Drug Class Review

Newer Diabetes Medications, TZDs, and Combinations

Final Original Report

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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STRUCTURED ABSTRACT

Purpose

To compare the effectiveness and adverse event profiles of amylin agonists, DPP-4 inhibitors, incretin mimetics, TZDs, and certain combination products for people with type 2 diabetes and for people with type 1 diabetes for pramlintide only.

Data Sources

To identify published studies, we searched MEDLINE, The Cochrane Library, Embase, International Pharmaceutical Abstracts, and reference lists of included studies through July 2010. We also requested dossiers of information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence (SOE), and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods.

Results

Most of the evidence was limited to adult populations. Most of the included studies evaluated intermediate outcomes, such as HbA1c or weight. Very few studies reported health outcomes and few studies were longer than 6 months. For the amylin agonists, DPP-IV inhibitors, and GLP-1 agonists, we found no studies that focused on health outcomes as primary outcomes. Some studies of these drug classes reported some health outcomes such as all-cause mortality or number of people with macrovascular disease among secondary outcomes or adverse events, but overall evidence was generally insufficient to determine how medications in these classes compare with other treatments for their impact on health outcomes.

For the newer diabetes drugs (pramlintide, sitagliptin, saxagliptin, exenatide, and liraglutide), all of the included medications were efficacious for reducing HbA1c compared with placebo. For reduction in HbA1c, pramlintide was similar to rapid acting insulin analog when added to insulin glargine or detemir (low SOE); sitagliptin monotherapy was less efficacious than metformin or glipizide monotherapy (low SOE); sitagliptin was not significantly different than rosiglitazone when either was added to metformin (moderate SOE); and there was no comparative evidence for saxagliptin (insufficient SOE). One head-to-head trial comparing exenatide with liraglutide reported a slightly greater reduction in HbA1c with liraglutide (between group difference −0.33%, 95% CI -0.47 to -0.18, low SOE). For reduction in HbA1c, exenatide was similar to glibenclamide (low SOE), rosiglitazone (low SOE), and insulin (with both groups also receiving oral diabetes agents, moderate SOE). Liraglutide-treated subjects had greater reductions in HbA1c than subjects treated with glargine (low SOE), rosiglitazone (low SOE), or sitagliptin (low SOE), and similar or greater reductions than those treated with glimepiride (insufficient SOE).

For weight, pramlintide, exenatide, and liraglutide (doses of 1.2 or greater) appear to cause weight loss compared with placebo. Sitagliptin and saxagliptin are likely weight neutral.

Most studies evaluating weight change were 6 months or less and it is uncertain whether weight loss is sustained long-term. Rates of hypoglycemia were lower with sitagliptin than with glipizide (moderate SOE), with liraglutide than exenatide (low SOE), and with liraglutide than glimepiride (high SOE). Hypoglycemia rates were similar to placebo for sitagliptin and saxagliptin (low SOE) and were similar between exenatide and insulin (moderate SOE). Rates of gastrointestinal side effects were higher with exenatide and liraglutide than with comparators.

For the TZDs, the available evidence indicates that pioglitazone and rosiglitazone are not statistically significantly different in their ability to reduce HbA1c (moderate SOE). Further, there were no significant differences in ability to reduce HbA1c between either TZD and sulfonylureas or metformin (moderate to high SOE). Both TZDs increase the risk of heart failure (high SOE), edema (high SOE), and fractures in women (moderate SOE). The risk of hypoglycemia is reduced with TZDs when compared with sulfonylureas; the risk is similar to the risk with metformin (high SOE). Both TZDs cause a similar degree of weight gain to that caused by sulfonylureas (moderate SOE). Although rosiglitazone now has restricted access due to an increased risk of cardiovascular adverse events, we found no evidence of increased all-cause mortality or cardiovascular mortality with pioglitazone; some studies suggest reduced risk of all-cause and cardiovascular mortality with pioglitazone (low SOE)

For the FDCPs, we found no head to head trials that compared HbA1c control between any 2 FDCPs (insufficient SOE). Therapy with Avandamet,® Avandaryl,® Actoplus Met, or dual therapy with metformin and sitagliptin produced statistically significantly greater reductions in HbA1c compared to monotherapy with any of their respective components.

Conclusion

All of the included medications were efficacious for reducing HbA1c and none of the newer medications appear to cause weight gain. Little data was available to evaluate the long-term effectiveness of the newer medications compared with more established treatments, limiting our ability to determine how to best incorporate newer medications into clinical practice.

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INTRODUCTION

Diabetes mellitus (diabetes) is a chronic and insidious disease affecting more than 23 million Americans, about 8% of the population.[1] Of those diagnosed, 90% to 95% have type 2 diabetes, while 5% to 10% have type 1 diabetes. Type 1 diabetes is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. Type 2 diabetes encompasses a heterogeneous group of disorders characterized by slow progressive loss of beta cell function and mass leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Higher glucagon levels relative to insulin also plays a significant role in the pathogenesis and management of type 2 diabetes.

The 2010 American Diabetes Association treatment guidelines recommend a hemoglobin A1c (HbA1c) goal of <7% in nonpregnant adults in order to prevent adverse microvascular outcomes.[2] The guidelines acknowledge that less stringent goals may be appropriate for certain populations. Insulin is the standard treatment for type 1 diabetes. Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, combination products, and insulin. Because of the progressive nature of diabetes, practitioners and patients often experience challenges in reaching and sustaining American Diabetes Association goals. In fact, it is estimated that more than 50% of persons with type 2 diabetes will require more than one oral hypoglycemic agent after 3 years of diagnosis and approximately 70% will require combination oral therapy with or without insulin 6 to 9 years from diagnosis.[3]

Newer Diabetes Medications

Within recent years, several new antihyperglycemic agents have been approved: pramlintide, exenatide, liraglutide, sitagliptin, and saxagliptin (Table 1). These agents offer mechanisms of glycemic control beyond that of "traditional" oral agents and insulin by targeting alternate gluco-regulatory receptors and hormones such as amylin, GLP-1, glucose-dependent insulinotropic peptide (GIP), and DPP-4. For the purposes of this report, we consider the following to be "newer diabetes medications": amylin agonists, DPP-4 inhibitors, and GLP-1 agonists. Amylin is a neuroendocrine hormone co-secreted with insulin from beta cells in response to elevated blood glucose concentrations and complements the actions of insulin. GLP-1 and GIP are secreted by L-and K-type cells in the intestinal tract in response to a combination of endocrine and neural signals initiated by the entry of food into the gut. Secretion of GLP-1 and GIP enhance insulin release. Both endogenous GLP-1 and GIP are rapidly degraded by the proteolytic enzyme DPP-4.

Thiazolidinediones

There are 2 thiazolidinediones approved for prescription use in the United States and Canada, rosiglitazone maleate (Avandia®), which has restrictions on its use described below, and pioglitazone hydrochloride (Actos®) (Table 1). A third thiazolidinedione (troglitazone) was removed from the market in 1999 due to adverse hepatic effects. Pioglitazone is approved in the United States and Canada for use in adults for the treatment of type 2 diabetes, either as monotherapy or in combination with insulin, metformin, or sulfonylurea when diet, exercise, and a single agent does not result in adequate glycemic control. In September 2010, the US Food and

Drug Administration (FDA) restricted access for rosiglitazone (Avandia®) and combination products that contain rosiglitazone due to an increased risk of cardiovascular adverse events. The FDA required that GlaxoSmithKline develop a restricted access program for rosiglitazone under a risk evaluation and mitigation strategy, or REMS.[4] Under the REMS, rosiglitazone will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone, the only other drug in this class. Current users of rosiglitazone who are benefiting from the drug will be able to continue using the medication if they choose to do so. Doctors will have to attest to and document their patients' eligibility; patients will have to review statements describing the cardiovascular safety concerns associated with this drug and acknowledge they understand the risks. Health Canada has added similar restrictions for rosiglitazone, which is now only indicated in patients with type 2 diabetes where other medications are either inappropriate (due to intolerance or to contraindications) or do not result in adequate glycemic control (as monotherapy or in combination).[5] Prior to initiation of rosiglitazone, there must be adequate documentation that the patient meets the eligibility criteria for rosiglitazone treatment, patients must be counseled on the risks (including cardiovascular) of treatment with rosiglitazone, and have written informed consent from the patient for treatment with rosiglitazone. Additionally, the Canadian Product Monographs for rosiglitazone and combination products containing rosiglitazone have been updated to reflect the restrictions and new boxed warnings have been added. Boxed warnings for all included medications are in Appendix A.

The mechanisms of action of thiazolidinediones in lowering plasma glucose among persons with type 2 diabetes are thought to include the following: increase in insulin sensitivity, decrease endogenous glucose production and postprandial gluconeogenesis, increase fasting and postprandial glucose clearance, and have beneficial effects on beta-cell function.[6] The glycemic effects of thiazolidinediones are thought to be mediated by binding to the peroxisome proliferators-activated receptor (PPAR) gamma receptors. These receptors are expressed in the liver, heart, adipose tissue, skeletal muscle, and smooth muscle, and endothelial cells of the vasculature of the kidneys and the gut.[7]

Dual therapy and Fixed-dose Combination Products

For this report, we've included 5 fixed-dose combination products (FDCPs) approved for the treatment of type 2 diabetes. These include 2 products that combine metformin with a thiazolidinedione, 2 that combine a sulfonylurea with a thiazolidinedione, and 1 that combines metformin with a DPP-4 inhibitor (Table 1). In addition to the 5 FDCPs, we've included studies of the individual components of those FDCPs when used together but in separate pills—we refer to this as "dual therapy" throughout the review.

Table 1. Characteristics of included drugs

Drug Class	Trade name Administration	Labeled indications	Dosing Country
Pramlintide Amylin agonist	Symlin® Injectable	Type 1 diabetes, Type 2 diabetes; Adjunct with insulin	Type 1: 15-60 mcg with meals Type 2: 60-120 mcg with meals US only

Drug Class	Trade name Administration	Labeled indications	Dosing Country
Sitagliptin DPP-4 Inhibitor	Januvia® Oral tablet	Type 2 diabetes; Monotherapy or combination with any antihyperglycemic	100 mg once daily (25 or 50 mg if renal dysfunction) US, Canada
Saxagliptin DPP-4 Inhibitor	Onglyza® Oral tablet	Type 2 diabetes; Monotherapy or combination with any antihyperglycemic	2.5-5 mg once daily (2.5 mg if renal dysfunction) US, Canada
Exenatide GLP-1 Agonists (Incretin mimetics)	Byetta® Injection	Type 2 diabetes; Not recommended with insulin (not studied)	5 or 10 mcg twice daily prior to meals US only
Liraglutide GLP-1 Agonists (Incretin mimetics)	Victoza® Injection	Type 2 diabetes; Not recommended with insulin (not studied)	0.6, 1.2, or 1.8 mg once daily US, Canada
Pioglitazone Thiazolidinediones	Actos® Oral tablet	Type 2 diabetes; Monotherapy or combination with sulfonylurea, metformin, insulin	15-45 mg once daily US, Canada
Rosiglitazone Thiazolidinediones	Avandia® Oral tablet	Type 2 diabetes; Monotherapy or combination with sulfonylurea, metformin (In Canada: monotherapy or combination with metformin, or combination with sulfonylurea if metformin is contraindicated)	4-8 mg once daily US, Canada
Rosiglitazone + Metformin	Avandamet® Oral tablet	Type 2 diabetes; Adjunct to diet and exercise in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.	2 mg/500 mg; 2 mg/1000 mg; 4 mg/500 mg; 4 mg/1000 mg US, Canada
Pioglitazone + Metformin	Actoplus Met® Actoplus Met XR® Oral tablet	Type 2 diabetes; Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.	15 mg/500 mg; 15 mg/850 mg for Actoplus Met®; 15 mg/1000 mg; 30 mg/1000 mg for Actoplus Met XR® US only
Rosiglitazone + Glimepiride	Avandaryl® Oral tablet	Type 2 diabetes; Adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate.	4 mg/1 mg; 4 mg/2 mg; 4 mg/4 mg; 8 mg/2 mg; 8 mg/4 mg US, Canada
Pioglitazone + Glimepiride	Duetact® Oral tablet	Type 2 diabetes; Adjunct to diet and exercise as a once-daily combination therapy	30 mg/2 mg; 30 mg/4 mg US only

Drug Class	Trade name Administration	Labeled indications	Dosing Country
		to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with a sulfonylurea alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.	
Sitagliptin + Metformin	Janumet® Oral tablet	Type 2 diabetes; Adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.	50 mg/500 mg; 50 mg/1000 mg US, Canada[a]

Abbreviations: DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; US, United States.
[a] A 50/850mg form is also available in Canada

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix B and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit

(experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures. Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to

practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The goal of this report is to compare the effectiveness and adverse event profiles of newer medications, TZDs, and combinations (Table 1) in the treatment of diabetes. The RTI-UNC Evidence-based Practice Center developed preliminary key questions to identify the populations, interventions, outcomes of interest, and eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. A group of clinicians specializing in treating patients with diabetes were consulted for clinical insight into the proposed key questions. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public and from clinical advisors and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients. These organizations approved the following key questions to guide the review for this report:

1. What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications, TZDs, and drug combinations (administered as combination products or dual therapy) differ in efficacy/effectiveness or frequency of adverse events?

The majority of this report focuses on type 2 diabetes mellitus. Studies enrolling subjects with type 1 diabetes are only included for one of the medications, pramlintide. Further details of the inclusion/exclusion criteria used to answer these key questions, including specific populations, interventions, comparisons, outcomes, and study designs, are provided in the methods section of this report.

METHODS

Inclusion Criteria

All citations were reviewed for inclusion using the criteria described in Table 2. Studies meeting these criteria and comparing at least one of the drugs of interest with an eligible comparator were included. Eligible drugs and comparators are listed in Table 3.

Literature Search

To identify articles relevant to each key question we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. Initially, we conducted 5 separate searches to ensure overlap and consistency with the 3 reports that were being updated and to capture additional references relevant to the new inclusion criteria. We used the generic and brand names of included drugs, and study designs as search terms. We combined the results of all the searches and removed duplicate references. The full search strategies are presented in Appendix C. Update searches were conducted on July 28, 2010 to ensure that recent publications were captured.

We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote®X.0.2, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using

the criteria above. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Table 2. Study inclusion and exclusion criteria

Included populations
• Adults and children with type 2 diabetes for all included medications • Adults and children with type 1 diabetes for Pramlintide (Symlin®) only
Excluded populations
• Individuals with gestational diabetes, pre-diabetes (impaired fasting glucose or impaired glucose tolerance), metabolic syndrome without diabetes, or polycystic ovary syndrome
Included intermediate outcomes
• Hemoglobin A1c (HbA1c) • Changes in weight[a] • Changes in lipid concentrations[b]
Included health and utilization outcomes
• All-cause mortality • Microvascular disease: chronic kidney disease, including renal dialysis, renal transplantation, end-stage renal disease; renal failure with proteinuria, retinopathy including proliferative retinopathy and blindness; peripheral neuropathy • Macrovascular disease: cardiovascular morbidity (e.g. myocardial infarction and peripheral arterial disease), cardiovascular mortality, stroke/transient ischemic attack, coronary heart disease, cardiovascular procedures, extremity amputation • Lower extremity ulcers • Quality of life • Hospitalization and medical visits related to diabetes care
Included harms/adverse events outcomes
• Overall adverse events • Withdrawals due to adverse events • Major adverse events (for example diabetic ketoacidosis, non-ketotic hyperosmolar coma) • Specific adverse events (for example cancers/neoplasms, infections, hypoglycemia, liver toxicity, liver function abnormalities, gastrointestinal effects, congestive heart failure, adverse changes in lipid concentrations, pancreatitis, weight gain, fractures)
Included study designs[c]
• For intermediate outcomes: randomized controlled trials and good-quality systematic reviews • For health and utilization outcomes: randomized controlled trials, good-quality systematic reviews, and observational studies if they were cohort studies with a comparison group or case-control studies • For harms: randomized controlled trials, controlled clinical trials, good and fair-quality systematic reviews, population-based comparative cohort studies focused on adverse events, case-control studies, and reports from voluntary adverse event reporting systems. For the TZDs, when evidence was available from good or fair-quality systematic reviews (such as for fractures and cardiovascular adverse events), we considered this the best available evidence and did not evaluate new observational studies published since the 2008 TZD report[8]. • Duration: all study designs for all key questions were required to have ≥ 12 weeks of follow-up • Sample size: Any size

[a] Change in weight is reported in the key question 1 section for exenatide, liraglutide, pramlintide, sitagliptin, and saxagliptin, and reported in the Key Question 2 section for all other drugs.
[b] Changes in lipid concentrations are reported in the key question 2 section.
[c] A Drug Effectiveness Review Project governance decision was made while the report was in progress not to evaluate new studies (since the 2008 TZD report) comparing TZDs with placebo because of resource limitations and availability of better evidence (e.g., active-control trials and systematic reviews).

Table 3. Eligible drugs and comparators

Drug class or drug[a]	Eligible comparators
Amylin Agonists	
Pramlintide vs.	Placebo, DPP4-Inhibitors, Thiazolidinediones (TZDs), GLP-1 Agonists, Fixed dose combination products, Dual therapy with the component medications of fixed dose combination products, Insulin, Second generation sulfonylureas and beyond, Biguanides (metformin), Meglitinides, Alpha Glucosidase Inhibitors
DPP-4 Inhibitors	
Sitagliptin or Saxagliptin vs.	Each other, Placebo, Thiazolidinediones (TZDs), Amylin Agonists, GLP-1 Agonists, Fixed dose combination products, Dual therapy with the component medications of fixed dose combination products, Insulin, Second generation sulfonylureas and beyond, Biguanides (metformin), Meglitinides, Alpha Glucosidase Inhibitors
GLP-1 Agonists	
Exenatide or Liraglutide vs.	Each other, placebo, DPP4-Inhibitors, Thiazolidinediones (TZDs), Amylin agonists, Fixed dose combination products, Dual therapy with the component medications of fixed dose combination products, Insulin, Second generation sulfonylureas, Biguanides (metformin), Meglitinides, Alpha Glucosidase Inhibitors
Thiazolidinediones (TZDs)[b]	
Rosiglitazone or Pioglitazone vs.	Each other, DPP4-Inhibitors, Amylin agonists, GLP-1 agonists, Fixed dose combination products, Dual therapy with the component medications of fixed dose combination products, Second generation sulfonylureas and beyond, Biguanides (metformin), Meglitinides, Alpha Glucosidase Inhibitors
Fixed-dose Combination Products[c]	
Avandamet® (Metformin + Rosiglitazone) or Actoplus Met® (Metformin + Pioglitazone) or Avandaryl® (Glimepiride + Rosiglitazone) or Duetact® (Glimepiride + Pioglitazone) or Janumet® (Metformin + Sitagliptin) vs.	Monotherapy with one of the component medications of the product or head to head studies comparing 2 fixed dose combination products
Dual Therapy	
Metformin + Rosiglitazone or Metformin + Pioglitazone or Glimepiride + Rosiglitazone or Glimepiride + Pioglitazone or Metformin + Sitagliptin vs.	Monotherapy with one of the component medications

[a] Evidence of these interventions (left column) used as monotherapy or as add-on therapy will be included when available.
[b] For TZDs, we did not include studies comparing TZDs with placebo, TZDs vs. insulin, or TZDs + insulin vs. an eligible comparator.
[c] In Drug Effectiveness Review Project reports, we traditionally refer to the drug products by their generic names wherever possible. For this report, however, we are using the trade names for the FDCPs in an effort to make reading easier.

Data Abstraction

The following data were abstracted from included trials: study design; population characteristics, including sex, age, and ethnicity; eligibility and exclusion criteria; interventions; comparisons; numbers randomized or treated, and the numbers analyzed; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we recorded these results and noted that they were modified intention-to-treat results. In cases where only per protocol results were reported, we recorded these results and noted that they were per protocol results. We considered whether results were intention-to-treat, modified intention-to-treat, or per protocol when assessing the internal validity of studies (as described below). Data abstraction was performed by one reviewer and independently checked by a second reviewer and differences were resolved by consensus. When studies reported duration in number of months, we converted this to number of weeks by multiplying months by 4.33 and rounding up or down. Number of weeks is presented in the tables of study characteristics throughout the report. When recording data on lipids, we converted mmol/L to mg/dL. To convert total cholesterol and HDL and LDL cholesterol, we used the following formula: divide mmol/L by 0.0259 to get mg/dL. To convert triglycerides, we used the following formula: divide mmol/L by 0.0113 to get mg/dL.

Validity Assessment

Two reviewers independently assessed each study and differences were resolved by consensus. We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).[9, 10] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, and attrition; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw may be reflected by one aspect introducing a high risk of bias or by failure to meet combinations of items of the quality assessment checklist. We did not include poor quality studies in our analysis. A particular randomized trial might receive 2 different ratings, for different outcomes.

Observational studies included for the assessment of adverse events were also rated for quality. The criteria used reflect aspects of the study design that are particularly important for assessing adverse event rates.

Included systematic reviews were also rated for quality. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. These studies were categorized as good when all criteria were met.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[11] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. We considered all placebo-controlled evidence to be indirect (not directly comparing medications). We considered all evidence from intermediate outcomes (e.g. HbA1c) to be indirect (not directly reporting health outcomes).

Table 4 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of the drugs included in this review. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers assessed each domain for each outcome and differences were resolved by consensus.

We graded the strength of evidence for the outcomes deemed to be of greatest importance to decision makers and those most commonly reported in the literature. For example, these included HbA1c and weight changes, among others. Because of time and resource constraints we did not grade the strength of evidence for every possible outcome reported everywhere in the included literature.

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition[11]
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one included drug of interest against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons (i.e., head-to-head comparisons of included medications) were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare included drugs of interest with other drug classes (i.e., active controls) or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. Since a large number of recent good quality meta-analyses were available for comparisons of the TZDs with other medications of interest to this review, we did not conduct our own meta-analyses for those comparisons (except for the head-to-head comparison of pioglitazone and rosiglitazone for HbA1c).

Random-effects models were used to estimate pooled effects.[12] Forest plots graphically summarize results of individual studies and of the pooled analysis.[13]

The Chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[14, 15] An I^2 from 0 to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and $\geq$ 75% represents considerable heterogeneity.[16] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2). Whenever including a meta-analysis with considerable statistical heterogeneity in this report, we provide an explanation for doing so, considering the magnitude and direction of effects. .[16] Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions. Quantitative analyses were conducted using Stata version 11.1 and Comprehensive Meta Analysis version 2.2.055.

When describing conclusions and key findings in this report, we sometimes refer to "no difference" between two treatments. We use this wording to indicate that the available evidence did not support a statistically or clinically significant difference between the two treatments.

Peer Review

We requested and received peer review of the report from 3 content or methodology experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment.

We received comments from 6 persons, 6 representing pharmaceutical companies, 0 representing professional or advocacy organizations, and 0 individuals with no reported affiliation.

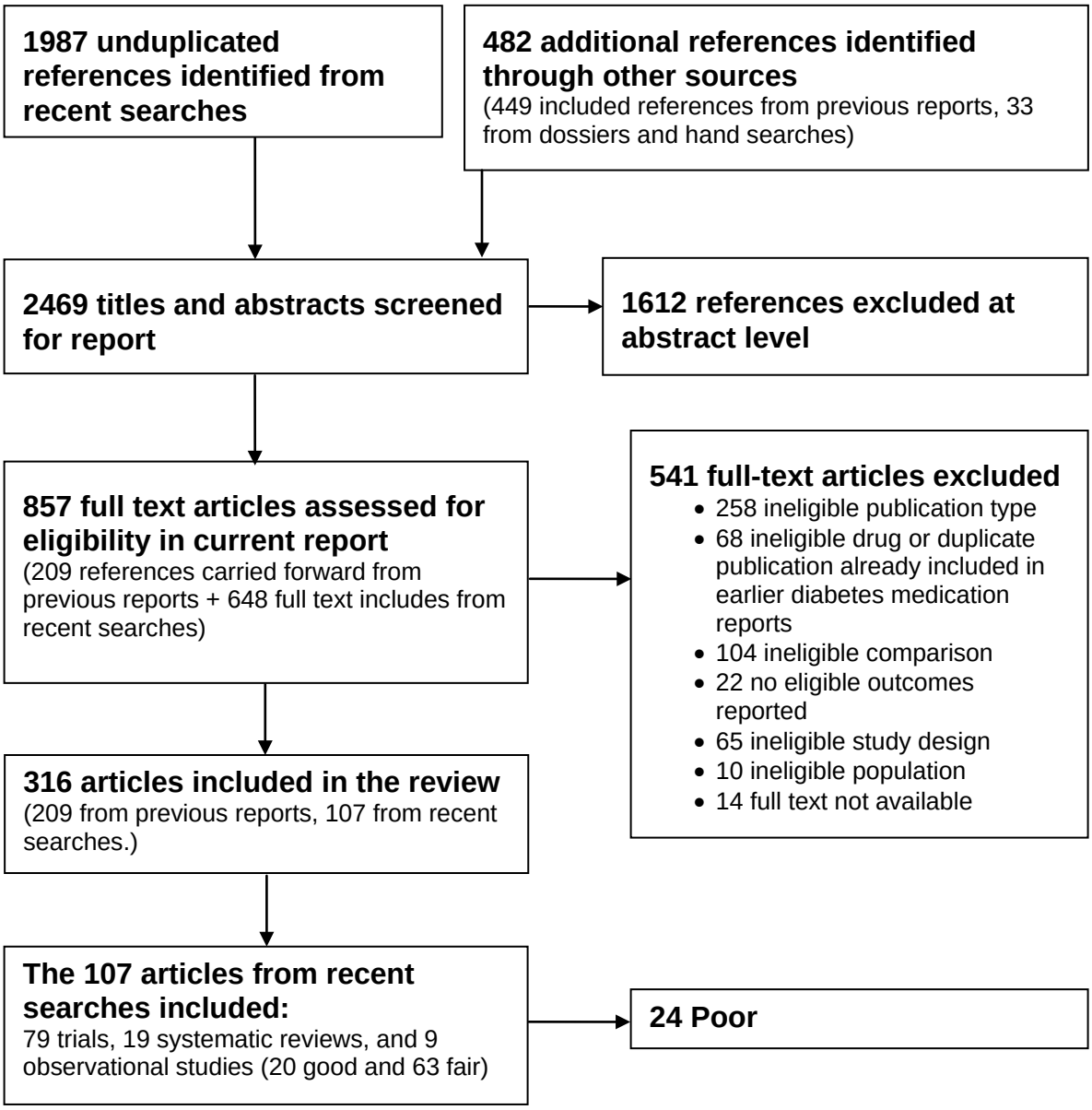
RESULTS

Overview

Literature searches through July 28, 2010 for the current report identified 1987 unduplicated citations. We received dossiers from 6 pharmaceutical manufacturers: Takeda Pharmaceuticals, GlaxoSmithKline, Bristol-Meyers Squibb, Amylin Pharmaceuticals, Novo Nordisk, and Merck. Twenty-two additional references were identified through hand searches of systematic reviews and other sources, and 11additional articles were identified from the dossiers, 4 from the pioglitazone (Actos®) dossier (Takeda Pharmaceuticals), 1 from the exenatide (Byetta®) dossier , 1 from the liraglutide (Victoza®) dossier (Novo Nordisk), 4 from the sitagliptin dossier (Merck), and 1 from the saxagliptin (Onglyza®) dossier (Bristol-Meyers Squibb). We also retrieved 240 excluded references from the reference database of the Fixed Dose Combination Drug Products for the Treatment of Type 2 Diabetes and Hyperlipidemia DERP report[17] in order to review these publications using new inclusion criteria. From all of these sources, we had a total of 2260 references. In addition to these, we carried forward 209 of the included studies from 3 previous DERP reports: Newer Drugs for the Treatment of Diabetes Mellitus,[8] Fixed Dose Combination Drug Products for the Treatment of Type 2 Diabetes and Hyperlipidemia,[17] and the Drug Class Review on Thiazolidinediones.[18]

By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 857 citations. After re-applying the criteria for inclusion, we ultimately included 107 new publications from our recent literature searches and other sources, plus the 209 includes from previous reports. See Appendix D for a list of excluded studies and reasons for exclusion at the full text stage. Figure 1 shows the flow of study selection. Among the 107 includes from our recent searches, 79 were trials, 19 were systematic reviews, and 9 were observational studies. Among these, 20 were rated good quality, 63 were fair quality, and 24 were poor quality. Poor-quality studies are listed in Appendix D.

