Annals of Clinical Diabetes and Endocrinology

Review Article
Published: 21 Jul, 2020

Is Liraglutide a Safe and Effective Medication to Treat Hyperglycaemia? A Systematic Review

*Ameera Al Onezei, Shahwar I Jiwani, Philemon Gyasi-Antwi, Andrew Meal and Gary G Adams**

Department of Medicine and Health Sciences, The University of Nottingham, UK

Abstract

Background: The aim of this systematic review is to examine the effectiveness of Liraglutide on glycemic control and Systolic Blood Pressure (SBP) in patients with Type 2 Diabetes (T2D) mellitus and to investigate whether Liraglutide leads to any Gastrointestinal (GI) adverse effects.

Materials and Methods: seven databases were searched, including CINAHL, MEDLINE, PubMed, EMBASE, Cochrane, Joana Briggs Institute (JBI). Only Randomized Controlled Trials (RCTs) that assessed safety and efficacy of Liraglutide in patients with type 2 diabetes were included. The extracted outcome measures were HbA1c, SBP, and GI disturbances.

Results: 40 RCTs were included with overall numbers of participants were 16,113. Liraglutide as monotherapy or as adjunct treatments to other diabetes treatments showed significant reduction in HbA1c levels in patients with T2D. Nine studies compared Liraglutide to a placebo and Liraglutide was superior to the placebo at HbA1c reduction. Four studies compared Liraglutide to Sitagliptin, five to Glimepiride, and one to Rosiglitazone, in these studies Liraglutide was also superior at HbA1c reduction. Two studies compared it to Metformin, in one of them Liraglutide was superior. One study compared Liraglutide to variety of Oral Anti-Diabetes Medications (OADs); Liraglutide was superior at HbA1c reduction. Ten studies compared Liraglutide to variety of insulin therapy, the combination of Liraglutide plus Insulin showed greater reduction at HbA1c levels than Liraglutide or Insulin alone. In addition, Liraglutide was superior when compared to insulin as part and insulin glargine at HbA1c reduction. Eight studies compared Liraglutide to glucagon-like peptide-1 receptor agonist (Exenatide, Dulaglutide, Lixisenatide, Albiglutide, and Semaglutide), Liraglutide was superior to Exenatide, Lixisenatide, and Albiglutide at HbA1c reduction. In most of the included studies Liraglutide showed significant reduction in SBP. Liraglutide can lead to different GI events, most frequently nausea, vomiting, and diarrhea, which are transient in nature.

Conclusion: The results of this systematic review indicated that Liraglutide as a monotherapy or as adjunct treatments to other diabetes treatments could significantly lower HbA1c levels and SBP. Although the gastrointestinal adverse event is common with Liraglutide, Liraglutide can be effective choice in T2D treatment.

OPEN ACCESS

Correspondence:
Gary G Adams, Department of Medicine and Health Sciences, The University of Nottingham, UK, E-mail: Gary.Adams@nottingham.ac.uk

Received Date: *28 Jun 2020*
Accepted Date: *13 Jul 2020*
Published Date: *21 Jul 2020*

Citation:
Al Onezei A, Jiwani SI, Gyasi-Antwi P, Meal A, Adams GG. Is Liraglutide a Safe and Effective Medication to Treat Hyperglycaemia? A Systematic Review. Ann Clin Diabetes Endocrinol. 2020; 3(2): 1017.

Abbreviations

T2D: Type 2 Diabetes; SBP: Systolic Blood Pressure; GI: Gastrointestinal; OADs: Oral Antidiabetes Medications; RCTs: Randomized Controlled Trials; GLP-1: Glucagon-Like Peptide-1

Introduction

Diabetes mellitus is defined as a heterogeneous metabolic disorder that clinically manifested by chronic hyperglycemia due to either impaired insulin secretion or defect in insulin action or both [1]. According to World Health Organization, diabetes mellitus is classified as one of four common major types of non-communicable disease worldwide. In 2014, it was estimated that 422 million adults around the world were diagnosed with diabetes, and in 2012, 1.5 million people died because of it (World Health Organization, 2016) [2]. Type 2 diabetes is more prevalent than type 1 [1]. The diagnosis of diabetes must be based on plasma-glucose values of Fasting Plasma Glucose (FPG) that are equal to or greater than 126 mg/dL (7.0 mmol/L), or 2-h plasma-glucose values during a 75 g oral glucose-tolerance test that are equal to or greater than 200 mg/dL (11.1 mmol/L) or an A1c Hemoglobin blood test (HbA1c) that is equal to or greater than 6.5% (48 mmol/mol) [3].

Duration of diabetes and intensity of hyperglycaemia are the main leading factors for the

development of diabetes complication [4]. Diabetes complications are divided into microvascular complications, which is due to damage to the small blood vessels and macrovascular complication that due to damage to larger blood vessels [4,5]. Examples of microvascular complications include 1) Diabetes retinopathy; 2) Diabetes nephropathy 3) Diabetes neuropathy and macrovascular complications.

The principal goal of diabetes treatment is to maintain glycemic control by implementing various lifestyle changes and undergoing pharmacological therapy [6]. There are many classes of drugs available for the treatment of type 2 diabetes, including alpha-glucosidase inhibitors, thiazolidinediones and Glucagon-Like Peptide-1 (GLP-1) receptor agonists [6,7]. However, the first choice for the treatment of type 2 diabetes is metformin [7-9]. If the target blood-glucose levels are not achieved within three months through the use of metformin, a second drug combination will be used [9].

Liraglutide

Liraglutide (Victoza®) is an injectable synthetic analogue of human Glucagon-Like Peptide-1 (GLP-1) that works as GLP-1 receptor agonist [10]. Liraglutide shares 97% amino acid homology to the amino acid structure of native Human GLP-1 [10-12]. This was obtained by substitution of lysine at position 34 to arginine 34 at N-terminal and addition of 16-carbon fatty-acid chain using a glutamic acid spacer that is chemically attached to the lysine at position 26 [11-12]. These changes prolonged the plasma half-life of Liraglutide to 13 hours compared to human GLP-1 half-life, which is ~2 min [11-12].

GLP-1 is gut-derived hormone produced by enteroendocrine L-cells in the distal ileum of the large intestine; the primary stimulus for GLP-1 secretion is food ingestion [13]. The most common action of GLP-1 is on islet beta cells as the effect of GLP-1 receptor activation leads to insulin secretion in glucose-dependent manner [14]. The glucoregulatory actions of GLP-1 is exhibited via slowing of gastric emptying; inhibition of glucagon secretion; promoting satiety, which is associated with weight reduction in both preclinical and clinical studies [13].

Liraglutide has similar effects of GLP-1 but with prolonged half-life of 13 h and maximum concentration reached after 8 h to 12 h of subcutaneous administration [11]. When blood-glucose levels are elevated, Liraglutide stimulates GLP-1 receptors to release insulin, reduce glucagon secretion and inhibit gastric emptying, thus leading to increased control of body weight [10]. This mode of glucose-dependent action is also associated with lower instances of hypoglycemic episodes [15].

Liraglutide was approved by the US Food and Drug Administration in January 2010 to improve glycemic control in type 2 diabetes mellitus in addition to when coupled with a balanced diet and exercise [13,16]. Liraglutide is an once-daily subcutaneous injection that can be injected at any time of the day, independently of meals [17]. It is available as 0.6 mg, 1.2 mg and 1.8 mg, the initiation dose is 0.6 mg and after week increase to 1.2 mg then it can be increased to 1.8 mg for more efficiency [17].

Liraglutide also leads to various other non-glycemic benefits such as improvement in systolic blood pressure and the functioning of β-cells [18]. A randomized controlled double-blind study of 9,340 patients over 3.8 years assessed the effect of Liraglutide on the cardiovascular outcome. It concluded that the rate of non-fatal myocardial infarction, non-fatal stroke or the occurrence of first death due to cardiovascular causes in type 2 diabetes patients was lower in patients receiving Liraglutide than placebo [19]. Liraglutide also assists with weight loss, especially for overweight and obese patients with type 2 diabetes [20]. The efficiency of Liraglutide in weight management was investigated in randomized clinical trial of 846 overweight diabetes patients. Patients were randomized to receive 1.8 mg Liraglutide (n=211), 3.0 mg Liraglutide (n=423), or placebo (n=212). The results show weight loss of 6.0% with 3.0 mg Liraglutide, 4.7% weight loss with 1.8 mg Liraglutide and 2.0% with placebo [20]. These features of GLP-1 receptor agonists have made them an attractive choice for patients with type 2 diabetes [15].

Multiple studies have assessed the efficacy and safety of Liraglutide. The Liraglutide Effect and Action in Diabetes (LEAD) program, which was founded by the manufacturer of Liraglutide, Novo Nordisk, consisted of six Randomized Controlled Trails (RCT) that assess the effect of Liraglutide as a form of monotherapy or in combination with other anti-diabetes drugs. In LEAD program, 3,900 patients were recruited from forty countries [11]. An overview of LEAD studies concluded that from the LEAD-1 to LEAD-5 trials, Liraglutide led to a reduction in HbA1c by up to 1.6%, a rapid reduction in FPG and a consistent reduction in postprandial glucose. Liraglutide was also associated with significant weight loss, reduced the risk of hypoglycemia and reduced systolic blood pressure [21].

No large scale systematic review has previously investigated the effectiveness and safety of Liraglutide itself.

The aim of this systematic review is to examine the effectiveness of Liraglutide on glycemic control and Systolic Blood Pressure (SBP) in patients with type 2 diabetes mellitus and to investigate whether Liraglutide leads to any gastrointestinal adverse effects.

Materials and Methods

Eligibility criteria

Participants: This systematic review considered RCTs that include adults over the age of 18 with type 2 diabetes mellitus who have inadequate control of their blood-glucose levels. Patients were excluded if they presented with conditions that affect their red blood cells, such as anemia or end-stage kidney disease, or patients who have recently undergone a blood transfusion.

Intervention

This systematic review considered studies that evaluated the effectiveness of Liraglutide as a combination to one or more other diabetes treatment (i.e., metformin, sulfonylurea, Pioglitazone, DPP-4 inhibitors, Glinides and insulin) or as a monotherapy in lowering blood-glucose levels and SBP. The key intervention of interest was the administering of Liraglutide. Any dosages of Liraglutide were considered in the review.

Study type

This systematic review considered only RCTs that investigated the effectiveness of Liraglutide in hyperglycemic control, SBP and GI adverse events.

Comparison

The effect of administering Liraglutide compared to placebo, metformin, insulin, Glucagon-like peptide-1 receptor agonist, Dipeptidyl peptidase-4 inhibitors or any other antidiabetes medications.

Primary outcomes

The primary outcome is to measure the effect of Liraglutide in lowering blood-glucose levels. All included studies assess this effect by measuring HbA1c in order to ensure homogeneous data for a reliable analysis.

Secondary outcomes

Systolic blood pressure: This secondary outcome is to assess the effectiveness of Liraglutide in lowering systolic blood pressure.

Gastrointestinal disturbance

This secondary outcome is to evaluate any gastrointestinal adverse events associated with Liraglutide.

Search strategy

First stage: An initial basic search of PubMed, CINAHL and EMBASE using the basic search words and phrases (i.e., Liraglutide, type 2 diabetes and glycemic control) was done to find potentially relevant studies with no specific time frame. After reviewing the title and abstract of these initial studies, the search words and phrases were expanded.

Second stage: Databases and grey literature sources were searched using the identified keywords and phrases. These databases included: CINAHL, MEDLINE, PubMed, EMBASE, Cochrane, Joana Briggs Institute (JBI). The grey literature included: American Diabetes Association, International Diabetes Federation, and Google Scholar.

Third stage: The reference lists of the identified studies also were examined. A search of authors' names who are known to have conducted research in the same field also were carried out in order to find more relevant studies.

Study selection

The titles and abstracts of the studies were examined during the search process and some studies full texts were examined for more details. The RCTs that met the inclusion criteria were included and studies that did not meet the inclusion criteria were excluded as well the duplicated studies.

Critical appraisal

All included studies were critically appraised for their methodological validity before being including in the review. Critical appraisal instruments were used from the Joanna Briggs Institute.

All RCTs in this systematic review were assessed for bias and judged according to high, low or unclear levels of bias, based on the Cochrane risk-of-bias tool criteria. The five elements of bias (i.e., selection, performance, attrition, detection and reporting bias) were assessed using this tool.

Selection bias: This can happened due to inadequate generation of randomized sequence or inadequate concealment of allocations before the assignment. All included studies were given either 'Low Risk' of bias if the study describe the way of randomized sequence generation and concealment of allocations or 'Unclear Risk' of bias if the study does not describe the way of randomized sequence generation and concealment of allocations. 'High Risk' of bias was given if the study did not perform the allocation concealment.

Performance bias: Can happen due to participant and personal knowledge of intervention allocation. All included studies were given either 'Low Risk' of bias if the study was double blinded and/or double dummy or 'High Risk' of bias if the study was not blinded.

Detection bias: This can happen due to outcome assessor knowledge of the allocated intervention. In all included studies this domain was not addressed by authors thus it was deleted from the figure chart.

Attrition bias: this can happened due to the way of dealing with incomplete data. All included studies were given either 'Low Risk' of bias if the study explained the way they handled incomplete data (most studies imputed the missing values by last observation carried forward), or 'High Risk' of bias if the study stated that they did not imputed the missing values, or 'Unclear Risk' if they did not mention anything about it.

Reporting bias: can happen due to selective reporting. All included studies were given either 'Low Risk' of bias if there is a protocol or clear listed outcome, or 'Unclear Risk' of bias if there was no protocol but clear listed outcome.

Other bias: In this review other bias is referred to the nature of funding that support the study as this medication is manufactured by Novo Nordisk Company that funded most of the included studies.

Data extraction and synthesis

Each included study was summarised and necessary details extracted using the Joanna Briggs Institute data extraction form.

Study method, type of participant, setting (i.e., where the study was done, sample size and interventions), in what dose Liraglutide was administered, was the participant on other medication such as metformin or sulfonylurea or insulin etc, the primary outcome measure of HbA1c, the secondary outcome measures of systolic blood pressure and the gastrointestinal adverse events (e.g., nausea, diarrhea, vomiting, decreased appetite or headache) and authors' conclusions.

Results

Search results: Seven electronic databases identified 1,679 studies: CINAHL (n=25), MEDLINE (n=469), PubMed (n=338), EMBASE (n=413), Cochrane (n=429), Joana Briggs Institute (JBI) (n=5). Initially, all the studies were assessed by title alone. If the titles were found to be relevant, the abstracts were then assessed for eligibility then a full text analysis was carried out. 552 duplicates were removed and 1,073 irrelevant studies were excluded after title and abstract review. Full text examination of the remaining 54 studies based on the inclusion and exclusion criteria and forty studies met the review inclusion criteria. Figure 1 shows PRISMA flow diagram of the studies identification.

