Outcomes with Albiglutide versus Standard of Care [EXAMINE]) [63] report no increased pancreatitis risk with either of these therapies compared with placebo. Furthermore, an EMA/FDA assessment has concluded that a causal association between incretin-based drugs and pancreatitis or pancreatic cancer is inconsistent with currently published data [64].
such as hypoglycemia, nausea and infections, and describe any notable differences between and within classes of incretin therapies.

**Systematic review of the safety and tolerability of incretin-based therapies**

**Search strategy**

The authors performed a PubMed search for articles published in English between 1 January 2000 and 1 February 2015 using the keywords ‘human’, ‘diabetes’ and ‘randomized controlled trial’. For this search, the authors applied limiting keywords related to each currently available treatment as outlined in Supplementary Appendix I. In addition, the authors performed a search of the ClinicalTrials.gov database for phase IV or post-marketing surveillance trials where results were available and these search parameters are outlined in Supplementary Appendix II.

**Selection criteria**

**Study inclusion**

From the PubMed search, publications of randomized controlled trials in patients with T2D involving the use of one or more incretin therapies were considered. Only studies that reported AE and/or safety outcomes were included (Supplementary Appendix III).

**Study exclusion**

Titles, abstracts and major subject headings (keywords) were screened based on the exclusion criteria. Studies were excluded if the primary focus of the article was not incretin-based therapies, there was no indication that safety data had been recorded, the study was of shorter duration than 24 weeks, contained fewer than 100 patients or investigated pharmacokinetic and/or pharmacodynamic characteristics (as these generally involve few patients and are of short duration). Studies performed in healthy individuals, patients with type 1 diabetes or in subjects with impaired fasting glucose or impaired glucose tolerance were also excluded. The authors also omitted studies that were not phase III trials, not appropriately controlled (i.e. had no comparator treatment or had used only data from AEs reporting systems or patient-reported outcomes) or where data were duplicated in publications or extension studies. Following the initial screening, full papers were obtained and scrutinized more closely for the exclusion criteria described above.

**Data extraction**

Data relating to the most frequently reported AEs from each study were extracted. In studies where more than one incretin therapy had been used, data for both were taken. Data were extracted regarding primary study incretin; treatment type: monotherapy or combination therapy and the detail of each combination; the three most frequently reported AEs; frequency of overall and treatment-emergent AEs; frequency of overall and treatment-emergent serious AEs; and rates of minor and major hypoglycemia and were placed in a summary table (Supplementary Appendix IV).

The authors then also considered other less frequently reported AEs of interest to incretin therapies. These included skin and subcutaneous disorders; lymphocyte disorders and specific reports of pancreatitis and/or C-cell tumors. Where data for comparator therapies were noted, these included metformin, sulfonylurea (SU: glyburide, gliclazide and glimepiride) and thiazolidinedione (TZD: pioglitazone and rosiglitazone).

**Results**

Searches in PubMed and Clinicaltrials.gov using the criteria outlined above identified 477 articles, of which 112 were considered relevant (Supplementary Appendices I–III). Safety data were extracted from these publications, which are listed in Supplementary Appendix IV. The distribution of papers by therapy used is shown in Table 3.

The percentage of patients experiencing an AE before it qualified for reporting ranged from ≥1 to ≥5% but the majority of publications reported AEs occurring in >3% or >5% of the patient population. Not all publications that were analyzed provided specific AE data, and some instead chose to report AE data in Medical Dictionary for Regulatory Activities (MedDRA) classification terms. For example, nausea, diarrhea and vomiting were frequently classified under GI disorders. Therefore, to standardize data extraction across all studies, the authors classified each specific AE according to its parent MedDRA classification term [142].

A summary table of the extracted data can be found in Supplementary Appendix IV.

**DPP-4i studies: data from randomized controlled trials**

A total of 72 DPP-4i mono- and combination therapy studies (104 trial arms) were analyzed. In general, the AEs that were reported as the most common, excluding hypoglycemia, were infection and infestation (51% of trial arms), followed by GI AEs (21% of trial arms), nervous system disorders (16% of trial arms), vascular disorders (7% of trial arms), and

| Table 3: Distribution of studies used for systematic review. |
|---------------------------------------------------------------|
| **Number of published studies** | **Monotherapy** | **Combination** | **References** |
| Sitagliptin | 7 | 18 | [30,37,40,42,67–87] |
| Saxagliptin | 2 | 12 | [43–45,62,79,88–96] |
| Linagliptin | 2 | 4 | [46,47,97–100] |
| Alogliptin | 0 | 3 | [49,63,101] |
| Vildagliptin | 10 | 15 | [52–54,102–123] |
| GLP-1 RAs | | | |
| Exenatide daily | 0 | 17 | [12,15,17,70,124–136] |
| Exenatide weekly | 1 | 6 | [13,14,24,39,67,69,137] |
| Liraglutide | 2 | 12 | [17,19–24,32,36,42,138–141] |
| (all doses) | | | |
| Dulaglutide | 1 | 3 | [36–39] |
| Albiglutide | 0 | 5 | [30–33,35] |

*Certain studies contained data for both mono- and combination therapy and also several different incretin-based therapies (GLP-1 RAs and DPP-4i).

DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist.
musculoskeletal and connective tissue disorders (2% of trial arms). Infection and infestation AEs, GI AEs, peripheral edema and musculoskeletal and connective tissue disorders were a feature of all DPP-4is. The highest rate of patient discontinuation due to study drug was in a saxagliptin trial in patients with T2D and renal impairment, where 11.8% of patients withdrew [88].

**DPP-4is and hypoglycemia**

Hypoglycemia is often associated with intensification of T2D therapies and may be a major hurdle to overcome for both patients and prescribers. In the trials included in this review, comparator OAD therapies combined with insulin typically led to 8–54% of patients experiencing minor hypoglycemia. In DPP-4i trials, minor hypoglycemia was fairly common, being reported as an AE in 41–100% of the trial arms analyzed. However, the actual proportion of patients experiencing this AE within the majority of DPP-4i trial arms, including those treated with monotherapy or with DPP-4i in combination with metformin, TZDs or SU, was very low (<13%) (Table 4). When DPP-4is were combined with ≥2 OAD therapies, minor hyperglycemia was experienced by up to 17.3% of patients and, when combined with insulin alone, this value reached the maximum proportion reported for DPP-4is (22.9%). Between different DPP-4is, similar proportions of patients experienced minor hypoglycemia (Table 5) and the overall proportion of patients experiencing minor hypoglycemia was 2.6%. Major hypoglycemia was less common than minor hypoglycemia, being reported as an AE in 3–67% of DPP-4i trial arms. Although this proportion appears moderate to high, the actual proportion of patients experiencing major hypoglycemia did not exceed 3% in any trial arm across all individual DPP-4i studies (Table 4) and the overall proportion of patients experiencing major hypoglycemia across DPP-4i trial arms was 0.2%.

