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Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis

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ABSTRACT

Objectives: To synthesise current evidence for the effects of exenatide and liraglutide on heart rate, blood pressure, and body weight.

Design: Meta-analysis of available data from randomised controlled trials comparing GLP-1 analogues with placebo, active anti-diabetic drug therapy, or lifestyle intervention.

Participants: Patients with type 2 diabetes.

Outcome measures: Weighted mean differences between trial arms for changes in heart rate, blood pressure and body weight, after a minimum of 12 weeks follow up.

Results: 32 trials were included. Liraglutide increased heart rate by 2.65 beats per minute (bpm) [95% confidence interval (CI), 1.78, 3.52] compared with placebo and by 1.61 bpm [1.10, 2.13] versus active control. Exenatide twice daily (BID) increased heart rate by 0.88 bpm [-0.47, 2.22] versus placebo but did not reach statistical significance, and by 1.36 [0.57, 2.14] versus active control. Exenatide long acting release (LAR) increased heart rate by 2.14 [1.11, 3.17] versus active control. GLP-1 agonists decreased systolic blood pressure by -1.79mmHg [-2.94, -0.64] and -2.39mmHg [-3.35, -1.42] compared to placebo and active control respectively. Reduction in diastolic blood pressure failed to reach statistical significance (-0.54mmHg [-1.15, 0.07] vs placebo and -0.50mmHg [-1.24, 0.24] vs active control). Body weight decreased by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

Conclusions: GLP-1 analogues are associated with a small increase in heart rate, and modest reductions in body weight and blood pressure. Mechanisms underlying the rise in heart rate require further investigation.

ARTICLE SUMMARY

Article focus

- GLP-1 agonists are increasingly used in the management of type 2 diabetes, but their long term cardiovascular safety is not yet confirmed.
- These agents are known to reduce body weight and blood pressure, but are also associated with an elevation in heart rate that has not previously been quantified.

Key messages

- Our analysis confirms the weight and blood pressure reducing effects of liraglutide and exenatide, and reports a small rise in heart rate.
- The weight reducing effects are substantially greater when compared with active control treatments than placebo, as alternative treatment options may promote weight gain.
- Heart rate rises were more evident for liraglutide than exenatide, and for exenatide long acting release (LAR) than exenatide twice daily (BID).

Strengths and limitations

- We included unpublished data obtained from pharmaceutical companies, enabling the effects of GLP-1 agonists on heart rate to be quantified for the first time by meta-analysis.
- Our analysis is limited by significant heterogeneity between studies, and suggests the need for more detailed investigation using more accurate measurements of heart rate than those typically used in clinical practice.

INTRODUCTION

In contrast to the weight increasing effects of several traditional anti-diabetic drug classes,[1] GLP-1 analogues have been shown to reduce both body weight and blood pressure.[2] The mechanisms producing weight loss have been extensively investigated, and involve improved satiety and reduced calorie ingestion both through effects on the central nervous system and through delayed gastric emptying.[3-6] Those leading to reduced blood pressure are less adequately understood, but this effect has been shown to occur as early as two weeks after commencing therapy, preceding significant weight loss, suggesting that a direct hypotensive effect is at least partly responsible.[7] Experimental studies of GLP-1 analogues have also reported direct effects on blood pressure, possibly via interaction with the autonomic nervous system.[8, 9]

Whilst a number of studies have reported heart rate increases, the associated mechanisms are unknown, and this effect is often dismissed as clinically unimportant. Given the safety implications attributed to raised heart rate in other contexts,[10-13] there is a surprising lack of concern over its possible implications in this setting. A recent review of liraglutide by Buse acknowledges the effect,[14] but a meta-analysis on safety of incretin based therapies published in 2010 did not mention heart rate,[15] nor does an overview of the LEAD trials of liraglutide by Blonde and Russell-Jones.[16] A large nationwide audit of exenatide designed by the Association of British Clinical Diabetologists (ABCD) did not include heart rate as an outcome, despite citing evidence for the effect in the main published report.[17] A subsequent (on-going) ABCD audit of liraglutide also aims to identify unknown safety issues but has similarly omitted heart rate from the protocol.[18]

GLP-1 analogues are an expanding drug class, with recent development of longer acting agents including the once weekly (LAR) form of exenatide, Bydureon. This drug has recently obtained approval from the National Institute for Health and Clinical Excellence for use in type 2 diabetes and its use is likely to increase.[19] A review of trial data from five long acting GLP-1 agonists (exenatide once weekly, taspoglutide, albiglutide, LY2189265 and CJC-1134-PC) concluded that they were more likely than shorter acting formulations to raise heart rate.[20] A more recently published study of the long acting GLP-1 agent PF-04603629 reported a substantial rise in heart rate (mean increase 23 bpm at 24 hours after injection of the higher dose studied), together with a rise in diastolic blood pressure.[21]

Whilst there is no evidence to date that these agents (short or long acting) increase cardiovascular event rates, safety data are limited by short follow up duration.[22] Longer term follow up is underway but will take a number of years to complete.

We aimed to identify and synthesise all available heart rate data from both published and unpublished sources, to quantify the effect of GLP-1 analogues on heart rate, as well as that on blood pressure and body weight.

METHODS

Literature searches

The following resources were systematically searched to identify completed, new or on-going controlled trials of liraglutide or exenatide: Clinical Trials Gov (www.clinicaltrials.gov); Entertrials.co.uk; Clinicaltrialssearch.org; Centerwatch; Drugsontrial; WebMD; MEDLINE (from 1960); EMBASE (from 1960); Cochrane Library Central Register of Controlled Trials (CENTRAL). We used a search strategy to capture "exenatide", "liraglutide" or "glucagon-like peptide-1" in any field, limited to "Randomised Controlled Trial," "Clinical Trial," or "Controlled Clinical Trial". Conference proceedings (British Endocrinology Society, Diabetes UK, European Association for the Study of Diabetes) and websites (American Diabetes Association, Federal Drug Agency and European Medicines Agency) were examined, and the reference lists of trials, meta-analyses and reviews were searched for further studies. Novo Nordisk and Amylin Pharmaceuticals were contacted directly to request unpublished data. The review is up to date at July 2012.

Inclusion and exclusion criteria

a) Participants

We only included trials involving participants with type 2 diabetes.

b) Study designs

We included all randomised trials with minimum follow up of 12 weeks. We excluded 'open-label' extension studies of phase 3 trials.

c) Interventions

Trials of liraglutide (1.2 or 1.8 mg daily), exenatide (5 or 10 µg BID), or exenatide LAR, either alone or in combination with an oral anti-diabetic drug (OAD) or insulin, were included.

c) Comparison groups(s)

Comparators included placebo, OAD, lifestyle intervention, or insulin.

d) Outcomes

We included all studies reporting heart rate, blood pressure, or body weight outcomes.

Data extraction

Retrieved studies were assessed for inclusion by two researchers independently using the above criteria and any discrepancies were resolved by consensus. Information on the participants, intervention, comparison group, outcomes and trial quality were extracted from included studies by two researchers independently. Where necessary, clarification of data was obtained by correspondence with trial co-ordinators.

Risk of Bias

We used the Cochrane tool to determine risk of selection bias (success of sequence generation and allocation concealment); performance bias (success of blinding to treatment received); detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data and selective outcome reporting) and other biases.[23] Funnel plots were used to detect publication bias.

Analysis

Means and standard deviations for baseline and outcome values for blood pressure, heart rate and body weight were extracted. Mean effect data from cross-over trials were extracted at the end of the initial phase. Where standard deviations for the outcome were not available they were imputed according to Cochrane Handbook for Systematic reviews version 5.[23] Standard deviations for changes from baseline were derived where necessary to account for correlation of baseline to follow up measurements within individuals, and where the correlation coefficient could not be calculated, methods were employed as recommended by Follman et al.[24] Study results were combined using RevMan version 5.2. Heterogeneity was estimated using the χ^2- test and I^2 statistic. Fixed and random effects weighted mean difference models using the Inverse Variance technique were used to compare outcomes between study drug and comparator with 95% confidence intervals (CI). Interaction effects were evaluated using pre-specified subgroup analyses (comparing various doses of study drug to active control or placebo) and type of GLP-1 agonist (liraglutide, exenatide BID and exenatide LAR preparations). Results are described using the random effects approach due to the heterogeneity of the included studies. Analyses were stratified by active control or placebo. Funnel plots were assessed for asymmetry.

RESULTS

Figure 1 describes the identification of included studies. A total of 521 articles were screened. Of these, 472 were excluded on the basis of the title or abstract being irrelevant to the aims of this review. Forty-nine studies were examined in full text. Out of these, 4 were excluded because the comparator was another form of GLP-1.[25-28] In 3 cases the doses were not as specified in our inclusion criteria,[29-31] and in a further 2 the study involved further analysis of data from trials that were already included.[32, 33] Finally, 8 were open label extension studies.[34-41] This left 32 trials included in our review (Figure 1 and Table 1).[42-73] Most studies did not report all of the outcomes of interest, or did not provide them as usable numerical data. Data were therefore obtained, where available directly from the pharmaceutical companies.

Methodological quality and risk of bias

Results of risk of bias assessment are given in Table 2. Explanation of sequence generation and allocation concealment was adequate for all trials. In nine trials at least one arm was open-label. Attrition was adequately described and was greater than 20% in nine studies. The proportion of the intention to treat (ITT) population completing the study varied with range 65.4-99.6% and median 83.7%. None of the trials were terminated prematurely. Funnel plots were broadly symmetrical with no evidence of publication bias.

Heterogeneity

For all outcomes, we found significant heterogeneity (Figures 2 to 6). We therefore chose to report results using the random effects approach, although the differences between random effects and fixed effect results were very small.

Heart rate

A total of 22 studies provided heart rate data. A summary from the Lead 1-5 trials of liraglutide[57, 64, 67, 69, 73] was obtained from Novo Nordisk and is given in Figure 2. Pooled results show a significant increase in heart-rate, with weighted mean difference 2.65 bpm [1.78, 3.52] versus placebo and 1.61 bpm [1.10, 2.13] versus active control. The data were provided grouped into quartiles of baseline heart rate and demonstrated significant variation in effect between these subgroups. Exenatide BID increased heart rate by 1.36 bpm [0.57, 2.14] versus active control and by 0.88 bpm [-0.47, 2.22] versus placebo, which did not reach statistical significance (Figure 3). Exenatide LAR produced a more significant change (2.14 bpm [1.11, 3.17] versus active control) but the number of studies involving this formulation was small.

Blood pressure

We included 31 trials measuring blood pressure changes (Figures 4 and 5). GLP-1 agonists reduced systolic blood pressure by -1.79mmHg [-2.94, -0.64] compared to placebo and by -2.39 [-3.35, -1.42] compared to active control. Reductions in diastolic blood pressure failed to reach statistical significance, and were -0.54mmHg [-1.15, 0.07] compared to placebo and -0.50mmHg [-1.24, 0.24] compared to active control.

Body weight

Twenty-one trials measuring changes in weight were included (Figure 6). We confirm a small but highly significant reduction in body weight as a result of GLP-1 therapy. Weight changed by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

DISCUSSION

We have confirmed and quantified the effects of liragutide and exenatide on heart rate, blood pressure and body weight. Our analysis benefited from the inclusion of unpublished data supplied by Novo Nordisk and Amylin Pharmaceuticals, as these were often missing from published trial reports. It was limited by the significant heterogeneity of effect size measurements between individual studies.

The weight reducing effects of these agents are a welcome contrast to the weight promoting effects of other treatment options, including sulphonylureas, thiazolidinediones, and insulin. We have derived a similar effect size to a previously reported value for weight loss,[2] although our study has distinguished between placebo and active comparators, in which effects sizes differ substantially. Together with the reduction in blood pressure, this may improve longer term cardiovascular risk. However, the small rise in heart rate is a reason for caution, as it might potentially be associated with adverse outcomes. This rise was more evident for liraglutide than exenatide BID, but exenatide LAR may produce a greater response than the BID formulation.

For most GLP-1 trials, heart rate is a secondary outcome measured as part of safety assessment, and is reported inconsistently. In clinic it is often measured using a very short sampling interval (perhaps one minute of data). One study was designed specifically to examine the effects of exenatide BID on change in heart rate as the primary outcome using 24 hour ambulatory monitoring.[58] The mean change from baseline at 12 weeks was 2.1 bpm for exenatide BID and -0.7 bpm for placebo. The sample size (54 randomised participants) in this pilot study was relatively small and the difference was not significant (p=0.16), but is similar to the values we have obtained generally for GLP-1

agonists in our meta-analysis. Measurement of heart rate using this 24-hour technique (compared with a traditional heart rate measurement in clinic) substantially improves the accuracy of measurement as heart rate is very variable within the individual. This technique could be used as a basis for a larger study powered to detect such a difference. This would enable investigation of pre-specified subgroups, including those with low baseline heart rate, who appeared in the LEAD studies of liraglutide to experience a more substantial change of 4.8 bpm versus placebo.

This review highlights the need to improve our understanding of the physiological mechanisms through which GLP-1 agonists act, whilst the results of longer term safety studies are awaited. There is also a clear need to improve the comprehensive reporting of all outcome data measured during clinical trials of anti-diabetic agents, particularly those relevant to cardiovascular risk.

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CONTRIBUTORSHIP STATEMENT

LR, PO'H and HR were involved in the design and conception of the study. LR and TH conducted the bibliographic searches, identified the included papers, and extracted the data independently. KR advised on methodological issues. All authors were involved in drafting the manuscript.

ETHICAL APPROVAL

None required.

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COMPETING INTERESTS

LR, TH and KR have no interests to declare. PO'H and HR have received research funding (paid to Warwick Medical School) from Novo Nordisk, and payments for speaking from Novo Nordisk.

DATA SHARING

All data used in this study are freely available by request to the corresponding author Dr Tim A. Holt.

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FIGURE LEGENDS

Figure 1: PRISMA flow diagram

Figure 2: Effect of liraglutide on heart rate in patients with type 2 diabetes

Figure 3: Effect of exenatide on heart rate in patients with type 2 diabetes

Figure 4: GLP-1 agonists' effect on systolic blood pressure in patients with type 2 diabetes

Figure 5: GLP-1 agonists' effect on diastolic blood pressure in patients with type 2 diabetes

Figure 6: GLP-1 agonists' effects on body weight

Table 1 Characteristics of included studies

Study	Comparisons	Duration (weeks)	Study population/ ethnicity	Country	Body weight groups included	Balanced Male/ Female?	Standardised diet/ exercise	Background OAD
Apovian, 2010	EX/PLAC	24	MR	US	OW	>60% F	Y	MET and/or SU
Barnett, 2007	EX/IG	16	MR	Multi-national	N/OW/ OB	Y	N	MET or SU
Bergenstal, 2009	EX/BIAsp	24	MR	US	N/OW	Y	N	MET and SU
Bergenstal, 2010	EX LAR vs PIO EX LAR vs SITA	26	MR	Multi-national	N/OW/ OB	Y	N	MET
Buse, 2004	EX/PLAC	30	MR	US	OW/OB	60% M	N	SU
Buse, 2011	IG+EX/ IG+PLAC	30	MR	Multi-national	N/OW/ OB	Y	N	MET or PIO

Davies, 2009	EX/IG	26	MR	GB	OW/OB	>60% M	N	Two or three OADS: MET, SU, or TZD
Defronzo, 2005	EX/PLAC	30	MR	US	OW/OB	Y	N	MET
Defronzo, 2010	EX vs ROSI	20	MR	US	OW/OB	Y	N	MET
Derosa, 2010	EX/GLIB	52	W	IT	OW/OB	Y	Y	MET
Derosa, 2011	EX/GLIM	52	CAUC	IT	OW/OB	Y	Y	MET
Diamant, 2010	EX LAR/IG	26	MR	Multi-national	OW/OB	Y	N	MET
Gallwitz, 2011	EX/BIAsp	26	MR	GER	OW/OB	Not reported	N	MET
Gallwitz 2012	EX/GLIM	Up to 4.5 years	MR	Multi-national	OW/OB	Y	N	MET
Gao,	EX/PLAC	12	C/I/K/T	Multi-national	N/OW/	Y	N	MET and/or SU

2009					OB			
Garber, 2009	LIR/GLIM	52	MR	US/MEX	N/OW/ OB	Y	N	Nil - previous OAD withdrawn
Gill, 2010	EX/PLAC	12	MR	CAN/NL	OW/OB	Y	N	MET and/or TZD
Heine, 2005	EX/IG	26	MR	Multi-national	OW/OB	Y	N	MET and SU
Kadowaki, 2009	EX/PLAC	12	JP	JP	N/OW/ OB	>60% M	N	SU, with or without either BG or TZD
Kendall, 2005	EX/PLAC	30	MR	US	OW/OB	Y	Y	MET and SU
Kim, 2007	EX LAR/PLAC	15	MR	US	OW/OB	60% M	Y	MET
Liutkus, 2010	EX/PLAC	26	MR	Multi-national	OW/OB	Y	N	TZD with or without MET
Marre, 2009	LIR/PLAC	26	MR	Multi-national	N/OW/	Y	N	SU with or

					OB			without ROSI
Moretto, 2008	EX/PLAC	24	MR	Multi-national	OW/OB	Y	Y	DRUG NAIVE
Nauck, 2007	EX/PIA	52	MR	Multi-national	OW/OB	Y	N	SU and MET
Nauck, 2009	LIR/GLIM/PLAC	26	MR	Multi-national	N/OW/ OB	Y	N	MET
Pratley, 2010	LIR/SIT	26	MR	Multi-national	N- OW- OB	Y	N	MET
Russell-Jones, 2009	LIR/IG/PLAC	26	MR	Multi-national	N/OW/ OB	Y	N	MET and SU
Russell-Jones, 2012	EX LAR/MET EX LAR/PIO EX LAR/SITA	26	MR	Multi-national	N/OW/ OB	Y	N	DRUG NAIVE
Yang, 2011	LIR/GLIM	16	C/K/I	Multi-national	N/OW/ OB	Y	N	MET
Zinman, 2007	EX/PLAC	16	MR	Multi-national	OW/OB	Y	N	TZD with or without MET

Zinman, 2009	LIR/PLAC	26	MR	US/CAN	N/OW/ OB	Y	N	MET and ROSI

EX, Exenatide; EX LAR, Exenatide long acting release; PLAC, placebo; IG, insulin glargine; BIAsp, biphasic insulin aspart; PIO, pioglitazone; SITA, sitagliptin; ROSI, rosiglitazone; GLIB, glibenclamide; GLIM, glimepiride; LIR, liraglutide; MET, metformin, BG, Biguanide.

MR, Multi-racial; C, Chinese; K, Korean; I, Indian; T, Taiwanese; JP, Japanese; W, White; CAUC, Caucasian.

GB, Great Britain; US, United States; GER, Germany; CAN, Canada; JP, Japan; NL, Netherlands; MEX, Mexico; IT, Italy.

N, normal weight; OW, overweight; OB, obese.

Table 2 Risk of bias across included studies

Included studies were assessed using the Cochrane Risk of Bias Tool for factors which may cause bias in the trial outcomes and subsequent evaluation by meta-analysis: A) Randomisation, B) Allocation concealment, C) Blinding of participants/investigators/sponsors, D) Blinding outcome assessment, E) Incomplete outcome data, F) Selective outcome reporting, G) Other bias.