Figure 1. Results of literature search



Key Question 1. What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

I. Newer Drugs for the Treatment of Diabetes Mellitus: Amylin Agonists, DPP-4 Inhibitors, and Incretin Mimetics

Summary of Findings for Amylin Agonists

Pramlintide for type 1 diabetes

Evidence in children

- No data on children were reported, although people as young as 16 years were eligible for study enrollment in 2 included trials (% of children enrolled was not reported) [19, 20] (insufficient strength of evidence).

Evidence in adults

- HbA1c was either slightly improved or no different with the addition of pramlintide 30 or 60 mcg/meal to a flexible-dose insulin regimen compared with placebo plus flexible-dose insulin regimen over 29 weeks[20] (between-group difference: 0.0%) and 52 weeks[19] (between-group difference: 0.27%, *P* value, not reported) of treatment (low strength of evidence).
- Greater reduction in HbA1c when pramlintide 60 mcg 3 or 4 times a day was added to fixed-dose insulin therapy (decreased from baseline by 0.29% to 0.34%, $P<0.01$) than when placebo was added to fixed-dose insulin (decrease by 0.04%, not statistically significant) at 52 weeks[21] (low strength of evidence).
- Slight weight loss with pramlintide in addition to insulin (range: −0.4 to −1.3 kg) compared with slight weight gain with placebo plus insulin in a fixed- or flexible-dose setting (range: +0.8 to +1.2 kg) over 29 and 52 weeks (moderate strength of evidence).

Pramlintide for type 2 diabetes

Evidence in children

- Children and adolescents ≤ 18 years were not enrolled in any of the included studies (insufficient strength of evidence).

Evidence in adults

- No included studies focused on health outcomes as the primary outcomes. One study reported some health outcomes among the adverse events.[22] Overall evidence was insufficient to determine how pramlintide compares with other treatments for their impact on health outcomes.
- Greater reduction in HbA_{1c} with pramlintide doses from 75 mcg to 120 mcg given 2 or 3 times daily added to fixed- or stable doses of insulin compared with placebo and insulin (range 0.13% to 0.4% at 52 weeks, moderate strength of evidence).
- Greater reduction in weight with pramlintide doses from 75 mcg to 120 mcg given 2 or 3 times daily added to fixed- or stable-doses of insulin compared with placebo and insulin

(range 1.1 kg to 1.85 kg, placebo-corrected differences at 52 weeks, moderate strength of evidence).

- No statistically significant difference for reduction in HbA1c between the addition of pramlintide 120 mcg at meals to glargine or detemir compared with rapid acting insulin analog at 24 weeks (1.1% compared with 1.3%, P=0.46, low strength of evidence).
- No change in weight reported with the addition of pramlintide 120 mcg at meals to glargine or detemir, compared with a 4.7 kg weight gain with rapid acting insulin analog at 24 weeks (+4.7 kg between group difference, P<0.0001, low strength of evidence).

Detailed Assessment for Pramlintide in Type 1 Diabetes

We found no active-control trials. We found 3 placebo-controlled trials. Characteristics of these trials are presented in Table 5 and results for HbA1c and weight are presented in Table 6. All 3 studies were fair-quality and were conducted in a double-blind manner with pramlintide or placebo added to their insulin regimen. None of these trials were similar enough for efficacy data to be pooled.

Table 5. Characteristics of pramlintide placebo-controlled trials in adults with type 1 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years)(SD)[a] % Male[a] % White[a] % Hispanic[a]	Baseline values: HbA1c (%) (SD)[a] Weight (kg)[a]	Interventions
Whitehouse, 2002[19] US Fair	480/342 52	40.3-40.4 (11.6-12.1) 55 92-96 NR	8.7-8.9 (1.3-1.5) 75.0-75.6 (13.8-13.3)	Pramlintide: 30 mcg, 60 mcg QID[b] Placebo + Insulin: No restrictions on use (flexible dosing)
Ratner, 2004[21] US, Canada Fair	651/479 52	39.2-41.9 (12.8-13.6) 47-53 89-92 NR	8.9-9.0 (0.9-1.1) 75.8-78.3 (14.5-15.8)	Pramlintide: 60 mcg TID, 60 mcg QID, 90 mcg TID[b,c] Placebo + Insulin: Dose adjustments not encouraged (fixed-stable dosing)
Edelman, 2006[20] US Fair	296/295 29	41 (12-14) 36.6-53.5 85.4-92 NR	8.1-8.2 (0.7−0.8) 77-83 (13-18)	Pramlintide: 30 mcg, 60 mcg, TID-QID[b] Placebo + Insulin: No restrictions on use (flexible dosing)

Abbreviations: BMI, body mass index; NR, not reported; SD, standard deviation; TID, 3 times daily; QID, 4 times daily.
[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] Pramlintide was administered before meals with insulin.
[c] Efficacy results from 90 mcg arm were excluded after another trial indicated that this dose exhibited an adverse tolerability profile.

Efficacy and effectiveness

Flexible-dose insulin

In a fair-quality trial the addition of pramlintide 30 mcg or 60 mcg 3 or 4 times a day with meals to a flexible-dose insulin regimen did not significantly improve HbA1c (−0.5% compared with −0.5%; Table 6) compared to patients receiving a combination of short- and long-acting insulin plus placebo adjusted to achieve specified glycemic targets over 29 weeks.[20] Pramlintide-treated patients lost slightly more weight than insulin-only patients (−1.3 kg compared with +1.2 kg).

All patients received stable doses (±10% change from baseline) of intensive insulin therapy using multiple daily injections or continuous insulin infusion before enrolling in the study. Patients were mainly middle-aged and white and had long-standing type 1 diabetes. Mean baseline HbA1c was 8.1%. A 30% to 50% reduction in mealtime insulin was recommended before starting pramlintide to avoid hypoglycemic events.

In a second trial using flexible insulin dosing,[19] the addition of pramlintide 30 mcg or 60 mcg 4 times a day to insulin with each meal was slightly more effective than insulin plus placebo in lowering HbA1c and weight (Table 6). The change in HbA1c at week 52 was −0.39% with pramlintide plus insulin and −0.12% with insulin plus placebo (between-group difference: 0.27%, *P* value, not reported).

This trial was rated fair quality, but there are some aspects of the design and reporting that limit the validity of the results: only 71% of patients completed the 52 weeks of therapy and data from only completers were examined. The total withdrawal rates of 28% to 29% were similar between the treatments, however, more pramlintide-treated patients discontinued due to adverse events than placebo-treated patients during the study (12.8% compared with 8.0%). Nausea was the most common reason for withdrawal. In addition, the authors reported no further details on insulin dose adjustments than that they were made according to "good medical practices."

Stable insulin dosing

The addition of pramlintide 60 mcg 3 or 4 times a day with meals to fixed or stable background insulin therapy improved HbA1c by 0.29% and 0.34% compared with 0.04% improvement in the insulin plus placebo group over 52 weeks of therapy.[21] Pramlintide-treated subjects also demonstrated nominal weight loss from baseline (−0.4 kg at 52 weeks, $P<0.05$), which was not seen with placebo (+0.8 kg at 52 weeks, $P>0.05$). This trial was rated fair quality, but there are some aspects of the design and reporting that limit the validity of the results, including high withdrawal rates (>35% in all treatment arms). However a greater proportion of pramlintide-treated patients discontinued due to adverse events (primarily nausea) compared with those in the placebo plus insulin arm (14% to 20% compared with 3% for adverse events).

This trial began with a 90 mcg dose arm, which was removed from efficacy analysis when another trial (identified as study #137-117 in US Food and Drug Administration reviews) revealed an adverse tolerability profile associated with this 90 mcg dose. Specific reasons for "intolerability" with the 90 mcg dose could not be found in either study #137-117 in the US Food and Drug Administration documents or from this trial by Ratner and colleagues. Only general statements were made by Ratner and colleagues: there was 2-fold increase in nausea, vomiting, anorexia and 4-fold increase in severe hypoglycemia event rates associated with pramlintide across the doses compared with placebo. Study #137-117 could not be found in a peer-reviewed publication.

Table 6. Efficacy outcomes of placebo-controlled trials of Pramlintide in type 1 diabetes

Author, year	HbA1c[a] (%)						Weight[a] (kg)		
	29 weeks						29 weeks		
Edelman, 2006[20]	30/60 TID-QID[b]		PBO				30/60 TID-QID[b]		PBO
	−0.5		−0.5				−1.3		+1.2
	26 weeks			52 weeks			52 weeks		
Whitehouse, 2002[19]	30/60[b] QID		PBO	30/60[b] QID		PBO	30/60[b] QID		PBO
	−0.58		−0.18	−0.39		−0.12	−0.5		+1.0
Ratner, 2004[21]	60 TID	60 QID	PBO	60 TID	60 QID	PBO	60 TID	60 QID	PBO
	−0.41	−0.39	−0.18	−0.29	−0.34	−0.04	−0.4	−0.4	+0.8

Abbreviations: PBO, placebo; TID, 3 times daily; QID, 4 times daily.
[a] Data represent change from baseline.
[b] Patients received 30 or 60 mcg with meals.

Detailed Assessment of Pramlintide in Type 2 Diabetes

Three placebo-controlled and one active-control trials were found. One post hoc analysis[23] of a placebo-controlled trial[24] addressing cardiovascular markers was identified. Characteristics of the included trials are presented in Table 7 and results for HbA1c and weight in Table 8. All of the studies were rated fair-quality. Three studies included patients who were not achieving glycemic goals on insulin with or without oral agents.[24-26] One study included patients not achieving glycemic goals regardless of insulin or oral agent use.[22] None of the trials were pooled due to significant heterogeneity.

Table 7. Characteristics of pramlintide trials (placebo and active controlled) in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a]	Intervention Dosages	Background therapy
Ratner, 2002[26] US Fair	538/538 52	55.5-57.5 (8.9-10.8) 38-44 76-81 8-10	9.0-9.3 (1.1-1.2) NR	Pramlintide: 30 mcg, 75 mcg, 150 mcg TID[b] Placebo + Insulin: Dose adjustments not encouraged (fixed-stable dosing)	Stable doses of MET or SU were allowed; doses to remain unchanged
Hollander, 2003[25] US Fair	656/498 52	56.4-57.0 (10.2-10.5) 48-52 73-77 8-13	9.0-9.3 (1.1-1.3) 96.7-97.1 (19.3-23.2)	Pram: 60 mcg TID, 90 mcg, 120 mcg BID[b] Placebo + Insulin: Dose adjustments not encouraged (fixed-stable dosing)[c]	Stable doses of MET or SU were allowed; doses to remain unchanged
Riddle, 2007,[24] Wysham 2008[23d] US Fair	212/211 16	55 (9-10) 48.1-54.3 72-73 8-13	8.5 (0.9) 103 (18)	Pram: 60 mcg, 120 mcg, BID-TID[e] Placebo + insulin glargine: dose adjustments allowed	Stable doses of MET, SU, +/- TZD were allowed
Riddle, 2009[22] US Fair	113/112 24	54-55(10-11) 34-39.3 NR NR	8.2-8.3(0.8) 103-108(18-22)	Pram: 120 mcg before major meals Rapid-acting insulin analog: 5 units before meals, titrated every 3-7 days	Insulin glargine or detemir, oral antihyerpglycemics were allowed

Abbreviations: BID, 2 times per day; BMI, body mass index; MET, metformin, NR, not reported; Pram, Pramlintide; SD, standard deviation; SU, sulfonylurea, TID, 3 times per day.

[a] Data presented are the range across treatment groups for mean and standard deviation.

[b] Pramlintide was administered before meals + insulin or insulin glargine ± oral hypoglycemic agent.

[c] Note: 60 mcg arm was excluded after another trial indicated that this dose was less effective than higher doses

[d] Wysham, 2008 is a post hoc analysis of Riddle. To avoid duplication, the data are not presented here.

[e] Pramlintide was administered with insulin glargine $\pm$ oral hypoglycemic agent.

Dose-ranging study

The addition of pramlintide 75 mcg/meal or 150 mcg/meal to fixed-dose insulin, with or without oral hypoglycemic agents (metformin or sulfonylureas), improved HbA1c by 0.3% to 0.4% and weight loss by 1.5 to 2.4 kg (placebo-corrected values) in a population with poorly controlled (HbA1c 9.0% to 9.3%) type 2 diabetes over 52 weeks.[26] No significant differences in HbA1c were observed between 2 pramlintide doses at the end of the trial: pramlintide 75 mcg (−0.5%) compared with 150 mcg (−0.6%). The largest reductions in HbA1c (almost 1%) occurred early on at week 13 for those on the 150 mcg dose.

This trial was rated fair quality, but there are some aspects of the design and reporting that limit the validity of the results. These include high withdrawal rates (~30%) which were similar for placebo, pramlintide 30 mcg and 75 mcg groups. Those randomized to pramlintide 150 mcg dose exhibited largest rates of total withdrawal and withdrawal due to adverse events (37.5% and 18%).

Stable insulin dosing

The addition of pramlintide 90 mcg or 120 mcg to fixed or stable doses of insulin with or without oral hypoglycemic agents (metformin or sulfonylureas) gave slightly larger improvements in HbA1c and weight at 52 weeks than patients randomized to placebo plus fixed-dose insulin (placebo-corrected values for HbA1c: 90 mcg: −0.13%, 120 mcg: −0.4% and for weight: 90 mcg: −1.1 kg; 120 mcg: −1.85 kg).[25] Effect on HbA1c was greatest at 26 weeks for both pramlintide groups ($P<0.05$ compared with placebo) and persisted only with the 120 mcg arm at 52 weeks (change in HbA1c from baseline −0.62%, $P<0.05$). Approximately 20% to 27% of all randomized patients were taking oral hypoglycemic agents at baseline.

During the course of this one fair-quality trial, [25] results from another study (identified as study #137-123 in the US Food and Drug Administration reviews) found that pramlintide 60 mcg was less effective than compared with higher doses. As a result, efficacy and safety information from the 60 mcg arm were not reported by this trial.

Flexible insulin dosing

In contrast to the previous study, another short-term fair-quality trial [24] evaluated pramlintide as a pre-meal medication in conjunction with glargine (without prandial insulin) with or without oral hypoglycemic agents (metformin, sulfonylureas, and/or thiazolidinediones). The comparison group was patients on flexible-dose glargine plus placebo. At 16 weeks, the addition of pramlintide to glargine reduced HbA1c by 0.36% and induced weight loss of 2.3 kg (placebo-corrected values) relative to placebo plus glargine.

Glargine, a basal insulin without pronounced peak effects, was allowed to be adjusted during the study to achieve prespecified fasting glucose targets once pramlintide doses were stabilized. Patients had diabetes for 10 to 11 years. At baseline HbA1c was moderately elevated at 8.5%, and patients were using insulin glargine 48 to 54 units per day, with 50% of patients concomitantly taking ≥2 oral hypoglycemic agents and 89% taking at least 1 oral agent.

Another fair-quality trial [22] compared pramlintide with rapid acting insulin analog (RAIA; lispro, aspart, or glulisine) in addition to basal insulin (glargine or detemir). Both basal and RAIA were allowed to be titrated at the investigators discretion, however basal insulin was titrated once or twice weekly to fasting glucose 70-100 mg/dL and RAIA could be titrated only after 4 weeks of basal titration to avoid hypoglycemia. RAIA was increased by 1-2 units every 3-7 days per the investigator based on glucose readings prior to the next meal. RAIA resulted in a

non-statistically significant greater HbA1c reduction over pramlintide by 0.2% (P=0.46). No change in weight was noted in the pramlintide group, however patients randomized to RAIA did experience significantly more weight gain, mean change from baseline 4.7 kg (P<0.0001).

Baseline HbA1c was similarly elevated to previously described studies at 8.2% to 8.3% and approximately 50% of patients were taking oral agents. Of the patients in the pramlintide group, 27% were using basal insulin at doses averaging 20-24 units per day, as were 24% of patients in the placebo group.

Table 8. Efficacy outcomes of placebo and active-control trials of pramlintide in type 2 diabetes

Author, year	Change in HbA1c from baseline (%)						Change in weight from baseline (kg)		
Riddle, 2007[24]	16 weeks						16 weeks		
	60/120 BID-TID	PBO					60/120 BID-TID	PBO	
	−0.7	−0.34					−1.6	+0.7	
Riddle, 2009[22]	24 Weeks						24 weeks		
	120 TID	RAIA					120 TID	RAIA	
	−1.1	−1.3					0	+4.7	
	26 weeks			52 weeks			52 weeks		
Ratner, 2002[26]	75 TID	150 TID	PBO	75 TID	150 TID	PBO	75 TID	150 TID	PBO
	−0.8	−0.79	−0.3	−0.5	−0.6	−0.2	−0.5	−1.4	+1.0
Hollander, 2003[25]	90 BID	120 BID	PBO	90 BID	120 BID	PBO	90 BID	120 BID	PBO
	−0.54	−0.68	−0.3	−0.35	−0.62	−0.22	−0.5	−1.25	+0.6

Abbreviations: BID, 2 times per day; PBO, placebo; RAIA, rapid acting insulin analog; TID, 3 times per day.

Summary of Findings for DPP-IV Inhibitors

Eighteen randomized controlled trials for sitagliptin and 5 randomized controlled trials for saxagliptin fulfilled inclusion criteria. Four of the sitagliptin randomized controlled trials were identified through dossier submission, 2 of which were extensions of other studies included. Two systematic reviews including sitagliptin also met inclusion criteria. No comparative cohort or case-control studies were identified reporting either long-term benefits or adverse events. In the US Food and Drug Administration Medical and Statistical Reviews we identified 10 relevant trials for sitagliptin, of which 7 were published in peer-reviewed journals. One of the trials[27] identified from the US Food and Drug Administration Reviews was not included because it did not meet inclusion criteria; the 3 remaining trials (study #P10X1, P014, and P014X1) could not be found in the medical literature. Details of included studies are found in Tables 9-17; their quality assessments are in Evidence Table 6 (Evidence Tables are published in a separate document).

Summary of Findings for Sitagliptin

Efficacy/Effectiveness

Sitagliptin compared with Saxagliptin

- We found no head-to-head studies of sitagliptin and saxagliptin meeting inclusion criteria (insufficient strength of evidence).

Evidence in children

- Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness or efficacy (insufficient strength of evidence).

Evidence in adults

- All studies focused on intermediate outcomes with none focusing on health outcomes as primary outcomes. Some studies reported some health outcomes such as all-cause mortality or number of people with macrovascular disease among secondary outcomes or adverse events. Overall evidence was insufficient to determine how sitagliptin compares with other treatments for their impact on health outcomes.
- No studies provided data on efficacy/effectiveness for follow up beyond 2 years.
- Sitagliptin monotherapy resulted in slightly less HbA1c reduction than either metformin monotherapy over 54 weeks (between group difference −0.16 for metformin 1000 and −0.47 for metformin 2000 mg/d) or glipizide monotherapy over 12 weeks (between group difference −0.22%) (low strength of evidence for both comparisons).
- Sitagliptin monotherapy resulted in slight weight gain, compared with slight weight loss for those treated with metformin monotherapy over 54 weeks (between group difference −1.6 to −2.1 at 54 weeks, low strength of evidence).
- Sitagliptin monotherapy resulted in slightly less weight gain compared with glipizide monotherapy over 12 weeks (+0.4 kg compared with +0.9 kg, low strength of evidence).
- Greater reduction in HbA1c with liraglutide 1.2 mg and 1.8 mg daily than with sitagliptin 100 mg daily in one trial (-1.24% to -1.5% compared with -0.6%; $P<0.0001$, low strength of evidence). Weight loss was significantly greater with both doses of liraglutide compared to sitagliptin.
- Greater reduction in HbA1c with sitagliptin 100 mg/d monotherapy than with placebo (weighted mean difference −0.79%, 95% CI −0.93 to −0.66) in patients inadequately controlled on diet and exercise over 12-24 weeks (moderate strength of evidence).
- Less weight loss with sitagliptin 100 mg/d monotherapy than with placebo (weighted mean difference 0.66, 95% CI 0.43 to 0.89, moderate strength of evidence).
- Studies comparing add-on of sitagliptin to other hypoglycemic agents (metformin, pioglitazone, or glimepiride) found sitagliptin-treated subjects to have either more weight gain, less weight loss, or similar changes in weight compared to placebo-treated subjects (low strength of evidence).
- Overall, in patients with inadequate glycemic control on one (metformin, pioglitazone, or glimepiride) or 2 hypoglycemic agents, the addition of sitagliptin resulted in greater reduction in HbA_{1c} than the addition of placebo (between group difference −0.5 to −1.0, moderate strength of evidence)

- No significant difference in reduction in HbA1c between rosiglitazone and sitagliptin when added to metformin therapy in two randomized controlled trials (moderate strength of evidence).

Detailed Assessment for Sitagliptin

Systematic reviews

Amori and colleagues[28] published a good-quality systematic review of US Food and Drug Administration approved and unapproved GLP-1 analogues (exenatide, linaclotide) and DPP-4 inhibitors (sitagliptin [8 studies] and vildagliptin [12 studies]). Sitagliptin and vildagliptin were examined together, rather than individually. Thus, we do not report results of that systematic review here because vildagliptin is not a medication of interest for this report. The Cochrane Collaboration published one good-quality systematic review of DPP-4 inhibitors vildagliptin and sitagliptin.[29] In contrast to Amori and colleagues, this review presented results separately by drug. Two studies compared sitagliptin with another single hypoglycemic agent and found less HbA1c lowering with sitagliptin (weighted mean difference 0.33 (95% CI 0.18 to 0.48). In contrast, when sitagliptin was used in combination with another hypoglycemic agent compared to another hypoglycemic combination (6 studies), sitagliptin combination resulted in slightly greater HbA1c lowering (weighted mean difference −0.40, 95% CI −0.47 to −0.33). Similarly, 6 studies were pooled that compared sitagliptin to placebo as monotherapy and found sitagliptin to reduce HbA1c to a greater extent than placebo (weighted mean difference −0.77, 95% CI –0.85 to −0.65). When changes in weight were examined sitagliptin resulted in less weight loss than either placebo (3 studies) or another single hypoglycemic agent (1 study). Our analysis found similar results in change in HbA1c and weight to the above systematic review.

Randomized controlled trials

Eighteen unique randomized controlled trials were identified, with three extension trials, all of fair-quality. We first address active controlled trials and then placebo-controlled trials. The placebo-controlled section is organized by whether sitagliptin was used as monotherapy or as add-on therapy.

Table 9. Characteristics of sitagliptin active-control trials (with or without placebo study arms) in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a]	Intervention Dosages
Scott, 2007[30] Multinational Fair	743 12	54.7-56.2 (9.0-10.7) 37.6-52 61.0-69.4 NR	7.8-7.9 (0.9-1.0) NR	Sitagliptin 5-, 12.5-, 25, 50 mg BID Glipizide 5-20 mg/day Placebo

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a]	Intervention Dosages
Goldstein, 2007[31] Williams-Herman, 2009[32e] Williams-Herman, 2010[33f] Multinational Fair	1091 (885) 24, 54, 104	53.2-54.1 (9.6-10.2) 44.7-57.7 46.0-58.2 21.4-30.2	8.8[b] NR	Sitagliptin 50+MET 500 mg BID Sitagliptin 50+MET 1000 mg BID Sitagliptin 100 mg daily Metformin 500 mg BID Metformin 1000 mg BID Placebo
Nauck, 2007[34] Seck, 2010 [35] Multinational Fair	1172 (per-protocol 793) 52, 104	56.6-56.8 (9.3-9.8) 38.7-42.9 73.5-74.3 7.3-7.9	7.5[c] 89.5-89.7 (17.4-17.5)	Sitagliptin 100 mg daily or Glipizide 5-20 mg/day Added-on to metformin >1500 mg/day
Scott, 2008[36] Multinational Fair	273 18	54.8-55.3 (9.3-10.5) 39-41 NR 4.6-5.4 (3.5-4.0)	7.7-7.8 (0.8-1.0) 157-160 (31.4-37.4)	Sitagliptin 100 mg or Rosiglitazone 8 mg or Placebo Added to metformin monotherapy ≥ 1500 mg/day
Chan, 2008[37d] Multinational Fair	91 12,54	65.3-68.9 (9.7-9.8) 38-52 31-34 26-35	7.6-7.8 (0.9) 68.3-71.5 (14.0-16.5)	Sitagliptin 25 mg daily or 50 mg daily Placebo /glipizide
Aschner, 2010 [38] Multinational Fair	1050 24	55.7-56.3 (10.3-10.7) 52-56 NR NR	7.2 (0.7) NR	Sitagliptin 100 mg Metformin (uptitrated to 1000 mg twice daily)
Derosa, 2010 [39] Italy Fair	151 52	57-58(5-6) 49-51 NR NR	8.4-8.5(0.8-0.9) 77.3-78.7(5.4-6.2)	Sitagliptin 100mg daily plus pioglitazone 30mg daily Metformin 850mg twice daily plus pioglitazone 15mg daily
Rigby 2010[40] Fair	169 16	Rosi group: 54.7 (10.9) 58.9 28.6 67.9	8.06-8.17 (0.75-0.91) 78.7-81.1 (17.9-18.5)	Rosiglitazone 4 mg or Sitagliptin 100 mg or Colesevelam 3.75 g daily Added to metformin 1500-2550 mg daily
Pratley 2010 [41] Multinational Fair	665 26	55.0-55.9 (9.0-9.6) 45-48 82-91 15-16	8.4-8.5 (0.7-0.8) 93.1-94.6 (18.1-18.9)	LIR 1.2 mg daily LIR 1.8 mg daily Sitagliptin 100 mg Added to metformin ≥ 1500 mg daily

Abbreviations: BID, twice daily; NR, not reported; SD, standard deviation.
[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] >50% had HbA1c <9% at baseline.
[c] >70% had HbA1c <8% at baseline.
[d] Glipizide added to placebo group after 12 weeks for remaining 42 weeks. Sitagliptin dose determine by renal function. Patients could be on insulin, number not reported.
[e] Williams-Herman, 2009 is an extension of Goldstein, 2007.
[f] Williams-Herman, 2010 is an extension of Goldstein 2007.

Active-control trials

Seven fair-quality trials (10 articles) compared various doses of sitagliptin to active treatment arms of glipizide or metformin (Table 9).[30-39] Four of these trials included comparisons of sitagliptin monotherapy with glipizide or metformin monotherapy.[30-33, 37, 38] The others compared sitagliptin with metformin, rosiglitazone, liraglutide, or glipizide as add-on therapy to active background therapy of metformin or pioglitazone.[34-36, 39-41]

Monotherapy: Sitagliptin compared with an active agent

In 4 fair-quality trials, various doses of sitagliptin were compared to active treatment arms of glipizide 5-20 mg/d or metformin 1000-2000 mg/d (Table 9).[30-33, 37, 38] Patients had baseline HbA1c of 7.2% to 8.9%. The trials ranged from 12-104 weeks and showed overall, patients on glipizide and metformin 1-2 g/d monotherapy had numerically larger reductions in HbA1c compared with sitagliptin monotherapy (Table 10). Pooled analysis was not conducted due to small number of studies with significant heterogeneity.

One study compared sitagliptin 100 mg/day with metformin 1000 mg/day and 2000 mg/day monotherapy (3 other arms included placebo, sitagliptin/metformin 1000 mg/day and sitagliptin 2000 mg/day discussed separately).[31-33] Initial results reported after 24 weeks showed greater HbA1c reduction with both doses of metformin when compared to sitagliptin (*P* value not reported). After 30 additional weeks (54 weeks total) slightly more HbA1c lowering was seen in each group however, the reduction remained greater in the metformin groups. After 104 weeks total, HbA1c changes were similar across all 3 groups. Weight loss was also greater after 24, 54, and 104 weeks in the metformin groups.