### Table 4. Number of trials and proportions of patients experiencing minor and major hypoglycemia with DPP-4is, GLP-1 RAs and insulin, combined with different oral antidiabetic drug therapies.

| Combination | Minor hypoglycemia | Major hypoglycemia |
|-------------|--------------------|--------------------|
|             | Number of trial arms | Proportions of patients (%) | Number of trial arms | Proportions of patients (%) |
| DPP-4is     |                   |                     |                   |                     |
| DPP-4i monotherapy | 14/34 (41%) | 0.6–3% | 1/34 (3%) | 0.4 |
| DPP-4i + metformin | 32/38 (84%) | 0.8–12.2% | 7/38 (18%) | 0–0.8 |
| DPP-4i + SU | 5/5 (100%) | 0–2.4% | 1/5 (20%) | 0.5 |
| DPP-4i + TZD | 7/9 (78%) | 6.3–22.9% | 1/9 (11%) | 0.5 |
| DPP-4i + insulin | 6/6 (100%) | 0.5–17.3% | 4/6 (67%) | 0–2.1 |
| DPP-4i + ≥2 OADs | 11/12 (92%) | 0.5–17.3% | 8/12 (67%) | 0–3.0 |
| GLP-1 RAs |                   |                     |                   |                     |
| GLP-1 RA monotherapy | 6/6 (100%) | 2–12.3% | 1/6 (17%) | 0.4 |
| GLP-1 RA + metformin | 26/26 (100%) | 10.0–28.0% | 6/26 (23%) | 0–0.4 |
| GLP-1 RA + SU | 4/4 (100%) | 14.0–36.0% | 0/4 (0%) | – |
| GLP-1 RA + thiazolidinediones | 1/1 (100%) | 3.4% | 0/1 (0%) | – |
| GLP-1 RA + insulin | 4/4 (100%) | 20.2–42.9% | 2/4 (50%) | 0.4–4.2 |
| GLP-1 RA + ≥2 OAD | 31/31 (100%) | 0.5–34.0% | 11/31 (35%) | 0–2.2 |
| Insulin |                   |                     |                   |                     |
| Insulin + metformin | 5/5 (100%) | 8.0–32.0% | 2/5 (40%) | 0–1.0 |
| Insulin + ≥2 OADs | 9/9 (100%) | 26.0–54.0% | 7/9 (70%) | 0.8–5.3 |

*Proportions were not available for one trial arm as a percentage.

*Proportions were not available for five trial arms as a percentage.

*Proportions were not available for two trial arms as a percentage.

*Proportions were not available for three trial arms as a percentage.

**DPP-4i**: dipeptidyl peptidase-4 inhibitor; **GLP-1 RA**: glucagon-like peptide-1 receptor agonist; **OAD**: oral antidiabetic drug; **SU**: sulfonylurea; **TZD**: thiazolidinedione.

### Table 5. Proportion of patients experiencing minor hypoglycemia with different DPP-4is, GLP-1 RAs and insulin, combined with different oral antidiabetic drug therapies.

| Combination | Saxagliptin | Sitagliptin | Vildagliptin | Linagliptin | Alogliptin | Exenatide daily/BID | Exenatide weekly | Liraglutide 0.6–1.2 mg | Liraglutide 1.8 mg | Lixisenatide | Dulaglutide (0.75–1.5 mg) | Albiglutide |
|-------------|-------------|-------------|-------------|-------------|-----------|--------------------|-----------------|---------------------|-----------------|-------------|-------------------------|-------------|
| DPP-4i monotherapy | 0 (6) | 0–3.2 (7) | 3.2–5.2 (2) | 0–1.0 (2) | 3.2–5.2 (2) | 0–1.0 (2) | 3.2–5.2 (2) | 0–1.0 (2) | 3.2–5.2 (2) | 0–1.0 (2) | 3.2–5.2 (2) | 0–1.0 (2) |
| + Metformin | 0–6.3 (8) | 0.5–8.4 (14) | 12.1 (2) | 1.1–2.4 (2) | 11.0–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) | 0.5–16.0 (2) |
| + SU | 0–1.2 (16) | 0–3.0 (12) | 1.2–3.6 (2) | 0–0.7 (4) | 22.9 (1) | 2.2–17.3 (4) | 2.2–17.3 (4) | 2.2–17.3 (4) | 2.2–17.3 (4) | 2.2–17.3 (4) | 2.2–17.3 (4) | 2.2–17.3 (4) |
| + Tzd | 0–0.3 (4) | 0–3.5 (3) | 1.2 (1) | 0–1.2 (1) | 7.0 (1) | 0–1.2 (1) | 7.0 (1) | 0–1.2 (1) | 7.0 (1) | 0–1.2 (1) | 7.0 (1) | 0–1.2 (1) |
| + Insulin | – | 1.0–1.5 (2) | – | – | – | – | – | – | – | – | – | – |
| + ≥2 OADs | – | 4.5–28.0 (6) | 20.8 (2) | 14.0–36.0 (2) | 31.4 (1) | 0.8–34.0 (11) | 0.8–34.0 (11) | 0.8–34.0 (11) | 0.8–34.0 (11) | 0.8–34.0 (11) | 0.8–34.0 (11) | 0.8–34.0 (11) |

*Proportions were not available for one trial arm as a percentage.

*Proportions were not available for three trial arms as a percentage.

*Proportions were not available for two trial arms as a percentage.