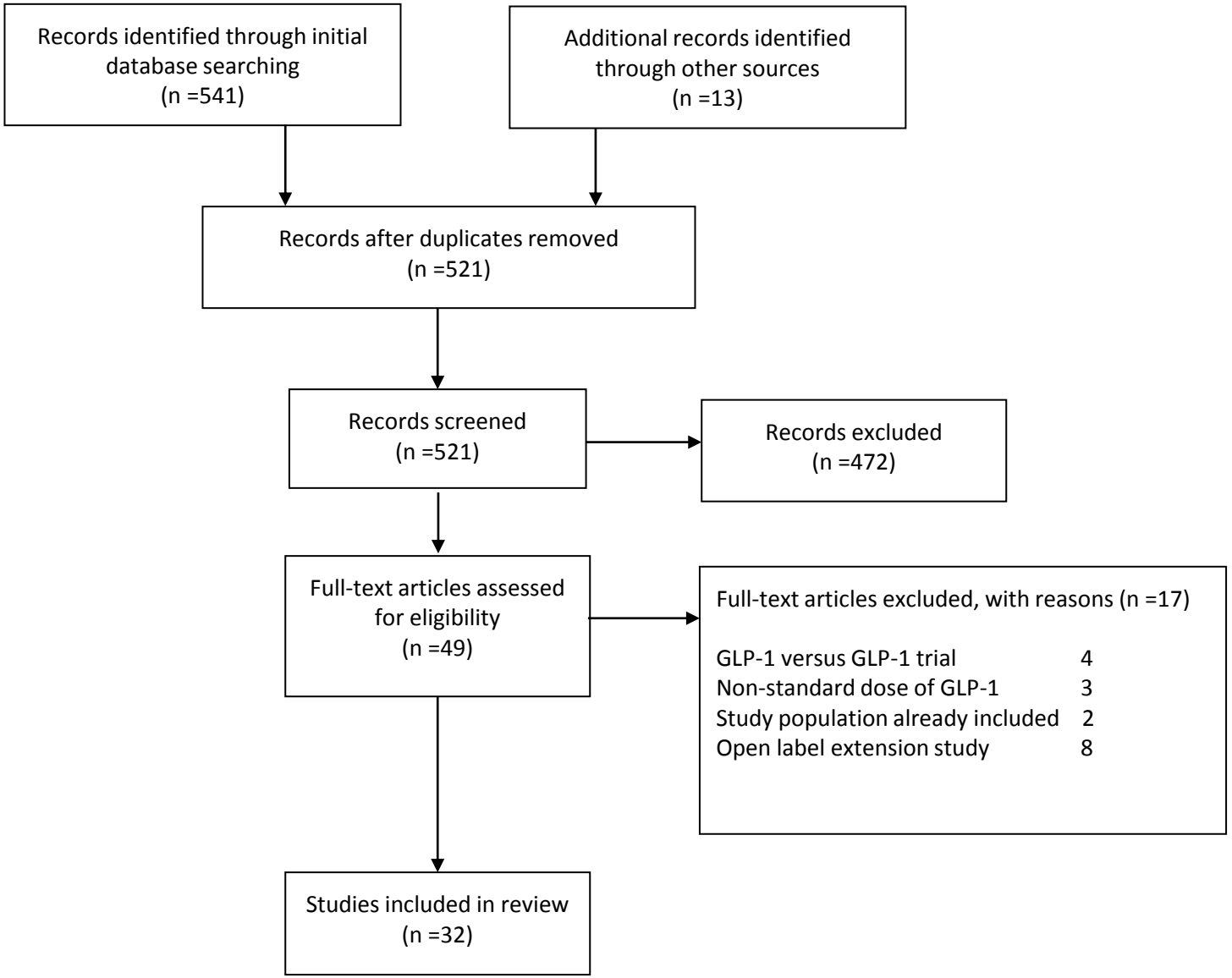
No.	Study	A	B	C	D	E	F	G	Comments
1	**Apovian, 2010**								Greater than 20% attrition.
2	**Barnett, 2007***								Open label cross-over study.
3	**Bergenstal, 2009***								Open label. Greater than 20% attrition and higher attrition in exenatide group.
4	**Bergenstal, 2010**								Greater than 20% attrition. Outcome assessors unblinded after finalisation of analysis plan.
5	**Buse, 2004**								Greater than 20% attrition. Higher attrition in the placebo arm.
6	**Buse, 2011**								Groups not balanced for sex and concomitant medication.
7	**Davies, 2009***								Open label.

8	**Defronzo, 2005**								
9	**Defronzo, 2010***								Open label. Greater than 20% attrition.
10	**Derosa, 2010**								Single blind.
11	**Derosa, 2011‡**								Single blind.
12	**Diamant, 2010***								Open label. Higher attrition in the exenatide arm.
13	**Gallwitz, 2011***								Open label.
14	**Gallwitz 2012***								Open label. Greater than 20% attrition. Higher attrition in the exenatide arm.
15	**Gao, 2009**								
16	**Garber, 2009**								Greater than 20% attrition.
17	**Gill, 2010**								
18	**Heine, 2005***								Open label. Higher attrition in the exenatide arm.
19	**Kadowaki,¥ 2009**								
20	**Kendall, 2005**								

21	**Kim, 2007**								
22	**Liutkus, 2010**[¥]								
23	**Marre, 2009**								Higher attrition in the placebo arm. Restriction of glimipiride and rosiglitazone in some countries precluded maximal dose regimes.
24	**Moretto, 2008**								Diet and exercise regimes not standardised.
25	**Nauck, 2007**[*]								Open label.
26	**Nauck, 2009**								Higher attrition in Liraglutide 1.8 mg and placebo arms.
27	**Pratley, 2010**[*]								Open label, but statistician was masked to the allocation.
28	**Russell-Jones, 2009***								Insulin glargine arm-open label.
29	**Russell-Jones 2012**								
30	**Yang, 2011**								Higher attrition in the liraglutide groups.

31	**Zinman, 2007**								Greater than 20% attrition. Higher attrition in exenatide group.
32	**Zinman, 2009**								Greater than 20% attrition. Higher attrition in placebo group.

* Open label; □ method of randomisation/allocation concealment consisted of a computer random-number generator and voice-response or telephone system; □ permuted block randomisation; ¥ randomised according to baseline biochemical values or background pharmacological agent; ŧ randomised according to coded envelopes designed by a statistician high risk; low risk; unclear risk.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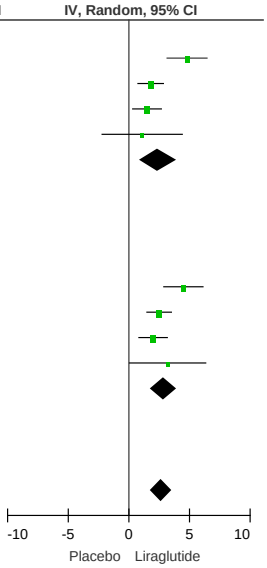
Records screened (n =521)
Records excluded (n =472)
Full-text articles assessed for eligibility (n =49)
Full-text articles excluded, with reasons (n =17)
GLP-1 versus GLP-1 trial 4
Non-standard dose of GLP-1 3
Study population already included 2
Open label extension study 8
Studies included in review (n =32)

Figure 2 Effect of liraglutide on heart rate in patients with type 2 diabetes

2(a) Liraglutide versus placebo

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.1.1 Liraglutide 1.2 mg vs placebo								
Q1 Baseline HR ≤ 68 b.p.m	8.5	6.47	233	3.7	5.13	50	12.2%	4.80 [3.15, 6.45]
Q2 68 < Baseline HR ≤ 74	3.5	3.41	168	1.7	3.29	50	16.5%	1.80 [0.75, 2.85]
Q3 74 Baseline HR ≤ 80	0.4	3.89	192	-1.1	3.78	50	15.5%	1.50 [0.32, 2.68]
Q4 Baseline HR > 80	-5.5	10.62	149	-6.6	8.91	38	5.3%	1.10 [-2.21, 4.41]
Subtotal (95% CI)			**742**			**188**	**49.5%**	**2.38 [0.85, 3.92]**
Heterogeneity: Tau² = 1.69; Chi² = 11.90, df = 3 (P = 0.008); I² = 75%								
Test for overall effect: Z = 3.05 (P = 0.002)								
4.1.2 Liraglutide 1.8 mg vs placebo								
Q1 Baseline HR ≤ 68 b.p.m	8.2	6.02	284	3.7	5.21	49	12.4%	4.50 [2.88, 6.12]
Q2 68 < Baseline HR ≤ 74	4.2	3.32	220	1.7	3.29	50	16.8%	2.50 [1.49, 3.51]
Q3 74 Baseline HR ≤ 80	0.9	3.9	234	-1.1	3.78	49	15.6%	2.00 [0.83, 3.17]
Q4 Baseline HR > 80	-3.4	9.62	192	-6.6	8.91	38	5.7%	3.20 [0.06, 6.34]
Subtotal (95% CI)			**930**			**186**	**50.5%**	**2.88 [1.80, 3.97]**
Heterogeneity: Tau² = 0.61; Chi² = 6.37, df = 3 (P = 0.09); I² = 53%								
Test for overall effect: Z = 5.21 (P < 0.00001)								
Total (95% CI)			**1672**			**374**	**100.0%**	**2.65 [1.78, 3.52]**
Heterogeneity: Tau² = 0.91; Chi² = 19.38, df = 7 (P = 0.007); I² = 64%								
Test for overall effect: Z = 5.96 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%								



2(b) Liraglutide versus active control

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.2.1 Liraglutide 1.2 mg vs active control								
Q1 Baseline HR ≤ 68 b.p.m	8.5	6.47	223	5.9	5.8	103	9.6%	2.60 [1.19, 4.01]
Q2 68 < Baseline HR ≤ 74	3.5	3.41	168	2	3.01	92	18.6%	1.50 [0.70, 2.30]
Q3 74 Baseline HR ≤ 80	0.4	3.89	192	-0.3	3.88	116	16.7%	0.70 [-0.20, 1.60]
Q4 Baseline HR > 80	-5.5	10.62	149	-5.6	9.15	87	3.6%	0.10 [-2.47, 2.67]
Subtotal (95% CI)			**732**			**398**	**48.5%**	**1.34 [0.49, 2.20]**
Heterogeneity: Tau² = 0.36; Chi² = 6.09, df = 3 (P = 0.11); I² = 51%								
Test for overall effect: Z = 3.09 (P = 0.002)								
4.2.2 Liraglutide 1.8 mg vs active control								
Q1 Baseline HR ≤ 68 b.p.m	8.2	6.02	284	5.9	5.89	103	10.3%	2.30 [0.96, 3.64]
Q2 68 < Baseline HR ≤ 74	4.2	3.32	220	2	3.12	92	19.2%	2.20 [1.43, 2.97]
Q3 74 Baseline HR ≤ 80	0.9	3.9	234	-0.3	3.69	116	17.9%	1.20 [0.36, 2.04]
Q4 Baseline HR > 80	-3.4	9.62	192	-5.6	9.15	87	4.2%	2.20 [-0.16, 4.56]
Subtotal (95% CI)			**930**			**398**	**51.5%**	**1.85 [1.27, 2.44]**
Heterogeneity: Tau² = 0.07; Chi² = 3.62, df = 3 (P = 0.31); I² = 17%								
Test for overall effect: Z = 6.18 (P < 0.00001)								
Total (95% CI)			**1662**			**796**	**100.0%**	**1.61 [1.10, 2.13]**
Heterogeneity: Tau² = 0.20; Chi² = 11.68, df = 7 (P = 0.11); I² = 40%								
Test for overall effect: Z = 6.15 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%								

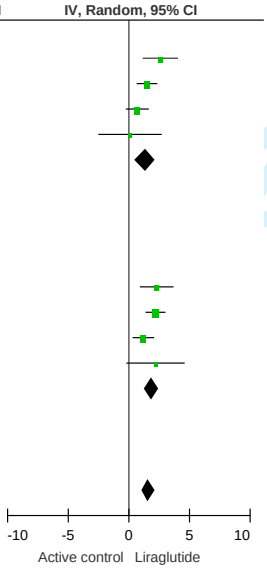
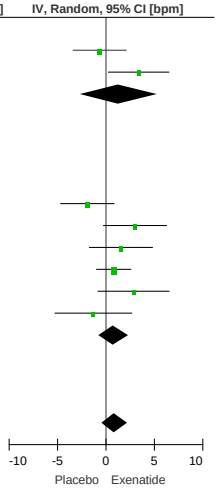


Figure 3 Effect of exenatide on heart rate in patients with type 2 diabetes

3(a) Exenatide versus placebo

Study or Subgroup	Experimental Mean [bpm]	Experimental SD [bpm]	Experimental Total	Control Mean [bpm]	Control SD [bpm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [bpm]
5.1.1 Exenatide 5mcg vs placebo								
Buse, 2004	0.47	9.054	125	1.12	8.911	62	13.8%	-0.65 [-3.38, 2.08]
DeFronzo, 2005	2.89	9.573	110	-0.49	9.815	57	11.7%	3.38 [0.27, 6.49]
Subtotal (95% CI)			**235**			**119**	**25.5%**	**1.29 [-2.65, 5.24]**
Heterogeneity: Tau² = 5.89; Chi² = 3.64, df = 1 (P = 0.06); I² = 73%								
Test for overall effect: Z = 0.64 (P = 0.52)								
5.1.2 Exenatide 10 mcg vs placebo								
Buse, 2004	-0.8	9.201	129	1.12	8.911	61	13.7%	-1.92 [-4.66, 0.82]
Buse, 2011	2.3	13.16	137	-0.7	13.42	122	11.1%	3.00 [-0.24, 6.24]
DeFronzo, 2005	1.06	10.746	113	-0.49	9.815	56	11.1%	1.55 [-1.70, 4.80]
Gao, 2009	0.1	9.82	234	-0.7	9.5	230	20.6%	0.80 [-0.96, 2.56]
Gill, 2010	2.14	6.52	26	-0.71	6.81	25	9.4%	2.85 [-0.81, 6.51]
Liutkus, 2010	0.5	13.72	111	1.8	11.31	54	8.5%	-1.30 [-5.25, 2.65]
Subtotal (95% CI)			**750**			**548**	**74.5%**	**0.76 [-0.76, 2.28]**
Heterogeneity: Tau² = 1.32; Chi² = 8.02, df = 5 (P = 0.16); I² = 38%								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**985**			**667**	**100.0%**	**0.88 [-0.47, 2.22]**
Heterogeneity: Tau² = 1.46; Chi² = 11.76, df = 7 (P = 0.11); I² = 40%								
Test for overall effect: Z = 1.28 (P = 0.20)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								



3(b) Exenatide versus active control

Study or Subgroup	Experimental Mean [bpm]	Experimental SD [bpm]	Experimental Total	Control Mean [bpm]	Control SD [bpm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [bpm]
5.2.1 Exenatide 10 mcg vs active control								
Barnett, 2007	-1.29	8.7	68	-0.93	8.95	70	5.3%	-0.36 [-3.30, 2.58]
Bunck, 2009	4.6	10.02	36	-2.2	9.82	33	2.5%	6.80 [2.12, 11.48]
Buse, 2011	2.3	17.25	137	-0.7	7.14	122	4.7%	3.00 [-0.15, 6.15]
DeFronzo, 2010	-0.6	9.34	73	-1.67	10.03	79	4.9%	1.07 [-2.01, 4.15]
Gallwitz, 2011	-0.5	11	181	0.1	9.1	173	8.3%	-0.60 [-2.70, 1.50]
Gallwitz, 2012	1.2	10.6	504	0.6	10.5	501	13.2%	0.60 [-0.70, 1.90]
Heine, 2005	-0.31	9.6	282	-1.2	9.52	267	11.1%	0.89 [-0.71, 2.49]
Nauck, 2007	1.53	10.27	253	1.19	9.17	248	10.5%	0.34 [-1.36, 2.04]
Subtotal (95% CI)			**1534**			**1493**	**60.5%**	**0.82 [-0.15, 1.79]**
Heterogeneity: Tau² = 0.64; Chi² = 10.83, df = 7 (P = 0.15); I² = 35%								
Test for overall effect: Z = 1.66 (P = 0.10)								
5.2.2 Exenatide LAR 2.0 mg vs active control								
Bergenstal, 2010 (Piogl)	1.6	9.27	80	-0.9	8.75	165	6.9%	2.50 [0.07, 4.93]
Bergenstal, 2010 (sita)	1.6	9.27	80	0.5	8.93	166	6.9%	1.10 [-1.34, 3.54]
Diamant, 2010	4	14.46	233	0	14.46	233	6.2%	4.00 [1.37, 6.63]
Russell-Jones,2012 (MET)	1.5	10	82	0.3	9.5	246	6.8%	1.20 [-1.27, 3.67]
Russell-Jones,2012 (Sita)	1.5	10	82	0.5	9.7	163	6.2%	1.00 [-1.63, 3.63]
Russell-Jones,2012(Piogl)	1.5	10	83	-1.7	8.7	163	6.5%	3.20 [0.67, 5.73]
Subtotal (95% CI)			**640**			**1136**	**39.5%**	**2.14 [1.11, 3.17]**
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 5 (P = 0.46); I² = 0%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Total (95% CI)			**2174**			**2629**	**100.0%**	**1.36 [0.57, 2.14]**
Heterogeneity: Tau² = 0.76; Chi² = 20.48, df = 13 (P = 0.08); I² = 37%								
Test for overall effect: Z = 3.40 (P = 0.0007)								
Test for subgroup differences: Chi² = 3.36, df = 1 (P = 0.07), I² = 70.3%								

