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Insulin secretagogues peptides (incretins) for diabetes

A systematic review and meta-analysis of randomized clinical trials

2011 - 2 - 22

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Contents

1 Executive Summary

1.1 Aim of the report

To systematically review the clinical effectiveness of insulin secretagogues peptides (incretins) for the treatment of diabetes

1.2 Methods

A systematic review was undertaken to compare the effectiveness of insulin secretagogues peptides (incretins) for the treatment of diabetes in all type of patients

1.2.1 Data sources

Major electronic databases were searched. Unpublished evidence such as conference abstracts, published reviews, and company submissions to the regulatory agencies (FDA review, EMEA - EPAR) were also reviewed.

1.2.2 Review methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and meta-analysis.

1.2.3 Trial selection

Trials were included if they fulfilled the following criteria:

1. **Types of intervention**: studies in which insulin secretagogues peptides (incretins) was used.
2. **Types of participants**: only those studies were included in which the participants had been diagnosed as having established diabetes.
3. **Outcome measures**: all studies were included in which clinical events were reported.
4. **Study design**: only randomised controlled trials (RCTs) were included. Trials were accepted as RCTs if the allocation of patients to treatment groups was described as randomised.

1.2.4 Data synthesis

The clinical effectiveness of insulin secretagogues peptides (incretins) was synthesised firstly through a narrative review with full tabulation of the results of the included studies and secondly by meta-analysis.

1.3 Results

We found 24 trials concerning Glucagon-like peptide analogs.
Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit

effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).
Reports of 22 trials (covering 25 comparisons and including 9571 patients) were identified .
Among these comparisons, 12 trials are about exenatide and 12 about liraglutide.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. One ongoing trial was identified.

Exenatide

Results obtained with exenatide for all the endpoints with data in at least one trial are summarized table **??**.

Table 1.1: *Results summary - Exenatide*

Benefit	Harmful	No evidence
	Exenatide versus insulin on-top of SU/MET	
	↑ nausea RR=7.91¶ [2.35;26.60] k=2 ↑ vomiting RR=3.21* [1.23;8.38] k=2	→ all hypoglycemia RR=0.73^{NS} [0.42;1.27] k=2 → severe hypoglycemia RR=0.35^{NS} [0.04;3.25] k=2 → diarrhoea RR=2.08^{NS} [0.42;10.44] k=2 → cardiovascular events RR=0.95^{NS} [0.08;12.11] k=2 → all cause death RR=0.67^{NS} [0.04;10.52] k=2
	Exenatide versus placebo	
		→ all hypoglycemia RR=3.52^{NS} [0.44;28.13] k=1 → severe hypoglycemia RR=0.50^{NS} [0.01;25.12] k=1 → nausea RR=12.08^{NS} [0.72;201.79] k=1 → vomiting RR=6.04^{NS} [0.34;106.74] k=1 → diarrhoea RR=2.01^{NS} [0.09;44.11] k=1 → cardiovascular events RR=0.50^{NS} [0.01;25.12] k=1 → all cause death RR=0.50^{NS} [0.01;25.12] k=1
	Exenatide versus placebo on-top of Metformin	
	↑ nausea RR=1.81¶ [1.26;2.62] k=2 ↑ vomiting RR=2.80* [1.03;7.59] k=2	→ all hypoglycemia RR=1.08^{NS} [0.43;2.70] k=2 → severe hypoglycemia RR=0.50^{NS} [0.03;7.89] k=2 → diarrhoea RR=1.75^{NS} [0.86;3.54] k=1 → cardiovascular events RR=0.50^{NS} [0.01;23.99] k=1 → all cause death RR=0.50^{NS} [0.03;7.89] k=2
	Exenatide versus placebo on-top of SU	
	↑ all hypoglycemia RR=7.02¶ [2.60;18.96] k=1 ↑ nausea RR=6.65¶ [3.49;12.66] k=1 ↑ vomiting RR=5.03† [1.56;16.19] k=1 ↑ diarrhoea RR=2.60* [1.02;6.63] k=1	→ severe hypoglycemia RR=0.52^{NS} [0.01;26.07] k=1 → cardiovascular events RR=0.26^{NS} [0.02;2.84] k=1 → all cause death RR=0.52^{NS} [0.01;26.07] k=1
	Exenatide versus placebo on-top of SU+/-MET	

continued...

Benefit	Harmful	No evidence
	↑ all hypoglycemia RR=3.92¶ [2.52;6.10] k=1	→ severe hypoglycemia RR=1.98NS [0.18;21.72] k=1 → cardiovascular events RR=0.25NS [0.01;5.47] k=1 → all cause death RR=0.99NS [0.02;49.76] k=1
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones		
		→ severe hypoglycemia RR=0.36NS [0.01;17.86] k=1 → nausea RR=14.41NS [0.89;233.03] k=1 → cardiovascular events RR=0.36NS [0.01;17.86] k=1 → all cause death RR=0.36NS [0.01;17.86] k=1
Exenatide versus placebo on-top of SU+MET		
	↑ all hypoglycemia RR=1.87¶ [1.30;2.70] k=1 ↑ nausea RR=2.12¶ [1.63;2.76] k=1 ↑ vomiting RR=3.19¶ [1.72;5.91] k=1 ↑ diarrhoea RR=2.13† [1.26;3.59] k=1	→ severe hypoglycemia RR=1.02NS [0.03;30.20] k=1 → cardiovascular events RR=0.59NS [0.20;1.75] k=1 → all cause death RR=0.25NS [0.01;7.55] k=1
Exenatide versus placebo on-top of thiazolidinediones+/-MET		
	↑ nausea RR=2.61¶ [1.60;4.27] k=1 ↑ vomiting RR=14.81† [2.00;109.86] k=1	→ all hypoglycemia RR=1.50NS [0.65;3.49] k=1 → diarrhoea RR=2.16NS [0.57;8.15] k=1 → cardiovascular events RR=0.93NS [0.02;46.26] k=1 → all cause death RR=0.93NS [0.02;46.26] k=1
Exenatide versus insulin on-top of SU+MET		
	↑ nausea RR=19.30* [1.68;221.62] H k=2 ↑ vomiting RR=4.65¶ [2.84;7.61] k=2 ↑ diarrhoea RR=3.49¶ [1.91;6.37] k=2	→ severe hypoglycemia RR=0.95NS [0.26;3.48] k=2 → cardiovascular events RR=1.81NS [0.78;4.24] k=2 → all cause death RR=1.61NS [0.21;12.40] k=2

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Liraglutide

Results obtained with liraglutide for all the endpoints with data in at least one trial are summarized table **??**.

Table 1.2: *Results summary - Liraglutide*

Benefit	Harmful	No evidence
Liraglutide versus placebo		

continued...

Benefit	Harmful	No evidence
		→ all hypoglycemia RR=0.34^{NS} [0.04;2.87] k=3 → severe hypoglycemia RR=0.26^{NS} [0.03;2.49] k=3 → nausea RR=2.93^{NS} [0.38;22.40] k=1 → vomiting RR=1.84^{NS} [0.23;14.75] k=2 → diarrhoea RR=1.73^{NS} [0.74;4.03] k=2 → cardiovascular events RR=0.26^{NS} [0.03;2.49] k=3 → all cause death RR=0.26^{NS} [0.03;2.49] k=3
Liraglutide versus placebo on-top of Metformin		
	↑ nausea RR=2.31¶ [1.55;3.44] k=1 ↑ vomiting RR=7.35* [1.02;52.88] k=1 ↑ diarrhoea RR=3.68† [1.38;9.83] k=1	→ all hypoglycemia RR=0.92^{NS} [0.32;2.62] k=1 → severe hypoglycemia RR=0.17^{NS} [0.00;8.38] k=1 → all cause death RR=0.17^{NS} [0.00;8.38] k=1
Liraglutide versus placebo on-top of SU		
	↑ nausea RR=4.30* [1.06;17.42] k=1	→ severe hypoglycemia RR=0.33^{NS} [0.01;9.81] k=1
Liraglutide versus placebo on-top of SU+MET		
	↑ nausea RR=4.14† [1.50;11.43] k=1	
Liraglutide versus placebo on-top of thiazolidinediones+MET		
		→ severe hypoglycemia RR=0.50^{NS} [0.01;24.95] k=1
Liraglutide versus glargine on-top of SU+MET		
	↑ nausea RR=10.76¶ [3.34;34.64] k=1	
Liraglutide versus glimepiride		
	↑ nausea RR=3.30¶ [2.14;5.08] k=1 ↑ diarrhoea RR=1.92† [1.24;2.98] k=2	→ all hypoglycemia RR=0.19^{NS} [0.02;1.50] H k=2 → severe hypoglycemia RR=0.31^{NS} [0.02;4.90] k=2 → vomiting RR=1.90^{NS} [0.42;8.71] k=2 → cardiovascular events RR=0.19^{NS} [0.00;9.49] k=1 → all cause death RR=0.22^{NS} [0.02;2.88] k=2
Liraglutide versus glimepiride on-top of Metformin		
↓ all hypoglycemia RR=0.18¶ [0.11;0.29] k=1	↑ nausea RR=2.31¶ [1.73;3.08] k=1 ↑ vomiting RR=7.35† [1.80;30.11] k=1 ↑ diarrhoea RR=3.68¶ [1.81;7.47] k=1	→ severe hypoglycemia RR=0.33^{NS} [0.01;16.80] k=1 → all cause death RR=0.33^{NS} [0.01;16.80] k=1
Liraglutide versus metformin		
		→ all hypoglycemia RR=0.48^{NS} [0.10;2.39] k=1 → severe hypoglycemia RR=0.19^{NS} [0.00;9.57] k=1 → nausea RR=0.68^{NS} [0.15;3.12] k=1 → vomiting RR=0.77^{NS} [0.09;6.70] k=1 → all cause death RR=0.19^{NS} [0.00;9.57] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

1.3.1 Interpret

Treatments for which trials demonstrate benefit

Treatments for which trials suggest possible benefit

liraglutide (versus glimepiride on-top of Metformin):
reductionin all hypoglycemia of 82 (95% CI between 0.11 and 0.29)(0 conclusif trials)

exenatide (versus insulin on-top of SU/MET): in HbA1c of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo): in HbA1c of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of Metformin): in HbA1c of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of SU): in HbA1c of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of SU+/-MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in nausea of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of SU+/-MET/thiazolidinediones): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of SU+MET): in HbA1c of NaN (95% CI between and)(conclusif trials)

exenatide (versus placebo on-top of thiazolidinediones+/-MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in severe hypoglycemia of NaN (95% CI between and)(conclusif trials)

exenatide (versus insulin on-top of SU+MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)

liraglutide (versus placebo): in HbA1c of NaN (95% CI between and)(conclusif trials)

liraglutide (versus placebo on-top of Metformin): in HbA1c of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)

liraglutide (versus placebo on-top of SU): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)
in All cause death of NaN (95% CI between and)(conclusif trials)

liraglutide (versus placebo on-top of SU+MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)
in severe hypoglycemia of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)
in All cause death of NaN (95% CI between and)(conclusif trials)

liraglutide (versus placebo on-top of thiazolidinediones+MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)
in nausea of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)
in All cause death of NaN (95% CI between and)(conclusif trials)

liraglutide (versus glargine on-top of SU+MET): in HbA1c of NaN (95% CI between and)(conclusif trials)
in all hypoglycemia of NaN (95% CI between and)(conclusif trials)
in severe hypoglycemia of NaN (95% CI between and)(conclusif trials)
in vomiting of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)
in All cause death of NaN (95% CI between and)(conclusif trials)

liraglutide (versus glimepiride): in HbA1c of NaN (95% CI between and)(conclusif trials)

liraglutide (versus glimepiride on-top of Metformin): in HbA1c of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)

liraglutide (versus metformin): in HbA1c of NaN (95% CI between and)(conclusif trials)
in diarrhoea of NaN (95% CI between and)(conclusif trials)
in cardiovascular events of NaN (95% CI between and)(conclusif trials)

Treatments for which trials do not show evidence of benefit

Treatments for which trials show harmful effect without demonstrated benefit

Treatments for which trials show a problematical benefit risk balance

Treatments for which trials demonstrate benefit difference (superiority or inferiority)

Treatments for which trials show a possible benefit difference (superiority or inferiority)

Treatments for which trials show safety difference without identified benefit difference

Treatments for which trials show possible safety difference without identified benefit difference

Treatments for which trials show benefit and safety differences

Treatments for which trials do not show evidence of difference

2 Introduction

2.1 Aim of the report

This report review all the randomized clinical trials of insulin secretagogues peptides (incretins) for the treatment of diabetes in all type of patients.

2.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of insulin secretagogues peptides (incretins) for the treatment of diabetes in all type of patients.

2.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2011 - 2 - 22:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science Science Citation Index Expanded,

Each database was searched as far back as possible, with no language restrictions.
Search strategies of relevant clinical keywords were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.
In addition, the reference lists of relevant articles were handsearched.
Attempts to identify further studies were made by consulting health technology assessment and guideline producing agencies, and research and trials registers via the Internet.
Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained.

2.2.2 Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

2.3 Inclusion criteria

Participants only those studies were included in which the participants had been diagnosed as having established diabetes.

Interventions studies in which insulin secretagogues peptides (incretins) was used.

Studies using other interventions in addition to insulin secretagogues peptides (incretins) therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of insulin secretagogues peptides (incretins).

Methodology randomised controlled trials (RCTs). Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

2.4 Exclusion criteria

Studies considered methodologically unsound. The list of excluded studies with reason of their exclusion are given in a separate section for each treatment categories considered.

2.5 Meta-analysis strategy

Studies that met the reviews entry criteria were eligible for inclusion in the meta-analyses provided that they reported outcomes in terms of the number of subjects suffering clinical outcomes, as only this would allow calculation of the relative risk of subjects in the intervention group developing each outcome, compared with subjects in the control group.

Studies that only presented results in the form of relative risks, relative hazards or odds ratios, without the underlying numbers were also include in the meta-analyses.

Binary outcomes were analysed using the fixed-effect model. For continuous outcomes, weighted mean differences (WMDs) were analysed, using a fixed-effect model.

Heterogeneity was tested by the chi-2 test and the I2 statistic was obtained to describe the proportion of the variability.

Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.

Meta-analyses were conducted for data on severe hypoglycemia, All cause death, nausea, vomiting, all hypoglycemia, diarrhoea, cardiovascular events, .

2.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part **??** to **??**, listed by therapeutic class. The therapeutic classes included Glucagon-like peptide analogs,

In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

3 Overview of glucagon-like peptide analogs24

3.1 Trials

A total of 24 randomized comparisons which enrolled 9571 patients were identified. In all, 12 randomized comparisons concerned exenatide and 12 liraglutide.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for exenatide and in section **??** (page **??**) for liraglutide.

The average study size was 398 patients (range 45 to 966). The first study was published in 2004, and the last study was published in 2009.
A total of 13 trials were double blind and 6 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

3.2 Summary of results

The meta-analysis of the available trials about glucagon-like peptide analogs provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

3.2.1 Exenatide

Data were insufficient to compare **exenatide** to **insulin on-top of SU/MET**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of nausea (RR=7.91, 95% CI 2.35 to 26.60, p=0.0000, 2 trials) and vomiting (RR=3.21, 95% CI 1.23 to 8.38, p=0.0171, 2 trials) .

Data were insufficient to compare **exenatide** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **exenatide** to **placebo on-top of Metformin**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of nausea (RR=1.81, 95% CI 1.26 to 2.62, p=0.0000, 2 trials) and vomiting (RR=2.80, 95% CI 1.03 to 7.59, p=0.0426, 2 trials) .

Data were insufficient to compare **exenatide** to **placebo on-top of SU**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of all hypoglycemia (RR=7.02, 95% CI 2.60 to 18.96, p=0.0000, 1 trial) , nausea (RR=6.65, 95% CI 3.49 to 12.66, p=0.0000, 1 trial) , vomiting (RR=5.03, 95% CI 1.56 to 16.19, p=0.0068, 1 trial) and diarrhoea (RR=2.60, 95% CI 1.02 to 6.63, p=0.0454, 1 trial) .

Data were insufficient to compare **exenatide** to **placebo on-top of SU+/-MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of all hypoglycemia (RR=3.92, 95% CI 2.52 to 6.10, p=0.0000, 1 trial) .

Data were insufficient to compare **exenatide** to **placebo on-top of SU+/-MET/thiazolidinediones**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **exenatide** to **placebo on-top of SU+MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of all hypoglycemia (RR=1.87, 95% CI 1.30 to 2.70, p=0.0000, 1 trial) , nausea (RR=2.12, 95% CI 1.63 to 2.76, p=0.0000, 1 trial) , vomiting (RR=3.19, 95% CI 1.72 to 5.91, p=0.0000, 1 trial) and diarrhoea (RR=2.13, 95% CI 1.26 to 3.59, p=0.0047, 1 trial) .

Data were insufficient to compare **exenatide** to **placebo on-top of thiazolidinediones+/-MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of nausea (RR=2.61, 95% CI 1.60 to 4.27, p=0.0000, 1 trial) and vomiting (RR=14.81, 95% CI 2.00 to 109.86, p=0.0084, 1 trial) .

Data were insufficient to compare **exenatide** to **insulin on-top of SU+MET**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis. Exenatide appear to be associated with significantly greater risk of nausea (RR=19.30, 95% CI 1.68 to 221.62, p=0.0174, 2 trials) with a random effect model in reason of a heterogeneity (Het. p=0.0138) , vomiting (RR=4.65, 95% CI 2.84 to 7.61, p=0.0000, 2 trials) and diarrhoea (RR=3.49, 95% CI 1.91 to 6.37, p=0.0000, 2 trials) .

3.2.2 Liraglutide

Data were insufficient to compare **liraglutide** to **placebo**. There were 3 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **liraglutide** to **placebo on-top of Metformin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=2.31, 95% CI 1.55 to 3.44, p=0.0000, 1 trial) , vomiting (RR=7.35, 95% CI 1.02 to 52.88, p=0.0474, 1 trial) and diarrhoea (RR=3.68, 95% CI 1.38 to 9.83, p=0.0095, 1 trial) .

Data were insufficient to compare **liraglutide** to **placebo on-top of SU**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=4.30, 95% CI 1.06 to 17.42, p=0.0409, 1 trial) .

Data were insufficient to compare **liraglutide** to **placebo on-top of SU+MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=4.14, 95% CI 1.50 to 11.43, p=0.0061, 1 trial) .

Data were insufficient to compare **liraglutide** to **placebo on-top of thiazolidinediones+MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **liraglutide** to **glargine on-top of SU+MET**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=10.76, 95% CI 3.34 to 34.64, p=0.0000, 1 trial) .

Data were insufficient to compare **liraglutide** to **glimepiride**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=3.30, 95% CI 2.14 to 5.08, p=0.0000, 1 trial) and diarrhoea (RR=1.92, 95% CI 1.24 to 2.98, p=0.0034, 2 trials) .

Data were insufficient to compare **liraglutide** to **glimepiride on-top of Metformin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis. Liraglutide appear to be associated with significantly greater risk of nausea (RR=2.31, 95% CI 1.73 to 3.08, p=0.0000, 1 trial) , vomiting (RR=7.35, 95% CI 1.80 to 30.11, p=0.0055, 1 trial) and diarrhoea (RR=3.68, 95% CI 1.81 to 7.47, p=0.0000, 1 trial) . There is a statistically significant difference in favour of liraglutide for all hypoglycemia (RR=0.18, 95% CI 0.11 to 0.29, p=0.0000, 1 trial) .