Another study compared sitagliptin 100 mg/day with metformin 2000 mg/day (titrated up over 5 weeks).[38] Similar to the previous trial discussed, metformin resulted in greater HbA1c lowering (difference in LS mean change 0.14 (95% CI 0.06 to 0.21) and greater weight loss than sitagliptin ($P<0.001$).

A 12 week dose-response study compared various doses of sitagliptin, all divided twice daily, to glipizide titrated according to the study's protocol.[30] Slightly less HbA1c reduction was seen in the sitagliptin 100 mg/day group than the glipizide group. However, patients randomized to sitagliptin gained less weight than those in the glipizide group.

Another study that stratified patients to sitagliptin 25 mg/day or 50 mg/ day based on their renal function, compared sitagliptin to placebo for the first 12 weeks and then glipizide 5-20 mg/day for the remaining 42 weeks.[37] Patients in this study all had chronic renal insufficiency and were allowed to continue insulin therapy if on it prior to randomization. After 54 weeks, the placebo/glipizide group had slightly greater HbA1c reduction than sitagliptin. There was minimal change in HbA1c from 12 weeks to 54 weeks with sitagliptin. After 54 weeks, the sitagliptin group had greater weight loss than the placebo/glipizide group however after 12 weeks the placebo group had greater weight loss (Table 10) Results were not stratified by whether or not patients were taking insulin, however 7 patients in the sitagliptin group (11%) and 2 patients in the placebo group (8%) were on insulin at baseline.

Table 10. Efficacy outcomes of sitagliptin monotherapy compared with an active agent

Author, year	Change in HbA1c from baseline at (%)			Change in weight from baseline at (kg)		
	S25/50	PBO/Glip		S25/50	PBO/Glip	
	54 weeks			54 weeks		
Chan, 2008[a 37]	−0.7	−0.8		−0.9	0	
	S100	Glip		S100	Glip	
	12 weeks			12 weeks		
Scott, 2007[30]	−0.54[d]	−0.76		+0.4	+0.9	
	S100	M1	M2	S100	M1	M2
	24 weeks			24 weeks		
Goldstein, 2007[31]	−0.66	−0.82	−1.13	0	−0.9	−1.1
	54 weeks			54 weeks		
Williams-Herman, 2009[32b]	−0.8	−1.0	−1.3	0.6	−1.0	−1.5
	104 weeks			104 weeks		
Williams-Herman, 2010[33c]	−1.2	−1.1	−1.3	+0.5	−0.8	−2.8
	S100	M2		S100	M2	
	24 weeks			24 weeks		
Aschner, 2010[38]	−0.43	−0.57		−0.6	−1.9	

Abbreviations: Glip, glipizide; M1, metformin 1000 mg/day; M2, metformin 2000 mg/day; PBO/Glip, placebo added to glipizide; S25/50, sitagliptin 25mg or 50mg daily; S100, sitagliptin 100 mg daily.
[a] Glipizide added to placebo group after 12 weeks for remaining 42 weeks. Sitagliptin dose determined by renal function. Patients could be on insulin, number not reported.
[b] Extension of Goldstein, 2007 to 54 weeks.
[c] Extension of Goldstein, 2007 to 104 weeks.
[d] *P* <0.001 for between group comparison.

Add-on therapy: Sitagliptin compared with active control (other oral hypoglycemic agent) added to metformin

Four fair-quality trials (4 articles) compared the addition of sitagliptin with the addition of another oral hypoglycemic agent to ongoing metformin therapy.[34-36, 40 Pratley, 2010 #5847, 41] Pooled analysis was not conducted due to small number of studies with significant heterogeneity.

One fair-quality trial compared the effects of adding either sitagliptin 100 mg/d or glipizide 5-20 mg/d in patients with inadequate glycemic control on metformin.[34, 35] Glycemic control was considered inadequate if the metformin dose was ≥ 1500 mg/d with baseline HbA1c 6.5% to 10% at initial screening or after several weeks of stabilizing the metformin dose prior to a 2-week single-blind, placebo run-in period before randomization.

Over the initial 52 weeks the 2 study groups showed no significant differences in treatment effects for HbA1c (between-group difference 0.04%, 95% CI -0.04, 0.13) (Table 11). There was a statistically significant difference between treatment groups in the change in weight. Sitagliptin-treated subjects experienced slight weight loss) compared with a small weight gain seen in glipizide-treated subjects (between-group difference -2.5kg, 95% CI -3.1, -2.0). Most patients had low baseline HbA1c (mean 7.5%) and more than 70% of patients were on oral

monotherapy while approximately 30% were on 2 oral agents at baseline. Results were similar in the 104 week extension.[35] Minimal changes were seen in HbA1c change from 52 week results and 104 week results, which is in contrast to a previously discussed trial and extensions investigating sitagliptin as monotherapy. [31-33]

Another fair quality trial[36] assessed the effects of sitagliptin, rosiglitazone, or placebo added to metformin monotherapy over 18 weeks. Prior to randomization patients had to have inadequate glycemic control (HbA1c 7% to 11%) and had to be taking metformin at stable doses ≥1500 mg/d for at least 10 weeks before entering a 2-week run-in period. The mean baseline HbA1c was 7.7%.

In these patients, the addition of sitagliptin or rosiglitazone to metformin was significantly more effective than the addition of placebo to metformin at lowering HbA1c (P≤0.001). The placebo-corrected mean change from baseline was −0.51% (95% CI, −0.70 to −0.32) for sitagliptin, and was −0.57% (95% CI, −0.76 to −0.37) for rosiglitazone. Also, comparisons between sitagliptin and rosiglitazone were conducted and showed no statistically significant differences in lowering HbA1c (between-group difference: −0.06%, 95% CI −0.25 to 0.14). Patients randomized to sitagliptin or placebo exhibited slight weight loss from baseline (sitagliptin, −0.4 kg, 95% CI −0.8 to 0.0 compared with placebo, −0.8 kg, 95% CI −1.2 to −0.4) while patients on rosiglitazone gained weight (from baseline: +1.5 kg, 95% CI 1.0 to 1.9) over 18 weeks of therapy (Table 11).

Another trial compared the addition of colesevelan, rosiglitazone, or sitagliptin to ongoing metformin.[40] The trial found no statistically significant difference between the rosiglitazone- and sitagliptin-treated subjects.[40]

An additional 26 week fair quality active-control trial compared liraglutide (1.2 or 1.8 mg daily) to sitagliptin 100 mg daily.[41] All study participants were on metformin ≥ 1500 mg daily as background therapy. The study found a greater improvement in HbA1c with both doses of liraglutide compared to sitagliptin (change in HbA1c: liraglutide 1.2 mg -1.24%; liraglutide 1.8 mg -1.5%; sitagliptin -0.6%; $P<0.0001$ for both doses of liraglutide compared to sitagliptin). Weight loss was significantly greater with both doses of liraglutide compared to sitagliptin (change in weight: liraglutide 1.2 mg -2.86 kg; liraglutide 1.8 mg -3.38 kg; sitagliptin -0.96 kg; $P<0.0001$ for both doses of liraglutide compared to sitagliptin). Treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) improved both with liraglutide and sitagliptin, but increased significantly more in the liraglutide 1.8 mg arm of the study than in the sitagliptin 100 mg arm of the study.[41]

Add-on therapy: Sitagliptin compared with active control (other oral hypoglycemic agent) added to pioglitazone

One fair-quality study was identified that compared sitagliptin 100mg daily to metformin 850mg twice daily as add-on therapy to pioglitazone.[39] All patients included were not controlled on pioglitazone 30mg daily as monotherapy. Patients were randomized to have sitagliptin added to pioglitazone 30mg daily or metformin added to pioglitazone 15mg daily. The rational for different doses of pioglitazone in the two groups was not addressed in the publication.

After 52 weeks of treatment, there was no difference in HbA1c reduction between the two treatment groups. Both groups had similar reduction in HbA1c (between group difference 0.1%, $P>0.05$). Patients taking metformin in addition to pioglitazone experienced more weight

loss the patients taking sitagliptin in addition to pioglitazone (between group difference 1.1kg, $P<0.05$) (Table 11).

Table 11. Efficacy outcomes of Sitagliptin compared with an active agent added to another oral hypoglycemic agent

Author, year	Change in HbA1c from baseline (%)		Change in weight from baseline (kg)	
	52 weeks		52 weeks	
	S/MET	Glip/MET	S/MET	Glip/MET
Nauck, 2007[34]	−0.51	−0.56	−1.5	+1.1
	104 weeks		104 weeks	
Seck, 2010[35]	−0.54	−0.51	−1.6	+0.7
	16-18 weeks		16-18 weeks	
	S/MET	Rosi/MET	S/MET	Rosi/MET
Scott, 2008[36]	−0.73	−0.79	−0.4	+1.5
Rigby 2010[40] Fair	-0.4	-0.6	NR	NR
	52 weeks		52 weeks	
	S/PIO	Met/PIO	S/PIO	Met/PIO
Derosa, 2010[39]	-1.1	-1.0	-1.1	-2.2
	26 weeks		26 weeks	
	S/MET	LIR/MET	S/MET	LIR/MET
Pratley, 2010[41]	-0.6	1.2mg: -1.24 1.8mg: -1.5	-0.96	1.2mg: -2.86 1.8mg: -3.38

Abbreviations: Glip/MET, glipizide added-on to metformin; PBO/MET, placebo added to metformin; Rosi/MET, rosiglitazone added-on to metformin; S/MET, sitagliptin added-on to metformin; S/PIO, sitagliptin added on to pioglitazone; Met/PIO, metformin added on to pioglitazone.

Placebo-controlled trials

Thirteen fair-quality trials compared various doses of sitagliptin to placebo (Tables 12 and 13).[30, 36, 37, 42-51] Six of these trials included comparisons of sitagliptin monotherapy with placebo (Table 12).[30, 42-46] The others compared add-on therapy with sitagliptin or placebo to a variety of ongoing treatments (Table 13).[36, 37, 47-51]

Table 12. Characteristics of sitagliptin monotherapy placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD) Weight (kg)	Intervention Dosages
Aschner, 2006[42] Multinational Fair	741 24	53.4-54.9 (9.5-10.1) 42.9-53.2 50.2-52.8 21.2-25.3	8.0 83.7-85.0 (18.1-19.2)	Sitagliptin 100 mg daily Sitagliptin 200 mg daily Placebo
Raz, 2006[43] Multinational Fair	521 18	54.5-55.5 (9.2-10.1) 37.3-49.5 61.8-70.9 18.0-20.0	8.1[a] 89.6-92.8 (18.8-19.4)	Sitagliptin 100 mg daily Sitagliptin 200 mg daily Placebo (randomized to 2:2:1 ratio)
Nonaka, 2008[44] Japan Fair	152 12	55.0-55.6 (8.0-8.6) 34-40 NR/Asian NR/Japanese	7.6 NR	Sitagliptin 100 mg daily Placebo
Scott, 2007[30] Multinational Fair	743 12	54.7-56.2 (9.0-10.7) 37.6-52 61.0-69.4 NR	7.8-7.9 (0.9-1.0) NR	Sitagliptin 5-, 12.5-, 25, 50 mg BID Glipizide 5-20 mg/day Placebo
Mohan, 2009[45] China, India, Korea Good	530/508 18	50.9 (9.3) 40-43 NR/Asian	8.7-8.8 (1.0-1.1) 66.6-66.8 (10.2-11.4)	Sitagliptin 100 mg daily Placebo
Hanefeld, 2007[46] Multinational Fair	555/552 12	55.1-56.0(7.9-10.3) 36.9-55.9 78.4-88.3 NR	7.6-7.8(0.9-1.0) NR	Sitagliptin 25 mg, 50 mg, 100 mg daily Sitagliptin 50 mg twice daily Placebo

Abbreviation: BID, 2 times per day; NR, not reported; SD, standard deviation.
[a] Data presented are the range across treatment groups for mean and standard deviation.

Table 13. Characteristics of sitagliptin add-on therapy placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a]	Intervention Dosages
Charbonnel, 2006[47] Multinational Fair	701 24	54.4-54.7 (9.7-10.4) 40.5-44.2 63.1-67.1 11.8-15.5	8.0[a] 171.5	Sitagliptin 100 mg or Placebo Added-on to metformin ≥ 1500 mg/day
Rosenstock, 2006[48] Multinational Fair	353 24	55.6-56.9 (10.4-11.1) 42.1-46.9 72.5-72.6 12.0-12.4	8.0-8.1 (0.8)[b] 165.6-168.3 (39.5-39.9)	Sitagliptin 100 mg or Placebo Added-on to Pioglitazone 30-45 mg/day
Hermansen, 2007[49] Denmark, USA Fair	441 24	55.6-56.5 (9.6) 46.6-47.3 61.3-63.9 14.6-17.6	8.34[c] 181.2	Sitagliptin 100 mg or Placebo Added on to glimepiride 4-8 mg/day or glimepiride+ metformin >1500 mg/day
Scott, 2008[36] Multinational Fair	273 18	54.8-55.3 (9.3-10.5) 39-41 NR 4.6-5.4 (3.5-4.0)	7.7-7.8 (0.8-1.0) 157-160 (31.4-37.4)	Sitagliptin 100 mg or Rosiglitazone 8 mg or Placebo Added to metformin monotherapy ≥ 1500 mg/day
Raz, 2008[50] Multinational Fair	190 18, 30	53.6-56.1 (9.5) 49.0-58.5 42-47 25-32	9.2[d] 200	Sitagliptin 100 mg or Placebo Added to metformin > 1500 mg/day
Vilsboll, 2010[51] Multinational Fair	641 24	57.2-58.3 (9.1-9.3) 47-51 69-71 12-16	8.6-8.7 (0.9) 86.5-87.3(17.9-18.6)	Sitagliptin Placebo Added to insulin (>15 units/day) ± metformin (>1500 mg/day)
Chan, 2008[37] Multinational Fair	91 12, 54	65.3-68.9 (9.7-9.8) 38-52 31-34 26-35	7.6-7.8 (0.9) 68.3-71.5 (14.0-16.5)	Sitagliptin 25 mg daily or 50 mg daily Placebo /glipizide

Abbreviation: NR, not reported.
[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] >50% had HbA1c <8% at baseline.
[c] > 30% had HbA1c <8% at baseline; means are reported as standard deviation unless otherwise specified.
[d] >50% had HbA1c >9% at baseline.
[e] Glipizide added to placebo group after 12 weeks for remaining 42 weeks. Sitagliptin dose determined by renal function. Patients could be on insulin, number not reported.

Monotherapy: Sitagliptin compared with placebo

Seven fair-quality trials ranging from 12-24 weeks in duration compared sitagliptin 100 mg/d to placebo (Table 12).[30, 31, 42, 43, 45, 46, 52] Approximately 50% to 60% of subjects were on 1 or more oral hypoglycemic agents at screening. These agents were discontinued before diet and exercise run-in periods. Patients not responding to diet and exercise were eligible for study inclusion but were required to participate in a 2-week single-blind, placebo run-in period prior to randomization. Three trials allowed use of prespecified rescue medications based on certain glycemic criteria. Mean baseline HbA1c was 7.6% to 8.8%.

Patients randomized to receive sitagliptin 100 mg/d showed significant reductions in HbA1c (weighted mean difference −0.79%, 95% CI, −0.93% to −0.66%, see Table 15), while placebo-treated patients generally showed worsening glycemic control (Table 14). One dose-ranging study [46] found similar HbA1c lowering across sitagliptin 50 mg daily, 100 mg daily, and 50 mg twice daily (−0.43% to +0.44%), however 25 mg daily resulted in less reduction (−0.25%).

Change in weight varied across the trials, generally decreasing in both treatment arms (range for change from baseline: sitagliptin −0.1 to −0.8 kg compared with placebo −0.5 to −1.1 kg). However, one trial[45] found weight gain in the sitagliptin arm (mean change from baseline, 0.6 kg) and no change in weight in the placebo arm. Overall, however, subjects randomized to sitagliptin lost slightly less weight than subjects randomized to placebo (weighted mean difference: 0.661, 95% CI 0.43 to 0.892; see Table 15).

Table 14. Efficacy outcomes of sitagliptin monotherapy compared with placebo

Author, year	Change in HbA1c from baseline at (%)					Change in weight from baseline (kg)				
	S25	S50	S100	S50BID	PBO	S25	S50	S100	S50BID	PBO
Hanefeld, 2007[46]	12 weeks					12 weeks				
	−0.28	−0.44	−0.44	−0.43	0.12	−0.5 to −0.8				−0.5
	S25/50		PBO			S25/50		PBO		
	12 weeks					12 weeks				
Chan, 2008[37]	−0.6		−0.1			0		−0.6		
	S100		PBO			S100		PBO		
	12 weeks					12 weeks				
Nonaka, 2008[44]	−0.65		+0.41			−0.1		−0.7[a]		
Scott, 2007[30]	−0.54		+0.23			NR		NR		
	18 weeks					18 weeks				
Raz, 2006[43]	−0.48		+0.12			−0.6		−0.7		
Mohan, 2009[45]	−0.7		+0.3			+0.6		0		
	24 weeks					24 weeks				
Aschner, 2006[42]	−0.61[a]		+0.18			−0.2		−1.1[a]		
Goldstein, 2007[31]	−0.66[a]		+0.17			0.0		−0.9[a]		

Abbreviation: NR, not reported; PBO, placebo; S25, sitagliptin 25mg daily; S50, sitagliptin 50mg daily, S100, sitagliptin 100 mg daily; S50BID, sitagliptin 50 mg twice daily; S25/50, sitagliptin 25 or 50 mg daily.

[a] $P<0.001$ for sitagliptin compared with placebo.

Table 15. Results of meta-analyses for mean change in HbA1c and weight for sitagliptin 100 mg compared with placebo

		Pooled analysis					Heterogeneity
Outcome	**N**	**Measure**	**Units**	**Estimate**	**95% CI**	***P* value**	**I^2**
HbA1c	7[a]	WMD	%	−0.79	(−0.933; −0.664)	<0.001	66%
Weight	5[b]	WMD	Kg	0.66	(0.43; 0.892)	<0.001	0.3%

[a] Included studies for this outcome: Aschner (2006), Raz (2006), Nonaka (2008), Goldstein (2007), Scott (2007), Mohan (2009), Hanefeld (2007)
[b] Included studies for this outcome: Aschner (2006), Raz (2006), Mohan (2009), Nonaka (2008), Goldstein (2007)

Add-on therapy: Sitagliptin or placebo added to one oral hypoglycemic agent

A total of 6 fair-quality trials compared the addition of sitagliptin or placebo to another oral hypoglycemic agent.[36, 47-51] Three trials assessed the effects of sitagliptin compared to placebo in patients who were considered to have "failed" therapy with metformin,[36, 47, 50] 2 studies assessed sitagliptin compared to placebo in patients who were considered to have "failed" therapy with pioglitazone or glimepiride,[48, 49] and 1 study assessed sitagliptin compared to placebo in patients who were inadequately controlled on metformin and insulin >15 units daily.[51]

Mean baseline HbA1c ranged from 7.7% to 9.2%. Approximately 60% of patients were on more than 1 oral hypoglycemic agent, while 30% were on more than 2 oral agents (Table 13). Patients were considered to have "failed" therapy with metformin, pioglitazone, or glimepiride at screening or after 10-19 weeks of dose stabilization and if HbA1c was between 7% and 10% or 7.5% and 10.5%. Patients also entered 2-week single-blind, placebo run-in periods prior to randomization.

The addition of sitagliptin to metformin, pioglitazone, or glimepiride appears to show larger reductions in HbA1c and compared with the addition of placebo over 18 to 30 weeks (Table 16). Subjects who received placebo plus glimepiride showed worsening glycemic control, while subjects on placebo plus metformin or placebo plus pioglitazone had slight improvements or no change in HbA1c from baseline. Weight gain was generally seen in patients taking sitagliptin in combination with pioglitazone or glimepiride to a similar extent of those taking pioglitazone alone, however no weight gain was seen in those taking glimepiride alone. Patients randomized to add sitagliptin or placebo to metformin lost weight by 0.4 kg to 0.8 kg compared with baseline (Table 16). Pooled analysis was not conducted due to small number of studies and significant heterogeneity.

One fair quality randomized trial[50] studied the effects of sitagliptin or placebo added to ongoing metformin therapy. Unlike the other studies[47-49], this trial evaluated the effects of sitagliptin in patients with worse glycemic control (baseline HbA1c between 8% and 11%). These patients were on metformin and diet and exercise for 6 weeks, had baseline HbA1c between 8% and 11%, and had ≥85% adherence to their regimens during a 2-week, placebo run-in period. No patients were naïve to oral hypoglycemic agents and approximately 50% were already taking metformin monotherapy or combination oral therapy at baseline. The addition of sitagliptin to ongoing metformin therapy was more effective than placebo plus metformin at lowering HbA1c (placebo-corrected difference: −1.0%, 95% CI −1.4 to −0.6) over 30 weeks. Both treatment groups exhibited weight loss of −0.5 kg over 30 weeks.

One study was unique in that it included patients who were inadequately controlled on insulin and/or metformin therapy.[51] Patients were randomized to sitagliptin 100 mg or placebo in addition to their pre-study doses insulin and metformin (if they were taking). Approximately 70% of patients in both groups were taking metformin at baseline. Doses of insulin and metformin were not increased, however insulin could be decreased if hypoglycemia occurred. Similar results were seen in this study as others, with greater HbA1c lowering seen in patients randomized to sitagliptin than placebo (difference in LS mean change −0.6, 95% CI −0.7 to −0.4). Authors reported no difference in HbA1c lowering in patients on metformin or not on metformin (p=0.44). No difference was noted in weight change from baseline between the two groups, *P* value NR (Table 16).

Table 16. Efficacy outcomes of sitagliptin or placebo added to one oral hypoglycemic agent

Author, year	Change in HbA1c from baseline at (%)				Change in weight from baseline at (kg)[a]			
	24 weeks				24 weeks			
	S/Pio		P/Pio		S/Pio		P/Pio	
Rosenstock, 2006[48]	−0.85[b]		−0.15		+1.8		+1.5	
	S/Glim		P/Glim		S/Glim		P/Glim	
Hermansen, 2007[49]	−0.3[b]		+0.27		+1.1		0.0	
	S/MET		P/MET		S/MET		P/MET	
Charbonnel, 2006[47]	−0.7[b]		−0.02		−0.7		−0.6	
	18 weeks				18 weeks			
	S/MET		P/MET		S/MET		P/MET	
Scott, 2008[36]	−0.73[b]		−0.22		−0.4		−0.8	
	24 weeks				24 weeks			
	S+Insulin/MET		P+Insulin/MET		S+Insulin/MET		P+Insulin/MET	
Vilsboll, 2010[51]	−0.6[b]		0		±0.1		+0.1	
	18 weeks		30 weeks		18 weeks		30 weeks	
	S/MET	P/MET	S/MET	P/MET	S/MET	P/MET	S/MET	P/MET
Raz, 2008[50]	−1.0[b]	0	−1.0[b]	0	--	--	−0.5	−0.5

Abbreviations: S/Pio, sitagliptin added to pioglitazone; S/MET, sitagliptin added to metformin; S/Glim, sitagliptin added to glimepiride; P/-, placebo added to.
[a] Weight data not reported in the publication were provided by the manufacturer.
[b] *P* <0.001 between group difference

Add-on therapy: Sitagliptin or placebo added to 2 existing oral hypoglycemic agents

One fair-quality trial evaluated the addition of sitagliptin or placebo in patients whose glycemia was inadequately controlled on glimepiride 4-8 mg/d alone or glimepiride plus metformin 1500-3000 mg/d.[49] Results of sitagliptin or placebo added to glimepiride alone have already been

reviewed. In this trial, mean baseline HbA1c was 8.3%, and more than 95% of patients were also taking combination oral hypoglycemic agents at baseline and were considered to have failed this regimen either at screening or after several weeks of dose-stabilization of glimepiride and metformin before participating in a 2-week placebo run-in phase prior to randomization.

In patients already on glimepiride plus metformin, the addition of sitagliptin improved HbA1c over 24 weeks of treatment whereas the addition of placebo showed worsening glycemic control (difference in LS mean change -0.89%, 95%CI -1.1 to -0.68). Weight, however, increased slightly (+0.4 kg, 95% CI −0.1 to 0.9) with sitagliptin relative to placebo; whereas, placebo-treated patients showed weight loss (−0.7 kg, 95% CI −1.4 to −0.1) (Table 17).

Table 17. Efficacy outcomes of sitagliptin or placebo added to 2 oral hypoglycemic agents

Author, year	Change in HbA1c from baseline (%)		Change in weight from baseline (kg)	
	24 weeks		24 weeks	
	S/G/M	P/G/M	S/G/M	P/G/M
Hermansen, 2006[a] [49]	−0.59[b]	+0.3	+0.4	−0.7

Abbreviations: S/G/M, sitagliptin added-on to glimepiride and metformin; P/G/M, placebo added-on to glimepiride and metformin.
[a] Note: this trial also included 2 other treatment arms: glimepiride alone, glimepiride plus metformin.
[b] *P*<0.001 compared with P/G/M.

Summary of Findings for Saxagliptin

Evidence in children

- We found no studies including children and adolescents ≤ 18 years

Evidence in adults

- All studies focused on intermediate outcomes with none focusing on health outcomes as primary outcomes. Some studies reported some health outcomes such as all-cause mortality or cardiac death among secondary outcomes or adverse events. Overall evidence was insufficient to determine how saxagliptin compares with other treatments for their impact on health outcomes.
- No studies provided data on efficacy or effectiveness for follow up beyond 24 weeks.
- We found no active-control studies meeting inclusion/exclusion criteria for saxagliptin.
- Greater reduction in HbA1c with saxagliptin monotherapy compared to placebo (between group difference −0.45 to −0.65%, moderate strength of evidence); reduction was greater with saxagliptin 5 mg than with saxagliptin 2.5 mg.
- Saxagliptin added on to either metformin, a thiazolidinedione, or glyburide resulted in greater HbA1c reduction than placebo added on to metformin, a thiazolidinedione, or glyburide (between group difference ranges were −0.72 to −0.82%, −0.36 to −0.64, and −0.62 to −0.72, respectively; one study was identified for each comparison, low strength of evidence for each comparison; moderate strength of evidence overall for saxagliptin add-on therapy compared with placebo).

- Weight loss was greater with placebo than with saxagliptin monotherapy and greater weight loss was seen with saxagliptin 2.5 mg than with 5 mg. (between group difference −0.09 to −0.2 kg for placebo compared with saxagliptin 2.5; −0.8 to −1.3 kg compared with saxagliptin 5, moderate strength of evidence).

Detailed Assessment for Saxagliptin

Randomized controlled trials

We found 5 fair-quality randomized placebo-controlled trials meeting our inclusion/exclusion criteria. This section is organized by how saxagliptin was used (monotherapy or add-on therapy). There were no active control studies identified that met inclusion criteria. Characteristics of included studies are shown in Table 18.

Table 18. Characteristics of saxagliptin placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a]	Intervention Dosages[b]
Monotherapy				
Rosenstock, 2008[53] Multinational Fair	338 12	52.5-55.2 37-60 85-87 NR	7.7-8.0(0.97-1.09) 86.6-93.1(14.17-19.21)	Saxagliptin 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg daily Placebo
Rosenstock, 2009[54] NR Fair	401 24	53.27-53.91(10.06-12.32) 43.1-50.5 79-93(83.2-87.7) NR	7.9-8.0(0.9-1.1) 86.56-92.1(16.9-18.30)	Saxagliptin 2.5 mg, 5 mg, 10 mg daily Placebo
Add-on therapy				
DeFronzo, 2009[55] Multinational Fair	743 24	54.7-54.8 (9.7-10.4)46.1-56.8 79.7-83.8 NR	8.0(0.8-1.0) NR 86.0-87.3(17.0-17.8)	Saxagliptin 2.5 mg, 5 mg, 10 mg Placebo Added-on to metformin
Hollander, 2009[56] Fair	565 24	53.2-54.9(9.7-10.6) 45.6-53.8 53.2-55.9 NR	8.2-8.4(1.1) 80.4-82.1(19.4-22)	Saxagliptin 2.5 mg, 5 mg daily Placebo Added-on to TZD
Chacra, 2009 Multinational Fair[57]	768 24	54.9-55.4(9.6-10.7) 54.4-56.5 56.9-59.7 NR	8.4-8.5(0.9) 75.2-76.2(14.4-17.6)	Saxagliptin 2.5 mg, 5 mg daily Placebo Added-on to open label, uptitrated glyburide

Abbreviation: NR, not reported; TZD, thiazolidinedione; SD, standard deviation.
[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] Results presented only for US Food and Drug Administration approved doses (Saxagliptin 2.5 mg and 5 mg).