**BID**: twice daily; **DPP-4i**: dipeptidyl peptidase-4 inhibitor; **GLP-1 RA**: glucagon-like peptide-1 receptor agonist; **OAD**: oral antidiabetic drug; **SU**: sulfonylurea; **TZD**: thiazolidinedione.
DPP-4is and infections and infestations

The most common infections and infestations reported for DPP-4is were upper respiratory tract infections (URTIs), nasopharyngitis and influenza. Proportions of patients across all of the different DPP-4is in use either as monotherapy or in combination with other OADs experiencing these infections as the most common AE were all low to moderate and were similar to the percentages observed for placebo or conventional therapy (saxagliptin, nasopharyngitis 5.6–9.6%; URTI 5.6–12.8%; sitagliptin, nasopharyngitis 8–12.1%; influenza 4.0–5.8%; vildagliptin, nasopharyngitis 4.8–15.8%; URTI 9.9%; lianglipitin, nasopharyngitis 3.9–16%; URTI 6.3–5.7%; alogliptin, nasopharyngitis 5.4%; URTI 7.2% all vs. placebo, nasopharyngitis 1.4–9.4% URTI, 3.0–16.0%; nasopharyngitis 6.0–22.0% SU; nasopharyngitis 2.8–8.6%; URTI 4.0–4.6%; metformin, nasopharyngitis 4.8–12.0%).

DPP-4is and Gl-related AEs

Among the GI disorders reported for DPP-4is, nausea was the most common, being reported as an AE in around 40% of trial arms. Actual proportions of patients experiencing nausea within DPP-4 trial arms were similar to, or lower than, those reported for placebo or conventional therapy, with a maximum value of 10.0% in patients who reported for a trial combining a DPP-4i with metformin (Table 6). Among the different DPP-4is, nausea was most frequent with use of sitagliptin and vildagliptin; proportions of patients experiencing nausea with these DPP-4is were similar and were most common in monotherapy and when used as an add-on to metformin treatment (Table 7).

DPP-4is and nervous system disorders

Nervous system disorders were reported as the main AE in approximately 16 of DPP-4i trial arms. These comprised headaches (7/17 trial arms), dizziness (5/17 trial arms) or tremor (3/17 trial arms). Headaches were reported only in vildagliptin (9.3% vs. metformin 7.0% and placebo 4.8%) and saxagliptin (6.3–11.2 % vs. metformin 5.2–5.5% and placebo 2.2–7.4%) trial arms. Dizziness was reported only in vildagliptin trial arms (4.8–8.8% vs. SU 5.0%, metformin 6.0% and placebo 2.2%). Tremor was reported in three vildagliptin trial arms (2.4–18.1% vs. placebo 4.2–4.9%).

DPP-4is and vascular disorders

In approximately 26% of the DPP-4i studies analyzed, peripheral edema was reported as a safety issue and was most

| Table 6. Number of trials reporting gastrointestinal adverse events, nausea and proportions of patients experiencing nausea among those using DPP-4is and GLP-1 RAs with different oral antidiabetic drug therapies. |

| DPP-4is         | Number of trial arms reporting GI AEs as most common disorder | Number of trial arms reporting nausea | Proportions of patients experiencing nausea vs. placebo or CT alone, % (number of trial arms) |
|-----------------|---------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------|
| DPP-4i monotherapy | 6/34 (18%)                                                   | 10/34 (29%)                          | 0–4.0 vs. 0–11.3 (9)                                                                    |
| DPP-4i + metformin | 13/38 (34%)                                                  | 22/38 (58%)                          | 10.0 vs. 0–27.0 (21)                                                                    |
| DPP-4i + SU      | 1/5 (20%)                                                    | 3/5 (60%)                            | 0–3.6 vs. 0–3.4 (3)                                                                     |
| DPP-4i + TZD     | 0/9 (0%)                                                     | 5/9 (56%)                            | 0–5.5 vs. 0–2.5 (5)                                                                     |
| DPP-4i + insulin | 6/6 (0%)                                                     | 1/6 (17%)                            | 5.0 vs. 2.0 (1)                                                                         |
| DPP-4i ≥2 OAD    | 2/12 (17%)                                                   | 4/12 (33%)                           | 0.9–5.9 vs. 0.9–7.1 (4)                                                                 |
| GLP-1 RAs        |                                                              |                                     |                                                                                          |
| GLP-1 RA monotherapy | 4/6 (67%)                                                   | 6/6 (100%)                           | 4.5–31.0 vs. 15.6–16.0 (5)                                                              |
| GLP-1 RA + metformin | 24/26 (92%)                                                 | 26/26 (100%)                         | 5.7–48.5 vs. 20.2–23.0 (21)                                                             |
| GLP-1 RA + SU    | 2/4 (50%)                                                    | 2/4 (50%)                            | 39.0–51.0 vs. 7.0 (2)                                                                   |
| GLP-1 RA + TZD   | 1/1 (100%)                                                   | 1/1 (100%)                           | 23.5 vs. 10.6 (1)                                                                       |
| GLP-1 RA + insulin | 3/4 (75%)                                                   | 3/4 (75%)                            | 3.7–48.3 vs. 2.6–5.7 (3)                                                                 |
| GLP-1 RA ≥2 OADs | 27/31 (87%)                                                  | 27/31 (87%)                          | 9.6–57.1 vs. 0.4–29.9 (22)                                                              |

AE: adverse event; CT: conventional diabetic therapy; DPP-4i: dipeptidyl peptidase-4 inhibitor; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide receptor agonist; OAD: oral antidiabetic drug; SU: sulfonylurea; TZD: thiazolidinedione.

| Table 7. Proportions of patients experiencing nausea among those using DPP-4is and GLP-1 RAs, combined with different oral antidiabetic drug therapies. |

| Combination therapy | Type of therapy and proportions of patients experiencing nausea, % (number of trial arms) |
|---------------------|------------------------------------------------------------------------------------------|
|                      | Monotherapy + Metformin + SU + TZD + Insulin ≥2 OADs                                      |
| Saxagliptin         | Not specified + 1.0 (1) + 0 (1) + 0.1 (1) + 0.9–5.9 (2)                                  |
| Sitagliptin         | 0–3.7 (5) + 0–10.0 (12) + 0–1.1 (2) + Not specified + Not specified                       |
| Vildagliptin        | 1.3–4.0 (6) + 0–6.5 (7) + 1.3–5.5 (2) + Not specified + Not specified                      |
| Linagliptin         | 0.7 (1) + 2.1–2.8 (2) + 0.4 (1) + Not specified + Not specified                           |
| Alogliptin          | – + Not specified + – + – + Not specified                                                |
| Exenatide daily/BID | 11.3 (1) + 18.8–48.5 (6) + 39.0–51.0 (2) + 48.3 (1) + 12.0–57.1 (10)                  |
| Exenatide weekly    | 0.6–1.2 mg + 24.0 (1) + 39.0–51.0 (2) + 48.3 (1) + 12.0–57.1 (10)                      |
| Liraglutide 0.6–1.2 mg | 4.5–29.0 (2) + 11.0–38.0 (5) + 10.5 (1) + Not specified + Not specified                   |
| Liraglutide 1.8 mg  | 31.0 (1) + 5.7–43.6 (6) + 3.7 (1) + 13.9–29.2 (3)                                        |
| Lixisenatide        | – + 21.2–35.4 (4) + 23.5 (1) + 39.6 (1) + 17.0–29.0 (2)                                  |
| Dulaglutide         | 11.5–19.7 (2) + 14.0–20.0 (3) + – + – + 9.6–10.7 (4)                                     |
| Albiglutide         | – + 10.3 (1) + – + – + –                                                             |