Excluded studies: Fourteen studies were excluded out of 54 studies after full text analysis due to: (n:2) studies the participants age was less than 18 years old; (n:1) study the participants with type 1 diabetes millets; (n:3) studies were assessing the efficacy and safety of switching from some types of medication to Liraglutide which can interfere with the study's results; (n:1) study short duration of intervention (5 weeks); (n:1) study analysis of three RCTs (LEAD 1, LEAD 2 and LEAD 4).

Characteristics of included studies: All the included studies are Randomized Control Trials. The publication date of included studies ranged from 2004 to 2016. Half of the included trials (n:20) are multinational; (n:7) were carried out in Japan; (n:5) in USA; (n:3) in China; (n:1) in Netherlands; (n:1) in Sweden; (n:1) in Germany; (n:1) in Scandinavia and UK; and one study did not mention the origin (Feinglos et al, 2004). Most of the trials (n:35) are multicentre

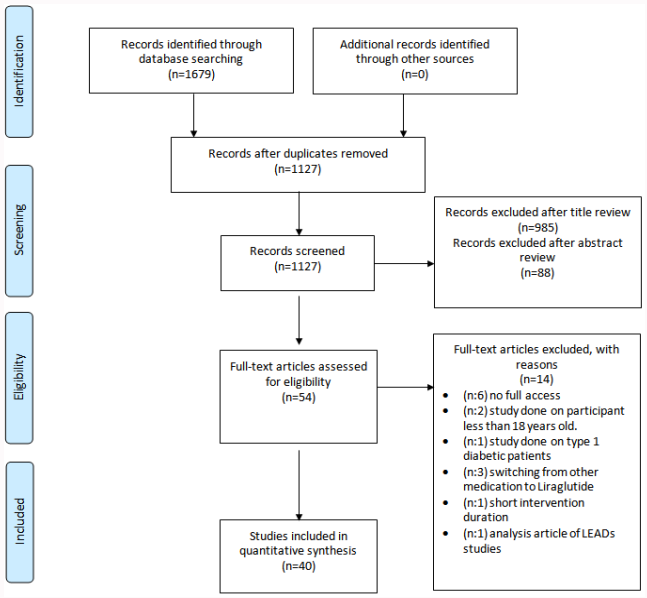

Figure 1: PRISMA flow diagram of studies identification.

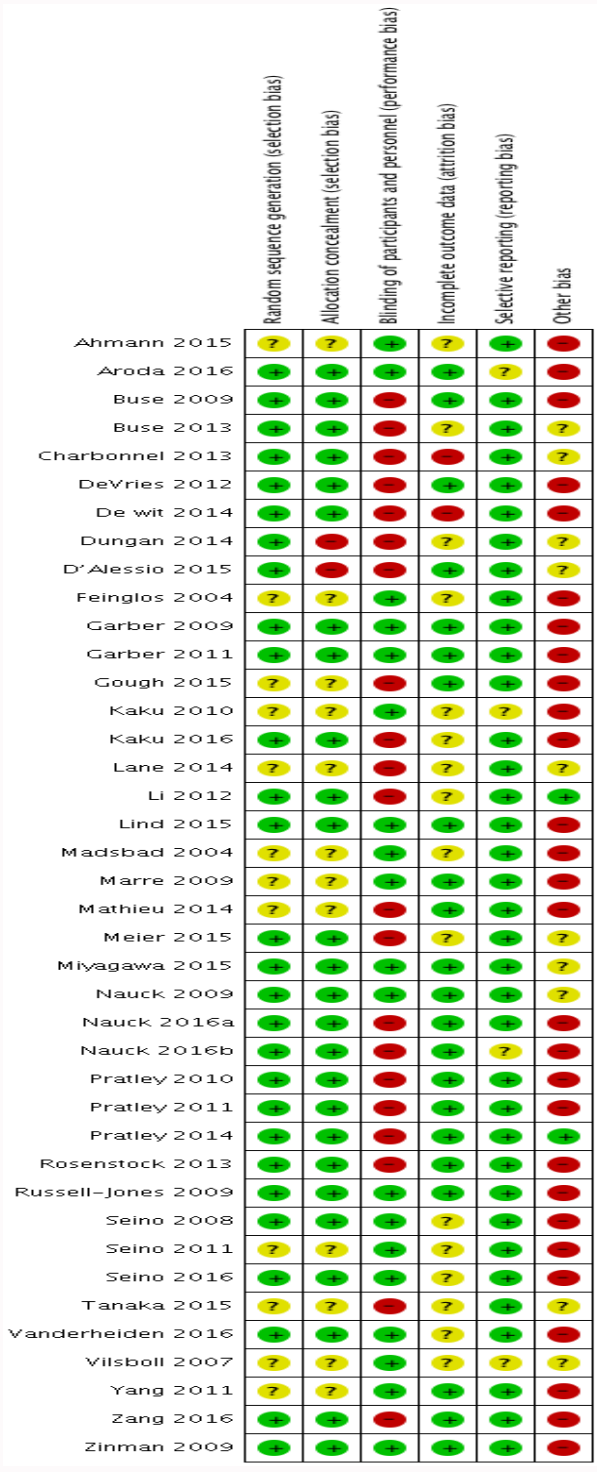

Figure 2: Summary of risk of bias in included studies (RevMan 5.3). (Key: (+) Low risk of bias, (-) High risk of bias, (?) Unclear risk of bias).

and the remaining are single-centre except in (Feinglos et al, 2004). The duration of the RCTs ranged from 8 weeks to 104 weeks: (n:17) studies for 26 weeks; (n:6) studies for 52 weeks; (n:6) studies for 24 weeks; (n:3) studies for 12 weeks; (n:2) studies for 16 weeks; (n:2) studies for 14 weeks; (n:1) study for 8 weeks; (n:1) study for 32 weeks; (n:1) study for 36 weeks; (n:1) study for 104 weeks.

See Table 1 for the summary of the studies characteristics.

Characteristics of participants: In all the trials, the overall number of participant is 16,113 with studies sample size ranged from 37 subjects to 1,663 subjects. Participants are aged 18 years old and above with mean age ranged between 52.0 ± 10.2 years and 61.8 ± 8.2 years. All the participants with type 2 diabetes and the mean duration of the disease ranged from 2.6 ± 2.9 years to 17.9 ± 8.4 years. All trials included both male and female subjects with varying percentages among studies. Mostly, each included study has a number of patients discontinuing the trial due to the side effect of Liraglutide, the number of participant and completers in each study (Table 1) [22-61].

Characteristics of intervention: The main intervention in all included studies is administering Liraglutide. The predominant doses of Liraglutide in most of the trials are: 0.6 mg, 1.2 mg or 1.8 mg all per day**.** Three studies were dose findings in which they used less doses [62].

Risk of bias in included studies: The Cochrane Collaboration's tool for assessing risk of bias consists of six domains: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [63]. Each domain were assessed by answering pre-specified questions and the level of bias expressed by 'Low Risk', 'High Risk' and 'Unclear Risk' (Figure 2).

Results and Discussion

The aim of this review was to assess the efficacy of Liraglutide in lowering HbA1c levels among type 2 diabetes patients as a primary outcome and its efficacy on SBP as a secondary outcome, as well as any associated GI disturbances. The results show that Liraglutide is effective on both HbA1c and SBP and that it can lead to various GI disturbances.

Theme 1: Liraglutide and HbA1c

The HbA1c level was the primary outcome measure of all included studies. The studies' results advocate Liraglutide's use as an effective treatment management of type 2 diabetes. In 16 of the studies (10, 11, 12, 14, 16, 19, 22, 24, 26, 27, 28, 32, 33, 37, 38, and 40), the interventions comprised multiple arms, including different dosages of Liraglutide and the comparator. In these trials, it is shown

Table 1: Summary of the included studies result.

	Author	Study type	Study duration	Participant	Intervention	Background medication	Outcomes			
1	Ahmann et al. [22]	RCT Multicenter Multinational Double-blind	26 weeks	· 450 Pts randomized · 364 Pts completed · Male: 56.8% · Female: 43.2% ·T2D duration: 12.1 ± 6.9 Years ·Mean (SD) Age: 58.4 ± 10.1.	· **Liraglutide: 1.8 mg/ day.** (pts number 225) · **Placebo:** (pts number 225)	Basal insulin analogue (≥ 20 U/day) ± metformin (≥ 1500 mg/day).	**1. HbA1c:** **Before**: mean SD 8.25% ± (0.85%) 7.0% to 10.0% **After Liraglutide**: estimated change -1.3% **After placebo:** estimated change -0.1% **2. SBP:** **After Liraglutide**: -5.78 mmHg ↓ from baseline. **After placebo:** -0.76 mmHg ↓ from baseline. **3. GI events:** Number of patients reporting GI events in each group:			
								Liraglutide	**placebo**	
							Nausea	50	7	
							Diarrhea	24	11	
							Vomiting	20	2	
							Dyspepsia	16	2	
							Nasopharyngitis	13	14	
							Headache	8	16	
							Lipase increased	17	5	
							Decreased appetite	22	5	
2	Aroda et al. [23]	RCT Multicenter Multinational Double-blind	26 weeks+15 weeks run-in period	·346 Pts randomized · 291 Pts completed · Male: 58.4% · Female: 41.6% ·T2D duration · Mean(SD): 9.5 ± 5.6 Years · Mean(SD)Age:57.1 ± 9.7 years	·**Liraglutide 1.8 mg/ day + Placebo.** (pts number 172) · **Liraglutide 1.8 mg/day + Insulin Degludec.** (pts number 174)	Metformin (≥ 1500 mg)	**1. HbA1c:** **Before**: mean SD 7.6 ± 0.6% **After Liraglutide 1.8 mg/day + Insulin Degludec**: estimated change -1.04% from baseline **After Liraglutide 1.8 mg/day + Placebo:** estimated change -0.16% from baseline **2. SBP:** From week 0 to week 26, mean blood pressure decreased slightly in both treatment groups. **3. GI events:** Number of patients reporting GI events in each group:			
								Liraglutide 1.8 mg/day + Placebo	**Liraglutide 1.8 mg/day + Insulin Degludec**	
							Diarrhea	13	10	
							Nasopharyngitis	11	14	
							Lipase increased	13	10	

3	Buse et al. [24]	RCT Multicenter Multinational open-label	26 weeks	·464 Pts randomized	· **Liraglutide 1.8 mg/ day:** (pts number 233	Maximum dose of metformin, sulphonylurea, or both.	**1. HbA1c:**			
							Before: mean SD 8.2 ± 1.0%			
							After Liraglutide 1.8 mg/day: estimated change -1.12% from baseline			
				· 389 Pts completed			**After Exenatide 10 µg twice a day:** estimated change -0.79% from baseline			
				· Male: 52%	· **Exenatide 10 µg twice a day:** pts number 231					
				· Female: 48%			**2. SBP:**			
							After Liraglutide 1.8 mg/day: -2.51 mmHg ↓ from baseline.			
							After Exenatide 10 µg twice a day: -2.0 mmHg ↓ from baseline.			
				· T2D duration			**3. GI events:**			
							Number of patients reporting GI events in each group:			
								Liraglutide	**Exenatide**	
				Mean (SD): 8.2 ± 6.0 Years			**Nausea**	60	65	
							Diarrhea	29	28	
							Vomiting	14	23	
							Dyspepsia	21	11	
							Nasopharyngitis	27	31	
				· Mean(SD)Age:56.7 ± 10.3 years			**Headache**	21	24	
							Constipation	12	6	
4	Buse et al. [25]	RCT Multicenter Multinational open-label	26 weeks	·911 Pts randomized	· **Liraglutide: 1.8 mg/ day.** (pts number 450)	maximum or near maximum dose of oral antihyper- glycaemic drugs (metformin, sulfonylurea, metformin plus sulfonylurea, or metformin plus pioglitazone)	**1. HbA1c:**			
							Before: mean SD 8.45 ± 1.0%			
				·791 Pts completed	· **Exenatide: 2 mg/ week** (pts number 461)		**After Liraglutide**: estimated change -1.48%			
							After Exenatide: estimated change -1.28%			
				· Male: 54.5%			**2. SBP:**			
							After Liraglutide: -3.45 mmHg ↓ from baseline.			
				· T2D duration: 8.5± 6 Years			**After Exenatide:** -2.48 mmHg ↓ from baseline.			
							3. GI events:			
							Number of patients reporting GI events in each group:			
								Liraglutide	**Exenatide**	
				· Mean(SD)Age: 57± 9.5 years			**Nausea**	93	43	
							Diarrhea	59	28	
							Vomiting	48	17	
							Dyspepsia	27	11	
							Nasopharyngitis	32	31	
							Headache	38	27	
							Decreased appetite	29	17	
							Constipation	22	21	
							Abdominal pain	8	12	

