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META-ANALYSIS

Risk of pancreatic adverse events associated with the use of glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitor drugs: A systematic review and meta-analysis of randomized trials

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Data sharing statement: All available data has been presented in the manuscript.

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Abstract

AIM: To systematically assess risk of pancreatic adverse events with glucagon-like peptide-1 (GLP-1) receptor agonist and dipeptidyl peptidase-4 (DPP-4) inhibitor drugs.

METHODS: We searched PubMed, Embase, CINAHL, Cochrane review of clinical trials, pharmaceutical company clinical trials register, United States Food and Drug Administration website, European Medicines Agency website and ClinicalTrials.gov for randomized controlled trials from inception to October 2013. Randomized control trial studies were selected for inclusion if they reported on pancreatic complication events and/or changes in pancreatic enzyme levels (serum amylase and serum lipase) as adverse events or as serious adverse events for patients who were on GLP-1 receptor agonist and DPP-4 inhibitor drugs. Two independent reviewers extracted data directly. We performed Peto odds ratio (OR) fixed effect meta-analysis of pancreatic adverse events a, and assessed heterogeneity with the I^2 statistic.

RESULTS: Sixty-eight randomized controlled trials were eligible. A total of 60720 patients were included in our analysis of the association of risk of pancreatic complication events with GLP-1 agents. A total of 89 pancreatic related adverse events occurred among the GLP-1 agents compared to 74 events among the controls. There was a statistically significant increased risk of elevation of pancreatic enzymes associated with GLP-1 agents compared with control (Peto OR = 3.15, 95%CI: 1.56-6.39, P = 0.001, I^2 = 0%). There was no statistically significant difference in the risk of pancreatic adverse event associated with GLP-1 agent compared with controls (Peto OR = 1.00, 95%CI: 0.73-1.37, P = 1.00, I^2 = 0%). There were a total of 71 pancreatitis events in patients on GLP-1 agents and 56 pancreatitis events occurred in the control patients. There were 36 reports of pancreatic cancer in these studies. Of these cases, 2 used linagliptin, 2 used alogliptin, 1 used vildagliptin, 7 used saxagliptin while 6 used sitagliptin. The remaining 18 cases occurred among controls.

CONCLUSION: Although GLP-1 based agents are associated with pancreatic enzyme elevation, we were unable to confirm a significant risk of pancreatitis or pancreatic cancer.

Key words: Diabetes mellitus; Pancreatitis; Glucagon-like peptide-1 agonists; Dipeptidyl peptidase-4 inhibitors; Meta-analysis

Core tip: There is conflicting data on the risk of pancreatitis with glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. We performed a meta-analysis of 68 randomized controlled trials of 11 different GLP-1 or DPP-4 targeted drugs. The incidence of pancreatic adverse events in the trials was generally low and we did not find any definitive evidence for pancreatitis or pancreatic cancer amongst the trials. However, we found a significantly raised risk of elevated pancreatic enzymes in a small number of trials that reported such enzyme elevations.

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a naturally occurring gut hormone that is mainly secreted by the intestinal L cell. It is a potent antihyperglycemic hormone, inducing glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. Once in the circulation, GLP-1 has a half-life of less than 2 min, due to the rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). The GLP-1 based therapies include GLP-1 receptor agonists and DPP-4 inhibitors. As GLP-1 is a gut hormone, it is possible that patients may experience adverse effects on the gastrointestinal system such as nausea or abdominal pain.

There are already several GLP-1 receptor agonists and DPP-4 inhibitor drugs approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), and we are aware of additional agents in development. However, sitagliptin and exenatide have been shown to cause acute pancreatitis in rodent models *via* amplification of ductal replication and induction of acinar to ductal metaplasia[1-4]. A recent case-control study showed a significant increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type-2 diabetes mellitus[5]. A meta-analysis of clinical trials reported no difference for sitagliptin use compared with placebo or other oral hypoglycemic in the incidence rates of pancreatitis[6]. Although complications involving the pancreas (acute pancreatitis, chronic pancreatitis and pancreatic cancer) are potentially serious adverse effects of GLP-1 receptor agonist drugs, there is a paucity of data available to clinicians regarding these effects of GLP-1 receptor agonist drugs. A recent meta-analysis[7] suggested that neither exenatide nor liraglutide increases the risk for acute pancreatitis when used in the treatment of type-2 diabetes mellitus. This analysis, however, was based on small studies, non-clinical evaluation of pancreatitis in the included RCTs and residual confounding in the observational studies that were included. None of the previous studies have adequately evaluated the role of pancreatic enzyme elevations. These studies have not evaluated the occurrence of reports of pancreatic cancer in these trials. Finally, the risk of pancreatic complication associated with individual therapies has not been evaluated.

Our objective was to conduct a systematic review to ascertain the risk of pancreatic complications (acute and chronic pancreatitis and pancreatic cancer) and pancreatic enzyme elevations associated with GLP-1 based therapies, as compared to placebo or other oral hypoglycemic drugs in randomized controlled trials of GLP-1 based therapies.

MATERIALS AND METHODS

Methods

We defined study aims and procedures in the study protocol registered with PROSPERO register of systematic reviews[8].

Data sources and searches

We searched MEDLINE, EMBASE, CINAHL and the Cochrane database from inception to October 2013 using the search terms: (drug name OR chemical com-

pound OR drug class) AND ["Pancreatic Neoplasms" (Mesh) OR "Pancreatitis"(Mesh) OR "pancreas"(tiab) OR "pancreatitis"(tiab) OR "pancreatic"(tiab) OR "pancreatic cancer"(tiab) OR "serum amylase"(tiab) OR "serum lipase"(tiab) OR "Islet Cell Adenoma" (tiab) OR "Insulinoma"(tiab) OR "Islet Cell Carcinoma" (tiab) OR "Gastrinoma"(tiab) OR "Glucagonoma"(tiab) OR "Somatostatinoma"(tiab) OR "Vipoma"(tiab) OR "Pancreatic Ductal Carcinoma"(tiab) OR "Islet Cell Adenomas"(tiab) OR "Insulinomas"(tiab) OR "Islet Cell Carcinomas"(tiab) OR "Gastrinomas"(tiab) OR "Glucagonomas"(tiab) OR "Somatostatinomas"(tiab) OR "Vipomas"(tiab) OR "Pancreatic Ductal Carcinomas" (tiab)] AND English(lang) NOT ["Animals"(Mesh)] NOT ["Animals"(Mesh) AND "Humans"(Mesh)].

We did not specify any language or population restrictions. To identify any unpublished studies, we keyed in the names of specific drug compounds into the search boxes of all GLP-1 agent pharmaceutical companies, three of which had publicly available clinical trials, these were Boehringer Ingelheim clinical trials register, Novartis clinical trials register and Takeda Pharmaceuticals register. We also searched the FDA, the EMA and ClinicalTrials.gov up to August 2013. Bibliographies of included studies and recent review articles were checked for additional relevant studies.

Study selection

We selected randomized controlled trials that enrolled participants using GLP-1 agonist and DPP-4 inhibitor drugs and reported on the risk of pancreatic complications either as adverse events or as serious adverse events. We included studies that reported on the use of FDA approved GLP-1 receptor agonists such as Exenatide (Byetta, Bydureon), Liraglutide (Victoza) and Albiglutide (Tanzeum). Other GLP-1 receptor agonists that were studied but have not yet been approved by FDA included Taspoglutide, Lixisenatide (Lyxumia), Dulaglutide and Semaglutide were included. Studies that also used FDA approved DPP-4 inhibitors such as Vidagliptin (Eucreas, Galvus, Icandra, Jalra, Xiliarx, Zomarist), Sitagliptin (Efficib, Januvia, Janumet, Ristaben, Ristfor, Tesavel, Velmetia, Xelevia), Saxagliptin (Komboglyze, Onglyza), Linagliptin (Jentadueto, Trajenta) and Alogliptin (Nesina) were included. Other DPP-4 inhibitors in development were included in our search. These include Septagliptin, Anagliptin, Biseglitpin, Carmegliptin, Denagliptin, Dutogliptin, Gosogliptin, Isoleucine Thiazolidide, Valine pyrrolidide, Evogliptin, Gemigliptin, Melogliptin, Omarigliptin, Tenegliptin and Trelagliptin. We did not restrict studies by healthcare settings, methods of diagnosing pancreatitis or by indication for the drug.

Data extraction and quality assessment

Two reviewers (HMS and TA) evaluated all titles and abstracts for studies that met the inclusion criteria, and excluded any articles that clearly did not meet the selection criteria. Full reports of potentially relevant studies were retrieved and independently checked for eligibility. Data from the included studies were then extracted independently by two reviewers (HMS and TA) who collected information on study design, study location, study population description, drug exposure, pancreatic complication (acute pancreatitis, chronic pancreatitis, pancreatic cancer) events, pancreatic enzyme derangement (elevated serum pancreatic amylase and/or pancreatic serum lipase) data, mortality from pancreatic events, how the pancreatic events were defined and monitored, confounders for pancreatic events and characteristics of participants onto a pre-formatted spreadsheet. Another reviewer (YKL or SS) then checked the data. Any uncertainties or discrepancies were resolved through rechecking against the source papers, and through discussion with a third reviewer.

We used a pre-specified spreadsheet to record the location and duration of the randomized controlled trials (in years), dose and frequency of GLP-1 agonist drug and DPP-4 inhibitor drug and placebo or alternative hypoglycemic agent, mean age and sex of participants, number of pancreatic complication events and confounders.

The Cochrane toolkit was used for the assessment of bias in evaluating each trial for the reporting of randomization, allocation concealment, the use of blinding of participants and staff, and information on loss to follow-up or withdrawal rates[9]. In accordance with the Cochrane handbook of systematic reviews, we assessed the quality of data on adverse events by recording how they were monitored and recorded by the investigators[10]. We aimed to generate funnel plots to assess the possibility of publication bias, provided that there were > 10 studies available in the meta-analysis, with no evidence of substantial statistical heterogeneity[11].

Statistical analysis

We used RevMan[12] 5.3 to conduct meta-analysis based on the summary statistic of Peto Odds Ratios, which is the recommended approach for rare events[9]. We assumed similarity between the risk ratio and OR because the incidence of adverse outcomes was low[13]. We evaluated both adjusted and unadjusted data from primary studies, although we preferentially used adjusted data where available.

Statistical heterogeneity was assessed using I^2 statistic[14], with I^2 values of 30%-60% representing a moderate level of heterogeneity. Pre-specified subgroup analysis was performed by evaluating the effect of study design, study setting and outcome ascertainment.

The statistical methods of this study were reviewed by Yoon K Loke, convenor of the Cochrane Adverse Effects Methods Group.

RESULTS

After a review of 3583 citations, we identified 68 randomized controlled trials (Figure 1) with a total of 60811

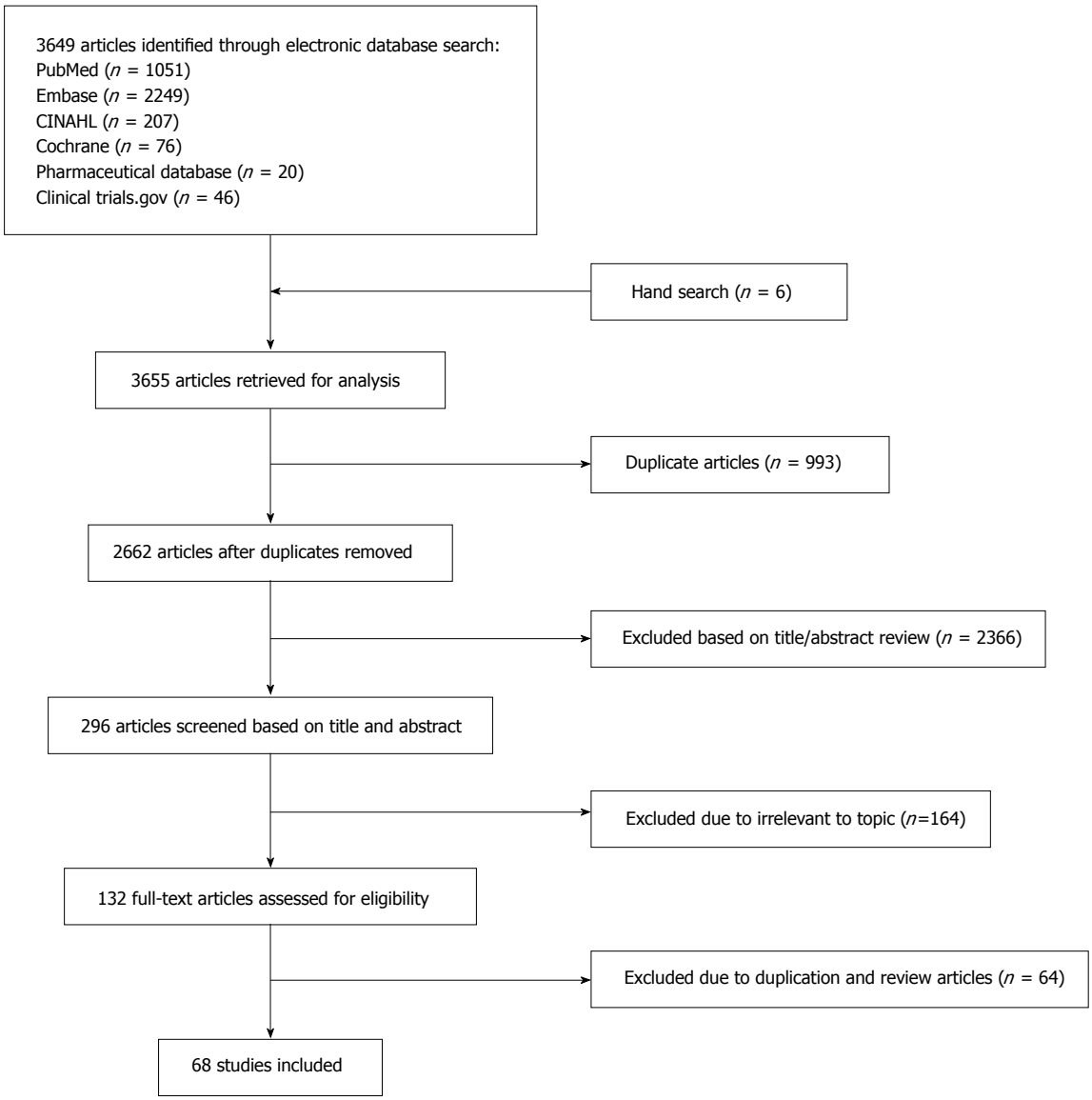

Figure 1 Flow diagram of studies identified and selected.

patients for inclusion in our analysis of the association of risk of pancreatic complication events with the use of GLP-1 agonist and DPP-4 inhibitor drugs.

Description of studies

The study characteristics are listed in Table 1 and quality assessment of the trials in Table 2.