Data were insufficient to compare **liraglutide** to **metformin**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 3.1: *Main study characteristics - Glucagon-like peptide analogs*

Trial	Patients	Treatments	Trial design and method
Exenatide			
Exenatide versus insulin on-top of SU/MET			
Davis, 2007 [?] n = 33 vs. 16		exenatide 20 microg daily **versus** insulin on-top of sulphonylureas/metformin add-on to: SU/Met	open parallel groups
Barnett, 2007 [?] n = 136 vs. 127		exenatide 20 microg daily **versus** insulin add-on to: SU/Met	open cross over Primary endpoint: hbA1c change 26 centres,NA
Exenatide versus placebo			
Moretto, 2008 [?] n = 155 vs. 78		exenatide 1020 microg daily **versus** placebo add-on to: None	double blind parallel groups
Exenatide versus placebo on-top of Metformin			
DeFronzo, 2005 [?] n = 223 vs. 113	patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses	exenatide 1020 microg daily **versus** placebo on-top of Metformin add-on to: Metformin	double blind parallel groups
Kim, 2007 [?] n = 30 vs. 15		exenatide 0.82 microg daily **versus** placebo on-top of metformin add-on to: Met/None	double blind parallel groups
Exenatide versus placebo on-top of SU			

continued...

Trial	Patients	Treatments	Trial design and method
Buse, 2004 [?] n = 248 vs. 129	patients with type 2 diabetes failing maximally effective doses of a sulfonylurea as monotherapy	exenatide 20 microg daily **versus** placebo on-top of SU add-on to: SU	double blind (not adequate) parallel groups
Exenatide versus placebo on-top of SU+/-MET			
Gao, 2009 [?] n = 234 vs. 232		exenatide 20 microg daily **versus** placebo on-top of sulphonylureas+/-metformin add-on to: SU+/-Met	double blind parallel groups
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones			
CT Register 8683, 0 n = 111 vs. 40		exenatide 51020 microg daily **versus** placebo on-top of sulphonylureas+/-metformin/thiazolidinediones add-on to: SU+/-Met/TZD	not reported parallel groups
Exenatide versus placebo on-top of SU+MET			
Kendall, 2005 [?] n = 486 vs. 247	patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy	exenatide 1020 microg daily **versus** placebo on-top of sulphonylureas+metformin add-on to: SU+/-Met	double blind parallel groups
Exenatide versus placebo on-top of thiazolidinediones+/-MET			
Zinman, 2007 [?] n = 121 vs. 112		exenatide 20 microg daily **versus** placebo on-top of thiazolidinediones+/-metformin add-on to: TZD+/-Met	double blind parallel groups

continued...

Trial	Patients	Treatments	Trial design and method
Exenatide versus insulin on-top of SU+MET			
Heine, 2005 [?] n = 282 vs. 267		exenatide 20 microg daily **versus** insulin on-top of sulphonylureas+metformin add-on to: SU+/-Met	open parallel groups
Nauck, 2007 [?] n = 253 vs. 248		exenatide 20 microg daily **versus** insulin on-top of sulphonylureas+metformin add-on to: SU+/-Met	open parallel groups
Liraglutide			
Liraglutide versus placebo			
Vilsboll, 2008 [?] n = 123 vs. 40		liraglutide 0.651.90 mg daily **versus** placebo add-on to: None	double blind (not adequate) parallel groups
Seino, 2008 [?] n = 180 vs. 46		liraglutide 0.10.9 mg daily **versus** placebo add-on to: None	double blind parallel groups
Madsbad (vs placebo), 2004 [?] n = 135 vs. 29		liraglutide 0.0450.75 mg daily **versus** placebo add-on to: None	open parallel groups
Liraglutide versus placebo on-top of Metformin			

continued...

Trial	Patients	Treatments	Trial design and method
Nauck (vs placebo), 2009 [?] n = 724 vs. 121		liraglutide 1.21.8 mg daily **versus** placebo on-top of Metformin add-on to: Metformin	double blind parallel groups
Liraglutide versus placebo on-top of SU			
LEAD-1, 0 n = 695 vs. 115		liraglutide 1.21.8 mg daily **versus** placebo on-top of sulphonylureas add-on to: SU	not reported parallel groups
Liraglutide versus placebo on-top of SU+MET			
LEAD-5 (vs placebo), 0 n = 230 vs. 119		liraglutide 1.8 mg daily **versus** placebo on-top of sulphonylureas+metformin add-on to: SU+/-Met	not reported parallel groups
Liraglutide versus placebo on-top of thiazolidinediones+MET			
LEAD-4, 0 n = 356 vs. 177		liraglutide 1.21.8 mg daily **versus** placebo on-top of thiazolidinediones+metformin add-on to: TZD+/-Met	not reported parallel groups
Liraglutide versus glargine on-top of SU+MET			
LEAD-5 (vs Glargine), 0 n = 230 vs. 232		liraglutide 1.8 mg daily **versus** glargine on-top of sulphonylureas+metformin add-on to: SU+/-Met	not reported parallel groups
Liraglutide versus glimepiride			

continued...

Trial	Patients	Treatments	Trial design and method
Garber, 2009 [**?**] n = 498 vs. 248		liraglutide 1.21.8 mg daily **versus** glimepiride add-on to: None	double blind parallel groups
Madsbad (vs Glimepiride), 2004 [**?**] n = 135 vs. 26		liraglutide 0.0450.75 mg daily **versus** glimepiride add-on to: None	open parallel groups
Liraglutide versus glimepiride on-top of Metformin			
Nauck (vs glimepiride), 2009 [**?**] n = 724 vs. 242		liraglutide 1.21.8 mg daily **versus** glimepiride on-top of Metformin add-on to: Metformin	double blind parallel groups
Liraglutide versus metformin			
Feinglos, 2005 [**?**] n = 176 vs. 34		liraglutide 0.0450.75 mg daily **versus** metformin add-on to: None	double blind (not adequate) parallel groups

Table 3.2: *Summary of all results for exenatide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
exenatide versus insulin on-top of SU/MET						
all hypoglycemia	RR=0.73	0.42;1.27	0.2663	0.2069 (0.37)	2	312
severe hypoglycemia	RR=0.35	0.04;3.25	0.3558	0.4235 (0.00)	2	312
nausea	RR=7.91	2.35;26.60	0.0000	0.1411 (0.54)	2	312
vomiting	RR=3.21	1.23;8.38	0.0171	0.8324 (0.00)	2	312
diarrhoea	RR=2.08	0.42;10.44	0.3723	0.2566 (0.22)	2	312
cardiovascular events	RR=0.95	0.08;12.11	0.9713	0.9885 (0.00)	2	312
all cause death	RR=0.67	0.04;10.52	0.7761	0.8155 (0.00)	2	312
exenatide versus placebo						
all hypoglycemia	RR=3.52	0.44;28.13	0.2349	1.0000 (0.00)	1	233
severe hypoglycemia	RR=0.50	0.01;25.12	0.7307	1.0000 (0.00)	1	233
nausea	RR=12.08	0.72;201.79	0.0829	1.0000 (1.00)	1	233
vomiting	RR=6.04	0.34;106.74	0.2198	1.0000 (0.00)	1	233
diarrhoea	RR=2.01	0.09;44.11	0.6569	1.0000 (0.00)	1	233
cardiovascular events	RR=0.50	0.01;25.12	0.7307	1.0000 (0.00)	1	233
all cause death	RR=0.50	0.01;25.12	0.7307	1.0000 (0.00)	1	233
exenatide versus placebo on-top of Metformin						
all hypoglycemia	RR=1.08	0.43;2.70	0.8723	0.3454 (0.00)	2	381
severe hypoglycemia	RR=0.50	0.03;7.89	0.6249	0.9962 (0.00)	2	381
nausea	RR=1.81	1.26;2.62	0.0000	0.5128 (0.00)	2	381
vomiting	RR=2.80	1.03;7.59	0.0426	0.3664 (0.00)	2	381
diarrhoea	RR=1.75	0.86;3.54	0.1225	1.0000 (1.00)	1	336
cardiovascular events	RR=0.50	0.01;23.99	0.7256	1.0000 (0.00)	1	45
all cause death	RR=0.50	0.03;7.89	0.6249	0.9962 (0.00)	2	381
exenatide versus placebo on-top of SU						
all hypoglycemia	RR=7.02	2.60;18.96	0.0000	1.0000 (0.00)	1	377
severe hypoglycemia	RR=0.52	0.01;26.07	0.7434	1.0000 (0.00)	1	377
nausea	RR=6.65	3.49;12.66	0.0000	1.0000 (0.00)	1	377
vomiting	RR=5.03	1.56;16.19	0.0068	1.0000 (0.00)	1	377
diarrhoea	RR=2.60	1.02;6.63	0.0454	1.0000 (0.00)	1	377
cardiovascular events	RR=0.26	0.02;2.84	0.2696	1.0000 (0.00)	1	377
all cause death	RR=0.52	0.01;26.07	0.7434	1.0000 (0.00)	1	377
exenatide versus placebo on-top of SU+/-MET						
all hypoglycemia	RR=3.92	2.52;6.10	0.0000	1.0000 (0.00)	1	466
severe hypoglycemia	RR=1.98	0.18;21.72	0.5751	1.0000 (0.00)	1	466
cardiovascular events	RR=0.25	0.01;5.47	0.3768	1.0000 (1.00)	1	466
all cause death	RR=0.99	0.02;49.76	0.9966	1.0000 (0.00)	1	466
exenatide versus placebo on-top of SU+/-MET/thiazolidinediones						
severe hypoglycemia	RR=0.36	0.01;17.86	0.6083	1.0000 (0.00)	1	151
nausea	RR=14.41	0.89;233.03	0.0602	1.0000 (0.00)	1	151
cardiovascular events	RR=0.36	0.01;17.86	0.6083	1.0000 (0.00)	1	151
all cause death	RR=0.36	0.01;17.86	0.6083	1.0000 (0.00)	1	151
exenatide versus placebo on-top of SU+MET						
all hypoglycemia	RR=1.87	1.30;2.70	0.0000	1.0000 (0.00)	1	733
severe hypoglycemia	RR=1.02	0.03;30.20	0.9925	1.0000 (0.00)	1	733
nausea	RR=2.12	1.63;2.76	0.0000	1.0000 (0.00)	1	733

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
vomiting	RR=3.19	1.72;5.91	0.0000	1.0000 (0.00)	1	733
diarrhoea	RR=2.13	1.26;3.59	0.0047	1.0000 (0.00)	1	733
cardiovascular events	RR=0.59	0.20;1.75	0.3427	1.0000 (1.00)	1	733
all cause death	RR=0.25	0.01;7.55	0.4285	1.0000 (0.00)	1	733
exenatide versus placebo on-top of thiazolidinediones+/-MET						
all hypoglycemia	RR=1.50	0.65;3.49	0.3422	1.0000 (0.00)	1	233
nausea	RR=2.61	1.60;4.27	0.0000	1.0000 (0.00)	1	233
vomiting	RR=14.81	2.00;109.86	0.0084	1.0000 (0.00)	1	233
diarrhoea	RR=2.16	0.57;8.15	0.2557	1.0000 (0.00)	1	233
cardiovascular events	RR=0.93	0.02;46.26	0.9691	1.0000 (0.00)	1	233
all cause death	RR=0.93	0.02;46.26	0.9691	1.0000 (0.00)	1	233
exenatide versus insulin on-top of SU+MET						
severe hypoglycemia	RR=0.95	0.26;3.48	0.9388	0.9869 (0.00)	2	1050
nausea	RR=19.30 [1]	1.68;221.62	0.0174	0.0138 (0.84) †	2	1050
vomiting	RR=4.65	2.84;7.61	0.0000	0.9943 (0.00)	2	1050
diarrhoea	RR=3.49	1.91;6.37	0.0000	0.4208 (0.00)	2	1050
cardiovascular events	RR=1.81	0.78;4.24	0.1692	0.8104 (0.00)	2	1050
all cause death	RR=1.61	0.21;12.40	0.6484	0.7560 (0.00)	2	1050

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 3.3: *Summary of all results for liraglutide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
liraglutide versus placebo						
all hypoglycemia	RR=0.34	0.04;2.87	0.3201	0.9804 (0.00)	3	553
severe hypoglycemia	RR=0.26	0.03;2.49	0.2431	0.9891 (0.00)	3	553
nausea	RR=2.93	0.38;22.40	0.3010	1.0000 (0.00)	1	163
vomiting	RR=1.84	0.23;14.75	0.5650	0.7408 (0.00)	2	327
diarrhoea	RR=1.73	0.74;4.03	0.2072	0.8763 (0.00)	2	327
cardiovascular events	RR=0.26	0.03;2.49	0.2431	0.9891 (0.00)	3	553
all cause death	RR=0.26	0.03;2.49	0.2431	0.9891 (0.00)	3	553
liraglutide versus placebo on-top of Metformin						
all hypoglycemia	RR=0.92	0.32;2.62	0.8748	1.0000 (0.00)	1	845
severe hypoglycemia	RR=0.17	0.00;8.38	0.3705	1.0000 (1.00)	1	845
nausea	RR=2.31	1.55;3.44	0.0000	1.0000 (0.00)	1	845
vomiting	RR=7.35	1.02;52.88	0.0474	1.0000 (0.00)	1	845
diarrhoea	RR=3.68	1.38;9.83	0.0095	1.0000 (0.00)	1	845
all cause death	RR=0.17	0.00;8.38	0.3705	1.0000 (1.00)	1	845
liraglutide versus placebo on-top of SU						
severe hypoglycemia	RR=0.33	0.01;9.81	0.5225	1.0000 (0.00)	1	810
nausea	RR=4.30	1.06;17.42	0.0409	1.0000 (0.00)	1	810
liraglutide versus placebo on-top of SU+MET						
nausea	RR=4.14	1.50;11.43	0.0061	1.0000 (0.00)	1	349
liraglutide versus placebo on-top of thiazolidinediones+MET						
severe hypoglycemia	RR=0.50	0.01;24.95	0.7265	1.0000 (0.00)	1	533

continued...

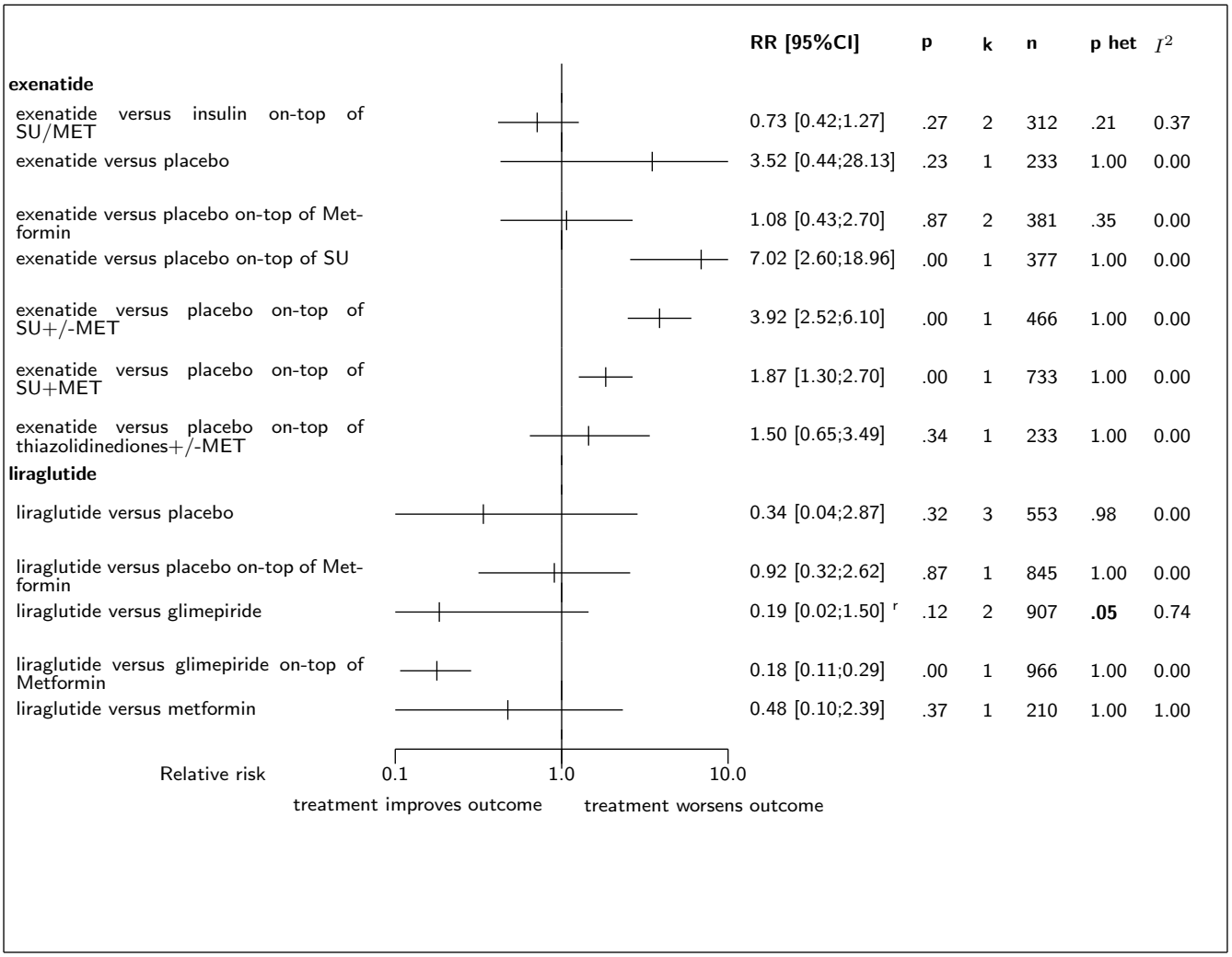
[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=7.34 95% CI 4.94;10.90

Endpoint	Effect	95% CI	p ass	p het	k	n
liraglutide versus glargine on-top of SU+MET						
nausea	RR=10.76	3.34;34.64	0.0000	1.0000 (0.00)	1	462
liraglutide versus glimepiride						
all hypoglycemia	RR=0.19 [2]	0.02;1.50	0.1150	0.0490 (0.74) †	2	907
severe hypoglycemia	RR=0.31	0.02;4.90	0.4047	0.7361 (0.00)	2	907
nausea	RR=3.30	2.14;5.08	0.0000	1.0000 (0.00)	1	746
vomiting	RR=1.90	0.42;8.71	0.4073	0.1529 (0.51)	2	907
diarrhoea	RR=1.92	1.24;2.98	0.0034	0.9995 (0.00)	2	907
cardiovascular events	RR=0.19	0.00;9.49	0.4075	1.0000 (0.00)	1	161
all cause death	RR=0.22	0.02;2.88	0.2502	0.9224 (0.00)	2	907
liraglutide versus glimepiride on-top of Metformin						
all hypoglycemia	RR=0.18	0.11;0.29	0.0000	1.0000 (0.00)	1	966
severe hypoglycemia	RR=0.33	0.01;16.80	0.5835	1.0000 (0.00)	1	966
nausea	RR=2.31	1.73;3.08	0.0000	1.0000 (0.00)	1	966
vomiting	RR=7.35	1.80;30.11	0.0055	1.0000 (0.00)	1	966
diarrhoea	RR=3.68	1.81;7.47	0.0000	1.0000 (1.00)	1	966
all cause death	RR=0.33	0.01;16.80	0.5835	1.0000 (0.00)	1	966
liraglutide versus metformin						
all hypoglycemia	RR=0.48	0.10;2.39	0.3721	1.0000 (1.00)	1	210
severe hypoglycemia	RR=0.19	0.00;9.57	0.4090	1.0000 (0.00)	1	210
nausea	RR=0.68	0.15;3.12	0.6157	1.0000 (0.00)	1	210
vomiting	RR=0.77	0.09;6.70	0.8150	1.0000 (0.00)	1	210
all cause death	RR=0.19	0.00;9.57	0.4090	1.0000 (0.00)	1	210

