PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: Systematic review and meta-analysis
AUTHORS	Holt, Tim; Robinson, Louise; Rees, Karen; Randeva, Harpal; O'Hare, Paul

VERSION 1 - REVIEW

REVIEWER	Dr Lindsay Govan Research Associate Health Economics and Health Technology Assessment Institute of Health and Wellbeing University of GlasgowGlasgow UK I have no competing interests related to this article.
REVIEW RETURNED	04-Oct-2012

THE STUDY	Are the methods adequately described? The methods used by the authors are adequately described but a clearer explanation of the data for the analysis of heart rate data for liraglutide obtained from Novo Nordisk is needed. The authors describe the data being provided as summaries by quartiles of heart rate. Does this mean that Novo Nordisk provided summary quartile data for each of the 5 trials individually, or did they provide a pooled estimate of the change in heart rate for the 5 trials? If it is the former, then the analysis for each of the individual trials should be shown in Figure 2 and Figure 3 or at least a description of how these were pooled. If it was the latter, a description of how Novo Nordisk pooled the data before providing it to the authors is necessary. If Novo Nordisk naively pooled the results of the 5 LEAD trials then this will have introduced bias. If Novo Nordisk appropriately pooled the data then this needs to be described along with any possible measures of heterogeneity. Are the statistical methods appropriate? I believe the most complex meta-analysis techniques could provide better results. Firstly, the authors point out that there was significant heterogeneity in the analysis, but have not investigated why this heterogeneity exists. This is worrying since the results may therefore not be interpretable: random-effects meta-analysis is not cure for heterogeneity. A discussion of possible explanations for the heterogeneity should be included in the discussion section of the paper. Explanations may include different subsets of subjects (should the studies have been examined by subset of patient characteristics, i.e. different age distributions in studies) or different study designs (i.e. RCT vs. cross-over). Any observed differences in study characteristics could be examined using meta-regression

	techniques to investigate the heterogeneity. The authors stratify the analysis by dose, but this may be better analysed as a meta-regression where dose is included as a covariate. Other characteristics could also be analysed in this way. Secondly, several treatments are of interest in this analysis (liraglutide, exenatide LAR and exenatide BID). There is overlap in the comparison of treatments and comparators (placebo, OAD, insulin, lifestyle intervention) of the 32 trials included, and I believe a network meta-analysis could be used instead of stratifying the analysis by types of comparators. Using network meta-analysis would allow not only the direct comparison of treatments to inform the difference in effects of treatments, but also includes indirect treatment comparison information. This provides more powerful comparisons between treatments. Additionally, the 4 trials that were excluded due to the comparator being another GLP-1 could be included in the analyses further increasing the study's power.
GENERAL COMMENTS	Further comments Although I believe the paper can be improved with the suggestions I have included in the score sheet, I believe this is a very interesting study and worthy of publication. My main concern is the significant heterogeneity in the analysis. The authors need to provide an explanation of the heterogeneity and investigate it or the results of the study cannot be interpreted, possibly through meta-regression of dosage. My second suggestion is a network meta-analysis. I am aware that opinions differ on the appropriateness of including indirect evidence as this can be considered observational in nature. However, I would recommend investigating the use of this approach as the heterogeneity may be explained by the difference in comparators across trials and the network meta-analysis could eliminated this potential source of heterogeneity. Overall, I would recommend this paper for publication after my concerns have been adequately addressed. Some further, minor comments: The authors do not explain why only certain doses of liraglutide and exenatide are included. Three papers were excluded due to incorrect dosage but no explanation was given why the doses stated were chosen. If meta-regression is performed then these additional trials could be included as they would inform the regression. The authors included all participants with type 2 diabetes. What is the age range for the included studies?