Of these 69 studies, data was abstracted from 28 published reports, 32 studies from clinicaltrials.gov and 9 studies were abstracted from pharmaceutical company databases (Boehringer Ingelheim, Novartis and Takeda Pharmaceutical Company). Almost all the trials were multicenter or multinational studies in patients with type Ⅱ diabetes mellitus.

The majority of studies did not report on the method of generating the random sequence, or on the means of concealing allocation. However, most of the trials (*n* = 55) were double-blinded, thus reducing risk of bias in the diagnosis of pancreatic adverse events. We found that most of the trials, except for two, did not specific pancreatitis as a part of their safety monitoring protocol. As such, there is a strong possibility that pancreatic adverse events may have been missed or wrongly diagnosed. Moreover, the included studies did not specify whether they applied similar criteria in defining cases of pancreatitis.

Overall

Total pancreatic related adverse events: With a total of 89 pancreatic related adverse events among the 34340 number of patients receiving GLP-1 agents and 74 events among 26380 patients receiving the control agents, there was no statistically significant difference in the risk of pancreatic adverse event associated with GLP-1 agent compared with controls (Peto OR = 0.99, 95%CI: 0.72-1.36, $P = 0.96$; $I^2 = 0\%$) (Figure 2).

Pancreatitis: There were a total of 71 pancreatitis

Table 1 Characteristics of glucagon-like peptide-1 based agents in randomized controlled trials included in analysis of pancreatic events

Ref.	Location (No. of centers)	Year of study completion	Total duration (wk)	Duration of GLP-1 exposure (wk)	Participant disease	Arms	No. of participants	Mean age, yr (SD)	Female, *n* (%)
Ross *et al*[21]	Multi-national (84 centers in 9 countries)	2010	43	12	Type 2 diabetes	Linagliptin 2.5 mg bid	223	58.7 (9.9)	85 (38.1)
						Linagliptin 5 mg qd	224	58.4 (10.6)	103 (46.0)
						Placebo	44	59.9 (10.7)	23 (52.3)
Haak *et al*[22]	Multi-national (133 clinics in 14 countries)	2010	73	24	Type 2 diabetes	Linagliptin 5 mg qd	142	56.2 (10.8)	62 (43.7)
						Metformin 500 mg bid	144	52.9 (10.4)	62 (43.1)
						Metformin 1000 mg bid	147	55.2 (10.6)	69 (46.9)
						Linagliptin 2.5 mg qd + Metformin 500 mg bid	143	55.6 (11.2)	73 (49.0)
						Linagliptin 2.5 mg qd + Metformin 1000 mg bid	143	56.4 (10.7)	66 (46.2)
						Placebo	72	55.7 (11.0)	36 (50)
NCT00328172[23]	Multi-national (71 sites in 6 countries)	2007	65	12	Type 2 diabetes	Linagliptin 0.5 mg	58	58.0 (9.4)	13 (22.4)
						Linagliptin 2.5 mg	57	59.8 (10.3)	30 (52.6)
						Linagliptin 5.0 mg	55	56.6 (9.6)	24 (43.6)
						Metformin	65	53.7 (10.7)	26 (40.0)
						Placebo	67	58.6 (8.9)	34 (50.7)
Yki-Jarvinen *et al*[24,25]	Multi-national (169 sites in 19 countries)	2011	108	52	Type 2 diabetes	Linagliptin 5.0 mg	631	59.7 (9.9)	302 (47.9)
						Placebo	630	60.4 (10.0)	301 (47.8)
NCT00654381[26]	Japan	2010	91	12	Type 2 diabetes	Linagliptin 5.0 mg	159	60.3 (9.4)	48 (30.2)
						Linagliptin 10.0 mg	160	61.3 (10.0)	48 (30.0)
						Voglibose	162	58.5 (9.9)	47 (29.0)
						Placebo	80	59.7 (8.9)	23 (28.7)
NCT00622284[27]	Multi-national (221 sites in 16 countries)	2010	146	104	Type 2 diabetes	Linagliptin	776	59.8 (9.4)	314 (40.5)
						Glimepiride	775	59.8 (9.4)	304 (39.2)
BI Trial No: 1218.15/ U09-2519-01[28]	Multi-national (43 sites in 7 countries)	2009	61	24	Type 2 diabetes	Linagliptin 5 mg + Pioglitazone 30 mg	259	NR	NR
						Pioglitazone 30 mg + Placebo	130	NR	NR
BI Trial No: 1218.52/ U11-1782-01[29]	Multi-national (101 sites in 14 countries)	2011	102	54	Type 2 diabetes	Linagliptin 2.5 mg + Metformin (500 mg and 1000 mg bid)	396	NR	NR
						Metformin 1000 mg bid	170	NR	NR
BI Trial No: 1218.63/ U11-1781-02[30]	Multi-national (33 sites in 5 countries)	2011	67	24	Type 2 diabetes	Linagliptin 5 mg	162	NR	46 (28.4)
						Placebo	79	NR	30 (38.0)
BI Trial No: 1218.75/ U12-3204-01[31]	Multi-center study (Black/African American patients only)	2011	55	24	Type 2 diabetes	Linagliptin 5 mg	106	NR	NR
						Placebo	120	NR	NR
BI Trial No: 1218.61/ U13-3124-01[32]	Multi-national study (4 countries)	2012	123	24	Type 2 diabetes	Linagliptin 5 mg	183	NR	NR
						Placebo	89	NR	NR
BI Trial No: 1218.65/ U12-2143-01[33]	Multi-national study (19 sites in 3 countries)	2012	74	24	Type 2 diabetes	Linagliptin 5 mg	205	82%(< 65 yr)	NR
						Placebo	100	83% (< 65 yr)	NR
BI Trial No: 1218.64/ U13-1283-01[34]	Multi-national study (52 sites in 9 countries)	2012	117	52	Type 2 diabetes	Linagliptin 5 mg	113	NR	43 (38.1)
						Placebo (first 12 wk)/ Glimepiride (next 40 wk)	122	NR	43 (35.2)
BI Trial No: 1218.66/ U12-2076-01[35]	Multi-national study (19 sites in 3 countries	2012	80	24	Type 2 diabetes	Linagliptin 5 mg	200	84.0% (< 65 yr)	NR
						Placebo	99	89.9% (< 65 yr)	NR
Rosenstock *et al*[36]	Multi-national study (110 sites in 13 countries)	2007	65	26	Type 2 diabetes	Alogliptin 12.5 mg	131	55.4 (9.8)	76 (58)
						Alogliptin 25 mg	129	55.9 (10.2)	85 (66)
						Placebo	130	55.0 (10.6)	68 (52)
White *et al*[37]	Multi-national study (898 centers in 49 countries)	2013	193	76 (median)	Type 2 diabetes	Alogliptin	2701	36.0% (≥ 65 yr)	873 (32.3)
						Placebo	2679	34.9% (≥ 65 yr)	856 (32.0)

NCT01318135[38]	Japan (58 sites)	2010	52	52	Type 2 diabetes	Alogliptin 12.5 mg qd + Glimepiride 1-6 mg qd or bid	150	38.0% (≥ 65 yr)	53 (35.3)
						Alogliptin 25 mg qd + Glimepiride 1-6 mg qd or bid	152	30.9% (≥ 65 yr)	52 (34.2)
NCT01289119[39]	Multi-national study (21 sites in 3 countries)	2011	52	16	Type 2 diabetes	Alogliptin monotherapy	92	51.6 (10.41)	37 (40.2)
						Metformin	98	53.2 (9.46)	50 (51.0)
						Metformin + Alogliptin Add-on Therapy	99	53.0 (9.88)	48 (48.5)
						Pioglitazone	63	51.8 (10.37)	24 (38.1)
						Pioglitazone + Alogliptin Add-on Therapy	61	52.6 (9.44)	33 (54.1)
						Placebo	93	53.1 (8.88)	39 (41.9)
NCT01263496[40]	Japan (58 sites)	2008	72	52	Type 2 diabetes	Alogliptin 6.25 mg qd	96	28.1 (≥ 65 yr)	26 (27.1)
						Alogliptin 12.5 mg qd	101	33.7 (≥ 6 5 yr)	29 (28.7)
						Alogliptin 25 mg qd	97	34.0 (≥ 65 yr)	22 (22.7)
						Alogliptin 50 mg qd	97	32.9 (≥ 65 yr)	29 (29.9)
						Voglibose 0.2 mg tid	83	38.6 (≥ 65 yr)	27 (32.5)
NCT00328627[41]	Multi-national study (90 sites in 19 countries)	2008	93	26	Type 2 diabetes	Alogliptin 12.5 mg + Placebo	128	53.1 (9.59)	61 (47.6)
						Alogliptin 25 mg + Placebo	129	53.7 (9.31)	79 (61.2)
						Placebo	129	55.2 (9.89)	68 (52.7)
NCT00395512[42]	Multi-national study (268 sites in 23 countries)	2008	67	26	Type 2 diabetes	Alogliptin 25 mg + Pioglitazone 30 mg	164	52.8 (11.01)	91 (55.5)
						Alogliptin 12.5 mg + Pioglitazone 30 mg	164	53.5 (11.37)	83 (50.6)
						Pioglitazone 30 mg	163	51.5 (10.72)	73 (44.8)
Kikuchi *et al*[43]	Japan (26 sites)	2007	52	12	Type 2 diabetes	Vildagliptin 50 mg bid + glimepiride	102	59.2 (9.8)	27 (26.5)
						Placebo + glimepiride	100	60.3 (10.1)	31 (31.0)
Lukashevich *et al*[44]	Multi-national study (12 countries)	2010	291	24	Type 2 diabetes	Vildagliptin 50 mg qd (moderate RI)	165	67.7 (8.8)	69 (41.8)
						Placebo (moderate RI)	129	69.7 (7.3)	49 (38.0)
						Vildagliptin 50 mg qd (severe RI)	124	64.1 (9.2)	59 (47.6)
						Placebo (severe RI)	97	64.5 (10.8)	44 (45.4)
Strain *et al*[45]	Multi-national study (45 centers in 7 countries)	2012	64	24	Type 2 diabetes	Vildagliptin	139	75.1 (4.3)	66 (47.5)
						Placebo	139	74.4 (4.0)	86 (61.9)
NCT00106340[46] (CLAF237A2308)	Multi-national study (402 centers in 25 countries)	2008	166	104	Type 2 diabetes	Vildagliptin 50 mg bid + Metformin	1562	57.5 (9.07)	733 (46.9)
						Glimepiride up to 6 mg qd + Metformin	1556	57.5 (9.19)	718 (46.1)
NCT00300287[47] (CLAF237A2307)	Multi-national study (69 centers in 6 countries)	2006	85	52	Type 2 diabetes	Vildagliptin 50 mg qd	156	63.27 (10.18)	63 (40.4)
						Placebo	150	62.84 (11.03)	61 (40.7)
CLAF237A1301[48]	Japan (51 centers)	2007	44	12	Type 2 diabetes	Vildagliptin 50 mg bid	188	60.3 (10.48)	67 (35.6)
						Voglibose 0.2 mg tid	192	58.0 (9.32)	62 (32.3)
CLAF237A23119[49]	United States (796 centers)	2007	53	12	Type 2 diabetes	Vildagliptin 100 mg + Metformin	1776	55.3	864 (48.6)
						Thiazolinedione + Metformin	888	56.2	467 (52.6)
NCT00110240[50] (CLAF237A2323)	Multi-national study (31 centers in 3 countries)	2006	87	24	Type 2 diabetes	Vildagliptin 50 mg bid	441	51.79 (10.13)	176 (40.0)
						Acarbose up to 100 mg tid	220	51.93 (10.34)	81 (37.0)
NCT00327015[51]	Multi-national study (211 sites in 13 countries)	2007	78	24	Type 2 diabetes	Saxagliptin 5 mg + Metformin 500 mg	320	51.95 (10.43)	155 (48.4)

						Saxagliptin 10 mg + Metformin 500 mg	323	52.08 (11.59)	177 (54.8)
						Metformin 500 mg + Placebo	328	51.83 (10.74)	165 (50.3)
Hollander *et al*[52] (NCT00295633)	Multi-national study (133 sites in 7 countries)	2007	82	24	Type 2 diabetes	Saxagliptin 2.5 mg + TZD	195	54.9 (9.7)	89 (45.6)
						Saxagliptin 5 mg + TZD	186	53.2 (10.6)	97 (52.2)
						Placebo + TZD	184	54.0 (10.1)	99 (53.8)
NCT00757588[53]	Multi-national study (80 sites in 10 countries)	2010	73	24	Type 2 diabetes	Saxagliptin 5 mg + Insulin	304	57.2 (9.4)	184 (60.5)
						Placebo + Insulin	151	57.3 (9.3)	83 (54.9)
Scirica *et al*[54]	Multi-national study (788 sites in 26 countries)	2013	156	109	Type 2 diabetes	Saxagliptin	8280	65.1 (8.5)	2768 (33.4)
						Placebo	8212	65 (8.6)	2687 (32.7)
Göke *et al*[55]	Multi-national study (130 sites in 11 countries)	2010	139	104	Type 2 diabetes	Saxagliptin + Metformin	428	57.5 (10.26)	216 (50.5)
						Glipizide + Metformin	430	57.59 (10.37)	198 (46.1)
NCT00316082[56]	Multi-national study (74 sites in 4 countries)	2007	74	24	Type 2 diabetes	Saxagliptin 2.5/5 mg QAM	71	54.28 (10.93)	34 (47.9)
						Saxagliptin 2.5 mg QAM	74	55.24 (10.44)	49 (66.2)
						Saxagliptin 5 mg QAM	74	54.66 (9.71)	36 (48.6)
						Saxagliptin 5 mg QPM	72	55.11 (10.35)	39 (54.2)
						Placebo	74	55.57 (10.32)	39 (52.7)
NCT00614939[57]	Multi-national study (74 sites in 14 countries)	2009	74	12	Type 2 diabetes	Saxagliptin	85	66.8 (8.3)	53 (62.4)
						Placebo	85	66.2 (9.1)	44 (51.8)
Chan *et al*[58,59]	Multi-national study (30 sites in 13 countries)	2006	NR	54	Type 2 diabetes	Sitagliptin 50 mg or 25 mg once daily	65	68.9 (9.8)	34 (52.3)
						Glipizide	26	65.3 (9.7)	10 (38.5)
Kojima *et al*[60]	Japan (Japanese Red Cross Medical Center)	2011	65	12	Type 2 diabetes	Sitagliptin	20	63.85 (12.92)	5 (0.25)
						Nateglinide	16	66.44 (9.02)	4 (0.25)
NCT00509262 (Arjona Ferreira *et al*[61,62])	Multi-national study	2011	178	54	Type 2 diabetes	Sitagliptin	211	64.2 (10.7)	80 (37.9)
						Glipizide	212	64.2 (9.4)	90 (42.5)
Henry *et al*[63,64]	Multi-national study	2010	108	54	Type 2 diabetes	Sitagliptin 100 mg/ Pioglitazone 15 mg	230	NR	112 (48.7)
						Sitagliptin 100 mg/ Pioglitazone 30 mg	231	NR	96 (41.6)
						Sitagliptin 100 mg/ Pioglitazone 45 mg	230	NR	95 (41.3)
						Pioglitazone 15 mg	230	NR	82 (35.7)
						Pioglitazone 30 mg	233	NR	106 (45.5)
						Pioglitazone 45 mg	230	NR	117 (50.9)
Raz *et al*[65,66]	Multi-national study (30 sites in 13 countries)	2007	47	30	Type 2 diabetes	Sitagliptin 100 mg	96	53.6 (9.5)	47 (48.9)
						Placebo	94	56.1 (9.5)	55 (58.5)
NCT01131182[67]	NR	2010	22	4	Type 2 diabetes	Sitagliptin	507	55.0 (11.0)	238 (46.9)
						Sulfonylurea	514	55.0 (11.0)	259 (50.4)
Goldstein *et al*[68,69]	Multi-national study	2006	69	54	Type 2 diabetes	Sitagliptin 50 mg bid + Metformin 500 mg bid	190	54.1 (10.0)	85 (44.7)
						Sitagliptin 50 mg bid + Metformin 1000 mg bid	182	53.3 (9.6)	105 (57.7)
						Sitagliptin 50 mg bid + Metformin 1000 mg bid (Open Label Cohort)	117	52.6 (10.0)	50 (42.7)
						Metformin 500 mg bid	182	53.4 (10.2)	93 (51.1)
						Metformin 1000 mg bid	182	53.2 (9.6)	100 (54.9)
						Placebo/Metformin 1000 mg bid	176	53.6 (10.0)	83 (47.2)
Arechavaleta *et al*[70,71]	Multi-national study	2009	74	30	Type 2 diabetes	Sitagliptin	516	56.3 (9.7)	232 (44.9)
						Glimepiride	519	56.2 (10.1)	240 (46.2)