<table>
<tr><td rowspan="16">5</td><td rowspan="16">Charbonnel et al. [26]</td><td rowspan="16">RCT Multicenter Multinational open-label</td><td rowspan="16">26 week</td><td>· 653 Pts randomized</td><td>· Liraglutide: 1.2 mg/ day. (pts number 253)</td><td rowspan="16">metformin monotherapy ≥ 1,500 mg/day</td><td colspan="3">1. HbA1c:</td></tr>
<tr><td rowspan="3">·532 Pts completed</td><td rowspan="15">· Sitagliptin: 100 mg/ day (pts number 269)</td><td colspan="3">Before: baseline 7.0-11.0%, mean SD 8.15 ± 1.0%</td></tr>
<tr><td colspan="3">After Liraglutide: estimated change -1.4% ↓ from baseline</td></tr>
<tr><td colspan="3">After Sitagliptin: estimated change -1.3% ↓ from baseline.</td></tr>
<tr><td>· Male: 55%</td><td colspan="3">2. SBP:</td></tr>
<tr><td rowspan="2">· T2D duration: 7.9 ± 5.5 Years</td><td colspan="3">After Liraglutide : -1.9 mmHg ↓ from baseline</td></tr>
<tr><td colspan="3">After Sitagliptin: 0.9 mmHg ↓ from baseline</td></tr>
<tr><td rowspan="9">· Mean(SD)Age: 57 ± 10.4 years</td><td colspan="3">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>Sitagliptin</td></tr>
<tr><td>Nausea</td><td>63</td><td>10</td></tr>
<tr><td>Diarrhea</td><td>35</td><td>7</td></tr>
<tr><td>Vomiting</td><td>21</td><td>6</td></tr>
<tr><td>Dyspepsia</td><td>11</td><td>4</td></tr>
<tr><td>Constipation</td><td>6</td><td>4</td></tr>
<tr><td>Abdominal pain</td><td>16</td><td>5</td></tr>
<tr><td rowspan="17">6</td><td rowspan="17">DeVries et al. [27]</td><td rowspan="17">RCT Multicenter Multinational open-label</td><td>26 weeks</td><td rowspan="2">· 323 Pts randomized</td><td rowspan="16">· Liraglutide: 1.8 mg/ day. (pts number 161)</td><td rowspan="17">metformin (≥ 1500 mg/day)</td><td colspan="3">1. HbA1c:</td></tr>
<tr><td rowspan="16">12 weeks run-in period (metformin + Liraglutide 1.8mg)</td><td colspan="3">Before: mean SD 8.25 ± 0.75%</td></tr>
<tr><td colspan="3">After Liraglutide 1.8 mg : estimated change +0.02% ↓ from baseline</td></tr>
<tr><td rowspan="3">· 271 Pts completed</td><td colspan="3">After insulin detemir + Liraglutide 1.8 mg : estimated change -0.51% ↓ from baseline</td></tr>
<tr><td colspan="3">2. SBP:</td></tr>
<tr><td colspan="3">After Liraglutide 1.8mg: -3.13 mmHg</td></tr>
<tr><td colspan="3">After insulin detemir + Liraglutide 1.8 mg: -1.65 mmHg</td></tr>
<tr><td colspan="3">3. GI events:</td></tr>
<tr><td rowspan="2">· Female: 45.2%</td><td colspan="3">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>insulin detemir + Liraglutide</td></tr>
<tr><td>Nausea</td><td>9</td><td>6</td></tr>
<tr><td>Diarrhea</td><td>11</td><td>19</td></tr>
<tr><td>· T2D duration</td><td></td><td>Nasopharyngitis</td><td>30</td><td>23</td></tr>
<tr><td rowspan="2">Mean (SD): 8.3 ± 5.9Years</td><td rowspan="2"></td><td>Headache</td><td>13</td><td>10</td></tr>
<tr><td>Lipase increased</td><td>6</td><td>18</td></tr>
<tr><td>· Mean(SD)Age: 57 ± 9.6 years</td><td></td><td colspan="3"></td></tr>
</table>

7	De wit et al. [28]	RCT Single center open-label	26 weeks	· 50 Pts randomized · 47 Pts completed · Male: 62% · Female: 38% · T2D duration Mean(SD): 7.9 ± 6.0 Years · Mean(SD) Age: 58 ± 9 years	· **Liraglutide 1.8 mg/ day added on Insulin** (pts number 26) · **Insulin:** (pts number 24)	Metformin, Sulfonylurea or Sulfonylurea and metformin.	**1. HbA1c:** **Before**: mean SD 7.4 ± 0.6% **After Liraglutide 1.8 mg added on Insulin**: estimated change -0.77% from baseline **After insulin:** estimated change +0.01% from baseline **2. SBP:** **After Liraglutide 1.8 mg added on Insulin**: -7.0 mmHg ↓ from baseline. **After insulin:** -3.0 mmHg **3. GI events:** Number of patients reporting GI events in each group:			
								Liraglutide	**insulin glargine**	
							Nausea	11	3	
							Diarrhea	10	6	
							Vomiting	6	1	
							Dyspepsia	20	1	
							Constipation	14	2	
							Nasopharyngitis	8	7	
							Headache	10	6	
							Decreased appetite	24	2	
							Abdominal pain	9	1	
8	Dungan et al. [29]	RCT Multicenter Multinational open-label	26 weeks	· 599 Pts randomized ·538 Pts completed · Male: 48% · Female: 52% · T2D duration: 7.2 ± 5.4 Years · Mean (SD)Age: 56.65 ± 9.6 years	· **Liraglutide: 1.8 mg/ day.** (pts number 300) · **Dulaglutide 1.5 mg/ week** (pts number 299)	metformin (≥ 1500 mg/day)	**1. HbA1c:** **Before**: baseline 7.0-10.0%, mean SD 8.1 ± 0.8% **After Liraglutide**: estimated change -1.36% from baseline **After Dulaglutide:** estimated change -1.42% from baseline. **2. SBP:** **After Liraglutide**: -2.82 mmHg ↓ from baseline. **After Dulaglutide:** -3.36 mmHg ↓ from baseline. **3. GI events:** Number of patients reporting GI events in each group:			
								Liraglutide	**Dulaglutide**	
							Nausea	54	61	
							Diarrhea	36	36	
							Vomiting	25	21	
							Dyspepsia	18	24	
							Constipation	17	11	
							Nasopharyngitis	21	23	
							Headache	25	22	
							Decreased appetite	20	16	
							Lipase increased	9	11	

<table>
<tr><td rowspan="16">9</td><td rowspan="16">D'Alessio et al. [30]</td><td rowspan="16">RCT Multicenter Multinational open-label</td><td rowspan="16">24 weeks</td><td rowspan="5">· 978 Pts randomized</td><td rowspan="5">· Liraglutide: 1.8 mg/ day. (pts number 470)</td><td rowspan="16">metformin at a minimum dose of 1 g/day, alone or in combination with sulphonylurea, glinides or a dipeptidyl peptidase-4 inhibitor for >3 months.</td><td colspan="3">1. HbA1c:</td><td></td></tr>
<tr><td colspan="3">Before: mean SD 9.0 ± 1.1%</td><td></td></tr>
<tr><td colspan="3">After Liraglutide 1.8 mg: estimated change -1.79% from baseline</td><td></td></tr>
<tr><td colspan="3">After insulin glargine: estimated change -1.94% from baseline</td><td></td></tr>
<tr><td colspan="3">2. SBP:</td><td></td></tr>
<tr><td rowspan="2">· Male: 54.4%</td><td rowspan="3">· insulin glargine: (pts number 474)</td><td colspan="3">After Liraglutide: -3.1 mmHg ↓ from baseline.</td><td></td></tr>
<tr><td colspan="3">After insulin glargine: no change.</td><td></td></tr>
<tr><td rowspan="2">· Female: 45.6%</td><td colspan="3">3. GI events:</td><td></td></tr>
<tr><td rowspan="3">· T2D duration</td><td rowspan="3"></td><td colspan="3">Number of patients reporting GI events in each group:</td><td></td></tr>
<tr><td></td><td>Liraglutide</td><td>insulin glargine</td><td></td></tr>
<tr><td rowspan="2">· Mean (SD): 9 ± 6 Years</td><td rowspan="2"></td><td>Nausea</td><td>146</td><td>13</td><td></td></tr>
<tr><td rowspan="2">· Mean (SD) Age: 57 ± 9 years</td><td rowspan="2"></td><td>Diarrhea</td><td>62</td><td>18</td><td></td></tr>
<tr><td>Vomiting</td><td>46</td><td>8</td><td></td></tr>
<tr><td rowspan="20">10</td><td rowspan="20">Feinglos et al. [31]</td><td rowspan="20">RCT Multicenter double-blind USA</td><td rowspan="20">12 weeks</td><td rowspan="4">· 210 Pts randomized</td><td rowspan="4">· Liraglutide 0.045 mg/day: (pts number 37)</td><td rowspan="20">None</td><td>Dyspepsia</td><td>25</td><td>4</td><td></td></tr>
<tr><td>Constipation</td><td>26</td><td>6</td><td></td></tr>
<tr><td>Nasopharyngitis</td><td>35</td><td>38</td><td></td></tr>
<tr><td>Headache</td><td>29</td><td>24</td><td></td></tr>
<tr><td colspan="3">1. HbA1c:</td><td></td></tr>
<tr><td colspan="3">Before: mean SD 7.0 ± 1.2%</td><td></td></tr>
<tr><td colspan="3">After Liraglutide:</td><td></td></tr>
<tr><td colspan="3">0.045 mg/day: estimated change +1.28% from baseline</td><td></td></tr>
<tr><td rowspan="5">· 179 Pts completed</td><td></td><td colspan="3">0.225 mg/day: estimated change +0.86% from baseline</td><td></td></tr>
<tr><td>· Liraglutide 0.225 mg/day</td><td colspan="3">0.45 mg/day: estimated change +0.22% from baseline</td><td></td></tr>
<tr><td></td><td colspan="3">0.6 mg/day: estimated change +0.16% from baseline</td><td></td></tr>
<tr><td>(pts number 35)</td><td colspan="3">0.75 mg/day: estimated change +0.30% from baseline</td><td></td></tr>
<tr><td></td><td colspan="3">After Metformin: estimated change +0.09% from baseline</td><td></td></tr>
<tr><td rowspan="2">·Male: 40%</td><td rowspan="3">· Liraglutide 0.45 mg/ day: (pts number 33)</td><td colspan="3">2. GI events:</td><td></td></tr>
<tr><td colspan="3">Number of patients reporting GI events in each group:</td><td></td></tr>
<tr><td rowspan="2">· Female: 60%</td><td></td><td>Lira groups</td><td>Metformin</td><td></td></tr>
<tr><td rowspan="5">· Liraglutide 0.6 mg/ day (pts number 34)</td><td>n:176</td><td>n:34</td><td></td></tr>
<tr><td>Nausea</td><td>7</td><td>2</td><td></td></tr>
<tr><td rowspan="2">· T2D duration</td><td>Vomiting</td><td>4</td><td>1</td><td></td></tr>
<tr><td colspan="3" rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td rowspan="2">· Mean(SD): 4.7 ± 4.8 Years</td></tr>
<tr><td>· Mean(SD)Age: 53.5 ± 8.8 years</td><td>· Liraglutide 0.75 mg/ day: (pts number 37)</td><td colspan="3"></td></tr>
<tr><td></td><td>· Metformin 1000 mg twice/day(pts number 34)</td><td colspan="3"></td><td></td></tr>
</table>

<table>
<tr><td rowspan="15">11</td><td rowspan="15">Garber et al. [32]</td><td rowspan="14">RCT Multicenter double-blind</td><td rowspan="15">52 week</td><td>· 746 Pts randomized</td><td>· Liraglutide: 1.2 mg/ day. (pts number 251)</td><td rowspan="15">None</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td colspan="4">Before: mean SD 8.3 ± 1.1%</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg : estimated change -0.84% from baseline</td></tr>
<tr><td rowspan="2">· 487 Pts completed</td><td></td><td colspan="4">After Liraglutide 1.8 mg : estimated change -1.14% from baseline</td></tr>
<tr><td></td><td colspan="4">After Glimepiride: 8 mg/day: estimated change -0.51% from baseline.</td></tr>
<tr><td rowspan="3">· Male: 50%

Female: 50%

·T2D duration: 5.3 ± 5.2 Years</td><td rowspan="3">Liraglutide: 1.8 mg/ day. (pts number 247)</td><td colspan="4">2. SBP:</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg: -2.1 mmHg</td></tr>
<tr><td colspan="4">After Liraglutide 1.8 mg: -3.6 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">· Mean(SD)Age: 53.0 ± 10.9 years</td><td rowspan="2">Glimepiride: 8 mg/ day (pts number 248)</td><td colspan="4">After Glimepiride: 8 mg/day: -0.7mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td></td><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide 1.2 mg</td><td>Liraglutide 1.8 mg</td><td>Glimepiride</td></tr>
<tr><td>Nausea</td><td>69</td><td>72</td><td>21</td></tr>
<tr><td>Diarrhea</td><td>39</td><td>46</td><td>22</td></tr>
<tr><td>Vomiting</td><td>31</td><td>23</td><td>9</td></tr>
<tr><td>Nasopharyngitis</td><td>17</td><td>9</td><td>13</td></tr>
<tr><td>Headache</td><td>27</td><td>18</td><td>23</td></tr>
<tr><td>Constipation</td><td>21</td><td>28</td><td>12</td></tr>
<tr><td>Flatulence</td><td>4</td><td>13</td><td>4</td></tr>
<tr><td rowspan="15">12</td><td rowspan="15">Garber et al. [33]</td><td rowspan="15">RCT Multicenter
*Participants completing the 1-year randomized, double-blind, double-dummy period (Garber et al, 2009) could continue open-label treatment for an additional year</td><td rowspan="15">2 years (104 week)</td><td>· 746 Pts randomized</td><td rowspan="2">· Liraglutide: 1.2 mg/ day. (pts number 110)</td><td rowspan="15">None</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td colspan="4">Before: mean SD 8.0 ± 1.0%</td></tr>
<tr><td>· 440 Pts entered the extension at 52 weeks</td><td colspan="4">After Liraglutide 1.2 mg : estimated change -0.9% from baseline</td></tr>
<tr><td rowspan="2">321 Pts completed 104 weeks</td><td rowspan="2">Liraglutide: 1.8 mg/ day. (pts number 114)</td><td colspan="4">After Liraglutide 1.8 mg : estimated change -1.1% from baseline</td></tr>
<tr><td colspan="4">After Glimepiride: 8 mg/day: estimated change -0.6% from baseline.</td></tr>
<tr><td rowspan="3">Male: 51.6%·

Female: 48.4%

T2D duration: 4.6 ± 4.9 Years</td><td rowspan="3"></td><td colspan="4">2. SBP:</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg: -1.35 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">After Liraglutide 1.8 mg : -2.37 mmHg</td></tr>
<tr><td rowspan="2">· Mean(SD)Age: 53.5 ± 9.6 years</td><td rowspan="2">Glimepiride: 8 mg/ day (pts number 97)</td><td colspan="4">After Glimepiride: 8 mg/day: -0.49 mmHg</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide 1.2 mg</td><td>Liraglutide 1.8 mg</td><td>Glimepiride</td></tr>
<tr><td>Nausea</td><td>72</td><td>75</td><td>21</td></tr>
<tr><td>Diarrhea</td><td>44</td><td>48</td><td>23</td></tr>
<tr><td>Vomiting</td><td>33</td><td>25</td><td>10</td></tr>
<tr><td>Nasopharyngitis</td><td>23</td><td>16</td><td>18</td></tr>
<tr><td>Headache</td><td>28</td><td>18</td><td>23</td></tr>
<tr><td>Constipation</td><td>21</td><td>29</td><td>12</td></tr>
<tr><td>Flatulence</td><td>4</td><td>13</td><td>5</td></tr>
</table>