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

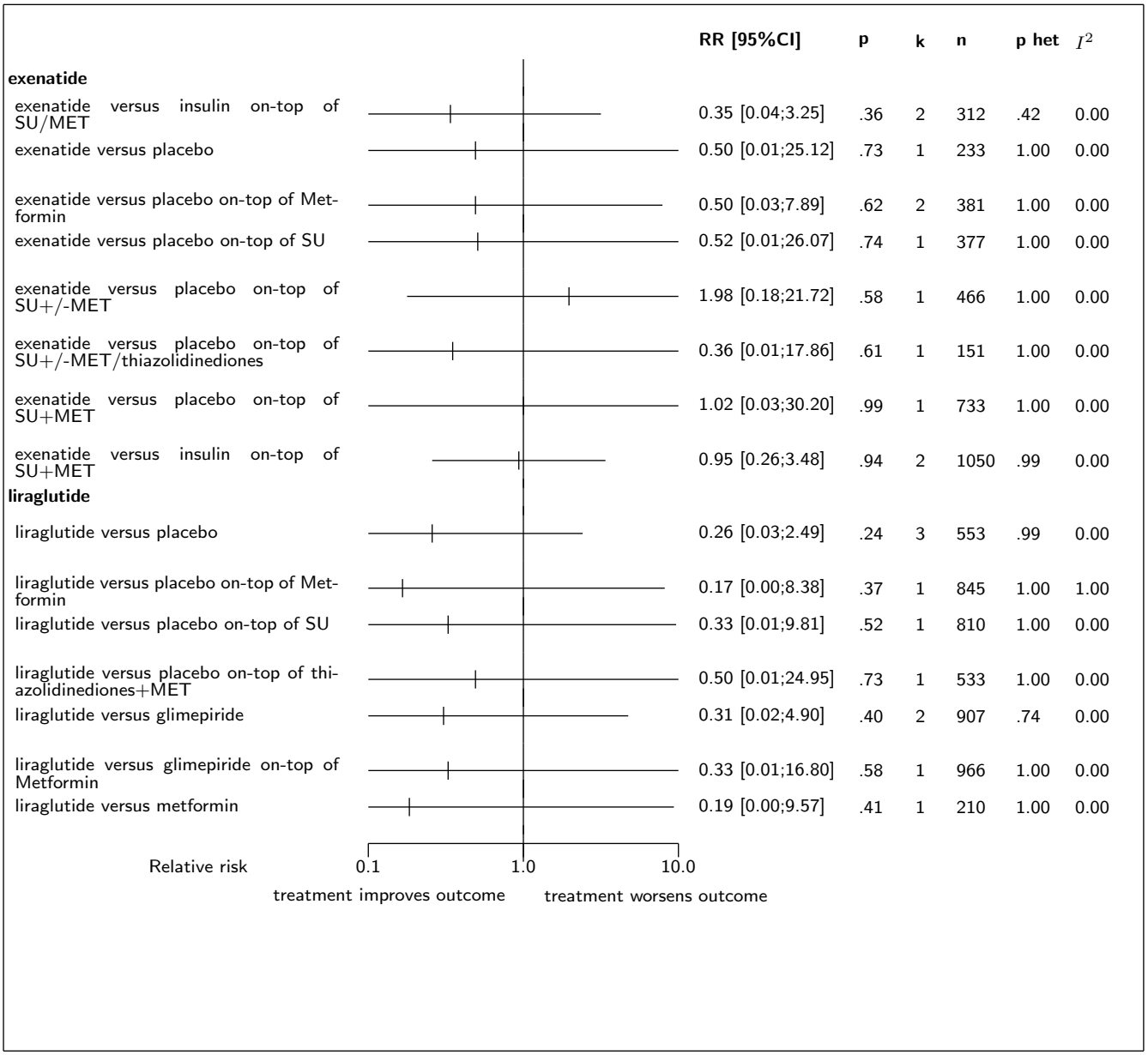
[2]with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.41 95% CI 0.29;0.57

Figure 3.1: *Forest's plot for all hypoglycemia*



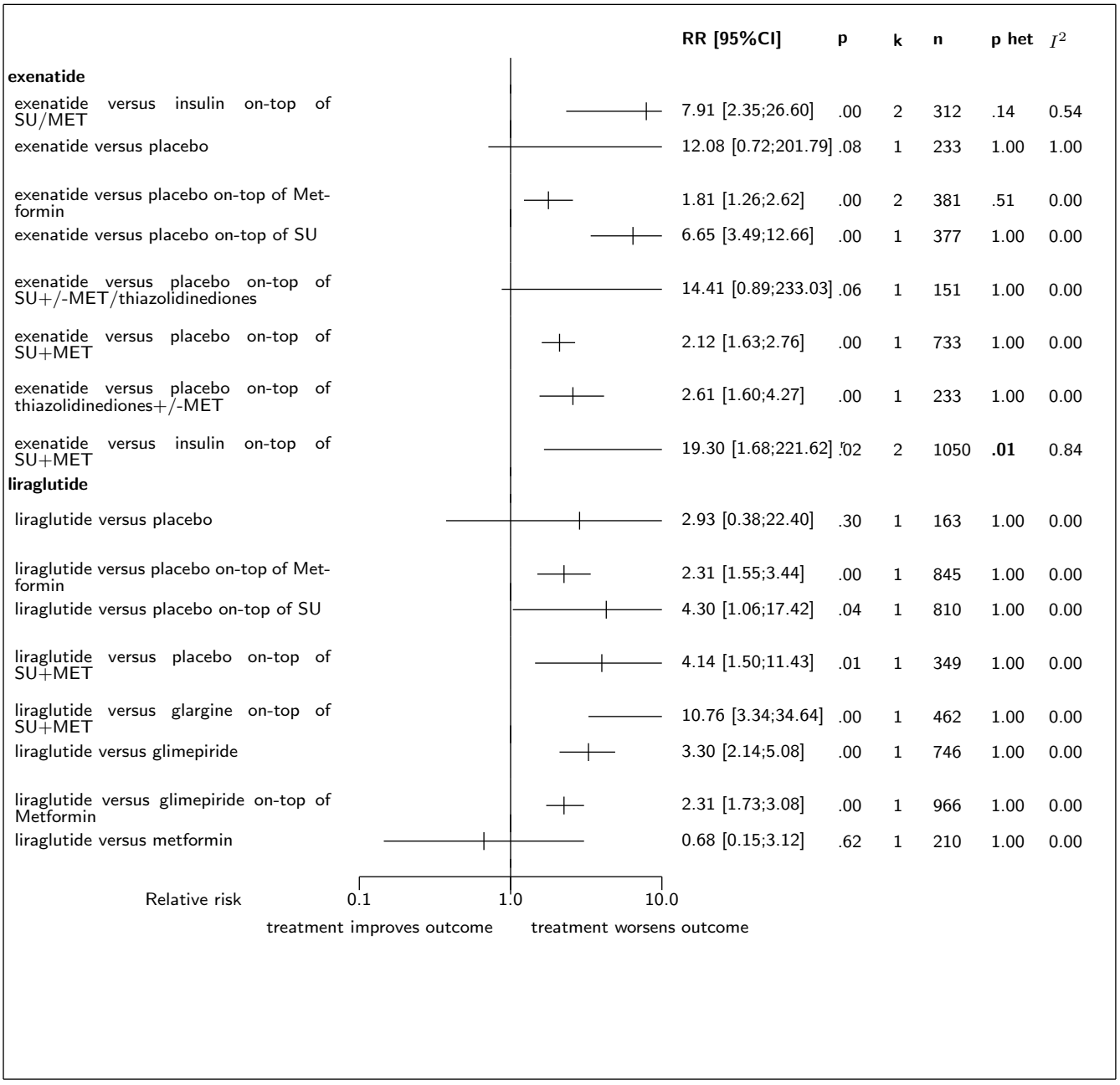
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 3.2: *Forest's plot for severe hypoglycemia*



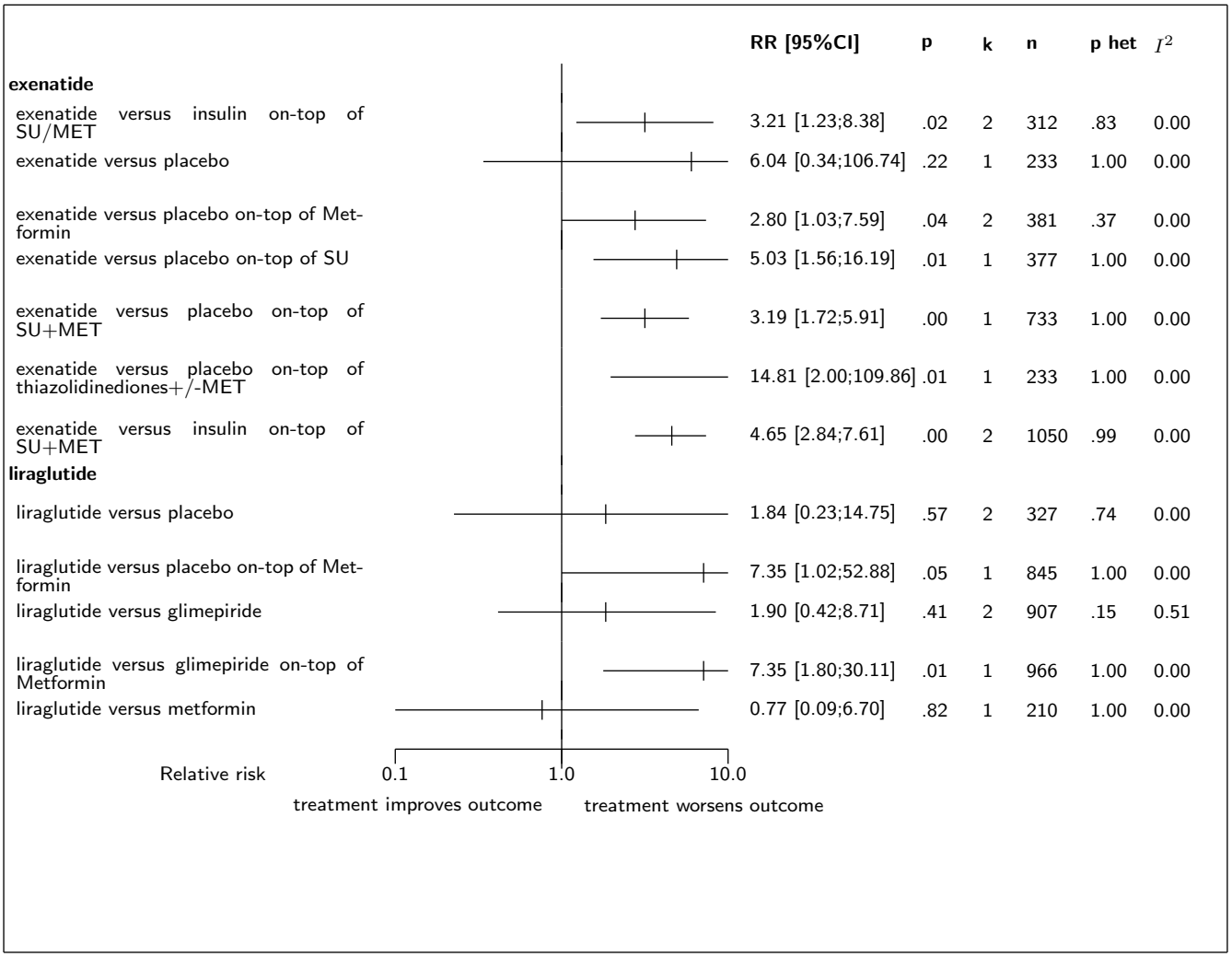
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 3.3: *Forest's plot for nausea*



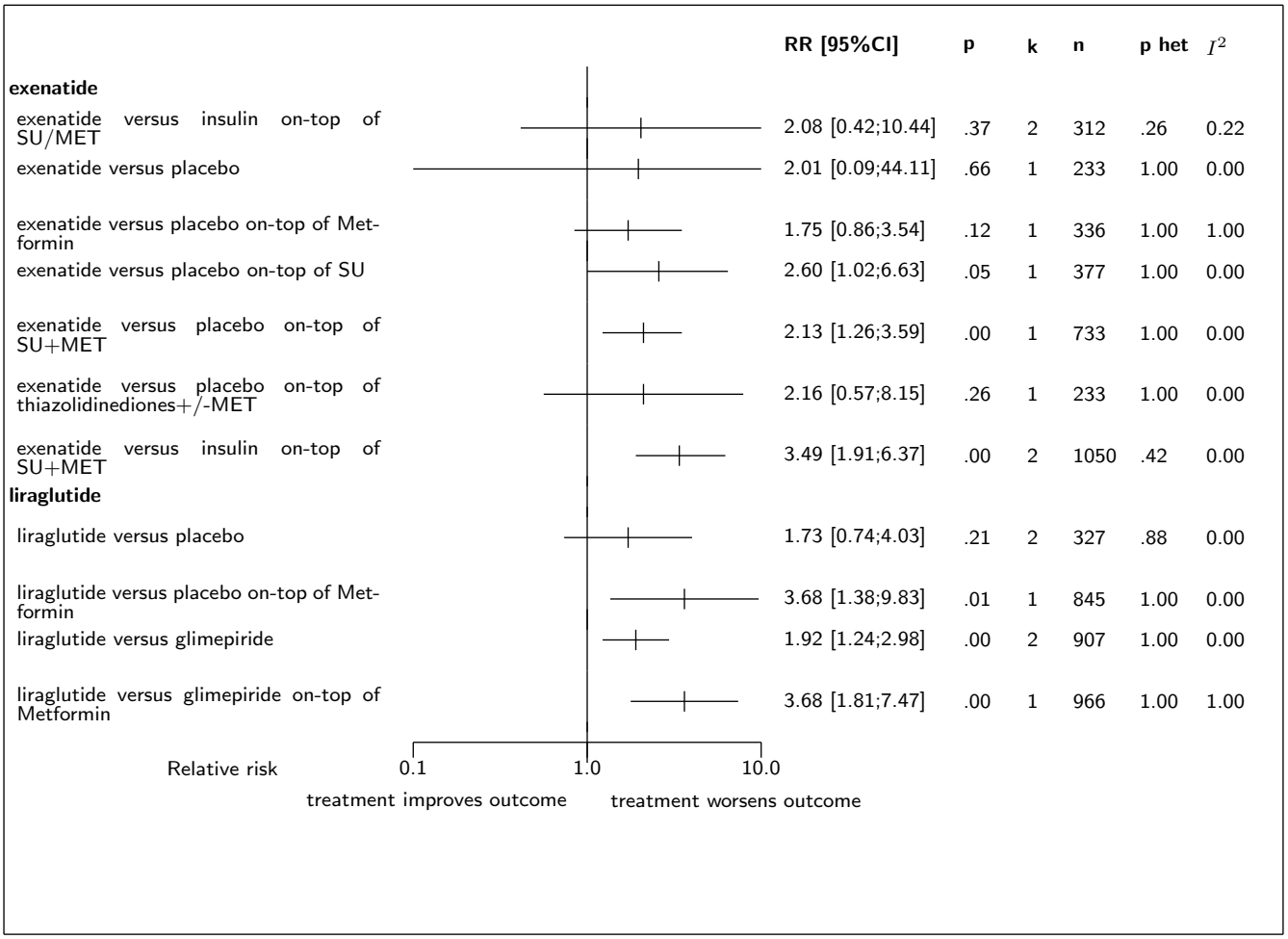
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

Figure 3.4: *Forest's plot for vomiting*



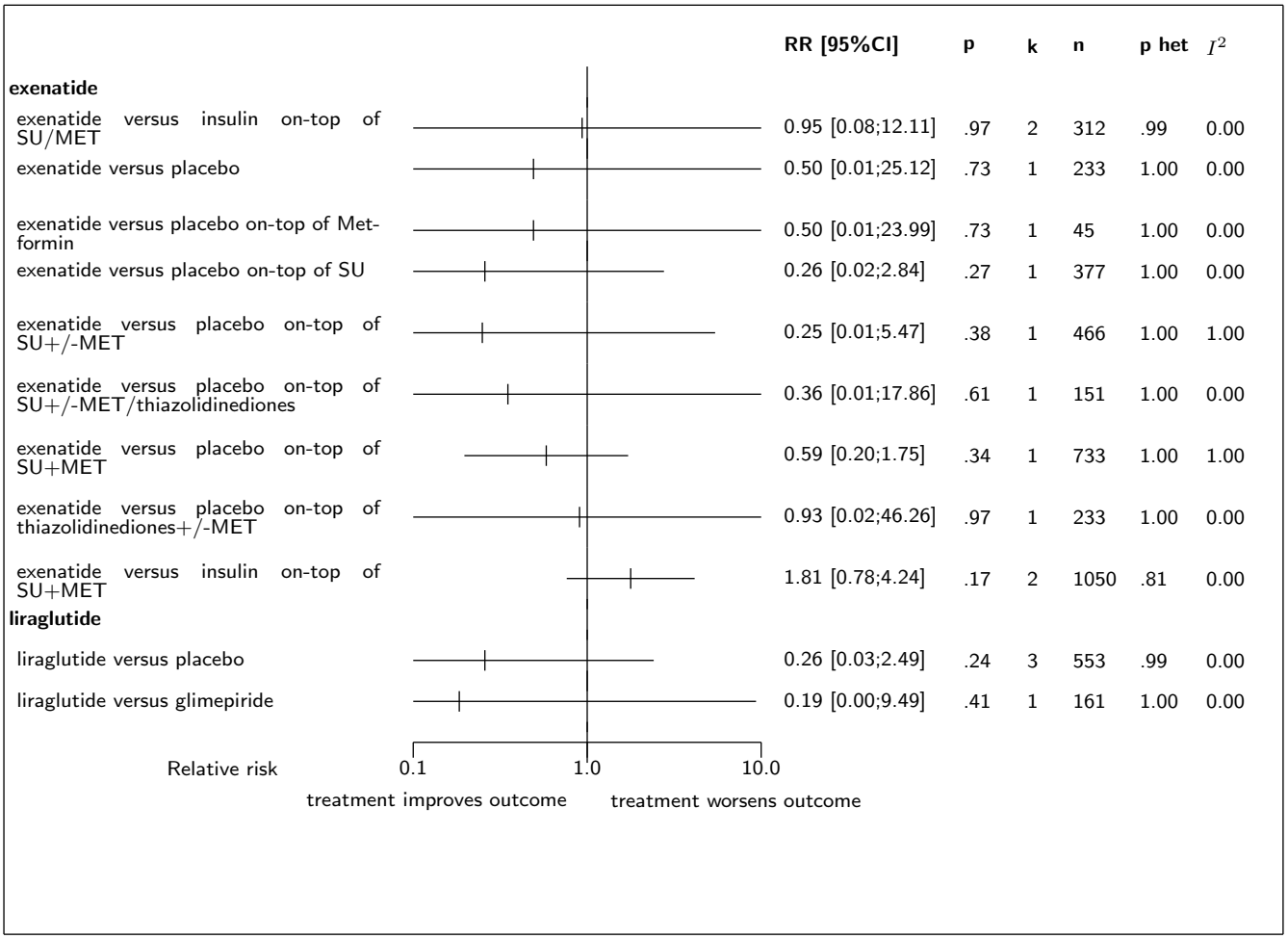
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 3.5: *Forest's plot for diarrhoea*