NCT00086515 *et al*[72,73]	Multi-national study	2007	135	24	Type 2 diabetes	Sitagliptin 100 mg	464	54.4 (10.4)	205 (44.2)
						Placebo/Glipizide 5 mg	237	54.7 (9.7)	96 (40.5)
Bergenstal *et al*[74,75]	Multi-national study (62 sites in 3 countries)	2009	56	26	Type 2 diabetes	Exenatide once weekly	160	52.4 (10.41)	71 (44.4)
						Sitagliptin	166	52.2 (10.54)	80 (48.2)
						Pioglitazone	165	53.0 (9.92)	86 (52.1)
NCT00094757[76]	Multi-national study	2006	78	54	Type 2 diabetes	Sitagliptin 100 mg	205	54.5 (10.0)	95 (46.3)
						Sitagliptin 200 mg	206	55.4 (9.2)	102 (49.5)
						Placebo/Pioglitazone	110	55.5 (10.1)	41 (37.3)
NCT00094770[77]	Multi-national study (173 sites in 27 countries)	2006	139	104	Type 2 diabetes	Sitagliptin 100 mg	588	56.8 (9.3)	252 (42.8)
						Glipizide	584	56.6 (9.8)	226 (38.7)
NCT01137812[78,79]	Multi-national study (182 sites in 17 countries)	2012	87	52	Type 2 diabetes	Sitagliptin 100 mg	378	56.6 (9.33)	163 (43.1)
						Canagliflozin 300 mg	377	56.5 (9.62)	170 (45.1)
NCT00482729[80]	Multi-national study (209 sites in United States)	2008	74	44	Type 2 diabetes	Sitagliptin/ Meformin-Fixed Dose Combination	625	49.5 (10.5)	272 (43.5)
						Metformin	621	50.0 (10.5)	266 (42.8)
Bunck *et al*[81]	Multi-national study (3 sites in 3 countries)	2007	154	52	Type 2 diabetes	Exenatide	36	58.4 (1.4)	13 (36.1)
						Insulin glargine	33	58.3 (1.3)	11 (33.3)
Diamant *et al*[82]	Multi-national study (72 sites in 7 countries)	2009	53	26	Type 2 diabetes	Exenatide	233	58.0 (10.0)	113 (48.0)
						Insulin glargine	223	58 (9.0)	100 (45.0)
Inagaki *et al*[83]	Japan (22 sites)	2010	61	26	Type 2 diabetes	Exenatide once weekly	215	57.07 (10.44)	73 (34.0)
						Insulin glargine once daily	212	56.44 (11.16)	64 (30.2)
Russell-Jones *et al*[84]	Multi-national study (106 sites in 22 countries)	2010	82	26	Type 2 diabetes	Exenatide 2 mg once weekly + Oral placebo	248	53.7 (10.91)	109 (43.9)
						Sitagliptin 100 mg/d + SC placebo	163	52.3 (11.05)	69 (42.3)
						Metformin starting at 1000 mg/d + SC placebo	246	53.7 (11.08)	92 (37.4)
						Pioglitazone starting at 30 mg/d+ SC placebo	163	55.3 (10.96)	66 (40.5)
NCT01003184[85]	34 sites in Ireland and United Kingdom	2011	91	26	Type 2 diabetes	Exenatide once weekly	111	59.2 (9.86)	40 (36.04)
						Insulin Detemir twice daily	105	57.8 (9.48)	33 (31.4)
Astrup *et al*[86]	Multi-national study (19 sites in 8 European countries)	2009	117	104	Type 2 diabetes	Liraglutide 1.2 mg	95	47.18 (9.72)	73 (76.8)
						Liraglutide 1.8 mg	90	45.53 (10.9)	68 (75.6)
						Liraglutide 2.4 mg	93	45.01 (11.09)	71 (76.3)
						Liraglutide 3.0 mg	93	45.91 (10.71)	70 (75.3)
						Placebo	98	45.86 (10.28)	74 (75.5)
Garber *et al*[87]	126 sites in United States and 12 sites in Mexico	2007	91	52	Type 2 diabetes	Liraglutide 1.2 mg	251	53.7 (11.0)	134 (53.4)
						Liraglutide 1.8 mg	247	52.0 (10.8)	126 (51.0)
						Glimepiride 8 mg	248	53.4 (10.9)	115 (46.4)
Nauck *et al*[88]	Multi-national study (170 sites in 21 countries)	2007	52	26	Type 2 diabetes	Once daily Liraglutide (0.6 mg)	242	56.0 (11.0)	91 (37.6)
						Once daily Liraglutide (1.2 mg)	241	57 (9.0)	111 (46.1)
						Once daily Liraglutide (1.8 mg)	242	57 (9.0)	100 (41.3)
						Once daily Glimepiride (4 mg)	244	57 (9.0)	103 (42.2)
						Placebo	122	56 (9.0)	49 (40.2)
Marre *et al*[89]	Multi-national study (116 sites in 21 countries)	NR	NR	26	Type 2 diabetes	Liraglutide 0.6 mg	233	55.7 (9.9)	107 (46.0)
						Liraglutide 1.2 mg	228	57.7 (9.0)	125 (55.0)
						Liraglutide 1.8 mg	234	55.6 (10.0)	110 (47.0)
						Placebo	114	54.7 (10.0)	60 (53.0)
Zinman *et al*[90]	90 sites in United States and Canada	2007	65	26	Type 2 diabetes	Liraglutide 1.2 mg	178	55.0 (10.0)	77 (43.0)
						Liraglutide 1.8 mg	178	55.0 (11.0)	87 (49.0)
						Placebo	177	55.0 (10.0)	67 (38.0)

Raz *et al*[91]	Multi-national study (53 centers in 11 countries)	2011	134	24	Type 2 diabetes	Taspoglutide 10 mg	116	NR	NR
						Taspoglutide 20 mg	129	NR	NR
						Placebo	123	NR	NR
Rosenstock *et al*[92]	Multi-national study (118 sites in 4 countries)	2008	56	16	Type 2 diabetes	Albiglutide 4 mg weekly	35	50.4 (10.3)	20 (57.1)
						Albiglutide 15 mg weekly	35	55.5 (10.5)	17 (48.6)
						Albiglutide 30 mg weekly	31	54.2 (9.7)	23 (74.2)
						Albiglutide 15 mg biweekly	33	52.5 (9.6)	19 (57.6)
						Albiglutide 30 mg biweekly	32	55.5 (9.9)	16 (50.0)
						Albiglutide 50 mg biweekly	35	51.1 (10.3)	16 (45.7)
						Albiglutide 50 mg monthly	35	54.1 (11.3)	18 (51.4)
						Albiglutide 100 mg monthly	34	54.4 (9.9)	15 (44.1)
						Placebo	51	54.0 (10.6)	23 (45.1)
Seino *et al*[93]	Multi-national study (57 centers in 4 Asian countries)	NR	NR	24	Type 2 diabetes	Lixisenatide (10 ug for 1 wk, 15 mg for 1 wk, then 20 mg-maintenance dose)	154	58.7 (10.2)	85 (55.2)
						Placebo	157	58.0 (10.1)	77 (49.0)
Umpierrez *et al*[94]	36 sites in United States and 3 in Puerto Rico	2008	39	16	Type 2 diabetes	LY2189265 (LY 0.5/1.0)	66	59.0 (12.0)	31 (47.0)
						LY2189265 (LY 1.0/1.0)	65	57.0 (12.0)	30 (46.0)
						LY2189265 (LY 1.0/2.0)	65	54.0 (11.0)	31 (48.0)
						Placebo	66	56.0 (12.0)	37 (56.0)

Table 2 Quality assessment of glucagon-like peptide-1 based agents in randomized controlled trials included in analysis of pancreatic events

Ref.	Sequence generation	Blinding	Allocation concealment	Was Pancreatitis an AE or SAE?	Adverse event monitoring	Arms	Withdrawal rate (%)	Loss to follow- up (%)
Ross *et al*[21]	Central computer based; randomization: block in a 5:5:1 ratio	Double blind	Adequate	AE	Safety and tolerability end-points were the incidence of adverse events (including adverse changes observed during physical examinations or ECGs), protocol-specified significant AEs, hypoglycemia and changes from baseline in vital signs, clinical laboratory parameters and body weight	Linagliptin 2.5 mg bid	7.2	0
						Linagliptin 5 mg qd	4.5	0
						Placebo	2.3	0
Haak *et al*[22]	NR	Double blind	Adequate	AE	Incidence of AEs, serious AEs, discontinuation due to AEs,12-lead ECGs, vital signs and clinical laboratory parameters. The causal relationships between study medications and AEs were evaluated by the investigators at the site	Linagliptin 5 mg qd	14.8	2.1
						Metformin 500 mg bid	11.8	2.1
						Metformin 1000 mg bid	14.3	2.7
						Linagliptin 2.5 mg qd + Metformin 500 mg bid	11.2	2.8
						Linagliptin 2.5 mg qd + Metformin 1000 mg bid	7.7	0
						Placebo	25.0	1.4

NCT00328172[23]	NR	Double blind	NR	SAE	NR	Linagliptin 0.5 mg	24.1	1.7
						Linagliptin 2.5 mg	17.5	3.5
						Linagliptin 5.0 mg	23.6	1.8
						Metformin	7.7	1.5
						Placebo	32.8	1.5
Yki-Jarvinen *et al*[24,25]	NR	Double blind	NR	SAE	NR	Linagliptin 5.0 mg	13.9	2.2
						Placebo	17.5	1.3
NCT00654381[26]	NR	Double blind	NR	SAE	NR	Linagliptin 5.0 mg	1.89	0
						Linagliptin 10.0 mg	3.13	0
						Voglibose	2.5	0
						Placebo	7.5	0
NCT00622284[27]	NR	Double blind	NR	SAE	NR	Linagliptin	24.4	1.4
						Glimepiride	22.1	1.7
BI Trial No: 1218.15/ U09-2519-01[28]	Randomized into 1;2 ratio to receive either placebo or linagliptin	Double blind	Adequate	SAE	Incidence and intensity of AEs, withdrawals due to AEs, physical examination, 12-lead ECG, vital signs, clinical laboratory parameters	Linagliptin 5 mg + Pioglitazone 30 mg	5.8	NR
						Pioglitazone 30 mg + Placebo	14.6	NR
BI Trial No: 1218.52/ U11-1782-01[29]	NR	Double blind	NR	SAE	Safety endpoints were the incidence and intensity of AEs, withdrawals due to AEs, clinically relevant new or worsening findings in physical examination, 12-lead ECG, vital signs and clinical laboratory parameters	Linagliptin 2.5 mg + Metformin (500 mg and 1000 mg bid)	0.0	NR
						Metformin 1000 mg bid	0.6	NR
BI Trial No: 1218.63/ U11-1781-02[30]	NR	Double blind	NR	SAE	Incidence and intensity of AEs, withdrawals due to AEs, physical examination, 12-lead ECG, vital signs, clinical laboratory parameters	Linagliptin 5 mg	1.23	NR
						Placebo	1.26	NR
BI Trial No: 1218.75/ U12-3204-01[31]	NR	Double blind	NR	AE	Incidence and intensity of AEs, withdrawals due to AEs, clinically relevant changes from baseline in vital signs (blood pressure and pulse rate), clinically relevant new or worsening findings in 12-lead ECG as reported as AEs, clinically relevant changes from baseline in clinical laboratory assessments, cardiac and cerebrovascular events adjudicated CEC	Linagliptin 5 mg	12.3	NR
						Placebo	12.5	NR
BI Trial No: 1218.61/ U13-3124-01[32]	NR	Double blind	NR	AE	Incidence and intensity of AEs, primarily based on spontaneous AEs; withdrawal due to AEs; clinically relevant new or worsening findings in physical examination reported as AEs; changes from baseline in vital signs (BP and pulse); clinically relevant new or worsening findings in 12 lead ECG reported as AEs; changes from baseline in clinical lab assessments; and hypoglycemic events	Linagliptin 5 mg	2.2	NR
						Placebo	0.0	NR