13	Gough et al. [34]	RCT Multicenter Multinational open-label	52 weeks	· 1663 Pts randomized	· **Liraglutide 1.8 mg/day**	metformin ± pioglitazone	**1. HbA1c:**
							Before: mean SD 8.3 ± 0.9%
				· 1311 Pts completed	(pts number 414)		**After Liraglutide**: estimated change -1.24% from baseline
					· **Insulin Degludec 100 U/ml:** (pts number 413)		**After Insulin Degludec:** estimated change -1.40% from baseline
							After IDegLira: estimated change -1.84% from baseline
							2. SBP:
							- No significant difference in systolic blood pressure between Liraglutide and IDegLira.
							- The mean change between IDegLira and insulin degludec was −1.54 mmHg.
				· Male: 50.3%			**3. GI events:**
				Female: 49.7%	· **(IDegLira) Insulin degludec 100 U/ml plus Liraglutide 3.6mg/m**(pts number 833)		The most frequently reported AEs were headache, nausea, diarrhoea, vomiting, nasopharyngitis and upper respiratory tract infection.
				· T2D duration			
				Mean (SD): 6.9 ± 5.5 Years			
				· Mean (SD) Age: 55 ± 9.9 years			
14	Kaku et al. [35]	RCT Japan double-blind	24 weeks	· 264 Pts randomized	· **Liraglutide 0.6 mg/day:** (pts number 88)	Sulphonylureas (glibenclamide, glicazide or glimeprimide)	**1. HbA1c:**
							Before: mean SD 8.42 ± 0.91%
				241 Pts completed	· **Liraglutide 0.9 mg/day** (pts number 88)		**After Liraglutide 0.6 mg/day:** estimated change -1.46% from baseline
							After Liraglutide 0.9 mg/day: estimated change -1.56% from baseline
							After Placebo: estimated change -0.40% from baseline
							2. SBP:
				· Male: 64%	**Placebo**(pts number 88)		Systolic blood pressure did not change in any of the treatment groups during the treatment period.
				· Female: 36%			**3. GI events:**
				· T2D duration			More subjects in the two Liraglutide groups reported gastrointestinal adverse events during the first 4 weeks
				Mean(SD): 10.3 ± 7.0 Years			
				· Mean(SD)Age:			
				59.7 ± 10.4 years			

15	Kaku et al. [36]	RCT Japan open-label	52 weeks	· • 360 Pts randomized	· **Liraglutide 0.9 mg/ day**(pts number 240)	single OAD (glinide, metformin, α-glucosidase inhibitor or thiazolidinedione)	**1. HbA1c:**			
				• 332 Pts completed			**Before**: mean SD 8.1 ± 0.8%			
							After Liraglutide 0.9 mg/day: estimated change -1.21% from baseline			
							After Additional OAD: estimated change -0.94% from baseline			
					Additional OAD (DPP-4 inhibitor, SU, glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) (pts number 120)					
							2. SBP:			
				· Male: 72.8%			**After Liraglutide:** -4.0 mmHg ↓ from baseline.			
				· Female: 27.2%			**After Additional OAD:** -3.91 mmHg ↓ from baseline.			
				· T2D duration			**3. GI events:**			
							Number of patients reporting GI events in each group:			
				Mean(SD): 8.02 ± 6.04 Years				**Liraglutide**	**Additional OAD**	
							Nausea	31	4	
							Diarrhea	20	9	
							Constipation	44	12	
				· Mean(SD)Age: 59.5 ± 11.1 years			**Nasopharyngitis**	89	47	
							Headache	12	4	
							Abdominal pain	19	1	
16	Lane et al. [37]	RCT Single center open-label USA	24 weeks	· 37 Pts randomized	· **Liraglutide 1.2mg or 1.8mg per day:** (pts number 21)	>100 units of insulin daily with or without metformin	**1. HbA1c:**			
				· Male: 46%			**Before**: mean SD 8.1 ± 0.8%			
				· Female: 54%			**After Liraglutide:** estimated change -0.65% from baseline			
				· T2D duration			**After Insulin up-titration:** estimated change -0.39% from baseline			
					· **Intensive insulin up-titration only:** (pts number 16)		**2. GI events:**			
				Mean(SD): 17.1 ± 7.1 Years			In Liraglutide group 24% experiencing mild to moderate nausea in the first 4 weeks which resolved by 12 weeks, and only one subject experienced vomiting.			
				Mean(SD)Age: 59.7 ± 10.8 years						
17	Li et al. [38]	RCT China open-label	16 weeks	· 90 Pts randomized	· **Liraglutide 1.2 mg/ day Added on Insulin:** (pts number 42)	Insulin injections for at least 3 months at a dose of at least 10 U/day	**1. HbA1c:**			
							Before: mean SD 8.7 ± 0.9%			
							After Liraglutide 1.2 mg/day Added on Insulin: estimated change -1.9% from baseline			
							After Insulin-increasing dose: estimated change -1.77% from baseline.			
				· 84 Pts completed			**2. GI events:**			
				· Male: 59.5%	· **Insulin-increasing dose:** (pts number 42)		GI events (diarrhoea, constipation, nausea and vomiting) are most frequently reported in Liraglutide-added group.			
				· Female: 40.5%						
				· T2D duration						
				Mean(SD): 9.0 ± 3.6 Years						
				· Mean(SD)Age: 52 ± 10.2 years						

<table>
<tr><td rowspan="11">18</td><td rowspan="11">Lind et al. [39]</td><td rowspan="11">RCT Multicenter double blind</td><td rowspan="11">24 weeks</td><td>· 124 Pts randomized</td><td>· Liraglutide 1.8mg/ day: (pts number 64)</td><td rowspan="11">Multiple daily insulin injections with or without Metformin.</td><td colspan="5">1. HbA1c:</td></tr>
<tr><td colspan="5">Before: mean SD 8.1 ± 0.8%</td></tr>
<tr><td colspan="5">After Liraglutide: estimated change -1.55% from baseline</td></tr>
<tr><td colspan="5">After Placebo: estimated change -0.42% from baseline</td></tr>
<tr><td>· 122 Pts completed</td><td rowspan="10">· Placebo : (pts number 60)</td><td colspan="5"></td></tr>
<tr><td colspan="5">2. SBP:</td></tr>
<tr><td colspan="5">After Liraglutide: -5.69 mmHg ↓ from baseline.</td></tr>
<tr><td>· Male: 64.6%</td><td colspan="5">After Placebo: +1.98 mmHg ↑ from baseline.</td></tr>
<tr><td colspan="5">3. GI events:</td></tr>
<tr><td>· Female: 35.4%</td><td colspan="5">Number of patients reporting GI events in each group:</td></tr>
<tr><td rowspan="2">· T2D duration</td><td></td><td>Liraglutide</td><td>Placebo</td><td></td></tr>
<tr><td>GI events</td><td>30</td><td>8</td><td></td></tr>
<tr><td>Mean(SD): 17.1 ± 7.8 Years</td><td>Nausea</td><td>21</td><td>1</td><td></td></tr>
<tr><td>· Mean(SD)Age: 63.6 ± 7.9 years</td><td>Diarrhea</td><td>5</td><td>3</td><td></td></tr>
<tr><td rowspan="19">19</td><td rowspan="19">Madsbad et al. [62]</td><td rowspan="19">RCT double blind</td><td rowspan="19">12 weeks</td><td>· 193 Pts randomized</td><td rowspan="5">· Liraglutide 0.045 mg/day: (pts number 26)</td><td rowspan="19">None</td><td colspan="5">1. HbA1c:</td></tr>
<tr><td rowspan="5">· 122 Pts completed</td><td colspan="5">Before: mean SD 7.6%</td></tr>
<tr><td colspan="5">After Liraglutide 0.045 mg/day: estimated change +0.25% from baseline</td></tr>
<tr><td colspan="5">After Liraglutide 0.225 mg/day: estimated change -0.34% from baseline</td></tr>
<tr><td colspan="5">After Liraglutide 0.45 mg/day: estimated change -0.30% from baseline</td></tr>
<tr><td rowspan="3">· Liraglutide 0.225 mg/day (pts number 24)</td><td colspan="5">After Liraglutide 0.60 mg/day: estimated change -0.70% from baseline</td></tr>
<tr><td colspan="5">After Liraglutide 0.75 mg/day: estimated change -0.75% from baseline</td></tr>
<tr><td rowspan="3">· Male: 64.6%</td><td colspan="5">After Glimepiride: estimated change -0.74% from baseline</td></tr>
<tr><td rowspan="4">· Liraglutide 0.45 mg/ day: (pts number 27)</td><td colspan="5">After Placebo: estimated change -0.42% from baseline</td></tr>
<tr><td colspan="5">2. GI events:</td></tr>
<tr><td rowspan="3">· Female: 35.4%</td><td colspan="5">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide groups 135 pts</td><td>Placebo</td><td>Glimepiride</td></tr>
<tr><td rowspan="4">· T2D duration</td><td>· Liraglutide 0.60 mg/ day(pts number 30)</td><td>Nausea</td><td>10</td><td>1</td><td>0</td></tr>
<tr><td rowspan="3">Liraglutide 0.75 mg/ day (pts number 28)</td><td>Diarrhea</td><td>5</td><td>0</td><td>0</td></tr>
<tr><td>Vomiting</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>Mean(SD): 17.1 ± 7.8 Years</td><td>Constipation</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>· Mean(SD)Age: 56.6 years</td><td colspan="5"></td></tr>
<tr><td></td><td>· Glimepiride 1-4mg (pts number 26)</td><td colspan="5"></td></tr>
<tr><td></td><td>· Placebo(pts number 29)</td><td colspan="5"></td></tr>
</table>

20	Marre et al. [40]	RCT Multicenter Multinational double-dummy	26 weeks	· 1041 Pts randomized	· **Liraglutide: 0.6 mg/ day.** (pts number 233)	Glimepiride (2– 4 mg/day)	**1. HbA1c:**			
							Before: mean SD 8.4 ± 1.0%			
							After Liraglutide 0.6 mg: estimated change -0.6% from baseline			
							After Liraglutide 1.2 mg: estimated change -1.08% from baseline			
				· 894 Pts completed	· **Liraglutide: 1.2 mg/ day.** (pts number 228)		**After Liraglutide 1.8 mg**: estimated change -1.13% from baseline			
							After Placebo: estimated change +0.23% from baseline			
				· Male: 49.2%			**After Rosiglitazone:** estimated change -0.44% from baseline.			
							2. SBP:			
				· Female: 50.8%	**Liraglutide: 1.8 mg/ day.** (pts number 234)		**After Liraglutide 1.2mg OR 1.8mg**: -2.6 to -2.8 mmHg ↓ from baseline.			
							After Placebo OR Rosiglitazone: -0.9 to -2.3 mmHg ↓ from baseline.			
				· T2D duration			**3. GI events:**			
							The percentage of GI events With **Liraglutide 1.2mg** which was the highest:			
				Mean(SD): 6.5 Years	· **Placebo:** (pts number 114)		**Nausea**	10.50%		
							Diarrhea	7.90%		
				Mean(SD)Age: 56 ± 10	· **Rosiglitazone: 4 mg/ day.** (pts number 232)		**Vomiting**	4.40%		
21	Mathieu et al. [41]	RCT Multicenter Multinational Multinational open-label	26 weeks	· 177 Pts randomized	· **Liraglutide 1.8 mg/ day:** (pts number 88)	insulin degludec (IDeg) once daily + metformin	**1. HbA1c:**			
							Before: mean SD 7.7 ± 0.7%			
							After Liraglutide: estimated change -0.74% from baseline			
				· 151 Pts completed	**Insulin Aspart once daily:** (pts number 89)		**After Insulin Aspart:** estimated change -0.39% from baseline			
							2. GI events:			
							Number of patients reporting GI events in each group:			
								Liraglutide	**Insulin Aspart**	
				· Male: 65.6%			**Nausea**	18	0	
				· Female: 34.4%			**Diarrhea**	9	0	
				· T2D duration			**Vomiting**	5	0	
				Mean(SD): 12.3 ± 6.4 Years			**Nasopharyngitis**	9	11	
				· Mean(SD)Age: 61 ± 9.1 years			**Lipase increase**	6	0	

<table>
<tr><td rowspan="22">22</td><td rowspan="22">Meier et al. [42]</td><td rowspan="22">RCT Multicenter open-label Germany</td><td rowspan="22">8 weeks</td><td>· 142 Pts randomized</td><td>· Liraglutide: 1.2 mg/ day. (pts number 47)</td><td rowspan="22">insulin glargine</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td rowspan="2">· 136 Pts completed</td><td rowspan="2"></td><td colspan="4">Before: mean SD 7.8 ± 0.8%</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg: estimated change -0.7% from baseline</td></tr>
<tr><td></td><td></td><td colspan="4">After Liraglutide 1.8 mg: estimated change -0.7% from baseline</td></tr>
<tr><td>· Male: 74%</td><td rowspan="3">· Liraglutide: 1.8 mg/ day. (pts number 47)</td><td colspan="4">After Lixisenatide: estimated change -0.6% from baseline</td></tr>
<tr><td rowspan="2">· Female: 26%</td><td colspan="4"></td></tr>
<tr><td colspan="4">2. SBP:</td></tr>
<tr><td rowspan="3">Mean (SD): 11.4 ± 7.4 Years</td><td rowspan="15">Lixisenatide 20 µg/ day (pts number 48)</td><td colspan="4">After Liraglutide 1.2 mg: -0.5 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">After Liraglutide 1.8 mg: -2.5 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">After Lixisenatide: +0.4 mmHg ↑ from baseline.</td></tr>
<tr><td rowspan="13">· Mean (SD) Age: 61.8 ± 8.2 years.</td><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide 1.2mg</td><td>Liraglutide 1.8mg</td><td>Lixisenatide</td></tr>
<tr><td>Nausea</td><td>8</td><td>11</td><td>9</td></tr>
<tr><td>Diarrhea</td><td>4</td><td>5</td><td>3</td></tr>
<tr><td>Vomiting</td><td>2</td><td>5</td><td>5</td></tr>
<tr><td>Constipation</td><td>5</td><td>3</td><td>0</td></tr>
<tr><td>Abdominal pain</td><td>2</td><td>1</td><td>3</td></tr>
<tr><td>Abdominal distention</td><td>7</td><td>4</td><td>3</td></tr>
<tr><td>Lipase increase</td><td>5</td><td>1</td><td>0</td></tr>
<tr><td rowspan="23">23</td><td rowspan="23">Miyagawa et al. [43]</td><td rowspan="23">RCT Multicenter Japan</td><td rowspan="23">26 week</td><td>· 487 Pts randomized</td><td rowspan="3">· Liraglutide: 0.9 mg/ day. (pts number 137)</td><td rowspan="23">None</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td rowspan="2">462 Pts completed</td><td colspan="4">Before: mean SD 8.14% ± (0.81%)</td></tr>
<tr><td colspan="4">After Liraglutide: estimated change -1.33%</td></tr>
<tr><td>· Male: 81%</td><td rowspan="3">· Dulaglutide: 0.75 mg/day. (pts number 280)</td><td colspan="4">After Dulaglutide: estimated change -1.43%</td></tr>
<tr><td>· Female: 19%</td><td colspan="4">After placebo: estimated change 0.14%</td></tr>
<tr><td>· Female: 19%</td><td colspan="4">2. SBP:</td></tr>
<tr><td>· T2D duration: 6.6 ± 5.6 Years</td><td rowspan="14">· placebo:(pts number 70)</td><td colspan="4">After Liraglutide: -2.10 mmHg ↓ from baseline.</td></tr>
<tr><td></td><td colspan="4">After Dulaglutide: 0.62 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="13">· Mean (SD) Age: 57.4 ± 9.6.</td><td colspan="4">After placebo: 0.53 mmHg ↑ from baseline.</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>Dulaglutide</td><td>placebo</td></tr>
<tr><td>Nausea</td><td>11</td><td>15</td><td>1</td></tr>
<tr><td>Diarrhea</td><td>5</td><td>16</td><td>1</td></tr>
<tr><td>Nasopharyngitis</td><td>16</td><td>37</td><td>4</td></tr>
<tr><td>Lipase increased</td><td>2</td><td>4</td><td>0</td></tr>
<tr><td>Decreased appetite</td><td>8</td><td>2</td><td>0</td></tr>
<tr><td>Constipation</td><td>8</td><td>19</td><td>3</td></tr>
<tr><td>Abdo distention</td><td>7</td><td>6</td><td>0</td></tr>
</table>