BID: twice daily; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1 RA: glucagon-like peptide receptor agonist; OAD: oral antidiabetic drug; SU: sulfonylurea; TZD: thiazolidinedione.
commonly observed in combination studies with TZDs. The cardiovascular impact of DPP-4i therapy has been robustly evaluated in two outcome trials (SAVOR-TIMI 53 and EXAMINE), both of which were primarily designed to demonstrate noninferiority with respect to cardiovascular events with DPP-4i therapy compared with usual care, evaluated in patients at high risk of cardiovascular events. In both SAVOR-TIMI 53 and EXAMINE trials, the cardiovascular safety of saxagliptin and alogliptin, respectively, was confirmed, while no excess cardiovascular morbidity/mortality was seen in SU-treated patients [62,63]. One important observation from SAVOR-TIMI 53 was an increase in hospitalization due to heart failure in saxagliptin-treated patients compared with placebo-treated patients (hazard ratio 1.27 [95% confidence interval 1.7–1.51], p = 0.007). However, a further analysis of this finding shows that the risk for increased hospitalization for saxagliptin-treated patients was greatest in individuals at a high overall risk of heart failure at baseline (i.e. prior heart failure, impaired renal function [estimated glomerular filtration rate <60 ml/min] or elevated baseline levels of N-terminal pro-brain natriuretic peptide [143], although it should be noted that brain natriuretic peptide is a substrate for DPP-4 and, thus, not a useful surrogate for assessing heart failure associated with DPP-4Is [144]. Similarly, a retrospective database study has found that sitagliptin was not associated with an increased risk of all-cause hospital admission or death, but that hospitalization for heart failure was more common in sitagliptin-treated patients with preexisting heart failure [145]. The effect of vildagliptin has been assessed in patients with established heart failure in the Vildagliptin in Ventricular Dysfunction Diabetes study [146]. While there was no difference in left ventricular function between the vildagliptin and placebo groups after 52 weeks, an excess in cardiovascular mortality was noted in the vildagliptin cohort, which was clustered in the New York Heart Association class III/IV subgroup of patients. This observation appears to be at variance with other cardiovascular safety data and may be accounted for by an imbalance in cardiovascular risk factors in this subgroup of patients at randomization, with an excess of cardiovascular risk factors in the vildagliptin-exposed cohort.

DPP-4is and musculoskeletal disorders
Musculoskeletal disorders were reported as the main AE in approximately 2% (n = 2) of DPP-4i trial arms.

Back pain was reported in both of these trial arms; vildagliptin 16.2% vs. placebo 4.8%; alogliptin 5.1% vs. pioglitazone 3.1%.

DPP-4is and skin-related AEs
Skin-related AEs were considered in the context of hypersensitivity reactions to DPP-4is. The proportion of patients experiencing skin and subcutaneous disorders as an AE across the different DPP-4i trial arms either with DPP-4i monotherapy or with DPP-4i in combination with other OADs was 31%. Skin and subcutaneous reactions were very common occurrences with saxagliptin (17 of 23 trial arms) and alogliptin (3 of 4 trial arms) but much less frequent with sitagliptin (4 of 29 trial arms), vildagliptin (5 of 39 trial arms) or linagliptin (3 of 9 trial arms). Within trial arms, the proportions of patients experiencing skin and subcutaneous AEs for all of the DPP-4is were low to moderate and were similar or slightly higher to those observed for placebo or comparator therapy (saxagliptin 0.5–11.3%; sitagliptin 1.5–9.8%; vildagliptin 0.3–4.9%; linagliptin 5.6–15%; alogliptin 1.2–8.2%; placebo 2.5–10.9%; metformin 2.7–4.9%; TZD 0.5–8.0%; SU 0.5–8.0%). Among those trials where the skin disorder was specified, one included a case of rash (3.6% vs. placebo 1.1%) and pruritus (1.3% vs. placebo 0%) with saxagliptin treatment [89] and another included rash (1.2% vs. 0.5%) and pruritus (1.2% vs. 0.8%) using alogliptin (25 mg) in combination with metformin and pioglitazone vs. metformin and pioglitazone. Two patients in the alogliptin in combination with metformin and pioglitazone arm discontinued the study due to these skin AEs, but both of these were reported to have been resolved [49].

DPP-4is and lymphocyte-related AEs
Lymphocyte disorders were considered in the context of immune system imbalances due to the use of DPP-4is. Lymphocyte disorders were uncommon across all DPP-4i studies (reported in only 4% of all DPP-4i trial arms). A small, numerical decrease in lymphocyte counts was observed during a study of saxagliptin in combination with metformin, but mean lymphocyte counts in all groups remained within normal limits [90]. Lymphopenia (reduced lymphocyte number) was also reported in three different saxagliptin DPP-4i trial arms but the proportions of patients experiencing lymphopenia within trial arms were very low, reported as ≤1.4% for saxagliptin monotherapy [91], 0.5% for saxagliptin in combination with metformin [92] and 0.3% for saxagliptin in combination with insulin or insulin and metformin. In the latter case, the lymphopenia was very mild and resolved without alterations to saxagliptin treatment dosing [93].