Monotherapy: Saxagliptin compared with placebo

In 2 fair-quality randomized controlled trials carried out over 12-24 weeks, a wide variety of doses were compared to placebo.[53, 54] Data abstracted was for approved doses in the United States, Saxagliptin 2.5 mg and 5 mg although other doses were studied in identified trials. All patients included in the trials were treatment naïve and mean baseline HbA1c for participants ranged from 7.7-8.0 (Table 18).

Overall, reduction in HbA1c was greater with saxagliptin compared to placebo and slightly greater with saxagliptin 5 mg compared to 2.5 mg (Table 19). With saxagliptin, HbA1c reduction ranged from −0.43 to −0.9% and placebo ranged from −0.27 to +0.19%. There was a numerically greater HbA1c reduction with saxagliptin in the 12 week trial[53] compared to the 24 week trial,[54] however the placebo corrected change was similar between the two trials. Patients were similar between the 2 trials except patients in the 24 week trial had diabetes for longer than those in the 12 week trial (mean duration 2.3-3.1 years compared to 0.8-1.8 years).

Weight loss was seen across all groups, however more weight loss was seen in the placebo group than in either saxagliptin 2.5 mg or 5 mg (−1.03 to −1.4 kg compared to −0.1 to −1.2 kg, Table 19). Patients randomized to saxagliptin 5 mg had less weight loss than those randomized to saxagliptin 2.5 mg.

Table 19. Efficacy outcomes for saxagliptin monotherapy compared with placebo

Author, year	Change in HbA1c from baseline (%)			Change in weight from baseline (kg)		
	12 Weeks			12 weeks		
	S2.5	S5	PBO	S2.5	S5	PBO
Rosenstock, 2008[53]	−0.72	−0.9	−0.27	−0.94	−0.23	−1.03
	24 Weeks			24 Weeks		
Rosenstock 2009[54]	−0.43[a]	−0.46[a]	0.19[a]	−1.2	−0.1	−1.4

Abbreviations: PBO, placebo; S2.5, saxagliptin 2.5 mg daily; S5, saxagliptin 5 mg daily.
[a] The adjusted mean change for each group was calculated from a mean baseline of 7.9%, although the actual mean baseline for each group was not 7.9%. The actual mean baseline values were: G1: 7.9%, G2: 8.0%, G3: 7.8%, G4: 7.9%.

Add-on therapy: Saxagliptin or placebo added to one oral hypoglycemic agent

Three fair-quality trials were identified that compared saxagliptin to placebo as add-on therapy in patients not achieving adequate glycemic control on either metformin, a thiazolidinedione, or glyburide.[55-57] Mean baseline HbA1c ranged from 8.0% to 8.4% and trials were all carried out over 24 weeks. Patients were deemed to have inadequate glycemic control if their HbA1c was ≥7% to ≤10% or ≥7% to ≤10.5% on their current therapy for the previous 8-12 weeks prior to screening.

In general, the addition of saxagliptin to metformin, a thiazolidinedione, or glyburide appears to show larger reductions in HbA1c compared with the addition of placebo over 24 weeks (Table 20). Results were not stratified by which thiazolidinedione patients were taking. Varying results were seen in regards to change in weight. The addition of placebo to glyburide or a thiazolidinedione resulted in less weight gain than the addition of saxagliptin to glyburide or a

thiazolidinedione. Slightly more weight loss was seen with the addition of saxagliptin 2.5 mg to metformin than with the addition of saxagliptin 5 mg or placebo. No statistical testing was done to determine the statistical significance of these differences.

One study randomized patients who had inadequate glycemic control on submaximal doses of sulfonylurea therapy.[57] Patients were switched from their current sulfonylurea to open label glyburide 7.5 mg/day. After a 4 week single blind run-in period, patients continued their open label glyburide and were randomized to either saxagliptin 2.5 mg/day, saxagliptin 5 mg/day or placebo + blinded glyburide 2.5 mg/day. Therefore patients randomized to placebo had a total daily dose of glyburide 10 mg daily as compared with glyburide 7.5 mg in the saxagliptin groups.

Table 20. Efficacy outcomes for saxagliptin or placebo added to one oral hypoglycemic agent

Author, year	Change in HbA1c from baseline (%)			Change in weight from baseline (kg)		
	24 Weeks			24 Weeks		
	S2.5/Met	S5/Met	PBO/Met	S2.5/Met	S5/Met	PBO/Met
DeFronzo, 2009[55a]	−0.59	−0.69	+0.13	−1.43	−0.87	−0.92
	S2.5/TZD	S5/TZD	PBO/TZD	S2.5/TZD	S5/TZD	PBO/TZD
Hollander, 2009[56]	−0.66	−0.94	−0.3	+1.3	+1.4	+0.9
	S2.5/Gly	S5/Gly	PBO/Gly	S2.5/Gly	S5/Gly	PBO/Gly
Chacra, 2009[57]	−0.54	−0.64	+0.08	+0.7	+0.8	+0.3

Abbreviations: Gly, glyburide; kg, kilogram; Met, metformin; PBO, placebo; S2.5, sitagliptin 2.5 mg; S5, sitagliptin 5 mg; TZD, thiazolidinediones.
[a] This study also had a saxagliptin 10 mg daily arm, however only data for approved doses were abstracted.

Summary of Findings for GLP-1 Agonists

Efficacy and effectiveness

Exenatide compared with liraglutide

- In the one included head-to-head trial (N=464), liraglutide 1.8 mg once daily reduced mean HbA1c significantly more than exenatide 10 mcg twice daily (−1.12% compared with −0.79%; estimated treatment difference −0.33; 95% CI −0.47 to −0.18, low strength of evidence).
- Exenatide and liraglutide resulted in similar weight loss (−2.87 compared with −3.24 kg, respectively; estimated treatment difference −0.38 kg; 95% CI −0.99 to 0.23, low strength of evidence)

Exenatide

Evidence in children

- No included study examined children or adolescents with type 2 diabetes.

Evidence in adults

- Except for one study reporting quality of life, no included studies examined the impact of treatment with exenatide on health outcomes (such as MI, death, stroke, or renal failure) (insufficient strength of evidence). The longest duration of an included study was 52 weeks.
- Four active-control trials compared exenatide to insulin, with both groups also receiving oral diabetes agents, and all found no significant difference between groups for reduction in HbA_{1c} (range for exenatide 10 mcg twice daily −1.0% to −1.4%; range for insulin −0.9% to −1.4%, moderate strength of evidence). In one of the trials, the substitution of exenatide for insulin did not improve HbA1c compared to continuing insulin.
- Active-control studies demonstrated significant weight loss in exenatide groups compared to weight gain with insulin (treatment difference range 4.1 kg to 5.4 kg, moderate strength of evidence).
- One active-control trial found no significant difference in improvement in HbA1c between exenatide and glibenclamide (-1.5% compared with -1.8%, $P>0.05$, low strength of evidence). Weight loss in the exenatide arm of the study was significantly greater than in the glibenclamide arm of the study (-8.0 kg compared with +4.3 kg, $P<0.001$, low strength of evidence).
- One trial comparing exenatide to rosiglitazone with all participants on background metformin therapy, found no significant difference in improvement in HbA1c (-0.9% vs. -1.0%, $P=0.720$), but greater weight loss in the exenatide arm of the study (-2.8 kg vs. +1.5, $P<0.001$).
- Greater reduction in HbA1c with exenatide than with placebo, both when added to various oral agents and as monotherapy. For exenatide 5 mcg twice daily compared with placebo (5 studies) weighted mean difference in HbA1c –0.72%, 95% CI –0.99% to –0.45% (moderate strength of evidence); for exenatide 10 mcg twice daily compared with placebo (8 studies) weighted mean difference in HbA1c –0.90%, 95% CI –1.08% to –0.73% (high strength of evidence).
- For change in weight, pooled analysis (5 studies) found no statistically significant difference between exenatide 5 mcg twice daily and placebo (weighted mean difference −0.61 kg, 95% CI −1.28 to 0.06). However, statistical heterogeneity was high for the pooled analysis ($I^2=74\%$), and a sensitivity analysis removing a single study resulted in significant weight loss for exenatide 5mcg compared to placebo (weighted mean difference −0.87, 95% CI −1.35 to −0.40, $P<0.001$, $I^2=33\%$) (low strength of evidence).
- For change in weight, exenatide 10 mcg twice daily resulted in significant weight loss compared to placebo (weighted mean difference –1.25 kg, 95% CI –1.60 to –0.90, high strength of evidence).
- Quality of life was examined in only one study of exenatide 10 mcg twice a day. No significant differences were seen between exenatide and insulin glargine (low strength of evidence).

Liraglutide

Evidence in children

- No study examined children or adolescents with type 2 diabetes

Evidence in adults

- No included studies focused on health outcomes as the primary outcomes. Several studies reported a health outcome among other secondary outcomes or in the adverse events section. Overall evidence was insufficient to determine how liraglutide compares with other treatments for their impact on health outcomes.
- The longest duration of an included study was 52 weeks.
- Three active-control trials comparing liraglutide to glimepiride demonstrated improvement in HbA1c in both treatment groups. Results indicate either no significant difference between treatment groups (2 trials) with liraglutide 0.6 mg daily and glimepiride 1 to 4 mg daily[58] and between liraglutide 1.2 mg and 1.8 mg daily and glimepiride 4 mg daily[59] or greater improvement in HbA1c with liraglutide (1.2 mg and 1.8 mg daily) than with glimepiride 8 mg daily (insufficient strength of evidence).[60]
- Liraglutide 1.2mg and 1.8 mg daily leads to weight loss whereas glimepiride causes weight gain (moderate strength of evidence).
- Greater reduction in HbA_{1c} in one good quality active-control trial comparing liraglutide 1.8 mg daily to open-label insulin glargine (−1.33% compared with −1.09%; *P*=0.0015, low strength of evidence)
- Weight loss with liraglutide compared with weight gain with insulin glargine in the same study (treatment difference −3.43 kg; *P*<0.0001, low strength of evidence)
- One trial comparing the addition of rosiglitazone with the addition of liraglutide (to ongoing glimepiride treatment) reported greater reduction in HbA1c with liraglutide (−1.1 compared with −0.4%, P<0.0001, low strength of evidence) and greater weight gain in the rosiglitazone arm compared to all doses of liraglutide (change in weight: liraglutide 0.6mg +0.7kg; liraglutide 1.2mg +0.3 kg; liraglutide 1.8mg -0.2 kg; rosiglitazone 4 mg +2.1 kg; *P*<0.0001 for all doses of liraglutide compared to rosiglitazone).
- Greater reduction in HbA1c with liraglutide 1.2 mg and 1.8 mg daily than with sitagliptin 100 mg daily in one trial (-1.24% to -1.5% compared with -0.6%; *P*<0.0001, low strength of evidence).[41]
- Greater weight loss with liraglutide 1.2 mg and 1.8 mg daily than with sitagliptin in the same study (-2.86 kg to -3.38 kg compared with -0.96 kg; *P*<0.0001, low strength of evidence).[41]
- Greater reduction in HbA_{1c} with liraglutide than with placebo (moderate strength of evidence), both when added to various oral agents and as monotherapy (liraglutide 0.6 to 0.65 mg daily weighted mean difference −1.10, 95% CI –1.45 to –0.75; liraglutide 1.2 to 1.25 mg daily weighted mean difference −1.28, 95% CI –1.56 to –1.00; liraglutide 1.8 to 1.9 mg daily weighted mean difference −1.26, 95% CI −1.50 to −1.03). Although all of the individual studies showed that liraglutide significantly decreased HbA1c compared to placebo, statistical heterogeneity in pooled analyses was substantial (I^2 71% to 82%).
- When compared with placebo, liraglutide 1.8 mg to 1.9 mg daily produced a significant decrease in weight (weighted mean difference −1.43 kg, 95% CI –2.33 to –0.56, moderate strength of evidence).
- There was no statistically significant weight loss for liraglutide 0.6 to 0.65 mg compared with placebo (moderate strength of evidence).
- Liraglutide 1.2 to 1.25 mg resulted in significant weight loss compared to placebo in all studies except for in the 1 included study in which all participants were on background sulfonylurea therapy; meta-analyses of 3 trials using the 1.2 to 1.25 dose indicated no

statistically significant difference in weight change between liraglutide and placebo (weighted mean difference −0.83 kg, 95% CI –1.85 to 0.19) but there was substantial statistical heterogeneity (I^2 76%); removing 1 trial where subjects were all on background sulfonylureas resulted in a finding of greater weight loss with liraglutide than with placebo (weighted mean difference −1.31 kg, 95% CI –1.85 to -0.77) (low strength of evidence).

Detailed Assessment of Exenatide Compared with Liraglutide

We found one fair quality randomized controlled trial comparing liraglutide to exenatide.[61] In this 26-week open-label study, 464 participants were randomized to liraglutide 1.8 mg once daily or exenatide 10 mcg twice daily. Participants were continued on their background oral antidiabetic therapy which was either metformin, a sulfonylurea, or both.

In this study, liraglutide reduced mean HbA1c significantly more than exenatide (−1.12% [SE 0.08] compared with −0.79% [SE 0.08]; estimated treatment difference −0.33; 95% CI −0.47 to −0.18; $P<0.0001$). Both liraglutide and exenatide resulted in similar weight loss (liraglutide −3.24 kg [0.33] compared with exenatide −2.87 [0.33]; estimated treatment difference −0.38 kg; 95% CI −0.99 to 0.23; $P=0.2235$).

Detailed Assessment for Exenatide

Active-control trials

Four open label studies compared exenatide 10 mcg twice a day to insulin therapy (various regimens). All studies used concurrent sulfonylurea and/or metformin in addition to the study treatment regimens (Table 21, Evidence Table 3). Three of these trials were fair-quality noninferiority studies,[62-64] and 1 was a fair-quality exploratory substitution study.[65] The outcomes in these 4 trials were too heterogeneous to pool in meta-analyses. In addition to the four trials comparing exenatide to insulin, we also identified one trial comparing exenatide to glibenclamide,[66] and one trial comparing exenatide to rosiglitazone.[67]

Table 21. Characteristics of exenatide active-control trials in adults with type 2 diabetes

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Barnett 2007[62] Fair	138 16	54.4-55.3 (1.1-1.2) 45.7 – 48.5 NR 6.6-8.3 (0.6−0.7)	8.89 (0.13) 84.0-85.6(2.0) 30.9-31.3 (0.5)	Exenatide: 10 mcg BID Insulin glargine	Both groups continued prior MET or SU
Davis, 2007[65] Fair	51 16	52-54 (8) 56-50 NR NR 10-12 (6-7)	8.0-8.3 (0.9-1.2) 95-102 (17-19) 33-35 (4)	Exenatide: 10 mcg BID Insulin: various	Both groups received MET +/- SU or SU

Heine, 2005[63] Boye, 2006 Fair	551 26	58-59.8 (8.8-9.5) 55-56.6 79.8-80.5 15-15.6 9.2-9.9 (5.7-6.0)	8.2-8.3(1.0) 87.5-88.3 (16.9 - 17.9) 31.3-31.4 (4.4 - 4.6)	Exenatide: 10 mcg BID Insulin glargine	Both groups received maximum MET and SU
Nauck, 2007[64] Fair	505 52	58-59 (9) 49-53 NR NR 9.8-10.0 (6.2-6.3)	8.6 (1.0-1.1) 83.4-85.5 (15.6-15.7) 30.4 (4.1)	Exenatide: 10 mcg BID Biphasic insulin aspart	Both groups received MET and SU
DeFronzo, 2010[67] Fair	137 20	56 (10) 51 61 23 4.7 (3.7)	7.8 (0.7) NR 32.5 (4.3)	Exenatide: 10 mcg BID Rosiglitazone 4 mg BID Exenatide and Rosiglitazone	All groups continued on prior MET
Derosa, 2010[66] Fair	128 52	56-57 (7-8) 48-50 NR NR NR	8.8-8.9 (0.7-0.8) 82.0-82.4 (8.3-9.1) 28.5-28.7 (1.4-1.5)	Exenatide: 10 mcg BID Glibenclamide 5 mg TID	Both groups continued on prior MET

Abbreviations: BID, twice daily; TID, three times daily; BMI, body mass index; MET, metformin; NR, not reported; SD, standard deviation; SU, sulfonylurea.
[a] Data presented are the range across treatment groups for mean and standard deviation.

Efficacy and effectiveness

Heine and colleagues[63] compared once-daily insulin glargine to exenatide twice daily over 26 weeks of follow-up in a noninferiority study, with both groups receiving metformin and a sulfonylurea. Reductions in HbA1c were 1.11% in both groups (between-group difference 0.017%, 95% CI −0.123 to 0.157%). Weight increased in the insulin glargine group throughout the trial, with progressive reduction in the exenatide group (weight change −2.3 kg with exenatide, +1.8 kg with insulin glargine; between-group difference −4.1 kg, 95% CI −4.6 to −3.5 kg).

Quality of life was assessed in this trial.[63, 68] A per protocol analysis of 455 of 549 original trial patients revealed no significant differences between the 2 treatments for measures of symptoms, quality of life, vitality, and treatment satisfaction. These similar outcomes occurred despite an additional injection daily and gastrointestinal adverse events with exenatide.

Another noninferiority study[62] also compared exenatide 10 mcg twice daily to insulin glargine, with both groups continuing pre-study single oral agents. Change in HbA1c at 16 weeks was identical in the 2 treatment arms (−1.36%, SE 0.09%, within group $P<0.001$). Both exenatide and insulin glargine reduced HbA1c by a similar amount in patients with baseline HbA1c ≥ 9% (approximate change −1.8%) and < 9% (change −0.9%).[62]

A third non-inferiority study[64] compared exenatide twice daily with biphasic insulin aspart in patients poorly controlled on sulfonylurea and metformin. The change in HbA1c was similar between groups (change with exenatide −1.04%, change with insulin aspart −0.89%; between group difference −0.15%, 95% CI −0.32 to 0.01). Exenatide patients lost weight while insulin-treated patients gained weight (between-group difference −5.4 kg, 95% CI −5.9 to −5.0 kg).

The fourth active-control trial[65] examined persons with type 2 diabetes who were already using insulin and sulfonylurea and/or metformin. In this small (N=51), exploratory randomized controlled trial, exenatide 5 and then 10 mcg twice daily was substituted for insulin, while oral agents were continued. Specific glycemic goals were not set. HbA1c did not change significantly in either group (P>0.05) and there was no significant between-group difference in HbA1c at 12-week follow-up. Exenatide patients noted a decrease in weight (mean weight change −4.2 kg, SD 3.0 kg, P<0.001), in contrast to the insulin group (mean weight change +0.5 kg, SD 1.7, P<0.001).

In addition to the four trials described above comparing exenatide to insulin, we also identified one trial comparing exenatide to glibenclamide, and one trial comparing exenatide to rosiglitazone. In the 12-month trial comparing exenatide to glibenclamide, all participants in the study continued on metformin.[66] There was no significant difference in improvement in HbA1c between those treated with exenatide and those treated with glibenclamide (change with exenatide -1.5%, change with glibenclamide -1.8%, P>0.05.) Weight loss in the exenatide arm of the study was significantly greater than in the glibenclamide arm of the study (change with exenatide -8.0 kg, change with glibenclamide +4.3 kg, P<0.001).

In the 20-week study comparing exenatide to rosiglitazone with all participants on background metformin therapy, there was no significant difference in improvement in HbA1c between the exenatide and rosiglitazone arms (change with exenatide -0.9%, change with rosiglitazone -1.0%, P=0.720).[67] Weight loss in the exenatide arm of the study was significantly greater than in the rosiglitazone arm of the study (change with exenatide -2.8 kg, change with rosiglitazone +1.5, P<0.001.)

Placebo-controlled trials

We identified 9 fair-to-good-quality placebo-controlled trials[69-77] of exenatide (Table 22, Evidence Table 3). Overall, study subjects were fairly homogeneous. Subjects were similar in age (mean 53 to 62 years) and sex (37 to 75% male) with some variation in race and ethnicity. Mean baseline HbA1c ranged from 7.1% to 8.6% and mean duration of diabetes from 2 to 14.8 years.

Table 22.Characteristics of exenatide placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Duration of diabetes (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Buse, 2004 US Fair	377 30	55 (10-11) 57-63 59.7-66.7 18.4-21.7 5.7-6.6 (4.7-6.6)	8.5-8.7 (1.1-1.2) 95-99(18-22) 33-34 (5-6)	5, 10 mcg BID	Maximum SU (but could be decreased by 50% based on hypoglycemic events)

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Duration of diabetes (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
DeFronzo, 2005 US Fair	336 30	52-54 (9-11) 51.8-60.2 72.6-79.6 7.3-10.6 4.9-6.6 (4.7-6.1)	8.2-8.3 (1.0-1.1) 100-101(19-22) 34 (6)	5, 10 mcg BID	High dose MET
Kendall, 2005 US Fair	733 30	55-56 (9-10) 55.9-59.3 66.4-69.0 15.8-16.6 8.7-9.4 (5.9-6.4)	8.5 (1.0-1.1) 97-99(19-21) 33-34 (5-6)	5, 10 mcg BID	High dose MET + SU
Zinman, 2007 Canada, Spain, US Fair	233 16	55.6-56.6 (10.2-10.8) 53.7-57.1 82.1-85.1 NR 7.3-8.2 (4.9-5.8)	7.9 (SE 0.1) 96.9-97.5 (18.8-19.0) 34 (5)	10 mcg BID	TZD +/- MET
Moretto, 2008 US Good	233 24	54 (10) 56 68 4 2 (3)	7.8 (0.9) 86 (16) 31 (5)	5, 10 mcg BID	None
Gao, 2009 Multinational Good	466 16	54-55 (9) 41-48 0 (All Asian/Indian) 0 8 (5-6)	8.3 (1.0) 69.6-67.9 (11.1-11.2) NR	5-10 mcg BID	MET +/- SU
Kadowaki, 2009 Japan, US Fair	153 12	57.8-62.2 (7.8-10.4) 62.2-75.0 0 (All Japanese) 0 9.6-14.8 (6.0-10.9)	7.9-8.1 (0.7-0.9) 64.9-71.1 (9.8-15.9) 24.2-26.1	2.5, 5, 10 mcg BID	SU alone or in combination with TZD or biguanide
Apovian, 2010 US Fair	196 24	54.5-55.1 (9.0-10.0) 37-38 NR NR 5.3-5.7 (5.1-5.5)	7.5-7.8 (0.8-0.9) 94.9-96.2 (15.6-16.5) 33.6-33.9 (3.7-4.3)	10 mcg BID	MET +/- SU
Gill, 2010 Canada, Netherlands Fair	54 12	54-57 (10-11) 42-68% 86-96% 0-4% 6-7 (4)	7.1-7.5 (0.7-0.9) 85.9-91.6 (12.2-15.2) 29.5-30.1 (3.4-3.9)	10 mcg BID	MET +/- TZD

Abbreviations: BID, twice daily; BMI, body mass index; MET, metformin; NR, not reported; SD, standard deviation; SU, sulfonylurea; TZD, thiazolidinedione.

[a] Data presented are the range across treatment groups for mean and standard deviation.

Efficacy and effectiveness

We included 9 trials comparing exenatide to placebo (Table 22). All found statistically significant weight loss with exenatide compared to placebo. All but one of the trials found

statistically significant reduction in HbA1c with exenatide compared to placebo. The one trial that did not find statistically significant reduction in HbA1c compared to placebo was different from the other trials in that participants in the study had relatively well controlled diabetes at baseline (HbA1c 7.1-7.5 at baseline).[77] In this section, we first describe the nine placebo-control trials, and then present the results of our meta-analyses for HbA1c and weight.

Three similar studies compared exenatide to placebo, with both treatment groups taking oral hypoglycemic agents.[69-71] Kendall and colleagues[71] randomized patients to exenatide 5 mcg or 10 mcg or placebo twice daily over 30 weeks. Patients continued their pre-study metformin and a sulfonylurea. Hemoglobin A1c decreased in the exenatide arms and steadily increased with placebo (placebo-adjusted change in HbA1c for exenatide 5 mcg, −0.8%; 10 mcg, −1.0%; $P<0.001$ for both treatment groups compared with placebo). Weight decreased progressively in both exenatide arms, more so than in the placebo arm (weight change −1.6 kg, SE 0.2 kg in both exenatide groups; −0.9 kg, SE 0.2 kg with placebo).

In a similarly designed study Buse and colleagues[69] compared exenatide to placebo in patients taking a sulfonylurea. Hemoglobin A1c improved in both treatment groups (HbA1c change with exenatide 5 mcg, −0.46%; 10 mcg, −0.86%) while increasing slightly in the placebo group (between-group $P\leq 0.0002$). Weight decreased more in the exenatide groups (weight change −1.6 kg, SE 0.3) than in the placebo group (weight change −0.6 kg, SE 0.3 kg). DeFronzo and colleagues[70] performed a similar study except that all subjects were taking metformin. The researchers noted very similar improvements in HbA1c with exenatide 10 mcg (HbA1c change −0.78%, SE 0.1%) compared with placebo (HbA1c change 0.08%, SE 0.10%) and also a similar decrease in weight with exenatide.

In a fourth placebo-controlled trial, subjects who were inadequately controlled with a thiazolidinedione (with or without metformin), were randomized to exenatide 10 mcg twice daily or placebo.[72] Exenatide improved HbA1c (mean between-group difference −0.98, 95% CI −1.21 to −0.74). Exenatide reduced weight but placebo did not (between-group difference −1.51 kg, 95% CI −2.15 to −0.88).

Three additional placebo-controlled trials of subjects inadequately controlled with oral antidiabetic agents found that HbA1c improved and weight was reduced with exenatide treatment compared with placebo, when subjects were continued on oral antidiabetic agents.[74-76] One study randomized subjects on metformin with or without a sulfonylurea to exenatide 10 mcg twice daily or placebo.[74] At 16 weeks, HbA1c reduction from baseline was significantly greater in the exenatide treatment group than with placebo (−1.2% compared with −0.4%; $P<0.001$). Weight reduction was also greater with exenatide than placebo (−1.2 kg compared with −0.1 kg; $P<0.001$). In a similarly designed study, Kadowaki and colleagues[75] randomized subjects with suboptimally controlled diabetes on oral antidiabetic agents (a sulfonylurea with or without biguanide or a thiazolidinedione) to exenatide 2.5 mcg twice daily, exenatide 5 mcg twice daily, exenatide 10 mcg twice daily, or placebo. This study found a dose-dependent effect on glycemic control with exenatide compared to placebo (HbA1c change with exenatide 2.5 mcg −0.9%; exenatide 5 mcg −1.2%; exenatide 10 mcg −1.4%; placebo +0.02%; all $P<0.001$ compared with placebo). This study did not find a significant weight reduction in the exenatide treatment groups compared with placebo. The third study randomized subjects on oral antidiabetic agents (metformin or a sulfonylurea) to exenatide or placebo.[76] All subjects continued on oral antidiabetic therapy, and started an intensive lifestyle modification program. The exenatide arm of the study showed greater improvement in HbA1c (-1.21% compared to -0.73%, $P<0.0001$), and greater weight loss (-6.16 kg compared to -3.97 kg, $P=0.003$).