<table>
<tr><td rowspan="12">24</td><td rowspan="12">Nauck et al. [44] LEAD2</td><td rowspan="12">RCT Multicenter Multinational double-blind, double- dummy</td><td rowspan="12">26 weeks</td><td rowspan="3">· 1091 Pts randomized</td><td rowspan="4">· Liraglutide: 0.6 mg/ day. (pts number 242)</td><td rowspan="12">Metformin</td><td>1. HbA1c:</td></tr>
<tr><td>Before: mean SD 8.4 ± 1.0%</td></tr>
<tr><td>After Liraglutide 0.6 mg : estimated change -0.69% from baseline</td></tr>
<tr><td rowspan="3">· 880 Pts completed</td><td>After Liraglutide 1.2 mg : estimated change -0.97% from baseline</td></tr>
<tr><td>After Liraglutide 1.8 mg : estimated change -1.0% from baseline</td></tr>
<tr><td>After Glimepiride: estimated change -0.98% from baseline.</td></tr>
<tr><td>· Liraglutide: 1.2 mg/ day. (pts number 241)</td><td>After Placebo: estimated change +0.09% from baseline</td></tr>
<tr><td>· Male: 58.4%</td><td rowspan="4">Liraglutide: 1.8 mg/ day. (pts number 242)</td><td>2. SBP:</td></tr>
<tr><td>· Female: 41.6%</td><td>After Liraglutide 0.6 mg: -0.6 mmHg ↓ from baseline.</td></tr>
<tr><td>T2D duration</td><td>After Liraglutide 1.2 mg: -3.2 mmHg ↓ from baseline.</td></tr>
<tr><td>Mean (SD): 11.4 ± 7.4 Years</td><td>After Liraglutide 1.8 mg: -2.7 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">Mean (SD) Age: 56.6 ± 9.4 years.</td><td rowspan="2">Placebo: (pts number 122)</td><td>After Glimepiride: +0.4 mmHg ↑ from baseline.</td></tr>
<tr><td>After Placebo: -1.8 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">25</td><td rowspan="2">Nauck et al. [45] (A)</td><td rowspan="2">RCT Multicenter Multinational Open-label</td><td rowspan="2">26 wee</td><td>· 404 Pts randomized</td><td>· Liraglutide: 1.8 mg/ day. (pts number 202)</td><td rowspan="2">Metformin 1000 to 3000 mg/day</td><td>1. HbA1c:</td></tr>
<tr><td>340 Pts completed</td><td>Lixisenatide: 20mg/ day, 1h prior to morning or evening meal.</td><td>Before: mean SD 8.4% ± (0.8%)</td></tr>
<tr><td></td><td></td><td>After Liraglutide: estimated change -1.8% with 74.2% of Pts reached <7%.</td></tr>
<tr><td>· Male: 60%</td><td rowspan="2">· Lixisenatide: 20mg/day, 1h prior to morning or evening meal. (pts number 202)</td><td>After Lixisenatide: estimated change -1.2% with 45.5% of Pts reached <7%.</td></tr>
<tr><td>· Female: 40%</td><td>2. SBP:</td></tr>
<tr><td>· T2D duration: 6.4 ± 5.1 Years</td><td rowspan="11"></td><td>After Liraglutide: -4.7 mmHg ↓ from baseline.</td></tr>
<tr><td>· Mean (SD) Age: 56 ± 10.3.</td><td>After Lixisenatide: -3.5 mmHg ↓ from baseline.</td></tr>
<tr><td></td><td>3. GI events:</td></tr>
<tr><td></td><td>Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Liraglutide</td><td>Lixisenatide</td><td></td></tr>
<tr><td>Nausea</td><td>44</td><td>44</td><td></td></tr>
<tr><td>Diarrhea</td><td>25</td><td>20</td><td></td></tr>
<tr><td>Vomiting</td><td>14</td><td>18</td><td></td></tr>
<tr><td>Dyspepsia</td><td>11</td><td>6</td><td></td></tr>
<tr><td>Nasopharyngitis</td><td>13</td><td>20</td><td></td></tr>
<tr><td>Headache</td><td>15</td><td>17</td><td></td></tr>
<tr><td>Lipase increased</td><td>17</td><td>5</td><td></td></tr>
<tr><td>Decreased appetite</td><td>13</td><td>5</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td rowspan="30">26</td><td rowspan="30">Nauck et al. [46] (B)</td><td rowspan="30">RCT Multicenter Multinational double-blind for Semaglutide open-label for the active control Liraglutide</td><td rowspan="30">12 weeks</td><td>· 415 Pts randomized</td><td rowspan="3">· Liraglutide: 1- 1.2 mg/day (n: 45)
2- 1.8 mg/day (n:50)</td><td rowspan="30">Diet and exercise or metformin monotherapy</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td>341 Pts completed</td><td colspan="4">Before: mean SD 8.1 ± 0.9 %</td></tr>
<tr><td rowspan="2"></td><td colspan="4">After Liraglutide:</td></tr>
<tr><td rowspan="2"></td><td colspan="4">1.2 mg/day: estimated change -1.2% from baseline</td></tr>
<tr><td rowspan="2"></td><td colspan="4">1.8 mg/day: estimated change -1.3% from baseline</td></tr>
<tr><td rowspan="2"></td><td colspan="4">After semaglutide:</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.1 mg/week: estimated change -0.6% from baseline</td></tr>
<tr><td rowspan="2">· Male: 64.8%</td><td rowspan="5">· Semaglutide: 1- 0.1 mg/week (n:47)
2- 0.2 mg/week (n:44)
3- 0.4mg/week (n49)
4- 0.8 mg/week (n:44)
5- 1.6 mg/week (n:45)</td><td colspan="4">0.2 mg/week: estimated change -0.9% from baseline</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.4 mg/week: estimated change -1.1% from baseline</td></tr>
<tr><td>· Female: 35.2%</td><td rowspan="2"></td><td colspan="4">0.8 mg/week: estimated change -1.4% from baseline</td></tr>
<tr><td rowspan="2">· T2D duration</td><td colspan="4">1.6 mg/week: estimated change -1.7% from baseline</td></tr>
<tr><td rowspan="2"></td><td colspan="4">After Placebo: estimated change -0.5% from baseline</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td colspan="4"></td></tr>
<tr><td rowspan="2">Mean (SD): 2.6 ± 2.9 Years</td><td rowspan="2"></td><td colspan="4">2. SBP</td></tr>
<tr><td rowspan="2">Mean (SD) Age: 54 ± 10.1 years</td><td rowspan="2">· Placebo (n:46)</td><td colspan="4">After Liraglutide:</td></tr>
<tr><td rowspan="2"></td><td colspan="4">1.2 mg/day: -4.9 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">1.8 mg/day: -5.7 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">After semaglutide:</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.1 mg/week: +2.4 mmHg ↑ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.2 mg/week: -3.8 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.4 mg/week: -1.8 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">0.8 mg/week: -6.2 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">1.6 mg/week: -6.2 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">After Placebo: -3.8 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2"></td><td colspan="4">3. GI events:</td></tr>
<tr><td rowspan="2"></td><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td rowspan="2"></td><td></td><td>Lira groups n:95</td><td>Sema groups n:227</td><td>Placebo n:46</td></tr>
<tr><td rowspan="2"></td><td>Nausea</td><td>14</td><td>74</td><td>2</td></tr>
<tr><td rowspan="2"></td><td>Diarrhea</td><td>9</td><td>33</td><td>0</td></tr>
<tr><td rowspan="2"></td><td>Vomiting</td><td>10</td><td>40</td><td>1</td></tr>
<tr><td rowspan="2"></td><td>Dyspepsia</td><td>9</td><td>19</td><td>1</td></tr>
<tr><td rowspan="2"></td><td>Nasopharyngitis</td><td>3</td><td>15</td><td>4</td></tr>
<tr><td rowspan="2"></td><td>Headache</td><td>6</td><td>22</td><td>3</td></tr>
<tr><td rowspan="2"></td><td>Decreased appetite</td><td>2</td><td>9</td><td>0</td></tr>
<tr><td>Constipation</td><td>4</td><td>8</td><td>0</td></tr>
</table>

<table>
<tr><td rowspan="15">27</td><td rowspan="15">Pratley et al. [47]</td><td rowspan="15">RCT Multinational Open-label</td><td rowspan="15">26 weeks</td><td>· 658 Pts randomized</td><td rowspan="3">· Liraglutide: 1.2 mg/ day. (pts number 221)</td><td rowspan="15">Metformin (≥ 1500 mg daily for ≥ 3 months)</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td rowspan="2">554 Pts completed</td><td colspan="4">Before: baseline 7.5% to 10.0% , mean 8.5%</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg : estimated change -1.24% from baseline</td></tr>
<tr><td rowspan="2">· Male: 53%</td><td rowspan="2">Liraglutide:</td><td colspan="4">After Liraglutide 1.8 mg : estimated change</td></tr>
<tr><td colspan="4">-1.50% from baseline</td></tr>
<tr><td rowspan="2">· Female: 47%</td><td rowspan="2">1.8 mg/day. (pts number 218)</td><td colspan="4">After Sitagliptin: estimated change -0.90% from baseline.</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td rowspan="2">· T2D duration: 6.2 ± 5.1 Years</td><td rowspan="2"></td><td colspan="4">2. SBP:</td></tr>
<tr><td colspan="4">After Liraglutide 1.2 mg: -0.55 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="3">· Mean(SD)Age: 55.3 ± 9.2</td><td rowspan="3">Sitagliptin: 100 mg/ day (pts number 219)</td><td colspan="4">After Liraglutide 1.8 mg : -0.72 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">After Sitagliptin: -0.94 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide 1.2 mg</td><td>Liraglutide 1.8 mg</td><td>Sitagliptin</td></tr>
<tr><td>Nausea</td><td>46</td><td>59</td><td>10</td></tr>
<tr><td>Diarrhea</td><td>16</td><td>25</td><td>10</td></tr>
<tr><td>Vomiting</td><td>17</td><td>21</td><td>9</td></tr>
<tr><td>Dyspepsia</td><td>7</td><td>14</td><td>5</td></tr>
<tr><td>Nasopharyngitis</td><td>21</td><td>28</td><td>26</td></tr>
<tr><td>Headache</td><td>20</td><td>25</td><td>22</td></tr>
<tr><td>Decreased appetite</td><td>7</td><td>12</td><td>2</td></tr>
<tr><td>Constipation</td><td>10</td><td>11</td><td>6</td></tr>
</table>

<table>
<tr><td rowspan="19">28</td><td rowspan="19">Pratley et al. [48]</td><td rowspan="19">RCT Multinational Open-label Extension to Pratley et al, 2010</td><td rowspan="19">52 weeks</td><td rowspan="2">· 497 Pts randomized</td><td rowspan="4">· Liraglutide: 1.2 mg/ day. (pts number 155)</td><td rowspan="19">metformin monotherapy (≥ 1500 mg/day</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td colspan="4">Before: baseline 8.4-8.5%</td></tr>
<tr><td rowspan="2">· 436 Pts completed</td><td colspan="4">After Liraglutide 1.2 mg : estimated change -1.29% from baseline</td></tr>
<tr><td colspan="4">After Liraglutide 1.8 mg : estimated change -1.51% from baseline</td></tr>
<tr><td>· Male: 53%</td><td rowspan="3">Liraglutide: 1.8 mg/ day. (pts number 176)</td><td colspan="4">After Sitagliptin: estimated change -0.88% from baseline.</td></tr>
<tr><td>· Female: 47%</td><td colspan="4">2. SBP:</td></tr>
<tr><td>· T2D duration: 6.2 ± 5.1 Years</td><td colspan="4">After Liraglutide 1.2 mg: -0.37 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">· Mean(SD)Age: 55.3 ± 9.2</td><td>· Sitagliptin: 100 mg/ day (pts number 166)</td><td colspan="4">After Liraglutide 1.8 mg: -2.55 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="17"></td><td colspan="4">After Sitagliptin: -1.03 mmHg ↓from baseline.</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide 1.2 mg</td><td>Liraglutide 1.8 mg</td><td>Sitagliptin</td></tr>
<tr><td></td><td>(Patients)</td><td>(Patients)</td><td>(Patients)</td></tr>
<tr><td>Nausea</td><td>48</td><td>60</td><td>12</td></tr>
<tr><td>Diarrhea</td><td>20</td><td>27</td><td>14</td></tr>
<tr><td>Vomiting</td><td>18</td><td>23</td><td>11</td></tr>
<tr><td>Dyspepsia</td><td>8</td><td>15</td><td>5</td></tr>
<tr><td>Nasopharyngitis</td><td>27</td><td>32</td><td>31</td></tr>
<tr><td>Headache</td><td>21</td><td>29</td><td>27</td></tr>
<tr><td>Decreased appetite</td><td>8</td><td>12</td><td>3</td></tr>
<tr><td>Constipation</td><td>10</td><td>13</td><td>8</td></tr>
<tr><td rowspan="19">29</td><td rowspan="19">Pratley et al. [49]</td><td rowspan="19">RCT Multicenter Multinational open-label</td><td rowspan="19">32 weeks</td><td>· 841 Pts randomized</td><td rowspan="2">· Liraglutide: 1.8 mg/ day. (pts number 406)</td><td rowspan="19">One or more oral antidiabetes drugs (metformin, thiazolidinedione or Sulfonylurea)</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td>686 Pts completed</td><td colspan="4">Before: mean SD 8.16 ± 0.86%</td></tr>
<tr><td rowspan="2">· Male: 50%</td><td rowspan="6">Albiglutide 50mg/ week (pts number 404)</td><td colspan="4">After Liraglutide: estimated change -0.99% from baseline</td></tr>
<tr><td colspan="4">After Albiglutide: estimated change -0.78% from baseline</td></tr>
<tr><td rowspan="2">· Female: 50%</td><td colspan="4">2. SBP:</td></tr>
<tr><td colspan="4">After Liraglutide: less than 1 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">· T2D duration</td><td colspan="4">After Albiglutide: less than 1 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td rowspan="2">Mean(SD): 8.3 ± 5.8 Years</td><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>Albiglutide</td><td></td></tr>
<tr><td rowspan="2">· Mean(SD)Age: 55.6 ± 10 years</td><td>Nausea</td><td>119</td><td>40</td><td></td></tr>
<tr><td>Diarrhea</td><td>55</td><td>60</td><td></td></tr>
<tr><td></td><td>Vomiting</td><td>38</td><td>20</td><td></td></tr>
<tr><td></td><td>Headache</td><td>22</td><td>22</td><td></td></tr>
<tr><td></td><td>Nasopharyngitis</td><td>28</td><td>24</td><td></td></tr>
<tr><td></td><td>Lipase increase</td><td>28</td><td>22</td><td></td></tr>
</table>