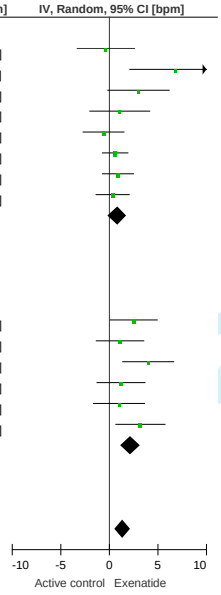
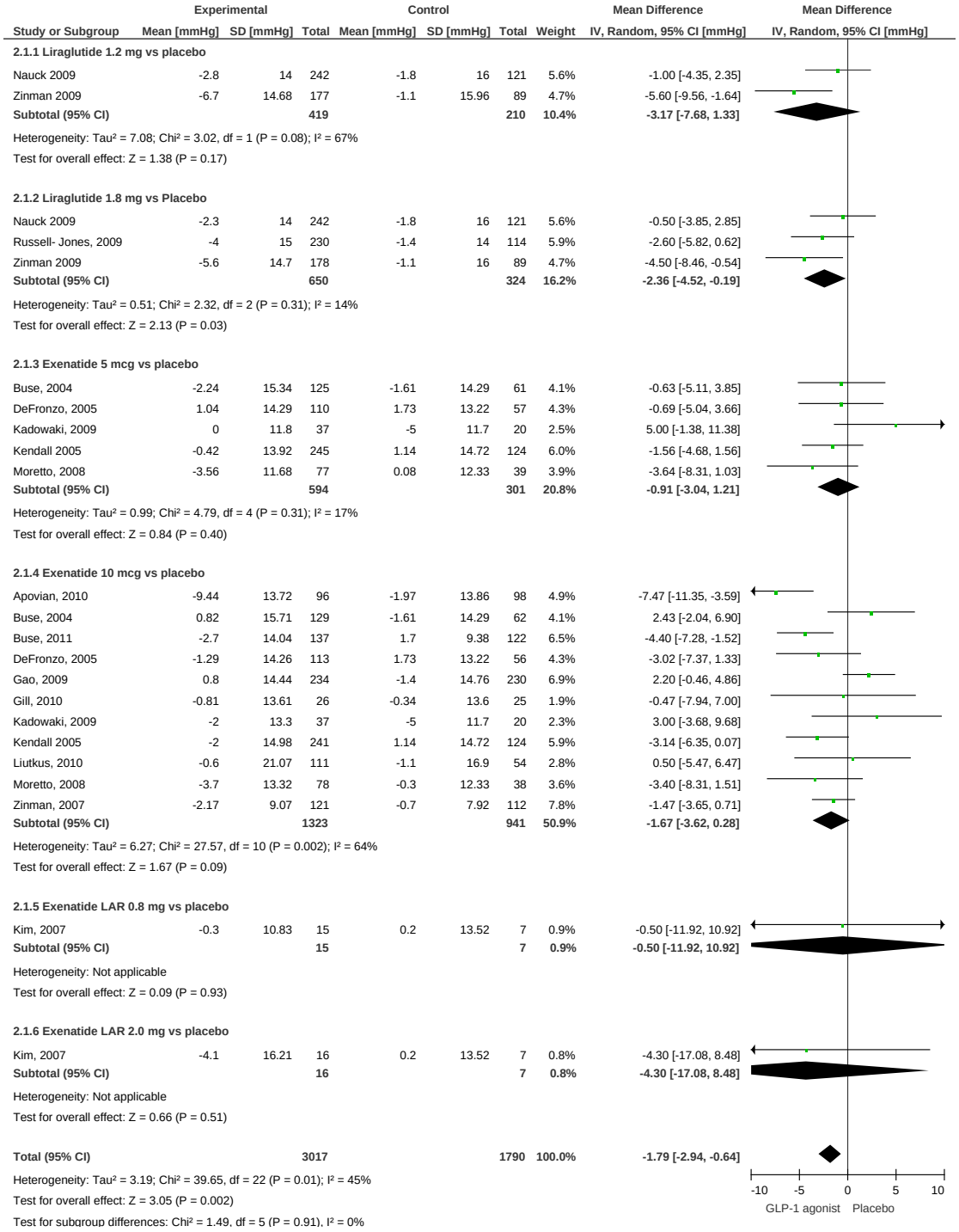


Figure 4 GLP-1 agonists' effect on systolic blood pressure in patients with type 2 diabetes

4(a) GLP-1 vs placebo



4(b) GLP-1 vs active control

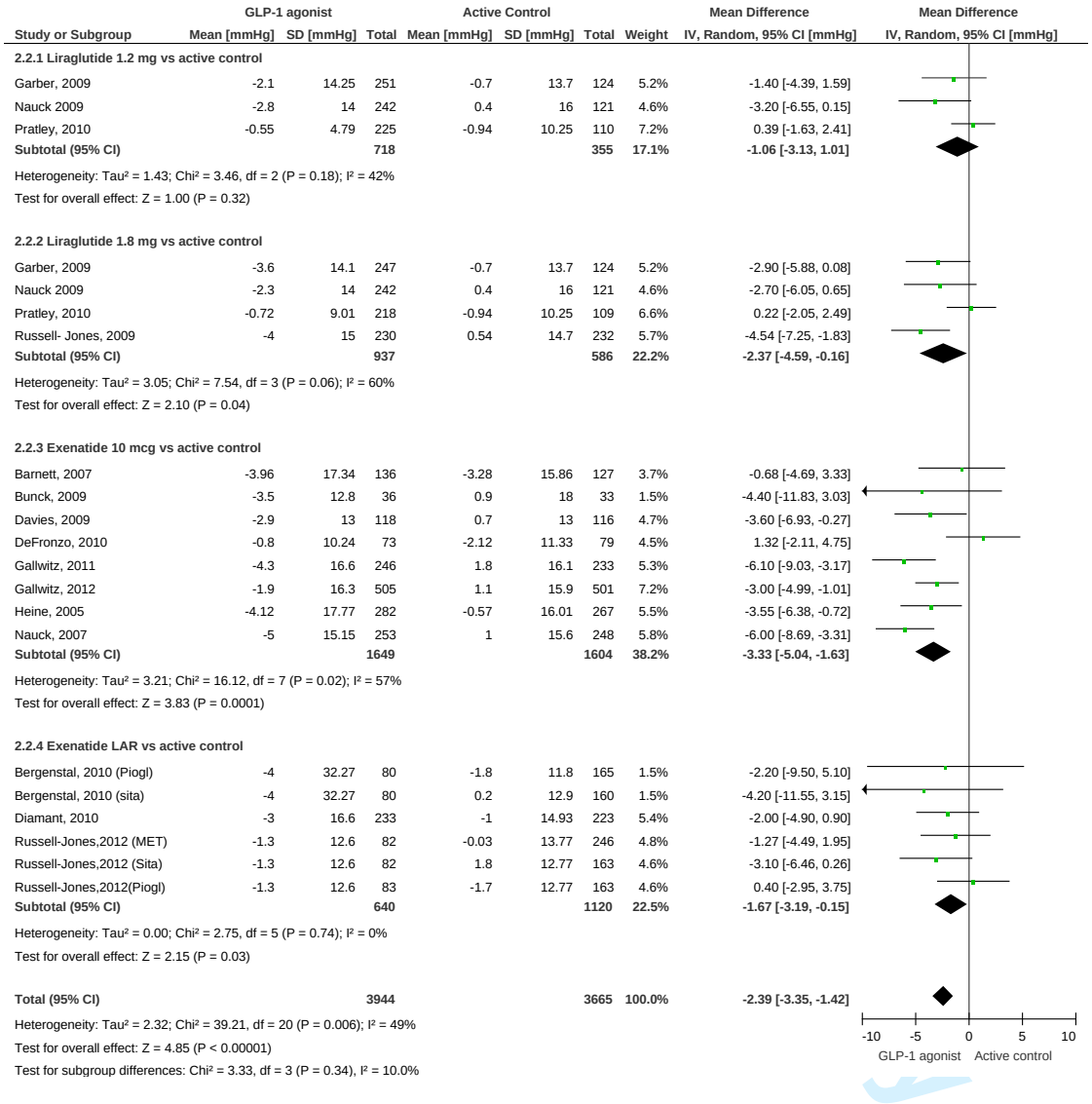
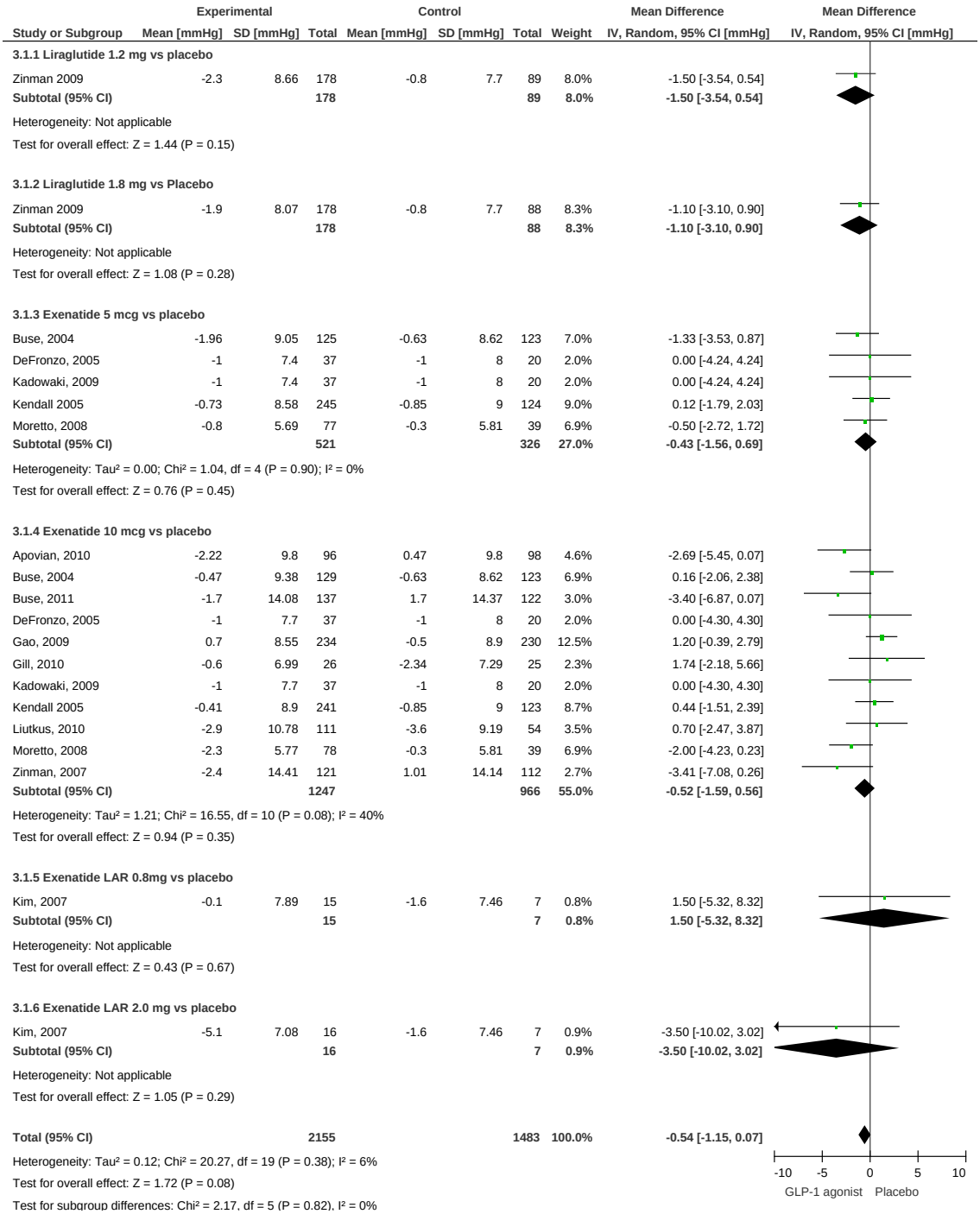


Figure 5 GLP-1 agonists' effect on diastolic blood pressure in patients with type 2 diabetes

5(a) GLP-1 vs placebo



5(b) GLP-1 vs active control

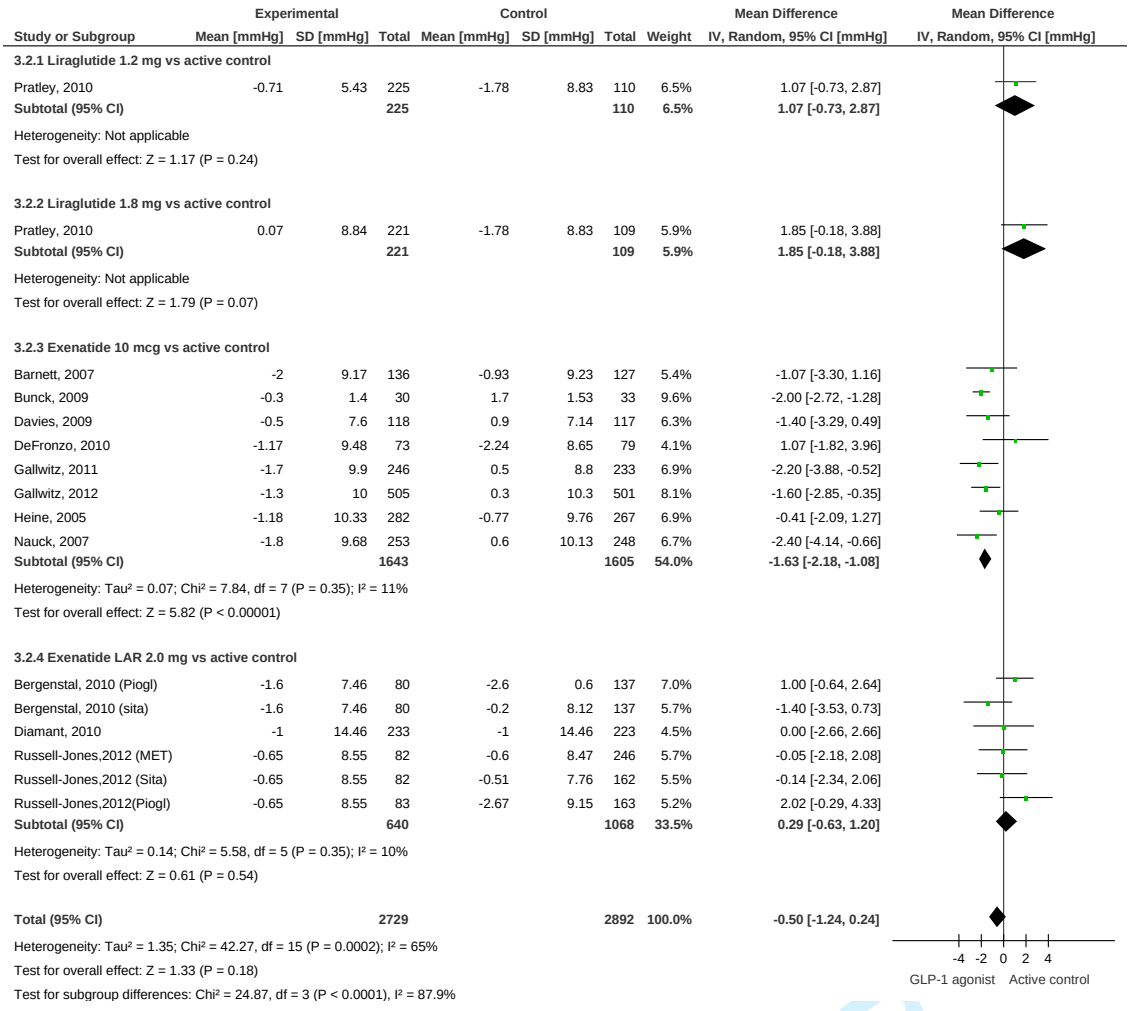
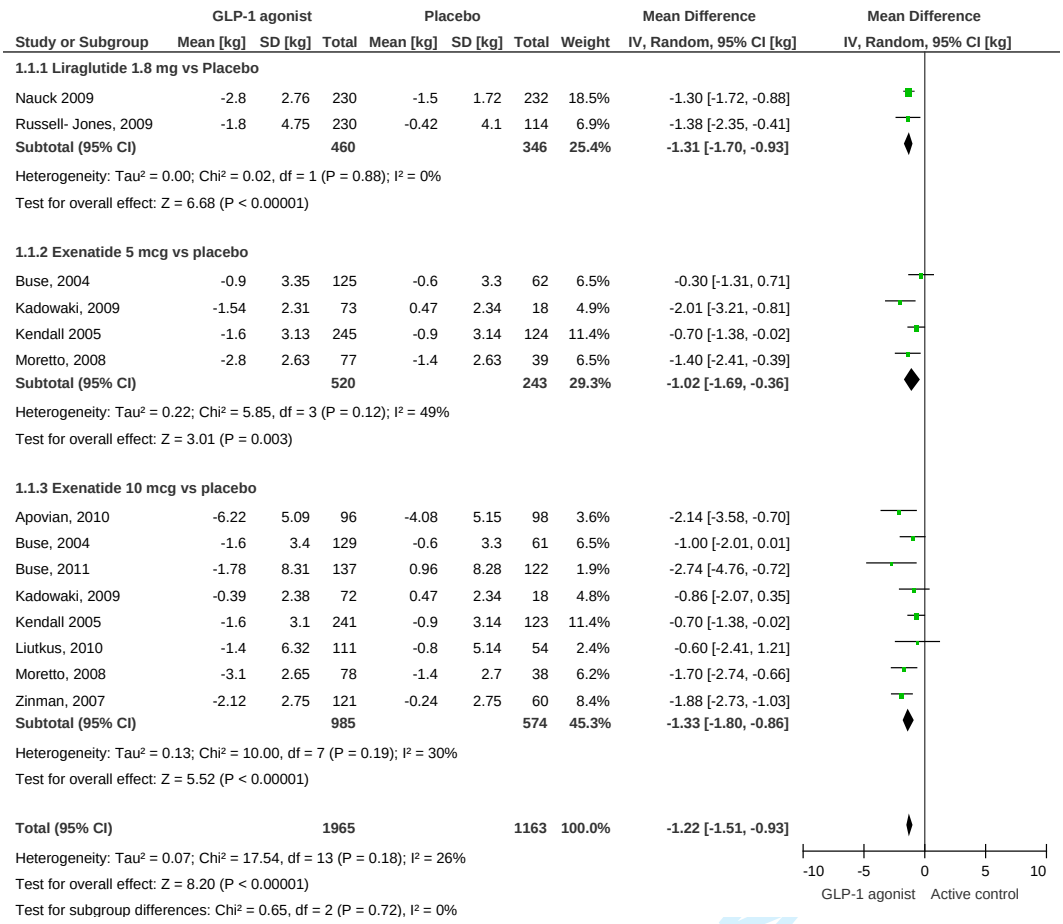
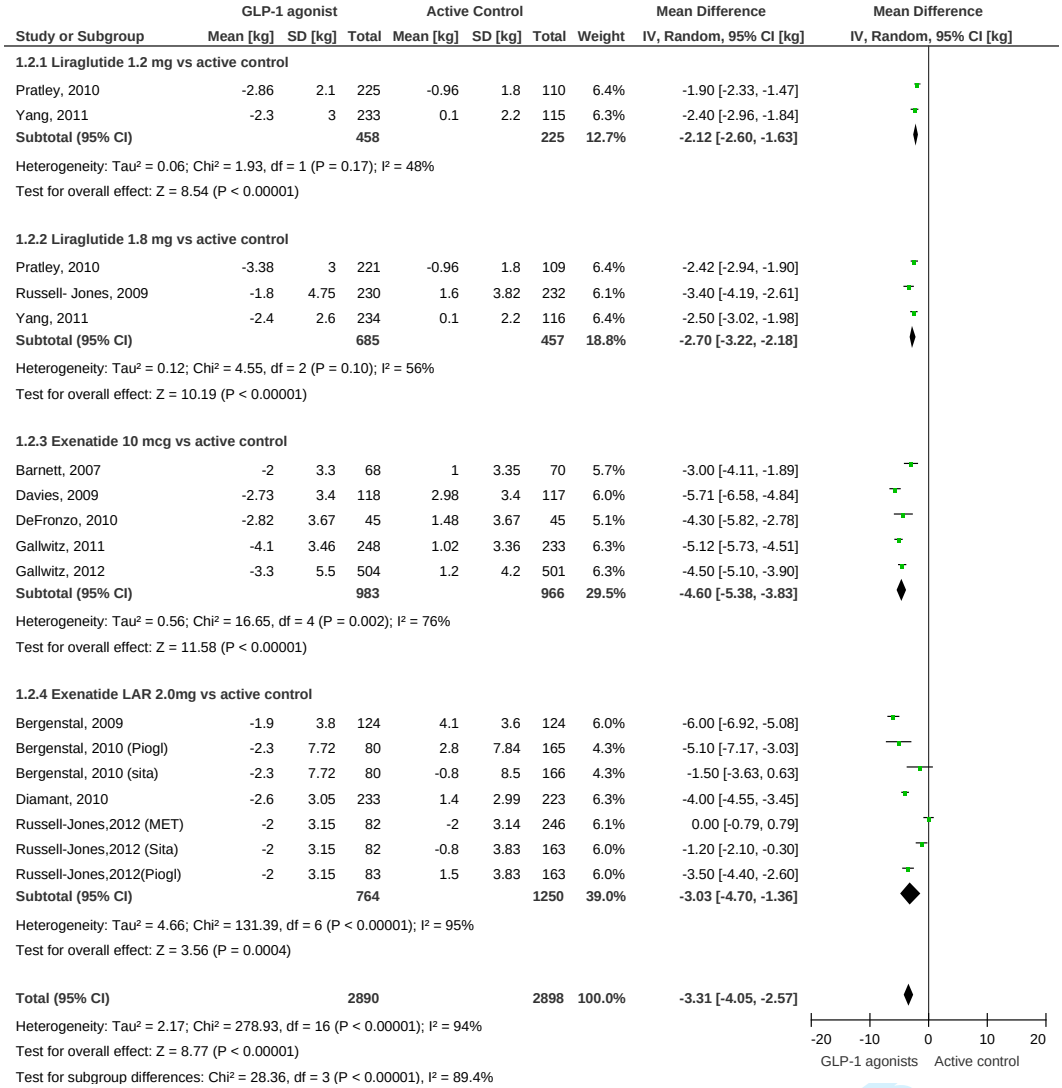