BI Trial No: 1218.65/ U12-2143-01[33]	NR	Double blind	NR	SAE	Incidence and intensity of adverse events, withdrawals due to AEs, physical examination, ECGs, change from baseline in clinical lab parameters and cardiovascular events (Clinical Event Committee adjudication results)	Linagliptin 5 mg Placebo	0.98 3.0	NR NR
BI Trial No: 1218.64/ U13-1283-01[34]	NR	Double blind	NR	AE	Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, vital signs, 12 lead ECG, change from baseline in clinical lab parameters	Linagliptin 5 mg Placebo (first 12 wk)/ Glimepiride (next 40 wk)	0.0 1.64	NR NR
BI Trial No: 1218.66/ U12-2076-01[35]	NR	Double blind	NR	SAE	Incidence and intensity of adverse events, withdrawals due to AEs, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments	Linagliptin 5 mg Placebo	5.1 2.0	NR NR
Rosenstock *et al*[36]	Automated interactive voice response system using a randomization schedule	Double blind	NR	SAE	During the treatment period, patients were reviewed for adverse event evaluations. Further safety assessments included clinical examination of skin and digits. Hematology, serum chemistry, vital signs, physical exam and ECG parameters were done	Alogliptin 12.5 mg Alogliptin 25 mg Placebo	36.6 40.3 57.7	3.05 2.33 1.54
White *et al*[37]	NR	Double blind	NR	SAE	The principal secondary safety end point was the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 h after hospital admission. Additional safety end points included angioedema, hypoglycemia, pancreatitis, cancer, and the results of laboratory testing	Alogliptin Placebo	NR NR	NR NR
NCT01318135[38]	NR	Open Label	Inadequate	SAE (Pancreatic cancer only)		Alogliptin 12.5 mg qd + Glimepiride 1-6 mg qd or bid Alogliptin 25 mg qd + Glimepiride 1-6 mg qd or bid	NR NR	NR NR
NCT01289119[39]	NR	Double blind	NR	SAE	TEAE were defined as any adverse events that started on or after the date of the first dose of double-blind study drug and within 14 d after the date of the last dose of double-blind study drug	Alogliptin monotherapy Metformin Metformin + Alogliptin Add-on Therapy Pioglitazone Pioglitazone + Alogliptin Add-on Therapy Placebo	9.78 9.18 6.06 7.94 6.56 9.78	3.26 0 0 0 1.64 0
NCT01263496[40]	NR	Open Label	Inadequate	SAE	A TEAE is defined as an adverse event with an onset that occurs after receiving study drug and within 30 d after receiving the last dose of study drug	Alogliptin 6.25 mg qd Alogliptin 12.5 mg qd Alogliptin 25 mg qd Alogliptin 50 mg qd Voglibose 0.2 mg tid	NR NR NR NR NR	NR NR NR NR NR

NCT00328627[41]	NR	Double blind	NR	SAE	NR	Alogliptin 12.5 mg + Placebo	24.2	1.56
						Alogliptin 25 mg + Placebo	21.7	1.55
						Placebo	45.7	3.1
NCT00395512[42]	NR	Double blind	Adequate	SAE	NR	Alogliptin 25 mg + Pioglitazone 30 mg	17.1	3.05
						Alogliptin 12.5 mg + Pioglitazone 30 mg	23.2	3.05
						Pioglitazone 30 mg	22.7	3.68
Kikuchi *et al*[43]	Dynamic randomization	Double blind	NR	SAE	Adverse events were recorded at each visit, and these AEs were assessed for severity and suspected relationship to the study drug. Hematology, biochemistry and urinalysis were performed at each scheduled visit. All laboratory assessments were processed at a central testing to ensure consistency	Vildagliptin 50 mg bid + glimepiride	2.9	NR
						Placebo + glimepiride	4	NR
Lukashevich *et al*[44]	NR	Double blind	NR	SAE	All treatment emergent AEs were recorded and assessed by the investigator as to severity and potential relationship to study drug. Particular attention was paid to hepatic, infections, skin, pancreatitis as well as edema and cardiovascular safety	Vildagliptin 50 mg qd (moderate RI)	10.3	2.4
						Placebo (moderate RI)	10.9	1.6
						Vildagliptin 50 mg qd (severe RI)	13.7	1.6
						Placebo (severe RI)	13.4	2.1
Strain *et al*[45]	Validated automated system	Double blind	Adequate	AE	All AEs and their severity, serious AEs, and their presumed relation with the study drug were monitored and recorded at each study visit	Vildagliptin	5.8	0.72
						Placebo	5.8	0
NCT00106340[46] (CLAF237A2308)	NR	Double blind	NR	SAE	Safety assessments included monitoring and recording all AEs, SAEs and pregnancies; regular monitoring of hematology, blood chemistry, and urine (performed at a central lab); and regular assessments of vital signs, ECG, physical condition and body weight. Severity and relationship to study drug were recorded for all AEs and SAEs	Vildagliptin 50 mg bid + Metformin	36.4	0
						Glimepiride up to 6 mg qd + Metformin	38.8	0
NCT00300287[47]	NR	Double blind	NR	SAE	Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs	Vildagliptin 50 mg qd	14.7	0.6
						Placebo	12.7	0.7

(CLAF237A2307) CLAF237A1301[48]	NR	Double blind	NR	AE (elevated pancreatic enzymes)	Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs	Vildagliptin	4.8	NR
						50 mg bid Voglibose 0.2 mg tid	5.2	NR
CLAF237A23119[49]	NR	Open Label	NA	SAE	Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs	Vildagliptin 100 mg + Metformin	10.4	2.5
						Thiazolinedione + Metformin	11.8	2.1
NCT00110240[50] (CLAF237A2323)	NR	Double Blind	NR	SAE	Safety assessments included adverse events, hypoglycemic events and serious adverse events, physical examination, vital signs, laboratory evaluations, and ECGs	Vildagliptin 50 mg bid	9.5	1.6
						Acarbose up to 100 mg tid	12.7	1.4
NCT00327015[51]	NR	Double Blind	NR	SAE	Safety and tolerability end-points included incidence of AEs, SAEs, discontinuation due to AEs, physical and ECG examinations, vital signs and results of clinical laboratory tests	Saxagliptin 5 mg + Metformin 500 mg	28.4	6.9
						Saxagliptin 10 mg + Metformin 500 mg	28.5	7.1
						Metformin 500 mg + Placebo	33.2	6.7
Hollander *et al*[52] (NCT00295633)	NR	Double Blind	NR	SAE	Safety assessments included incidence of AEs, SAEs and discontinuation due to AEs, changes from baseline lab parameters; changes from baseline vital signs; and incidence of marked clinical laboratory abnormalities	Saxagliptin 2.5 mg + TZD	31.8	NR
						Saxagliptin 5 mg + TZD	36	NR
						Placebo + TZD	41.3	NR
NCT00757588[53]	Interactive voice response system	Double Blind	NR	SAE	Safety end points included AEs, hypoglycemia and weight gain	Saxagliptin 5 mg + Insulin	11.8	0.98
						Placebo + Insulin	11.3	3.31
Scirica *et al*[54]	Central computerized telephone or web based system	Double Blind	NR	NR (Safety End Point)	A clinical events committee comprising specialists in cardiovascular and pancreatic medicine, all of whom were unaware of the study group assignments, adjudicated	Saxagliptin	NR	NR
						Placebo	NR	NR
Goke *et al*[55]	NR	Double Blind	NR	SAE	Safety and tolerability assessments included AEs and SAEs, lab measurements, vital signs, physical examination and ECG testing	Saxagliptin + Metformin	61.4	0.23
						Glipizide + Metformin	65.8	0.69
NCT00316082[56]	NR	Double Blind	NR	SAE	NR	Saxagliptin 2.5/5 mg QAM	38.0	9.9
						Saxagliptin 2.5 mg QAM	44.6	9.5
						Saxagliptin 5 mg QAM	29.7	8.1
						Saxagliptin 5 mg QPM	36.1	11.1
						Placebo	35.1	8.1

NCT00614939[57]	Interactive voice response system	Double Blind	NR	SAE	Safety and tolerability assessments included AEs, SAEs, treatment-related AEs, discontinuations of randomized study medication because of AEs, deaths, AEs of special interest and hypoglycemic events	Saxagliptin Placebo	71.8 80.0	NR NR
Chan *et al*[58,59]	Computer generated randomization schedule	Double Blind	Adequate	SAE	Assessment of safety and tolerability included evaluation of the data from physical examinations, vital signs and ECGs collected at specified study visits. All adverse experiences were rated by the investigators for intensity and relationship to study drug	Sitagliptin 50 mg or 25 mg once daily Placebo/ Glipizide	29.2 23.1	NR NR
Kojima *et al*[60]	Random allocation sequence performed centrally	Open label	NA	AE	NR	Sitagliptin Nateglinide	NR NR	NR NR
NCT00509262 (Arjona Ferreira JC *et al*[61,62])	Computer generated randomization schedule	Double	NR	SAE	Safety measurements included evaluation of AEs, physical exam and vital signs, and ECG. Lab safety studies included serum chemistry, hematology and urinalysis. All AEs were rated by the investigator for intensity and relationship to study drug	Sitagliptin Glipizide	210 212	
Henry RR *et al*[63,64]	NR	Blind Double blind	NR	SAE	Safety and tolerability were evaluated throughout the study by physical examination, monitoring of vital signs and safety lab measurements that included serum chemistry, hematology and urinalysis. AEs were monitored and evaluated by the investigators for intensity (severity), duration, outcome and relationship to study drug	Sitagliptin 100 mg/ Pioglitazone 15 mg Sitagliptin 100 mg/ Pioglitazone 30 mg Sitagliptin 100 mg/ Pioglitazone 45 mg Pioglitazone 15 mg Pioglitazone 30 mg Pioglitazone 45 mg	20.9 22.9 22.2 31.3 27.9 27.4	3.5 6.9 5.7 6.1 9 5.7
Raz I *et al*[65,66]	Computer generated schedule	Double blind	NR	SAE	Safety and tolerability were evaluated by physical examination, vital signs and lab measurements that included routine serum chemistry, hematology, urinalysis and pregnancy testing. AEs were monitored through the study for intensity, duration, outcome, relationship to study drug and level of severity	Sitagliptin 100 mg Placebo	17.7 14.9	3.13 3.19
NCT01131182[67]	NR	Open label	NA	SAE	NR	Sitagliptin Sulfonylurea	NR NR	NR NR

Goldstein *et al*[68,69]	NR	Double blind	NR	SAE	Data were collected regarding AEs, physical exam, vital signs, ECGs and body weight throughout the study. All AEs were rated by investigators for intensity and relationship to study drug	Sitagliptin 50 mg bid + Metformin 500 mg bid	22.1	2.6
						Sitagliptin 50 mg bid + Metformin 1000 mg bid	22.5	5.5
						Sitagliptin 50 mg bid + Metformin 1000 mg bid (OLC)	32.5	2.6
						Metformin 500 mg bid	30.8	2.2
						Metformin 1000 mg bid	25.8	3.8
						Placebo/ Metformin 1000 mg bid	34.7	5.1
Arechavaleta *et al*[70,71]	Concealed computer-generated allocation schedule	Double blind	Adequate	SAE	Safety and tolerability were assessed by a review of all safety parameters including adverse experiences, laboratory safety parameters, body weight and vital signs	Sitagliptin	9.3	1.7
						Glimepiride	9.8	1.7
NCT00086515 *et al*[72,73]	NR	Double blind	NR	SAE	Safety and tolerability were assessed throughout the study. Monitoring for adverse experiences, physical examinations, vital signs, body weight, 12-lead ECGs (read at a central reading laboratory), and safety laboratory measurements comprising routine hematology, serum chemistry, and urinalysis were performed	Sitagliptin 100 mg	10.6	0.86
						Placebo/ Glipizide 5 mg	18.9	2.11
Bergenstal *et al*[74,75]	Interactive voice response system	Double blind	Adequate	SAE	NR	Exenatide once weekly	26.9	5
						Sitagliptin	16.9	5.4
						Pioglitazone	24.8	7.8
NCT00094757[76]	NR	Double blind	NR	SAE	Data for adverse experiences, physical examinations, vital signs, ECGs, and body weight were collected throughout the study	Sitagliptin 100 mg	25.8	1.5
						Sitagliptin 200 mg	30.1	2.4
						Placebo/ Pioglitazone	27.3	5.4
NCT00094770[77]	NR	Double blind	NR	SAE	Data on adverse experiences, physical examinations, vital signs, ECGs and body weight were collected throughout the study. All adverse experiences were rated by the study site investigators for intensity and relationship to study drug. Laboratory safety evaluations included blood chemistry, haematology and urinalysis	Sitagliptin 100 mg	34.4	3.2
						Glipizide	29.5	1.7
NCT01137812[78,79]	Interactive Voice Response System/ Interactive Web Response System	Double blind	Adequate	SAE	Safety evaluations included AEs, clinical laboratory tests, vital sign measurements, physical examinations, self-monitored blood glucose, 12-lead electrocardiograms, and documentation of hypoglycemic episodes	Sitagliptin 100 mg	44.4	2.1
						Canagliflozin 300 mg	32.6	1.6

NCT00482729[80]	NR	Double blind	NR	SAE	NR	Sitagliptin/ Meformin-Fixed Dose Combination	34.7 (217/626)	13.7 (86/626)
						Metformin	34.9 (218/624)	10.6 (66/624)
Bunck *et al*[81]	NR	Open label	NA	SAE	NR	Exenatide	16.7	0
						Insulin glargine	9.1	3.03
Diamant *et al*[82]	Computer generated randomization sequence	Open label	NA	SAE	Safety endpoints were adverse events, clinical lab assessments, vital signs, and hypoglycemia. We defined adverse events as those occurring at or after randomization or worsening during the study	Exenatide	10.3	0.86
						Insulin glargine	6.3	0.45
Inagaki *et al*[83]	Computer generated randomization sequence	Open label	NA	AE	Safety profile end points included AEs and hypoglycemia	Exenatide once weekly	10.2	0.47
						Insulin glargine once daily	5.2	0
Russell-Jones *et al*[84]	Computer generated randomization sequence	Double blind	Adequate	SAE	Safety end points were adverse events, clinical lab assessments, vital signs, hypoglycemia and antibodies to exenatide. Treatment emergent adverse events were defined as those occurring or worsening after the first dose of study drug	Exenatide 2 mg once weekly + Oral placebo	15.3	1.6
						Sitagliptin 100 mg/d + SC placebo	14.1	2.4
						Metformin starting at 1000 mg/d + SC placebo	13.4	0.4
						Pioglitazone starting at 30 mg/d + SC placebo	1.8	1.8
NCT01003184[85]	NR	Open label	NR	SAE	NR	Exenatide once weekly	17.1	0.9
						Insulin Detemir twice daily	11.4	0
Astrup *et al*[86]	NR	Double blind (first 20 wk) Weeks 20-104: Open label	NR	SAE	Safety assessments included adverse events, recorded at every visit, standard lab tests and serum liraglutide antibodies. A safety committee for data surveillance was established	Liraglutide 1.2 mg	10.5	0
						Liraglutide 1.8 mg	17.8	0
						Liraglutide 2.4 mg	21.5	0
						Liraglutide 3.0 mg	11.8	0
						Placebo	19.4	0
Garber *et al*[87]	Telephone based or web-based systems	Double blind	Adequate	SAE	Key safety assessments were tolerability (including nausea and other gastrointestinal adverse events), serum calcitonin and hypoglycemic episodes	Liraglutide 1.2 mg	35.5	NR
						Liraglutide 1.8 mg	29.7	NR
						Glimepiride 8 mg	38.7	NR
Nauck *et al*[88]	Telephone based or web-based randomization systems	Double blind	Adequate	SAE	Safety variables included adverse events, vital signs, ECG, biochemical and hematology measures and subject reported hypoglycemic episodes	Once daily Liraglutide (0.6 mg)	14.0	0
						Once daily Liraglutide (1.2 mg)	18.0	0.4
						Once daily Liraglutide (1.8 mg)	21.0	0
						Once daily Glimepiride (4 mg)	14.0	0
						Placebo	39.0	0