DPP-4is and pancreatitis
There were few investigator-reported cases of pancreatitis in the DPP-4i studies evaluated. One occurred in a patient receiving saxagliptin (5 mg) as add-on to TZD, which resolved with treatment in 18 days [45], and another one occurred in a patient receiving linagliptin (5 mg) as an add-on to metformin [97]. Given the increased risk of pancreatitis in patients with TZD [147], this number is somewhat lower than expected. In another study, pancreatitis was not reported in the saxagliptin treatment group, but two cases were observed in the glipizide comparator group [92]. There were no reports of pancreatic cancer in any of the trials analyzed. In the long-term (median follow-up 2.1 years) SAVOR-TIMI 53 trial, adjudicated acute pancreatitis occurred infrequently and in similar proportions of saxagliptin- and placebo-treated patients (0.3% vs. 0.2%). In the long-term EXAMINE trial (median follow-up 18 months), investigator-reported pancreatitis occurred in 0.4% vs. 0.3% of patients in alogliptin- vs. placebo-treated patients, respectively [62,63].

DPP-4is and thyroid tumors
There were no reported instances of C-cell tumors, and in a study where changes in serum calcitonin concentrations were specifically monitored, changes were similar across all groups
GLP-1 RA studies: data from randomized controlled trials

A total of 47 GLP-1 RA mono- and combination therapy studies (72 trial arms) were analyzed. In 86 of these trial arms, GI-related AEs were reported as the most common. Additionally, in approximately one-quarter of all GLP-1 RA trial arms, GI symptoms accounted for the three most frequently occurring AEs. Infections and infestations were reported as the most common AE in 10% of trial arms. Discontinuations of the nervous system were reported in around 27% of trial arms, but were generally reported as the third most common AE. In two trial arms using exenatide once-weekly, skin and subcutaneous disorders were reported as the most common disorder due to injection-site reactions [24,137], although, in general, these nodules are transient, lasting around 4–8 weeks [148]. In one GLP-1 RA study investigating liraglutide in combination with metformin and rosiglitazone, peripheral edema was reported; however, the rate of edema reported was lower than that for placebo [23]. Musculoskeletal and connective tissue disorders were rarely reported for GLP-1 RAs, only occurring as one of the three most frequently reported AEs in a single study [138]. Discontinuations with GLP-1 RAs were low, typically <10%, and, on average, around 6.0% of patients withdrew from GLP-1 RA trials. Discontinuations were often related to GI-related AEs and occurred within the first few weeks of treatment. The highest rate of patient discontinuation due to AEs occurred in a study of liraglutide in combination with metformin and TZD. In this study, 15% of patients receiving liraglutide withdrew compared with 3% in the placebo arm (in combination with metformin and TZD) [23]. A similar proportion (13.4%) of discontinuations was reported in an exenatide trial arm [17]. Rates of withdrawal were slightly lower in other exenatide studies, ranging from 7.1% to 9.6% if combined with metformin [124,125] and around 8–9% if combined with SU [15,126,127] or basal insulin [128].

GLP-1 RAs and hypoglycemia

Minor hypoglycemia was reported as an AE at least once in all GLP-1 RA trial arms. However, actual proportions of patients experiencing minor hypoglycemia within trial arms remained low to moderate, ranging from 1.0% to 42.9%. Proportions were lowest with GLP-1 RA monotherapy (8.2–12.3%) or GLP-1 RA in combination with metformin (1.0–28%) and increased with the addition of an SU (14.0–36%) (Table 4). When a GLP-1 RA was used in conjunction with ≥1 OADs or insulin, the proportion of patients experiencing minor hypoglycemia ranged from 3.0% to 42.9%, with the highest rate of 42.9% being observed in a study of lixisenatide combined with an SU and insulin [28]. The proportions of patients experiencing minor hypoglycemia with dulaglutide and liraglutide (all doses) were largely comparable for monotherapy (8.2–12.3%). With metformin combination therapy, rates of minor hypoglycemia across the GLP-1 RAs ranged from 1% to 28%. When combined with an SU, exenatide (10 µg twice daily) was associated with more minor hypoglycemia (proportions of 30% and 36% were reported in two trial arms vs. proportions of 14.7–25.2% of patients for all other SU trial arms) [129,130]. The overall proportion of patients experiencing minor hypoglycemia with GLP-1 RA therapy was 10.9%. Major hypoglycemia was reported with GLP-1 RAs less often than minor hypoglycemia (Table 4). The overall proportion of patients experiencing major hypoglycemia with GLP-1 RA therapy was 0.2%. Only three studies reported proportions of >1%, which occurred in combination regimens where patients also received SU or TZD [12,15,22].

GLP-1 RAs and GLI-related AEs

Nausea was the most common GI AE in GLP-1 RA studies, reported in 85% of trial arms. Actual proportions of patients experiencing nausea were similar among different trial arms, including either GLP-1 RA monotherapy (5–31%), or GLP-1 RA in combination with metformin (6–49%), SU (39–51%) or two or more OADs (10–57%) (Table 6). When different GLP-1 RA therapies were compared, the proportion of patients experiencing nausea only increased to above 50% where exenatide was administered twice daily (Table 7). In all GLP-1 RA studies, GI symptoms were transient, generally subsiding within 4 weeks with liraglutide and 8 weeks with exenatide [55]; furthermore, there is no established relationship between nausea levels and the degree of retarded gastric emptying resulting from GLP-1 therapy [149].

GLP-1 RAs and skin and lymphocyte-related AEs

Skin and subcutaneous disorders were reported as an AE in 10 of 71 (13.2%) GLP-1 RA trial arms. Of these 10 trial arms, 8 were associated with liraglutide one with exenatide twice daily and one with lixisenatide. Actual proportions of patients within trial arms who experienced these AEs were generally low (liraglutide 3.4–13%; exenatide 6.9%; lixisenatide 0.9% [discontinuation]). In the majority of trials, the nature of the skin disorder was not specified but the proportions of patients experiencing them were similar in OAD comparator therapies such as glimepiride (8%) and glibenclamide (11.4%). Injection-site nodules were more common with exenatide once weekly [14,24,69] and albiglutide [30,31,33] compared with placebo. With regard to lymphocyte disorders, in one trial arm using exenatide once weekly, a serious AE of B-cell lymphoma was reported in one patient; however, the patient did not discontinue the trial [13].