Figure 6 GLP-1 agonists' effects on body weight

6(a) GLP-1 agonists versus placebo



6(b) GLP-1 agonists versus active control



Study or Subgroup	GLP-1 agonist Mean [kg]	SD [kg]	Total	Active Control Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.2.1 Liraglutide 1.2 mg vs active control								
Pratley, 2010	-2.86	2.1	225	-0.96	1.8	110	6.4%	-1.90 [-2.33, -1.47]
Yang, 2011	-2.3	3	233	0.1	2.2	115	6.3%	-2.40 [-2.96, -1.84]
Subtotal (95% CI)			**458**			**225**	**12.7%**	**-2.12 [-2.60, -1.63]**
Heterogeneity: Tau² = 0.06; Chi² = 1.93, df = 1 (P = 0.17); I² = 48%								
Test for overall effect: Z = 8.54 (P < 0.00001)								
1.2.2 Liraglutide 1.8 mg vs active control								
Pratley, 2010	-3.38	3	221	-0.96	1.8	109	6.4%	-2.42 [-2.94, -1.90]
Russell- Jones, 2009	-1.8	4.75	230	1.6	3.82	232	6.1%	-3.40 [-4.19, -2.61]
Yang, 2011	-2.4	2.6	234	0.1	2.2	116	6.4%	-2.50 [-3.02, -1.98]
Subtotal (95% CI)			**685**			**457**	**18.8%**	**-2.70 [-3.22, -2.18]**
Heterogeneity: Tau² = 0.12; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%								
Test for overall effect: Z = 10.19 (P < 0.00001)								
1.2.3 Exenatide 10 mcg vs active control								
Barnett, 2007	-2	3.3	68	1	3.35	70	5.7%	-3.00 [-4.11, -1.89]
Davies, 2009	-2.73	3.4	118	2.98	3.4	117	6.0%	-5.71 [-6.58, -4.84]
DeFronzo, 2010	-2.82	3.67	45	1.48	3.67	45	5.1%	-4.30 [-5.82, -2.78]
Gallwitz, 2011	-4.1	3.46	248	1.02	3.36	233	6.3%	-5.12 [-5.73, -4.51]
Gallwitz, 2012	-3.3	5.5	504	1.2	4.2	501	6.3%	-4.50 [-5.10, -3.90]
Subtotal (95% CI)			**983**			**966**	**29.5%**	**-4.60 [-5.38, -3.83]**
Heterogeneity: Tau² = 0.56; Chi² = 16.65, df = 4 (P = 0.002); I² = 76%								
Test for overall effect: Z = 11.58 (P < 0.00001)								
1.2.4 Exenatide LAR 2.0mg vs active control								
Bergenstal, 2009	-1.9	3.8	124	4.1	3.6	124	6.0%	-6.00 [-6.92, -5.08]
Bergenstal, 2010 (Piogl)	-2.3	7.72	80	2.8	7.84	165	4.3%	-5.10 [-7.17, -3.03]
Bergenstal, 2010 (sita)	-2.3	7.72	80	-0.8	8.5	166	4.3%	-1.50 [-3.63, 0.63]
Diamant, 2010	-2.6	3.05	233	1.4	2.99	223	6.3%	-4.00 [-4.55, -3.45]
Russell-Jones,2012 (MET)	-2	3.15	82	-2	3.14	246	6.1%	0.00 [-0.79, 0.79]
Russell-Jones,2012 (Sita)	-2	3.15	82	-0.8	3.83	163	6.0%	-1.20 [-2.10, -0.30]
Russell-Jones,2012(Piogl)	-2	3.15	83	1.5	3.83	163	6.0%	-3.50 [-4.40, -2.60]
Subtotal (95% CI)			**764**			**1250**	**39.0%**	**-3.03 [-4.70, -1.36]**
Heterogeneity: Tau² = 4.66; Chi² = 131.39, df = 6 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
Total (95% CI)			**2890**			**2898**	**100.0%**	**-3.31 [-4.05, -2.57]**
Heterogeneity: Tau² = 2.17; Chi² = 278.93, df = 16 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 8.77 (P < 0.00001)								
Test for subgroup differences: Chi² = 28.36, df = 3 (P < 0.00001), I² = 89.4%								

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, and 28 (Fig 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 (citations), and 19-23 (Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, 24-27 (Table 2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	29-36 (Figs 2-6)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	29-36 (Figs 2-6)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	29-36 (Figs 2-6)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ open

Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis

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Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis

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Key MeSH terms: Diabetes Mellitus, Type 2; Glucagon-Like Peptide 1; Heart Rate; Blood Pressure; Body Weight.

Word count: 2381 words

ABSTRACT

Objectives: To synthesise current evidence for the effects of exenatide and liraglutide on heart rate, blood pressure, and body weight.

Design: Meta-analysis of available data from randomised controlled trials comparing GLP-1 analogues with placebo, active anti-diabetic drug therapy, or lifestyle intervention.

Participants: Patients with type 2 diabetes.

Outcome measures: Weighted mean differences between trial arms for changes in heart rate, blood pressure and body weight, after a minimum of 12 weeks follow up.

Results: 32 trials were included. Overall, GLP-1 agonists increased heart rate by 1.86 beats per minute (bpm) [95% confidence interval (CI) 0.85, 2.87] versus placebo and 1.90 bpm [1.30, 2.50] versus active control. This effect was more evident for liraglutide and exenatide long acting release (LAR) than for exenatide BID. GLP-1 agonists decreased systolic blood pressure by -1.79mmHg [-2.94, -0.64] and -2.39mmHg [-3.35, -1.42] compared to placebo and active control respectively. Reduction in diastolic blood pressure failed to reach statistical significance (-0.54mmHg [-1.15, 0.07] vs placebo and -0.50mmHg [-1.24, 0.24] vs active control). Body weight decreased by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

Conclusions: GLP-1 analogues are associated with a small increase in heart rate, and modest reductions in body weight and blood pressure. Mechanisms underlying the rise in heart rate require further investigation.

ARTICLE SUMMARY

Article focus

- GLP-1 agonists are increasingly used in the management of type 2 diabetes, but their long term cardiovascular safety is not yet confirmed.

- These agents are known to reduce body weight and blood pressure, but are also associated with an elevation in heart rate that has not previously been quantified.

Key messages

- Our analysis confirms the weight and blood pressure reducing effects of liraglutide and exenatide, and reports a small rise in heart rate.
- The weight reducing effects are substantially greater when compared with active control treatments than placebo, as alternative treatment options may promote weight gain.
- Heart rate rises were more evident for liraglutide than exenatide, and for exenatide long acting release (LAR) than exenatide twice daily (BID).

Strengths and limitations

- We included unpublished data obtained from pharmaceutical companies, enabling the effects of GLP-1 agonists on heart rate to be quantified for the first time by meta-analysis.
- Our analysis is limited by significant heterogeneity between studies, and suggests the need for more detailed investigation using more accurate measurements of heart rate than those typically used in clinical practice.

INTRODUCTION

In contrast to the weight increasing effects of several traditional anti-diabetic drug classes,[1] GLP-1 analogues have been shown to reduce both body weight and blood pressure.[2] The mechanisms producing weight loss have been extensively investigated, and involve improved satiety and reduced

calorie ingestion both through effects on the central nervous system and through delayed gastric emptying.[3-6] Those leading to reduced blood pressure are less adequately understood, but this effect has been shown to occur as early as two weeks after commencing therapy, preceding significant weight loss, suggesting that a direct hypotensive effect is at least partly responsible.[7] Experimental studies of GLP-1 analogues have also reported direct effects on blood pressure, possibly via interaction with the autonomic nervous system.[8, 9]

Whilst a number of studies have reported heart rate increases, the associated mechanisms are unknown, and this effect is often dismissed as clinically unimportant. Given the safety implications attributed to raised heart rate in other contexts,[10-13] there is a surprising lack of concern over its possible implications in this setting. A recent review of liraglutide by Buse acknowledges the effect,[14] but a meta-analysis on safety of incretin based therapies published in 2010 did not mention heart rate,[15] nor does an overview of the LEAD trials of liraglutide by Blonde and Russell-Jones.[16] A large nationwide audit of exenatide designed by the Association of British Clinical Diabetologists (ABCD) did not include heart rate as an outcome, despite citing evidence for the effect in the main published report.[17] A subsequent (on-going) ABCD audit of liraglutide also aims to identify unknown safety issues but has similarly omitted heart rate from the protocol.[18]

GLP-1 analogues are an expanding drug class, with recent development of longer acting agents including the once weekly (LAR) form of exenatide, Bydureon. This drug has recently obtained approval from the National Institute for Health and Clinical Excellence for use in type 2 diabetes and its use is likely to increase.[19] A review of trial data from five long acting GLP-1 agonists (exenatide once weekly, taspoglutide, albiglutide, LY2189265 and CJC-1134-PC) concluded that they were more likely than shorter acting formulations to raise heart rate.[20] A more recently published study of the long acting GLP-1 agent PF-04603629 reported a substantial rise in heart rate (mean increase 23 bpm at 24 hours after injection of the higher dose studied), together with a rise in diastolic blood pressure.[21]

Whilst there is no evidence to date that these agents (short or long acting) increase cardiovascular event rates, safety data are limited by short follow up duration.[22] Longer term follow up is underway but will take a number of years to complete.

We aimed to identify and synthesise all available heart rate data from both published and unpublished sources, to quantify the effect of GLP-1 analogues on heart rate, as well as that on blood pressure and body weight.

METHODS

Literature searches

The following resources were systematically searched to identify completed, new or on-going controlled trials of liraglutide or exenatide: Clinical Trials Gov (www.clinicaltrials.gov); Entertrials.co.uk; Clinicaltrialssearch.org; Centerwatch; Drugsontrial; WebMD; MEDLINE (from 1960); EMBASE (from 1960); Cochrane Library Central Register of Controlled Trials (CENTRAL). We used a search strategy to capture "exenatide", "liraglutide" or "glucagon-like peptide-1" in any field, limited to "Randomised Controlled Trial," "Clinical Trial," or "Controlled Clinical Trial". Conference proceedings (British Endocrinology Society, Diabetes UK, European Association for the Study of Diabetes) and websites (American Diabetes Association, Federal Drug Agency and European Medicines Agency) were examined, and the reference lists of trials, meta-analyses and reviews were searched for further studies. Novo Nordisk and Amylin Pharmaceuticals were contacted directly to request unpublished data. The review is up to date at July 2012.

Inclusion and exclusion criteria

a) Participants

We only included trials involving participants with type 2 diabetes.

b) Study designs

We included all randomised trials with minimum follow up of 12 weeks. We excluded 'open-label' extension studies of phase 3 trials.

c) Interventions

Trials of liraglutide (1.2 or 1.8 mg daily), exenatide (5 or 10 µg BID), or exenatide LAR, either alone or in combination with an oral anti-diabetic drug (OAD) or insulin, were included. These doses were chosen to coincide with those most commonly used in clinical practice.

c) Comparison groups(s)

Comparators included placebo, OAD, lifestyle intervention, or insulin.

d) Outcomes

We included all studies reporting heart rate, blood pressure, or body weight outcomes.

Data extraction

Retrieved studies were assessed for inclusion by two researchers independently using the above criteria and any discrepancies were resolved by consensus. Information on the participants, intervention, comparison group, outcomes and trial quality were extracted from included studies by two researchers independently. Where necessary, clarification of data was obtained by correspondence with trial co-ordinators.

Risk of Bias

We used the Cochrane tool to determine risk of selection bias (success of sequence generation and allocation concealment); performance bias (success of blinding to treatment received); detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data and selective outcome reporting) and other biases.[23] Funnel plots were used to detect publication bias.

Analysis

Means and standard deviations for baseline and outcome values for blood pressure, heart rate and body weight were extracted. Mean effect data from cross-over trials were extracted at the end of the initial phase. Where standard deviations for the outcome were not available they were imputed according to Cochrane Handbook for Systematic reviews version 5.[23] Standard deviations for changes from baseline were derived where necessary to account for correlation of baseline to follow up measurements within individuals, and where the correlation coefficient could not be calculated, methods were employed as recommended by Follman et al.[24] Study results were combined using RevMan version 5.2. Heterogeneity was estimated using the χ^2- test and I^2 statistic. Fixed and random effects weighted mean difference models using the Inverse Variance technique were used to compare outcomes between study drug and comparator with 95% confidence intervals (CI). Interaction effects were evaluated using pre-specified subgroup analyses (comparing various doses of study drug to active control or placebo) and type of GLP-1 agonist (liraglutide, exenatide BID and exenatide LAR preparations). Results are described using the random effects approach due to the heterogeneity of the included studies. Analyses were stratified by active control or placebo. We compared heterogeneity measures between these subgroups and according to GLP-1 agent. We also undertook sensitivity analyses to investigate the influence of trial designs on heterogeneity measures, including the background OAD treatment common to both arms. Funnel plots were assessed for asymmetry.

RESULTS

Figure 1 describes the identification of included studies. A total of 521 articles were screened. Of these, 472 were excluded on the basis of the title or abstract being irrelevant to the aims of this review. Forty-nine studies were examined in full text. Out of these, 4 were excluded because the comparator was another form of GLP-1.[25-28] In 3 cases the doses were not as specified in our inclusion criteria,[29-31] and in a further 2 the study involved further analysis of data from trials that were already included.[32, 33] Finally, 8 were open label extension studies.[34-41] This left 32 trials included in our review (Figure 1 and Table 1).[42-73] Most studies did not report all of the outcomes of interest, or did not provide them as usable numerical data. Data were therefore obtained, where available directly from the pharmaceutical companies.

Methodological quality and risk of bias

Results of risk of bias assessment are given in Table 2. Explanation of sequence generation and allocation concealment was adequate for all trials. In nine trials at least one arm was open-label. Attrition was adequately described and was greater than 20% in nine studies. The proportion of the intention to treat (ITT) population completing the study varied with range 65.4-99.6% and median 83.7%. None of the trials were terminated prematurely. Funnel plots were broadly symmetrical with no evidence of publication bias.

Heterogeneity

The trials varied in terms of duration of follow up, location, type of active comparator drug, and background therapy. One study was a cross-over trial[43] and one was of prolonged follow up.[55] The mean age of participants ranged from 52.3 to 60.3 years. For most outcomes, we found significant heterogeneity (Figures 2 to 6). We therefore chose to report results using the random effects approach, although the differences between random effects and fixed effect results were very small. Heterogeneity varied significantly between comparisons. For the effect of Liraglutide on heart rate compared with placebo the I^2 value was 55%. However this value reduced to 0% when the data from a single trial (LEAD-1) was withheld.

Heart rate

A total of 22 studies provided heart rate data. GLP-1 agonists overall produce a significant increase in heart rate with weighted mean difference 1.86 beats per minute (bpm) [0.85, 2.87] versus placebo and 1.90 bpm [1.30, 2.50] versus active control. Looking at specific agents, liraglutide increases heart rate by 2.71 bpm [1.45, 3.97] versus placebo and 2.49 [1.77, 3.21] versus active control. Data from the LEAD trials of liraglutide[57, 64, 67, 69, 73] were initially provided grouped into quartiles of baseline heart rate and demonstrated significant variation in effect between these subgroups, with

greatest increase seen in those with lowest baseline values. Exenatide BID increased heart rate by 0.82 bpm [-0.15, 1.79] versus active control and by 0.88 bpm [-0.47, 2.22] versus placebo, which did not reach statistical significance (Figure 3). Exenatide LAR produced a more significant change (2.14 bpm [1.11, 3.17] versus active control) but the number of studies involving this formulation was small.

Blood pressure

We included 31 trials measuring blood pressure changes (Figures 4 and 5). GLP-1 agonists reduced systolic blood pressure by -1.79mmHg [-2.94, -0.64] compared to placebo and by -2.39 [-3.35, -1.42] compared to active control. Reductions in diastolic blood pressure failed to reach statistical significance, and were -0.54mmHg [-1.15, 0.07] compared to placebo and -0.50mmHg [-1.24, 0.24] compared to active control.

Body weight

Twenty-one trials measuring changes in weight were included (Figure 6). We confirm a small but highly significant reduction in body weight as a result of GLP-1 therapy. Weight changed by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

DISCUSSION

We have confirmed and quantified the effects of liragutide and exenatide on heart rate, blood pressure and body weight. Our analysis benefited from the inclusion of unpublished data supplied by Novo Nordisk and Amylin Pharmaceuticals, as these were often missing from published trial reports. It was limited by the significant heterogeneity of effect size measurements between individual studies. We examined pre-specified subgroups according to GLP-1 agent and type of comparator (placebo or active control). Active control treatments varied between trials and included different classes of OAD and insulins, which may explain some of the variation in measured effect. Other potential sources of heterogeneity include the characteristics of background OAD treatments common to both arms as these treatments differed between trials. For the heart rate effect of liraglutide versus placebo the heterogeneity was largely attributable to a single trial (LEAD-1), but the cause of the higher heart rate effect in this trial is unclear.

The weight reducing effects of these agents are a welcome contrast to the weight promoting effects of other treatment options, including sulphonylureas, thiazolidinediones, and insulin. We have derived a similar effect size to a previously reported value for weight loss,[2] although our study has distinguished between placebo and active comparators, in which effects sizes differ substantially.

Together with the reduction in blood pressure, this may improve longer term cardiovascular risk. However, the small rise in heart rate is a reason for caution, as it might potentially be associated with adverse outcomes. This rise was more evident for liraglutide than exenatide BID, but exenatide LAR may produce a greater response than the BID formulation. The clinical significance of this heart rate rise is still unknown from the perspective of cardiovascular risk.