One placebo-controlled trial of exenatide did not find improvement in HbA1c with exenatide compared to placebo, but subjects in this study at baseline had relatively well controlled diabetes on background therapy with metformin and/or a thiazolidinedione.[77] Exenatide did result in a statistically significant reduction in weight compared to placebo (weight change exenatide -1.8 kg, placebo 0.3 kg, $P<0.05$).

One placebo-controlled trial evaluated exenatide monotherapy in patients with type 2 diabetes naive to antidiabetic agents.[73] Subjects were randomized to exenatide 5 mcg, exenatide 10 mcg, or placebo, and were on no oral hypoglycemic agents. At 24 weeks, HbA1c reduction from baseline was significantly greater in both exenatide treatment groups than with placebo (HbA1c change with exenatide 5 mcg −0.7%; 10 mcg −0.9%; placebo −0.2%; $P<0.01$ for both treatment groups compared with placebo). Weight reduction was also greater with exenatide than with placebo (weight change with exenatide 5 mcg −2.8 kg; 10 mcg −3.1 kg; placebo −1.4 kg; $P<0.01$ for both treatment groups compared with placebo).

In several placebo-controlled trials of exenatide combined with oral agents, patients with a baseline HbA1c more than 9.0% achieved greater reductions in HbA1c than subjects with baseline less than 9.0%.[69, 71, 78] Weight reductions were greater in persons who had higher body mass index at baseline.[79, 80]

These studies were sufficiently homogeneous to obtain pooled estimates of effect (Table 23). When compared with placebo, exenatide 5 mcg twice daily produced a significant decrease in HbA1c (weighted mean difference –0.72, 95% CI –0.99 to –0.45, $P<0.001$, Appendix E).

A larger improvement in HbA1c was noted with exenatide 10 mcg twice daily (weighted mean difference –0.90, 95% CI –1.08 to –0.73, $P<0.001$). There was considerable statistical heterogeneity between the studies in these analyses (I^2=76% for exenatide 10 mcg, I^2=78% for exenatide 5 mcg). Because of the considerable heterogeneity, we repeated these meta-analyses without the study by Kadowaki et al. (Table 23). After removing it from the analysis, the statistical heterogeneity was reduced (I^2=57% for exenatide 10 mcg, I^2=1% for exenatide 5 mcg) and the magnitude of effect size from our pooled estimates was almost the same, but was slightly decreased (exenatide 10 mcg twice daily compared with placebo weighted mean difference −0.84, 95% CI −0.97 to −0.70, $P<0.001$; exenatide 5 mcg twice daily compared with placebo weighted mean difference −0.60, 95% CI −0.74 to −0.46, $P<0.001$). We hypothesize that the high heterogeneity when including Kadowaki et al. is due to the study being conducted in a different population (all Japanese participants) and having a small sample size.

When compared with placebo, exenatide 10 mcg twice daily produced a statistically significant decrease in weight (weighted mean difference –1.25 kg, 95% CI –1.60 to –0.90, $P<0.001$). The decrease for exenatide 5 mcg twice daily was not statistically significant in the meta-analysis including Kadowaki et al. (weighted mean difference −0.61 kg, 95% CI −1.28 to 0.06, $P=0.074$). There was substantial statistical heterogeneity prior to removing Kadowaki et al. from this analysis (I^2=74%). After removing Kadowaki et al, the heterogeneity was not statistically significant, and pooled estimates of effect were increased (exenatide 10 mcg twice daily compared with placebo weighted mean difference −1.34, 95% CI −1.71 to −0.97, $P<0.001$; exenatide 5 mcg twice daily compared with placebo weighted mean difference −0.87, 95% CI −1.35 to −0.40, $P<0.001$).

Table 23. Placebo-control trials of exenatide: Summary of meta-analyses

Exenatide dosage	Outcome	N	Pooled analysis						
			Measure	Units	Estimate	95% CI	*P* value	I^2	p
10 mcg BID	HbA1c	8[a]	WMD	%	−0.90	(−1.08 to −0.73)	<0.001	76%	<0.001
		7[b]	WMD	%	−0.84	(-0.97 to −0.70)	<0.001	57%	0.03
	Weight	9[c]	WMD	kg	−1.25	(−1.60 to −0.90)	<0.001	47%	0.057
		8[b]	WMD	kg	−1.34	(−1.71 to −0.97)	<0.001	44%	0.085
5 mcg BID	HbA1c	5[d]	WMD	%	−0.72	(−0.99 to −0.45)	<0.001	78%	0.001
		4[b]	WMD	%	−0.60	(−0.74 to −0.46)	<0.001	1%	0.389
	Weight	5[d]	WMD	kg	−0.61	(−1.28 to 0.06)	0.074	74%	0.004
		4[b]	WMD	kg	−0.87	(−1.35 to −0.40)	<0.001	33%	0.217

Abbreviations: BID, twice daily; CI, confidence interval; WMD, weighted mean difference.
[a] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009), Apovian (2010)
[b] Included the same studies as the row above, except for Kadowaki (2009), which was removed because of heterogeneity
[c] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009), Gill (2010) Apovian (2010)
[d] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Moretto (2008), Kadowaki (2009)

Systematic reviews

Three systematic reviews which included exenatide met our inclusion criteria and were rated fair or good quality.[28, 81, 82] In 2007, Amori and colleagues[28] published a review of published and unpublished English-language studies of US Food and Drug Administration-approved and unapproved DPP-4 inhibitors (sitagliptin and vildagliptin) and GLP-1 agonists including exenatide. These reviewers derived the following pooled estimates of change from baseline for exenatide compared with placebo (both groups combined with various oral diabetes agents): HbA1c –1.01% (95% CI −1.18% to −0.84%) and weight −1.44 kg (95% CI −2.13 to −0.75 kg). When exenatide was compared with various insulin regimens, the following pooled estimates of change from baseline for exenatide compared with insulin were noted: HbA1c −0.06% (95% CI −0.22% to 0.10%) and weight −4.8 kg (95% CI −6.0 to −3.5 kg). Weight loss was dose-dependent and progressive, with no apparent plateau by week 30.

A second systematic review, published by Pinelli and colleagues in 2008, also compared exenatide to placebo and insulin and in terms of glycemic control and weight loss.[81] In a meta-analysis of the 3 included studies, exenatide improved HbA1c compared to placebo (weighted mean difference −0.97% (95% CI −1.11 to −0.83), and also showed a slight improvement in HbA1c compared to insulin in 2 included studies (weighted mean difference −0.08%, 95% CI -.23 to 0.07). A meta-analysis of all 5 included studies on exenatide found significant weight loss with exenatide compared to placebo or insulin therapy (weighted mean difference −2.74 kg, 95% CI −4.85 to 0.64 kg).

Another systematic review of GLP-1 receptor agonists, including exenatide and liraglutide, was also included.[82] This study combined trials of both exenatide and liraglutide into one meta-analysis for HbA1c and one meta-analysis for weight loss. Combining the included trials of exenatide and liraglutide derived the following pooled estimates of GLP-1 agonists compared to placebo: HbA1c -1.0% (95% CI -1.1% to -0.8%). Similar results were obtained with separate analyses of exenatide and liraglutide compared to placebo. In our meta-analyses, we separated pooled estimates by dose of liraglutide, and found greater reduction in HbA1c at the higher doses of liraglutide. Monami et al. found significant weight loss with exenatide compared to placebo, and a nonsignificant trend toward weight loss with liraglutide compared to placebo. For our liraglutide analyses (described in the following section), we separated pooled estimates by dose of liraglutide and did find significantly greater weight loss with liraglutide compared to placebo at the higher dose of liraglutide (1.8mg daily).

Detailed Assessment for Liraglutide

Active-control trials

We found 6 fair or good quality active-control trials. Three fair quality active-control trials with a similar design compared liraglutide to glimepiride in terms of HbA1c reduction and weight loss.[58-60] In 2 of these studies, subjects were on no other antidiabetic agents.[58, 60] In one study, all subjects were taking metformin 1 g twice daily in addition to the study treatment regimes. We did not attempt to pool data for these 6 trials due to heterogeneity of study designs, outcome reporting and comparisons.

One good quality active-control trial compared liraglutide to open-label insulin glargine, with all subjects on combination therapy with metformin and glimepiride.[83] One fair quality active-control trial compared liraglutide to rosiglitazone.[84] An additional fair quality active-

control trial compared liraglutide to sitagliptin.[41] These studies are summarized in Table 24, Evidence Table 3.

Table 24. Characteristics of liraglutide active-control trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Madsbad[b] 2004[58] Scandinavia and UK Fair	193 12	53-58 (7.5-11.3) 57-85 NR NR 3.4-6.1 (2.9-7.9)	7.4-7.9 (0.8-1.2) NR 30.1-32.0 (4.2-5.4)	LIR 0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, or 0.75 mg daily Placebo Glimepiride 1-4 mg	None
Garber, 2009[60] Bode, 2010[85] US and Mexico Fair	746 52	52-53.7 (10.8-11.0) 47-54 75-80 32-38 5.2-5.6 (5.1-5.5)	8.3-8.3 (1-1.2) 92.5-93.4 (19.2-20.7) 32.8-33.2 (5.6-6.3)	LIR 1.2 mg daily LIR 1.8 mg daily Glimepiride 8 mg daily	None
Nauck[b] 2009[59] Multinational Fair	1091 26	56-57 (9-11) 54-62 84-89 NR 7-8 (5-6)	8.3-8.4 (0.9-1.1) NR 30.5-31.6 (4.4-4.8)	LIR 0.6 mg daily LIR 1.2 mg daily LIR 1.8 mg daily Placebo Glimepiride 4 mg daily	All groups received metformin 1 g BID
Russell-Jones[b] 2009[83] Multinational Good	581 26	57.5-57.6 (9.5-10.5) 49-60 NR NR 9.2-9.7 (5.8-6.4)	8.2-8.3 (0.9) 85.0-85.7 (16.7-17.9) 30.3-31.3 (5-5.3)	LIR 1.8 mg daily Placebo Insulin glargine	All groups received metformin 1 g BID and glimepiride 4 mg daily
Marre[b] 2009[84] Multinational Fair	1041 26	54.7-57.7 (9.0-10.0) 45-54 NR NR 6.5-6.7 (NR)	8.4-8.5 (0.9-1.1) 80.0-83.0 (17.0-18.1) 29.4-30.3 (4.8-5.4)	LIR 0.6 mg daily LIR 1.2 mg daily LIR 1.8 mg daily Placebo Rosiglitazone 4 mg	All groups on glimepiride 2-4 mg daily
Pratley 2010[41] Multinational Fair	665 26	55.0-55.9 (9.0-9.6) 52-55 82-91 15-16 6.0-6.4 (4.5-5.4)	8.4-8.5 (0.7-0.8) 93.1-94.6 (18.1-18.9) 32.6-33.1 (5.1-5.4)	LIR 1.2 mg daily LIR 1.8 mg daily Sitagliptin 100 mg	All groups on metformin ≥ 1500 mg daily

Abbreviations: BID, twice daily; BMI, body mass index; LIR, liraglutide; NR, not reported; SD, standard deviation.

[a] Data presented are the range across treatment groups for mean and standard deviation.

[b] Studies with both placebo and active control arms repeated in Tables 25 and 26.

Efficacy and effectiveness

Three fair quality studies compared the efficacy of liraglutide to glimepiride.[58-60] In a phase 2, dose-finding study Madsbad and colleagues[58] compared 5 fixed dosage groups of liraglutide (0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, and 0.75 mg daily) to glimepiride 1-4 mg daily and to placebo. Liraglutide 0.60 mg daily was the only approved dose of liraglutide in this study; we will focus on the outcomes for this arm only. After 12 weeks of therapy, there was a significant reduction in HbA1c compared to placebo for the liraglutide 0.6 mg arm, and the glimepiride arm (HbA1c change: liraglutide 0.60 mg compared to placebo −0.70%, glimepiride compared to placebo −0.74%). Treatment with liraglutide 0.6 mg daily or glimepiride did not significantly increase or decrease body weight in this study. According to the prescribing information for liraglutide, liraglutide 0.6 mg is a dose intended to be used for reduction of gastrointestinal side effects during the initial titration, and should not be used for glycemic control.

Two later studies compared the efficacy of liraglutide to glimepiride with higher doses of liraglutide.[59, 60] Nauck and colleagues, as part of the LEAD-2 study, randomized subjects to liraglutide 0.6 mg, liraglutide 1.2 mg, liraglutide 1.8 mg daily, glimepiride 4 mg daily, or placebo. All subjects were also on metformin 1 g twice daily. At 26 weeks, all of the treatment arms showed improvement in HbA1c (change in HbA1c: liraglutide 0.6 mg −0.7%; liraglutide 1.2 mg −1.0%; liraglutide 1.8 mg −1.0%, glimepiride 4 mg −1.0%.) Improvement in HbA1c in the liraglutide 1.2 mg and 1.8 mg arms was noninferior to treatment with glimepiride. There was a statistically significant difference between the weight loss in all of the liraglutide treatment groups and the weight gain in the glimepiride group (weight change liraglutide 0.6 mg −1.8 kg; liraglutide 1.2 mg −2.6 kg; liraglutide 1.8 mg −2.8 kg, glimepiride +1.0 kg; $P<0.0001$.)

Garber and colleagues, as part of the LEAD-3 Mono (Liraglutide Effect and Action in Diabetes-3 Mono) study, randomized subjects to liraglutide 1.2 mg daily, liraglutide 1.8 mg daily, or glimepiride 8 mg daily. At 52 weeks, all of the treatment arms showed improvement in HbA1c (change in HbA1c: liraglutide 1.2 mg −0.84%; liraglutide 1.8 mg −1.14%, glimepiride 8 mg −0.51%). Reduction in HbA1c was significantly greater in both liraglutide arms than in the glimepiride arm ($P<0.01$ for both comparisons). There was a statistically significant difference between the weight loss in the liraglutide arms and the weight gain in the glimepiride arm ($P<0.0001$, exact values of weight change not reported).

Patient-reported outcomes were also followed as part of the LEAD-3 Mono study.[85] This study used a survey to assess a composite health-related quality of life score, and found that this score improved more favorably with treatment with liraglutide 1.8 mg compared to glimepiride ($P = 0.004$). There was no statistical difference for this scale between liraglutide 1.2 mg and glimepiride.

In summary, Garber and colleagues found statistically significantly greater improvement in HbA1c with liraglutide 1.2 mg and 1.8 mg daily compared to glimepiride 8 mg daily with subjects on no other antidiabetic therapy, and Nauck and colleagues showed noninferiority of liraglutide 1.2 mg and 1.8 mg daily compared with glimepiride. Both studies showed significantly greater weight loss with liraglutide compared to glimepiride.

One good quality active-control trial compared liraglutide 1.8 mg daily to open-label insulin glargine, with all subjects on combination therapy with metformin and glimepiride. [83] Liraglutide reduced HbA1c significantly compared to glargine (−1.33% compared with −1.09%; $P=0.0015$). The study also found greater weight loss with liraglutide compared with insulin glargine (treatment difference −3.43 kg; $P<0.0001$).

One fair quality 26 week active-control trial compared liraglutide (0.6, 1.2, or 1.8 mg daily) to rosiglitazone. All subjects were on glimepiride 2 to 4 mg daily.[84]. The study found a greater improvement in HbA1c with the two higher doses of liraglutide compared to rosiglitazone 4 mg daily (change in HbA1c: liraglutide 1.2 mg -1.1%; liraglutide 1.8 mg -1.1%; rosiglitazone -0.4%). The difference was statistically significant ($P<0.0001$ for liraglutide 1.2 and 1.8 mg daily compared to placebo). The study also found significant weight gain in the rosiglitazone arm compared to all doses of liraglutide (change in weight: liraglutide 0.6mg +0.7kg; liraglutide 1.2mg +0.3 kg; liraglutide 1.8mg -0.2 kg; rosiglitazone 4 mg +2.1 kg; $P<0.0001$ for all doses of liraglutide compared to rosiglitazone).

One 26 week fair quality active-control trial compared liraglutide (1.2 or 1.8 mg daily) to sitagliptin 100 mg daily.[41] All study participants were on metformin ≥ 1500 mg daily as background therapy. The study found a greater improvement in HbA1c with both doses of liraglutide compared to sitagliptin (change in HbA1c: liraglutide 1.2 mg -1.24%; liraglutide 1.8 mg -1.5%; sitagliptin -0.6%; $P<0.0001$ for both doses of liraglutide compared to sitagliptin). Weight loss was significantly greater with both doses of liraglutide compared to sitagliptin (change in weight: liraglutide 1.2 mg -2.86 kg; liraglutide 1.8 mg -3.38 kg; sitagliptin -0.96 kg; $P<0.0001$ for both doses of liraglutide compared to sitagliptin. Treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) improved both with liraglutide and sitagliptin, but increased significantly more in the liraglutide 1.8 mg arm of the study than in the sitagliptin 100 mg arm of the study.[41] None of the other active-control trials examined treatment satisfaction or quality of life.

Placebo-controlled trials

We found 7 fair or good quality liraglutide placebo-control trials (Table 25).[58, 59, 83, 84, 86-88] Four of these included an active-control arm in addition to a placebo arm and are described above in the previous section.[58, 59, 83, 84] Overall, study subjects were fairly homogeneous. Subjects were similar in age (mean 53 to 60 years). Race was not reported in 5 of the 7 studies, and was 81% to 89% white when it was reported. Sex ranged from 45% to 85% male. Mean baseline HbA1c ranged from 7.1% to 8.6% and mean duration of diabetes from 3 to 10 years.

In 3 of the studies, study participants were on no other antidiabetic therapy.[58, 87, 88] In the other 4 studies, participants were on combination therapy with metformin,[59] metformin and glimepiride,[83] metformin and rosiglitazone,[86] and glimepiride.[84]

Table 25. Characteristics of liraglutide placebo-controlled trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Duration of diabetes (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Madsbad[b] 2004[58] Scandinavia and UK Fair	193 12	53-58 (7.5-11.3) 57-85 NR NR 3.4-6.1 (2.9-7.9)	7.4-7.9 (0.8-1.2) NR 30.1-32.0 (4.2-5.4)	LIR 0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, or 0.75 mg daily Placebo Glimepiride 1-4 mg daily	None
Vilsboll 2007[87] Multinational Fair	165 14	53.4-57.7 (8.2-11.4) 47-73 NR NR 4-7	8.1-8.5 (0.6-0.9) NR 28.9-31.2	IR 1.9 mg daily LIR 1.25 mg daily LIR 0.65 mg daily Placebo	None
Seino 2008[88] Japan Good	226 14	55.5-60.0 (7.0-8.8) 62-70 NR NR 6.78-8.87 (4.69-6.77)	8.12-8.50 (0.83-1.02) 61.97-64.82 (9.4-11.18) 23.59-24.26 (2.63-3.09)	LIR 0.1 mg daily LIR 0.3 mg daily LIR 0.6 mg daily LIR 0.9 mg daily Placebo	None
Nauck[b] 2009[59] Multinational Fair	1091 26	56-57 (9-11) 54-62 84-89 NR 7-8 (5-6)	8.3-8.4 (0.9-1.1) NR 30.5-31.6 (4.4-4.8)	LIR 0.6 mg daily LIR 1.2 mg daily LIR 1.8 mg daily Placebo Glimepiride 4 mg daily	All groups received metformin 1 g BID
Russell-Jones[b] 2009[83] Multinational Good	581 26	57.5-57.6 (9.5-10.5) 49-60 NR NR 9.2-9.7 (5.8-6.4)	8.2-8.3 (0.9) 85.0-85.7 (16.7-17.9) 30.3-31.3 (5-5.3)	LIR 1.8 mg daily Placebo Insulin glargine	All groups received metformin 1 g BID and glimepiride 4 mg daily

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Duration of diabetes (years)[a]	Baseline HbA1c (%) (SD)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy
Zinman 2009[86] Canada, US Fair	533 26	55 (10-11) 51-62 81-84 13-16 9 (6)	8.4-8.6 (1.2) NR 33.2-33.9 (5.1-5.4)	LIR 1.2 mg daily LIR 1.8 mg daily Placebo	All groups received metformin 1 g BID and rosiglitazone 4 mg BID
Marre[b] 2009 [84] Multinational Fair	1041 26	54.7-57.7 (9.0-10.0) 45-54 NR NR 6.5-6.7 (NR)	8.4-8.5 (0.9-1.1) 80.0-83.0 (17.0-18.1) 29.4-30.3 (4.8-5.4)	LIR 0.6 mg daily LIR 1.2 mg daily LIR 1.8 mg daily Placebo Rosiglitazone 4 mg	All groups on glimepiride 2-4 mg daily

Abbreviations: BID, twice daily; BMI, body mass index; LIR, liraglutide; NR, not reported; SD, standard deviation.
[a] Data presented are the range across treatment groups for mean and standard deviation.
[b] Studies with both placebo and active control arms repeated in Table 24.

Efficacy and effectiveness

All of the studies showed that liraglutide therapy resulted in a significant decrease in HbA1c compared to placebo. Pooled estimates of effect were obtained through meta-analyses for three doses of liraglutide. (Table 26, Appendix E) There was substantial statistical heterogeneity (I^2 71% to 82%) for all of the doses of liraglutide, most likely secondary to differences in background therapy between studies. However, all of the studies found a significant decrease in HbA1c compared to placebo. When compared with placebo, liraglutide 0.6 to 0.65 mg daily produced a significant decrease in HbA1c (weighted mean difference −1.10, 95% CI –1.45 to –0.75, P<0.001, Table 26). A similar improvement in HbA1c was noted with liraglutide 1.2 to 1.25 mg daily (weighted mean difference −1.28, 95% CI –1.56 to –1.00, P<0.001) and 1.8 to 1.9 mg daily (weighted mean difference −1.26, 95% CI −1.50 to −1.03, P<0.001).

When compared with placebo, liraglutide 1.8 mg to 1.9 mg daily produced a significant decrease in weight (liraglutide 1.8 mg to 1.9 mg weighted mean difference -1.43 kg, 95% CI –2.33 to –0.53, P=0.002). There was no statistically significant weight loss for liraglutide 0.6 to 0.65 mg or liraglutide 1.2 mg to 1.25 mg daily compared with placebo, although there was considerable heterogeneity in the meta-analysis of liraglutide 1.2 mg to 1.25 mg daily (Table 26). In reviewing the results, this considerable heterogeneity was largely secondary to the inclusion of the LEAD-1 SU study by Marre et al.[84] In this study, participants in all arms were on background therapy with glimepiride, and participants in the liraglutide 0.6 mg and 1.2 mg arms of the study gained, rather than lost, weight. Because of this difference, we ran the meta-analyses for weight both including and excluding Marre et al. (Table 26). With the exclusion of Marre et al., there was significant weight loss with liraglutide 1.2 mg compared to placebo (weighted mean difference -1.31 kg, 95% CI –1.85 to –0.77, P<0.001). This suggests that the 1.2 mg dose of liraglutide may lead to weight loss as monotherapy or combined with metformin, but not in combination with a sulfonylurea.

Table 26. Placebo-controlled trials of liraglutide: Summary of meta-analyses

Liraglutide dosage	Outcome	N	Pooled analysis						
			Measure	Units	Estimate	95% CI	*P* value	I^2	p
0.6 mg to 0.65 mg daily	HbA1c	4[a]	WMD	%	−1.10	(−1.45; −0.75)	<0.001	82 %	<0.001
	Weight	3[b]	WMD	kg	+0.27	(−0.71; 0.76)	0.942	12 %	0.320
	Weight without Marre	2[c]	WMD	kg	-0.27	(-0.97; 0.43)	0.450	0%	0.597
1.2 mg to 1.25 mg daily	HbA1c	4[d]	WMD	%	−1.28	(−1.56; −1.00)	<0.001	77 %	<0.001
	Weight	3[e]	WMD	kg	−0.83	(−1.85; 0.19)	0.111	76 %	0.014
	Weight without Marre	2[f]	WMD	kg	-1.31	(-1.85; -0.77)	<0.001	0%	0.369
1.8 mg to 1.9 mg daily	HbA1c	5[g]	WMD	%	−1.26	(−1.50;−1.03)	<0.001	71 %	0.008
	Weight	4[h]	WMD	kg	−1.43	(−2.33; −0.53)	0.002	73 %	0.010
	Weight without Marre	3[i]	WMD	kg	-1.76	(-2.61; -0.92)	<0.001	67 %	0.047

Abbreviations: CI, confidence interval; WMD, weighted mean difference.
[a] Studies included in the analysis: Vilsboll (2007), Seino (2008), Nauck (2009), Marre (2009).
[b] Studies included in the analysis: Seino (2008), Nauck (2009), Marre (2009).
[c] Studies included in the analysis: Seino (2008), Nauck (2009).
[d] Studies included in the analysis: Vilsboll (2007), Nauck (2009), Zinman (2009), Marre (2009).
[e] Studies included in the analysis: Nauck (2009), Zinman (2009), Marre (2009).
[f] Studies included in the analysis: Nauck (2009), Zinman (2009).
[g] Studies included in the analysis: Vilsboll (2007), Nauck (2009), Zinman (2009), Russell-Jones (2009), Marre (2009).
[h] Studies included in the analysis: Nauck (2009), Zinman (2009), Russell-Jones (2009), Marre (2009).
[h] Studies included in the analysis: Nauck (2009), Zinman (2009), Russell-Jones (2009).

II. Thiazolidinediones (TZDs)

Summary of Findings for Thiazolidinediones (TZDs)

Evidence in children

- No data on children were reported.

Evidence in adults

- Pioglitazone compared with rosiglitazone. Meta-analysis of 8 head-to-head randomized controlled trials found no statistically significant difference between pioglitazone and rosiglitazone for their ability to improve glycemic control (for change in HbA1c, weighted mean difference −0.09, 95% CI −0.23, 0.05, I^2 0.0%) (moderate strength of evidence). Prior systematic reviews found both drugs appear to have similar effects on HbA1c, producing a decrease of approximately 1%, similar to the change produced with other oral agents (including metformin, glibenclamide, or glimepiride). Effect of both

pioglitazone and rosiglitazone appears to be similar when used in either monotherapy or combination therapy.

- Pioglitazone compared with rosiglitazone. None of the included head-to-head trials reported comparative efficacy/effectiveness of health outcomes or utilization outcomes.
- Overall, no difference in reduction in HbA1c between pioglitazone and sulfonylureas (moderate strength of evidence). We included 10 trials, 7 finding no statistically significant difference, 2 favoring pioglitazone by 0.19 to 0.32%, and one favoring glimepiride by 0.63%.
- No significant difference in 7 trials for reduction in HbA1c between pioglitazone and metformin (high strength of evidence).
- No significant difference in reduction in HbA1c between rosiglitazone and sulfonylureas (moderate strength of evidence). We included 9 trials, 7 finding no statistically significant difference, one favoring rosiglitazone by 0.42%, and one favoring the sulfonylurea group by 0.4%.
- No significant difference in reduction in HbA1c between rosiglitazone and metformin (moderate strength of evidence). We included 4 trials, 3 finding no statistically significant difference and one favoring rosiglitazone by 0.13%.
- For reduction in HbA1c, consistent with our findings, prior systematic reviews reported no between-group differences between thiazolidinediones and metformin or second-generation sulfonylureas.
- Thiazolidinedione plus metformin compared with a second-generation sulfonylurea plus metformin (4 randomized controlled trials) did not show a consistent effect favoring 1 of the combinations, nor did a randomized controlled trial comparing thiazolidinediones with repaglinide.
- No significant difference in reduction in HbA1c between rosiglitazone and sitagliptin in two randomized controlled trials (moderate strength of evidence).
- One trial comparing the addition of rosiglitazone with the addition of liraglutide (to ongoing glimepiride treatment) reported greater reduction in HbA1c with liraglutide (−1.1 compared with −0.4%, P<0.0001, low strength of evidence)
- One trial comparing exenatide to rosiglitazone with all participants on background metformin therapy, found no significant difference in improvement in HbA1c (-0.9% vs. -1.0%, *P*=0.720).
- Data were not sufficient to determine the comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes; there were no head-to-head data (insufficient strength of evidence).