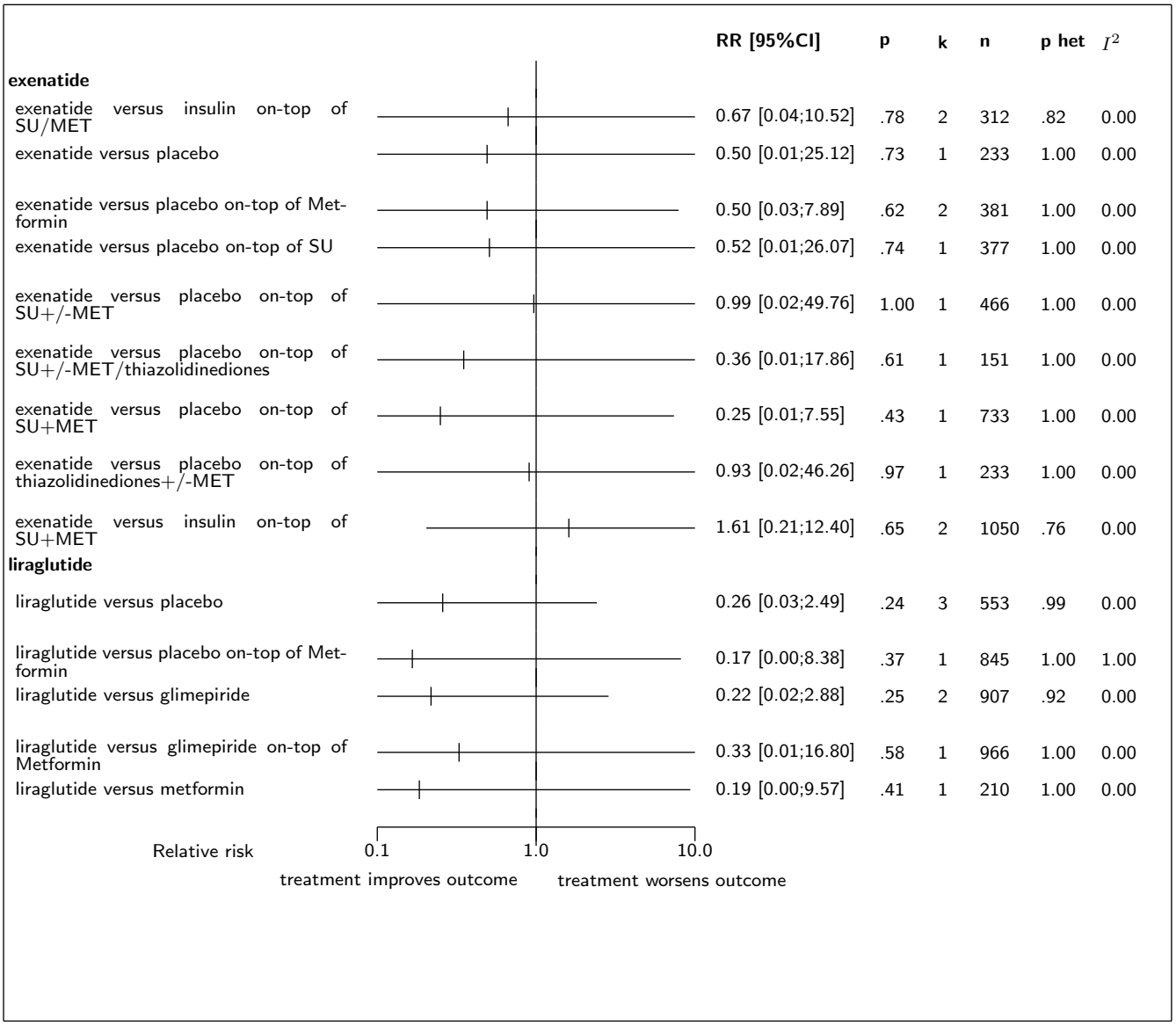
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 3.6: *Forest's plot for cardiovascular events*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 3.7: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

4 Detailed results for exenatide

4.1 Available trials

A total of 12 RCTs which randomized 3936 patients were identified: 2 trials compared exenatide with insulin on-top of SU/MET , it compared exenatide with placebo , 2 trials compared exenatide with placebo on-top of Metformin , it compared exenatide with placebo on-top of SU , it compared exenatide with placebo on-top of SU+/-MET , it compared exenatide with placebo on-top of SU+/-MET/thiazolidinediones , it compared exenatide with placebo on-top of SU+MET , it compared exenatide with placebo on-top of thiazolidinediones+/-MET and 2 trials compared exenatide with insulin on-top of SU+MET.
The average study size was 328 patients (range 45 to 733). The first study was published in 2004, and the last study was published in 2009.
A total of 7 trials were double blind and 4 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 12 trials; 11 trials reported data on nausea; 11 trials reported data on severe hypoglycemia; 10 trials reported data on vomiting; 9 trials reported data on all hypoglycemia; 9 trials reported data on diarrhoea; and 11 trials reported data on cardiovascular events.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of exenatide.

Table 4.1: *Treatment description - Glucagon-like peptide analogs - exenatide*

Trial	Studied treatment	Control treatment
Exenatide versus insulin on-top of SU/MET		
Davis (2007) [?]	Exenatide 20 microg daily	Insulin on-top of sulphonylureas/metformin
	Concomittant treatment: sulphonylureas or metformin	
Barnett (2007) [?]	Exenatide 20 microg daily subcutaneous injection, 10 g/dayfor 4 weeks then 20 g/day for 12weeks, administered twice daily	Insulin titrated to FBG <= 5.6 mmol/l, initiated at 10 IU and increased weekly, four times daily
	Concomittant treatment: sulphonylureas or metformin	
Exenatide versus placebo		
Moretto (2008) [?]	Exenatide 1020 microg daily	Placebo
	Concomittant treatment: None	
Exenatide versus placebo on-top of Metformin		
DeFronzo (2005) [?]	Exenatide 1020 microg daily	Placebo on-top of Metformin
	Concomittant treatment: Metformin	
Kim (2007) [?]	Exenatide 0.82 microg daily	Placebo on-top of metformin
	Concomittant treatment: metformin or None	
Exenatide versus placebo on-top of SU		
Buse (2004) [?]	Exenatide 20 microg daily	Placebo on-top of SU
	Concomittant treatment: SU	

continued...

Trial	Studied treatment	Control treatment
Exenatide versus placebo on-top of SU+/-MET		
Gao (2009) [?]	Exenatide 20 microg daily	Placebo on-top of sulphonylureas+/-metformin
	Concomittant treatment: sulphonylureas+/-metformin	
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones		
CT Register 8683 (0)	Exenatide 51020 microg daily	Placebo on-top of sulphonylureas+/-metformin/thiazolidinediones
	Concomittant treatment: sulphonylureas+/-metformin or TZD	
Exenatide versus placebo on-top of SU+MET		
Kendall (2005) [?]	Exenatide 1020 microg daily	Placebo on-top of sulphonylureas+metformin
	Concomittant treatment: SU+/-metformin	
Exenatide versus placebo on-top of thiazolidinediones+/-MET		
Zinman (2007) [?]	Exenatide 20 microg daily	Placebo on-top of thiazolidinediones+/-metformin
	Concomittant treatment: TZD+/-metformin	
Exenatide versus insulin on-top of SU+MET		
Heine (2005) [?]	Exenatide 20 microg daily	Insulin on-top of sulphonylureas+metformin
	Concomittant treatment: sulphonylureas+/-metformin	
Nauck (2007) [?]	Exenatide 20 microg daily	Insulin on-top of sulphonylureas+metformin
	Concomittant treatment: sulphonylureas+/-metformin	

Table 4.2: *Descriptions of participants - Glucagon-like peptide analogs - exenatide*

Trial	Patients	
Exenatide versus insulin on-top of SU/MET		
Davis (2007) [?]		
Barnett (2007) [?]	**Inclusion criteria:** type 2 diabetes, equal to or more than 30 years of age, receiving treatment with either a stable dose of immediate- or extended-release MET equal to or greater than 1500 mg/day or an optimally effective dose of SFU for 3 months, HbA1c level equal to, or more than, 7.1% and equal to, or less than, 11%, BMI more than 25 kg/m2 and less than 40 kg/m2, stable body weight (not varying by more than 10% for at least 3 months prior to screening)	**Exclusion criteria:**
Exenatide versus placebo		
Moretto (2008) [?]		
Exenatide versus placebo on-top of Metformin		
DeFronzo (2005) [?]	Patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses	
Kim (2007) [?]		
Exenatide versus placebo on-top of SU		

continued...

Trial	Patients
Buse (2004) [?]	Patients with type 2 diabetes failing maximally effective doses of a sulfonylurea as monotherapy
Exenatide versus placebo on-top of SU+/-MET	
Gao (2009) [?]	
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones	
CT Register 8683 (0)	
Exenatide versus placebo on-top of SU+MET	
Kendall (2005) [?]	Patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy
Exenatide versus placebo on-top of thiazolidinediones+/-MET	
Zinman (2007) [?]	
Exenatide versus insulin on-top of SU+MET	
Heine (2005) [?]	
Nauck (2007) [?]	

Table 4.3: *Main patients characteristics - Glucagon-like peptide analogs - exenatide*

Trial	Characteristics
Exenatide versus insulin on-top of SU/MET	
Davis, 2007 [?]	age (year): 53 duration of diabetes (year): 11.0 y BMI: 34.0 hbA1c (%): 8.1
Barnett, 2007 [?]	age (year): 55 women (%): 51% duration of diabetes (year): 7.4 y BMI: 31.1 hbA1c (%): 8.9
Exenatide versus placebo	
Moretto, 2008 [?]	age (year): 54 duration of diabetes (year): 2.0 y BMI: 32.0 hbA1c (%): 7.8
Exenatide versus placebo on-top of Metformin	
DeFronzo, 2005 [?]	age (year): 53 duration of diabetes (year): 5.8 y BMI: 34.0 hbA1c (%): 8.2
Kim, 2007 [?]	age (year): 54 duration of diabetes (year): 5.0 y BMI: 36.0 hbA1c (%): 8.5
Exenatide versus placebo on-top of SU	
Buse, 2004 [?]	age (year): 55 duration of diabetes (year): 6.3 y BMI: 33.3 hbA1c (%): 8.6
Exenatide versus placebo on-top of SU+/-MET	
Gao, 2009 [?]	age (year): NA duration of diabetes (year): NA BMI: NA hbA1c (%): 8.3
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones	
CT Register 8683, 0	age (year): 61 duration of diabetes (year): 11.8 y BMI: 25.1 hbA1c (%): NA
Exenatide versus placebo on-top of SU+MET	
Kendall, 2005 [?]	age (year): 55 duration of diabetes (year): 9.0 y BMI: 34.0 hbA1c (%): 8.5
Exenatide versus placebo on-top of thiazolidinediones+/-MET	
Zinman, 2007 [?]	age (year): 56 duration of diabetes (year): 7.7 y BMI: 34.0 hbA1c (%): 7.9
Exenatide versus insulin on-top of SU+MET	
Heine, 2005 [?]	age (year): 59 duration of diabetes (year): 9.5 y BMI: 31.3 hbA1c (%): 8.2
Nauck, 2007 [?]	age (year): 59 duration of diabetes (year): 9.9 y BMI: 30.4 hbA1c (%): 8.6

Table 4.4: *Design and methodological quality of trials - Glucagon-like peptide analogs - exenatide*

Trial	Design	Duration	Centre	Primary endpoint
Exenatide versus insulin on-top of SU/MET				
Davis, 2007 [?] n=49	parallel groups open	16 weeks		
Barnett, 2007 [?] n=263	Cross over open exploratory trial	16 weeks	NA 26 centres	HbA1c change
Exenatide versus placebo				
Moretto, 2008 [?] n=233	parallel groups double blind	24 weeks		
Exenatide versus placebo on-top of Metformin				
DeFronzo, 2005 [?] n=336	parallel groups double blind	30 weeks		
Kim, 2007 [?] n=45	parallel groups double blind	15 weeks		
Exenatide versus placebo on-top of SU				
Buse, 2004 [?] n=377	parallel groups double blind (not adequate)	30 weeks		
Exenatide versus placebo on-top of SU+/-MET				
Gao, 2009 [?] n=466	parallel groups double blind	16 weeks		
Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones				
CT Register 8683, 0 n=151	parallel groups not reported	12 weeks		
Exenatide versus placebo on-top of SU+MET				
Kendall, 2005 [?] n=733	parallel groups double blind	30 weeks		
Exenatide versus placebo on-top of thiazolidinediones+/-MET				
Zinman, 2007 [?] n=233	parallel groups double blind	16 weeks		
Exenatide versus insulin on-top of SU+MET				
Heine, 2005 [?] n=549	parallel groups open	26 weeks		
Nauck, 2007 [?] n=501	parallel groups open	52 weeks		

4.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Exenatide versus insulin on-top of SU/MET

Exenatide versus placebo

Exenatide versus placebo on-top of Metformin

Exenatide versus placebo on-top of SU

Exenatide versus placebo on-top of SU+/-MET

Exenatide versus placebo on-top of SU+/-MET/thiazolidinediones

Exenatide versus placebo on-top of SU+MET

Exenatide versus placebo on-top of thiazolidinediones+/-MET

Exenatide versus insulin on-top of SU+MET

Table 4.5: *Results details - Glucagon-like peptide analogs - exenatide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
exenatide versus insulin on-top of SU/MET						
all hypoglycemia	RR=0.73	[0.42;1.27]	0.2663	0.2069 (I^2=0.37)	2	312
severe hypoglycemia	RR=0.35	[0.04;3.25]	0.3558	0.4235 (I^2=0.00)	2	312
nausea	RR=7.91	[2.35;26.60]	0.0000	0.1411 (I^2=0.54)	2	312
vomiting	RR=3.21	[1.23;8.38]	0.0171	0.8324 (I^2=0.00)	2	312
diarrhoea	RR=2.08	[0.42;10.44]	0.3723	0.2566 (I^2=0.22)	2	312
cardiovascular events	RR=0.95	[0.08;12.11]	0.9713	0.9885 (I^2=0.00)	2	312
all cause death	RR=0.67	[0.04;10.52]	0.7761	0.8155 (I^2=0.00)	2	312
exenatide versus placebo						
all hypoglycemia	RR=3.52	[0.44;28.13]	0.2349	1.0000 (I^2=0.00)	1	233
severe hypoglycemia	RR=0.50	[0.01;25.12]	0.7307	1.0000 (I^2=0.00)	1	233
nausea	RR=12.08	[0.72;201.79]	0.0829	1.0000 (I^2=1.00)	1	233
vomiting	RR=6.04	[0.34;106.74]	0.2198	1.0000 (I^2=0.00)	1	233
diarrhoea	RR=2.01	[0.09;44.11]	0.6569	1.0000 (I^2=0.00)	1	233
cardiovascular events	RR=0.50	[0.01;25.12]	0.7307	1.0000 (I^2=0.00)	1	233
all cause death	RR=0.50	[0.01;25.12]	0.7307	1.0000 (I^2=0.00)	1	233
exenatide versus placebo on-top of Metformin						
all hypoglycemia	RR=1.08	[0.43;2.70]	0.8723	0.3454 (I^2=0.00)	2	381
severe hypoglycemia	RR=0.50	[0.03;7.89]	0.6249	0.9962 (I^2=0.00)	2	381
nausea	RR=1.81	[1.26;2.62]	0.0000	0.5128 (I^2=0.00)	2	381
vomiting	RR=2.80	[1.03;7.59]	0.0426	0.3664 (I^2=0.00)	2	381

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
diarrhoea	RR=1.75	[0.86;3.54]	0.1225	1.0000 (I^2=1.00)	1	336
cardiovascular events	RR=0.50	[0.01;23.99]	0.7256	1.0000 (I^2=0.00)	1	45
all cause death	RR=0.50	[0.03;7.89]	0.6249	0.9962 (I^2=0.00)	2	381
exenatide versus placebo on-top of SU						
all hypoglycemia	RR=7.02	[2.60;18.96]	0.0000	1.0000 (I^2=0.00)	1	377
severe hypoglycemia	RR=0.52	[0.01;26.07]	0.7434	1.0000 (I^2=0.00)	1	377
nausea	RR=6.65	[3.49;12.66]	0.0000	1.0000 (I^2=0.00)	1	377
vomiting	RR=5.03	[1.56;16.19]	0.0068	1.0000 (I^2=0.00)	1	377
diarrhoea	RR=2.60	[1.02;6.63]	0.0454	1.0000 (I^2=0.00)	1	377
cardiovascular events	RR=0.26	[0.02;2.84]	0.2696	1.0000 (I^2=0.00)	1	377
all cause death	RR=0.52	[0.01;26.07]	0.7434	1.0000 (I^2=0.00)	1	377
exenatide versus placebo on-top of SU+/-MET						
all hypoglycemia	RR=3.92	[2.52;6.10]	0.0000	1.0000 (I^2=0.00)	1	466
severe hypoglycemia	RR=1.98	[0.18;21.72]	0.5751	1.0000 (I^2=0.00)	1	466
cardiovascular events	RR=0.25	[0.01;5.47]	0.3768	1.0000 (I^2=1.00)	1	466
all cause death	RR=0.99	[0.02;49.76]	0.9966	1.0000 (I^2=0.00)	1	466
exenatide versus placebo on-top of SU+/-MET/thiazolidinediones						
severe hypoglycemia	RR=0.36	[0.01;17.86]	0.6083	1.0000 (I^2=0.00)	1	151
nausea	RR=14.41	[0.89;233.03]	0.0602	1.0000 (I^2=0.00)	1	151
cardiovascular events	RR=0.36	[0.01;17.86]	0.6083	1.0000 (I^2=0.00)	1	151
all cause death	RR=0.36	[0.01;17.86]	0.6083	1.0000 (I^2=0.00)	1	151
exenatide versus placebo on-top of SU+MET						
all hypoglycemia	RR=1.87	[1.30;2.70]	0.0000	1.0000 (I^2=0.00)	1	733
severe hypoglycemia	RR=1.02	[0.03;30.20]	0.9925	1.0000 (I^2=0.00)	1	733
nausea	RR=2.12	[1.63;2.76]	0.0000	1.0000 (I^2=0.00)	1	733
vomiting	RR=3.19	[1.72;5.91]	0.0000	1.0000 (I^2=0.00)	1	733
diarrhoea	RR=2.13	[1.26;3.59]	0.0047	1.0000 (I^2=0.00)	1	733
cardiovascular events	RR=0.59	[0.20;1.75]	0.3427	1.0000 (I^2=1.00)	1	733
all cause death	RR=0.25	[0.01;7.55]	0.4285	1.0000 (I^2=0.00)	1	733
exenatide versus placebo on-top of thiazolidinediones+/-MET						
all hypoglycemia	RR=1.50	[0.65;3.49]	0.3422	1.0000 (I^2=0.00)	1	233
nausea	RR=2.61	[1.60;4.27]	0.0000	1.0000 (I^2=0.00)	1	233
vomiting	RR=14.81	[2.00;109.86]	0.0084	1.0000 (I^2=0.00)	1	233
diarrhoea	RR=2.16	[0.57;8.15]	0.2557	1.0000 (I^2=0.00)	1	233
cardiovascular events	RR=0.93	[0.02;46.26]	0.9691	1.0000 (I^2=0.00)	1	233
all cause death	RR=0.93	[0.02;46.26]	0.9691	1.0000 (I^2=0.00)	1	233
exenatide versus insulin on-top of SU+MET						
severe hypoglycemia	RR=0.95	[0.26;3.48]	0.9388	0.9869 (I^2=0.00)	2	1050
nausea	RR=19.30	[1.68;221.62]	0.0174	0.0138 (I^2=0.84)	2	1050
vomiting	RR=4.65	[2.84;7.61]	0.0000	0.9943 (I^2=0.00)	2	1050
diarrhoea	RR=3.49	[1.91;6.37]	0.0000	0.4208 (I^2=0.00)	2	1050
cardiovascular events	RR=1.81	[0.78;4.24]	0.1692	0.8104 (I^2=0.00)	2	1050
all cause death	RR=1.61	[0.21;12.40]	0.6484	0.7560 (I^2=0.00)	2	1050

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 4.1: *Forest's plot for all hypoglycemia*