Marre *et al*[89]	NR	Double blind	NR	SAE	Safety variables included hypoglycemic episodes, liraglutide antibodies, tolerability (gastrointestinal complaints) and pulse. AEs, vital signs, ECG, biochemical and hematology measures including calcitonin were also monitored	Liraglutide 0.6 mg	10.7	NR
						Liraglutide 1.2 mg	14.0	NR
						Liraglutide 1.8 mg	8.9	NR
						Placebo	27.2	NR
Zinman *et al*[90]	Telephone based or web-based randomization systems	Double blind	Adequate	SAE	Safety variables included AEs, vital signs, ECG, biochemical and hematology measures and subject reported hypoglycemic episodes	Liraglutide 1.2 mg	14.0	NR
						Liraglutide 1.8 mg	25.0	NR
						Placebo	32.0	NR
Raz *et al*[91]	NR	Double blind	NR	SAE	Safety assessments included AEs, vital signs, physical examinations, clinical lab tests, ECG and hypoglycemia	Taspoglutide 10 mg	11.2	NR
						Taspoglutide 20 mg	13.2	NR
						Placebo	3.3	NR
Rosenstock *et al*[92]	NR	Double blind	NR	SAE	Adverse event assessments and safety analyses were conducted throughout the study	Albiglutide 4 mg weekly	48.6	5.7
						Albiglutide 15 mg weekly	31.4	8.6
						Albiglutide 30 mg weekly	32.3	3.2
						Albiglutide 15 mg biweekly	45.5	9.1
						Albiglutide 30 mg biweekly	24.2	0
						Albiglutide 50 mg biweekly	42.9	2.9
						Albiglutide 50 mg monthly	14.3	2.9
						Albiglutide 100 mg monthly	44.1	2.9
						Placebo	23.5	0
Seino *et al*[93]	Interactive voice response system	Double blind	Adequate	SAE	Safety and tolerability included reported AEs and other safety information such as symptomatic hypoglycemia	Lixisenatide (10 ug for 1 wk, 15 ug for 1 wk, then 20 ug-maintenance dose)	NR	NR
						Placebo	NR	NR
Umpierrez *et al*[94]	Computer generated random sequence	Double blind	Adequate	SAE	Safety measures included AEs, vital signs, hypoglycemia events and lab tests	LY2189265 (LY 0.5/1.0)	12.1	1.5
						LY2189265 (LY 1.0/1.0)	10.8	1.5
						LY2189265 (LY 1.0/2.0)	13.8	1.5
						Placebo	9.1	1.5

NR: Not reported; AE: Adverse event; SAE: Serious adverse event; ECGs: Electrocardiograms; TEAE: Treatment-emergent adverse events; CEC: Clinical events committee.

events in patients on GLP-1 agents and 56 pancreatitis events occurred in the control patients. There was no statistically significant difference in the risk of pancreatic adverse event associated with GLP-1 agent compared with controls (Peto OR = 1.07, 95%CI: 0.75-1.52, P = 0.72, I^2 = 0%) (Figure 3).

Elevated pancreatic enzymes: Eight studies reported on elevated pancreatic enzymes. There was a statistically significant increased risk of elevation of pancreatic enzymes associated with GLP-1 agents compared with control (Peto OR = 3.15, 95%CI: 1.56-6.39, P = 0.001, I^2 = 0%) (Figure 4).

Pancreatic cancer: Eighteen studies reported on pancreatic cancer (Table 3). There were a total of 35 cases of pancreatic cancer reported from studies that used GLP-1 agents. Seventeen cases of pancreatic occurred among 18259 patients taking GLP-1 agents compared to 18 cases among 15785 controls. Of these cases, 2 used linagliptin, 2 used alogliptin, 1 used vildagliptin, 7 used saxagliptin while 5 used sitagliptin. The remaining 18 cases occurred among controls.

Individual GLP-1 agents

DPP-4 inhibitors: (1) Linagliptin: Fifteen studies that used Linagliptin had a total of 7263 patients. There

A

Study or subgroup	GLP1 agent Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, Fixed, 95%CI
Active control						
1218.52/U11-1782-01	0	396	0	170		Not estimable
1218.64/U13-1283-01	0	113	0	122		Not estimable
Bunk 2009	1	36	0	33	0.6%	6.80 [0.13, 343.88]
Chan 2008	1	65	0	26	0.5%	4.06 [0.05, 310.62]
CLAF237A23119	2	1756	2	871	2.3%	0.47 [0.06, 3.75]
Diamant 2010	1	233	0	223	0.6%	7.08 [0.14, 357.08]
Garber 2009	2	498	0	248	1.1%	4.48 [0.24, 85.11]
Goke 2013	0	428	2	430	1.3%	0.14 [0.01, 2.17]
Haak LM v M 2012	0	286	0	291		Not estimable
Inagaki 2012	0	215	0	212		Not estimable
Kojima 2013	0	20	0	16		Not estimable
Nauck LvG 2009	1	725	1	244	1.0%	0.27 [0.01, 6.53]
NCT00086515	1	464	0	237	0.6%	4.53 [0.07, 285.42]
NCT00094757	0	411	2	110	0.9%	0.01 [0.00, 0.26]
NCT00094770	1	588	0	584	0.6%	7.34 [0.15, 369.87]
NCT00103857	1	489	2	540	1.9%	0.57 [0.06, 5.46]
NCT00106340	3	1553	2	1546	3.2%	1.49 [0.26, 8.59]
NCT00110240	1	440	0	220	0.6%	4.48 [0.07, 286.49]
NCT00327015	1	643	1	328	1.2%	0.48 [0.03, 9.08]
NCT00328627	1	257	0	129	0.6%	4.49 [0.07, 286.28]
NCT00395512	1	328	0	163	0.6%	4.47 [0.07, 286.84]
NCT00482729	1	625	2	621	1.9%	0.51 [0.05, 4.91]
NCT00509262	1	210	0	212	0.6%	7.46 [0.15, 375.96]
NCT00622284	2	776	2	775	2.6%	1.00 [0.14, 7.10]
NCT00637273 E v P	0	160	1	82	0.6%	0.05 [0.00, 3.29]
NCT00637273 SvP	0	166	1	83	0.6%	0.05 [0.00, 3.18]
NCT00701090	1	516	0	518	0.6%	7.42 [0.15, 373.83]
NCT00722371	1	691	1	693	1.3%	1.00 [0.06, 16.05]
NCT01131182	0	507	1	514	0.6%	0.14 [0.00, 6.91]
NCT01137812	0	378	1	377	0.6%	0.13 [0.00, 6.80]
NCT01263496	2	391	0	83	0.7%	3.37 [0.09, 129.71]
NCT01289119 A + M	0	99	0	98		Not estimable
NCT01289119 A + P	0	61	0	63		Not estimable
NCT01318135	1	142	0	145	0.6%	7.55 [0.15, 380.42]
Russell-Jones E v P 2012	0	242	0	254		Not estimable
Russell-Jones S v P 2012	1	163	0	255	0.6%	12.99 [0.23, 722.62]
Subtotal (95%CI)		15071		11516	29.1%	0.96 [0.53, 1.70]
Total events	28		21			

Heterogeneity: χ^2 = 28.87, df = 27 (P = 0.37); I^2 = 6%

Test for overall effect: Z = 0.18 (P = 0.86)

B

Study or subgroup	GLP1 agent Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, Fixed, 95%CI
Placebo control						
1218.15/U09-2519-01	0	259	1	130	0.6%	0.05 [0.00, 3.20]
1218.61/U13-3124-01	0	183	0	89		Not estimable
1218.63/U11-1781-02	0	162	0	79		Not estimable
1218.65/U12-2143-01	0	205	0	100		Not estimable
1218.66/U12-2076-01	0	200	0	99		Not estimable
1218.75/U12-3204-01	0	106	0	120		Not estimable
Astrup 2012	1	371	0	98	0.4%	3.54 [0.03, 439.21]
Haak LvP 2012	0	142	0	72		Not estimable
Hollander 2011	1	381	0	184	0.6%	4.41 [0.07, 288.68]
Kikuchi 2010	0	102	0	100		Not estimable
Lukashevich 2011	0	289	0	226		Not estimable
Marre 2009	1	695	0	114	0.3%	3.20 [0.01, 895.32]
Nauck LvP 2009	1	725	0	122	0.3%	3.22 [0.01, 854.21]
NCT00300287	0	156	1	150	0.6%	0.13 [0.00, 6.56]
NCT00316082	1	291	0	74	0.4%	3.51 [0.03, 459.13]
NCT00328172	1	170	0	67	0.5%	4.03 [0.05, 313.12]
NCT00328627	1	257	0	129	0.6%	4.49 [0.07, 286.28]
NCT00337610	0	96	1	94	0.6%	0.13 [0.00, 6.68]
NCT00614939	0	85	1	85	0.6%	0.14 [0.00, 6.82]
NCT00654381	1	319	0	80	0.4%	349 [0.03, 466.89]
NCT00757588	1	304	1	151	1.1%	0.47 [0.02, 8.90]
NCT00954447	2	631	1	630	1.9%	1.95 [0.20, 18.75]
NCT01289119 A alone	0	92	1	93	0.6%	0.14 [0.00, 6.89]
Raz 2012	0	245	0	123		Not estimable
Rosenstock Albi 2009	0	270	0	51		Not estimable
Rosenstock Aloglip 2009	2	260	0	130	1.1%	4.50 [0.24, 85.42]
Ross 2012	0	447	0	44		Not estimable
Scirica 2013	29	8280	34	8212	40.4%	0.85 [0.52, 1.39]
Seino 2012	0	154	0	157		Not estimable
Strain 2013	0	139	0	139		Not estimable
Umpierrez 2011	2	196	0	66	1.0%	3.83 [0.16, 93.74]
White 2013	17	2701	12	2679	18.6%	1.40 [0.68, 2.91]
Zinman 2009	0	356	0	177		Not estimable
Subtotal (95%CI)		19269		14864	70.9%	1.01 [0.70, 1.47]
Total events	61		53			
Heterogeneity: χ^2 = 12.05, df = 18 (P = 0.84); I^2 = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95%CI)		34340		26380	100.0%	0.99 [0.72, 1.36]
Total events	89		74			
Heterogeneity: χ^2 = 40.95, df = 46 (P = 0.68); I^2 = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subqroup differences: χ^2 = 0.03, df = 1 (P = 0.85); I^2 = 0%						

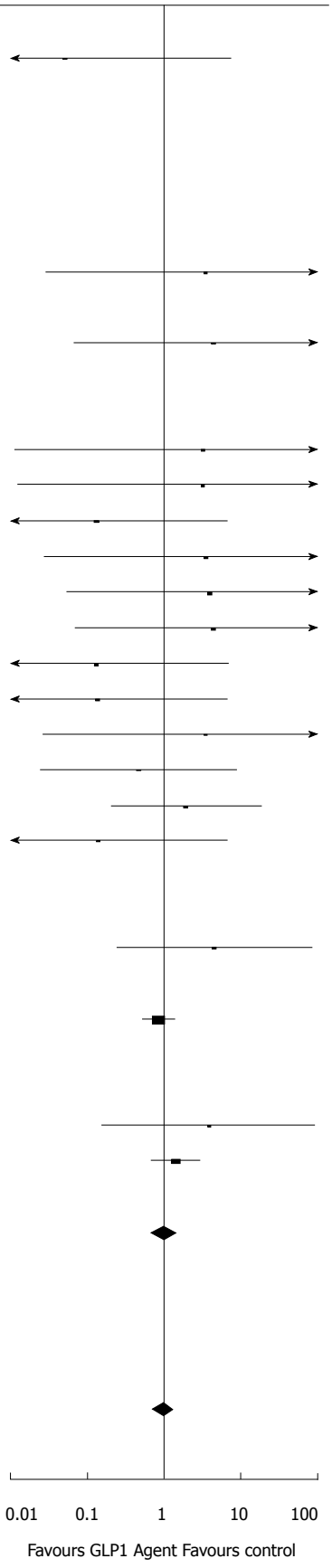

Figure 2 Risk of pancreatic adverse events in patients treated with glucagon-like peptide-1 based therapies (A and B).

A

Study or subgroup	GLP1 agent Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, Fixed, 95%CI
Active control						
1218.52/U11-1782-01	0	396	0	170		Not estimable
1218.64/U13-1283-01	0	113	0	122		Not estimable
Bunk 2009	1	36	0	33	0.8%	6.80 [0.13, 343.88]
Chan 2008	0	65	0	26		Not estimable
CLAF237A23119	1	1756	2	871	2.2%	0.22 [0.02, 2.44]
Diamant 2010	1	233	0	223	0.8%	7.08 [0.14, 357.08]
Garber 2009	2	498	0	248	1.5%	4.48 [0.24, 85.11]
Goke 2013	0	428	2	430	1.6%	0.14 [0.01, 2.17]
Haak LM v M 2012	0	286	0	291		Not estimable
Inagaki 2012	0	215	0	212		Not estimable
Kojima 2013	0	20	0	16		Not estimable
Nauck LvG 2009	1	725	1	244	1.2%	0.27 [0.01, 6.53]
NCT00086515	0	464	0	237		Not estimable
NCT00094757	0	411	1	110	0.5%	0.01 [0.00, 1.07]
NCT00094770	1	588	0	584	0.8%	7.34 [0.15, 369.87]
NCT00103857	1	489	1	540	1.6%	1.10 [0.07, 17.74]
NCT00106340	3	1553	2	1546	4.1%	1.49 [0.26, 8.59]
NCT00110240	1	440	0	220	0.7%	4.48 [0.07, 286.49]
NCT00327015	1	643	1	328	1.5%	0.48 [0.03, 9.08]
NCT00395512	1	328	0	163	0.7%	4.47 [0.07, 286.84]
NCT00482729	1	625	2	621	2.5%	0.51 [0.05, 4.91]
NCT00509262	0	210	0	212		Not estimable
NCT00622284	1	776	0	775	0.8%	7.38 [0.15, 371.91]
NCT00637273 E v P	0	160	1	82	0.7%	0.05 [0.00, 3.29]
NCT00637273 SvP	0	166	1	83	0.7%	0.05 [0.00, 3.18]
NCT00701090	0	516	0	518		Not estimable
NCT00722371	0	691	1	693	0.8%	0.14 [0.00, 6.84]
NCT01131182	0	507	1	514	0.8%	0.14 [0.00, 6.91]
NCT01137812	0	378	1	377	0.8%	0.13 [0.00, 6.80]
NCT01263496	1	391	0	83	0.5%	3.36 [0.02, 583.65]
NCT01289119 A + M	0	99	0	98		Not estimable
NCT01289119 A + P	0	61	0	63		Not estimable
NCT01318135	0	142	0	145	0.6%	Not estimable
Russell-Jones E v P 2012	0	242	0	254		Not estimable
Russell-Jones S v P 2012	1	163	0	255	0.8%	12.99 [0.23, 722.62]
Subtotal (95%CI)		14814		11387	26.7%	0.75 [0.38, 1.50]
Total events	18		17			