GLP-1 RAs and pancreatitis

A small number of cases of nonadjudicated pancreatitis were reported in the GLP-1 RA-treated trial arms analyzed. In the liraglutide trial arms, one patient withdrew due to acute pancreatitis in the 1.2 mg arm of the LEAD-2 trial [20] and a case of chronic pancreatitis was reported in the 0.6 mg liraglutide arm of the 26-week-long LEAD-1 trial [19]. In another trial, pancreatitis was reported for two patients using liraglutide, one during the 12-week run-in period (acute case) and another during the randomization period (chronic case) [139]. A mild case of acute pancreatitis, considered unrelated to treatment, was recorded for liraglutide therapy in a head-to-head trial with exenatide twice daily [17]. During a trial comparing liraglutide monotherapy with SU treatment, acute and chronic pancreatitis...
(unrelated to therapy) were also noted at autopsy [140]. Acute pancreatitis was reported in two studies using exenatide once weekly, one in a head-to-head trial with liraglutide and another in a trial comparing exenatide once weekly with insulin [13,24]. In a trial comparing exenatide daily with glimepiride, both groups reported one case of pancreatitis (type not stated) [131]. Although pancreatitis was not reported in any of the lixisenatide studies that met the inclusion criteria for this systematic review, the EMA report on lixisenatide notes that, throughout the clinical development program of this drug, more patients receiving lixisenatide (9 [0.3%]) experienced pancreatitis-specific AEs than those receiving placebo (2 [0.1%]) [150]. Cases of adjudicated pancreatitis were also reported. In a dulaglutide trial, one patient with transient elevations in pancreatic enzymes throughout the study from baseline experienced adjudicated chronic pancreatitis around 7 months after study duration [39]. Adjudicated pancreatitis was confirmed as probable in three patients treated with albiglutide [30,31] and as definite or probable in one patient treated with albiglutide and two patients with liraglutide [32]. There were no reports of pancreatic cancer in any of the trials analyzed.

In several studies using GLP-1 RAs, concentrations of pancreatic lipase were routinely measured. In some of these, lipase levels varied across trial arms, but these variations were not predictive of GI symptoms or pancreatitis [24,139]. In other trials, no clinically significant changes in amylase or lipase levels were reported [69,137].

It has been suggested that increased pancreatic lipase levels may be indicative of pancreatitis; however, levels are also commonly raised in patients with T2D [151]. In one trial using lixisenatide, a small number of patients (lixisenatide: n = 2; 0.6% and placebo: n = 2; 1.2%) was reported to have increased lipase levels; however, no confirmed diagnoses of pancreatitis were reported in either treatment group [27]. In another lixisenatide trial, a protocol prespecified increase in pancreatic enzymes (amylase and/or lipase) was reported in 2.5% of both lixisenatide arms and in 3.1% of the placebo trial arm [26]. In a trial using exenatide once weekly, a few patients had either amylase or lipase concentrations raised to more than three times the upper limit of normal (3× ULN) at both baseline (exenatide: n = 2, 1.2%; insulin glargine: n = 3, 2.2%) and at end point (exenatide: n = 5, 3.1%; no insulin glargine). However, changes were generally asymptomatic, with the exception of one patient taking exenatide who was diagnosed with edematous pancreatitis; the patient was not hospitalized and abdominal pain resolved a day after onset [13,14]. In a trial comparing dulaglutide and liraglutide, significantly higher lipase concentrations were reported at end point in patients receiving liraglutide; however, the proportion of patients with lipase levels 3× ULN was low and did not differ between treatment groups (dulaglutide 4% and liraglutide 3%) [36].

GLP-1 RAs and thyroid tumors

There was one report of medullary thyroid cancer in all of the GLP-1 RA trial arms evaluated [30]. A slight increase in calcitonin was seen in <1% of patients in one other trial [26]. In a study comparing liraglutide monotherapy with SU treatment, where serum calcitonin concentrations were specifically measured, these did not increase over 2 years and the mean values remained in the lower end of the normal range [140].

GLP-1 RAs and vascular disorders

Peripheral edema was not reported for GLP-1 RA therapy, even when used in combination with TZDs [12,23,132].

Immunogenicity with GLP-1 RAs

In humans, both twice-daily and once-weekly formulations of exenatide have been linked to the formation of high titer anti-exenatide antibodies that have the potential to reduce efficacy in a small number of patients (exenatide twice daily: 1–4% [1]; exenatide once weekly: 6% [2]). The proportion of patients experiencing high titer antibody formation with lixisenatide treatment was similarly low (5.2%) [5]. In patients treated with albiglutide and dulaglutide, the proportions developing anti-drug antibodies were similarly low (5.5% and 1.6%, respectively). Treatment with liraglutide also resulted in infrequently observed treatment-emergent antibodies in a small proportion (<10%) of patients [152].

Evaluation of data from postmarketing clinical trials with results

Only one postmarketing clinical trial (phase IV) meeting the inclusion criteria was identified. This study investigated the effect of adding exenatide to sitagliptin and metformin in comparison with switching from sitagliptin to exenatide. The results of this trial were in agreement with those of premarketing studies [70,153] (Supplementary Appendix IV).

Discussion

This systematic review has focused on safety data from large, long-duration, randomized studies of incretin-based therapies. For DPP-4is, infections and infestations were the most frequently reported AEs and for GLP-1 RA studies, GI symptoms were the most common AEs, and this highlights a key difference in the AE profile between the two therapy classes.

Since DPP-4 also plays a key role in regulating the immune system, it has been suggested that the apparent increase in risk for infections in patients receiving DPP-4is could be due to an immune system imbalance. Preclinical studies indicate that after an immune challenge DPP-4-deficient (DPP-4-/-) mice have fewer T-cells and natural killer cells, lowered interleukin (IL)-4, and increased IL-10 and interferon-γ levels compared to control mice [154]. However, another study showed that DPP-4-/- mice had normal levels of T-cells and that T-cell proliferation, immune responses and IL-2 production were unaffected [155]. In cancer biology, DPP-4 may also play a pivotal role as a tumor suppressor. Loss of DPP-4 in human ovarian and prostate cancer cells led to reduced apoptosis, prolonged survival and more metastatic events [156]. However, published clinical trials using saxagliptin have been unable to demonstrate clinically relevant adverse reactions related to immunological parameters to corroborate these findings [9].
The orally administered DPP-4is result in a modest (approximately 2-fold) increase in native GLP-1 levels. On the other hand, the subcutaneously injected GLP-1 RAs result in plasma concentrations 6- to 10-fold greater than native GLP-1, which could explain the observed differences in GI side effect profiles [157]. It has been proposed that gastric discomfort is mediated via GLP-1 neural pathways and that this may be, in part, responsible for the reduction in food intake and increased satiety in patients receiving GLP-1 RA treatment [158]. In studies where GLP-1 RAs were compared head to head, nausea rates were broadly similar [17,42] and, in other studies, were found to be clearly dose dependent [159]. However, across all studies analyzed, the highest rates of nausea were generally found to be associated with exenatide 10 µg twice daily, in agreement with a meta-analysis and a mixed treatment comparison study [160]. The mechanism underlying the transient nature of GLP-1 RA-related GI symptoms is not clearly understood.