<table>
<tr><td rowspan="15">30</td><td rowspan="15">Rosenstock et al. [50]</td><td rowspan="15">RCT Multicenter Multinational</td><td rowspan="15">52 weeks + 12 weeks run-in period</td><td>· 323 Pts randomized</td><td>· Liraglutide: 1.8 mg/ day. (pts number 161)</td><td rowspan="15">Metformin</td><td colspan="5">1. HbA1c:</td></tr>
<tr><td></td><td></td><td colspan="5">Before: mean SD 7.6 ± 0.65%</td></tr>
<tr><td>randomized</td><td>1.8 mg/day. (pts number 161)</td><td colspan="5">After Liraglutide: no change from baseline.</td></tr>
<tr><td>· 222 Pts completed</td><td></td><td colspan="5">After Liraglutide + insulin detemir: estimated change -0.45% from baseline</td></tr>
<tr><td rowspan="4">Male: 54.8%</td><td rowspan="13">Liraglutide: 1.8 mg/ day + insulin detemir. (pts number 162)</td><td colspan="5">2. SBP:</td></tr>
<tr><td colspan="5">After Liraglutide: -4.89 mmHg ↓ from baseline.</td></tr>
<tr><td rowspan="2">· Female: 45.2%</td><td colspan="5">After Liraglutide + insulin detemir: -2.07 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="5">3. GI events:</td></tr>
<tr><td rowspan="2">· T2D duration</td><td colspan="5">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>Liraglutide + insulin detemir</td><td></td></tr>
<tr><td>Mean(SD): 8.5 ± 5.9 Years</td><td>Nausea</td><td>12</td><td>9</td><td></td></tr>
<tr><td rowspan="3">· Mean (SD) Age: 57 ± 9.6 years</td><td>Diarrhea</td><td>14</td><td>21</td><td></td></tr>
<tr><td>Vomiting</td><td>9</td><td>10</td><td></td></tr>
<tr><td>Headache</td><td>15</td><td>13</td><td></td></tr>
<tr><td rowspan="15">31</td><td rowspan="15">Russell-Jones et al. [51] LEAD5</td><td rowspan="15">RCT Multicenter Multinational</td><td rowspan="15">26 weeks</td><td>· 581 Pts randomized</td><td rowspan="4">· Liraglutide: 1.8 mg/ day. (pts number 232)</td><td rowspan="15">All in combination with metformin (1 g twice daily) and glimepiride (4 mg once daily)</td><td colspan="5">1. HbA1c:</td></tr>
<tr><td>· 522 Pts completed</td><td colspan="5">Before: mean SD 8.26% ± (0.9%)</td></tr>
<tr><td>· Male: 55.4%</td><td colspan="5">After Liraglutide: estimated change -1.33%</td></tr>
<tr><td>· Female: 44.6%</td><td colspan="5">After placebo: estimated change -0.24%</td></tr>
<tr><td rowspan="4"></td><td rowspan="4">· Placebo. (pts number 115)</td><td colspan="5">After insulin glargine: estimated change -1.09%</td></tr>
<tr><td colspan="5">2. SBP:</td></tr>
<tr><td colspan="5">After Liraglutide: -4.0 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="5">After placebo: -1.4 mmHg ↓ from baseline.</td></tr>
<tr><td>· T2D duration: 9.4 ± 6.1 Years</td><td rowspan="11">· open-label insulin glargine (pts number 234) (100 IU/ml injected once daily)</td><td colspan="5">After insulin glargine: 0.54 mmHg ↑ from baseline.</td></tr>
<tr><td rowspan="2">· Mean(SD)Age: 57.5 ± 9.8 years</td><td colspan="5">3. GI events:</td></tr>
<tr><td colspan="5">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td>Liraglutide</td><td>placebo</td><td>insulin glargine</td></tr>
<tr><td>Nausea</td><td>32</td><td>4</td><td>3</td></tr>
<tr><td>Diarrhea</td><td>23</td><td>6</td><td>3</td></tr>
<tr><td>Vomiting</td><td>15</td><td>4</td><td>1</td></tr>
<tr><td>Dyspepsia</td><td>15</td><td>1</td><td>4</td></tr>
<tr><td>Nasopharyngitis</td><td>21</td><td>10</td><td>26</td></tr>
<tr><td>Headache</td><td>22</td><td>9</td><td>13</td></tr>
</table>

<table>
<tr><td rowspan="10">32</td><td rowspan="10">Seino et al. [52]</td><td rowspan="10">RCT Multicenter double-blind Japan</td><td rowspan="10">14 weeks</td><td>· 226 Pts randomized</td><td rowspan="2">· Liraglutide 0.1 mg/ day: (pts number 45)</td><td rowspan="10">With or without oral antidiabetes drug monotherapy</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td></td><td colspan="4">Before: mean SD 8.30%</td></tr>
<tr><td rowspan="2">· 210 Pts completed</td><td rowspan="2">Liraglutide 0.3 mg/ day (pts number 46)</td><td colspan="4">After Liraglutide 0.1 mg/day: estimated change -0.79% from baseline</td></tr>
<tr><td colspan="4">After Liraglutide 0.3 mg/day: estimated change -1.22% from baseline</td></tr>
<tr><td>· Male: 66.8%</td><td colspan="4">After Liraglutide 0.6 mg/day: estimated change -1.64% from baseline</td></tr>
<tr><td>· Female: 33.2%</td><td>· Liraglutide 0.6 mg/ day: (pts number 45)</td><td colspan="4">After Liraglutide 0.9 mg/day: estimated change -1.85% from baseline</td></tr>
<tr><td>· T2D duration</td><td></td><td colspan="4">After placebo: estimated change +0.09% from baseline</td></tr>
<tr><td>Mean(SD): 7.6 ± 5.4 Years</td><td>· Liraglutide 0.9 mg/ day (pts number 44)</td><td colspan="4">2. GI events:</td></tr>
<tr><td>Mean(SD)Age: 57.3 years</td><td>Placebo (pts number 46)</td><td colspan="4">Incidences of gastrointestinal disorders were placebo, 24%; Liraglutide 0.1 mg/day, 18%; 0.3 mg/day, 15%; 0.6 mg/day, 31%; 0.9 mg/day, 30%.</td></tr>
<tr><td rowspan="13">33</td><td rowspan="13">Seino et al. [53]</td><td rowspan="13">RCT Multicenter double-blind Japan</td><td rowspan="13">52 weeks</td><td>· 264 Pts randomized</td><td>· Liraglutide 0.6 mg/ day: (pts number 88)</td><td rowspan="13">sulfonylurea (glibenclamide, gliclazide or glimepiride)</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td>· 210 Pts completed</td><td>Liraglutide 0.9 mg/ day (pts number 88)</td><td colspan="4">Before: mean SD 8.82 ± 0.91 %</td></tr>
<tr><td>Male: 64%</td><td></td><td colspan="4"></td></tr>
<tr><td>Female: 36%</td><td></td><td colspan="4">After Liraglutide 0.6 mg/day: estimated change -1.09% from baseline</td></tr>
<tr><td>· T2D duration</td><td></td><td colspan="4">After Liraglutide 0.9 mg/day: estimated change -1.28% from baseline</td></tr>
<tr><td></td><td>.</td><td colspan="4">After placebo: estimated change -0.06% from baseline</td></tr>
<tr><td>Mean(SD): 10.3 ± 7.0 Years</td><td>Placebo (pts number 88)</td><td colspan="4">2. GI events:</td></tr>
<tr><td>Mean(SD)Age: 59.7 ± 10.4 years</td><td></td><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td></td><td></td><td></td><td>Liraglutide 0.6 mg</td><td>Liraglutide 0.9 mg</td><td>placebo</td></tr>
<tr><td></td><td></td><td>Diarrhea</td><td>4</td><td>6</td><td>6</td></tr>
<tr><td></td><td></td><td>Constipation</td><td>6</td><td>7</td><td>3</td></tr>
<tr><td rowspan="19">34</td><td rowspan="19">Seino et al. [54]</td><td rowspan="19">RCT Multicenter double-blind Japan</td><td rowspan="19">36 weeks</td><td>· 257 Pts randomized</td><td rowspan="5">· Liraglutide 0.9 mg/ day(pts number 127)</td><td rowspan="19">Insulin therapy (basal insulin, premixed insulin or basal–bolus regimen)</td><td colspan="4">1. HbA1c:</td></tr>
<tr><td>· 246 Pts completed</td><td colspan="4">Before: mean SD 8.8 ± 0.9 %</td></tr>
<tr><td>· 246 Pts completed</td><td colspan="4">After Liraglutide 0.9 mg/day: estimated change -1.68% from baseline</td></tr>
<tr><td>· Male: 56%</td><td colspan="4">After placebo: estimated change -0.88% from baseline</td></tr>
<tr><td rowspan="4">· Female: 44%</td><td colspan="4"></td></tr>
<tr><td rowspan="14">· Placebo (pts number 130)</td><td colspan="4">2. SBP</td></tr>
<tr><td colspan="4">After Liraglutide: −3.12 mmHg ↓ from baseline.</td></tr>
<tr><td colspan="4">After placebo: +2.46 mmHg ↑ from baseline.</td></tr>
<tr><td colspan="4">3. GI events:</td></tr>
<tr><td></td><td colspan="4">Number of patients reporting GI events in each group:</td></tr>
<tr><td rowspan="2"></td><td></td><td>Liraglutide</td><td>placebo</td><td></td></tr>
<tr><td rowspan="2">· T2D duration</td><td>Nausea</td><td>14</td><td>7</td><td></td></tr>
<tr><td>Diarrhea</td><td>15</td><td>4</td><td></td></tr>
<tr><td>· Mean (SD): 14.51 ± 8.73 Years</td><td>Dyspepsia</td><td>7</td><td>0</td><td></td></tr>
<tr><td rowspan="3">· Mean (SD) Age: 60.5 ± 11.2 years</td><td>Constipation</td><td>15</td><td>2</td><td></td></tr>
<tr><td>Headache</td><td>8</td><td>6</td><td></td></tr>
<tr><td>Nasopharyngitis</td><td>55</td><td>40</td><td></td></tr>
</table>

35	Tanaka et al. [55]	RCT Japan open-labele	24 weeks	· 47 Pts randomized	· **Liraglutide 0.9 mg/ day** (pts number 22)	None	**1. HbA1c:**
				· 46 Pts completed			**Before**: mean SD 7.85 ± 0.7%
				· Male: 63%			**After Liraglutide:** estimated change -0.80% from baseline
				· Female: 37%			**After metformin:** estimated change -0.95% from baseline
				· T2D duration	· **Metformin 1500 mg/day or more** (pts number 24)		**2. SBP**
				Mean(SD): 5.15 ± 4.0 Years			No significant change in systolic blood pressure.
				Mean(SD)Age: 53 ± 11 years			**3. GI events**
							Constipation was more frequent in the Liraglutide group.
							Diarrhea more frequent in the metformin group.
36	Vanderheiden et al. [56]	RCT Single-center double-blind	6 Month	· 71 Pts randomized	· **Liraglutide: 1.8 mg/ day.** (pts number 35)	Total daily dose of insulin exceeding 1.5 U/kg/d	**1. HbA1c:**
				· 66 Pts completed		Insulin mean (SD): 247 ± 95.1U/d	**Before**: mean SD 9.0% ± 1.2%
				· Male: 37%			**After Liraglutide**: estimated change -1.1%
				· Female: 63%	· **Placebo:** (pts number 36)		**After Placebo:** No change 0%
				· T2D duration: 17.9 ± 8.4Years			**2. SBP:**
							After Liraglutide: -1 mmHg ↓ from baseline.
				Mean (SD) Age: 54.2 ± 7.4.			**After Placebo:** -3 mmHg ↓ from baseline.
							3. GI events:
							In Liraglutide: 13 of 35 adverse events
							In placebo: 13 of 36 adverse events
37	Vilsboll et al. [57]	RCT double-blind	14 weeks	· 165 Pts randomized	· **Liraglutide 0.65 mg/ day** (pts number 40)	None	**1. HbA1c:**
				· 140 Pts completed	· **Liraglutide 1.25 mg/ day:** (pts number 42)		**Before**: mean SD 8.30 %
				· Male: 60.7%			**After Liraglutide 0.65 mg/day:** estimated change -0.98% from baseline
				· Female: 39.3%			**After Liraglutide 1.25 mg/day:** estimated change -1.40% from baseline
				· T2D duration	· **Liraglutide 1.90 mg/ day** (pts number 41)		**After Liraglutide 1.90 mg/day:** estimated change -1.45% from baseline
					· **Placebo:** (pts number 40)		**After placebo:** estimated change +0.29% from baseline
							2. SBP:
				· Male: 60.7%	· **Liraglutide 1.90 mg/ day** (pts number 41)		Systolic blood pressure decreased significantly
				Mean(SD): 5.5 ± 9.8 Years			1.90 mg *vs.* placebo: −7.9 mmHg [−12.9 to −2.9], *P*=0.0023;
							1.25 mg *vs.* placebo: −5.2 mmHg [−10.2 to −0.2], *P*=0.0417;
							0.65 mg *vs.* placebo: −7.4 mmHg [−12.4 to −2.4], *P*=0.0041.
							3. GI events:
							Number of patients reporting GI events in each group:
				Mean(SD)Age: 55.8 ± 9.9 years			