Heterogeneity: χ^2 = 22.59 df =21 (P = 0.37); I^2 = 7%

Test for overall effect: Z = 0.81 (P = 0.42)

B

Study or subgroup	GLP1 agent Events	GLP1 agent Total	Control Events	Control Total	Weight	Peto odds ratio Peto, Fixed, 95%CI
Placebo control						
1218.15/U09-2519-01	0	259	0	130		Not estimable
1218.61/U13-3124-01	0	183	0	89		Not estimable
1218.63/U11-1781-02	0	162	0	79		Not estimable
1218.65/U12-2143-01	0	205	0	100		Not estimable
1218.66/U12-2076-01	0	200	0	99		Not estimable
1218.75/U12-3204-01	0	106	0	120		Not estimable
Astrup 2012	1	371	0	98	0.5%	3.54 [0.03, 439.21]
Haak LvP 2012	0	142	0	72		Not estimable
Hollander 2011	1	381	0	184	0.7%	4.41 [0.07, 288.68]
Kikuchi 2010	0	102	0	100		Not estimable
Lukashevich 2011	0	289	0	226		Not estimable
Marre 2009	1	695	0	114	0.4%	3.20 [0.01, 895.32]
Nauck LvP 2009	1	725	0	122	0.4%	3.22 [0.01, 854.21]
NCT00300287	0	156	1	150	0.8%	0.13 [0.00, 6.56]
NCT00316082	0	291	0	74		Not estimable
NCT00328172	1	170	0	67	0.7%	4.03 [0.05, 313.12]
NCT00328627	1	257	0	129	0.7%	4.49 [0.07, 286.28]
NCT00337610	0	96	0	94		Not estimable
NCT00614939	0	85	1	85	0.8%	0.14 [0.00, 6.82]
NCT00654381	0	319	0	80		Not estimable
NCT00757588	0	304	1	151	0.7%	0.05 [0.00, 3.16]
NCT00954447	2	631	1	630	2.5%	1.95 [0.20, 18.75]
NCT01289119 A alone	0	92	1	93	0.8%	0.14 [0.00, 6.89]
Raz 2012	0	245	0	123		Not estimable
Rosenstock Aloglip 2009	2	260	0	130	1.5%	4.50 [0.24, 85.42]
Ross 2012	0	447	0	44		Not estimable
Scirica 2013	24	8280	22	8212	37.7%	1.08 [0.61, 1.93]
Seino 2012	0	154	0	157		Not estimable
Strain 2013	0	139	0	139		Not estimable
Umpierrez 2011	2	196	0	66	1.2%	3.83 [0.16, 93.74]
White 2013	17	2701	12	2679	23.7%	1.40 [0.68, 2.91]
Zinman 2009	0	356	0	177		Not estimable
Subtotal (95%CI)		18999		14813	73.3%	1.21 [0.80, 1.84]
Total events	53		39			
Heterogeneity: χ^2 = 9.11, df = 14 (P = 0.82); I^2 = 0%						
Test for overall effect: Z = 0.06 (P = 0.36)						
Total (95%CI)		33813		26200	100.0%	0.99 [0.72, 1.36]
Total events	71		56			
Heterogeneity: χ^2 = 33.06, df = 36 (P = 0.61); I^2 = 0%						
Test for overall effect: Z = 0.05 (P = 0.72)						
Test for subqroup differences: χ^2 = 1.36, df = 1 (P = 0.24); I^2 = 26.3%						

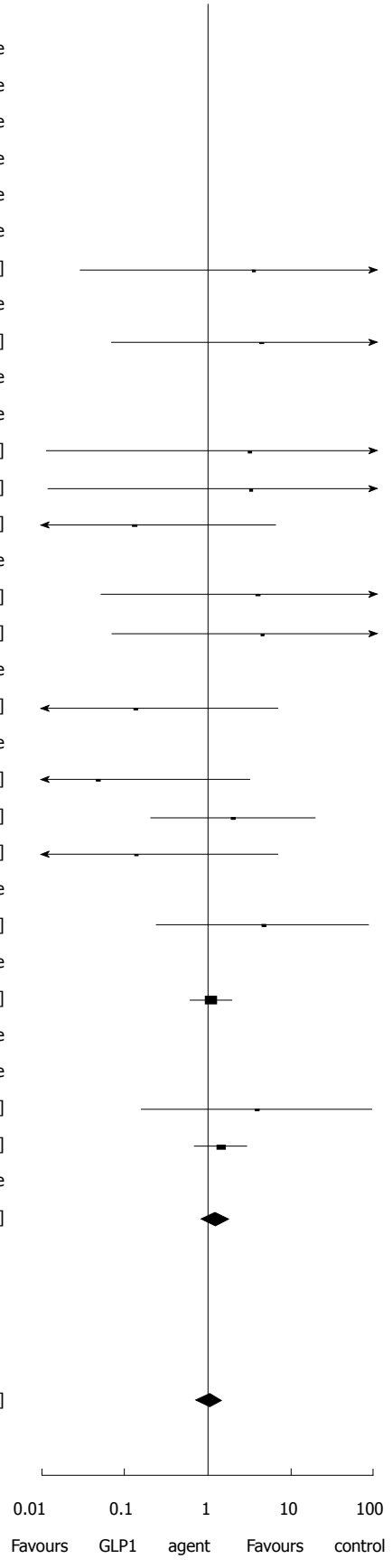

Figure 3 Risk of pancreatitis in patients treated with glucagon-like peptide-1 based therapies (A and B).

Table 3 Pancreatic cancer events in randomized controlled trials of glucagon-like peptide-1 agents

Ref.	Duration of GLP-1 exposure (wk)	Arms	No. of participants	No. of cases
NCT00654381[26]	52	Linagliptin 5 mg	159	0
		Linagliptin 10 mg	160	1
		Voglibose	162	0
		Placebo	80	0
NCT00622284[27]	104	Linagliptin	776	1
		Glimepiride	775	2
BI Trial No: 1218.15/ U09-2519-01[28]	24	Linagliptin 5 mg + Pioglitazone 30 mg	130	0
		Pioglitazone 30 mg + Placebo	259	1
White *et al*[37]	76	Alogliptin	2701	0
		Placebo	2679	0
NCT01318135[38]	52	Alogliptin 12.5 mg qd + Metformin 500 mg bid or 750 mg tid	142	1
		Metformin 500 mg bid or 750 mg tid	145	0
NCT01263496[40]	52	Alogliptin 6.25 mg qd	96	0
		Alogliptin 12.5 mg qd	101	0
		Alogliptin 25 mg qd	97	1
		Alogliptin 50 mg qd	97	0
		Voglibose 0.2 mg tid	83	0
CLAF237A23119[49]	12	Vildagliptin 100 mg + Metformin	1756	1
		Thiazolinedione + Metformin	871	NR
NCT00757588[53]	52	Saxagliptin 5 mg + Insulin	304	1
		Placebo + Insulin	151	0
Scirica *et al*[54]	109	Saxagliptin	8280	5
		Placebo	8212	12
NCT00316082[56]	24	Saxagliptin 2.5/5 mg QAM	71	1
		Saxagliptin 2.5 mg QAM	74	0
		Saxagliptin 5 mg QAM	74	0
		Saxagliptin 5 mg QPM	72	0
		Placebo	74	0
Chan *et al*[58,59]	54	Sitagliptin 50 mg or 25 mg once daily	65	1
		Placebo/Glipizide	26	0
Ferreira *et al*[61,62]	54	Sitagliptin	210	1
		Glipizide	212	0
Henry *et al*[63,64]	54	Pioglitazone 15 mg	230	0
		Pioglitazone 30 mg	233	0
		Pioglitazone 45 mg	230	0
		Sitagliptin 100 mg/Pioglitazone 15 mg	230	0
		Sitagliptin 100 mg/Pioglitazone 30 mg	231	1
		Sitagliptin 100 mg/Pioglitazone 45 mg	230	0
Raz *et al*[65,66]	30	Sitagliptin 100 mg	96	0
		Placebo	94	1
Goldstein *et al*[68,69]	104	Metformin 500 mg bid	182	0
		Metformin 1000 mg bid	182	0
		Sitagliptin 50 mg bid + Metformin 500 mg bid	190	0
		Sitagliptin 50 mg bid + Metformin 1000 mg bid	182	0
		Sitagliptin 50 mg bid + Metformin 1000 mg bid	117	0
		Placebo/Metformin 1000 mg bid	176	1
Arechavaleta *et al*[70,71]	30	Sitagliptin	516	1
		Glimepiride	518	0
Charbonnel *et al*[72,73]	104	Sitagliptin 100 mg	464	1
		Placebo/Glipizide 5 mg	237	0
NCT00094757[76]	54	Sitagliptin 100 mg	205	0
		Sitagliptin 200 mg	206	0
		Placebo/Pioglitazone	110	1

GLP-1: Glucagon-like peptide-1.

was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 1.14, 95%CI: 0.32-4.13) or pancreatitis (Peto OR = 2.90, 95%CI: 0.49-17.36) associated with linagliptin compared with controls; (2) Alogliptin: Nine studies that used Alogliptin had a total of 7914 patients. In comparison with control, there was no increased risk of having a pancreatic adverse event (Peto OR = 1.59, 95%CI: 0.82-3.07) or pancreatitis (Peto OR = 1.50, 95%CI: 0.77-2.94) with alogiptin; (3) Vildagliptin: Seven studies that used Vildagliptin had a total of 7687 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 0.87, 95%CI: 0.26-2.94) or pancreatitis (Peto OR = 0.75, 95%CI: 0.21-2.67) with vildagliptin; (4) Saxagliptin: Seven studies that used Saxagliptin had

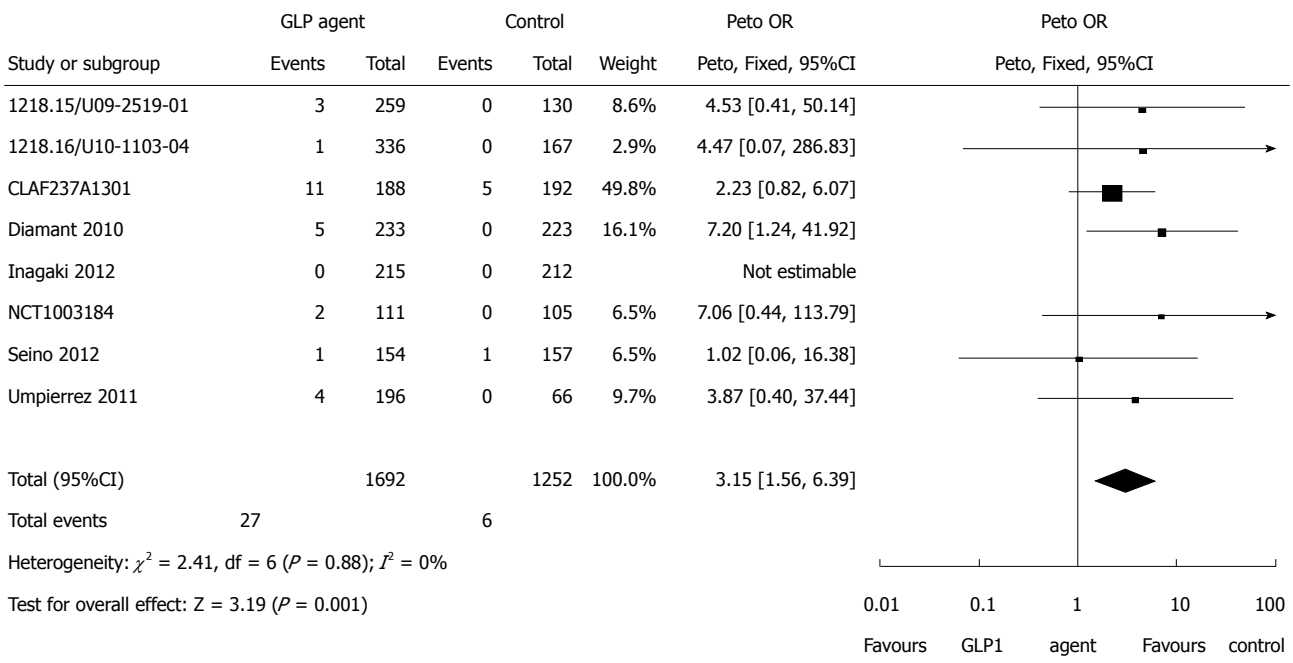

Figure 4 Risk of elevated pancreatic enzymes for glucagon-like peptide-1 based agents.

a total of 19876 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 0.79, 95%CI: 0.49-1.25) or pancreatitis (Peto OR 0.91, 95%CI: 0.53-1.56) with saxaglipitin; and (5) sitagliptin: Sixteen studies that used Sitagliptin had a total of 10360 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 0.66, 95%CI: 0.27-1.63) or pancreatitis (Peto OR = 0.45, 95%CI: 0.14-1.43) with sitagliptin.

GLP-1 receptor agonists

Exenatide: Five studies that used Exenatide had a total of 1690 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 1.53, 95%CI: 0.15-15.29) or pancreatitis (Peto OR = 1.53, 95%CI: 0.15-15.29) with exenatide.

Liraglutide: Six studies that used Liraglutide had a total of 4373 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 1.71, 95%CI: 0.29-10.04) or pancreatitis (Peto OR = 1.71, 95%CI: 0.29-10.04 with liraglutide.

Dulaglutide: One study that used Dulaglutide had 262 patients. In comparison with control, there was no statistically significant difference in the risk of pancreatic adverse event (Peto OR = 3.83, 95%CI: 0.16-93.74) or pancreatitis (Peto OR = 3.83, 95%CI: 0.16-93.74) with dulaglutide.

Taspoglutide, albiglutide and lixisenatide: Taspoglutide, Albiglutide and Lixisenatide all had 1 study each with 368, 321 and 311 patients each. The effect estimates were not estimable due to the small number of events.

In a post-hoc analysis, we examined whether there was any difference between DPP-4 inhibitors and GLP-1 based therapies. The results showed that neither the DPP-4 inhibitors nor the GLP- 1 based therapies were associated with a risk of pancreatic complications (Figure 5).

Publication bias

We did not detect any publication bias in the funnel plot (Figure 6).