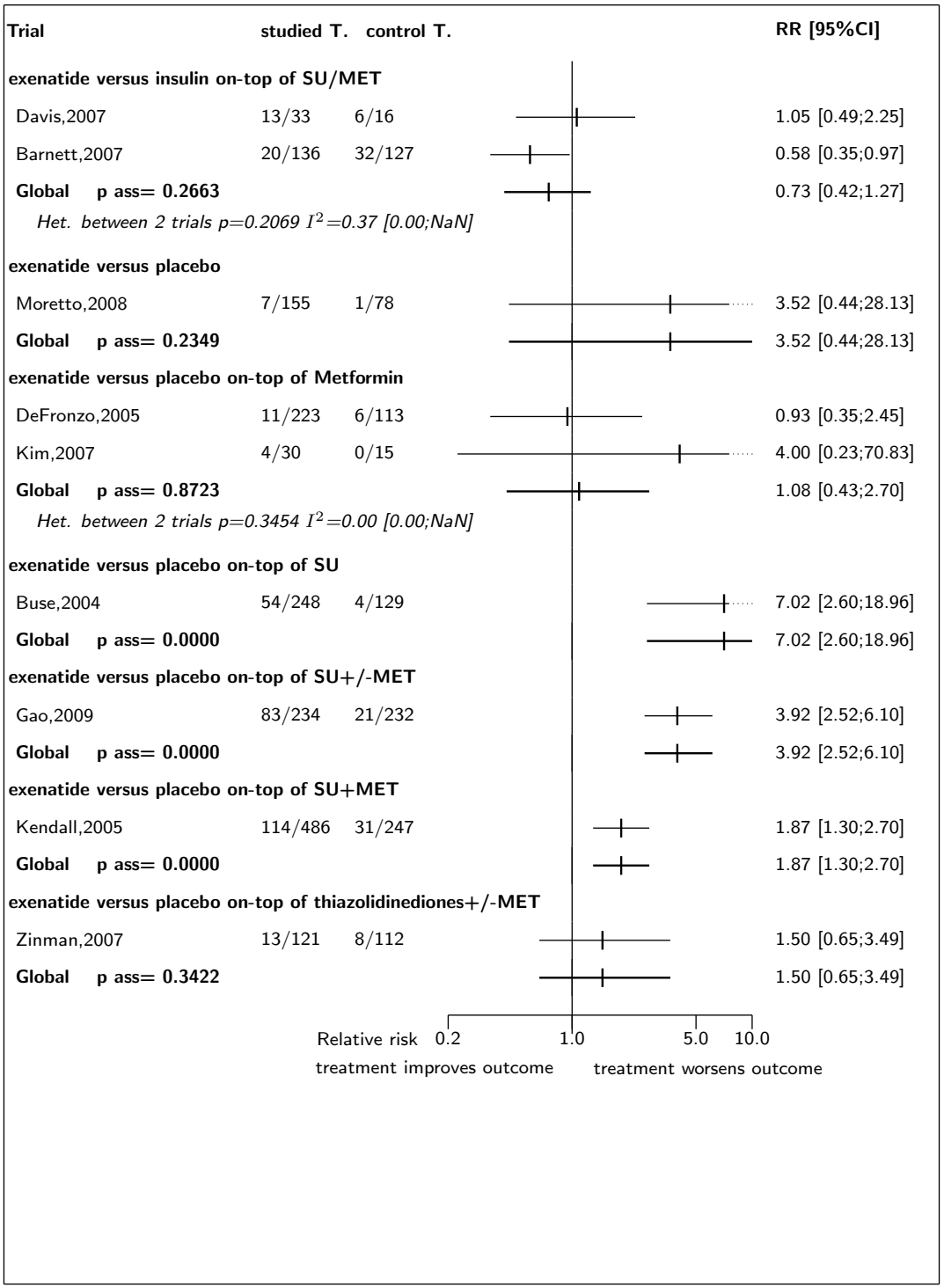


Figure 4.2: *Forest's plot for severe hypoglycemia*

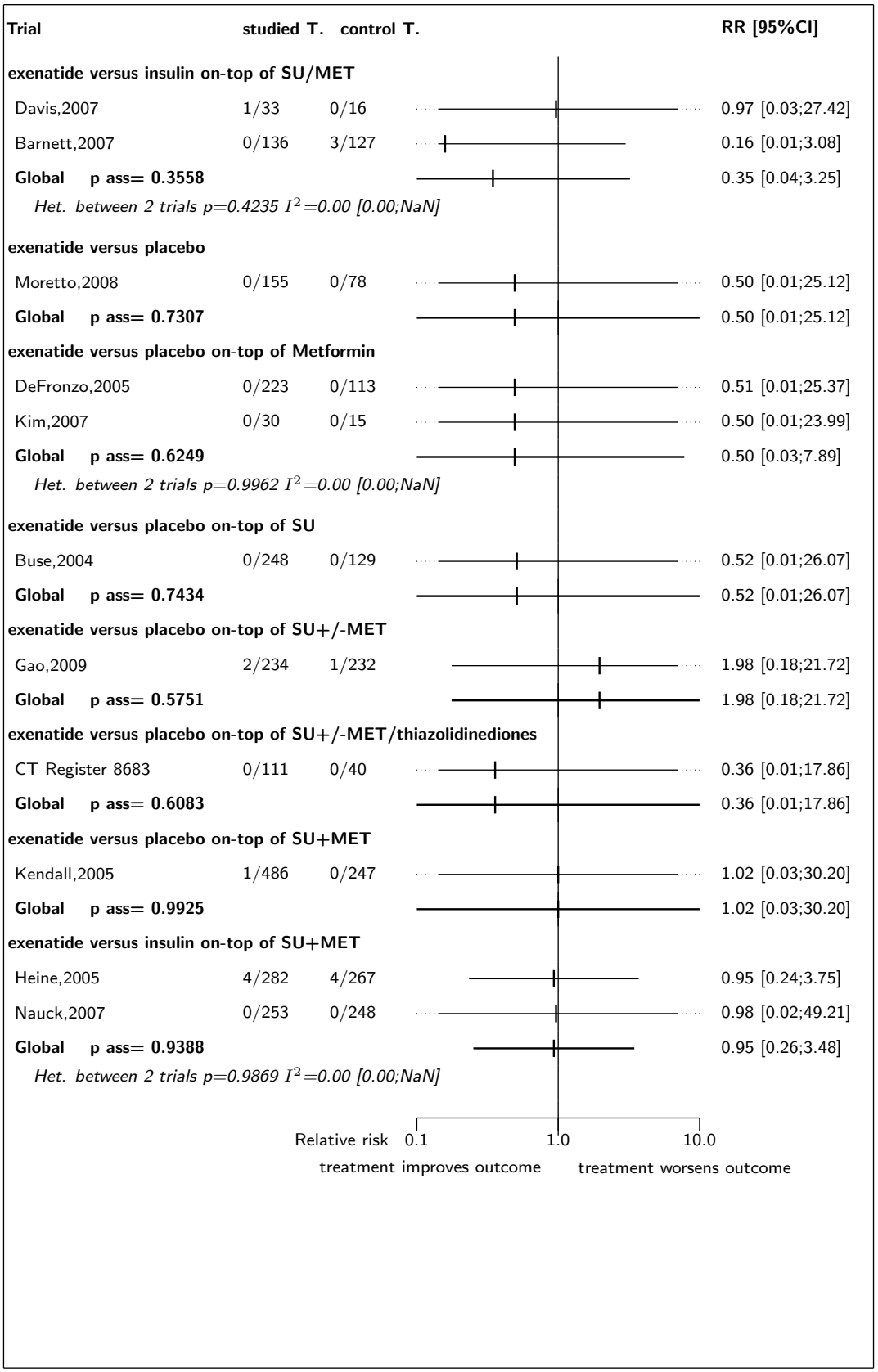


Figure 4.3: *Forest's plot for nausea*

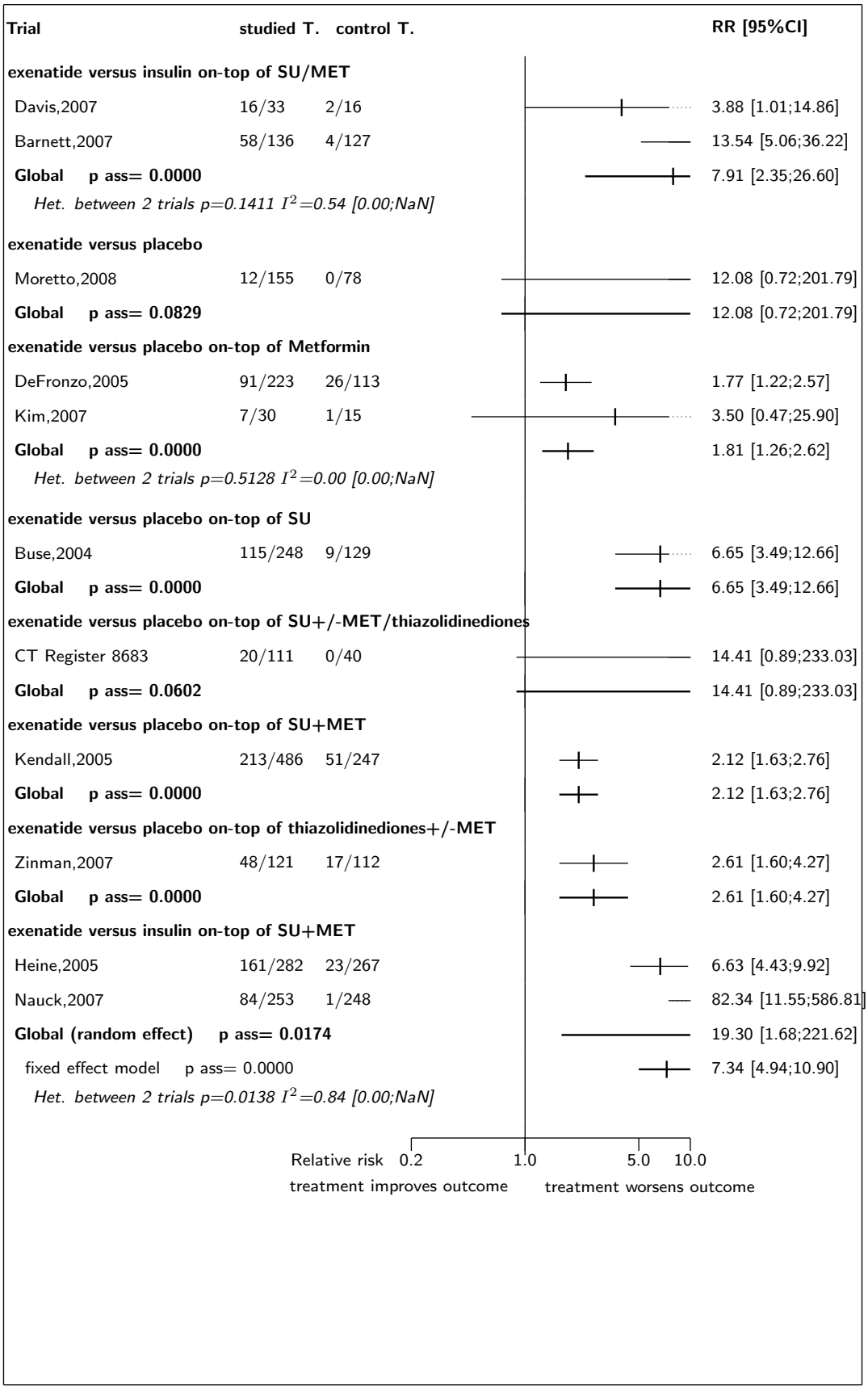


Figure 4.4: *Forest's plot for vomiting*

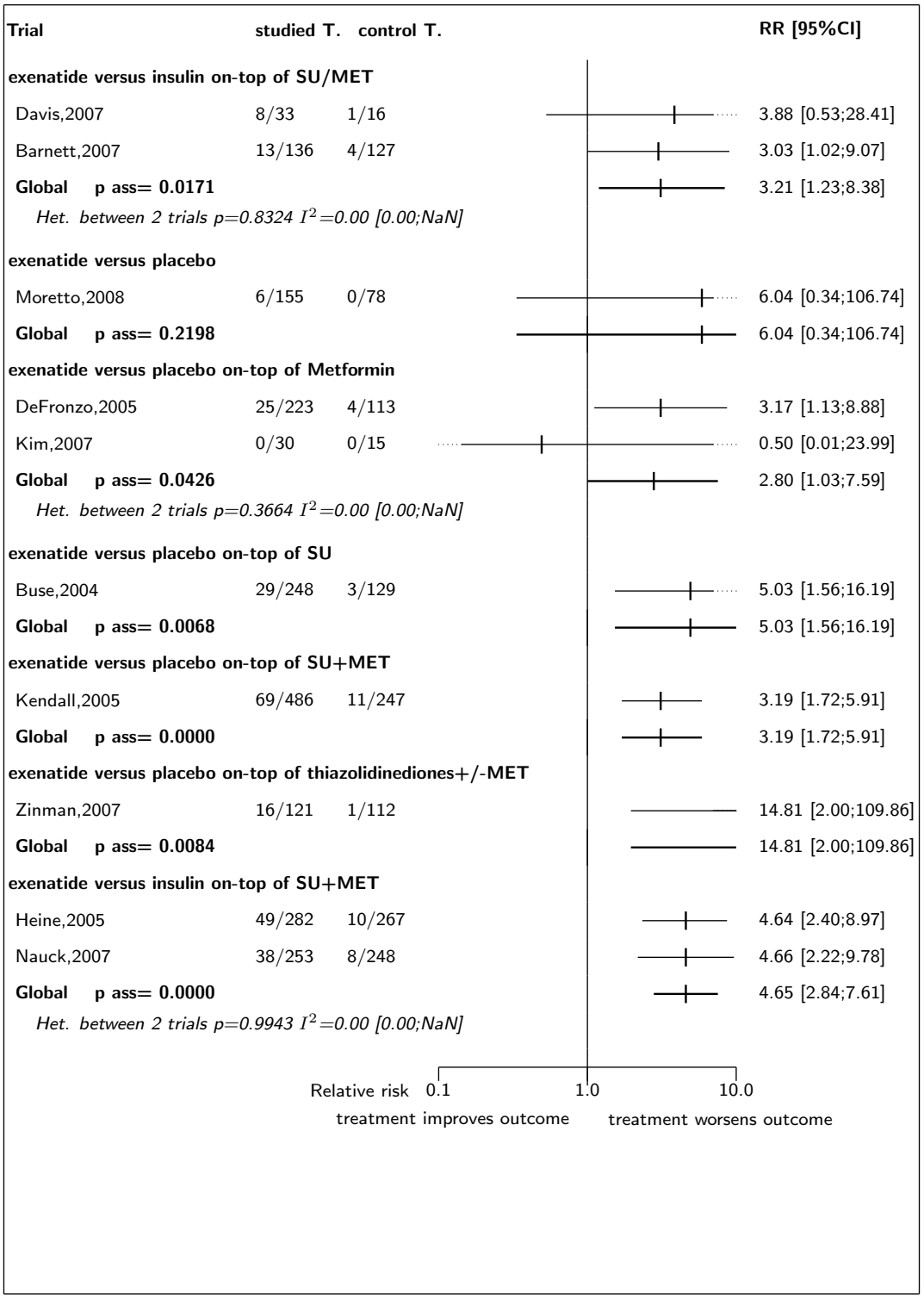


Figure 4.5: *Forest's plot for diarrhoea*

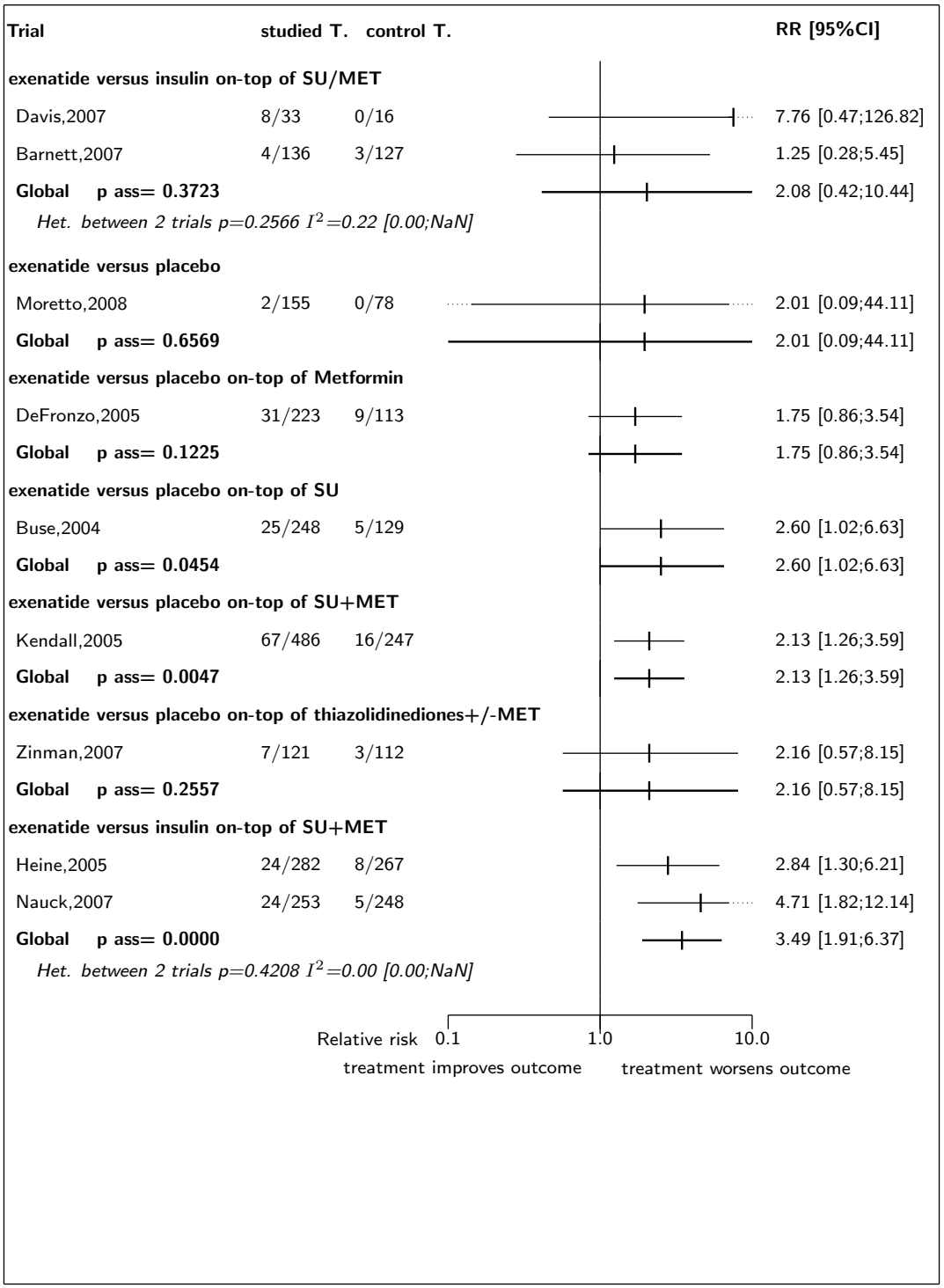


Figure 4.6: *Forest's plot for cardiovascular events*

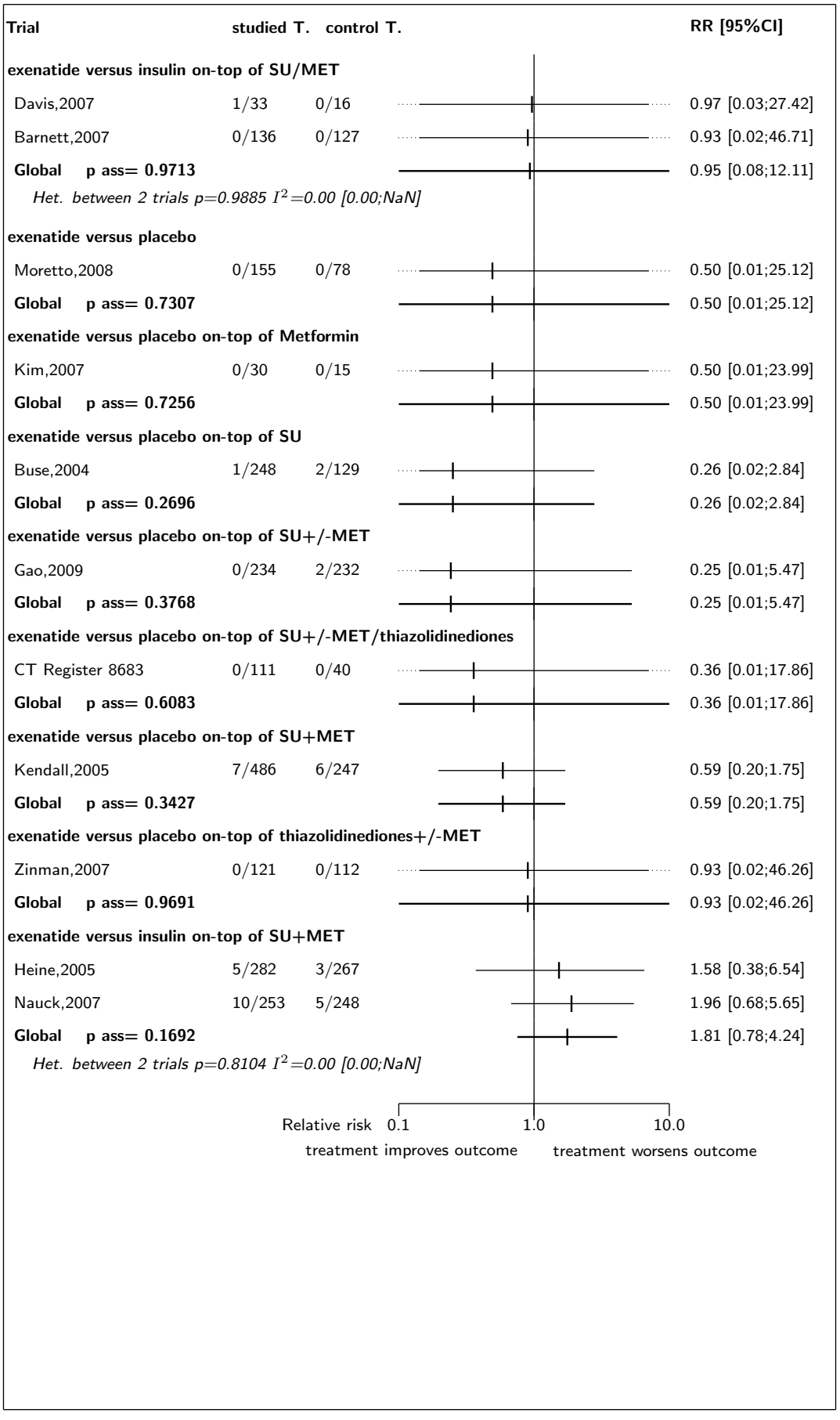
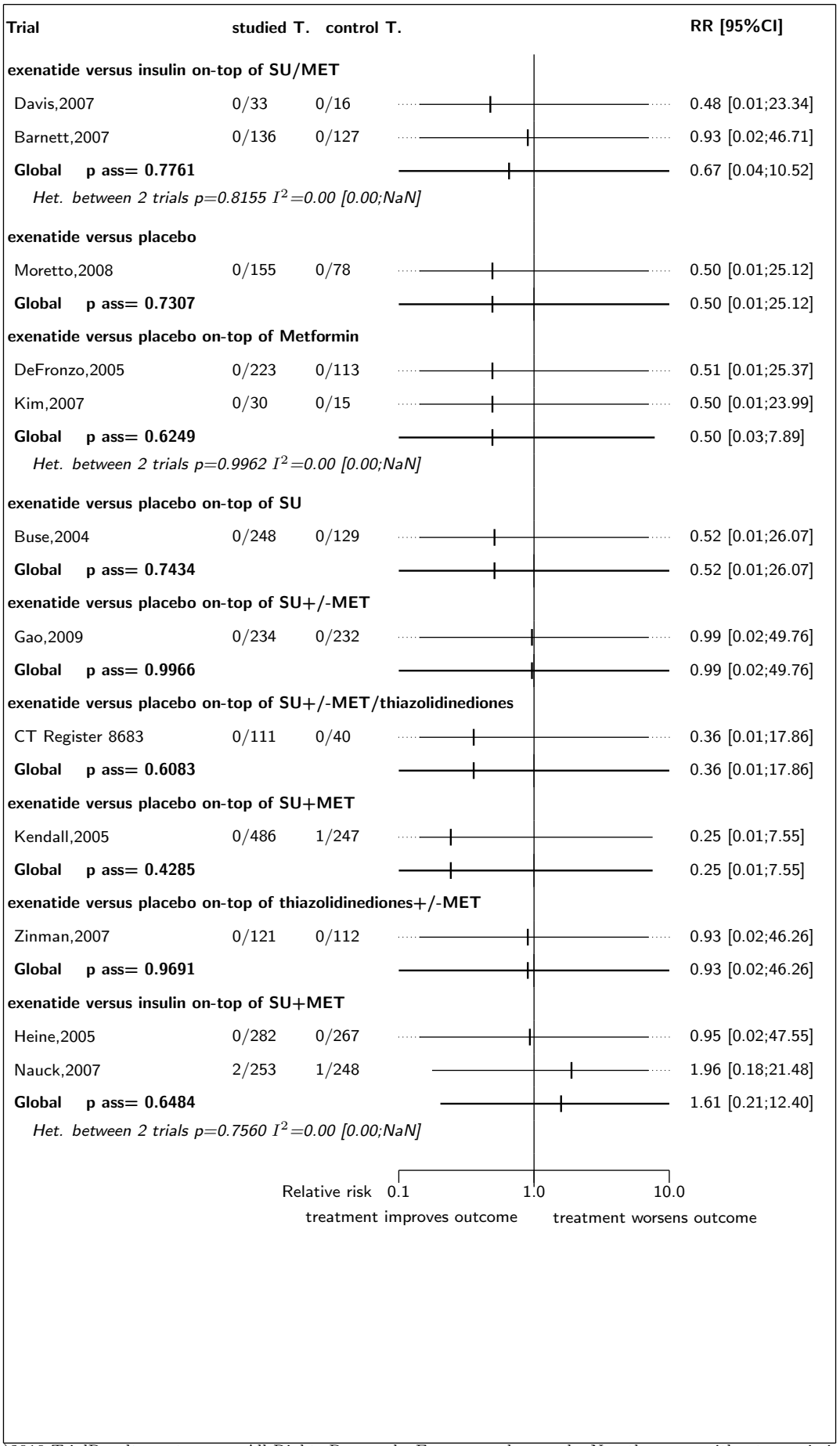


Figure 4.7: *Forest's plot for all cause death*



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5 Detailed results for liraglutide

5.1 Available trials

A total of 12 RCTs which randomized 5635 patients were identified: 3 trials compared liraglutide with placebo , it compared liraglutide with placebo on-top of Metformin , it compared liraglutide with placebo on-top of SU , it compared liraglutide with placebo on-top of SU+MET , it compared liraglutide with placebo on-top of thiazolidinediones+MET , it compared liraglutide with glargine on-top of SU+MET , 2 trials compared liraglutide with glimepiride , it compared liraglutide with glimepiride on-top of Metformin and it compared liraglutide with metformin.
The average study size was 469 patients (range 161 to 966). The first study was published in 2004, and the last study was published in 2009.
A total of 6 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Severe hypoglycemia data was reported in 10 trials; 8 trials reported data on all hypoglycemia; 8 trials reported data on all cause death; 8 trials reported data on nausea; 7 trials reported data on vomiting; 6 trials reported data on diarrhoea; and 4 trials reported data on cardiovascular events.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of liraglutide.

Table 5.1: *Treatment description - Glucagon-like peptide analogs - liraglutide*

Trial	Studied treatment	Control treatment
Liraglutide versus placebo		
Vilsboll (2008) [**?**]	Liraglutide 0.651.90 mg daily **Concomittant treatment:** None	Placebo
Seino (2008) [**?**]	Liraglutide 0.10.9 mg daily **Concomittant treatment:** None	Placebo
Madsbad (vs placebo) (2004) [**?**]	Liraglutide 0.0450.75 mg daily **Concomittant treatment:** None	Placebo
Liraglutide versus placebo on-top of Metformin		
Nauck (vs placebo) (2009) [**?**]	Liraglutide 1.21.8 mg daily **Concomittant treatment:** Metformin	Placebo on-top of Metformin
Liraglutide versus placebo on-top of SU		
LEAD-1 (0)	Liraglutide 1.21.8 mg daily **Concomittant treatment:** sulphonylureas	Placebo on-top of sulphonylureas
Liraglutide versus placebo on-top of SU+MET		
LEAD-5 (vs placebo) (0)	Liraglutide 1.8 mg daily **Concomittant treatment:** sulphonylureas+/-metformin	Placebo on-top of sulphonylureas+metformin
Liraglutide versus placebo on-top of thiazolidinediones+MET		

continued...

Trial	Studied treatment	Control treatment
LEAD-4 (0)	Liraglutide 1.21.8 mg daily	Placebo on-top of thiazolidinediones+metformin
	Concomittant treatment: TZD+/-metformin	
Liraglutide versus glargine on-top of SU+MET		
LEAD-5 (vs Glargine) (0)	Liraglutide 1.8 mg daily	Glargine on-top of sulphonylureas+metformin
	Concomittant treatment: sulphonylureas+/-metformin	
Liraglutide versus glimepiride		
Garber (2009) [?]	Liraglutide 1.21.8 mg daily	Glimepiride
	Concomittant treatment: None	
Madsbad (vs Glimepiride) (2004) [?]	Liraglutide 0.0450.75 mg daily	Glimepiride
	Concomittant treatment: None	
Liraglutide versus glimepiride on-top of Metformin		
Nauck (vs glimepiride) (2009) [?]	Liraglutide 1.21.8 mg daily	Glimepiride on-top of Metformin
	Concomittant treatment: Metformin	
Liraglutide versus metformin		
Feinglos (2005) [?]	Liraglutide 0.0450.75 mg daily	Metformin
	Concomittant treatment: None	

Table 5.2: *Descriptions of participants - Glucagon-like peptide analogs - liraglutide*

Trial	Patients
Liraglutide versus placebo	
Vilsboll (2008) [?]	
Seino (2008) [?]	
Madsbad (vs placebo) (2004) [?]	
Liraglutide versus placebo on-top of Metformin	
Nauck (vs placebo) (2009) [?]	
Liraglutide versus placebo on-top of SU	
LEAD-1 (0)	
Liraglutide versus placebo on-top of SU+MET	
LEAD-5 (vs placebo) (0)	
Liraglutide versus placebo on-top of thiazolidinediones+MET	
LEAD-4 (0)	
Liraglutide versus glargine on-top of SU+MET	
LEAD-5 (vs Glargine) (0)	
Liraglutide versus glimepiride	

continued...

Trial	Patients
Garber (2009) [?]	
Madsbad (vs Glimepiride) (2004) [?]	
Liraglutide versus glimepiride on-top of Metformin	
Nauck (vs glimepiride) (2009) [?]	
Liraglutide versus metformin	
Feinglos (2005) [?]	

Table 5.3: *Main patients characteristics - Glucagon-like peptide analogs - liraglutide*

Trial	Characteristics
Liraglutide versus placebo	
Vilsboll, 2008 [**?**]	age (year): 55 duration of diabetes (year): 5.0 y BMI: 30.0 hbA1c (%): 8.3
Seino, 2008 [**?**]	age (year): 57 duration of diabetes (year): 8.0 y BMI: 23.9 hbA1c (%): 8.3
Madsbad (vs placebo), 2004 [**?**]	age (year): 57 duration of diabetes (year): 4.5 y BMI: 30.4 hbA1c (%): 7.5
Liraglutide versus placebo on-top of Metformin	
Nauck (vs placebo), 2009 [**?**]	age (year): 57 duration of diabetes (year): 7.9 y BMI: 31.0 hbA1c (%): 8.4
Liraglutide versus placebo on-top of SU	
LEAD-1, 0	age (year): 56 duration of diabetes (year): 7.9 y BMI: 30.0 hbA1c (%): 8.4
Liraglutide versus placebo on-top of SU+MET	
LEAD-5 (vs placebo), 0	age (year): 57 duration of diabetes (year): 9.4 y BMI: 30.5 hbA1c (%): 8.2
Liraglutide versus placebo on-top of thiazolidinediones+MET	