	Liraglutide groups (n:123)	**Placebo (n:40)**	
Nausea	9	1	
Diarrhea	26	5	
Vomiting	4	0	

<table>
<tr><td rowspan="12">38</td><td rowspan="12">Yang et al. [58]</td><td rowspan="12">RCT Multicenter Multinational double-blind double-dummy</td><td rowspan="12">16 weeks</td><td>· 929 Pts randomized</td><td rowspan="2">· Liraglutide: 0.6 mg/ day. (pts number 231)</td><td rowspan="12">Metformin (2000 mg daily).</td><td>1. HbA1c:</td></tr>
<tr><td>Before: mean SD 8.6 ± 1.0%</td></tr>
<tr><td>· 779 Pts completed</td><td>After Liraglutide 0.6 mg : estimated change -1.14% from baseline</td></tr>
<tr><td rowspan="3">· Male: 55.3%</td><td>After Liraglutide 1.2 mg : estimated change -1.36% from baseline</td></tr>
<tr><td rowspan="2">· Liraglutide: 1.2 mg/ day. (pts number 233)</td><td>After Liraglutide 1.8 mg : estimated change -1.45% from baseline</td></tr>
<tr><td>After Glimepiride 4 mg: estimated change -1.39% from baseline</td></tr>
<tr><td rowspan="2">· Female: 44.7%</td><td rowspan="2">· Liraglutide: 1.8 mg/ day. (pts number 233)</td><td>2. SBP:</td></tr>
<tr><td>In Liraglutide groups: -3 mmHg ↓ from baseline</td></tr>
<tr><td rowspan="2">Mean(SD): 7.5 ± 5.5 Years</td><td rowspan="2">· Glimepiride: 4 mg/ day (pts number 231)</td><td>In Glimepiride group: -0.91 mmHg ↓ from baseline</td></tr>
<tr><td>3. GI events:</td></tr>
<tr><td>· Mean(SD)Age: 53.3 ± 9.5 years</td><td></td><td>GI events (diarrhoea, nausea, vomiting) are most frequently reported in Liraglutide groups than in Glimepiride group.</td></tr>
<tr><td rowspan="13">39</td><td rowspan="13">Zang et al. [59]</td><td rowspan="13">RCT Multicenter open-labele China</td><td rowspan="13">26 weeks</td><td>· 368 Pts</td><td rowspan="13">· Liraglutide: 1.8 mg/ day (pts number 184)</td><td rowspan="13">metformin monotherapy</td><td>1. HbA1c:</td></tr>
<tr><td>Male: 59.6%</td><td>Before: baseline 8.4-8.5%</td></tr>
<tr><td>Female: 40.4%</td><td>After Liraglutide: estimated change -1.51% from baseline</td></tr>
<tr><td rowspan="10">· T2D duration:</td><td>After Sitagliptin: estimated change -0.88% ↓ from baseline.</td></tr>
<tr><td>2. SBP:</td></tr>
<tr><td>After Liraglutide: -4.31 mmHg ↓ from baseline.</td></tr>
<tr><td>After Sitagliptin: -2.76 mmHg ↓ from baseline.</td></tr>
<tr><td>3. GI events:</td></tr>
<tr><td>Number of patients reporting GI events in each group:</td></tr>
<tr><td>
<table>
<tr><th></th><th>Liraglutide 1.8 mg</th><th>Sitagliptin</th><th></th></tr>
<tr><td>Nausea</td><td>27</td><td>1</td><td></td></tr>
<tr><td>Diarrhea</td><td>15</td><td>4</td><td></td></tr>
<tr><td>Lipase increased</td><td>11</td><td>8</td><td></td></tr>
<tr><td>Decreased appetite</td><td>20</td><td>1</td><td></td></tr>
</table>
</td></tr>
<tr><td rowspan="12">40</td><td rowspan="12">Zinman et al. [60] LEAD4</td><td rowspan="12">RCT Multicenter Multinational Double-blind</td><td rowspan="12">26 weeks</td><td>· 533 Pts randomized</td><td>Liraglutide 1.2 mg/ day (pts number 178)</td><td rowspan="12">metformin (1 g twice daily)</td><td>1. HbA1c:</td></tr>
<tr><td>· 407 Pts completed</td><td rowspan="3">Liraglutide 1.8 mg/ day (pts number 178)</td><td>Before: mean SD 8.6 ± 1.0%</td></tr>
<tr><td>Male: 56.6%</td><td>After Liraglutide: estimated change -1.1 from baseline.</td></tr>
<tr><td>Female: 43.4%</td><td>After Liraglutide 1.8 mg: estimated change -1.1 from baseline.</td></tr>
<tr><td>· T2D duration: Mean(SD): 9 ± 6 Years</td><td rowspan="6">Placebo: (pts number 177)</td><td>After Placebo: estimated change -0.8 from baseline.</td></tr>
<tr><td rowspan="6">· Mean(SD) Age: 55 ± 10 Years</td><td>2. SBP:</td></tr>
<tr><td>After Liraglutide: -6.7 ± 1.1 mmHg ↓from baseline.</td></tr>
<tr><td>After Liraglutide 1.8 mg: -5.6 ± 1.1 mmHg ↓from baseline.</td></tr>
<tr><td>After Placebo: -1.1 ± 1.2 mmHg ↓from baseline.</td></tr>
<tr><td>3. GI events:</td></tr>
<tr><td>GI events (diarrhoea, nausea, vomiting) are most frequently reported in Liraglutide groups than in placebo. It was reported by 45% in 1.2 mg Liraglutide, 56% in 1.8mg Liraglutide and 19% in Placebo.</td></tr>
</table>

that higher doses of Liraglutide are more effective in lowering HbA1c levels. Scott [64] states that Liraglutide is dose-dependent when it comes to reducing HbA1c levels, postprandial plasma glucose levels, and fasting plasma glucose, and that it improves glucose levels over a 24 h dosage interval.

Based on the results of the included studies, Liraglutide is proven to be effective in lowering HbA1c levels as a monotherapy or as adjunct treatments to other oral antidiabetes agents or insulin.

Liraglutide was assessed as a monotherapy in 7 trials (10, 11, 12, 19, 23, 35 and 37). In study (10), Liraglutide showed a greater reduction in HbA1c level compared to metformin while in study (35), there was no significant difference between them, with the estimated mean changes in HbA1c level being- 0.80% for Liraglutide and -0.95% for Metformin. However, in both trials (10, 35), the maximum Liraglutide dose used was less than 1 mg/day. In addition, when comparing Liraglutide to Dulaglutide (23), there was no significant difference between them as the estimated change in HbA1c level after 26 weeks was- 1.33% for Liraglutide and - 1.43% for Dulaglutide. Studies (11, 12, and 19), showed that Liraglutide monotherapy reduces HbA1c significantly more than Glimepiride monotherapy and more than a placebo (37). 12 studies (3, 4, 7, 9, 13, 14, 15, 20, 29, 31, 32 and 33) assessed Liraglutide's efficacy as an adjunct treatment to different oral antidiabetes drugs, such as sulphonylureas, dipeptidyl peptidase-4 inhibitor, and metformin. The results of these studies showed a significant reduction in HbA1c levels among Liraglutide groups. In addition, Liraglutide was given together with insulin therapy as a background treatment in some studies (1, 16, 17, 18, 21, 22, 34, and 36). These studies showed a significant reduction in HbA1c levels, with the mean estimated changes ranging from 0.65% to 1.9% from the baseline. Another 12 studies (2, 5, 6, 8, 24, 25, 27, 28, 30, 38, 39, and 40) assessed Liraglutide's efficacy as an adjunct treatments to metformin, with metformin being the background treatment in both the Liraglutide and control groups. When Liraglutide was compared to Liraglutide plus insulin therapy, both arms in combination with metformin (2, 6, and 30), Liraglutide plus insulin therapy was more effective than Liraglutide, with the estimated mean changes in HbA1c levels in these studies (2, 6, and 30) for Liraglutide and Liraglutide plus insulin therapy being -0.16% and -1.04%, +0.02% and -0.51% and no change and -0.45%, respectively. In addition, in study (8), Dulaglutide was more effective than Liraglutide (both with metformin), with the estimated mean changes in HbA1c being -1.42% and -1.36%, respectively. However, Liraglutide was superior to Glimepiride (24 and 38), Lixisenatide (25), and the placebo (40) when both arms were given in combination with metformin, with a significant reduction in HbA1c levels in the Liraglutide groups and the mean estimated changing from -1.0% to -1.8% from the baseline in these studies. In studies (5, 27, 28, and 39), Liraglutide was superior to Sitagliptin when both were given in combination with metformin, with a significant reduction in HbA1c levels in the Liraglutide groups. The estimated mean changes in HbA1c levels in the Liraglutide groups in these studies were -1.4%, -1.50%, and -1.51 respectively.

The efficacy of Liraglutide on HbA1c has also been proven in observational studies. Kesavadev et al. [65] carried out a prospective, open label, single arm, and single centre observational study over 24 weeks to assess the efficacy 1.8 mg of Liraglutide in 195 Indian patients with type 2 diabetes. The study results showed a reduction in HbA1c level from 8.14% to 6.96% at week 24, with 49.23% of the treated patients reaching HbA1c <7.0% and 41.03% reaching HbA1c ≤ 6.5%. In addition, Feher et al. [66] performed a real-world observational study to assess the efficacy of Liraglutide compared to Lixisenatide by utilizing The Health Improvement Network Database, which includes electronic medical records for over 13 million patients in the United Kingdom. They assessed 579 patients using Liraglutide and 213 patients using Lixisenatide, all with type 2 diabetes and aged over 18 years old, and it was found that Liraglutide decreases HbA1c levels significantly more than Lixisenatide and that patients are more likely to achieve their target HbA1c level with Liraglutide.

Theme 2: Liraglutide and SBP

The overall results of the included studies that measured SBP showed a significant reduction in SBP. However, the included studies did not assess SBP as a primary end point. In studies comparing Liraglutide to GLP-1 receptors agents, Liraglutide was not always better at reducing SBP. As GLP-1 receptors agents are known to be associated with lowering SBP ≈2 mmHg [67]. Study (8) compared Liraglutide with Dulaglutide and the results were -2.82 mmHg decreased from the baseline with Liraglutide and -3.36 mmHg decreased from the baseline with Dulaglutide. However, in study (23), the significant reduction of Liraglutide was more than that of Dulaglutide at -2.10 mmHg and -0.62 mmHg, respectively.

Also, when Liraglutide was compared to Semaglutide (26), Semaglutide was superior in reducing SBP but without a significant difference (-6.2 mmHg from the baseline with Semaglutide and -5.7 mmHg with Liraglutide). The results of studies (22 and 25), showed a superior significant reduction in SBP with Liraglutide compared to Lixisenatide. This is also supported by an observational study comparing Liraglutide and Lixisenatide. In this observational study, the reduction of SBP was greater in the Liraglutide group than the Lixisenatide one, but the results were not significantly different [66].

The efficacy of Liraglutide on SBP was also proven in a real-world observational study that found that mean SBP reduced from 129.31 mmHg to 119.59 mmHg [65]. The efficacy of Liraglutide in reducing SBP is agreed on by many studies and reviews [34,46,64,68]. However, a recent analysis study they suggests that this blood pressure reduction effect is more likely to happen in patients with better glycemic control while patients with higher HbA1c are more likely to respond with glycemic control improvement [69-74]. Therefore, treatment based on individualized evaluation is encouraged.

Theme 3: Liraglutide and GI disturbances

It is known that Liraglutide can cause different types of GI disturbance as in all included studies the percentage of patients who experienced GI events varied from low to high percentages. These adverse GI events, especially nausea, are not only seen with Liraglutide but with all GLP-1 receptor agonist agents and one possible cause is the delayed gastric emptying effect of GLP-1 receptors [75-82]. The results of the included studies that compared Liraglutide to a placebo, OAD medications, and insulin showed a higher rate of patients reporting GI events among the Liraglutide groups. Contrastingly, in the studies that compare Liraglutide to GLP-1 receptor agents such as Exenatide, Dulaglutide, Lixisenatide, and Semaglutide, the number of patients reporting GI events tends to be high in both groups [82-88].

Although GI disturbances are frequently reported with Liraglutide, it appears to be dose dependent and transient [46,64,75,89-95]. Less cases of GI events were reported in the trials that used a small doses of Liraglutide. For example, in study (10), Liraglutide was given in 5 arms and the given doses were between 0.045 mg to 0.75 mg for 176

patients and nausea was reported by 7 patients and vomiting by only 4 patients. The same situation occurred in study (19), which compared 135 patients, with 10 of them reporting nausea, 5 reporting diarrhea, 3 reporting vomiting, and 3 reporting constipation.

It is noticeable that in the studies that initiated a run-in period of about 12 weeks prior to randomization (2, 6, and 30), the rate of reported GI events was less than in the other studies. This is due to dose titration and the transient GI effects of Liraglutide. Most of the included studies indicate that the GI disturbances are transient in nature and resolved within the first four to eight weeks of Liraglutide initiation. Also, to minimize the GI side effects, starting with a small dose and gradually increasing the dose is recommended [46,75,96-103].

Conclusion

Liraglutide is effective in lowering HbA1c levels and maintaining it within the normal range. Liraglutide as a monotherapy or in a combination with other diabetes treatment showed a significant reduction in HbA1c levels in most of the included studies. Liraglutide was superior to placebo, metformin, sitagliptin, glimepiride, rosiglitazone, exenatide, lixisenatide and albiglutide at HbA1c reduction.

Furthermore, beside glycemic control, Liraglutide could lead to significant reduction in systolic blood pressure, which can reach up to -7.0 mmHg. The gastrointestinal adverse events mostly nausea, vomiting, and diarrhea, were also common with Liraglutide use, which can affect the continuity of treatment. However, based on the included studies, these GI disturbances are transient in nature and can be resolved within 4 to 8 weeks of Liraglutide initiation.