Hypoglycemia was consistently low across incretin mono- and combination therapy, which is in agreement with what is known about the glucose-dependent mechanism of action of these drugs [161]. Interestingly, low hypoglycemia rates are maintained when either GLP-1 RAs or DPP-4is are used in combination with metformin, allowing them to be used safely in a wide range of treatment regimens; caution should still be observed when SU use is continued alongside GLP-1 RA therapy.

The occurrence of peripheral edema appears to be a treatment-related AE, which occurred with DPP-4is but not with GLP-1 RA agents. In the case of TZD-related edema, reduced free water clearance, increased sodium reabsorption, endothelial permeability and expanded plasma volume have all been proposed. For DPP-4is, it has been hypothesized that their inhibition of the degradation of vasoactive peptides such as substance P and bradykinin may be responsible. Substance P and bradykinin are normally degraded by angiotensin-converting enzyme (ACE) and diminished degradation of these peptides is proposed to contribute to ACE inhibitor-associated angioedema [162].

Patients with T2D are generally at high risk of cardiovascular disease (CVD) [163]. Of the currently available OAD therapies, only metformin has been shown to reduce cardiovascular morbidity and mortality [164–166]. Long-term studies on the effect of insulin and SUs on cardiovascular outcomes are generally inconclusive, with some studies suggesting a decrease [167], and others an increase, in macrovascular complications [168]. Glitazones have also been associated with both favorable and unfavorable cardiovascular outcomes [169,170].

Clinical trials of exenatide and liraglutide have demonstrated positive effects on key cardiovascular risk factors such as weight, systolic blood pressure, lipid profiles and surrogate markers of CVD [67,171,172]. A meta-analysis of the cardiovascular safety profile of GLP-1 RAs has also shown no increase in adverse effects on cardiovascular outcomes [173]. Regarding DPP-4i therapies, emerging data also suggest an improvement in cardiovascular risk factors for patients using these therapies, [174] although caution should be exercised in patients already at high risk of heart failure [145].

Patients with T2D have approximately a 3-fold increase in the risk of developing pancreatitis compared with the general population [175]. The overall occurrences of pancreatitis in the studies that the authors considered in this systematic review were low and contrasted with the claims made by Elashoff and Butler [57,58] that exenatide and sitagliptin are associated with an increased risk of pancreatitis compared with other antidiabetic medicines. These claims were made following analysis of data from the FDA AEs reporting system, which has several limitations, including the addition of incomplete data, over-reporting and reporting bias. A study by Raschi et al. [176] also evaluated the association of pancreatitis with incretin-based therapies using the FDA AEs reporting system and demonstrated that reporting trends were often heavily influenced by FDA regulatory activity, that is, the publication of a new indication or safety alert. These reporting peaks may, therefore, contribute to the overestimation of AEs for certain drugs, indicating the need to be cautious when interpreting AE databases. Regarding acute pancreatitis, several large claims database studies, including over one million patients, have found no association between this disorder and exenatide or sitagliptin use [177–179].

A preclinical study has reported the incidence of chronic pancreatitis in mice genetically predisposed to developing pancreatic neoplasia following 12 weeks of exenatide treatment [180], and another has reported that chronic pancreatitis in rats is associated with increased expression of the GLP-1 receptor on acinar cells, ductal cells and activated pancreatic stellar cells [181]. In a cohort of T2D patients (n = 1269) previously hospitalized for pancreatitis, sitagliptin and exenatide were found to be associated with an increased risk of acute pancreatitis, regardless of the period of time that had elapsed between taking the therapy and the diagnosis of pancreatitis [59].

Regarding pancreatic cancer, 2 years of liraglutide treatment in mice, rats and monkeys and 2 years of vildagliptin exposure in rats did not lead to an increased risk of pancreatic neoplasia [182]; pancreatic intraepithelial neoplasia was increased after 12 weeks of exenatide treatment in mice [180]; however, the limitations of the study, which used a mouse model of pancreatic neoplasia, should be considered when interpreting the data [180]. An increase in total pancreatic mass was also reported after 6 weeks in liraglutide-treated mice; however, a decrease in both α- and β-cell mass was also observed [183]. In humans, augmented cell proliferation and dysplasia, leading to up to a 40% increase in pancreatic mass, was observed in seven human pancreata isolated from organ donors, six of whom were treated with sitagliptin and one with exenatide [58]. However, the duration of incretin therapy was not specified, few histological sections of pancreata per patient were analyzed and controls were not adequately matched for age, diabetes status, body mass index or concomitant medications.

From both the preclinical and clinical data available, it appears difficult to find a common link between the different cases of pancreatic neoplasia described. A recent commentary has concluded that results from the study on human tissues do not provide a mechanism of action for
GLP-1 RAs and pancreatitis risk that can be substantiated by evidence from animal studies [184]. A large cohort study on around 70,000 patients has also shown no increased risk of pancreatitis with incretin therapies compared with SU therapy [185]. Furthermore, meta-analyses of randomized controlled trials involving GLP-1 RAs [186,187] do not confirm the increased risk of pancreatic hyperplasia or acute pancreatitis; Butler and Singh, respectively [57,58]. An assessment by the FDA and EMA has, however, been published in response to the published literature, stating that a causal association between incretin-based drugs and pancreatitis or pancreatic cancer is inconsistent with the current data. However, it is also included that ‘pancreatitis will continue to be considered a risk associated with these drugs until more data are available’ [64].

Following the identification of a link between GLP-1 receptor expression levels and C-cell carcinoma in rats, C-cell proliferation and the incidence of medullary thyroid carcinoma have been of particular interest in patients receiving chronic GLP-1 RA treatment. However, while rats and mice have large numbers of C-cells that are very sensitive to GLP-1, humans have far fewer C-cells [65]. In our analysis, there were no specific reports of C-cell tumors or elevated levels of plasma calcitonin, a specific biomarker for both C-cell activation and increased C-cell number. This observation is in line with studies in primates that indicate GLP-1R activation does not result in C-cell activation or proliferation [65]. In addition, of the 5000 patients treated with liraglutide in clinical trials, none developed C-cell cancer and all studies, including long-term 2-year data, showed no increase in calcitonin levels compared to any active comparators [188]. However, long-term consequences of GLP-1 signaling on GLP-1 receptor-expressing cells in the human thyroid gland remain unknown, and further investigation in this area is warranted.