Detailed Assessment for TZDs

Systematic reviews: Pioglitazone compared with rosiglitazone

In a report for the Agency for Healthcare Research and Quality report,[89] Bolen and colleagues examined 4 head-to-head studies comparing pioglitazone with rosiglitazone and did not find a significant difference for HbA1c between these 2 drugs.

Head-to-head trials: Pioglitazone compared with rosiglitazone

Eight fair-quality, head-to-head, randomized controlled trials (in 14 publications) were identified (Table 27 and Evidence Table 4).[90-102]

Details of the trials comparing pioglitazone with rosiglitazone are presented in Table 27 and Evidence Table 4. Some trials compared monotherapy with either medication,[92, 93, 99, 101, 102] while others compared adding pioglitazone or rosiglitazone to existing treatment.[90, 91, 94-98, 100] All trials reporting improvement in HbA1c (%) for subjects treated with either pioglitazone or rosiglitazone found no statistically significant difference between groups. The range of improvement (change from baseline in HbA1c[%]) with either treatment was from a 0.6 to a 1.4.

Our meta-analysis including 7 of these trials found no statistically significant difference between pioglitazone and rosiglitazone (weighted mean difference −0.09, 95% CI −0.23, 0.05, I^2 0.0%, Appendix E). One of the trials did not report sufficient outcome data to be included.[93]

Table 27. Head-to-head trials comparing pioglitazone with rosiglitazone in persons with type 2 diabetes

Study Sample size	Dosages	Concurrent therapy	Follow-up; Other characteristics	HbA1c (%) baseline; Change from baseline (mean, SD)	Quality; Funder
Derosa 2004[90], 2005[91] Derosa 2006[95] [103] N=87	Pio 15 mg daily Rosi 4 mg daily	Both groups glimepiride 4 mg daily	12 mo; participants had metabolic syndrome	Pio: 8.2 (0.7); −1.4 (NR) Rosi: 8.0 (0.8); −1.3 (NR) Within groups *P*<0.01; NSD between groups	Fair; NR
Derosa 2006[94] Derosa 2006[96] Derosa 2007[97] Derosa 2007[98] N=103	Pio 15 mg daily Rosi 4 mg daily	Both groups metformin 1500-3000 mg daily	12 mo; participants had metabolic syndrome	Pio: 8.2 (0.8); - 1.4 (NR) Rosi: 8.1 (0.9); - 1.3 (NR) Within-group *P*<0.01 both groups Between-group *P* value NR	Fair; NR
Goldberg 2005[92] N=735[a]	Pio 30-45 mg daily Rosi 4 mg daily or twice a day	Monotherapy	24 wk Participants had untreated dyslipidemia	Pio: 7.6 (1.2); −0.7 (1.9) Rosi: 7.5 (1.2); −0.6 (1.9) Between-group *P*=0.129	Fair; Eli Lilly and Takeda Pharmaceuticals, North America
Kahn 2002[93] N=127	Pio 15-45 mg daily Rosi 2 mg daily to 4 mg twice a day	Monotherapy; troglitazone withdrawn	16 wk Open-label	Pio: 8.0 (1.7); NR Rosi: 7.9 (1.9); NR NSD at follow-up in either group	Fair; NR
Vijay 2009[99] N = 50[b]	Pio 30 – 45 mg daily Rosi 4 mg 1 to 2 times a day	Monotherapy	16 wk Open-label	Pio: 9.27 (0.97); −1.27 (0.17) Rosi: 9.1 (0.80); −1.26 (0.72) [Within groups P<.001; Between group *P* NR]	Fair; UGC, India
Beysen 2008[100] N =12	Pio 15-45 mg daily Rosi 4 mg	Metformin or metformin plus a sulfonylurea	20 wk Open-label	Pio: 8.1 (0.6); −1.1 (0.6) Rosi: 8.2 (1.1); −1.3 (0.8)	Fair; Takeda Pharmaceuticals

Study Sample size	Dosages	Concurrent therapy	Follow-up; Other characteristics	HbA1c (%) baseline; Change from baseline (mean, SD)	Quality; Funder
	daily to twice a day				North America, Inc.
Oz Gul 2009[101] N=60[c]	Pio 30 mg daily Rosi 4 mg once a day	Monotherapy	12 wk; all participants of Turkish descent and naïve to therapy	Pio: 7.6 (1.5); −1.1 (NR) Rosi: 7.3 (1.3); −1.1 (NR) Within groups *P*<.001 and *P*<.003 Between groups *P*=NR	Fair; NR
Oz 2008[102] N = 35[d]	Pio 30 mg daily Rosi 4 mg daily	Monotherapy	12 wk	Pio: 7.82 (1.7); −1.2 (NR) Rosi: 7.0 (1.07);- 0.8 (NR) Within groups *P*<0.003 and 0.019 Between group *P*=NR	Fair; NR

Abbreviations: wk, weeks; mo, months; NR, not reported; NSD, no significant difference; pio, pioglitazone; rosi, rosiglitazone; SD, standard deviation

[a] Deeg (2007) [104] reports HbA1c for a subset (N = 650) of participants described in the Goldberg 2005 article. These data are not presented here.

[b] N=50 including the control group: 20 pioglitazone; 20 rosiglitazone; 10 control.

[c] N=60 including the placebo group: 19 pioglitazone; 20 rosiglitazone; 21 placebo.

[d] N=35 including nutrition therapy group: 14 pioglitazone; 11 rosiglitazone; 10 medical nutrition therapy.

Systematic reviews: Active- and placebo-controlled trials with TZDs

Original report

For the original Drug Effectiveness Review Project drug class report on TZDs, 10 reviews reporting comprehensive searches were identified (Evidence Tables 1 and 2 from that report).[18] Six of the reviews were rated poor quality, as they lacked 1 or more of the following: explicit inclusion criteria, specification of the search strategy, quality assessment of individual studies, or sufficient detail on the individual studies.[105, 106 107-110] Details of the 4 fair- to good-quality systematic reviews are provided in Evidence Table 1 from the 2008 TZD report.[18]

Three systematic reviews examined both pioglitazone and rosiglitazone.[111-113] Boucher and colleagues[111] compared the 2 thiazolidinediones to other antidiabetic drugs; they did not directly compare pioglitazone and rosiglitazone. They concluded that as monotherapy these 2 drugs have effects on HbA1c similar to the other antidiabetic drugs, and when added to one of those drugs significantly improved HbA1c compared with the original treatment regimen.

Chiquette and coauthors[112] reviewed placebo-controlled trials of pioglitazone and rosiglitazone and noted the need for head-to-head studies. They concluded that both drugs decreased HbA1c and increased weight to a similar degree.

In a systematic review for the Health Technology Assessment Programme of the National Health Service,[113] Czoski-Murray and colleagues also noted that both pioglitazone and rosiglitazone produced similar improvements in HbA1c (approximately 1.0%). They did not identify any randomized controlled trials comparing the 2 drugs and noted that there were no peer-reviewed data on long-term effects.

Updated report

For the 2008 update of the Drug Effectiveness Review Project drug class review on TZDs, an additional 11 systematic reviews were identified (Evidence Table 1 for 2008 TZD Report).[89, 114-123]

In these reviews both pioglitazone and rosiglitazone reduced HbA1c by approximately 1.0 absolute percentage point, similar to the change produced with other oral agents, including metformin, glibenclamide, and glimepiride.[89, 114, 117, 119, 124] This reduction was also similar to the changes noted in placebo-controlled trials in this report. These reviews did not provide additional direct head-to-head data for HbA1c change for pioglitazone and rosiglitazone. In placebo-controlled trials, Phatak and Yin[117] noted a weighted mean change in HbA1c from baseline of −1.03% (standard deviation 0.19) for pioglitazone and −0.98% (standard deviation 0.18) for rosiglitazone. Head-to-head studies were not examined and indirect comparisons were not performed.

Detailed Assessment for TZDs Compared With Active Controls

For the original Drug Effectiveness Review Project TZD report, active-control studies for the outcome of HbA1c were not included. These were, however, included for examination of effectiveness outcomes and for examination of patient subgroups.

For the updated report (2008), active-control studies for both pioglitazone and rosiglitazone were included for the outcome of HbA1c in order to update the Agency for Healthcare Research and Quality report on oral hypoglycemic agents whose search ended January 2006.[89] Bolen and colleagues concluded that there were no between-group differences between thiazolidinediones and metformin (7 randomized controlled trials) or second generation sulfonylureas (13 randomized controlled trials). Thiazolidinedione plus metformin compared with a second-generation sulfonylurea plus metformin (2 randomized controlled trials) did not show a consistent effect favoring 1 of the combinations, nor did 2 randomized controlled trials comparing thiazolidinediones compared with repaglinide. One trial comparing pioglitazone to acarbose favored pioglitazone for HbA1c reduction.

In the sections below, we include the active-control good- and fair-quality TZD studies included in the 2008 Drug Effectiveness Review Project drug class review on TZDs (searches through Nov 2007), as well as new good- and fair-quality studies identified since that time (searches through July 28, 2010).

Pioglitazone compared with an active control

Characteristics of studies

We included 16 trials comparing pioglitazone with an active control (Tables 28 and 29).[125-140] Seven of these are new to this section in this report.[128, 129, 136-140] Seven monotherapy trials compared pioglitazone to a sulfonylurea[126, 130, 133, 135] or to metformin.[135, 137, 139, 140] Trials examining combination therapy compared pioglitazone to a sulfonylurea with both groups receiving various oral hypoglycemic agents or insulin[125, 127-129, 131] or metformin.[134] Pioglitazone was compared to metformin as add-on to other diabetic therapy in 3 trials.[132, 136, 138] Drug dosing across studies was fairly consistent, with most study populations 50-60 years of age. Studies ranged between 3 and 18 months; 5 trials had follow-up of greater than 6 months.[127, 128, 130, 135, 137]

Table 28. Characteristics of pioglitazone active-control trials with sulfonylureas in adults with type 2 diabetes

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Agarwal 2005[125] Fair	44 16	67 (8.5) 0 NR NR 68% on insulin at baseline; All had overt diabetic nephropathy	Glipizide: start 5 mg daily; mean maximal dosage 41 mg daily Pio: start 15 mg daily, mean maximal dosage 19 mg daily	Combined with various oral hypoglycemic agents or insulin
Basu 2006[126] Fair	19 12	56 (2) 33 NR NR	Glipizide: 10 mg daily (median dose) Pio: 45 mg daily	None
Mazzone 2006[127] Fair	458 72	59.9 (8.2) 37 NR NR Newly diagnosed on any therapy	Pio 15-45 mg daily Glimepiride 1-4 mg daily	Add-on metformin or insulin as needed (12%-13% took insulin during study)
Nissen 2008[128] Multinational Fair	360 78	59.7 (9.1) 34 81 NR At least 1 angiographic stenosis with at least 20% narrowing	Pio 15-45 mg daily Glimepiride 1-4 mg daily	Added to ongoing diabetic treatment (metformin in 63 to 65%; insulin in 18 to 23%)
Papathanassiou 2009[129] Greece Fair	28 26	63.6 (7.3) 79 NR NR Treated with metformin only	Pio 30 mg daily Glimepiride 4 mg daily	Added to metformin
Perriello 2006[130] Fair	283 52	59 (assume SD 7) 36 NR NR HbA1c>7.5%	Pio 30-45 mg daily Gliclazide 80-320 mg daily	Appears to be monotherapy (some patients on 1 oral agent prior to study)
Pfutzner 2005[131] Fair	179 26	63.0 (7.4) 38 NR NR Failed various oral agents; no prior TZD use	Pio 24 mg daily Glimepiride 1-6 mg daily and TZDs with glimepiride	Other oral agents permitted in both groups, except metformin with pio

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Teramoto 2007[133] Fair	92 24	56.4 (10.5) 24 NR NR Triglycerides 150-500 mg/dL	Pio 15-30 mg daily Glibenclamide 1.25-2.5 mg daily	None
Umpierrez 2006[134] Fair	210 26	51.6 (11.8) 45 NR NR Inadequately controlled on metformin monotherapy	Pio 30-45 mg daily Glimepiride 2-8 mg daily	Add-on to metformin therapy
Yamanouchi 2005[135] Japan Fair	114 52	Metformin group: 54.7 (9.8) 49 NR NR Not on oral agents previously	Pio 30-45 mg daily Metformin 750 mg daily Glimepiride 1.0-2.0 mg daily	None

Abbreviations: NR, not reported; Pio, pioglitazone; SD, standard deviation; SE, standard error; TZD, thiazolidinedione.
[a] Data shown are mean (SD) unless otherwise indicated.

Table 29. Characteristics of pioglitazone active-control trials with metformin in adults with type 2 diabetes

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Kato 2009[140] Fair	50 12	51.4 (15.2), 58.6 (12.4) 48 NR NR	Pioglitazone 15 mg daily Metformin 500 mg daily	None
Kusaka 2008[136] Japan Fair	35 17	60 (2) 41 NR NR Inadequate glycemic control with sulfonylurea and/or diet and exercise	Pioglitazone 15 mg daily (women); 30 mg daily (men) Metformin 750 mg daily	Added to current therapy (either sulfonylurea or diet and exercise)
Perez, 2009[139] Fair	600 24	54.1 (12.2) 57.7 89	Pioglitazone 30mg daily Metformin 1700 daily	None

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
		25.5 Treatment naive	Pioglitazone + Metformin (same total doses)	
Schernthaner 2004[137] Multinational Good	1,194 52	56 (9.3) 42 NR NR Inadequate treatment with diet alone	Pioglitazone 30-45 mg daily Metformin 850-2,550 mg daily	None
Sharma 2006[132] Fair	35 12	47.7 (9.5) 33 NR NR Newly diagnosed type 2 diabetes	Pio 15-30 mg daily Metformin 1000-2000 mg daily	Gliclazide 30-60 mg daily added to both arms if needed
Van der Meer 2009[138] Netherlands Good	78 24	56.4 (0.9) 0 NR NR	Pioglitazone 30 mg daily Metformin 2,000 mg daily	Added to glimepiride
Yamanouchi 2005[135] Japan Fair	114 52	Metformin group: 54.7 (9.8) 49 NR NR Not on oral agents previously	Pioglitazone 30-45 mg daily Metformin 750 mg daily Glimepiride 1.0-2.0 mg daily	None
Range Fair 5 Good 2	19-2,097 12-156	47.7-67.0 year 0-79 % female	Pioglitazone: 15-45 mg daily Sulfonylureas: various drugs and doses Metformin: 750-2,550 mg daily	

Abbreviations: NR, not reported; pio, pioglitazone; SD, standard deviation; SE, standard error; TZD, thiazolidinedione.
[a] Data shown are mean (SD) unless otherwise indicated.

Efficacy results

HbA1c results for active-control trials of pioglitazone are presented in Tables 30 and 31. Effects on HbA1c were similar between treatment groups, with no statistically significant difference noted between groups in 13 of the 16 trials. The 3 trials reporting a statistically significant difference compared pioglitazone to a sulfonylurea and reported small between-group differences in HbA1c (0.19% to 0.63%).[127, 128, 133] None of the trials comparing pioglitazone to metformin reported a statistically significant difference. In a small (N=92), monotherapy study in

Japan,[133] HbA1c decreased more with glibenclamide (change in HbA1c −1.43%) than with pioglitazone (change in HbA1c −0.80%, between-group $P<0.05$) at 24 weeks follow-up. In an 18-month trial of glibenclamide compared with pioglitazone in newly-diagnosed diabetic subjects taking a variety of concurrent hypoglycemic agents including insulin,[127] HbA1c improved in both groups to a similar degree to week 32, then the improvement was maintained with pioglitazone but not with glimepiride. At the final follow-up (week 72), the between-group difference (in favor of pioglitazone) was −0.32% (95% CI −0.52 to −0.12). In the PERISCOPE trial (N=543), greater improvement in HbA1c was reported for subjects treated with pioglitazone (−0.55%) than for those treated with glimepiride (−0.36%, between group $P=0.03$) at 18 months.[128]

Table 30. Change in HbA1c for pioglitazone compared with sulfonylureas in adults with type 2 diabetes

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for pioglitazone	HbA1c (%) change from baseline (mean, SD) for active control	*P* value of between-group difference
Agarwal 2005[125] Fair	Glipizide: start 5 mg daily; mean maximal dosage 41 mg daily Pio: start 15 mg daily, mean maximal dosage 19 mg daily	−0.1 (1.2)	−0.4 (1.8)	0.52
Basu 2006[126] Fair	Glipizide: 10 mg daily (median dose) Pio: 45 mg daily	0.6 (NR)	0.4 (NR)	*P*>0.05
Mazzone 2006[127] Fair	Pio 15-45 mg daily Glimepiride 1-4 mg daily	(At week 72; from graph) −0.32	(At week 72; from graph) 0	(At week 72) 0.002
Nissen 2008[128] Multinational Fair	Pio 15-45 mg daily Glimepiride 1-4 mg daily	−0.55 (NR)	−0.36	0.03
Papathanassiou 2009[129] Greece Fair	Pio 30 mg daily Glimepiride 4 mg daily	−0.60 (0.85)	−0.56 (0.57)	0.398
Perriello 2006[130] Fair	Pio 30-45 mg daily Gliclazide 80-320 mg daily	−0.79 (NR)	−0.79 (NR)	*P*>0.05
Pfutzner 2005[131] Fair	Pio 24 mg daily Glimepiride 1-6 mg daily and TZDs with glimepiride	−0.8 (0.9)	−0.6 (0.8)	*P*>0.05
Teramoto 2007[133] Fair	Pio 15-30 mg daily Glibenclamide 1.25-2.5 mg daily	−0.80 (1.14)	−1.43 (1.09)	<0.05
Umpierrez 2006[134] Fair	Pio 30-45 mg daily Glimepiride 2-8 mg daily	−1.23 (SE 0.073)	−1.30 (SE 0.077)	0.4825
Yamanouchi 2005[135] Japan Fair	Pio 30-45 mg daily Glimepiride 1.0-2.0 mg daily	−2.3 (NR)	−2.1 (NR)	NSD
Range Fair 10 Good 0	Pio: 15-45 mg daily Sulfonylureas: various drugs and doses	−2.3 – 0.6	−2.1 – 0.4	

Abbreviations: CI, confidence interval; NR, not reported; NSD, no significant difference; pio, pioglitazone; SE, standard error; SD, standard deviation.

Table 31. Change in HbA1c for pioglitazone compared with metformin in adults with type 2 diabetes

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for pioglitazone	HbA1c change from baseline (mean, SD) for active control	*P* value of between-group difference
Kato 2009[140]	Pio 15 mg daily Metformin 500 mg daily	-1.05 (NR)	-0.83 (NR)	NSD
Kusaka 2008[136] Japan Fair	Pio 15 mg daily (women); 30 mg daily (men) Metformin 750 mg daily	−1.1 (NR)	−1.0 (NR)	NR
Perez, 2009[139]	Pio 30mg daily Metformin 1700 daily	-0.96 (NR)	-0.99 (NR)	NSD
Schernthaner 2004[137] Multinational Good	Pio 30-45 mg daily Metformin 850-2,550 mg daily	−1.41 (0.04)	−1.50 (0.04)	NSD
Sharma 2006[132] Fair	Pio 15-30 mg daily Metformin 1000-2000 mg daily	−0.42 (NR)	−0.47 (NR)	0.43
Van der Meer 2009[138] Netherlands Good	Pio 30 mg daily Metformin 2,000 mg daily	−0.6 (NR)	−0.7 (NR)	0.146
Yamanouchi 2005[135] Japan Fair	Pio 30-45 mg daily Metformin 750 mg daily	−2.3 (NR)	−2.1 (NR)	NSD
Range Fair 3 Good 2	Pio: 15-45 mg daily Metformin: 750-2,550 mg daily	−2.3 to −0.42	−2.1 to −0.47	

Abbreviations: CI, confidence interval; NR, not reported; NSD, no significant difference; Pio, pioglitazone; SE, standard error; SD, standard deviation.

Rosiglitazone compared with an active control

Characteristics of studies

We included 14 active-control trials comparing rosiglitazone with an active control (Tables 32 and 33).[141-154] Six of these are new to this section in this report.[144, 148, 149, 152-154] There were 4 monotherapy trials comparing rosiglitazone to metformin[147, 148] or rosiglitazone to a sulfonylurea.[145, 147, 149] The combined therapy trials compared rosiglitazone to a sulfonylurea with both groups receiving metformin or insulin[141-144, 152, 154] or compared rosiglitazone to metformin with both groups receiving sulfonylureas[151] or various hypoglycemic agents.[146] Raskin and colleagues[150] compared rosiglitazone to repaglinide and to the combination of the 2 drugs. Kadoglou and colleagues[153] compared the addition of rosiglitazone with increasing the

dose of metformin for people with inadequately controlled diabetes while taking metformin 850mg daily.

Across active-control studies, rosiglitazone dosing was either 4 or 8 mg daily. Follow-up intervals ranged from 24 weeks to 4 years,[147] with 7 trials having follow-up of 1 year or more.[142, 144-148, 154] Mean age of study subjects was mid-50s for most studies, with 4 studies enrolling older subjects, with mean ages between 60 and 65 years.[141, 151, 153, 154]

Table 32. Characteristics of rosiglitazone active-control trials with sulfonylurea in adults with type 2 diabetes

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Bakris 2006[141] Fair	374 32	58.8 (SE 9.8) 31 NR NR	Rosi: start 4 mg daily Glyburide: start 5 mg daily	Metformin ≥ 1000 mg daily
Derosa 2006[142] Good	95 52	52 (5) 48 NR NR All subjects had the metabolic syndrome (ATPIII definition) in addition to type 2 diabetes	Rosi 4 mg daily Glimepiride 2 mg daily	Metformin 1500 mg daily
Garber 2006[143] Fair	318 24	56 (NR) 44 80 NR Inadequately controlled on metformin at baseline	Rosi 4-8 mg daily and metformin 1,500-2,000 mg daily Glibenclamide-metformin 5/1,000 mg to 10/2,000 mg daily (combination product)	Yes
Gerstein 2010[154] Fair	672 78	Glipizide group: 60.2 34.2 NR NR	Rosi 4-8 mg daily Glipizide 10-15mg daily	Tapered off other oral agents over month 1; could add metformin or insulin if needed
Hamann 2008[144] Multinational Fair	573 52	59.3 (9.2) 48 95 NR Overweight subjects (BMI >=25 kg/m^2 having received metformin	Rosiglitazone 4-8 mg daily Sulfonylurea (glibenclamide 5-15 mg daily or gliclazide 80-320 mg daily)	Added to metformin 2000 mg daily

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Hanefeld 2007[145] Fair	587 52	Glibenclamide group: 60.1 (3.8) 32 NR NR	Rosi 4 mg daily Rosi 8 mg daily Glibenclamide 2.5-15 mg daily	None
Kahn 2006,[147] Viberti 2006, 2002[155, 156] ADOPT Fair	4,351 208 (median)	Glyburide group: 56.4 (10.2) 58 NR NR Failed lifestyle therapy, recently diagnosed, not on oral agents previously	Rosi 4-8 mg daily Glyburide: 2.5-7.5 mg daily Metformin: 500-2,000 mg daily	None
Pop-Busui 2009[149] USA Fair	27 26	49.5 (10) 23 NR NR Treated with diet/exercise or SU alone	Rosiglitazone 8 mg daily Glyburide 10 mg daily	None
Von Bibra 2008[152] Germany Fair	12 32	59 (12) [b] 33 NR NR	Rosiglitazone 8 mg daily Glimepiride 3 mg daily	Added to metformin monotherapy
Range **Fair 8** **Good 1**	**12 - 4,351** **12-208**	**49.5 – 60.2** **23 – 58**	**Rosi 4 mg – 8 mg daily**	

Abbreviations: BMI, body mass index; CI, confidence interval; NR, not reported; rosi, rosiglitazone; SU, sulfonylurea; wk, week(s); yr, year(s).
[a] Baseline data are from the comparison group. Data shown are mean (SD) unless otherwise indicated.
[b] Because this was a cross-over study, population characteristics were reported for the entire cohort.

Table 33. Characteristics of rosiglitazone active-control trials with metformin or other in adults with type 2 diabetes

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
Home 2007[146b] Multinational RECORD Fair	4447 195 (mean, for interim analysis)	58.5 (8.3) 48 NR NR Inadequate control on SU or metformin	Rosi 4-8 mg daily Metformin (up to 2550 mg daily) or SU	Preexisting SU or metformin continued; SU or metformin or insulin added

Author, year Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
		monotherapy		as needed
Kadoglou 2010[153] Fair	100 14	Rosi group: 62 (8.3) 74 NR NR Poor glycemic control while taking Metformin 850 mg daily	Rosi 8 mg daily Metformin, titrating up to 2550 mg daily	Metformin 850 mg daily
Kahn 2006,[147] Viberti 2006, 2002[155, 156] ADOPT Fair	4,351 208 (median)	Glyburide group: 56.4 (10.2) 58 NR NR Failed lifestyle therapy, recently diagnosed, not on oral agents previously	Rosi 4-8 mg daily Glyburide: 2.5-7.5 mg daily Metformin: 500-2,000 mg daily	None
Kiyici 2009[148] Turkey Fair	35 52	52.4 (8.3) NR NR NR Drug naïve	Rosi 4 mg daily Metformin 850 mg daily	Medical nutrition therapy
Stocker 2007[151] Fair	92 24	65 (10) 47 NR NR Failed diet and/or sulfonylurea therapy	Rosi 4 mg daily Metformin 850 mg twice daily	Monotherapy or combined therapy: could continue SU taken prior to study (unknown %)
Rosiglitazone vs. other active control				
Raskin 2004[150] Fair	252 24	Rosi+repaglinide group: 57.5 (10.8) 49 NR NR Failed monotherapy	Rosi: 2-4 mg twice daily Repaglinide: 0.5-4 mg per meal Rosi + repaglinide	None
Range **Fair 6** **Good 0**	**12 - 4,447** **12-208**	**52.4 – 65** **47 – 74**	**Rosi 4 mg – 8 mg daily** **Metformin 500 mg – 2550 mg daily**	

Abbreviations: CI, confidence interval; NR, not reported; rosi, rosiglitazone; SU, sulfonylurea; wk, week(s); yr, year(s).
[a] Baseline data are from the comparison group. Data shown are mean (SD) unless otherwise indicated.
[b] Additional outcomes (cardiovascular risk factors) are reported in Home 2009[157]; that paper is not added to this table because it would mean duplication of HbA1c data.

Efficacy results

HbA1c results for active-control trials of rosiglitazone are presented in Tables 34 and 35. One of the 14 trials, A Diabetes Outcomes Progression Trial (ADOPT),[147] reported a statistically significantly greater improvement in HbA1c for subjects treated with rosiglitazone than those treated with active controls and one[143] reported greater improvement for the active control than for rosiglitazone. The other 12 trials reported no statistically significant difference between groups. ADOPT was a large (N=4360), multicenter, double-blind, randomized controlled trial designed to evaluate monotherapy with rosiglitazone, metformin, or glyburide. The trial reported greater improvement in HbA1c at 4 years for subjects treated with rosiglitazone than for those treated with metformin (treatment difference −0.13%, 95% CI −0.22 to −0.05) and those treated with glyburide (treatment difference −0.42%, 95% CI −0.50 to −0.33). Garber and colleagues reported greater improvement in glycemic control for subjects treated with a combination of glibenclamide 5 mg/metformin 1000 mg (once or twice daily) than for those treated with rosiglitazone 4-8 mg daily combined with metformin 1500-2000 mg daily (between-group difference in HbA1c 0.4%, $P<0.001$).[143]

Among the monotherapy trials, ADOPT (N=4360) was designed to evaluate monotherapy with rosiglitazone, metformin, or glyburide among subjects recently diagnosed (within 3 years) with type 2 diabetes and who had failed lifestyle therapy but had not started on oral hypoglycemic agents.[147] The primary outcome was monotherapy failure defined as fasting plasma glucose level of >180 mg/dL. Median duration of treatment with rosiglitazone was 4 years. The cumulative incidence of monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide ($P<0.001$ for both rosiglitazone comparisons).