For most GLP-1 trials, heart rate is a secondary outcome measured as part of safety assessment, and is reported inconsistently. In clinic it is often measured using a very short sampling interval (perhaps one minute of data). One study was designed specifically to examine the effects of exenatide BID on change in heart rate as the primary outcome using 24 hour ambulatory monitoring.[58] The mean change from baseline at 12 weeks was 2.1 bpm for exenatide BID and -0.7 bpm for placebo. The sample size (54 randomised participants) in this pilot study was relatively small and the difference was not significant (p=0.16), but is similar to the values we have obtained generally for GLP-1 agonists in our meta-analysis. Measurement of heart rate using this 24-hour technique (compared with a traditional heart rate measurement in clinic) substantially improves the accuracy of measurement as heart rate is very variable within the individual. This technique could be used as a basis for a larger study powered to detect such a difference and to investigate the influence of alternative background medications..

This review highlights the need to improve our understanding of the physiological mechanisms through which GLP-1 agonists act, whilst the results of longer term safety studies are awaited. Both autonomic nervous system-dependent and -independent effects have been suggested in animal studies as a basis for the rise in heart rate.[74, 75] The heart rate response in the presence or absence of autonomic neuropathy in human patients might therefore justify further study. There is also a clear need to improve the comprehensive reporting of all outcome data measured during clinical trials of anti-diabetic agents, particularly those relevant to cardiovascular risk.

ACKNOWLEDGEMENTS

We would like to thank Amylin Pharmaceuticals and Novo Nordisk for providing us with unpublished data for this meta-analysis.

CONTRIBUTORSHIP STATEMENT

LR, PO'H and HR were involved in the design and conception of the study. LR and TH conducted the bibliographic searches, identified the included papers, and extracted the data independently. KR advised on methodological issues. All authors were involved in drafting the manuscript.

ETHICAL APPROVAL

None required.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS

LR, TH and KR have no interests to declare. PO'H and HR have received research funding (paid to Warwick Medical School) from Novo Nordisk, and payments for speaking from Novo Nordisk.

DATA SHARING

All data used in this study are freely available by request to the corresponding author Dr Tim A. Holt.

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FIGURE LEGENDS

Figure 1: PRISMA flow diagram

Figure 2: Effect of liraglutide on heart rate in patients with type 2 diabetes

Figure 3: Effect of exenatide on heart rate in patients with type 2 diabetes

Figure 4: GLP-1 agonists' effect on systolic blood pressure in patients with type 2 diabetes

Figure 5: GLP-1 agonists' effect on diastolic blood pressure in patients with type 2 diabetes

Figure 6: GLP-1 agonists' effects on body weight

Table 1 Characteristics of included studies

Study	Comparisons	Duration (weeks)	Study population /ethnicity	Country	Body weight groups included	Balanced Male/ Female?	Mean age	Standardised diet/ exercise	Background OAD
Apovian, 2010	EX/PLAC	24	MR	US	OW	>60% F	54.8	Y	MET and/or SU
Barnett, 2007	EX/IG	16	MR	Multi-national	N/OW/ OB	Y	54.9	N	MET or SU
Bergenstal, 2009	EX/BIAsp	24	MR	US	N/OW	Y	52.6	N	MET and SU
Bergenstal, 2010	EX LAR vs PIO EX LAR vs SITA	26	MR	Multi-national	N/OW/ OB	Y	52.3	N	MET
Buse, 2004	EX/PLAC	30	MR	US	OW/OB	60% M	55.3	N	SU
Buse, 2011	IG+EX/ IG+PLAC	30	MR	Multi-national	N/OW/ OB	Y	59.0	N	MET or PIO

Davies, 2009	EX/IG	26	MR	GB	OW/OB	>60% M	56.5	N	Two or three OADS: MET, SU, or TZD
Defronzo, 2005	EX/PLAC	30	MR	US	OW/OB	Y	53.0	N	MET
Defronzo, 2010	EX vs ROSI	20	MR	US	OW/OB	Y	56.0	N	MET
Derosa, 2010	EX/GLIB	52	W	IT	OW/OB	Y	56.5	Y	MET
Derosa, 2011	EX/GLIM	52	CAUC	IT	OW/OB	Y	55.5	Y	MET
Diamant, 2010	EX LAR/IG	26	MR	Multi-national	OW/OB	Y	58.0	N	MET
Gallwitz, 2011	EX/BIAsp	26	MR	GER	OW/OB	Not reported	57.0	N	MET
Gallwitz 2012	EX/GLIM	Up to 4.5 years	MR	Multi-national	OW/OB	Y	56.0	N	MET
Gao,	EX/PLAC	12	C/I/K/T	Multi-national	N/OW/	Y	54.0	N	MET and/or SU

2009					OB				
Garber, 2009	LIR/GLIM	52	MR	US/MEX	N/OW/ OB	Y	53.0	N	Nil - previous OAD withdrawn
Gill, 2010	EX/PLAC	12	MR	CAN/NL	OW/OB	Y	55.6	N	MET and/or TZD
Heine, 2005	EX/IG	26	MR	Multi-national	OW/OB	Y	58.9	N	MET and SU
Kadowaki, 2009	EX/PLAC	12	JP	JP	N/OW/ OB	>60% M	60.3	N	SU, with or without either BG or TZD
Kendall, 2005	EX/PLAC	30	MR	US	OW/OB	Y	55.3	Y	MET and SU
Kim, 2007	EX LAR/PLAC	15	MR	US	OW/OB	60% M	53.7	Y	MET
Liutkus, 2010	EX/PLAC	26	MR	Multi-national	OW/OB	Y	54.7	N	TZD with or without MET
Marre,	LIR/PLAC/ROSI	26	MR	Multi-	N/OW/	Y	56.0	N	SU

2009				national	OB				
Moretto, 2008	EX/PLAC	24	MR	Multi-national	OW/OB	Y	54.0	Y	DRUG NAIVE
Nauck, 2007	EX/PIA	52	MR	Multi-national	OW/OB	Y	58.5	N	SU and MET
Nauck, 2009	LIR/GLIM/PLAC	26	MR	Multi-national	N/OW/ OB	Y	56.7	N	MET
Pratley, 2010	LIR/SIT	26	MR	Multi-national	N- OW-OB	Y	55.3	N	MET
Russell-Jones, 2009	LIR/IG/PLAC	26	MR	Multi-national	N/OW/ OB	Y	57.5	N	MET and SU
Russell-Jones, 2012	EX LAR/MET EX LAR/PIO EX LAR/SITA	26	MR	Multi-national	N/OW/ OB	Y	54.0	N	DRUG NAIVE
Yang, 2011	LIR/GLIM	16	C/K/I	Multi-	N/OW/	Y	53.3	N	MET

				national	OB				
Zinman, 2007	EX/PLAC	16	MR	Multi-national	OW/OB	Y	56.1	N	TZD with or without MET
Zinman, 2009	LIR/PLAC	26	MR	US/CAN	N/OW/OB	Y	55.0	N	MET and ROSI

EX, Exenatide; EX LAR, Exenatide long acting release; PLAC, placebo; IG, insulin glargine; BIAsp, biphasic insulin aspart; PIO, pioglitazone; SITA, sitagliptin; ROSI, rosiglitazone; GLIB, glibenclamide; GLIM, glimepiride; LIR, liraglutide; MET, metformin, BG, Biguanide.

MR, Multi-racial; C, Chinese; K, Korean; I, Indian; T, Taiwanese; JP, Japanese; W, White; CAUC, Caucasian.

GB, Great Britain; US, United States; GER, Germany; CAN, Canada; JP, Japan; NL, Netherlands; MEX, Mexico; IT, Italy.

N, normal weight; OW, overweight; OB, obese.

Table 2 Risk of bias across included studies

Included studies were assessed using the Cochrane Risk of Bias Tool for factors which may cause bias in the trial outcomes and subsequent evaluation by meta-analysis: A) Randomisation, B) Allocation concealment, C) Blinding of participants/investigators/sponsors, D) Blinding outcome assessment, E) Incomplete outcome data, F) Selective outcome reporting, G) Other bias.

No.	Study	A	B	C	D	E	F	G	Comments
1	**Apovian, 2010**								Greater than 20% attrition.
2	**Barnett, 2007***								Open label cross-over study.
3	**Bergenstal, 2009***								Open label. Greater than 20% attrition and higher attrition in exenatide group.
4	**Bergenstal, 2010**								Greater than 20% attrition. Outcome assessors unblinded after finalisation of analysis plan.
5	**Buse, 2004**								Greater than 20% attrition. Higher attrition in the placebo arm.

6	**Buse, 2011**								Groups not balanced for sex and concomitant medication.
7	**Davies, 2009***								Open label.
8	**Defronzo, 2005**								
9	**Defronzo, 2010***								Open label. Greater than 20% attrition.
10	**Derosa, 2010**								Single blind.
11	**Derosa, 2011‡**								Single blind.
12	**Diamant, 2010***								Open label. Higher attrition in the exenatide arm.
13	**Gallwitz, 2011***								Open label.
14	**Gallwitz 2012***								Open label. Greater than 20% attrition. Higher attrition in the exenatide arm.
15	**Gao, 2009**								
16	**Garber, 2009**								Greater than 20% attrition.
17	**Gill, 2010**								
18	**Heine, 2005***								Open label. Higher attrition in the exenatide arm.

19	**Kadowaki,[¥] 2009**								
20	**Kendall, 2005**								
21	**Kim, 2007**								
22	**Liutkus, 2010[¥]**								
23	**Marre, 2009**								Higher attrition in the placebo arm. Restriction of glimipiride and rosiglitazone in some countries precluded maximal dose regimes.
24	**Moretto, 2008**								Diet and exercise regimes not standardised.
25	**Nauck, 2007[*]**								Open label.
26	**Nauck, 2009**								Higher attrition in Liraglutide 1.8 mg and placebo arms.
27	**Pratley, 2010[*]**								Open label, but statistician was masked to the allocation.
28	**Russell-Jones, 2009***								Insulin glargine arm-open label.
29	**Russell-Jones 2012**								

30	**Yang, 2011**								Higher attrition in the liraglutide groups.
31	**Zinman, 2007**								Greater than 20% attrition. Higher attrition in exenatide group.
32	**Zinman, 2009**								Greater than 20% attrition. Higher attrition in placebo group.

* Open label; □ method of randomisation/allocation concealment consisted of a computer random-number generator and voice-response or telephone system; □ permuted block randomisation; ¥ randomised according to baseline biochemical values or background pharmacological agent; ŧ randomised according to coded envelopes designed by a statistician high risk; low risk; unclear risk.

Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis

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ABSTRACT

Objectives: To synthesise current evidence for the effects of exenatide and liraglutide on heart rate, blood pressure, and body weight.

Design: Meta-analysis of available data from randomised controlled trials comparing GLP-1 analogues with placebo, active anti-diabetic drug therapy, or lifestyle intervention.

Participants: Patients with type 2 diabetes.

Outcome measures: Weighted mean differences between trial arms for changes in heart rate, blood pressure and body weight, after a minimum of 12 weeks follow up.

Results: 32 trials were included. ~~Liraglutide increased heart rate by 2.65 beats per minute (bpm) [95% confidence interval (CI), 1.78, 3.52] compared with placebo and by 1.61 bpm [1.10, 2.13] versus active control. Exenatide twice daily (BID) increased heart rate by 0.88 bpm [-0.47, 2.22] versus placebo but did not reach statistical significance, and by 1.36 [0.57, 2.14] versus active control. Exenatide long acting release (LAR) increased heart rate by 2.14 [1.11, 3.17] versus active control.~~ Overall, GLP-1 agonists increased heart rate by 1.86 beats per minute (bpm) [95% confidence interval (CI) 0.85, 2.87] versus placebo and 1.90 bpm [1.30, 2.50] versus active control. This effect was more evident for liraglutide and exenatide long acting release (LAR) than for exenatide BID. GLP-1 agonists decreased systolic blood pressure by -1.79mmHg [-2.94, -0.64] and -2.39mmHg [-3.35, -1.42] compared to placebo and active control respectively. Reduction in diastolic blood pressure failed to reach statistical significance (-0.54mmHg [-1.15, 0.07] vs placebo and -0.50mmHg [-1.24, 0.24] vs active control). Body weight decreased by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

Conclusions: GLP-1 analogues are associated with a small increase in heart rate, and modest reductions in body weight and blood pressure. Mechanisms underlying the rise in heart rate require further investigation.

ARTICLE SUMMARY

Article focus

- GLP-1 agonists are increasingly used in the management of type 2 diabetes, but their long term cardiovascular safety is not yet confirmed.
- These agents are known to reduce body weight and blood pressure, but are also associated with an elevation in heart rate that has not previously been quantified.

Key messages

- Our analysis confirms the weight and blood pressure reducing effects of liraglutide and exenatide, and reports a small rise in heart rate.
- The weight reducing effects are substantially greater when compared with active control treatments than placebo, as alternative treatment options may promote weight gain.
- Heart rate rises were more evident for liraglutide than exenatide, and for exenatide long acting release (LAR) than exenatide twice daily (BID).

Strengths and limitations

- We included unpublished data obtained from pharmaceutical companies, enabling the effects of GLP-1 agonists on heart rate to be quantified for the first time by meta-analysis.
- Our analysis is limited by significant heterogeneity between studies, and suggests the need for more detailed investigation using more accurate measurements of heart rate than those typically used in clinical practice.

INTRODUCTION

In contrast to the weight increasing effects of several traditional anti-diabetic drug classes,[1] GLP-1 analogues have been shown to reduce both body weight and blood pressure.[2] The mechanisms producing weight loss have been extensively investigated, and involve improved satiety and reduced calorie ingestion both through effects on the central nervous system and through delayed gastric emptying.[3-6] Those leading to reduced blood pressure are less adequately understood, but this effect has been shown to occur as early as two weeks after commencing therapy, preceding significant weight loss, suggesting that a direct hypotensive effect is at least partly responsible.[7] Experimental studies of GLP-1 analogues have also reported direct effects on blood pressure, possibly via interaction with the autonomic nervous system.[8, 9]

Whilst a number of studies have reported heart rate increases, the associated mechanisms are unknown, and this effect is often dismissed as clinically unimportant. Given the safety implications attributed to raised heart rate in other contexts,[10-13] there is a surprising lack of concern over its possible implications in this setting. A recent review of liraglutide by Buse acknowledges the effect,[14] but a meta-analysis on safety of incretin based therapies published in 2010 did not mention heart rate,[15] nor does an overview of the LEAD trials of liraglutide by Blonde and Russell-Jones.[16] A large nationwide audit of exenatide designed by the Association of British Clinical Diabetologists (ABCD) did not include heart rate as an outcome, despite citing evidence for the effect in the main published report.[17] A subsequent (on-going) ABCD audit of liraglutide also aims to identify unknown safety issues but has similarly omitted heart rate from the protocol.[18]

GLP-1 analogues are an expanding drug class, with recent development of longer acting agents including the once weekly (LAR) form of exenatide, Bydureon. This drug has recently obtained approval from the National Institute for Health and Clinical Excellence for use in type 2 diabetes and its use is likely to increase.[19] A review of trial data from five long acting GLP-1 agonists (exenatide once weekly, taspoglutide, albiglutide, LY2189265 and CJC-1134-PC) concluded that they were more likely than shorter acting formulations to raise heart rate.[20] A more recently published study of the long acting GLP-1 agent PF-04603629 reported a substantial rise in heart rate (mean increase 23 bpm at 24 hours after injection of the higher dose studied), together with a rise in diastolic blood pressure.[21]

Whilst there is no evidence to date that these agents (short or long acting) increase cardiovascular event rates, safety data are limited by short follow up duration.[22] Longer term follow up is underway but will take a number of years to complete.

We aimed to identify and synthesise all available heart rate data from both published and unpublished sources, to quantify the effect of GLP-1 analogues on heart rate, as well as that on blood pressure and body weight.

METHODS

Literature searches

The following resources were systematically searched to identify completed, new or on-going controlled trials of liraglutide or exenatide: Clinical Trials Gov (www.clinicaltrials.gov); Entertrials.co.uk; Clinicaltrialssearch.org; Centerwatch; Drugsontrial; WebMD; MEDLINE (from 1960); EMBASE (from 1960); Cochrane Library Central Register of Controlled Trials (CENTRAL). We used a search strategy to capture "exenatide", "liraglutide" or "glucagon-like peptide-1" in any field, limited to "Randomised Controlled Trial," "Clinical Trial," or "Controlled Clinical Trial". Conference proceedings (British Endocrinology Society, Diabetes UK, European Association for the Study of Diabetes) and websites (American Diabetes Association, Federal Drug Agency and European Medicines Agency) were examined, and the reference lists of trials, meta-analyses and reviews were searched for further studies. Novo Nordisk and Amylin Pharmaceuticals were contacted directly to request unpublished data. The review is up to date at July 2012.

Inclusion and exclusion criteria

a) Participants

We only included trials involving participants with type 2 diabetes.

b) Study designs

We included all randomised trials with minimum follow up of 12 weeks. We excluded 'open-label' extension studies of phase 3 trials.

c) Interventions

Trials of liraglutide (1.2 or 1.8 mg daily), exenatide (5 or 10 µg BID), or exenatide LAR, either alone or in combination with an oral anti-diabetic drug (OAD) or insulin, were included. These doses were chosen to coincide with those most commonly used in clinical practice.

c) Comparison groups(s)

Comparators included placebo, OAD, lifestyle intervention, or insulin.

d) Outcomes

We included all studies reporting heart rate, blood pressure, or body weight outcomes.

Data extraction

Retrieved studies were assessed for inclusion by two researchers independently using the above criteria and any discrepancies were resolved by consensus. Information on the participants, intervention, comparison group, outcomes and trial quality were extracted from included studies by two researchers independently. Where necessary, clarification of data was obtained by correspondence with trial co-ordinators.

Risk of Bias

We used the Cochrane tool to determine risk of selection bias (success of sequence generation and allocation concealment); performance bias (success of blinding to treatment received); detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data and selective outcome reporting) and other biases.[23] Funnel plots were used to detect publication bias.

Analysis

Means and standard deviations for baseline and outcome values for blood pressure, heart rate and body weight were extracted. Mean effect data from cross-over trials were extracted at the end of the initial phase. Where standard deviations for the outcome were not available they were imputed according to Cochrane Handbook for Systematic reviews version 5.[23] Standard deviations for changes from baseline were derived where necessary to account for correlation of baseline to follow up measurements within individuals, and where the correlation coefficient could not be calculated, methods were employed as recommended by Follman et al.[24] Study results were combined using RevMan version 5.2. Heterogeneity was estimated using the χ^2- test and I^2 statistic. Fixed and random effects weighted mean difference models using the Inverse Variance technique were used to compare outcomes between study drug and comparator with 95% confidence intervals (CI). Interaction effects were evaluated using pre-specified subgroup analyses (comparing various doses of study drug to active control or placebo) and type of GLP-1 agonist (liraglutide, exenatide BID and exenatide LAR preparations). Results are described using the random effects approach due to the heterogeneity of the included studies. Analyses were stratified by active control or placebo. We compared heterogeneity measures between these subgroups and according to GLP-1 agent. We also undertook sensitivity analyses to investigate the influence of trial designs on heterogeneity

measures, including the background OAD treatment common to both arms. Funnel plots were assessed for asymmetry.