There are several limitations to this study. Firstly, the authors have only summarized the available safety data from large, long-duration studies with incretin therapies. Therefore, the authors have not been able to report data on less frequently occurring AEs that may be specific to a particular drug class or type. To compensate for this, the authors took note of AEs that were of particular interest to the authors, and this approach is clearly open to some degree of bias. Secondly, the number of studies identified for each agent differed greatly and, consequently, more data were available for certain agents. This may have contributed to an under- or over-reporting of certain AEs. Thirdly, data have been extracted from controlled trial populations, so data are not fully generalizable to the population as a whole since they do not necessarily include the highest risk individuals, with the exception of the data from the two long-term cardiovascular outcome trials [62,63].

Finally, many of the studies considered in this review reported AE data as MedDRA terms only. Data for specific events, such as nausea and vomiting, were not always available and were reported under the MedDRA term ‘gastrointestinal disorder’ instead. The authors, therefore, continued with this approach when extracting data and, consequently, it has not been possible to report the incidences of specific AEs (such as nausea and vomiting) across all studies.

Conclusions

This analysis has demonstrated that, overall, incretin-based therapies are well tolerated but are associated with some AEs, which will be important when considering individualized therapy in patients with T2D. Minor hypoglycemia rates were found to be consistently low. GI symptoms are a frequently occurring AE common to both GLP-1 RA and DPP-4i treatment; however, their mild and transient nature ensures that the risk-to-benefit profile of these therapies is generally favorable. Fortunately, the increasingly widespread use of these therapies is generating a large body of data; it is important that these data are reviewed periodically to update information about safety concerns and enable physicians to make informed treatment decisions.

Expert commentary

In this systematic review, we have summarized the AE profiles of the incretin-based therapies. The body of evidence to date suggests that both DPP-4is and GLP-1 RAs have a favorable benefit-to-risk ratio for treatment of T2D, with effective glucose control and absence of weight gain being achievable in conjunction with low rates of hypoglycemia and no apparent increase in CVD risk or other serious drug-related AEs such as pancreatitis, pancreatic cancer or thyroid cancer. The most commonly reported side effects for DPP-4is and GLP-1 RAs are minor infections/infestations and GI-related disorders, respectively.

Incretin therapy was first included in clinical T2D treatment algorithms in 2009, with the recommendation that exenatide be used for more complex or advanced stages of disease progression only, due to a warning that insufficient safety information was available at that time [189]. Over the last 5 years, the safety data that have accumulated on the range of currently approved DPP-4is and GLP-1 RAs have supported important shifts in clinical recommendations for incretin therapies in T2D treatment algorithms. Incretin therapies, with their consistently effective glucose-lowering capability and propensity for weight loss, are now recommended for use in all stages of the treatment pathway, including as an add-on to metformin [190,191]. This new paradigm could potentially have a large impact on diabetes management, with clinicians being able to provide patients with a safe and effective therapy early in the disease pathway, thereby reducing the likelihood of complications associated with advancing T2D without the risks of hypoglycemia or weight gain, which are undesirable for the patient and clinician alike.

However, early treatment with incretin therapies will also result in long-term exposure of patients to these drugs. Therefore, despite currently available safety information, in-depth and long-term safety assessments of incretin therapies such as this one continue to be critical for the continued use of these drugs for T2D, and may be particularly
important in the future for patients with CVD or other debilitating conditions such as hepatic or renal insufficiency.

**Five-year view**

In 5 years from now, around 14 years will have elapsed since the approval of exenatide in 2005, and at least 10 years since the approval of sitagliptin, saxagliptin and lixisenatide, allowing at least a decade’s worth of safety data to be assembled for a clear and balanced picture of these key therapies. In addition, new incretin therapies developed between 2010 and 2014 will have accumulated at least 5 years of safety data. A number of ongoing and planned safety trials will also have been completed, providing important data on long-term use. These trials include TECOS (sitagliptin, n = 14,000, completion in 2015), CAROLINA (linagliptin, n = 6000, completion in 2018), CARMELINA (linagliptin, n = 8300, completion in 2018), LEADER (lixisenatide, n = 9341, completion in 2016), ELIXA (lixisenatide, n = 6000, completion in 2015), EXSCEL (exenatide extended release, n = 9500, completion in 2017) and REWIND (dulaglutide, n = 9622, completion in 2019). Apart from building the individual safety profile of each individual drug, the information from these trials will assist in providing a reliable overall assessment of the effects of long-term incretin-based therapies in patients who suffer from T2D.

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**Key issues**

- Since 2005, several different incretin-based therapies have been approved by the US FDA and the European Medicines Agency (EMA).
- As with all newly approved drugs, the benefits of incretin-based therapies for patients must be balanced against the risk of any associated adverse events (AEs); thus, it is important to periodically assess their safety profile.
- The action of both dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is glucose dependent and, thus, these therapies carry a lower risk of hypoglycemia compared to insulin and traditional oral antidiabetic drugs.
- The use of DPP-4is and GLP-1 RAs is linked to other AEs. These principally include infections and infestations for DPP-4is and transient gastrointestinal AEs for GLP-1 RAs.
- More serious AEs such as pancreatitis and pancreatic cancer have also been suggested to be associated with incretin-based therapies; however, in response, an assessment from the FDA/EMA has concluded that such a causal association is inconsistent with currently available data.
- A large proportion of patients with type 2 diabetes (T2D) are at high risk of cardiovascular disease, and some previous therapies have been withdrawn due to their elevated cardiovascular event risk profile. The long-term cardiovascular safety of incretin-based therapies must, therefore, be assessed. To date, two long-term studies on the use of DPP-4is have provided evidence that these therapies are not associated with an increased risk of cardiovascular events, and for other DPP-4is and GLP-1 RAs, long-term cardiovascular risk studies are ongoing.
- Since the approval of the first incretin-based therapy in 2005, a large number of clinical trials have provided a consistently favorable safety profile for both GLP-1 RAs and DPP-4is. Further long-term trials will continue to assess the safety of incretin therapies, which is of great importance due to the chronic nature of T2D and the associated long-term requirements of patients with this disease.

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