REVIEWER	Bruce W. Bode MD Atlanta Diabetes Associates Emory University School of Medicine
REVIEW RETURNED	20-Oct-2012

GENERAL COMMENTS	1. I would delete the following line from the conclusion because this does not pertain to the main part of the paper and is an outlier ("This would enable investigation of prespecified 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"). 2. Since you discussed GLP-1 agonists as a group regarding a

	reduction in weight and blood pressure, would do the same for the increase in heart rate; would thus change the wording to all GLP-1 receptor agonists show a small increase in heart rate with the longer acting GLP 1 receptor agonists showing a statically significant rise in heart rate compared to both comparator drugs as well as placebo. 3. You must state in the discussion that the clinical significance of a small increase in heart rate shown by GLP-1 receptor agonists is unknown from a cardiovascular risk prospective; You could also discuss the potential mechanisms of increase heart rate by GLP-1 receptor agonists but this may beyond the purpose of this manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer comment: The methods used by the authors are adequately described but a clearer explanation of the data for the analysis of heart rate data for liraglutide obtained from Novo Nordisk is needed. The authors describe the data being provided as summaries by quartiles of heart rate. Does this mean that Novo Nordisk provided summary quartile data for each of the 5 trials individually, or did they provide a pooled estimate of the change in heart rate for the 5 trials? If it is the former, then the analysis for each of the individual trials should be shown in Figure 2 and Figure 3 or at least a description of how these were pooled. If it was the latter, a description of how Novo Nordisk pooled the data before providing it to the authors is necessary. If Novo Nordisk naively pooled the results of the 5 LEAD trials then this will have introduced bias. If Novo Nordisk appropriately pooled the data then this needs to be described along with any possible measures of heterogeneity.

Our response: The data from Novo Nordisk were originally presented to us grouped into quartiles of baseline heart rate. To address this Reviewer's concern over possible bias we have identified the raw data specific to each trial and repeated the analysis for this revised submission. For each trial, the mean change in heart rate from baseline, and the number of participants in each arm were available. The standard deviations in change scores were available from the quartile data for each dose/type of comparator. This re-analysis has led to slightly altered estimates for the effect size on heart rate but the differences are small and do not affect interpretation. It has also identified that the heterogeneity in heart rate estimation for liraglutide vs placebo is largely attributable to a single study (LEAD-1) and reduces to I2=0% if this trial is removed, with slight reductions in estimated effect size. However the reason for the higher heart rate effect estimate in this trial is unclear.

Reviewer comment: I believe the most complex meta-analysis techniques could provide better results. Firstly, the authors point out that there was significant heterogeneity in the analysis, but have not investigated why this heterogeneity exists. This is worrying since the results may therefore not be interpretable: random-effects meta-analysis is not cure for heterogeneity. A discussion of possible explanations for the heterogeneity should be included in the discussion section of the paper. Explanations may include different subsets of subjects (should the studies have been examined by subset of patient characteristics, i.e. different age distributions in studies) or different study designs (i.e. RCT vs. cross-over). Any observed differences in study characteristics could be examined using meta-regression techniques to investigate the heterogeneity. The authors stratify the analysis by dose, but this may be better analysed as a meta-regression where dose is included as a covariate. Other characteristics could also be analysed in this way.

Our response: We agree there is a need to look further into the issue of heterogeneity. Some of this is likely to be due to differences in the type of active comparator (which includes different classes of oral drug and insulin). Background OAD (oral anti-diabetic drug common to both arms) may also be relevant.

We have not conducted a meta-regression analysis for two reasons:

1) The number of trials should ideally be at least 10 to perform a meta-regression and as we do not

have 10 trials for all comparisons, we would be doing it for some but not others.
2) Meta-regression is used mainly for continuous variables and we don't have any pre-specified covariates that are continuous. Useful things to look at would be age for example but we only have mean age for each trial and not individual patient data so this is less informative.
We have however already included subgrouping for dose and have reported effect size estimates for the different subgroups. We have also added a new column to Table 1 to report the mean age in each trial as this Reviewer suggested. Only one study was a cross over design and the variation in mean age of participants was not great. Sources of heterogeneity are therefore likely to be due to differences in types of active comparator, or in type of background OAD, as these factors differed between the trials.
Reviewer comment: Secondly, several treatments are of interest in this analysis (liraglutide, exenatide LAR and exenatide BID). There is overlap in the comparison of treatments and comparators (placebo, OAD, insulin, lifestyle intervention) of the 32 trials included, and I believe a network meta-analysis could be used instead of stratifying the analysis by types of comparators. Using network meta-analysis would allow not only the direct comparison of treatments to inform the difference in effects of treatments, but also includes indirect treatment comparison information. This provides more powerful comparisons between treatments. Additionally, the 4 trials that were excluded due to the comparator being another GLP-1 could be included in the analyses further increasing the study's power.
Our response: We considered this Reviewer's suggestion of a conducting a network meta-analysis. However very few of the trials had multiple intervention and comparison arms and we therefore chose to keep with the simpler approach of stratifying by the different drug groupings and their comparison group (placebo or active control) to examine the potential differences in effect.
Conducting a network meta-analysis would not have been achievable within the 2 week timescale of this minor revision invitation.