RESULTS

Figure 1 describes the identification of included studies. A total of 521 articles were screened. Of these, 472 were excluded on the basis of the title or abstract being irrelevant to the aims of this review. Forty-nine studies were examined in full text. Out of these, 4 were excluded because the comparator was another form of GLP-1.[25-28] In 3 cases the doses were not as specified in our inclusion criteria,[29-31] and in a further 2 the study involved further analysis of data from trials that were already included.[32, 33] Finally, 8 were open label extension studies.[34-41] This left 32 trials included in our review (Figure 1 and Table 1).[42-73] Most studies did not report all of the outcomes of interest, or did not provide them as usable numerical data. Data were therefore obtained, where available directly from the pharmaceutical companies.

Methodological quality and risk of bias

Results of risk of bias assessment are given in Table 2. Explanation of sequence generation and allocation concealment was adequate for all trials. In nine trials at least one arm was open-label. Attrition was adequately described and was greater than 20% in nine studies. The proportion of the intention to treat (ITT) population completing the study varied with range 65.4-99.6% and median 83.7%. None of the trials were terminated prematurely. Funnel plots were broadly symmetrical with no evidence of publication bias.

Heterogeneity

The trials varied in terms of duration of follow up, location, type of active comparator drug, and background therapy. One study was a cross-over trial[43] and one was of prolonged follow up.[55] The mean age of participants ranged from 52.3 to 60.3 years. For ~~all~~ most outcomes, we found significant heterogeneity (Figures 2 to 6). We therefore chose to report results using the random effects approach, although the differences between random effects and fixed effect results were very small. Heterogeneity varied significantly between comparisons. For the effect of Liraglutide on heart rate compared with placebo the I^2 value was 55%. However this value reduced to 0% when the data from a single trial (LEAD-1) was withheld.

Heart rate

A total of 22 studies provided heart rate data. ~~A summary from the Lead 1-5 trials of liraglutide[57, 64, 67, 69, 73] was obtained from Novo Nordisk and is given in Figure 2. Pooled results show a significant increase in heart rate, with weighted mean difference 2.65 bpm [1.78, 3.52] versus placebo and 1.61 bpm [1.10, 2.13] versus active control.~~ GLP-1 agonists overall produce a significant increase in heart rate with weighted mean difference 1.86 beats per minute (bpm) [0.85, 2.87] versus placebo and 1.90 bpm [1.30, 2.50] versus active control. Looking at specific agents, liraglutide increases heart rate by 2.71 bpm [1.45, 3.97] versus placebo and 2.49 [1.77, 3.21] versus active control. ~~The LEAD 1-5 trial data~~Data from the LEAD trials of liraglutide[57, 64, 67, 69, 73] were initially provided grouped into quartiles of baseline heart rate and demonstrated significant variation in effect between these subgroups, with greatest increase seen in those with lowest baseline values. Exenatide BID increased heart rate by ~~1.36 bpm [0.57, 2.14]~~0.82 bpm [-0.15, 1.79] versus active control and by 0.88 bpm [-0.47, 2.22] versus placebo, which did not reach statistical significance (Figure 3). Exenatide LAR produced a more significant change (2.14 bpm [1.11, 3.17] versus active control) but the number of studies involving this formulation was small.

Blood pressure

We included 31 trials measuring blood pressure changes (Figures 4 and 5). GLP-1 agonists reduced systolic blood pressure by -1.79mmHg [-2.94, -0.64] compared to placebo and by -2.39 [-3.35, -1.42] compared to active control. Reductions in diastolic blood pressure failed to reach statistical significance, and were -0.54mmHg [-1.15, 0.07] compared to placebo and -0.50mmHg [-1.24, 0.24] compared to active control.

Body weight

Twenty-one trials measuring changes in weight were included (Figure 6). We confirm a small but highly significant reduction in body weight as a result of GLP-1 therapy. Weight changed by -3.31kg [-4.05, -2.57] compared to active control but by only -1.22kg [-1.51, -0.93] compared to placebo.

DISCUSSION

We have confirmed and quantified the effects of liragutide and exenatide on heart rate, blood pressure and body weight. Our analysis benefited from the inclusion of unpublished data supplied by Novo Nordisk and Amylin Pharmaceuticals, as these were often missing from published trial reports. It was limited by the significant heterogeneity of effect size measurements between individual studies. We examined pre-specified subgroups according to GLP-1 agent and type of comparator (placebo or active control). Active control treatments varied between trials and included different classes of OAD and insulins, which may explain some of the variation in measured effect. Other

potential sources of heterogeneity include the characteristics of background OAD treatments common to both arms as these treatments differed between trials. For the heart rate effect of liraglutide versus placebo the heterogeneity was largely attributable to a single trial (LEAD-1), but the cause of the higher heart rate effect in this trial is unclear.

The weight reducing effects of these agents are a welcome contrast to the weight promoting effects of other treatment options, including sulphonylureas, thiazolidinediones, and insulin. We have derived a similar effect size to a previously reported value for weight loss,[2] although our study has distinguished between placebo and active comparators, in which effects sizes differ substantially. Together with the reduction in blood pressure, this may improve longer term cardiovascular risk. However, the small rise in heart rate is a reason for caution, as it might potentially be associated with adverse outcomes. This rise was more evident for liraglutide than exenatide BID, but exenatide LAR may produce a greater response than the BID formulation. The clinical significance of this heart rate rise is still unknown from the perspective of cardiovascular risk.

For most GLP-1 trials, heart rate is a secondary outcome measured as part of safety assessment, and is reported inconsistently. In clinic it is often measured using a very short sampling interval (perhaps one minute of data). One study was designed specifically to examine the effects of exenatide BID on change in heart rate as the primary outcome using 24 hour ambulatory monitoring.[58] The mean change from baseline at 12 weeks was 2.1 bpm for exenatide BID and -0.7 bpm for placebo. The sample size (54 randomised participants) in this pilot study was relatively small and the difference was not significant (p=0.16), but is similar to the values we have obtained generally for GLP-1 agonists in our meta-analysis. Measurement of heart rate using this 24-hour technique (compared with a traditional heart rate measurement in clinic) substantially improves the accuracy of measurement as heart rate is very variable within the individual. This technique could be used as a basis for a larger study powered to detect such a difference and to investigate the influence of alternative background medications. ~~This would enable investigation of pre-specified subgroups, including those with low baseline heart rate, who appeared in the LEAD studies of liraglutide to experience a more substantial change of 4.8 bpm versus placebo~~.

This review highlights the need to improve our understanding of the physiological mechanisms through which GLP-1 agonists act, whilst the results of longer term safety studies are awaited. Both autonomic nervous system-dependent and -independent effects have been suggested in animal studies as a basis for the rise in heart rate.[74, 75] The heart rate response in the presence or absence of autonomic neuropathy in human patients might therefore justify further study. There is

also a clear need to improve the comprehensive reporting of all outcome data measured during clinical trials of anti-diabetic agents, particularly those relevant to cardiovascular risk.

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CONTRIBUTORSHIP STATEMENT

LR, PO'H and HR were involved in the design and conception of the study. LR and TH conducted the bibliographic searches, identified the included papers, and extracted the data independently. KR advised on methodological issues. All authors were involved in drafting the manuscript.

ETHICAL APPROVAL

None required.

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COMPETING INTERESTS

LR, TH and KR have no interests to declare. PO'H and HR have received research funding (paid to Warwick Medical School) from Novo Nordisk, and payments for speaking from Novo Nordisk.

DATA SHARING

All data used in this study are freely available by request to the corresponding author Dr Tim A. Holt.

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FIGURE LEGENDS

Figure 1: PRISMA flow diagram

Figure 2: Effect of liraglutide on heart rate in patients with type 2 diabetes

Figure 3: Effect of exenatide on heart rate in patients with type 2 diabetes

Figure 4: GLP-1 agonists' effect on systolic blood pressure in patients with type 2 diabetes

Figure 5: GLP-1 agonists' effect on diastolic blood pressure in patients with type 2 diabetes

Figure 6: GLP-1 agonists' effects on body weight

Table 1 Characteristics of included studies

Study	Comparisons	Duration (weeks)	Study population /ethnicity	Country	Body weight groups included	Balanced Male/ Female?	Mean age	Standardised diet/ exercise	Background OAD
Apovian, 2010	EX/PLAC	24	MR	US	OW	>60% F	54.8	Y	MET and/or SU
Barnett, 2007	EX/IG	16	MR	Multi-national	N/OW/ OB	Y	54.9	N	MET or SU
Bergenstal, 2009	EX/BIAsp	24	MR	US	N/OW	Y	52.6	N	MET and SU
Bergenstal, 2010	EX LAR vs PIO EX LAR vs SITA	26	MR	Multi-national	N/OW/ OB	Y	52.3	N	MET
Buse, 2004	EX/PLAC	30	MR	US	OW/OB	60% M	55.3	N	SU
Buse, 2011	IG+EX/ IG+PLAC	30	MR	Multi-national	N/OW/ OB	Y	59.0	N	MET or PIO

Davies, 2009	EX/IG	26	MR	GB	OW/OB	>60% M	56.5	N	Two or three OADS: MET, SU, or TZD
Defronzo, 2005	EX/PLAC	30	MR	US	OW/OB	Y	53.0	N	MET
Defronzo, 2010	EX vs ROSI	20	MR	US	OW/OB	Y	56.0	N	MET
Derosa, 2010	EX/GLIB	52	W	IT	OW/OB	Y	56.5	Y	MET
Derosa, 2011	EX/GLIM	52	CAUC	IT	OW/OB	Y	55.5	Y	MET
Diamant, 2010	EX LAR/IG	26	MR	Multi-national	OW/OB	Y	58.0	N	MET
Gallwitz, 2011	EX/BIAsp	26	MR	GER	OW/OB	Not reported	57.0	N	MET
Gallwitz 2012	EX/GLIM	Up to 4.5 years	MR	Multi-national	OW/OB	Y	56.0	N	MET
Gao,	EX/PLAC	12	C/I/K/T	Multi-national	N/OW/	Y	54.0	N	MET and/or SU

2009					OB				
Garber, 2009	LIR/GLIM	52	MR	US/MEX	N/OW/ OB	Y	53.0	N	Nil - previous OAD withdrawn
Gill, 2010	EX/PLAC	12	MR	CAN/NL	OW/OB	Y	55.6	N	MET and/or TZD
Heine, 2005	EX/IG	26	MR	Multi-national	OW/OB	Y	58.9	N	MET and SU
Kadowaki, 2009	EX/PLAC	12	JP	JP	N/OW/ OB	>60% M	60.3	N	SU, with or without either BG or TZD
Kendall, 2005	EX/PLAC	30	MR	US	OW/OB	Y	55.3	Y	MET and SU
Kim, 2007	EX LAR/PLAC	15	MR	US	OW/OB	60% M	53.7	Y	MET
Liutkus, 2010	EX/PLAC	26	MR	Multi-national	OW/OB	Y	54.7	N	TZD with or without MET
Marre,	LIR/PLAC/ROSI	26	MR	Multi-	N/OW/	Y	56.0	N	SU ~~with or~~

2009				national	OB				~~without ROSI~~
Moretto, 2008	EX/PLAC	24	MR	Multi-national	OW/OB	Y	54.0	Y	DRUG NAIVE
Nauck, 2007	EX/PIA	52	MR	Multi-national	OW/OB	Y	58.5	N	SU and MET
Nauck, 2009	LIR/GLIM/PLAC	26	MR	Multi-national	N/OW/ OB	Y	56.7	N	MET
Pratley, 2010	LIR/SIT	26	MR	Multi-national	N- OW-OB	Y	55.3	N	MET
Russell-Jones, 2009	LIR/IG/PLAC	26	MR	Multi-national	N/OW/ OB	Y	57.5	N	MET and SU
Russell-Jones, 2012	EX LAR/MET EX LAR/PIO EX LAR/SITA	26	MR	Multi-national	N/OW/ OB	Y	54.0	N	DRUG NAIVE
Yang, 2011	LIR/GLIM	16	C/K/I	Multi-	N/OW/	Y	53.3	N	MET

				national	OB				
Zinman, 2007	EX/PLAC	16	MR	Multi-national	OW/OB	Y	56.1	N	TZD with or without MET
Zinman, 2009	LIR/PLAC	26	MR	US/CAN	N/OW/OB	Y	55.0	N	MET and ROSI

EX, Exenatide; EX LAR, Exenatide long acting release; PLAC, placebo; IG, insulin glargine; BIAsp, biphasic insulin aspart; PIO, pioglitazone; SITA, sitagliptin; ROSI, rosiglitazone; GLIB, glibenclamide; GLIM, glimepiride; LIR, liraglutide; MET, metformin, BG, Biguanide.

MR, Multi-racial; C, Chinese; K, Korean; I, Indian; T, Taiwanese; JP, Japanese; W, White; CAUC, Caucasian.

GB, Great Britain; US, United States; GER, Germany; CAN, Canada; JP, Japan; NL, Netherlands; MEX, Mexico; IT, Italy.

N, normal weight; OW, overweight; OB, obese.

Table 2 Risk of bias across included studies

Included studies were assessed using the Cochrane Risk of Bias Tool for factors which may cause bias in the trial outcomes and subsequent evaluation by meta-analysis: A) Randomisation, B) Allocation concealment, C) Blinding of participants/investigators/sponsors, D) Blinding outcome assessment, E) Incomplete outcome data, F) Selective outcome reporting, G) Other bias.

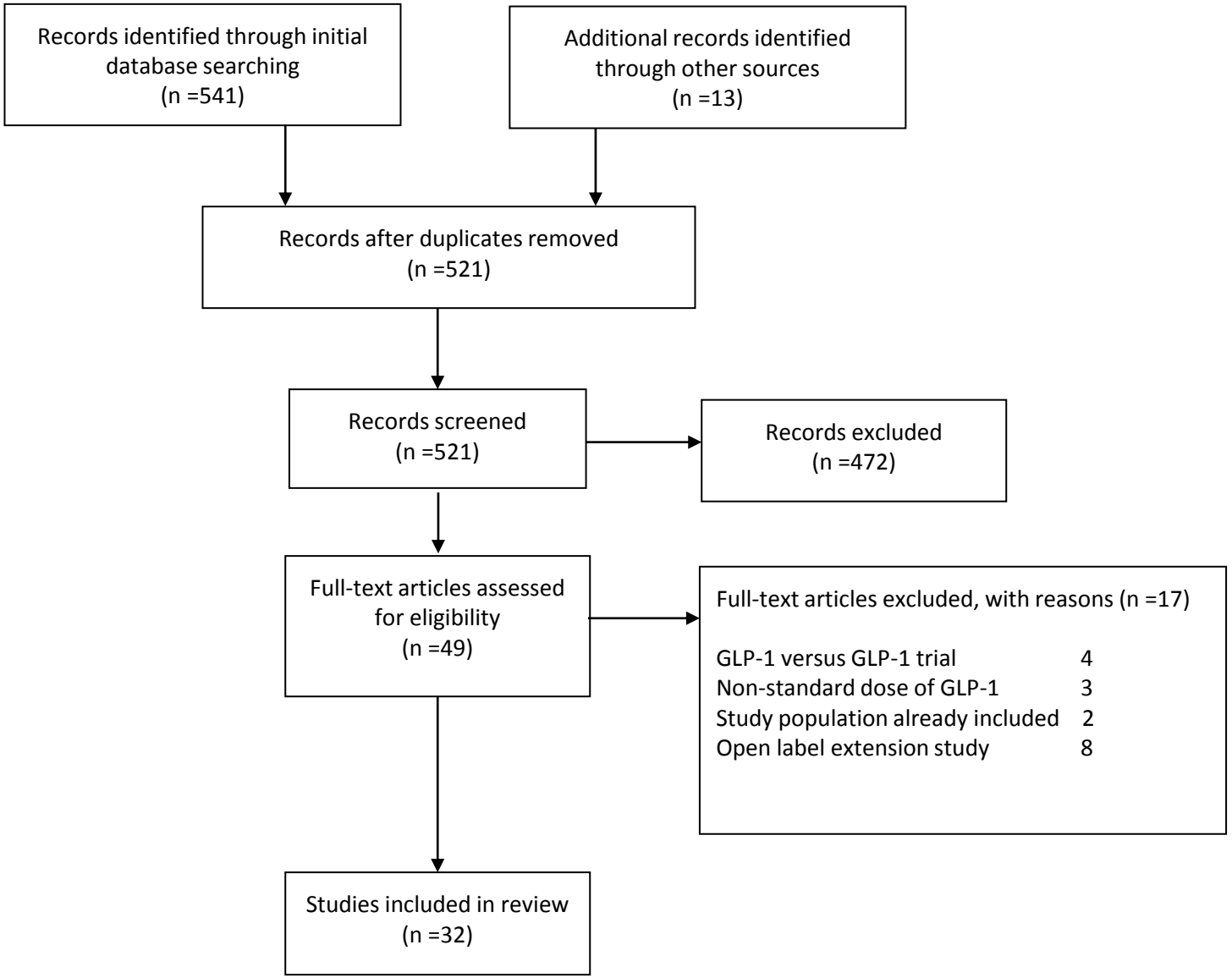
No.	Study	A	B	C	D	E	F	G	Comments
1	**Apovian, 2010**								Greater than 20% attrition.
2	**Barnett, 2007***								Open label cross-over study.
3	**Bergenstal, 2009***								Open label. Greater than 20% attrition and higher attrition in exenatide group.
4	**Bergenstal, 2010**								Greater than 20% attrition. Outcome assessors unblinded after finalisation of analysis plan.
5	**Buse, 2004**								Greater than 20% attrition. Higher attrition in the placebo arm.

6	**Buse, 2011**								Groups not balanced for sex and concomitant medication.
7	**Davies, 2009***								Open label.
8	**Defronzo, 2005**								
9	**Defronzo, 2010***								Open label. Greater than 20% attrition.
10	**Derosa, 2010**								Single blind.
11	**Derosa, 2011‡**								Single blind.
12	**Diamant, 2010***								Open label. Higher attrition in the exenatide arm.
13	**Gallwitz, 2011***								Open label.
14	**Gallwitz 2012***								Open label. Greater than 20% attrition. Higher attrition in the exenatide arm.
15	**Gao, 2009**								
16	**Garber, 2009**								Greater than 20% attrition.
17	**Gill, 2010**								
18	**Heine, 2005***								Open label. Higher attrition in the exenatide arm.

19	**Kadowaki,[¥] 2009**								
20	**Kendall, 2005**								
21	**Kim, 2007**								
22	**Liutkus, 2010[¥]**								
23	**Marre, 2009**								Higher attrition in the placebo arm. Restriction of glimipiride and rosiglitazone in some countries precluded maximal dose regimes.
24	**Moretto, 2008**								Diet and exercise regimes not standardised.
25	**Nauck, 2007[*]**								Open label.
26	**Nauck, 2009**								Higher attrition in Liraglutide 1.8 mg and placebo arms.
27	**Pratley, 2010[*]**								Open label, but statistician was masked to the allocation.
28	**Russell-Jones, 2009***								Insulin glargine arm-open label.
29	**Russell-Jones 2012**								

30	**Yang, 2011**								Higher attrition in the liraglutide groups.
31	**Zinman, 2007**								Greater than 20% attrition. Higher attrition in exenatide group.
32	**Zinman, 2009**								Greater than 20% attrition. Higher attrition in placebo group.