DISCUSSION

Summary of results

Our study showed a significantly increased risk of pancreatic enzyme elevation with GLP-1 based therapies**.** However, the use of GLP-1 based therapies was not associated with a statistically significant increased risk of pancreatic complication events in patients with type 2 diabetes in randomized controlled trials. Additionally, when we examined individual agents, none of the DPP-4 inhibitors or GLP-1 agonists was associated with a statistically significant increased risk of pancreatitis (Figure 3). Despite the lack of statistical significance the upper bounds of the CI in several analyses, particularly for the GLP-1 receptor agonists (exenatide, liraglutide and albiglutide) exceeded 1 and could not rule out a clinically significant hazard. There were an insufficient number

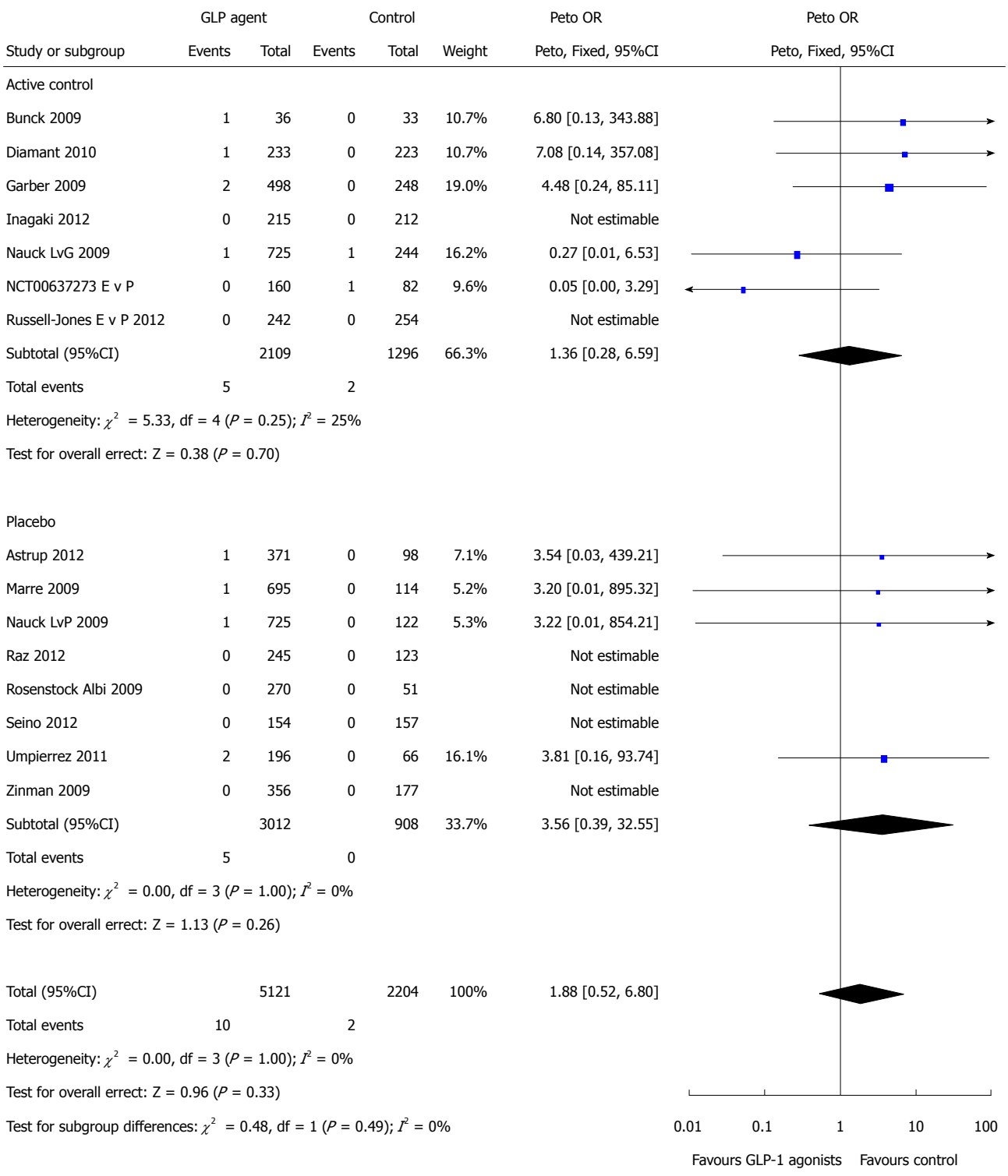

Figure 5 Risk of pancreatic events for glucagon-like peptide-1 receptor agonist drugs only.

of cases of pancreatic cancer to allow for the estimation of meaningful differences between GLP-1 based agents and controls.

Explanations

These discordant results-no significant effect on the outcome of acute pancreatitis but significant increase in the risk of pancreatic enzyme elevation associated with GLP-1 based therapies in a small number of studies may have two alternative explanations.

These could indicate that injury with GLP-1 based therapies is sub-threshold and result in pancreatic inflammation that may not reach the level of acute pancreatitis. Alternatively, the ascertainment of pancreatic adverse events/complications may have been more complete in this subset of studies showing an elevation in pancreatic

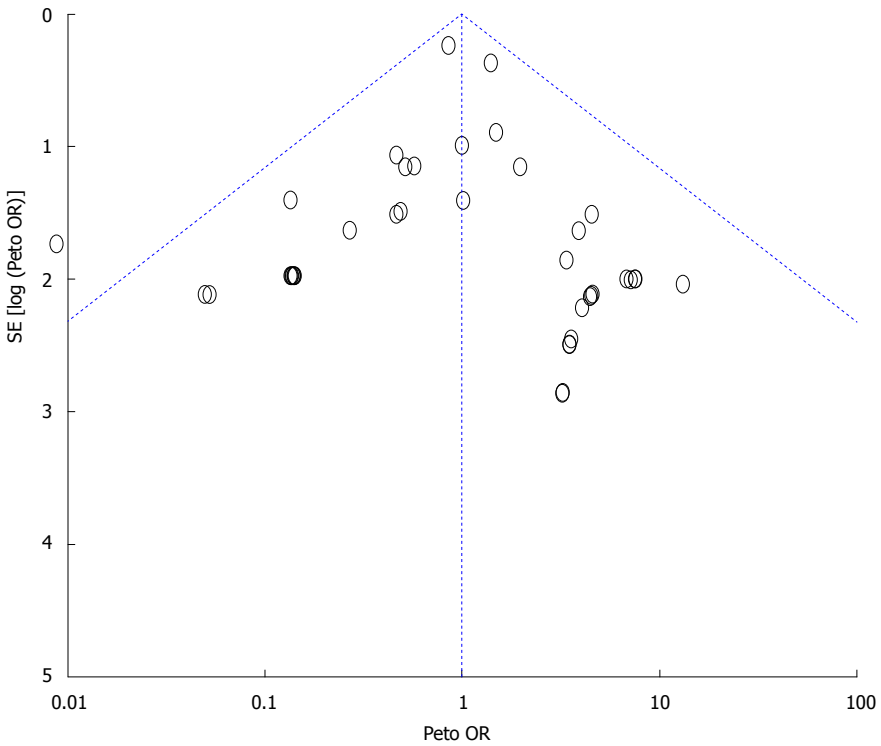

Figure 6 Funnel plot for risk of pancreatic adverse events.

enzymes. It was not clear whether pancreatitis adverse events were rigorously defined or captured in an objective rather than subjective manner across the trials, potentially biasing towards the null due to misclassification. In contrast, measurement of elevated pancreatic enzymes is a more objective measure, serial enzyme measurements should be regularly checked in trial participants on GLP-1 agents who present with gastrointestinal symptoms. Lack of awareness for the need to assess pancreatic enzymes could lead to under-ascertainment of pancreatic adverse events in patients presenting with upper abdominal symptoms. Among patients with type 2 diabetes, one previous study reported an increase in enzyme associated with DPP-4 inhibitors compared to controls (36% *vs* 18%), suggesting that this adverse reaction deserves further investigation[15].

Our meta-analysis should be seen in the light of other recent studies. A recent review reported a slightly increased trend for reporting of acute pancreatitis associated with GLP-1 receptor agonists but not with DPP-Ⅳ inhibitors[16]. Two other systematic reviews reported no increased risk of acute pancreatitis, but with very wide confidence intervals that could not rule out a significant increase[6,17]. However, one such meta-analysis included observational studies, which may be prone to confounding[17]. The difference in meta-analysis should reflect differences in inclusion of trials and ascertainment of events. Importantly none of the previous meta-analysis have reported on elevations in pancreatic enyzmes associated with GLP-1 based therapies. However, the CIs were wide in all meta-analyses and we could not rule out a significant increase in the risk of pancreatitis with GLP-1 based therapies. The lack of statistical significance may reflect incomplete ascertainment of pancreatic adverse events in clinical trials of GLP-1 based therapies or inadequate statistical power to detect rare but serious complication such as pancreatitis. Observational studies have also shown inconsistent results between GLP-1 based therapies and acute pancreatitis due to incomplete ascertainment of covariates, or poor performance of the diagnostic codes for acute pancreatitis[5,18-20]. It is also unclear whether the inflammatory process from recurrent or chronic pancreatitis is a predisposing factor to subsequent development of pancreatic cancer.

Limitations

Our study has some limitations. We limited our analysis to published RCTs. However; there may be unpublished studies that report on this outcome. We did not have access to data to conduct individual patient data meta-analysis and ascertain time to the occurrence of pancreatic enzyme elevations. Importantly, clinical trials may not have ascertained the occurrence of pancreatitis on participants who withdrew from the trial (as a result of the complication). This may bias our estimates towards the null. The availability of sponsors of individual patient data to independent investigators may allow for further analyses.

Our meta-analysis shows a three-fold increased risk of pancreatic enzyme elevation with GLP-1 based agents compared to controls, without an a significant increased risk of pancreatitis or pancreatic cancer due to small number of cases. Future adequately powered observational studies with well validated codes for pancreatitis

and pancreatic cancer and careful control of confounding are needed to evaluate the risk of pancreatic enzyme elevation, pancreatitis and pancreatic cancer with GLP-1 based therapies.

COMMENTS

Background

Recent developments have led to an increasingly wide range of glucose lowering drugs being trialed for treatment of type II diabetes mellitus. However, a variety of concerns have been raised regarding the safety of these new agents for long-term chronic use. This has led to tightening of the regulatory landscape and closer scrutiny of data regarding serious rare adverse events.

Research frontiers

Many trials have been conducted to demonstrate the efficacy of glucagon-like-peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in reducing blood glucose levels. However, there have been suggestions of a potential increase in risk of pancreatic adverse events with these drugs due to a postulated proliferative effect on pancreatic cells. The existing evidence base is conflicting, and difficult to interpret due to the very low incidence of pancreatic adverse events.

Innovations and breakthroughs

The findings of this meta-analysis are that risks of pancreatitis or pancreatic cancer have not been definitively established with any of the GLP-1 agonists or DPP-4 inhibitors. However, there is a signal suggesting increased risk of elevated pancreatic enzymes, which has not previously been described in other systematic reviews.

Applications

GLP-1 agonists or DPP-4 inhibitors may have some relationship with elevations in the pancreatic enzyme levels. Further large scale studies are needed to determine if these elevations may or may not be associated with adverse clinical outcomes.

Terminology

GLP-1 belongs to the incretin group of hormones which act to stimulate insulin secretion dependent on glucose levels. GLP-1 receptor agonists are drugs developed as incretin-mimetics. DPP-4 is an enzyme that breaks down GLP-1, thus causing GLP-1 to have a short half-life. Drugs that inhibit DPP-4 would be expected to increase the availability of endogenous GLP-1.

Peer-review

This manuscript has a great collecting data about this topic.

REFERENCES

1 **Butler PC**, Dry S, Elashoff R. GLP-1-based therapy for diabetes: what you do not know can hurt you. *Diabetes Care* 2010; **33**: 453-455 [PMID: 20103562 DOI: 10.2337/dc09-1902]

2 **Drucker DJ**, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010; **33**: 428-433 [PMID: 20103558]

3 **Nachnani JS**, Bulchandani DG, Nookala A, Herndon B, Molteni A, Pandya P, Taylor R, Quinn T, Weide L, Alba LM. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. *Diabetologia* 2010; **53**: 153-159 [PMID: 19756486 DOI: 10.1007/s00125-009-1515-4]

4 **Matveyenko AV**, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R, Butler AE, Butler PC. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. *Diabetes* 2009; **58**: 1604-1615 [PMID: 19403868 DOI: 10.2337/db09-0058]

5 **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**: 534-539 [PMID: 23440284 DOI: 10.1001/jamainternmed.2013.2720]

6 **Monami M**, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011; **27** Suppl 3: 57-64 [PMID: 22106978 DOI: 10.1185/03007995.2011.602964]

7 **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**: 271-284 [PMID: 23010561]

8 **Shihab HM,** Akande T, Loke YK, Singh S. Risk of pancreatic complication events associated with the use of GLP-1 receptor agonist and DPP-4 inhibitor drugs: A systematic review and meta-analysis. PROSPERO: International prospective register of systematic reviews. Available from: URL: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004742. Accessed June 23, 2014

9 **Higgins JPT,** Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011

10 **Loke YK,** Price D, Herxheimer A. Chapter 14: Adverse Effects. In: Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley and Sons, 2008

11 **Ioannidis JP**, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007; **176**: 1091-1096 [PMID: 17420491 DOI: 10.1503/cmaj.060410]

12 Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014

13 **Davies HT**, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ* 1998; **316**: 989-991 [PMID: 9550961]

14 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

15 **Lando HM**, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. *Endocr Pract* 2012; **18**: 472-477 [PMID: 22440997]

16 **Meier JJ**, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia* 2014; **57**: 1320-1324 [PMID: 24723174 DOI: 10.1007/s00125-014-3231-y]

17 **Li L**, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, Rios LP, Malaga G, Wong E, Sohani Z, Guyatt GH, Sun X. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ* 2014; **348**: g2366 [PMID: 24736555 DOI: 10.1136/bmj.g2366]

18 **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**: 2349-2354 [PMID: 20682680 DOI: 10.2337/dc10-0482]

19 **Dore DD,** Hussein M, Hoffman C, Pelletier EM, Smith DB, Seeger JD. A pooled analysis of exenatide use and risk of acute pancreatitis. *Curr Med Res Opin* 2013; **29**: 1577-1586 [PMID: 23981106 DOI: 10.1185/03007995.2013.838550]

20 **Chou HC**, Chen WW, Hsiao FY. Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors: a population-based nested case-control study. *Drug Saf* 2014; **37**: 521-528 [PMID: 24859164 DOI: 10.1007/s40264-014-0171-x]

21 **Ross SA**, Rafeiro E, Meinicke T, Toorawa R, Weber-Born S, Woerle HJ. Efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. *Curr Med Res Opin* 2012; **28**: 1465-1474 [PMID: 22816729 DOI: 10.1185/03007995.2012.714360]

22 **Haak T**, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind

1-year extension study. *Int J Clin Pract* 2013; **67**: 1283-1293 [PMID: 24118640 DOI: 10.1111/j.1463-1326.2012.01590.x]

23 **Boehringer Ingelheim Pharmaceuticals.** Efficacy and safety of 3 doses of BI1356 (linagliptin) in type 2 diabetes patients. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 8]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00328172 NLM Identifier: NCT00328172

24 **Yki-Järvinen H**, Rosenstock J, Durán-Garcia S, Pinnetti S, Bhattacharya S, Thiemann S, Patel S, Woerle HJ. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study. *Diabetes Care* 2013; **36**: 3875-3881 [PMID: 24062327 DOI: 10.2337/dc12-2718]