Reviewer comment: Although I believe the paper can be improved with the suggestions I have included in the score sheet, I believe this is a very interesting study and worthy of publication. My main concern is the significant heterogeneity in the analysis. The authors need to provide an explanation of the heterogeneity and investigate it or the results of the study cannot be interpreted, possibly through meta-regression of dosage. My second suggestion is a network meta-analysis. I am aware that opinions differ on the appropriateness of including indirect evidence as this can be considered observational in nature. However, I would recommend investigating the use of this approach as the heterogeneity may be explained by the difference in comparators across trials and the network meta-analysis could eliminated this potential source of heterogeneity.
Our response: As above, we have explored the issue of heterogeneity and included more on it in the Discussion section. We have also considered the pros and cons of conducting a meta-regression and a network meta-analysis. We decided against these approaches but have however investigated and discussed the heterogeneity more thoroughly in this revised submission.

Reviewer comment: The authors do not explain why only certain doses of liraglutide and exenatide are included. Three papers were excluded due to incorrect dosage but no explanation was given why the doses stated were chosen. If meta-regression is performed then these additional trials could be included as they would inform the regression.
Our response: We have included a statement explaining that our choice of dosages was designed to fit with the dosages used in clinical practice. This makes the findings interpretable by clinicians wishing to know how much of an effect (for instance on weight) these agents might confer when used during routine care.

Reviewer comment: The authors included all participants with type 2 diabetes. What is the age range for the included studies?
Our response: We have added a new column to Table 1 giving the mean age of included participants in each trial.

Reviewer 2
Reviewer comment: I would delete the following line from the conclusion because this does not pertain to the main part of the paper and is an outlier ("This would enable investigation of prespecified 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").
Our response: We agree and have deleted this statement.

Reviewer comment: Since you discussed GLP-1 agonists as a group regarding a reduction in weight and blood pressure, would do the same for the increase in heart rate; would thus change the wording to all GLP-1 receptor agonists show a small increase in heart rate with the longer acting GLP 1 receptor agonists showing a statically significant rise in heart rate compared to both comparator drugs as well as placebo.
Our response: We have followed this advice and combined the analyses of individual GLP-1 agents to report an overall GLP-1 effect on heart rate in the Abstract and Results section. However we would like to include the subgroup analyses according to individual agents in the Results section as we believe this will be of interest. The effect is more evident for liraglutide and exenatide LAR than it is for exenatide BID. The heart rate effect is the focus of this paper as it has not been quantified before so we believe it is justifiable to include a more detailed analysis of this effect than that for body weight and blood pressure.

Reviewer comment: You must state in the discussion that the clinical significance of a small increase in heart rate shown by GLP-1 receptor agonists is unknown from a cardiovascular risk prospective;
Our response: We have added a new sentence in the Discussion to re-emphasise this point.

Reviewer comment: You could also discuss the potential mechanisms of increase heart rate by GLP-1 receptor agonists but this may beyond the purpose of this manuscript.
Our response: We have added a sentence to the Discussion section to speculate on possible underlying mechanisms and provided two further references to support it. However we hope that this paper will serve to open up a wider discussion on this issue.

We have made appropriate (highlighted) changes to the text in response to all of these suggestions. We hope that our changes will be acceptable and look forward to hearing from you.

VERSION 2 – REVIEW

REVIEWER	Lindsay Govan, BSc (Hons), PhD Research Associate Health Economics and Health Technology Assessment Institute of Health and Wellbeing University of Glasgow
REVIEW RETURNED	30-Nov-2012

GENERAL COMMENTS	The authors have addressed each of my previous comments, making appropriate revisions to the manuscript or responding to my questions and providing justification where no changes have been made. Overall this is an interesting piece of work which makes a constructive contribution to the literature. The authors have addressed my initial concerns and queries with the manuscript and I have no further concerns.