* Open label; □ method of randomisation/allocation concealment consisted of a computer random-number generator and voice-response or telephone system; □ permuted block randomisation; ¥ randomised according to baseline biochemical values or background pharmacological agent; ŧ randomised according to coded envelopes designed by a statistician high risk; low risk; unclear risk.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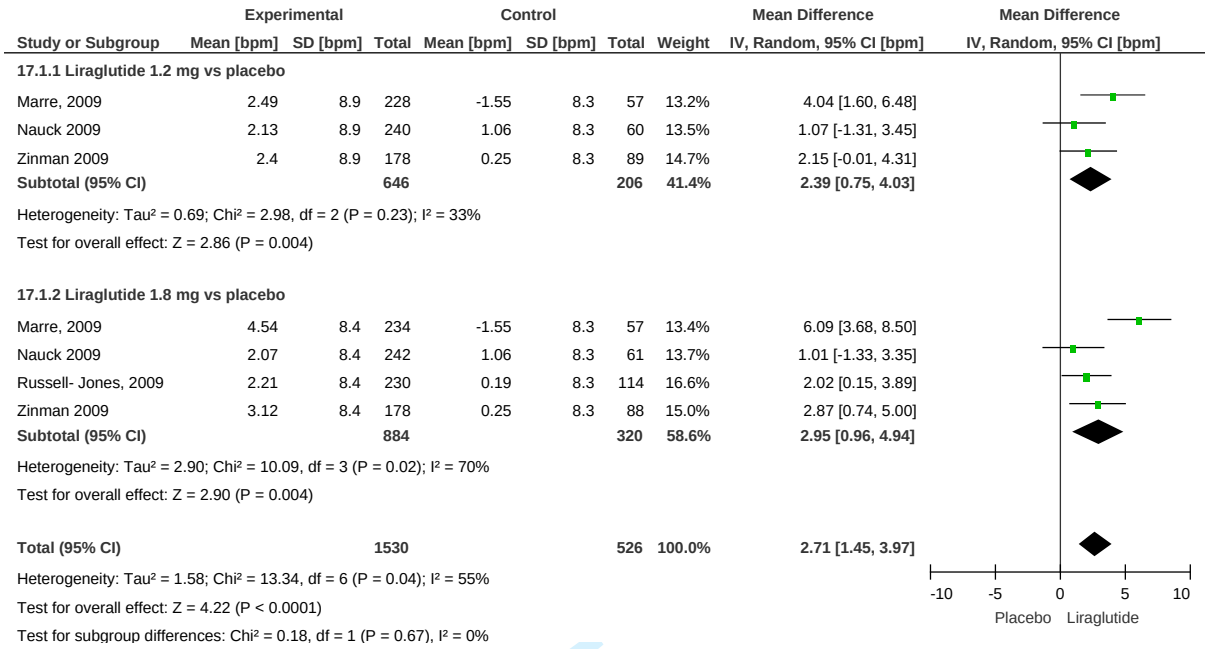
Full-text articles excluded, with reasons (n =17)
GLP-1 versus GLP-1 trial 4
Non-standard dose of GLP-1 3
Study population already included 2
Open label extension study 8
Studies included in review (n =32)

Figure 2 Effect of Liraglutide on heart rate in patients with type 2 diabetes

2a Liraglutide versus placebo



2b Liraglutide versus active control

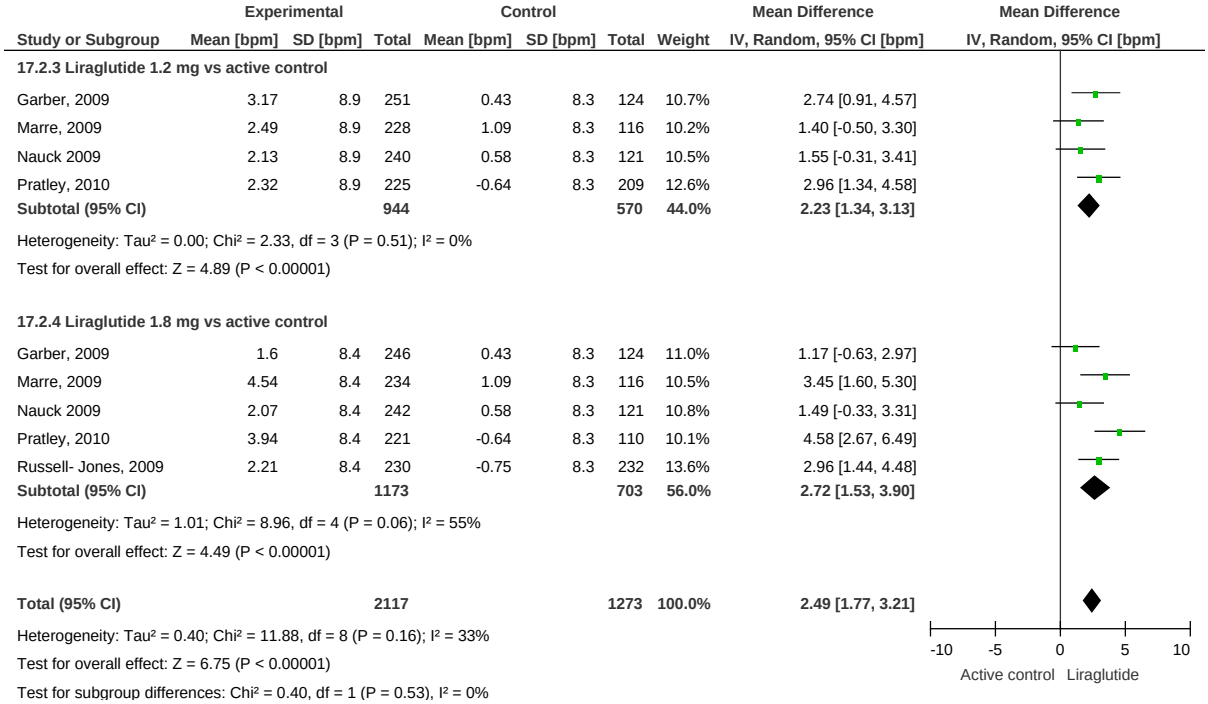
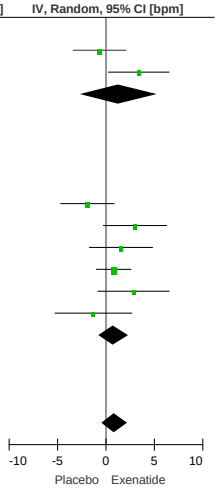


Figure 3 Effect of exenatide on heart rate in patients with type 2 diabetes

3(a) Exenatide versus placebo

Study or Subgroup	Experimental Mean [bpm]	Experimental SD [bpm]	Experimental Total	Control Mean [bpm]	Control SD [bpm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [bpm]
5.1.1 Exenatide 5mcg vs placebo								
Buse, 2004	0.47	9.054	125	1.12	8.911	62	13.8%	-0.65 [-3.38, 2.08]
DeFronzo, 2005	2.89	9.573	110	-0.49	9.815	57	11.7%	3.38 [0.27, 6.49]
Subtotal (95% CI)			**235**			**119**	**25.5%**	**1.29 [-2.65, 5.24]**
Heterogeneity: Tau² = 5.89; Chi² = 3.64, df = 1 (P = 0.06); I² = 73%								
Test for overall effect: Z = 0.64 (P = 0.52)								
5.1.2 Exenatide 10 mcg vs placebo								
Buse, 2004	-0.8	9.201	129	1.12	8.911	61	13.7%	-1.92 [-4.66, 0.82]
Buse, 2011	2.3	13.16	137	-0.7	13.42	122	11.1%	3.00 [-0.24, 6.24]
DeFronzo, 2005	1.06	10.746	113	-0.49	9.815	56	11.1%	1.55 [-1.70, 4.80]
Gao, 2009	0.1	9.82	234	-0.7	9.5	230	20.6%	0.80 [-0.96, 2.56]
Gill, 2010	2.14	6.52	26	-0.71	6.81	25	9.4%	2.85 [-0.81, 6.51]
Liutkus, 2010	0.5	13.72	111	1.8	11.31	54	8.5%	-1.30 [-5.25, 2.65]
Subtotal (95% CI)			**750**			**548**	**74.5%**	**0.76 [-0.76, 2.28]**
Heterogeneity: Tau² = 1.32; Chi² = 8.02, df = 5 (P = 0.16); I² = 38%								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**985**			**667**	**100.0%**	**0.88 [-0.47, 2.22]**
Heterogeneity: Tau² = 1.46; Chi² = 11.76, df = 7 (P = 0.11); I² = 40%								
Test for overall effect: Z = 1.28 (P = 0.20)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								



3(b) Exenatide versus active control

Study or Subgroup	Experimental Mean [bpm]	Experimental SD [bpm]	Experimental Total	Control Mean [bpm]	Control SD [bpm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [bpm]
5.2.1 Exenatide 10 mcg vs active control								
Barnett, 2007	-1.29	8.7	68	-0.93	8.95	70	5.3%	-0.36 [-3.30, 2.58]
Bunck, 2009	4.6	10.02	36	-2.2	9.82	33	2.5%	6.80 [2.12, 11.48]
Buse, 2011	2.3	17.25	137	-0.7	7.14	122	4.7%	3.00 [-0.15, 6.15]
DeFronzo, 2010	-0.6	9.34	73	-1.67	10.03	79	4.9%	1.07 [-2.01, 4.15]
Gallwitz, 2011	-0.5	11	181	0.1	9.1	173	8.3%	-0.60 [-2.70, 1.50]
Gallwitz, 2012	1.2	10.6	504	0.6	10.5	501	13.2%	0.60 [-0.70, 1.90]
Heine, 2005	-0.31	9.6	282	-1.2	9.52	267	11.1%	0.89 [-0.71, 2.49]
Nauck, 2007	1.53	10.27	253	1.19	9.17	248	10.5%	0.34 [-1.36, 2.04]
Subtotal (95% CI)			**1534**			**1493**	**60.5%**	**0.82 [-0.15, 1.79]**
Heterogeneity: Tau² = 0.64; Chi² = 10.83, df = 7 (P = 0.15); I² = 35%								
Test for overall effect: Z = 1.66 (P = 0.10)								
5.2.2 Exenatide LAR 2.0 mg vs active control								
Bergenstal, 2010 (Piogl)	1.6	9.27	80	-0.9	8.75	165	6.9%	2.50 [0.07, 4.93]
Bergenstal, 2010 (sita)	1.6	9.27	80	0.5	8.93	166	6.9%	1.10 [-1.34, 3.54]
Diamant, 2010	4	14.46	233	0	14.46	233	6.2%	4.00 [1.37, 6.63]
Russell-Jones,2012 (MET)	1.5	10	82	0.3	9.5	246	6.8%	1.20 [-1.27, 3.67]
Russell-Jones,2012 (Sita)	1.5	10	82	0.5	9.7	163	6.2%	1.00 [-1.63, 3.63]
Russell-Jones,2012(Piogl)	1.5	10	83	-1.7	8.7	163	6.5%	3.20 [0.67, 5.73]
Subtotal (95% CI)			**640**			**1136**	**39.5%**	**2.14 [1.11, 3.17]**
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 5 (P = 0.46); I² = 0%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Total (95% CI)			**2174**			**2629**	**100.0%**	**1.36 [0.57, 2.14]**
Heterogeneity: Tau² = 0.76; Chi² = 20.48, df = 13 (P = 0.08); I² = 37%								
Test for overall effect: Z = 3.40 (P = 0.0007)								
Test for subgroup differences: Chi² = 3.36, df = 1 (P = 0.07), I² = 70.3%								

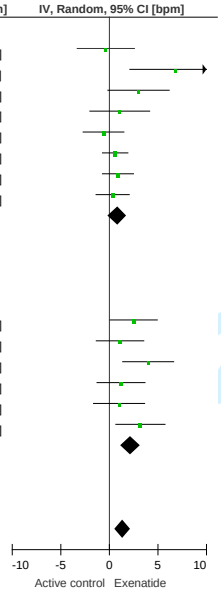
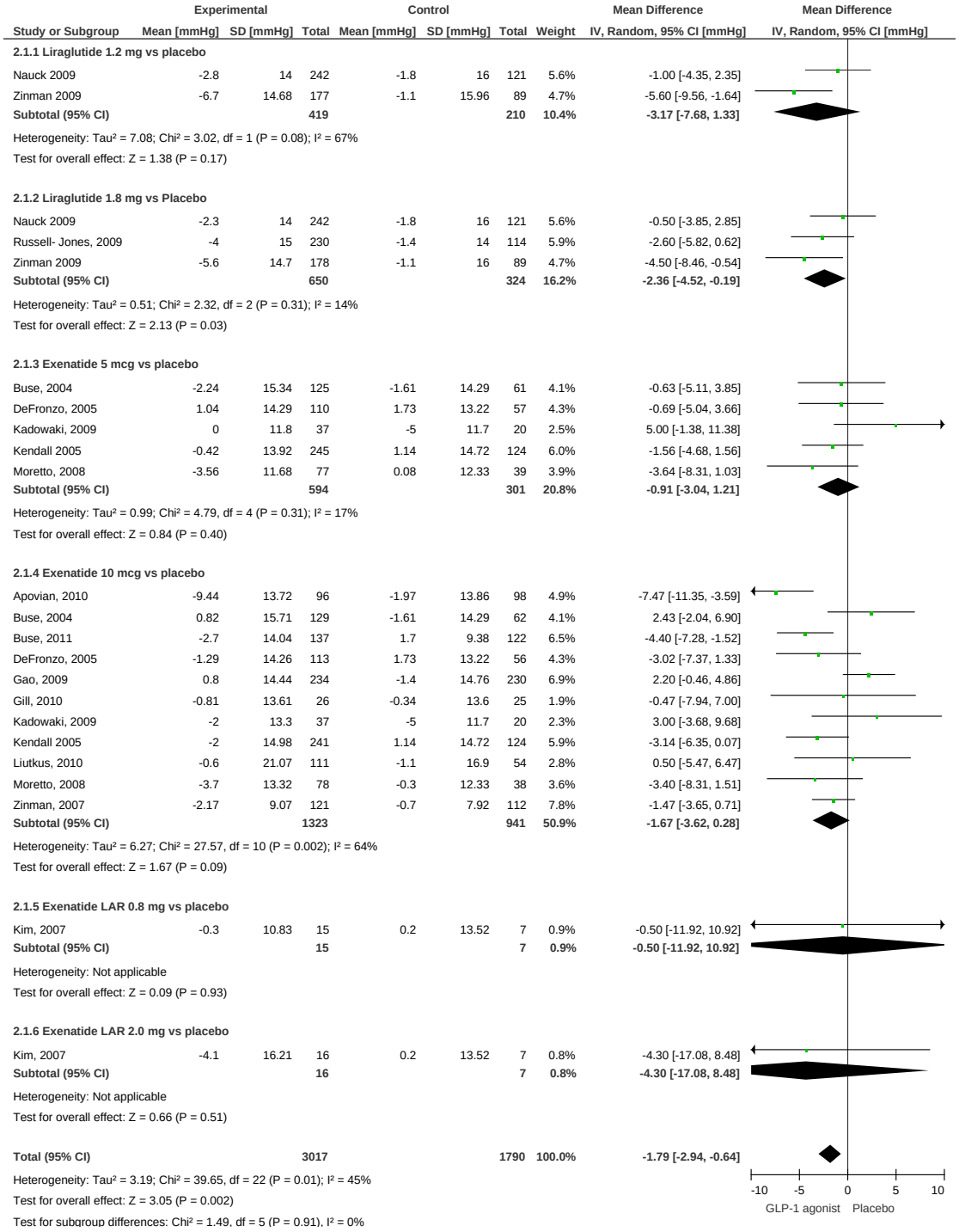


Figure 4 GLP-1 agonists' effect on systolic blood pressure in patients with type 2 diabetes