The results of 2 smaller rosiglitazone monotherapy trials were similar to the results from ADOPT when the appropriate follow-up intervals were compared. Hanefeld and colleagues found no significant difference between glibenclamide and rosiglitazone at 52-week follow-up[145] and Pop-Busui and colleagues found no significant difference between glyburide and rosiglitazone at 26 weeks.[149] Likewise, Kiyici and colleagues reported similar changes from baseline in HbA1c for subjects treated with rosiglitazone and those treated with metformin.[148]

Among the combination therapy trials where rosiglitazone was added to ongoing metformin therapy compared with adding various sulfonylureas to ongoing metformin, 4 trials did not show significant differences between rosiglitazone and active comparators.[141, 142, 144, 152] On the other hand, Garber and colleagues[143] reported greater improvement in HbA1c for the fixed combination of glibenclamide 5 mg/metformin 1000 mg (once or twice daily) than for rosiglitazone 4-8 mg daily combined with metformin 1500-2000 mg daily (between-group difference in HbA1c 0.4%, $P<0.001$).

Combination therapy studies comparing rosiglitazone to metformin with both groups receiving other oral agents did not show significant differences between treatment groups.[146, 151] A combination of rosiglitazone and repaglinide[150] demonstrated superiority for the combination product over rosiglitazone monotherapy. Rosiglitazone was superior to repaglinide (each as monotherapy; no statistics provided).

In the large RECORD trial[158] (discussed further in Key Question 2), subjects who were already taking a sulfonylurea were randomized to add-on rosiglitazone 4 mg daily (titrated up to 8 mg daily) or metformin (titrated up to 2550 mg daily). Subjects taking metformin at study entry were randomized to add-on sulfonylurea. If adequate glycemic control (HbA1c ≤ 8.5%) was not obtained on maximal dosage dual therapy, a third drug was added (either a sulfonylurea or metformin to rosiglitazone subjects and insulin in the control group). HbA1c decreased by

approximately 0.5% at 18 months follow-up[146] in all 4 treatment groups, with no statistically significant difference between rosiglitazone and other drugs in the background metformin and background sulfonylurea groups.

Table 34. Change in HbA1c in rosiglitazone active-control trials with sulfonylurea in adults with type 2 diabetes

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for rosiglitazone	HbA1c (%) change from baseline (mean, SD) for active control	*P* value of between-group difference
Bakris 2006[141] Fair	Rosi: start 4 mg daily Glyburide: start 5 mg daily	−0.72 (SE 0.10)	−0.92 (SE 0.08)	NR
Derosa 2006[142] Good	Rosi 4 mg daily Glimepiride 2 mg daily	−1.8[a] (NR)	−0.9[a] (NR)	>0.05
Garber 2006[143] Fair	Rosi 4-8 mg daily and metformin 1,500-2,000 mg daily Glibenclamide-metformin 5/1,000 mg to 10/2,000 mg daily (combination product)	−1.1 (NR)	−1.5 (NR)	<0.001
Gerstein 2010[154]	Rosi 4-8 mg daily Glipizide 10-15mg daily	-0.3 (NR)	-0.2 (NR)	*P*= 0.44
Hamann 2008[144] Multinational Fair	Rosi 4-8 mg daily Glibenclamide 5-15 mg daily or gliclazide 80-320 mg daily)	−0.78 (0.06)	−0.86 (0.06)	NSD
Hanefeld 2007[145] Fair	Rosi 4 mg daily Rosi 8 mg daily Glibenclamide 2.5-15 mg daily	Rosi 4 mg: −0.3 (NR) Rosi 8 mg: −0.5 (NR)	−0.7 (NR)	Rosi 8 mg: *P*>0.05
Kahn 2006,[147] Viberti 2006, 2002 [155, 156] ADOPT Fair	Rosi 4-8 mg daily Glyburide: 2.5-7.5 mg daily	NR[b]	NR[b]	Rosi vs. metformin *P*=0.002 Rosi vs. glyburide *P*<0.001[b]
Pop-Busui 2009[149] USA Fair	Rosi 8 mg daily Glyburide 10 mg daily	−0.5[a] (NR)	−1.1[a] (NR)	NSD

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for rosiglitazone	HbA1c (%) change from baseline (mean, SD) for active control	*P* value of between-group difference
Von Bibra 2008[152] Germany Fair	Rosi 8 mg daily Glimepiride 3 mg daily	−0.4[a] (NR)	−0.2[a] (NR)	NR
Range	**Rosi:** **4 mg - 8 mg daily** **Sulfonylureas:** **various drugs and doses**	**−1.8 to −0.3**	**−1.5 to −0.2**	

Abbreviations: NR, not reported; NSD, no significant difference; Rosi, rosiglitazone; SD, standard deviation; SE standard Error; SU, sulfonylurea.
[a] % change calculated from reported baseline and follow-up value.
[b] Improvement in HbA1c at 4 years for subjects treated with rosiglitazone than for those treated with metformin (treatment difference −0.13%, 95% CI −0.22 to −0.05) and those treated with glyburide (treatment difference −0.42%, 95% CI −0.50 to −0.33).

Table 35. Change in HbA1c in rosiglitazone active-control trials with metformin or other in adults with type 2 diabetes

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for rosiglitazone	HbA1c (%) change from baseline (mean, SD) for active control	*P* value of between-group difference
Home 2007[146c] Multinational RECORD Fair	Rosi 4-8 mg daily Metformin (up to 2,550 mg daily) or SU	Rosi + metformin: −0.48 % (95% CI −0.59 to −0.36) Rosi + SU: −0.55% (95% CI −0.67 to −0.44)	SU (background metformin) −0.55% (CI −0.66 to −0.44%) Metformin (background SU) −0.61% (−0.70 to −0.51%)	vs. background SU: *P*>0.05 vs. background metformin: *P*>0.05
Kadoglou 2010[153] Fair	Rosi 8 mg daily Metformin, titrating up to 2550 mg daily	-0.87 (NR)	-0.54 (NR)	*P*=0.291
Kahn 2006,[147] Viberti 2006, 2002[155, 156] ADOPT Fair	Rosi 4-8 mg daily Metformin: 500-2,000 mg daily	NR[b]	NR[b]	Rosi vs. metformin *P*=0.002 Rosi vs. glyburide *P*<0.001[b]
Kiyici 2009[148] Turkey Fair	Rosi 4 mg daily Metformin 850 mg daily	−0.7[a] (NR)	−0.3[a] (NR)	NR

Author, year Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for rosiglitazone	HbA1c (%) change from baseline (mean, SD) for active control	*P* value of between-group difference
Stocker 2007[151] Fair	Rosi 4 mg daily Metformin 850 mg twice daily	−1.08 (0.14)	−1.19 (0.13)	*P*>0.05
Rosiglitazone vs. other active-control				
Raskin 2004[150] Fair	Rosi: 2-4 mg twice daily Repaglinide: 0.5-4 mg per meal Rosi + repaglinide	−0.56 (SE 0.14)	Repaglinide: −0.17 (SE 0.14) Rosiglitazone: −0.56 (SE 0.14) Rosi + repaglinide: −1.43 (SE 0.10)	Rosi vs. rosi + repaglinide: *P*<0.001
Range	**Rosi: 4 mg - 8 mg daily** **Metformin: 500 mg – 2,550 mg daily**	**−1.08 to −0.48**	**−1.43 to −0.17**	

Abbreviations: NR, not reported; NSD, no significant difference; Rosi, rosiglitazone; SD, standard deviation; SE, standard error; SU, sulfonylurea.
[a] Percent change calculated from reported baseline and follow-up value.
[b] Improvement in HbA1c at 4 years for subjects treated with rosiglitazone than for those treated with metformin (treatment difference −0.13%, 95% CI −0.22 to −0.05) and those treated with glyburide (treatment difference −0.42%, 95% CI −0.50 to −0.33).
[c] Additional outcomes (cardiovascular risk factors) are reported in Home 2009[157]; that paper is not added to this table because it would mean duplication of HbA1c data.

TZDs compared with newer diabetes drugs

Characteristics of studies

We found 4 trials comparing rosiglitazone with a newer diabetes drug of primary interest to this report (Table 36).[36, 40, 67, 84] One compared the addition of rosiglitazone with the addition of sitagliptin to ongoing metformin;[36] one compared the addition of rosiglitazone with the addition of liraglutide to ongoing glimepiride;[84] one compared the addition of colesevelan, rosiglitazone, or sitagliptin to ongoing metformin;[40] and one compared the addition of exenatide, rosiglitazone, or exenatide and rosiglitazone to ongoing metformin.[67]

Table 36. Characteristics of TZD interclass head-to-head trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Combination therapy
DeFronzo, 2010[67] Fair	137 20	56 (10) 51 61 23	Rosiglitazone 8 mg daily Exenatide 20 mcg daily Exenatide and Rosiglitazone	Added to metformin
Marre 2009[84b] LEAD-1 Multinational Fair	1040[c] 26	54.7-57.7 (9.0-10.0) 55 NR NR Inadequate glycemic control after >=3 month OGLAs	Rosiglitazone 4 mg daily Liraglutide 0.6-1.8 mg daily	Added to glimepiride 2-4 mg daily
Rigby 2010[40] Fair	169 16	Rosi group: 54.7 (10.9) 58.9 28.6 67.9	Rosi 4 mg daily Sitagliptin 100 mg daily Colesevelam 3.75 g daily	Metformin 1500-2550 mg daily
Scott 2008[36] Multinational Fair	273 18	55.2 (9.8) 45 61 NR Inadequate glycemic control with metformin monotherapy	Rosiglitazone 8 mg daily Sitagliptin 100 mg daily	Added to metformin ≥1500 mg daily

Abbreviations: mth, month(s); NR, not reported; OAD, oral antidiabetic drug; OGLA, oral glucose-lowering agent; SD, standard deviation; SE, standard error; TZD, thiazolidinedione.
[a] Baseline data are from the comparator arms. Data shown are mean (SD) unless otherwise indicated.
[b] Nauck 2009[159] includes analyses of data from this trial.
[c] 1041 subjects were randomized; 1040 received at least 1 dose of medication and were included in data analysis.

Efficacy results

HbA1c results for these are presented in Table 37. One 18 week trial (N=273) found no significant difference in reduction of HbA1c between those treated with the addition of rosiglitazone and those treated with the addition of sitagliptin.[36] The trial that randomized subjects to add-on either rosiglitazone, sitagliptin, or colesevelam to ongoing metformin found no statistically significant difference between the rosiglitazone- and sitagliptin-treated subjects.[40]

One 26 week trial (N=1040) comparing the addition of rosiglitazone with the addition of liraglutide (to ongoing glimepiride treatment) reported greater reduction in HbA_{1c} with liraglutide (−1.1 compared with −0.4%, $P<0.0001$).[84]

One 20-week trial comparing exenatide to rosiglitazone with all participants on background metformin therapy, found no significant difference in improvement in HbA1c between the exenatide and rosiglitazone arms (-0.9% compared with -1.0%, *P*=0.720).[67]

Table 37. Change in HbA1c in TZD interclass head-to-head trials in adults with type 2 diabetes

Author, year Country Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for rosiglitazone	HbA1c change from baseline (mean, SD) for active comparator	*P* value of between-group difference
DeFronzo, 2010[67] Fair	Rosiglitazone 8 mg daily Exenatide 20 mcg daily Exenatide and Rosiglitazone	-1.0	-0.9	0.720
Marre 2009[84a] LEAD-1 Multinational Fair	Rosiglitazone 4 mg daily Liraglutide 0.6-1.8 mg daily	−0.44	0.6 mg: −0.60 1.2 mg: −1.08 1.8 mg −1.13	NSD *P*<0.0001 *P*<0.0001
Rigby 2010[40] Fair	Rosi 4 mg daily Sitagliptin 100 mg daily Colesevelam 3.75 g daily	-0.6 (95% CI: -0.83 to -0.32)	-0.4 (-0.64 to -0.13) for sitagliptin	NSD
Scott 2008[36] Multinational Fair	Rosiglitazone 8 mg daily Sitagliptin 100 mg daily	−0.79 (95% CI −0.92 to −0.65)	−0.73 (95% CI −0.87 to −0.60)	NSD

Abbreviations: SD, standard deviation; NSD, no significant difference.
[a] Nauck 2009[159] presented data for a subset of patients from LEAD-1[84] and LEAD-2.[59] We do not report those results in this table to avoid double-counting subjects. That study reported a mean change for HbA1c of −0.8 for rosiglitazone, −0.3 for placebo, and −1.4 for liraglutide 1.8 mg (*P*<0.001 for liraglutide vs. rosiglitazone).

Detailed Assessment of TZDs Compared with Placebo

Placebo-controlled trials of pioglitazone

For this report, we did not update the comparisons of pioglitazone or rosiglitazone compared with placebo. This information was included in the 2008 Drug Effectiveness Review Project drug class review on TZDs. We briefly summarize the findings of that report here.[18]

In the original report, 16 trials comparing pioglitazone to placebo in at least 1 study arm were identified. All but 1 of these trials had sufficient data to permit a meta-analysis; a study by Saad and colleagues[160] did not provide a measure of dispersion. In the updated review 4 new

placebo-controlled trials were identified, 2 of combination therapy[161, 162] and 2 of monotherapy,[163, 164] along with a no-treatment comparison[165] study.

The mean difference between groups for all good- and fair-quality studies comparing pioglitazone with placebo ranged from −3.0% to −0.5% and the pooled weighted mean difference was −0.95 (95% CI −1.24 to −0.67) (95% CI −1.27 to −0.84) (Table 38). In other words, overall, pioglitazone improved HbA1c about 1.0% compared with placebo. Results were somewhat more pronounced when pioglitazone monotherapy was compared with placebo than when combined therapy (the addition of pioglitazone to another hypoglycemic drug) was compared with placebo added to the other hypoglycemic drug, although the differences between monotherapy and combined therapy were not significant (Table 38).

Table 38. Meta-analysis results for HbA1c from 2008 Drug Effectiveness Review Project TZDs report

	Number of studies	Total N 11,148	Weighted mean difference in HbA1c (95% CI)[a]	Test for heterogeneity (*P* value)
Pioglitazone				
Good/fair-quality studies	9	6787	−0.95 (−1.24 to −0.67)	<0.0001
All studies	19	7324	−0.90 (−1.16 to −0.65)	<0.0001
Monotherapy	10	929	−0.92 (−1.33 to −0.51)	<0.0001
Combined therapy	9	6395	−0.90 (−1.26 to −0.55)	<0.0001
Rosiglitazone				
Good/fair-quality studies	23	3417	−0.92 (−1.15 to −0.68)	<0.0001
All studies	27	3824	−0.95 (−1.17 to −0.73)	<0.0001
Monotherapy	11	1196	−0.82 (−1.30 to −0.34)	<0.0001
Combined therapy	16	2628	−1.02 (−1.20 to −0.85)	<0.0028

Abbreviations: CI, confidence interval; N, sample size.
[a] HbA1c given as %. Net change is the difference in HbA1c between the end of the study period and baseline.

Placebo-controlled trials of rosiglitazone

In the original report, 25 trials compared the efficacy or effectiveness of rosiglitazone to placebo. Four rosiglitazone studies did not provide adequate information for inclusion in the meta-analysis: Honisett et al.[166] did not provide a measure of dispersion; the units for HbA1c in a paper by Raskin and colleagues[167] were difficult to interpret; Wang et al.[168] provided graphical data only; and Nolan and colleagues[169] provided a measure of fasting glucose but not HbA1c. In the updated review of placebo-controlled trials of rosiglitazone, 8 new studies were identified,[162, 170-176] including 3 poor-quality studies.[162, 173, 174] All but 1 study[162] were combination therapy studies.

Mean differences are presented in Table 38 above. Results are similar to those noted for pioglitazone, with a mean change in HbA1c for all good and fair-quality studies of −0.92 (95% CI −1.15 to −0.68). Again, heterogeneity was significant among studies and there were no

significant differences between monotherapy and combined therapy. Adjusted indirect comparisons of pioglitazone and rosiglitazone revealed no significant differences between the 2 drugs for HbA1c.

Using meta-regression, the 2008 Drug Effectiveness Review Project TZDs report examined placebo-controlled trials of either pioglitazone or rosiglitazone and found no significant relationships between change in HbA1c and follow-up interval or funder (industry or other). When studies using combination therapy (either thiazolidinedione combined with insulin, sulfonylurea, or metformin) were examined, there were no significant differences among the various treatment combinations for change in HbA1c.

Detailed Assessment of Health outcomes (microvascular and macrovascular disease, lower extremity ulcers, all-cause mortality, and quality of life) for TZDs

None of the head-to-head studies identified in the original or updated review examined macro- or microvascular outcomes. Three placebo-controlled or no-treatment comparison studies identified in the original review examined cardiovascular outcomes; all examined patients with known macrovascular disease and type 2 diabetes,[168, 177, 178] including the PROACTIVE trial.[177] These 3 trials did not provide sufficient data to determine comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes. In the updated review several additional trials provided evidence on macrovascular outcomes and on mortality, with 5 trials providing additional evidence on pioglitazone. Here we summarize the information related to health outcomes and TZDs. Of note, we address adverse events (including congestive heart failure and cardiovascular adverse events) in the Key Question 2 section of this report, rather than in this section.

In the PROACTIVE trial,[177] a good-quality, European, multicenter, randomized, placebo-controlled trial of 5238 patients with type 2 diabetes and evidence of macrovascular disease, treatment patients received pioglitazone titrated from 15 mg up to 45 mg daily. Ninety-six percent of patients were taking other glucose-lowering agents, including insulin. The average follow-up period was 34.5 months. The primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The hazard ratio for this endpoint was 0.90 (95% CI 0.80 to 1.02). Congestive heart failure was not included in this composite endpoint, although congestive heart failure was examined as an adverse event. When examined individually (as secondary endpoints), none of the components of the primary endpoint changed significantly ($P>0.05$). The hazard ratio of the main secondary endpoint (a composite of all-cause mortality, myocardial infarction [excluding silent myocardial infarction], and stroke) was 0.84 (95% CI 0.72 to 0.98).

Wang and colleagues[168] performed a randomized controlled trial comparing rosiglitazone 4 mg daily to no treatment (N=70) over 6 months. Included patients were aged 50 to 73 years, had a diagnosis of coronary artery disease (>50% stenosis as proven on angiography), had established type 2 diabetes, and had undergone a percutaneous coronary intervention (Evidence Table 9 from 2008 DERP TZD Report Update 1). Forty-one percent took other anti-diabetic medications. At 6-month follow-up the incidence of coronary events was decreased in the rosiglitazone group (between-group $P<0.05$ for the composite endpoint), with 4 events in the rosiglitazone group (recurrent angina[179] and coronary artery bypass grafting [1]) and 12 in the

control group (recurrent angina [5], repeated angioplasty,[179] and coronary artery bypass grafting[179]).

A single-center poor-quality study examined the preventive effects of rosiglitazone on restenosis after coronary stent implantation among 95 persons with type 2 diabetes.[178] In this open-label, randomized controlled trial, the treatment group was placed on rosiglitazone 8 mg before undergoing catheterization and 4 mg daily thereafter, combined with conventional antidiabetic therapy using a variety of agents (details of concurrent therapy were not provided). The comparison group received conventional therapy only. The rate of restenosis was 18% in the rosiglitazone group and 38% in the control group (between-group P=0.03). There was also a significant difference in stenosis diameter between groups at 6 months (P=0.004) in favor of the rosiglitazone group.

The available data provided no information on the comparative effectiveness of pioglitazone and rosiglitazone on macro- and microvascular outcomes when used as monotherapy or when added to or substituted for other oral hypoglycemic agents. Dormandy and colleagues[177] addressed the question of combined therapy as pioglitazone was added to other anti-diabetic therapy in 96% of patients. In the study by Wang and coauthors[168] monotherapy and combined therapy patients were aggregated, so conclusions cannot be drawn about each of these 2 approaches.

In the updated review several additional trials provided evidence on macrovascular outcomes and on mortality, with 5 trials providing additional evidence on pioglitazone.

The CHICAGO trial[127] was a multicenter study of pioglitazone 15 to 45 mg per day compared with glimepiride 1 to 4 mg per day in 462 adults who were newly diagnosed with type 2 diabetes. The primary endpoint was the change in carotid artery intima-media thickness after 72 weeks. Secondary endpoints included the composite of cardiovascular mortality, non-fatal myocardial infarction, or nonfatal stroke, and the composite of these outcomes plus coronary revascularization, carotid endarterectomy/carotid stenting, hospitalization for unstable angina, or hospitalization for heart failure. There were few events reported, and no cardiovascular deaths. There were 2 instances of the first composite endpoint in the glimepiride group and none in the pioglitazone group. On the second composite endpoint, there were 10 events in the glimepiride group (8 of which were coronary revascularization) and 4 in the pioglitazone group (3 coronary revascularization).

PERISCOPE was another trial of pioglitazone compared to glimepiride designed to measure progression of atherosclerosis in patients with type 2 diabetes.[128] After 18 months of follow-up, there was no difference between groups in the occurrence of clinical endpoints, including the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (2.2% for glimepiride compared with 1.9% for pioglitazone; P=0.78), the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or congestive heart failure 4.8% for glimepiride compared with 4.1% for pioglitazone; P=0.70) or any components of the composite outcomes. There were 3 cardiovascular deaths in the pioglitazone group and 1 in the glimepiride group (P=0.37).

In a small, fair-quality, randomized controlled trial (N=47), patients with impaired glucose tolerance or type 2 diabetes (combined in the analysis) in addition to nonalcoholic steatohepatitis, received either pioglitazone 45 mg daily or placebo, in addition to a weight loss intervention.[180] Glycemic control improved with pioglitazone compared with placebo (P<0.001), with a decrease in weight and body mass index with treatment compared with placebo (P=0.003 and 0.005, respectively). Plasma aspartate and alanine aminotransferase levels and hepatic fat

content all decreased with treatment compared with placebo ($P<0.05$) and liver aminotransferase levels normalized with pioglitazone. Histologic changes in the liver also improved significantly with pioglitazone.

In another small trial,[181] patients with acute coronary syndrome received pioglitazone or no additional treatment starting 2 weeks after percutaneous, bare metal stent placement. At 6-months follow-up these researchers demonstrated that late luminal loss was less in the pioglitazone group than in the control group ($P=0.0008$); the same was found for restenosis rate (between-group $P=0.0052$; both assessed with quantitative angiography). Major cardiac events (myocardial infarction or revascularization of the target lesion) were significantly decreased in the pioglitazone group at 6 months compared with the control group (7.7% compared with 60.7%, $P<0.0001$). There were no deaths in either group.

Takagi and colleagues compared pioglitazone with placebo in 44 patients with type 2 diabetes who had undergone coronary stent implantation.[182] After 6 months of follow-up, angiographic in-stent restenosis (19% compared with 46%; $P=0.0994$) and target lesion revascularization (12% compared with 38%; $P=0.0835$) were less frequent in the pioglitazone group, but the differences were not statistically significant. There was no difference in HbA1c levels at follow-up in this study (See Key Question 1).

The updated search identified several important recent trials of rosiglitazone reporting vascular or mortality outcomes: the RECORD trial[146, 157] and ADOPT.[147] The RECORD trial was an open-label, multicenter, noninferiority, randomized controlled trial (N=4447). Subjects who were already taking metformin or a sulfonylurea were randomized to add-on rosiglitazone 4 mg daily (titrated up to 8 mg daily) or to metformin (titrated up to 2550 mg daily) plus a sulfonylurea (glyburide, gliclazide or glimepiride, depending on physician preference). If adequate glycemic control (HbA1c $\leq$ 8.5%) was not obtained on maximal dosage dual therapy, a third drug was added (either a sulfonylurea or metformin for rosiglitazone subjects and insulin in the control group).

The primary outcome for the RECORD study was time to first occurrence of cardiovascular hospitalization or cardiovascular death. 321 people in the rosiglitazone group and 323 in the active control group experienced the primary outcome during a mean 5.5 year follow up. The hazard ratio for rosiglitazone (plus metformin or a sulfonylurea) compared with metformin plus a sulfonylurea was 0.99 (95% CI 0.85 to 1.16), meeting the criterion of non-inferiority. Heart failure causing admission to the hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group(hazard ratio 2.10, 95% CI 1.35 to 3.27).

The large ADOPT[147], discussed above for the outcome of monotherapy failure, compared rosiglitazone, glyburide, and metformin in subjects newly diagnosed with type 2 diabetes. Subjects with significant renal or hepatic disease, unstable or severe angina, or congestive heart failure of any New York Heart Association class were excluded. Approximately half of subjects had hypertension, 81% had metabolic syndrome, and 45% were smokers.[156] The number of deaths from all causes was similar across the 3 groups, but more cardiovascular events were reported in the rosiglitazone group (4.3%) than in the metformin (4.0%) or glyburide groups (2.8%; no significant differences among groups). Congestive heart failure events were higher with rosiglitazone than with glyburide (further details are presented in Key Question 8). The lower rates of cardiovascular events in the glyburide group were primarily due to lower rates of nonfatal myocardial infarction and congestive heart failure in this group.

Several additional, smaller rosiglitazone trials were also identified in the updated search.[174, 176] In a very small (N=16), poor-quality, randomized controlled trial, subjects with

coronary stent implantation were randomized to rosiglitazone 4-8 mg daily or placebo for 6 months. Rosiglitazone did not reduce in-stent restenosis and there were no differences in cardiac events between the groups.[174]

In a study of older adults with type 2 diabetes, Rosenstock and colleagues[176] noted no significant difference between rosiglitazone and placebo (both groups received glipizide) in SF-36 component scores, although the rosiglitazone group had greater improvement on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) than the glipizide only group (1.15 point increase compared with 1.61 point decrease, $P<0.001$).

III. Fixed-dose Combination Products (FDCPs) or Dual Therapy

Summary of findings for FDCPs or Dual Therapy

Evidence in children

- We did not find any evidence meeting inclusion/exclusion criteria for children (insufficient strength of evidence).

Evidence in adults

- We found no studies that focused on health outcomes as the primary outcomes for any available FDCP. Two studies reported health outcomes among other secondary outcomes or in the adverse events section.[183, 184] Overall evidence was insufficient to determine how FDCPs compare with other treatments for their impact on health outcomes.
- We found no head to head trials that compared HbA1c control between any 2 FDCPs (insufficient strength of evidence).
- We found no trials that evaluated the following FDCPs: Duetact®, Janumet® (insufficient strength of evidence).
- Therapy with Avandamet,® Avandaryl,® or Actoplus Met produced statistically significantly greater reductions in HbA1c compared to monotherapy with any of their respective components.
- The magnitudes of the differences in HbA1c reductions between the FDCPs and their respective monotherapy components ranged from 0.13% to 0.7% for Avandamet®, 0.6% to 0.8% for Avandaryl®, and 0.2% to 0.9% for Actoplus Met®.
- Greater reduction in HbA1c with Avandamet® or dual therapy with metformin and rosiglitazone than with component monotherapy in trials of 24 to 32 weeks (reduction in the intervention arms ranged from 0.13% to 0.7%, moderate strength of evidence)
- Greater reduction in HbA1c with Avandaryl® or dual therapy with rosiglitazone and glimepiride than with component monotherapy in trials from 20 to 28 weeks (reduction in the intervention arms ranged from 0.6% to 0.8%, moderate strength of evidence)
- Greater reduction in HbA1c with Actoplus Met® or dual therapy with pioglitazone and metformin than with component monotherapy in trials of 24 weeks and 15 months (reduction in the intervention arms ranged from 0.2% to 0.9%, moderate strength of evidence)
- Greater reduction in HbA1c with dual therapy with metformin and sitagliptin than with component monotherapy in a 24 week trial with additional 30 and 52 week extensions (range 0.4% to 1.2%, moderate strength of evidence).

Detailed Assessment for FDCPs and Dual Therapy

We identified studies that have been conducted specifically using fixed-dose combination tablets comprised of rosiglitazone/metformin (Avandamet®),[183, 185] rosiglitazone/glimepiride (Avandaryl®),[186] and pioglitazone/metformin (Actoplus Met®).[139] Two of these were new since the 2007 Drug Effectiveness Review Project report on FDCPs.[139, 183] We found no head-to-head studies comparing FDCPs.