LEAD-4, 0	age (year): 55 duration of diabetes (year): 9.2 y BMI: 33.5 hbA1c (%): 8.5
Liraglutide versus glargine on-top of SU+MET	
LEAD-5 (vs Glargine), 0	age (year): 57 duration of diabetes (year): 9.4 y BMI: 30.5 hbA1c (%): 8.2
Liraglutide versus glimepiride	
Garber, 2009 [**?**]	age (year): 53 duration of diabetes (year): 5.4 y BMI: 33.1 hbA1c (%): 8.3
Madsbad (vs Glimepiride), 2004 [**?**]	age (year): 57 duration of diabetes (year): 4.5 y BMI: 30.4 hbA1c (%): 7.5
Liraglutide versus glimepiride on-top of Metformin	
Nauck (vs glimepiride), 2009 [**?**]	age (year): 57 duration of diabetes (year): 7.4 y BMI: 31.0 hbA1c (%): 8.4
Liraglutide versus metformin	
Feinglos, 2005 [**?**]	age (year): 53 duration of diabetes (year): 4.7 y BMI: 34.5 hbA1c (%): 7.0

Table 5.4: *Design and methodological quality of trials - Glucagon-like peptide analogs - liraglutide*

Trial	Design	Duration	Centre	Primary endpoint
Liraglutide versus placebo				
Vilsboll, 2008 [?] n=163	parallel groups double blind (not adequate)	14 weeks		
Seino, 2008 [?] n=226	parallel groups double blind	14 weeks		
Madsbad (vs placebo), 2004 [?] n=164	parallel groups open	12 weeks		
Liraglutide versus placebo on-top of Metformin				
Nauck (vs placebo), 2009 [?] n=845	parallel groups double blind	26 weeks		
Liraglutide versus placebo on-top of SU				
LEAD-1, 0 n=810	parallel groups not reported	26 weeks		
Liraglutide versus placebo on-top of SU+MET				
LEAD-5 (vs placebo), 0 n=349	parallel groups not reported	26 weeks		
Liraglutide versus placebo on-top of thiazolidinediones+MET				
LEAD-4, 0 n=533	parallel groups not reported	26 weeks		
Liraglutide versus glargine on-top of SU+MET				
LEAD-5 (vs Glargine), 0 n=462	parallel groups not reported	26 weeks		
Liraglutide versus glimepiride				
Garber, 2009 [?] n=746	parallel groups double blind	52 weeks		
Madsbad (vs Glimepiride), 2004 [?] n=161	parallel groups open	12 weeks		
Liraglutide versus glimepiride on-top of Metformin				
Nauck (vs glimepiride), 2009 [?] n=966	parallel groups double blind	26 weeks		
Liraglutide versus metformin				
Feinglos, 2005 [?] n=210	parallel groups double blind (not adequate)	12 weeks		

5.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Liraglutide versus placebo

Liraglutide versus placebo on-top of Metformin

Liraglutide versus placebo on-top of SU

Liraglutide versus placebo on-top of SU+MET

Liraglutide versus placebo on-top of thiazolidinediones+MET

Liraglutide versus glargine on-top of SU+MET

Liraglutide versus glimepiride

Liraglutide versus glimepiride on-top of Metformin

Liraglutide versus metformin

Table 5.5: *Results details - Glucagon-like peptide analogs - liraglutide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
liraglutide versus placebo						
all hypoglycemia	RR=0.34	[0.04;2.87]	0.3201	0.9804 (I^2=0.00)	3	553
severe hypoglycemia	RR=0.26	[0.03;2.49]	0.2431	0.9891 (I^2=0.00)	3	553
nausea	RR=2.93	[0.38;22.40]	0.3010	1.0000 (I^2=0.00)	1	163
vomiting	RR=1.84	[0.23;14.75]	0.5650	0.7408 (I^2=0.00)	2	327
diarrhoea	RR=1.73	[0.74;4.03]	0.2072	0.8763 (I^2=0.00)	2	327
cardiovascular events	RR=0.26	[0.03;2.49]	0.2431	0.9891 (I^2=0.00)	3	553
all cause death	RR=0.26	[0.03;2.49]	0.2431	0.9891 (I^2=0.00)	3	553
liraglutide versus placebo on-top of Metformin						
all hypoglycemia	RR=0.92	[0.32;2.62]	0.8748	1.0000 (I^2=0.00)	1	845
severe hypoglycemia	RR=0.17	[0.00;8.38]	0.3705	1.0000 (I^2=1.00)	1	845
nausea	RR=2.31	[1.55;3.44]	0.0000	1.0000 (I^2=0.00)	1	845
vomiting	RR=7.35	[1.02;52.88]	0.0474	1.0000 (I^2=0.00)	1	845
diarrhoea	RR=3.68	[1.38;9.83]	0.0095	1.0000 (I^2=0.00)	1	845
all cause death	RR=0.17	[0.00;8.38]	0.3705	1.0000 (I^2=1.00)	1	845
liraglutide versus placebo on-top of SU						
severe hypoglycemia	RR=0.33	[0.01;9.81]	0.5225	1.0000 (I^2=0.00)	1	810
nausea	RR=4.30	[1.06;17.42]	0.0409	1.0000 (I^2=0.00)	1	810
liraglutide versus placebo on-top of SU+MET						
nausea	RR=4.14	[1.50;11.43]	0.0061	1.0000 (I^2=0.00)	1	349
liraglutide versus placebo on-top of thiazolidinediones+MET						

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
severe hypoglycemia	RR=0.50	[0.01;24.95]	0.7265	1.0000 (I^2=0.00)	1	533
liraglutide versus glargine on-top of SU+MET						
nausea	RR=10.76	[3.34;34.64]	0.0000	1.0000 (I^2=0.00)	1	462
liraglutide versus glimepiride						
all hypoglycemia	RR=0.19	[0.02;1.50]	0.1150	0.0490 (I^2=0.74)	2	907
severe hypoglycemia	RR=0.31	[0.02;4.90]	0.4047	0.7361 (I^2=0.00)	2	907
nausea	RR=3.30	[2.14;5.08]	0.0000	1.0000 (I^2=0.00)	1	746
vomiting	RR=1.90	[0.42;8.71]	0.4073	0.1529 (I^2=0.51)	2	907
diarrhoea	RR=1.92	[1.24;2.98]	0.0034	0.9995 (I^2=0.00)	2	907
cardiovascular events	RR=0.19	[0.00;9.49]	0.4075	1.0000 (I^2=0.00)	1	161
all cause death	RR=0.22	[0.02;2.88]	0.2502	0.9224 (I^2=0.00)	2	907
liraglutide versus glimepiride on-top of Metformin						
all hypoglycemia	RR=0.18	[0.11;0.29]	0.0000	1.0000 (I^2=0.00)	1	966
severe hypoglycemia	RR=0.33	[0.01;16.80]	0.5835	1.0000 (I^2=0.00)	1	966
nausea	RR=2.31	[1.73;3.08]	0.0000	1.0000 (I^2=0.00)	1	966
vomiting	RR=7.35	[1.80;30.11]	0.0055	1.0000 (I^2=0.00)	1	966
diarrhoea	RR=3.68	[1.81;7.47]	0.0000	1.0000 (I^2=1.00)	1	966
all cause death	RR=0.33	[0.01;16.80]	0.5835	1.0000 (I^2=0.00)	1	966
liraglutide versus metformin						
all hypoglycemia	RR=0.48	[0.10;2.39]	0.3721	1.0000 (I^2=1.00)	1	210
severe hypoglycemia	RR=0.19	[0.00;9.57]	0.4090	1.0000 (I^2=0.00)	1	210
nausea	RR=0.68	[0.15;3.12]	0.6157	1.0000 (I^2=0.00)	1	210
vomiting	RR=0.77	[0.09;6.70]	0.8150	1.0000 (I^2=0.00)	1	210
all cause death	RR=0.19	[0.00;9.57]	0.4090	1.0000 (I^2=0.00)	1	210