4(a) GLP-1 vs placebo



4(b) GLP-1 vs active control

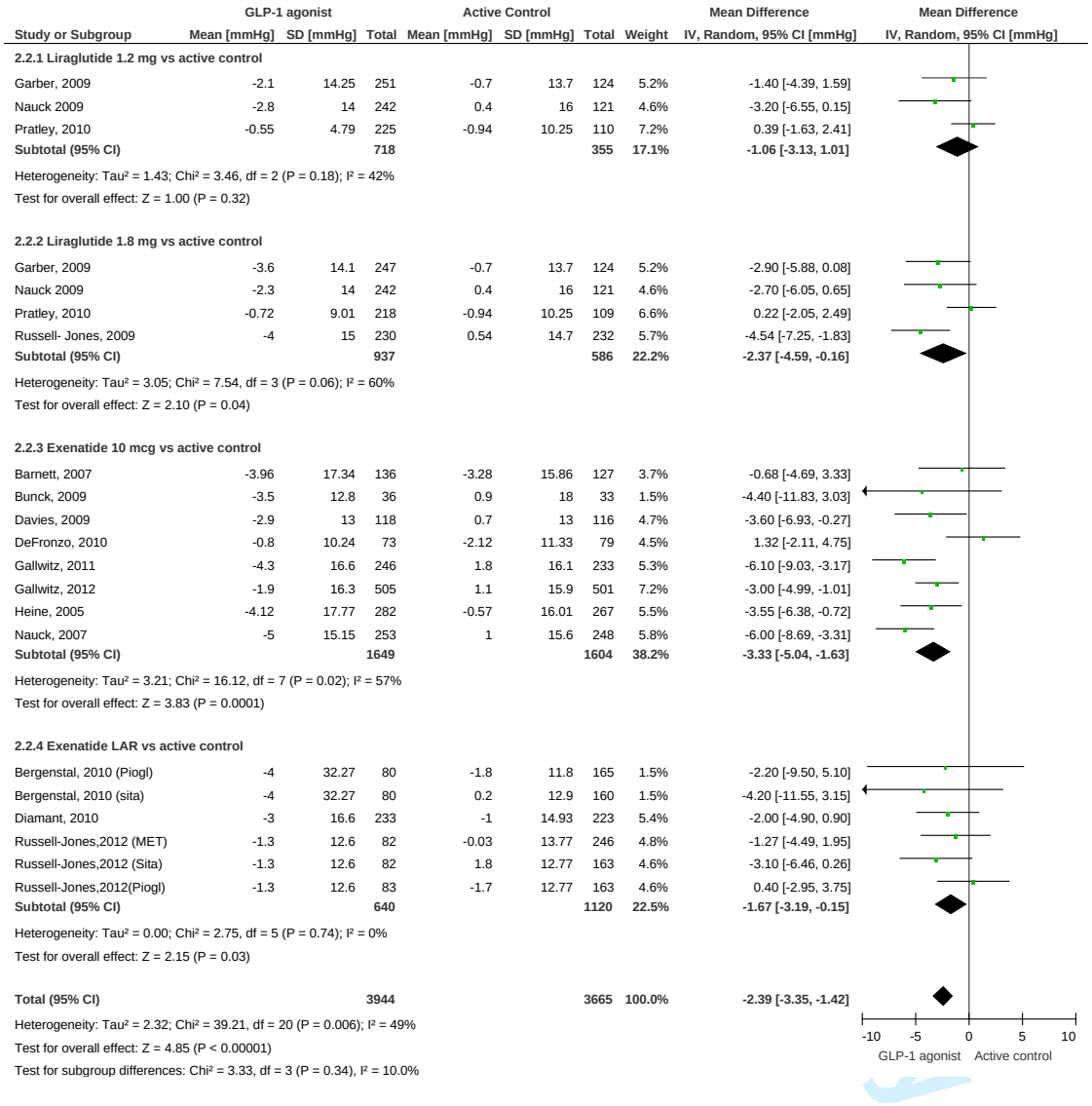
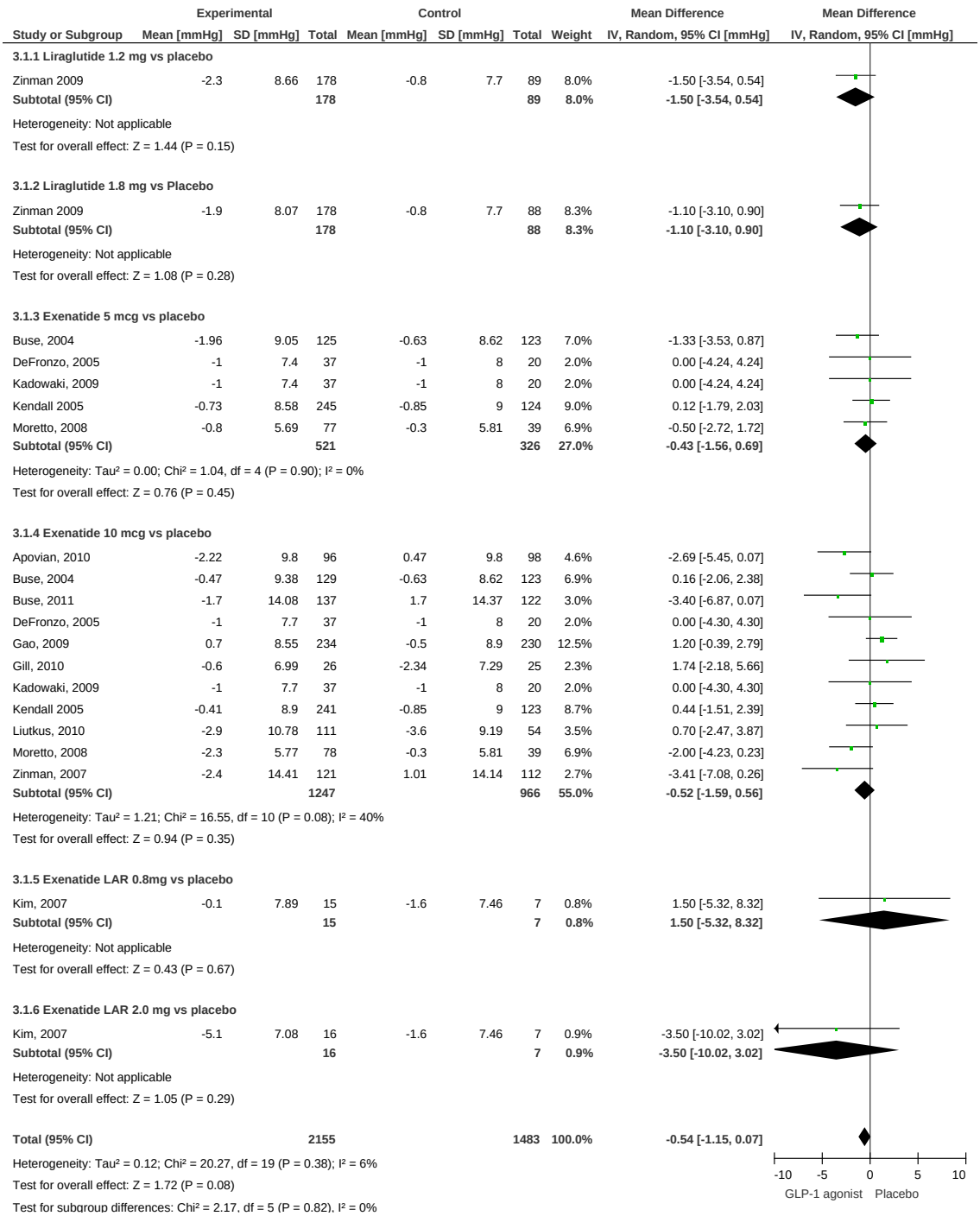


Figure 5 GLP-1 agonists' effect on diastolic blood pressure in patients with type 2 diabetes

5(a) GLP-1 vs placebo



5(b) GLP-1 vs active control

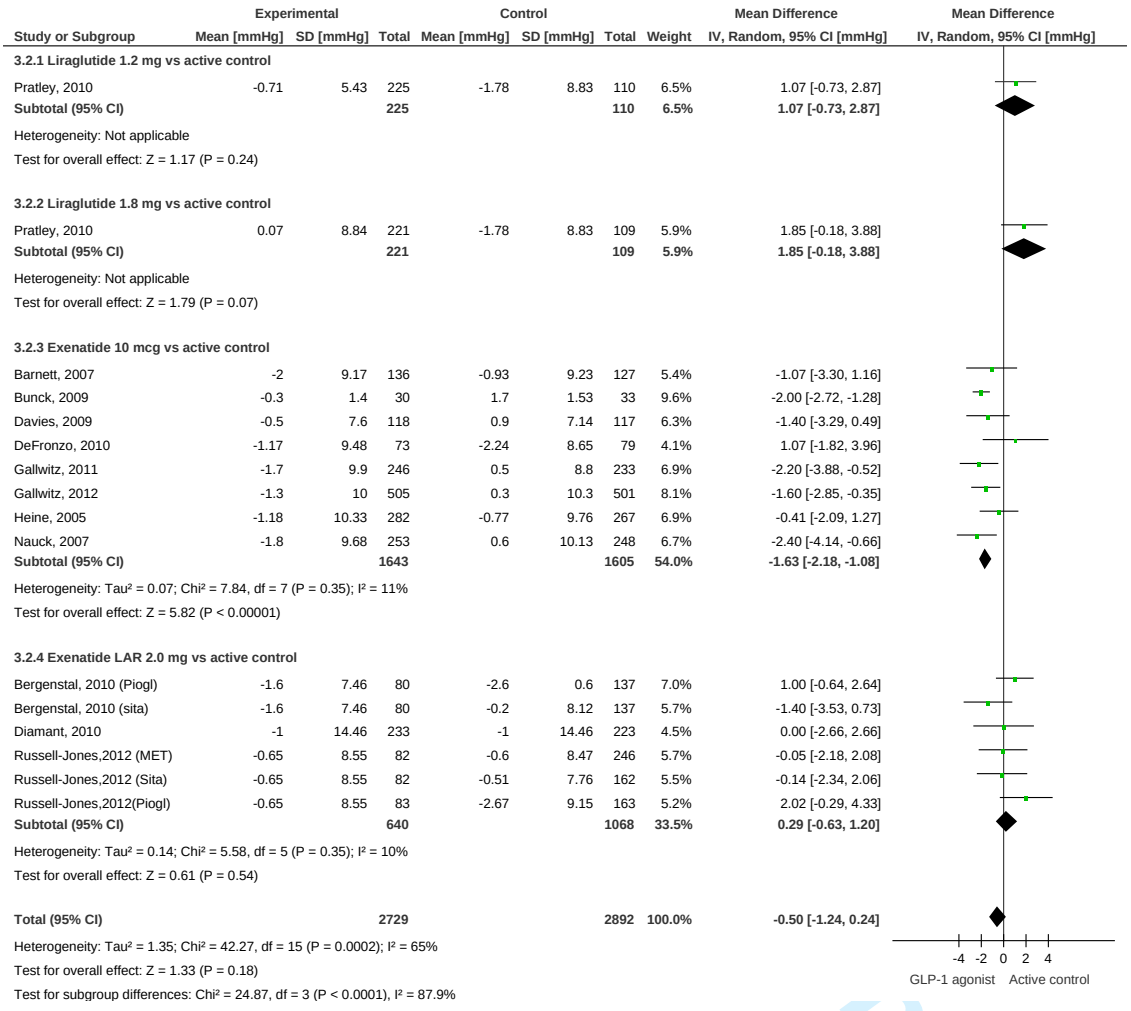
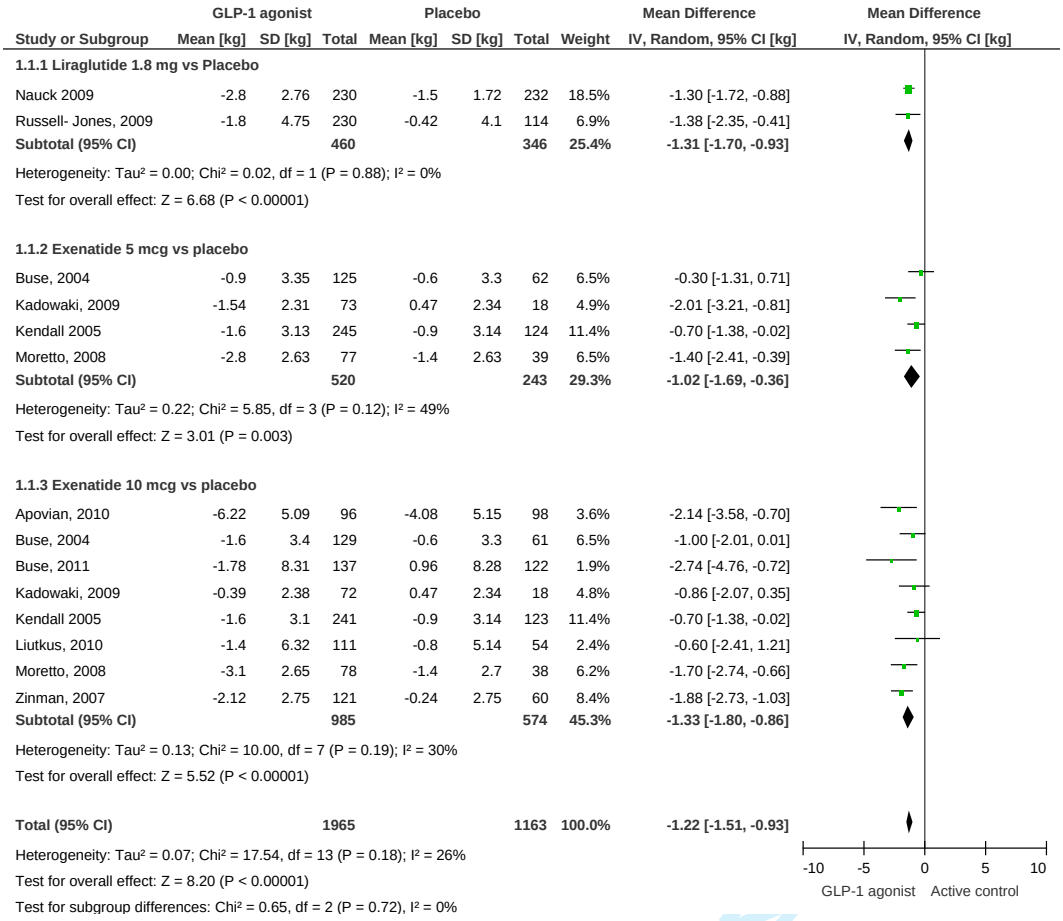
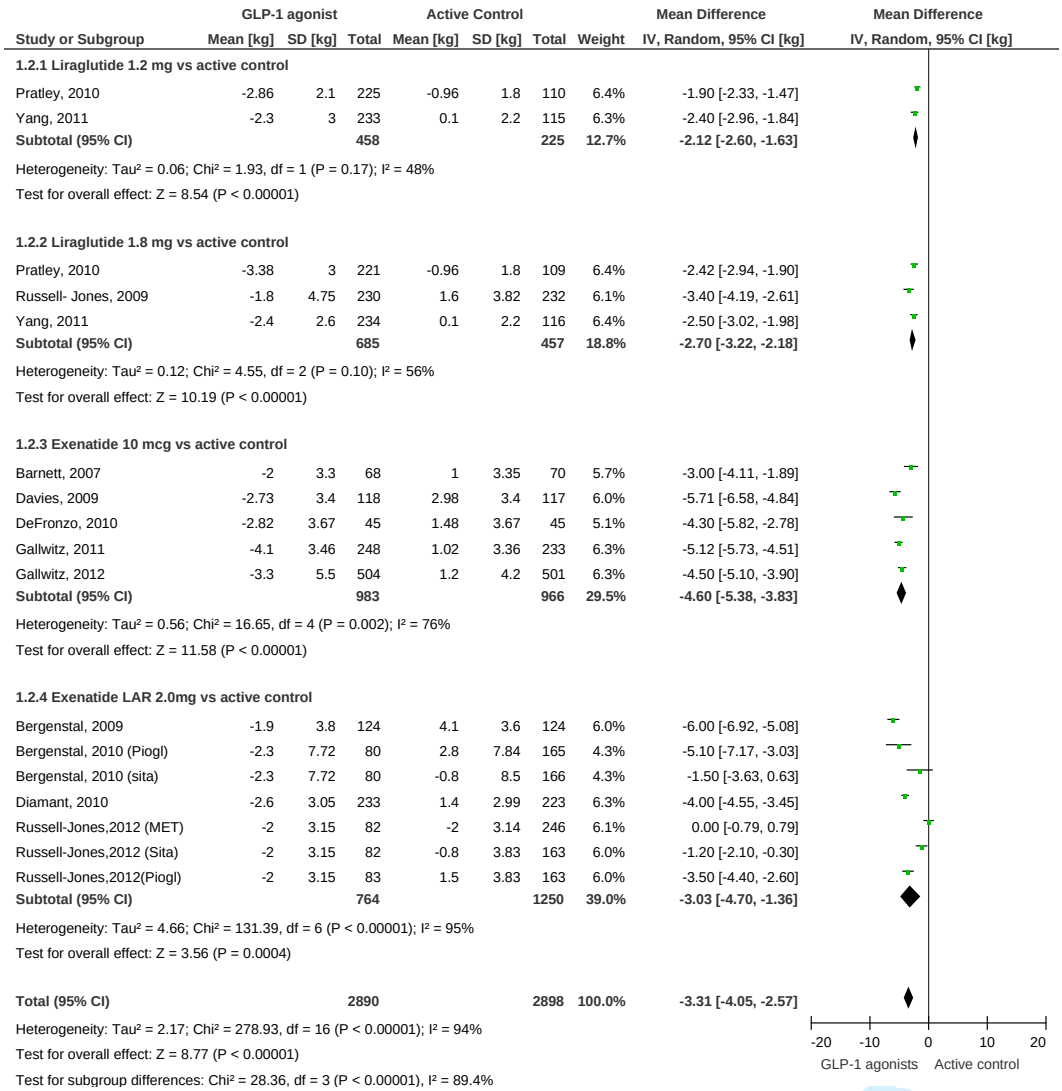


Figure 6 GLP-1 agonists' effects on body weight

6(a) GLP-1 agonists versus placebo



6(b) GLP-1 agonists versus active control



Study or Subgroup	GLP-1 agonist Mean [kg]	SD [kg]	Total	Active Control Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.2.1 Liraglutide 1.2 mg vs active control								
Pratley, 2010	-2.86	2.1	225	-0.96	1.8	110	6.4%	-1.90 [-2.33, -1.47]
Yang, 2011	-2.3	3	233	0.1	2.2	115	6.3%	-2.40 [-2.96, -1.84]
Subtotal (95% CI)			**458**			**225**	**12.7%**	**-2.12 [-2.60, -1.63]**
Heterogeneity: Tau² = 0.06; Chi² = 1.93, df = 1 (P = 0.17); I² = 48%								
Test for overall effect: Z = 8.54 (P < 0.00001)								
1.2.2 Liraglutide 1.8 mg vs active control								
Pratley, 2010	-3.38	3	221	-0.96	1.8	109	6.4%	-2.42 [-2.94, -1.90]
Russell- Jones, 2009	-1.8	4.75	230	1.6	3.82	232	6.1%	-3.40 [-4.19, -2.61]
Yang, 2011	-2.4	2.6	234	0.1	2.2	116	6.4%	-2.50 [-3.02, -1.98]
Subtotal (95% CI)			**685**			**457**	**18.8%**	**-2.70 [-3.22, -2.18]**
Heterogeneity: Tau² = 0.12; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%								
Test for overall effect: Z = 10.19 (P < 0.00001)								
1.2.3 Exenatide 10 mcg vs active control								
Barnett, 2007	-2	3.3	68	1	3.35	70	5.7%	-3.00 [-4.11, -1.89]
Davies, 2009	-2.73	3.4	118	2.98	3.4	117	6.0%	-5.71 [-6.58, -4.84]
DeFronzo, 2010	-2.82	3.67	45	1.48	3.67	45	5.1%	-4.30 [-5.82, -2.78]
Gallwitz, 2011	-4.1	3.46	248	1.02	3.36	233	6.3%	-5.12 [-5.73, -4.51]
Gallwitz, 2012	-3.3	5.5	504	1.2	4.2	501	6.3%	-4.50 [-5.10, -3.90]
Subtotal (95% CI)			**983**			**966**	**29.5%**	**-4.60 [-5.38, -3.83]**
Heterogeneity: Tau² = 0.56; Chi² = 16.65, df = 4 (P = 0.002); I² = 76%								
Test for overall effect: Z = 11.58 (P < 0.00001)								
1.2.4 Exenatide LAR 2.0mg vs active control								
Bergenstal, 2009	-1.9	3.8	124	4.1	3.6	124	6.0%	-6.00 [-6.92, -5.08]
Bergenstal, 2010 (Piogl)	-2.3	7.72	80	2.8	7.84	165	4.3%	-5.10 [-7.17, -3.03]
Bergenstal, 2010 (sita)	-2.3	7.72	80	-0.8	8.5	166	4.3%	-1.50 [-3.63, 0.63]
Diamant, 2010	-2.6	3.05	233	1.4	2.99	223	6.3%	-4.00 [-4.55, -3.45]
Russell-Jones,2012 (MET)	-2	3.15	82	-2	3.14	246	6.1%	0.00 [-0.79, 0.79]
Russell-Jones,2012 (Sita)	-2	3.15	82	-0.8	3.83	163	6.0%	-1.20 [-2.10, -0.30]
Russell-Jones,2012(Piogl)	-2	3.15	83	1.5	3.83	163	6.0%	-3.50 [-4.40, -2.60]
Subtotal (95% CI)			**764**			**1250**	**39.0%**	**-3.03 [-4.70, -1.36]**
Heterogeneity: Tau² = 4.66; Chi² = 131.39, df = 6 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
Total (95% CI)			**2890**			**2898**	**100.0%**	**-3.31 [-4.05, -2.57]**
Heterogeneity: Tau² = 2.17; Chi² = 278.93, df = 16 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 8.77 (P < 0.00001)								
Test for subgroup differences: Chi² = 28.36, df = 3 (P < 0.00001), I² = 89.4%								