Funding

We gratefully acknowledge the InDependent Diabetes Trust for funding.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014;37(Suppl 1):S81-S90.
2. World Health Organization. Global report on diabetes. 2016.
3. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes—2018. Diabetes care. 2018;41(Suppl 1):S13-S27.
4. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clinical Diabetes. 2008;26(2):77-82.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.
6. Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, del Cañizo-Gómez FJ. Update on the treatment of type 2 diabetes mellitus. World J Diabet. 2016;7(17):354-95.
7. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193-203.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
9. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2015;38(1):140-49.
10. Drucker DJ, Dritselis A, Kirkpatrick P. Liraglutide. Nat Rev Drug Discov. 2010;9(4):267-8.
11. Jackson SH, Martin TS, Jones JD, Seal D, Emanuel F. Liraglutide (victoza): The first once-daily incretin mimetic injection for type-2 diabetes. P T. 2010;35(9):498-529.
12. Wajcberg E, Amarah A. Liraglutide in the management of type 2 diabetes. Drug Des Devel Ther. 2010;4:279–90.
13. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-57.
14. Peterson GE, Pollom RD. Liraglutide in clinical practice: Dosing, safety and efficacy. Int J Clin Practice. 2010;64:35-43.
15. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes Obes Metab. 2016;18(3):203-16.
16. U.S Food and Drug Administration (2010) FDA Approved Drug Products.
17. Novo Nordisk. Victoza® (Liraglutide). 2017.
18. McGill JB. Liraglutide: Effects beyond glycaemic control in diabetes treatment. Int J Clin Pract Suppl. 2010;(167):28-34
19. Marso S, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-22.
20. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of Liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA. 2015;314(7):687-99.
21. Blonde L, Russell-Jones D. The safety and efficacy of Liraglutide with or without oral antidiabetes drug therapy in type 2 diabetes: An overview of the LEAD 1–5 studies. Diabetes Obes Metab. 2009;11(Suppl 3):26-34.
22. Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, De Loredo L, Tornøe K, et al. Efficacy and safety of Liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial. Diabetes Obes Metab. 2015;17(11):1056-64.
23. Aroda VR, Bailey TS, Cariou B, Kumar S, Leiter LA, Raskin P, et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and Liraglutide: A double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 S tudy). Diabetes Obes Metab. 2016;18(7):663-70.
24. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). The Lancet. 2009;374(9683):39-47.
25. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus Liraglutide once daily in patients with type 2 diabetes (DURATION-6): A randomised, open-label study. The Lancet. 2013;381(9861):117-24.
26. Charbonnel B, Steinberg H, Eymard E, Xu L, Thakkar P, Prabhu V, et al. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with Liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: A randomised clinical trial. Diabetologia. 2013;56(7):1503-11.

27. DeVries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, et al. Sequential intensification of metformin treatment in type 2 diabetes with Liraglutide followed by randomized addition of basal insulin prompted by A1C targets. Diabetes care. 2012;35(7):1446-54.

28. De Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, de Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: A 26 week, randomised clinical trial (ELEGANT). Diabetologia. 2014;57(9):1812-19.

29. Dungan KM, Povedano ST, Forst T, González JGG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily Liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): A randomised, open-label, phase 3, non-inferiority trial. The Lancet. 2014;384(9951):1349-57.

30. D'Alessio D, Häring HU, Charbonnel B, de Pablos-Velasco P, Candelas C, Dain MP, et al. Investigators. Comparison of insulin glargine and Liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabet Obes Metab. 2015;17(2):170-78.

31. Feinglos MN, Saad MF, Pi-Sunyer F, An B, Santiago O. Effects of Liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with type 2 diabetes. Diabet Med. 2005;22(8):1016-23.

32. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. 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(9662):473-81.

33. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):348-56.

34. Gough SCL, Bode BW, Woo VC, Rodbard HW, Linjawi S, Zacho M, et al. One-year efficacy and safety of a fixed combination of insulin degludec and Liraglutide in patients with type 2 diabetes: Results of a 26-week extension to a 26-week main trial. Diabetes Obes Metab. 2015;17(10):965-73.

35. Kaku K, Rasmussen MF, Clauson P, Seino Y. Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue Liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes Diabetes Obes Metab. 2010;12(4):341-7.

36. Kaku K, Kiyosue A, Ono Y, Shiraiwa T, Kaneko S, Nishijima K, et al. Liraglutide is effective and well tolerated in combination with an oral antidiabetes drug in Japanese patients with type 2 diabetes: A randomized, 52-week, open-label, parallel-group trial. J Diabetes Investig. 2016;7(1):76–84.

37. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of Liraglutide to high-dose intensive insulin therapy: A randomized prospective trial. Diabetes Obes Metab. 2014;16(9):827-32.

38. Li CJ, Li J, Zhang QM, Lv L, Chen R, Lv CF, et al. Efficacy and safety comparison between Liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. Cardiovasc Diabetol. 2012;11:142.

39. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahrén B, Torffvit O, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: Randomised clinical trial (MDI Liraglutide trial). BMJ. 2015;351:h5364.

40. Marre M, Shaw J, Brändle M, Bebakar WW, Kamaruddin NA, Strand J, et al. 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(3):268-78.

41. Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Philis-Tsimikas A, Ocampo Francisco AM, et al. A comparison of adding Liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab. 2014;16(7):636-44.

42. Meier JJ, Rosenstock J, Hincelin-Méry A, Roy-Duval C, Delfolie A, Coester HV, et al. Contrasting effects of lixisenatide and Liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: A randomized, open-label trial. Diabetes Care. 2015;38(7):1263-73.

43. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily Liraglutide and superior to placebo in Japanese patients with type 2 diabetes: A 26-week randomized phase III study. Diabetes Obes Metab. 2015;17(10):974-83.

44. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. 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(1):84-90.

45. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courrèges JP, Lindegaard ML, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label Liraglutide in patients with type 2 diabetes. Diabetes Care. 2016;39(2):231-41.

46. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J. Once-daily Liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: A 26-week randomized controlled clinical trial. Diabetes Care. 2016;39(9):1501-09.

47. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: A 26-week, randomised, parallel-group, open-label trial. Lancet. 2010;375(9724):1447-56.

48. Pratley R, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. One year of Liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: A randomised, parallel-group, open-label trial. Int J Clin Pract. 2011;65(4):397–07.

49. Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, et al. Once-weekly albiglutide versus once-daily Liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): A randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol. 2014;2(4):289-97.

50. Rosenstock J, Rodbard HW, Bain SC, D'Alessio, D, Seufert J, Thomsen AB, et al. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of Liraglutide to metformin followed by insulin detemir according to HbA1c target. J Diabetes Complications. 2013;27(5):492-500.

51. Russell-Jones D, Vaag, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide *vs.* insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+ SU): A randomised controlled trial. Diabetologia. 2009;52(10):2046-55.

52. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily Liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract. 2008;81(2):161-8.

53. Seino Y, Rasmussen MF, Nishida T, Kaku K. Glucagon-like peptide-1

analog Liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial. J Diabetes Investig. 2011;2(4):280-6.

54. Seino Y, Kaneko S, Fukuda S, Osonoi T, Shiraiwa T, Nishijima K, et al. Combination therapy with Liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial. J Diabetes Investig. 2016;7(4):565-73.

55. Tanaka K, Saisho Y, Kawai T, Tanaka M, Meguro S, Irie J, et al. Efficacy and safety of Liraglutide monotherapy compared with metformin in Japanese overweight/obese patients with type 2 diabetes. Endocr J. 2015;62(5):399-409.

56. Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Effect of adding Liraglutide *vs.* placebo to a high-dose insulin regimen in patients with type 2 diabetes: A randomized clinical trial. JAMA Intern Med. 2016;176(7):939-47.

57. Vilsbøll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courrèges JP, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care. 2007;30(6):1608-10

58. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial. Diabetes Obes Metab. 2011;13(1):81-8.

59. Zang L, Liu Y, Geng J, Luo Y, Bian F, Lv X, et al. Efficacy and safety of Liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: A 26-week, open-label, randomized, active comparator clinical trial. Diabetes Obes Metab. 2011;13(1):81-8.

60. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human GLP-1 analog Liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met+ TZD). Diabetes Care. 2009;32(7):1224-30.

61. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Retinopathy in diabetes. Diabetes Care. 2004;27(Suppl 1):S84-7.

62. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog Liraglutide (NN2211): A 12-week, double-blind, randomized, controlled trial. Diabetes Care. 2004;27(6), 1335-42.

63. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

64. Scott LJ. Liraglutide: A review of its use in adult patients with type 2 diabetes mellitus. Drugs. 2014;l74(18):2161-74.

65. Kesavadev J, Shankar A, Gopalakrishnan G, Jothydev S. Efficacy and safety of Liraglutide therapy in 195 Indian patients with type 2 diabetes in real world setting. Diabetes Metab Syndr. 2015;9(1):30-3.

66. Feher M, Vega-Hernandez G, Mocevic E, Buysse B, Myland M, Power GS, et al. Effectiveness of Liraglutide and lixisenatide in the treatment of type 2 diabetes: Real-world evidence from The Health Improvement Network (THIN) database in the United Kingdom. Diabetes Ther. 2017;8(2):417-31.

67. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: A review of the evidence. Curr Hypertens Rep. 206;18(2):16.

68. Fonseca VA, DeVries JH, Henry RR, Donsmark M, Thomsen HF, Plutzky J. Reductions in systolic blood pressure with Liraglutide in patients with type 2 diabetes: Insights from a patient-level pooled analysis of six randomized clinical trials. J Diabetes Complications. 2014;28(3):399-405.

69. Wijkman MO, Dena M, Dahlqvist S, Sofizadeh S, Hirsch I, Tuomilehto J, et al. Predictors and correlates of systolic blood pressure reduction with Liraglutide treatment in patients with type 2 diabetes. J Clin Hypertens (Greenwich). 2019;21(1):105-15.

70. Bagger JI, Knop FK, Lund A, Holst JJ, Vilsbøll T. Glucagon responses to increasing oral loads of glucose and corresponding isoglycaemic intravenous glucose infusions in patients with type 2 diabetes and healthy individuals. Diabetologia. 2014;57(8):1720-25.

71. Bradley E, Campbell P, Nolan P. Nurse prescribers: Who are they and how do they perceive their role? Jof Adv Nurs. 2005;51(5):439-48.

72. Cersosimo E, Triplitt C, Solis-Herrera C, Mandarino LJ, DeFronzo RA, Feingold KR, et al. Pathogenesis of type 2 diabetes mellitus. In: Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000 [Internet].

73. Cullen L, Adams S. What is evidence-based practice? J Perianesth Nurs. 2010;25(3):171-73.

74. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835.

75. Gross B. Clinical pearls for initiating and utilizing Liraglutide in patients with type 2 diabetes. J Pharm Pract. 2013;26(2):144-150.

76. Evans D. Hierarchy of evidence: A framework for ranking evidence evaluating healthcare interventions. J Clin Nurs. 2003;12(1):77-84.

77. Gray A. Advanced or advancing nursing practice: What is the future direction for nursing? Br J Nurs. 2016;25(1):8, 10, 12-3.

78. Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T, et al. Diabetes nephropathy: Diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164-76.

79. Gu J, Xin M, Yan G, Lei W, Hongzhi Z, Yixuan L, et al. The efficacy and safety of Liraglutide added to metformin in patients with diabetes: A meta-analysis of randomized controlled trials. Sci Rep. 2016;6:32714.

80. International Diabetes Federation (2017) IDF Diabetes Atlas, 8th ed. Brussels, Belgium: International Diabetes Federation [accessed 4 September 2019] [online].

81. Jensen MD, Haymond MW, Gerich J, Cryer PE, Miles JM. Lipolysis during fasting. Decreased suppression by insulin and increased stimulation by epinephrine. J Clin Invest. 1987;79(1):207-13.

82. Jimmy B, Jose J. Patient medication adherence: Measures in daily practice. Oman Med J. 2011;26(3):155–59.

83. Lau D, Shen G. Cardiovascular complications of diabetes. Can J Diabetes. 2013;37(5):279-81.

84. Leibiger IB, Leibiger B, Berggren PO. Insulin feedback action on pancreatic β-cell function. FEBS letters. 2002;532(1-2):1-6.

85. Li M, Yang Y, Jiang D, Ying M, Wang Y, Zhao R. Efficacy and safety of Liraglutide versus sitagliptin both in combination with metformin in patients with type 2 diabetes a systematic review and meta-analysis. Medicine. 2017;96(39):e8161.

86. Lund A, Bagger JI, Christensen M, Knop FK, Vilsbøll T. Glucagon and type 2 diabetes: The return of the alpha cell. Curr Diab Rep. 2014;14(12):555.

87. Mallett R, Hagen-Zanker J, Slater R, Duvendack M. The benefits and challenges of using systematic reviews in international development research. J Develop Effectiveness. 2012;4(3):445-55.

88. Meetoo D. Diabetes: Complications and the economic burden. Br J Healthc Manag. 2014;20(2):60-67.

89. Nolan P, Bradley E. The role of the nurse prescriber: The views of mental health and non-mental health nurses. J Psychiatr Ment Health Nurs. 2007;14(3):258-66.

90. Ostawal A, Mocevic E, Kragh N, Xu W. Clinical effectiveness of Liraglutide in type 2 diabetes treatment in the real-world setting: A systematic literature review. Diabetes Ther. 2016;7(3):411–38.

91. Pearce L. A prescription. Nursing Standard. 2003;17(26):14-5.

92. Ramcharan P, Hemingway S, Flowers K. A client-centered case for nurse prescribing. Mental Health Nursing. 2001;21(5):6-11.

93. Pellerin L. Food for thought: The importance of glucose and other energy substrates for sustaining brain function under varying levels of activity. Diabetes Metabolism. 2010;36(10):S59-S63.

94. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetes neuropathy: A position statement by the American Diabetes Association. Diabetes Care. 2017; 40(1):136–54.

95. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes. 2018;42(Suppl 1):S10-S15.

96. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016;48(3):e219.

97. Schlosser RW. The role of systematic reviews in evidence-based practice, research, and development. Focus. 2006;15:1-4.

98. Sigma Theta Tau International 2005-2007 Research and Scholarship Advisory Committee. Sigma theta tau international position statement on evidence-based practice February 2007 summary. Worldviews Evid Based Nurs. 2008;5(2):57-9.

99. Stevens KR. Systematic reviews: The heart of evidence-based practice. AACN Clin Issues. 2001;12(4):529-38.

100. Stumvoll M, Goldstein BJ, van Haeften TW. Pathogenesis of type 2 diabetes. In Type 2 Diabetes. CRC Press. 2016;27-40.

101. Thyer BA. What is evidence-based practice? Brief treatment and crisis intervention. 2004;4(2):167.

102. World Health Organization. Classification of diabetes mellitus. 2019.

103. Xue X, Ren Z, Zhang A, Yang Q, Zhang W, Liu F. Efficacy and safety of once-weekly glucagon-like peptide-1 receptor agonists compared with exenatide and Liraglutide in type 2 diabetes: A systemic review of randomised controlled trials. Int J Clin Pract. 2016;70(8):649-56.

104. Schlosser RW. The role of systematic reviews in evidence-based practice, research, and development. Focus. 2006;15:1-4.