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 5.1: *Forest's plot for all hypoglycemia*

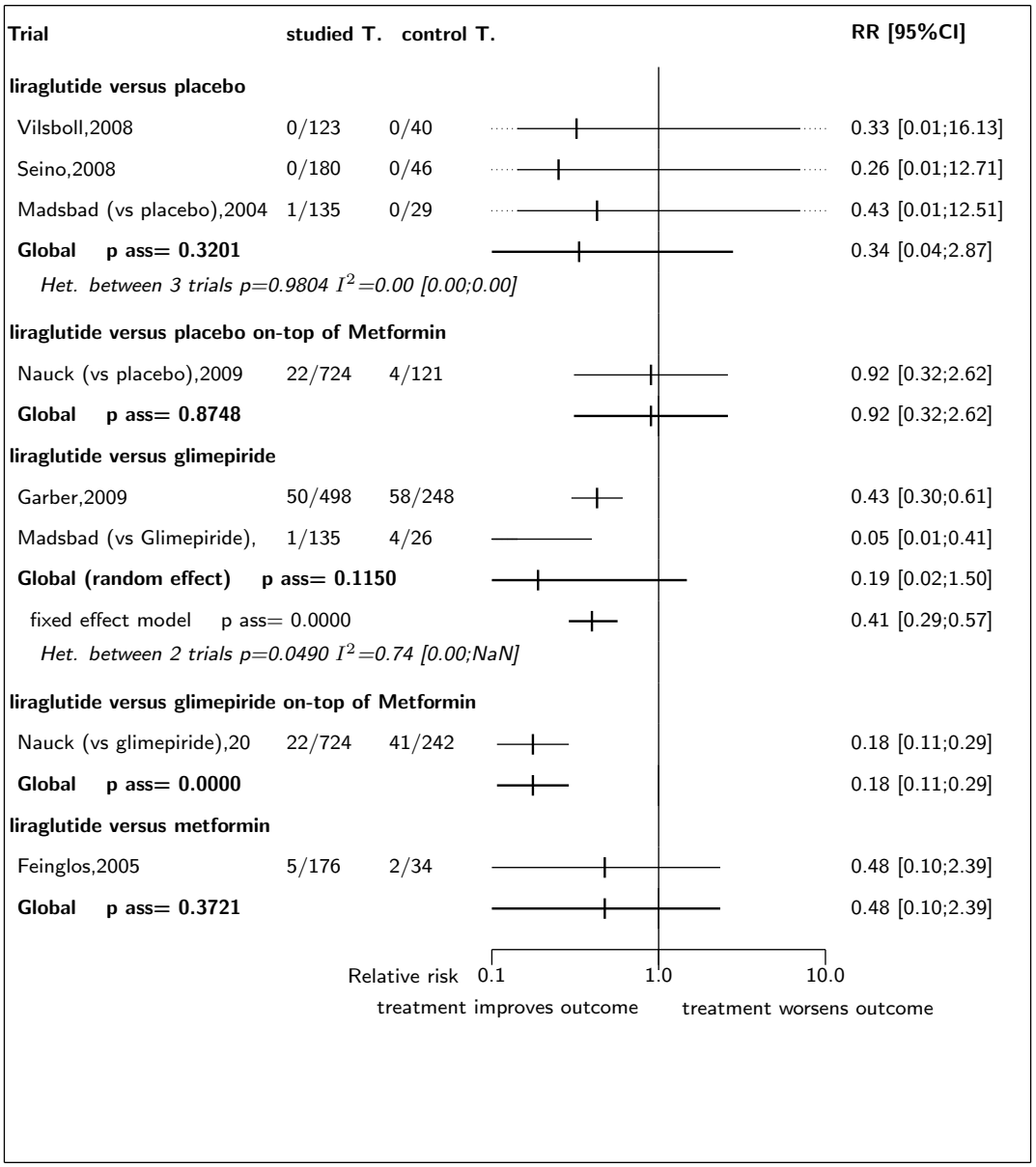


Figure 5.2: *Forest's plot for severe hypoglycemia*

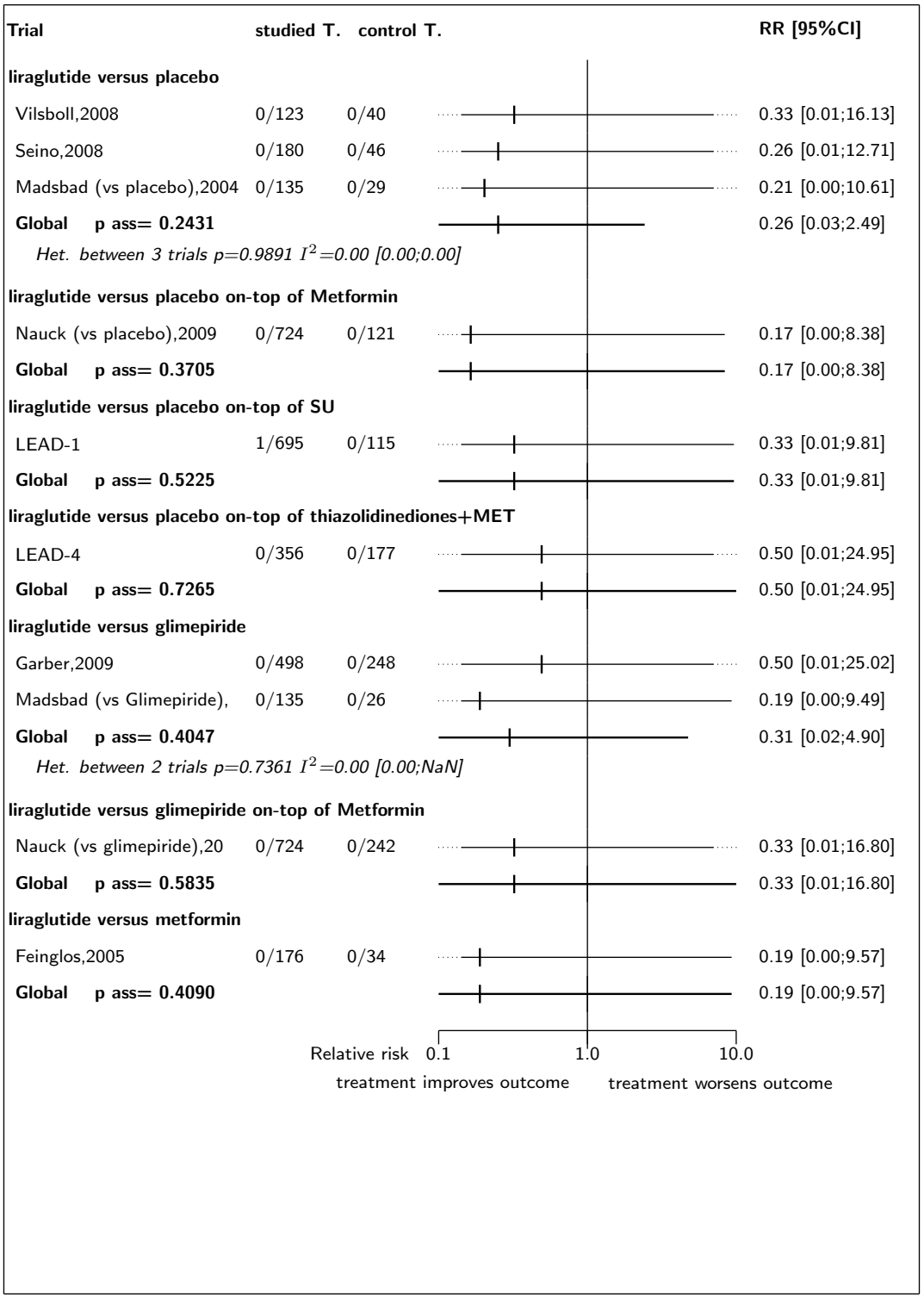


Figure 5.3: *Forest's plot for nausea*

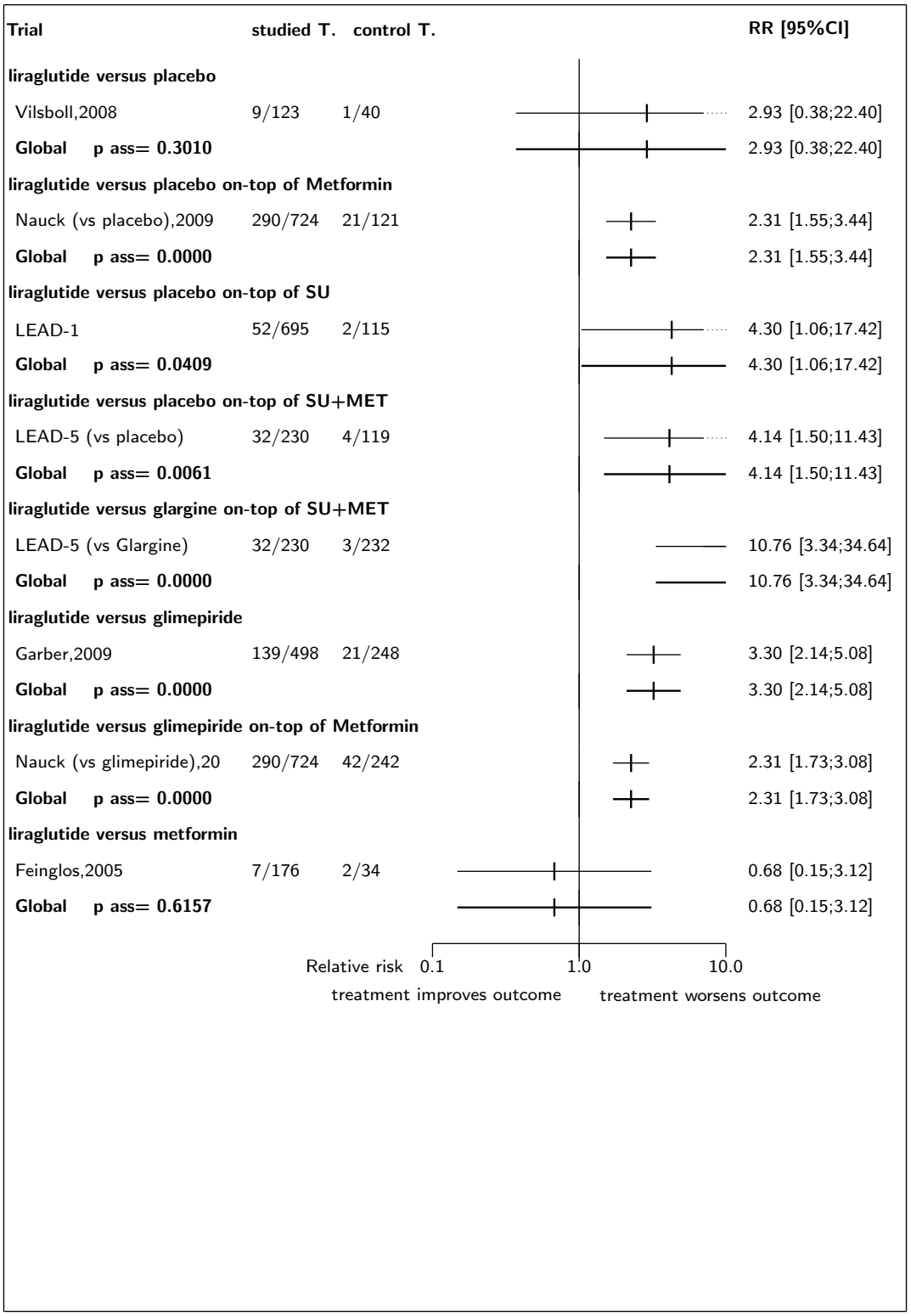


Figure 5.4: *Forest's plot for vomiting*

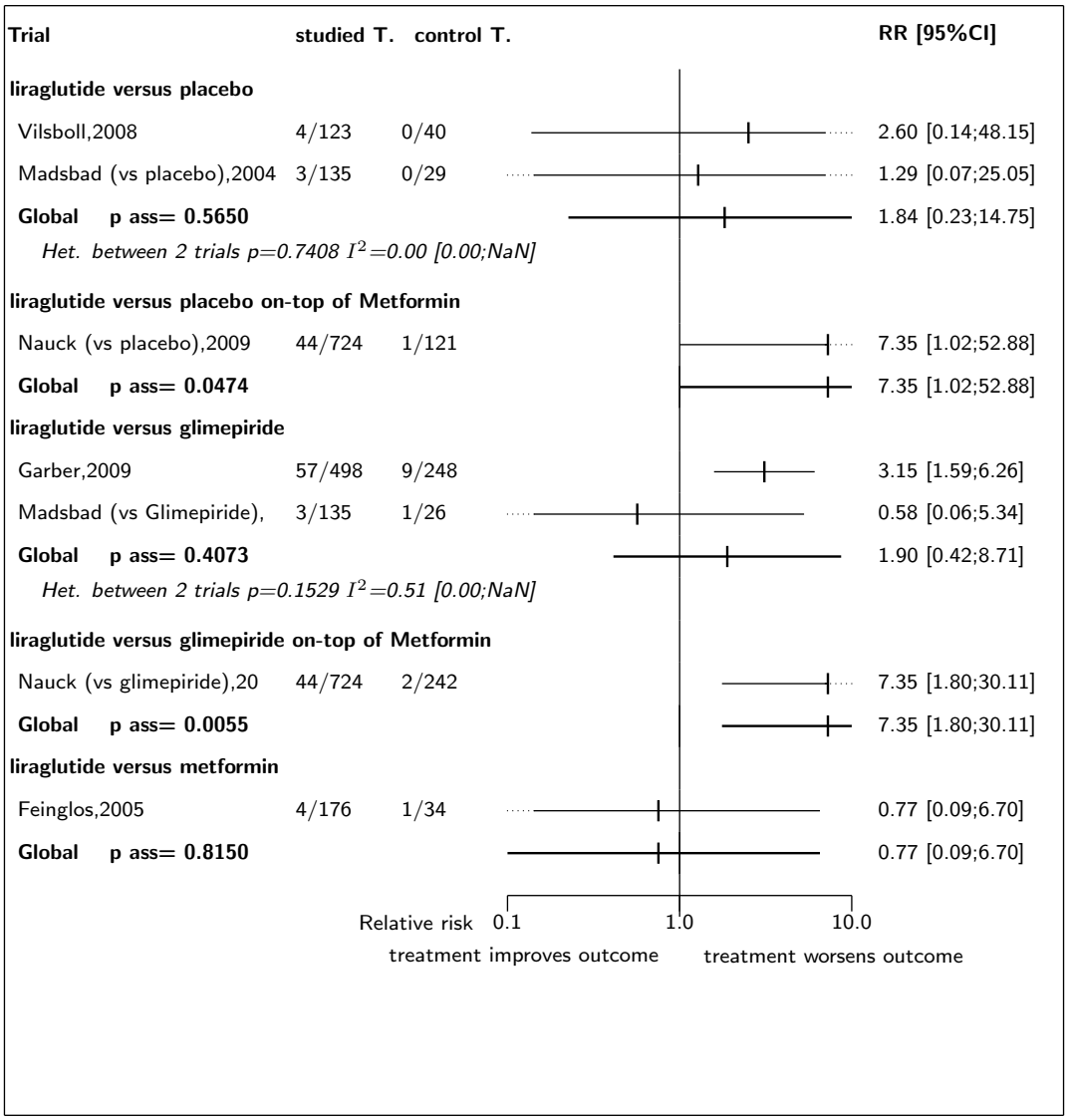


Figure 5.5: *Forest's plot for diarrhoea*

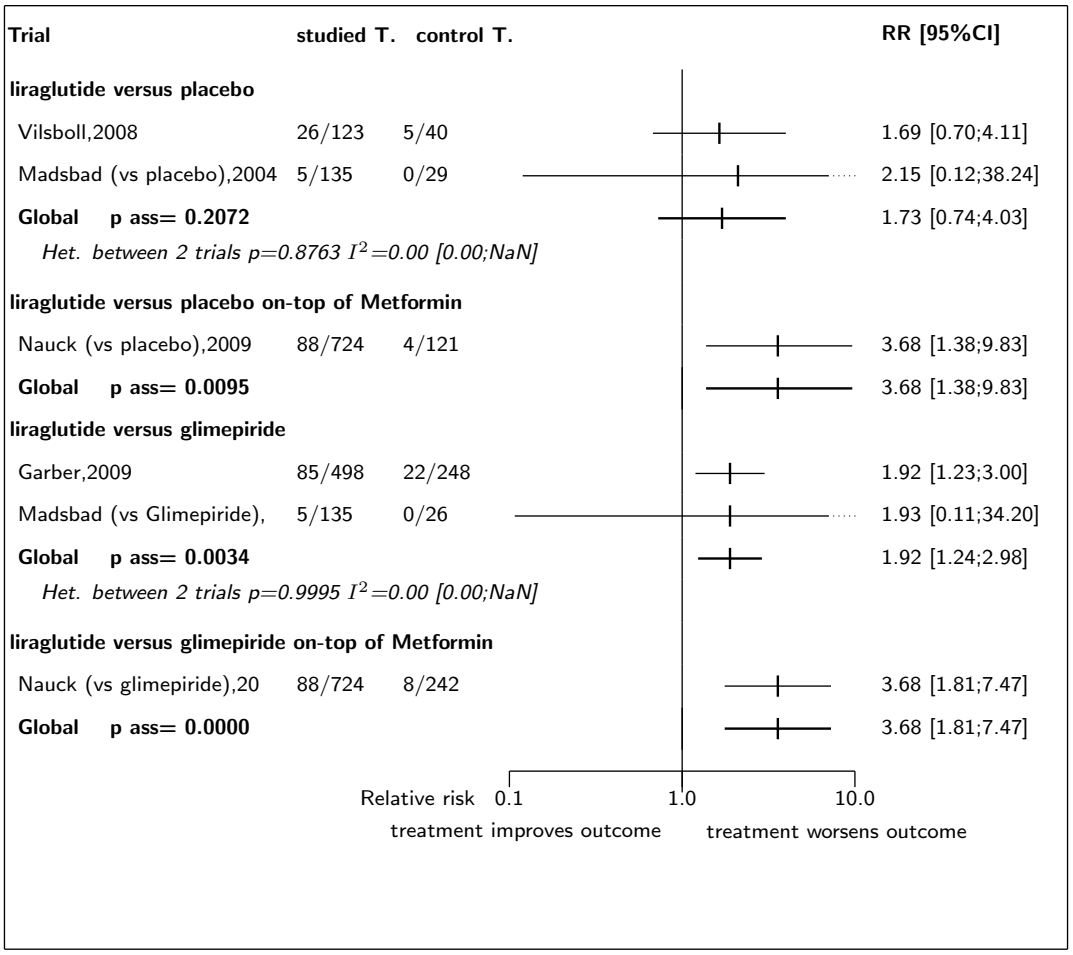


Figure 5.6: *Forest's plot for cardiovascular events*

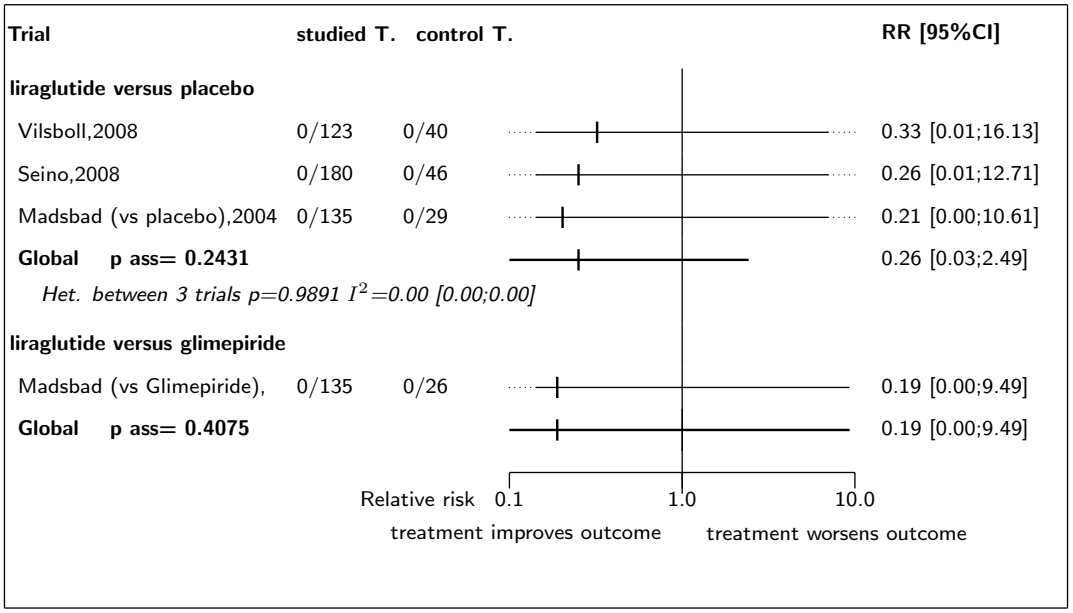
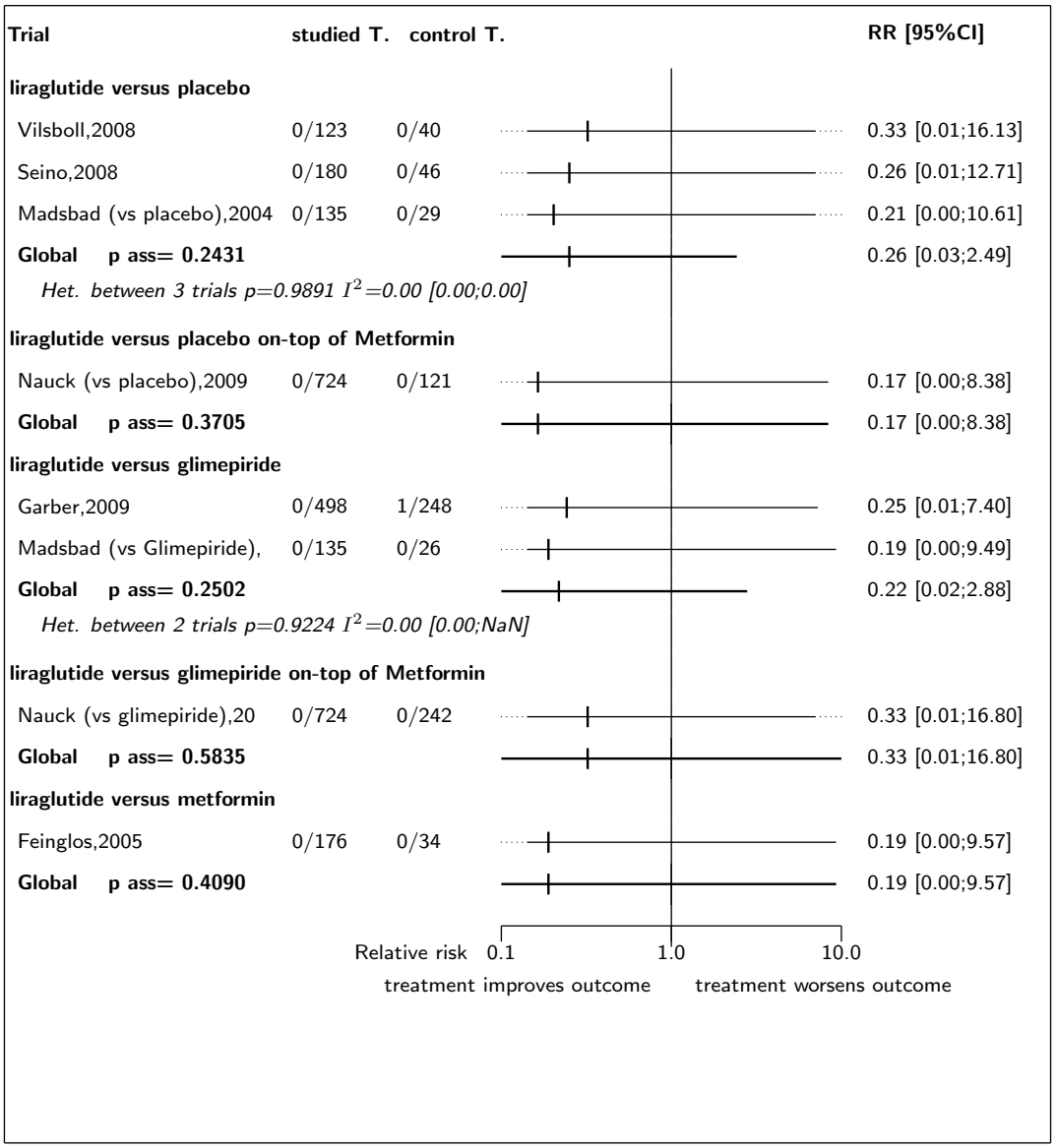


Figure 5.7: *Forest's plot for all cause death*



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

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

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6 Global meta-analysis: all Glucagon-like peptide analogs

6.1 Global meta-analysis: all Glucagon-like peptide analogs versus glargine on-top of SU+MET

Table 6.1: *All Glucagon-like peptide analogsversus glargine on-top of SU+MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.2 Global meta-analysis: all Glucagon-like peptide analogs versus glimepiride

Table 6.2: *All Glucagon-like peptide analogsversus glimepiride*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.3 Global meta-analysis: all Glucagon-like peptide analogs versus glimepiride on-top of Metformin

Table 6.3: *All Glucagon-like peptide analogsversus glimepiride on-top of Metformin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.4 Global meta-analysis: all Glucagon-like peptide analogs versus insulin on-top of SU+MET

Table 6.4: *All Glucagon-like peptide analogsversus insulin on-top of SU+MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.5 Global meta-analysis: all Glucagon-like peptide analogs versus insulin on-top of SU/MET

Table 6.5: *All Glucagon-like peptide analogsversus insulin on-top of SU/MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.6 Global meta-analysis: all Glucagon-like peptide analogs versus metformin

Table 6.6: *All Glucagon-like peptide analogsversus metformin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.7 Global meta-analysis: all Glucagon-like peptide analogs versus placebo

Table 6.7: *All Glucagon-like peptide analogsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.8 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of Metformin

Table 6.8: *All Glucagon-like peptide analogsversus placebo on-top of Metformin*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.9 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of SU

Table 6.9: *All Glucagon-like peptide analogsversus placebo on-top of SU*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.10 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of SU+/-MET

Table 6.10: *All Glucagon-like peptide analogsversus placebo on-top of SU+/-MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.11 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of SU+/-MET/thiazolidinediones

Table 6.11: *All Glucagon-like peptide analogsversus placebo on-top of SU+/-MET/thiazolidinediones*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.12 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of SU+MET

Table 6.12: *All Glucagon-like peptide analogsversus placebo on-top of SU+MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.13 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of thiazolidinediones+/-MET

Table 6.13: *All Glucagon-like peptide analogsversus placebo on-top of thiazolidinediones+/-MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

6.14 Global meta-analysis: all Glucagon-like peptide analogs versus placebo on-top of thiazolidinediones+MET

Table 6.14: *All Glucagon-like peptide analogsversus placebo on-top of thiazolidinediones+MET*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot

legend B

7 Ongoing studies

Only one ongoing study was identified. A brief description of this trial is given table **??**

Table 7.1: *Ongoing studies for Glucagon-like peptide analogs*

Study	**Description**
LEADER	**vs.**

8 Excluded studies

No trial was excluded.

Part I

Trial's summary - Evidence table

Table 8.1: *Davis, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=49 (33 vs. 16) **Follow-up duration:** 16 weeks **Study design:** Randomized controlled trial parallel groups Open		**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Insulin on-top of sulphonylureas/metformin **Concomittant treat.:**sulphonylureas or metformin	All hypoglycemia RR=1.05 [0.49;2.25] Nausea RR=3.88 [1.01;14.86] Vomiting RR=3.88 [0.53;28.41]

Reference

Davis SN, Johns D, Maggs D, Xu H, Northrup JH, Brodows RG. Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents. Diabetes Care 2007;30:2767-72 [PMID=17595353]

Table 8.2: *Barnett, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=263 (136 vs. 127) **Follow-up duration:** 16 weeks **Study design:** Randomized controlled trial Cross over Open Exploratory trial NA, 26 centres	**Inclusion criteria:** Type 2 diabetes, equal to or more than 30 years of age, receiving treatment with either a stable dose of immediate- or extended-release MET equal to or greater than 1500 mg/day or an optimally effective dose of SFU for 3 months, HbA1c level equal to, or more than, 7.1% and equal to, or less than, 11%, BMI more than 25 kg/m2 and less than 40 kg/m2, stable body weight (not varying by more than 10% for at least 3 months prior to screening)	**Studied treatment:** Exenatide 20 microg daily subcutaneous injection, 10 g/dayfor 4 weeks then 20 g/day for 12weeks, administered twice daily **Control treatment:** Insulin titrated to FBG <= 5.6 mmol/l, initiated at 10 IU and increased weekly, four times daily **Concomittant treat.:**sulphonylureas or metformin	All hypoglycemia RR=0.58 [0.35;0.97] Nausea RR=13.54 [5.06;36.22] Vomiting RR=3.03 [1.02;9.07] Diarrhoea RR=1.25 [0.28;5.45]

Reference

Barnett AH, Burger J, Johns D, Brodows R, Kendall DM, Roberts A, Trautmann ME. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther 2007;29:2333-48 [PMID=18158075]

Table 8.3: *Moretto, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=233 (155 vs. 78) **Follow-up duration:** 24 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Exenatide 1020 microg daily **Control treatment:** Placebo **Concomittant treat.:**None	All hypoglycemia RR=3.52 [0.44;28.13]

Reference

Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, Brodows RG. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2008;30:1448-60 [PMID=18803987]

Table 8.4: *DeFronzo, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=336 (223 vs. 113) **Follow-up duration:** 30 weeks **Study design:** Randomized controlled trial parallel groups Double blind	Patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses	**Studied treatment:** Exenatide 1020 microg daily **Control treatment:** Placebo on-top of Metformin **Concomittant treat.:**Metformin	All hypoglycemia RR=0.93 [0.35;2.45] Nausea RR=1.77 [1.22;2.57] Vomiting RR=3.17 [1.13;8.88] Diarrhoea RR=1.75 [0.86;3.54]

Reference

DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092-100 [PMID=15855572]

Table 8.5: *Kim, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=45 (30 vs. 15) **Follow-up duration:** 15 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Exenatide 0.82 microg daily **Control treatment:** Placebo on-top of metformin **Concomittant treat.:**metformin or None	Nausea RR=3.50 [0.47;25.90]

Reference

Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, Taylor K. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care 2007;30:1487-93 [PMID=17353504]

Table 8.6: *Buse, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=377 (248 vs. 129) **Follow-up duration:** 30 weeks **Study design:** Randomized controlled trial parallel groups Double blind (not adequate)	Patients with type 2 diabetes failing maximally effective doses of a sulfonylurea as monotherapy	**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Placebo on-top of SU **Concomittant treat.:**SU	All hypoglycemia RR=7.02 [2.60;18.96] Nausea RR=6.65 [3.49;12.66] Vomiting RR=5.03 [1.56;16.19] Diarrhoea RR=2.60 [1.02;6.63] Cardiovascular events RR=0.26 [0.02;2.84]

Reference
Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27:2628-35 [PMID=15504997]

Table 8.7: *Gao, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=466 (234 vs. 232) **Follow-up duration:** 16 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Placebo on-top of sulphonylureas+/-metformin **Concomittant treat.:**sulphonylureas+/-metformin	All hypoglycemia RR=3.92 [2.52;6.10] Severe hypoglycemia RR=1.98 [0.18;21.72]