25 **Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company.** Efficacy and safety of linagliptin in combination with insulin in patients with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 8]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00954447 NLM Identifier: NCT00954447

26 **Boehringer Ingelheim Pharmaceuticals.** Japanese P III vs voglibose and placebo. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 8]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00654381 NLM Identifier: NCT00654381

27 **Boehringer Ingelheim Pharmaceuticals.** Efficacy and safety of BI 1356 in combination with metformin in patients with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 8]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00622284 NLM Identifier: NCT00622284

28 **Boehringer Ingelheim Pharmaceuticals.** A randomised, double-blind, placebo controlled, parallel group 24 week study to assess the efficacy and safety of linagliptin (5mg) in combination with 30mg pioglitazone (both administered orally once daily), compared to 30mg pioglitazone plus placebo in drug-naive or previously treated type 2 diabetic patients with insufficient glycaemic control. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.15_U09-2519.pdf

29 **Boehringer Ingelheim Pharmaceuticals.** A phase III randomised, double-blind parallel group extension study to investigate the safety and efficacy of twice daily administration of the free combination of linagliptin 2.5 mg metformin 500 mg or of linagliptin 2.5 mg metformin 1000mg versus monotherapy with metformin 1000 mg twice daily over 54 weeks in type 2 diabetic patients previously completing the double-blind part of study 1218.46. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.52_U11-1782-01.pdf

30 **Boehringer Ingelheim Pharmaceuticals.** A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5mg), administered orally once daily over 24 weeks in type 2 diabetic patients (age 70 years) with insufficient glycaemic control (HbA1c 7.0%) despite metformin and/or sulphonylurea and/or insulin therapy. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.63_U11-1781-02.pdf

31 **Boehringer Ingelheim Pharmaceuticals.** A phase IIIb, 24 week, randomised, placebo-controlled, double-blinded, efficacy and safety study of linagliptin in black/african american patients with type 2 diabetes with a MTT sub-study. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.75_U12-3204-01.pdf

32 **Boehringer Ingelheim Pharmaceuticals.** A phase III, randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin 5mg administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with pioglitazone. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.61_U13-3124-01.pdf

33 **Boehringer Ingelheim Pharmaceuticals.** A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy in asian population. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.65_U12-2143-01.pdf

34 **Boehringer Ingelheim Pharmaceuticals.** A phase III, randomised, double-blind, placebo-controlled parallel group safety and efficacy study of linagliptin (5mg administered orally once daily) over 12 weeks followed by a 40 week double-blind extension period (placebo patients switched to glimepiride) in drug naive or previously treated type 2 diabetic patients with moderate to severe renal impairment and insufficient glycaemic control. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.64_U13-1283-01-DS.pdf

35 **Boehringer Ingelheim Pharmaceuticals.** A randomised, double-blind, placebo-controlled parallel group, efficacy and safety study of linagliptin (5mg administered orally once daily) over 24 weeks, in drug naive or previously treated type 2 diabetic patients with insufficient glycaemic control. [accessed 2014 Jun 8]. Available from: URL: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.66_U12-2076-01.pdf

36 **Rosenstock J**, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. *Diabetes Obes Metab* 2009; **11**: 1145-1152 [PMID: 19758359 DOI: 10.1111/j.1463-1326.2009.01124.x]

37 **White WB**, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369**: 1327-1335 [PMID: 23992602 DOI: 10.1056/NEJMoa1305889]

38 **Takeda.** Long-term safety study of alogliptin used in combination with sulfonylurea or metformin in participants with type 2 diabetes in japan. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01318135 NLM Identifier: NCT01318135

39 **Takeda.** Efficacy and safety of alogliptin in participants with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01289119 NLM Identifier: NCT01289119

40 **Takeda**. Long-term safety study of alogliptin in participants with type 2 diabetes in japan. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/results?term=NCT01263496 NLM Identifier: NCT01263496

41 **Takeda.** Efficacy and safety of alogliptin combined with pioglitazone in treating subjects with type 2 diabetes mellitus. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00328627 NLM Identifier: NCT00328627

42 **Takeda**. Efficacy of alogliptin with pioglitazone (actos) in subjects with type 2 diabetes mellitus. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00395512 NLM Identifier: NCT00395512

43 **Kikuchi M**, Haneda M, Koya D, Tobe K, Onishi Y, Couturier A, Mimori N, Inaba Y, Goodman M. Efficacy and tolerability of vildagliptin as an add-on to glimepiride in Japanese patients with Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2010; **89**:

216-223 [PMID: 20537746 DOI: 10.1016/j.diabres.2010.04.017]
44 **Lukashevich V**, Schweizer A, Shao Q, Groop PH, Kothny W. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. *Diabetes Obes Metab* 2011; **13**: 947-954 [PMID: 21733061 DOI: 10.1111/j.1463-1326.2011.01467.x]
45 **Strain WD**, Lukashevich V, Kothny W, Hoellinger MJ, Paldánius PM. Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study. *Lancet* 2013; **382**: 409-416 [PMID: 23706759 DOI: 10.1016/S0140-6736(13)60995-2]
46 **Novartis Pharmaceuticals.** Vildagliptin compared to glimepiride in combination with metformin in patients with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00106340 NLM Identifier: NCT00106340
47 **Novartis Pharmaceuticals**. A 56-week extension to a clinical study to assess the efficacy and safety of vildagliptin compared to placebo in drug naive patients with type 2 diabetes and mild hyperglycemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00300287 NLM Identifier: NCT00300287
48 **Novartis Pharmaceuticals.** A multicenter, randomized, double-blind, active-controlled study to compare the effects of 12 weeks treatment with vildagliptin 50 mg b.i.d. to voglibose 0.2 mg t.i.d. in patients with type 2 diabetes. [accessed 2014 Jun 22]. Available from: URL: http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult=2524
49 **Novartis Pharmaceuticals.** A multi-center, randomized, open-label, active controlled, parallel arm study to compare the efficacy of 12 weeks of treatment with vildagliptin 100 mg, once daily (qd) to thiazolidinedione (TZD) as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy in a community-based practice setting. [accessed 2014 Jun 22]. Available from: URL: http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult=2567.
50 **Novartis Pharmaceuticals.** Efficacy and safety of vildagliptin compared to acarbose in drug naive patients with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT00110240 NLM Identifier: NCT00110240
51 **AstraZeneca**. A phase 3 study of BMS-477118 in combination with metformin in subjects with type 2 diabetes who are not controlled with diet and exercise. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00327015 NLM Identifier: NCT00327015
52 **Hollander PL**, Li J, Frederich R, Allen E, Chen R. Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. *Diab Vasc Dis Res* 2011; **8**: 125-135 [PMID: 21562064 DOI: 10.1177/1479164111404575]
53 **AstraZeneca.** Safety and efficacy of saxagliptin plus insulin with or without metformin. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00757588 NLM Identifier: NCT00757588
54 **Scirica BM**, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]
55 **Göke B**, Gallwitz B, Eriksson JG, Hellqvist Å, Gause-Nilsson I. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. *Int J Clin Pract* 2013; **67**: 307-316 [PMID: 23638466 DOI: 10.1111/ijcp.12119]
56 **AstraZeneca.** Study of BMS-477118 as monotherapy with titration in subjects with type 2 diabetes who are not controlled with diet and exercise. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT00316082 NLM Identifier: NCT00316082
57 **AstraZeneca**. Treatment effect of saxagliptin compared with placebo in patients with type 2 diabetes and renal impairment. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00614939 NLM Identifier: NCT00614939
58 **Merck Sharp and Dohme Corp.** An investigational drug in patients with type 2 diabetes mellitus and chronic renal insufficiency. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00095056 NLM Identifier: NCT00095056
59 **Chan JC**, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, Stein PP, Kaufman KD, Amatruda JM, Williams-Herman D. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008; **10**: 545-555 [PMID: 18518892 DOI: 10.1111/j.1463-1326.2008.00914.x]
60 **Kojima Y**, Kaga H, Hayashi S, Kitazawa T, Iimura Y, Ohno M, Yoshitsugu M, Fujiwara M, Hiyoshi T. Comparison between sitagliptin and nateglinide on postprandial lipid levels: The STANDARD study. *World J Diabetes* 2013; **4**: 8-13 [PMID: 23493856 DOI: 10.4239/wjd.v4.i1.8]
61 **Arjona Ferreira JC**, Marre M, Barzilai N, Guo H, Golm GT, Sisk CM, Kaufman KD, Goldstein BJ. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. *Diabetes Care* 2013; **36**: 1067-1073 [PMID: 23248197 DOI: 10.2337/dc12-1365]
62 **Merck Sharp and Dohme Corp**. Sitagliptin versus glipizide in participants with type 2 diabetes mellitus and chronic renal insufficiency (MK-0431-063 AM1). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00509262 NLM Identifier: NCT00509262
63 **Merck Sharp and Dohme Corp**. MK0431 and pioglitazone co-administration factorial study in patients with type 2 diabetes mellitus (0431-102 AM2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00722371 NLM Identifier: NCT00722371
64 **Henry RR**, Staels B, Fonseca VA, Chou MZ, Teng R, Golm GT, Langdon RB, Kaufman KD, Steinberg H, Goldstein BJ. Efficacy and safety of initial combination treatment with sitagliptin and pioglitazone--a factorial study. *Diabetes Obes Metab* 2014; **16**: 223-230 [PMID: 23909985 DOI: 10.1111/dom.12194]
65 **Merck Sharp and Dohme Corp.** Sitagliptin metformin add-on study in patients with TYpe 2 diabetes mellitus. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00337610 NLM Identifier: NCT00337610
66 **Raz I**, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, Langdon RB, Stein PP, Alba M. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 2008; **24**: 537-550 [PMID: 18194595 DOI: 10.1185/030079908X260925]
67 **Merck Sharp and Dohme Corp.** Study of sitagliptin treatment in patients with type 2 diabetes during ramadhan (0431-263). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01131182 NLM Identifier: NCT01131182

68 **Goldstein BJ**, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2007; **30**: 1979-1987 [PMID: 17485570]

69 **Merck Sharp and Dohme Corp.** MK0431 (sitagliptin) and metformin co-administration factorial study in patients with type 2 diabetes mellitus (0431-036). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00103857 NLM Identifier: NCT00103857

70 **Merck Sharp and Dohme Corp**. A study to test the safety and efficacy of sitagliptin compared to glimepiride in patients with type 2 diabetes on a stable dose of metformin (0431-803). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00701090 NLM Identifier: NCT00701090

71 **Arechavaleta R**, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, Kaufman KD, Williams-Herman D, Goldstein BJ. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2011; **13**: 160-168 [PMID: 21199268 DOI: 10.1111/j.1463-1326.2010.01334.x]

72 **Merck Sharp and Dohme Corp**. Metformin add-on study in patients with type 2 diabetes mellitus (0431-020). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00086515 NLM Identifier: NCT00086515

73 **Charbonnel B**, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29**: 2638-2643 [PMID: 17130197 DOI: 10.2337/dc06-0706]

74 **Merck Sharp and Dohme Corp**. A study to compare the glycemic effects, safety, and tolerability of exenatide once weekly to those of sitagliptin and pioglitazone in subjects with type 2 diabetes treated with metformin (DURATION-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00637273 NLM Identifier: NCT00637273

75 **Bergenstal RM**, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J, Porter LE. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010; **376**: 431-439 [PMID: 20580422 DOI: 10.1016/S0140-6736(10)60590-9]

76 **Merck Sharp and Dohme Corp.** An investigational drug study in patients with type 2 diabetes mellitus (MK0431-023). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00094757 NLM Identifier: NCT00094757

77 **Merck Sharp and Dohme Corp.** An investigational drug study in patients with type 2 diabetes mellitus (0431-024). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00094770 NLM Identifier: NCT00094770

78 **Janssen Research and Development, LLC.** The CANTATA-D2 trial (CANagliflozin treatment and trial analysis-DPP-4 inhibitor second comparator trial). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01137812 NLM Identifier: NCT01137812

79 **Schernthaner G**, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 2013; **36**: 2508-2515 [PMID: 23564919 DOI: 10.2337/dc12-2491]

80 **Merck Sharp and Dohme Corp.** MK0431 A comparative study in patients with type 2 diabetes (0431A-079). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT00482729 NLM Identifier: NCT00482729

81 **Bunck MC**, Diamant M, Cornér A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Järvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2009; **32**: 762-768 [PMID: 19196887 DOI: 10.2337/dc08-1797]

82 **Diamant M**, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010; **375**: 2234-2243 [PMID: 20609969 DOI: 10.1016/S0140-6736(10)60406-0]

83 **Inagaki N**, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther* 2012; **34**: 1892-1908.e1 [PMID: 22884767 DOI: 10.1016/j.clinthera.2012.07.007]

84 **Russell-Jones D**, Cuddihy RM, Hanefeld M, Kumar A, González JG, Chan M, Wolka AM, Boardman MK. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care* 2012; **35**: 252-258 [PMID: 22210563 DOI: 10.2337/dc11-1107]

85 **AstraZeneca.** Efficacy of once-weekly exenatide versus once or twice daily insulin detemir in patients with type 2 diabetes. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2014 Jun 22]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01003184 NLM Identifier: NCT01003184

86 **Astrup A**, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes* (Lond) 2012; **36**: 843-854 [PMID: 21844879 DOI: 10.1038/ijo.2011.158]

87 **Garber A**, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**: 473-481 [PMID: 18819705 DOI: 10.1016/S0140-6736(08)61246-5]

88 **Nauck M**, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009; **32**: 84-90 [PMID: 18931095 DOI: 10.2337/dc08-1355]

89 **Marre M**, Shaw J, Brändle M, Bebakar WM, Kamaruddin NA, Strand J, Zdravkovic M, Le Thi TD, Colagiuri S. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009; **26**: 268-278 [PMID: 19317822 DOI: 10.1111/j.1464-5491.2009.02666.x]

90 **Zinman B**, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde L. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009; **32**: 1224-1230 [PMID: 19289857 DOI: 10.2337/dc08-2124]

91 **Raz I**, Fonseca V, Kipnes M, Durrwell L, Hoekstra J, Boldrin M,

Balena R. Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabetic patients after 24 weeks of treatment: results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1). *Diabetes Care* 2012; **35**: 485-487 [PMID: 22301126 DOI: 10.2337/dc11-1942]

92 **Rosenstock J**, Reusch J, Bush M, Yang F, Stewart M. 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**: 1880-1886 [PMID: 19592625 DOI: 10.2337/dc09-0366]

93 **Seino Y**, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab* 2012; **14**: 910-917 [PMID: 22564709 DOI: 10.1111/j.1463-1326.2012.01618.x]

94 **Umpierrez GE**, Blevins T, Rosenstock J, Cheng C, Anderson JH, Bastyr EJ. The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study. *Diabetes Obes Metab* 2011; **13**: 418-425 [PMID: 21251180 DOI: 10.1111/j.1463-1326.2011.01366.x]

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