Reference

Gao Y, Yoon KH, Chuang LM, Mohan V, Ning G, Shah S, Jang HC, Wu TJ, Johns D, Northrup J, Brodows R. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. Diabetes Res Clin Pract 2009;83:69-76 [PMID=19019476]

Table 8.8: *CT Register 8683, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=151 (111 vs. 40) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial parallel groups Not reported		**Studied treatment:** Exenatide 51020 microg daily **Control treatment:** Placebo on-top of sulphonylureas+/- metformin/thiazolidinediones **Concomittant treat.:**sulphonylureas+/-metformin or TZD	
Reference			

Table 8.9: *Kendall, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=733 (486 vs. 247) **Follow-up duration:** 30 weeks **Study design:** Randomized controlled trial parallel groups Double blind	Patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy	**Studied treatment:** Exenatide 1020 microg daily **Control treatment:** Placebo on-top of sulphonylureas+metformin **Concomittant treat.:**SU+/-metformin	All hypoglycemia RR=1.87 [1.30;2.70] Nausea RR=2.12 [1.63;2.76] Vomiting RR=3.19 [1.72;5.91] Diarrhoea RR=2.13 [1.26;3.59] Cardiovascular events RR=0.59 [0.20;1.75]

Reference

Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083-91 [PMID=15855571]

Table 8.10: *Zinman, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=233 (121 vs. 112) **Follow-up duration:** 16 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Placebo on-top of thiazolidinediones+/-metformin **Concomittant treat.:**TZD+/-metformin	All hypoglycemia RR=1.50 [0.65;3.49] Nausea RR=2.61 [1.60;4.27] Vomiting RR=14.81 [2.00;109.86] Diarrhoea RR=2.16 [0.57;8.15]

Reference

Zinman B, Hoogwerf BJ, Durn Garca S, Milton DR, Giaconia JM, Kim DD, Trautmann ME, Brodows RG. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2007;146:477-85 [PMID=17404349]

Table 8.11: *Heine, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=549 (282 vs. 267) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Open		**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Insulin on-top of sulphonylureas+metformin **Concomittant treat.:**sulphonylureas+/-metformin	Severe hypoglycemia RR=0.95 [0.24;3.75] Nausea RR=6.63 [4.43;9.92] Vomiting RR=4.64 [2.40;8.97] Diarrhoea RR=2.84 [1.30;6.21] Cardiovascular events RR=1.58 [0.38;6.54]

Reference

Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005;143:559-69 [PMID=16230722]

Table 8.12: *Nauck, 2007 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=501 (253 vs. 248) **Follow-up duration:** 52 weeks **Study design:** Randomized controlled trial parallel groups Open		**Studied treatment:** Exenatide 20 microg daily **Control treatment:** Insulin on-top of sulphonylureas+metformin **Concomittant treat.:**sulphonylureas+/-metformin	Nausea RR=82.34 [11.55;586.81] Vomiting RR=4.66 [2.22;9.78] Diarrhoea RR=4.71 [1.82;12.14] Cardiovascular events RR=1.96 [0.68;5.65] All cause death RR=1.96 [0.18;21.48]

Reference

Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, Brodows R, Trautmann M. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 2007;50:259-67 [PMID=17160407]

Table 8.13: *Vilsboll, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=163 (123 vs. 40) **Follow-up duration:** 14 weeks **Study design:** Randomized controlled trial parallel groups Double blind (not adequate)		**Studied treatment:** Liraglutide 0.651.90 mg daily **Control treatment:** Placebo **Concomittant treat.:**None	Nausea RR=2.93 [0.38;22.40] Diarrhoea RR=1.69 [0.70;4.11]

Reference

Vilsbll T, Brock B, Perrild H, Levin K, Lervang HH, Klendorf K, Krarup T, Schmitz O, Zdravkovic M, Le-Thi T, Madsbad S. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus. Diabet Med 2008;25:152-6 [PMID=18201212]

Table 8.14: *Seino, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=226 (180 vs. 46) **Follow-up duration:** 14 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Liraglutide 0.10.9 mg daily **Control treatment:** Placebo **Concomittant treat.:**None	

Reference

Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2008;81:161-8 [PMID=18495285]

Table 8.15: *Madsbad (vs placebo), 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=164 (135 vs. 29) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial parallel groups Open		**Studied treatment:** Liraglutide 0.0450.75 mg daily **Control treatment:** Placebo **Concomittant treat.:**None	

Reference

Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 2004;27:1335-42 [PMID=15161785]

Table 8.16: *Nauck (vs placebo), 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=845 (724 vs. 121) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Liraglutide 1.21.8 mg daily **Control treatment:** Placebo on-top of Metformin **Concomittant treat.:**Metformin	All hypoglycemia RR=0.92 [0.32;2.62] Nausea RR=2.31 [1.55;3.44] Vomiting RR=7.35 [1.02;52.88] Diarrhoea RR=3.68 [1.38;9.83]

Reference

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

Table 8.17: *LEAD-1, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=810 (695 vs. 115) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Not reported		**Studied treatment:** Liraglutide 1.21.8 mg daily **Control treatment:** Placebo on-top of sulphonylureas **Concomittant treat.:**sulphonylureas	Nausea RR=4.30 [1.06;17.42]
Reference			

Table 8.18: *LEAD-5 (vs placebo), 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=349 (230 vs. 119) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Not reported		**Studied treatment:** Liraglutide 1.8 mg daily **Control treatment:** Placebo on-top of sulphonylureas+metformin **Concomittant treat.:**sulphonylureas+/-metformin	Nausea RR=4.14 [1.50;11.43]
Reference			

Table 8.19: *LEAD-4, 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=533 (356 vs. 177) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Not reported		**Studied treatment:** Liraglutide 1.21.8 mg daily **Control treatment:** Placebo on-top of thiazolidinediones+metformin **Concomittant treat.:**TZD+/-metformin	
Reference			

Table 8.20: *LEAD-5 (vs Glargine), 0 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=462 (230 vs. 232) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Not reported		**Studied treatment:** Liraglutide 1.8 mg daily **Control treatment:** Glargine on-top of sulphonylureas+metformin **Concomittant treat.:**sulphonylureas+/-metformin	Nausea RR=10.76 [3.34;34.64]
Reference			

Table 8.21: *Garber, 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=746 (498 vs. 248) **Follow-up duration:** 52 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Liraglutide 1.21.8 mg daily **Control treatment:** Glimepiride **Concomittant treat.:**None	All hypoglycemia RR=0.43 [0.30;0.61] Nausea RR=3.30 [2.14;5.08] Vomiting RR=3.15 [1.59;6.26] Diarrhoea RR=1.92 [1.23;3.00]

Reference

Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-81 [PMID=18819705]

Table 8.22: *Madsbad (vs Glimepiride), 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=161 (135 vs. 26) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial parallel groups Open		**Studied treatment:** Liraglutide 0.0450.75 mg daily **Control treatment:** Glimepiride **Concomittant treat.:**None	All hypoglycemia RR=0.05 [0.01;0.41] Vomiting RR=0.58 [0.06;5.34]

Reference

Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 2004;27:1335-42 [PMID=15161785]

Table 8.23: *Nauck (vs glimepiride), 2009 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=966 (724 vs. 242) **Follow-up duration:** 26 weeks **Study design:** Randomized controlled trial parallel groups Double blind		**Studied treatment:** Liraglutide 1.21.8 mg daily **Control treatment:** Glimepiride on-top of Metformin **Concomittant treat.:**Metformin	All hypoglycemia RR=0.18 [0.11;0.29] Nausea RR=2.31 [1.73;3.08] Vomiting RR=7.35 [1.80;30.11] Diarrhoea RR=3.68 [1.81;7.47]

Reference

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

Table 8.24: *Feinglos, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=210 (176 vs. 34) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial parallel groups Double blind (not adequate)		**Studied treatment:** Liraglutide 0.0450.75 mg daily **Control treatment:** Metformin **Concomittant treat.:**None	All hypoglycemia RR=0.48 [0.10;2.39] Nausea RR=0.68 [0.15;3.12] Vomiting RR=0.77 [0.09;6.70]

Reference

Feinglos MN, Saad MF, Pi-Sunyer FX, An B, Santiago O. Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes. Diabet Med 2005;22:1016-23 [PMID=16026367]