We also included studies using dual therapy of rosiglitazone plus metformin,[184] rosiglitazone plus glimepiride,[187], pioglitazone plus metformin,[188] and sitagliptin plus metformin.[31-33] All of these were new for this report. For this report, dual therapy was defined as using the individual components of a FDCP in separate pills/tablets. Studies were required to randomize subjects to the components of a FDCP or to monotherapy with one of the components of the FDCP to be eligible for this report. Studies continuing a 'background' therapy (e.g., with metformin) and randomizing subjects to add-on one medication (e.g., rosiglitazone or pioglitazone) or to add-on placebo were classified as comparing that medication (e.g., rosiglitazone or pioglitazone) with placebo.

No studies were identified that used the fixed-dose combination tablets comprised of pioglitazone/glimepiride (Duetact®)[189] or sitagliptin/metformin (Janumet®).[190] The efficacy and safety of Duetact® and Janumet® have been established based on trials using the co-administration of their separate components.

The majority of the trials were 4- to 6-month evaluations of glycemic control and general adverse events with FDCPs or dual therapy compared to component monotherapy when used as initial treatment for patients with type 2 diabetes. Studies that compared type 2 diabetes combination tablet products to co-administration of their components were few, nonrandomized, and limited to analyses based on refill data from pharmacy claims databases.[191-193]

We found no evidence to address the effectiveness of combination tablet products in improving long-term health.

Throughout this section, meta-analyses were not performed due to an insufficient number of studies or heterogeneity of study populations, outcomes, and designs.

Avandamet® or dual therapy with metformin plus rosiglitazone

Three randomized controlled trials including either Avandamet® or dual therapy with metformin and rosiglitazone met inclusion criteria. No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Head-to-head trials

We found no head-to-head trials of Avandamet® or dual therapy with metformin and rosiglitazone comparing them with other FDCPs that met inclusion criteria.

Trials comparing Avandamet® or dual therapy with component monotherapy

Three fair-quality trials compared Avandamet® (2 trials) or dual therapy (one trial) with metformin and rosiglitazone to monotherapy with metformin or rosiglitazone. (Table 39) Two trials compared Avandamet® with metformin monotherapy; one of them also compared Avandamet® with rosiglitazone monotherapy. The dual therapy trial compared concurrent use of metformin and rosiglitazone with metformin monotherapy.

Table 39. Characteristics of Avandamet® (metformin/rosiglitazone) and rosiglitazone plus metformin dual therapy trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Control(s)
Fixed-dose combination				
Rosenstock 2006[185] Multinational Fair	468 32	50.1-51.5 (10.3-10.7) 42-44 54-59 21-26	Avandamet®: 2 mg/500 mg to 8 mg/2,000 mg daily	Metformin: 500-2,000 mg daily Rosiglitazone: 4-8 mg daily
Stewart 2006[183] Multinational Fair	509 32	58.9-59.0 (7.9-8.4) 44-45 98-99 <1	Avandamet®: 4 mg/500 mg to 8 mg/2,000 mg daily	Metformin: 500 mg to 3,000 mg daily
Dual therapy				
Weissman 2005[184b] United States Fair	709 24	55.5-55.7 (10.2-11.2) NR NR NR	Dual therapy (rosi + met): 4 mg/1,000 mg daily	Metformin: 1,500 mg-2,000 mg daily
Range **3 Fair** **0 Good**	**468-709** **24-32**	**50.1-59.0 (7.9-11.2)** **42-45** **54-99** **<1-26**	**Avandamet®: 2 mg/500 mg to 8 mg/2,000 mg daily** **Dual therapy: 4 mg/100 mg daily**	**Rosiglitazone: 4-8 mg daily** **Metformin: 500-3,000 mg daily**

Abbreviations: NR, not reported; SD, standard deviation; met, metformin; rosi, rosiglitazone
[a] Unless otherwise noted, data presented are the range across treatment groups for mean and standard deviation.
[b] Goldstein et al, 2006[194] analyzed a subset of this trial; that study is not included in this section in order to avoid duplication of data

Overall, both Avandamet® and dual therapy with metformin and rosiglitazone were associated with greater reductions in HbA1c values, compared with monotherapy (Table 40).

Both trials comparing Avandamet® with metformin monotherapy found that Avandamet® reduced HbA1c levels by a greater amount than metformin alone. In one of the trials,[185] HbA1c was reduced by a mean of 2.3% after 32 weeks in subjects on Avandamet® (mean daily dose = 7.2 mg rosiglitazone + 1,799 mg metformin) compared with 1.8% for subjects on metformin (mean daily dose = 1,847 mg) (P=0.0008). In the other,[183] mean HbA1c reduction in the Avandamet® group (mean daily dose = 6.8 mg rosiglitazone + 1,812 mg metformin) was 0.51% over 32 weeks, compared with a 0.38% reduction in the metformin monotherapy group (mean daily dose 2,628 mg) (P=0.0357).

In the 32-week trial comparing Avandamet® with rosiglitazone monotherapy,[185] rosiglitazone (mean daily dose = 7.7 mg) reduced HbA1c by a mean of 1.6% - an amount smaller than the 2.3% reduction with Avandamet® (P<0.001).

A 24-week trial of dual therapy (metformin plus rosiglitazone) compared with metformin monotherapy reported that dual therapy (8 mg rosiglitazone + 1,000 mg metformin daily) reduced HbA1c by a mean of 0.93% compared with a mean reduction in the metformin monotherapy group (2,000 mg daily) of 0.71% (*P* value for the between-group difference was NR; 95% CI indicated statistical significance between the arms (mean change from baseline −0.36, −0.04).

Table 40. Change in HbA1c in Avandamet® (metformin/rosiglitazone) or rosiglitazone plus metformin trials in adults with type 2 diabetes

Author, year Country Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for FDCP or dual therapy	HbA1c change from baseline (mean, SD) for active control	*P* value of between-group difference
Fixed-dose combination				
Rosenstock 2006[185] Multinational Fair	Avandamet®: 7.2 mg/1,799 mg final mean daily dose Metformin: 1,847 mg final mean daily dose Rosiglitazone: 7.7 mg final mean daily dose	−2.3 (NR)	Metformin: −1.8 (NR) Rosiglitazone: −1.6 (NR)	0.0008 <0.0001
Stewart 2006[183] Multinational Fair	Avandamet®: 6.8 mg/1,812 mg final mean daily dose Metformin: 2,627.9 mg final mean daily dose	−0.51 (NR)	−0.38 (NR)	0.0357
Dual therapy				
Weissman 2005[a 184] United States Fair	Dual therapy (rosi + met): 8 mg/1,000 mg daily Metformin: 2,000 mg daily	−0.93 (95%CI −1.06 to −0.80)	−0.71 (95%CI −0.83 to −0.60)	NR but 95%CI of difference = significant (−0.36 to −0.04)
Range **3 Fair** **0 Good**	**Avandamet®: 2 mg/500 mg to 8 mg/2,000 mg daily** **Dual therapy: 4 mg/100 mg daily**	**−2.3 to −0.51**	**−1.8 to −0.38**	

Abbreviations: CI, confidence interval; FDCP, fixed-dose combination product; met, metformin; NR, not recorded; NSD, no significant difference; rosi, rosiglitazone.

[a] Goldstein et al, 2006 [194] analyzed a subset of this trial; that study is not included in this section in order to avoid duplication of data.

Avandaryl® or dual therapy with rosiglitazone plus glimepiride

Two randomized controlled trials including either Avandaryl® or dual therapy with rosiglitazone and glimepiride met inclusion criteria. No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Head-to-head trials

We found no head-to-head trials of Avandaryl® or dual therapy with rosiglitazone and glimepiride comparing them with other FDCPs that met inclusion criteria.

Trials comparing Avandaryl® or dual therapy with component monotherapy

Two trials compared Avandaryl® or dual therapy with rosiglitazone plus glimepiride to monotherapy with rosiglitazone or glimepiride. (Table 41) One good-quality trial compared 2 dosages of Avandaryl® with glimepiride monotherapy and with rosiglitazone monotherapy.[186] One fair-quality dual therapy trial compared concurrent use of rosiglitazone and glimepiride with rosiglitazone monotherapy.[187]

Table 41. Characteristics of Avandaryl® (rosiglitazone /glimepiride) and rosiglitazone plus glimepiride dual therapy trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics[a]	Intervention	Control(s)
Fixed-dose combination				
Chou 2008[186] Multinational Good	874 28	53.0-54.9 (10.6-11.6) 40.0-42.3 76.1-78.4 7.7-10.6	Avandaryl®: 4 mg/1 mg – 4 mg/4 mg daily Avandaryl®: 4 mg/1 mg – 8 mg/4 mg daily	Glimepiride: 1 mg-4 mg daily Rosiglitazone: 4 mg-8 mg daily
Dual therapy				
McCluskey 2004[187] United States Fair	40 20	50.8-60.2 (7.8-9.7) 56.0-60.0 80.0-96.0 NR	Dual therapy (rosi + glimep): 8 mg/1 mg – 8 mg/8 mg daily	Rosiglitazone: 4 mg-8 mg daily
Range **1 Fair** **1 Good**	**40-874** **20-28**	**50.8-60.2 (7.8-11.6)** **40.0-60.0** **76.1-96.0** **7.7-10.6**	**Avandaryl®: 4 mg/1 mg to 8 mg/4 mg daily** **Dual therapy: 8 mg/1 mg to 8 mg/8 mg daily**	**Rosiglitazone: 4-8 mg daily** **Glimepiride: 1 mg-4 mg daily**

Abbreviations: glimep, glimepiride; NR, not reported; rosi, rosiglitazone; SD, standard deviation.
[a] Unless otherwise noted, data presented are the range across treatment groups for mean and standard deviation.

In both trials, Avandaryl® or dual therapy with rosiglitazone and glimepiride were associated with greater reductions in HbA1c values, compared with monotherapy (Table 42).The trial comparing 2 dosages of Avandaryl® with glimepiride or rosiglitazone monotherapy[186] found that Avandaryl® (4 mg/1 mg daily titrated to 4 mg/4 mg)reduced HbA1c levels by a greater amount (mean reduction 2.41%) than glimepiride monotherapy (1.72%; $P<0.0001$) or rosiglitazone monotherapy (1.75%; $P<0.0001$) after 28 weeks. In the 4 mg/1 mg daily titrated to 8 mg/4 mg daily formulation of Avandaryl®, mean HbA1c reduction was 2.52%. This was also a significantly greater reduction compared with glimepiride and rosiglitazone monotherapies ($P<0.0001$).

In the other trial, dual therapy with rosiglitazone and glimepiride also resulted in greater improvement in HbA1c than monotherapy.[187] Dual therapy with 8 mg of rosiglitazone and 8 mg of glimepiride daily (titrated up from 8 mg/1 mg daily) was associated with a mean HbA1c reduction of 1.2% after 20 weeks. This was a significantly larger decrease than was found with glimepiride (4 mg titrated to 8 mg daily) monotherapy (mean reduction 0.3%; $P<0.001$).

Table 42. Change in HbA1c in Avandaryl® (rosiglitazone/glimepiride) or rosiglitazone plus glimepiride trials in adults with type 2 diabetes

Author, year Country Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for FDCP or dual therapy	HbA1c change from baseline (mean, SD) for active control	*P* value of between-group difference
Fixed-dose combination				
Chou 2008[186] Multinational Good	Avandaryl®(A): 4 mg/1 mg – 4 mg/4 mg daily Avandaryl®(B): 4 mg/1 mg – 8 mg/4 mg daily Glimepiride: 1 mg-4 mg daily Rosiglitazone: 4 mg-8 mg daily	(A): −2.41 (1.4) (B): −2.52 (1.4)	Glimep: −1.72 (1.4) Rosi: −1.75 (1.5)	<0.0001 (All)
Dual therapy				
McCluskey 2004[187] United States Fair	Dual therapy (rosi + glimep): 8 mg/1 mg – 8 mg/8 mg daily Rosiglitazone: 4 mg-8 mg daily	−1.2 (SE −0.1)	−0.3 (SE 0.2)	<0.001
Range **1 Fair** **1 Good**	**Avandaryl®: 4 mg/1 mg to 8 mg/4 mg daily** **Dual therapy: 8 mg/1 mg to 8 mg/8 mg daily**	**−2.52 to −1.2**	**−0.3 to −1.75**	

Abbreviations: SD, standard deviation; FDCP, fixed dose combination product; rosi, rosiglitazone; glimep, glimepiride; SE, standard error.

Actoplus Met® or dual therapy with pioglitazone plus metformin

We found one study including Actoplus Met® and one controlled trial including dual therapy with pioglitazone and metformin that met inclusion criteria. No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Head-to-head trials

We found no head-to-head trials of Actoplus Met® or dual therapy with pioglitazone and metformin comparing them with other FDCPs that met inclusion criteria.

Trials comparing Actoplus Met® or dual therapy with component monotherapy

One fair-quality trial compared Actoplus Met® with pioglitazone and metformin monotherapies (Table 43). One good-quality trial compared dual therapy with pioglitazone and metformin to monotherapy with each component.

Table 43. Characteristics of Actoplus Met® (pioglitazone/metformin) or pioglitazone plus metformin dual therapy active-control trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Control(s)
Actoplus Met®				
Perez 2009[139] Multinational Fair	600 24	53.7-54.7 (12.0-12.2) 53.3-65.1 87.3-91.5 NR	Actoplus Met®: 30 mg/1,700 mg daily	Pio: 30 mg daily Met: 1,700 mg daily
Dual Therapy				
Derosa 2009[188] Italy Good	271 52	54-57.7 (5-7) 49.3-53.6 NR NR	Dual therapy (pio + met): 45 mg/2,550 mg daily	Pio: 45 mg daily Met: 3,000 mg daily

Abbreviations: met, metformin; NR, not reported pio, pioglitazone; SD, standard deviation.
[a] Unless otherwise noted, data presented are the range across treatment groups for mean and standard deviation.

In the active-control FDCP trial, Actoplus Met® (30 mg/1,700 mg daily) was associated with a greater reduction in HbA1c value, compared with either monotherapy (Table 44). At the end of this 24-week RCT, the mean HbA1c reduction in the Actoplus Met® group was 1.83%. Mean reductions in the pioglitazone and metformin monotherapy groups were 0.96% and 0.99%, respectively. The *P* value of the between-group difference for both Actoplus Met® comparisons was <0.0001.

In the active-control dual therapy trial, treatment with both pioglitazone (45 mg daily) and metformin (2,550 mg daily) was associated with greater reductions in HbA1c values, compared with monotherapy (Table 44). After 12 months of treatment, the dual therapy group

achieved a mean HbA1c reduction of 0.9%, a change significantly greater than the decreases achieved with 45mg daily pioglitazone monotherapy (mean reduction = 0.6%; $P<0.01$) or 3,000 mg daily metformin monotherapy (mean reduction = 0.7%; $P<0.05$).

Table 44. Change in HbA1c in Actoplus Met® (pioglitazone/metformin) or pioglitazone plus metformin trials in adults with type 2 diabetes

Author, year Country Quality	Intervention	HbA1c (%) change from baseline (mean, SD) for dual therapy	HbA1c change from baseline (mean, SD) for active control	*P* value of between-group difference
Actoplus Met®				
Perez 2009[139] Multinational Fair	FDCP (pio/met): 30 mg/1,700 mg daily Pio: 30 mg daily Met: 1,700 mg daily	-1.83 (NR)	Pio:-0.96 (NR) Met: -0.99 (NR)	Pio: <0.0001 Met: <0.0001
Dual therapy				
Derosa 2009[188] Italy Good	Dual therapy (pio + met): 45 mg/2,550 mg daily Pio: 45 mg daily Met: 3,000 mg daily	-0.9 (NR)	Pio: −0.6 (NR) Met: −0.7 (NR)	Pio: <0.01 Met: <0.05

Abbreviations: FDCP, fixed-dose combination product; Met, metformin; NR, not reported; pio, pioglitazone; SD, standard deviation.

Janumet® or dual therapy with sitagliptin plus metformin

No studies including Janumet® were found that met inclusion criteria. One randomized controlled trial including dual therapy with sitagliptin and metformin met inclusion criteria. This trial resulted in 3 publications; one reporting results after 24 weeks,[31] one reporting results after 54 weeks,[32] and the other after 104 weeks[33] No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Head-to-head trials

We found no head-to-head trials of Janumet® or dual therapy with sitagliptin plus metformin comparing them with other FDCPs that met inclusion criteria.

Trials comparing Janumet® or dual therapy with component monotherapy

One 24 week trial[31] with an optional additional 30 weeks[32] and further additional 50 weeks [33](Table 45) compared initial dual therapy of sitagliptin plus metformin to sitagliptin monotherapy and metformin monotherapy in subjects who were inadequately controlled only on diet and exercise. Patients in this study were taken off prior oral hypoglycemic agents and put through a diet and exercise run-in phase in addition to a 2-week single-blind placebo run-in period before enrollment. Approximately 50% of patients were taking oral hypoglycemic agents

at baseline, implying that the remainder were medication naive. Mean HbA1c was close to 9% and duration of diabetes was less than 5 years. In all treatment arms metformin was titrated to increase tolerability. Patients were followed initially for 24 weeks, and then had the option to continue for 30 additional weeks and then an additional 50 weeks. Patients originally randomized to placebo were automatically put in the metformin 1000 mg twice daily group for the additional 30 weeks. Since the study was designed to examine the potential benefit of a fixed-dose combination tablet of these 2 agents, sitagliptin was up titrated when metformin was up titrated as it would be with the use of a fixed-dose combination tablet (50 mg daily increased after 1 week to the stable study dose of 50 mg twice daily).

Table 45. Characteristics of metformin/sitagliptin dual therapy active-control trials in adults with type 2 diabetes

Author, year Country Quality	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Female[a] % White[a] % Hispanic[a] Other population characteristics	Intervention	Control(s)
Goldstein 2007[31] Multinational Fair	1,091 24	53.2-54.1 (9.6-10.2) 44.7-57.7 46.0-58.2 21.4-30.2	Dual therapy (sitagliptin + metformin): 100 mg/1,000 mg daily 100 mg/2,000 mg daily	Sitagliptin: 100 mg daily Metformin: 1,000 mg daily 2,000 mg daily
Williams-Herman 584[32] Multinational Fair	670 (748) 54	53.5-54.2 (9.1-10.0) 47-59 NR NR	Dual therapy (sitagliptin + metformin): 100 mg/1,000 mg daily 100 mg/2,000 mg daily	Sitagliptin: 100 mg daily Metformin: 1,000 mg daily 2,000 mg daily
Williams-Herman, 2010[33c] Multinational Fair	517 104	53.9-55.9(8.6-11.0) 42-63 NR NR	Dual therapy (sitagliptin + metformin): 100 mg/1,000 mg daily 100 mg/2,000 mg daily	Sitagliptin: 100 mg daily Metformin: 1,000 mg daily 2,000 mg daily
Range **2 Fair** **0 Good**	**670-1,091** **24-54**	**53.2-54.2 (9.1-10.2)** **44.7-59** **46.0-58.2** **21.4-30.2**	**Dual therapy: 100 mg/2,000 mg daily**	**Sitagliptin: 100 mg daily** **Metformin: 1,000 mg-3,000 mg daily**

Abbreviations: NR, not reported; SD, standard deviation.
[a] Unless otherwise noted, data presented are the range across treatment groups for mean and standard deviation.
[b] Williams-Herman et al, 2009 is a 30-week extension of Goldstein et al, 2007.
[c] Williams-Herman 2010 is an additional 50 week extension of Goldstein 2007 and Williams-Herman 2009.

The use of sitagliptin 100 mg/d plus metformin 2000 mg/d or sitagliptin 100 mg/d plus metformin 1000 mg/d significantly improved HbA1c compared with sitagliptin monotherapy or metformin monotherapy over 24 weeks (Table 46). For the subjects continuing for the additional

30 weeks, subjects on sitagliptin and metformin combination therapy maintained HbA1c levels without much change; those on metformin and sitagliptin monotherapy continued to have minimal HbA1c improvement (between group *P*=NR). Magnitude of benefit remained greater in the combination groups, but statistical significance was not reported. Similar results were seen in patients who continued for an additional 50 weeks (total of 104 week treatment).

Table 46. Change in HbA1c in metformin plus sitagliptin dual therapy trials in adults with type 2 diabetes

Author, year Country Quality	HbA1c (%) change from baseline (mean, 95% CI) for dual therapy	HbA1c (%) change from baseline (mean, 95% CI) for active control	*P* value of between-group difference
Goldstein 2007[31] Multinational Fair	Sitagliptin + Metformin: 100 mg/1000 mg daily −1.40 (−1.56 to −1.24) 100 mg/2000 mg daily −1.90 (−2.06 to −1.74)	Sitagliptin: 100 mg daily −0.66 (−0.83 to −0.50) Metformin: 1000 mg daily −0.82 (−0.98 to −0.66) 2000 mg daily −1.13 (−1.29 to −0.97)	<0.001 for either coadministration dose vs. either monotherapy
Williams-Herman, 2009[32a] Multinational Fair	Sitagliptin + Metformin: 100 mg/1000 mg daily −1.4 (−1.6 to −1.3) 100 mg/2000 mg daily −1.8 (−2.0 to −1.7)	Sitagliptin: 100 mg daily −0.8 (−1.0 to −0.6) Metformin: 1,000 mg daily −1.0 (−1.2 to −0.8) 2,000 mg daily −1.3 (−1.5 to −1.2)	NR
Williams-Herman, 2010[33b] Multinational Fair	Sitagliptin + Metformin: 100 mg/1000 mg daily −1.4 (−1.6 to −1.2) 100 mg/2000 mg daily −1.7 (−1.8 to −1.5)	Sitagliptin: 100 mg daily −1.2 (−1.4 to −0.9) Metformin: 1,000 mg daily −1.1 (−1.3 to −0.9) 2,000 mg daily −1.3 (−1.5 to −1.2)	NR
Range **2 Fair** **0 Good**	**Dual therapy:** **100 mg/1000 mg to 100 mg/2000 mg daily** **−1.9 to −1.4**	**Sitagliptin:** **100 mg daily** **−1.2 to −0.66** **Metformin:** **1000 mg to 2000 mg daily** **-1.3 to -0.82**	

Abbreviations: CI, confidence interval; NR, not reported.
[a] Williams-Herman et al, 2009 is a 30-week extension of Goldstein et al, 2007.
[b] Williams-Herman 2010 is an additional 50 week extension of Goldstein 2007 and Williams-Herman 2009.

Key Question 2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

I. Newer Drugs for the Treatment of Diabetes Mellitus: Amylin Agonists, DPP-4 Inhibitors, and GLP-1 Agonists

Summary of Findings for Amylin Agonists: Harms

Pramlintide for type 1 diabetes

Evidence in children

- No data on children were reported, although people as young as 16 years were eligible for study enrollment in 2 included trials.[19, 20]

Evidence in adults

- Greater withdrawals due to adverse effects for pramlintide-treated subjects than for insulin-treated subjects (ranges across trials were 5% to 20% compared with 2% to 8%, respectively, moderate strength of evidence).
- Gastrointestinal adverse events including nausea, vomiting, and anorexia were more commonly reported with the use of pramlintide plus insulin than with placebo plus insulin (moderate strength of evidence).
- Severe hypoglycemia occurred more frequently with pramlintide plus insulin during the first 4 weeks of treatment compared with placebo plus insulin (moderate strength of evidence). Rates of severe hypoglycemia declined once pramlintide doses stabilized but continued to remain slightly higher than with placebo plus insulin at up to 52 weeks of follow-up (moderate strength of evidence).
- Studies beyond 52 weeks are lacking.

Pramlintide for type 2 diabetes

Evidence in children

- Children and adolescents ≤ 18 years were not included in any of the published studies on efficacy or effectiveness.

Evidence in adults

- Both pramlintide- and placebo-treated subjects exhibited similar rates of withdrawal and withdrawal due to adverse events.
- The most commonly reported adverse event was nausea, which occurred more frequently with pramlintide plus insulin than with placebo plus insulin especially during the first 4 weeks of treatment, but declined thereafter (moderate strength of evidence).
- Severe hypoglycemia occurred more frequently with pramlintide compared with placebo (moderate strength of evidence).
- Hypoglycemia occurred less frequently in subjects taking pramlintide than those taking rapid acting insulin analogs (RAIA) in one 24 week study (low strength of evidence).

Detailed Assessment of Pramlintide in Type 1 Diabetes: Harms

We found no active-control trials. We found 3 placebo-controlled trials. [19-21] Details of these trials are presented in Table 5 in the corresponding section in Key Question 1.

Patients receiving pramlintide in addition to insulin had greater rates of withdrawal due to all causes and withdrawal due to adverse events than patients receiving placebo plus insulin. This was found with both fixed- and flexible-dose insulin (see Evidence Table 7). No included trial reported deaths or listed rare adverse events. There were no significant cardiac, hepatic, renal, or drug-related idiosyncratic adverse events observed in any treatment arm. Adverse events reported in the included studies are summarized in Table 47.

Hypoglycemia

During the first 4 weeks of treatment severe hypoglycemia occurred more frequently with pramlintide plus insulin than with insulin plus placebo, with both fixed and flexible insulin regimens. The rate of severe hypoglycemia declined once pramlintide doses were stabilized and not being titrated; however, at weeks 26-52[19, 21] and weeks 0-29[20] the rate of severe hypoglycemia associated with pramlintide was still slightly higher than placebo (event rates 0.42 to 1.10 compared with 0.30 to 0.52) (Table 47). Only 1 trial[20] reported that a 30% to 50% reduction in prandial insulin was allowed before the use of pramlintide. Even in this study, pramlintide-treated patients exhibited slightly higher rates of severe hypoglycemia compared with insulin plus placebo-treated patients (Table 47). No trials reported the overall incidence of mild to moderate hypoglycemic episodes. All 3 trials predefined the term "severe hypoglycemia" to mean: those requiring either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

Nausea and vomiting

A significant proportion of pramlintide-treated patients experienced nausea during the trials: Across trials overall rates of nausea for pramlintide groups ranged from 46% to 95%; for placebo groups, 12% to 36%. Specifically, patients who did not tolerate pramlintide 60 mcg also frequently experienced nausea with the 30 mcg dose, and the highest reported rates of nausea (95%) were in subjects who received 30 mcg 3 times a day.[20] Higher rates of nausea were reported with pramlintide 90 mcg 3 times a day[21] than with lower dosages in the same trial.

Severe nausea was much less common than nausea overall, ranging between 5.8% and 8.5% for pramlintide plus insulin and 0.7% to 1.7% for placebo plus insulin across studies.[19-21]

More than 10% of patients randomized to pramlintide plus insulin experienced vomiting, compared with rates of up to 8.0% with placebo plus insulin. Severe vomiting occurred in up to 2% of patients taking pramlintide compared with 0.4% to 0.7% taking placebo.[19-21]

Of note, 2 of 3 placebo-controlled trials[19, 21] reported that most cases of nausea and vomiting tended to occur within 2-4 weeks of treatment but no data were provided to verify these statements.

Anorexia or reduced appetite

Rate of anorexia was significantly more frequent with pramlintide plus insulin (11% to 18% across trials) than with placebo plus insulin (approximately 2%). Severe anorexia occurred in <2% of pramlintide patients and no placebo patients.[19, 21]

Other adverse events

One trial reported sinusitis at a rate of 14.0% with pramlintide and 8.8% with placebo (P>0.05).[20] Two non-comparative observational studies[195, 196] were also evaluated for rare adverse events and neither reported any additional information.

Table 47. Adverse events from placebo-controlled trials of pramlintide in type 1 diabetes

	Whitehouse 2002[19]		Ratner 2004[21]				Edelman 2006[20]		
	30/60[a] QID	Placebo	60 TID	60 QID	90 TID	Placebo	30 TID-QID	60 TID-QID	Placebo
Mean number of severe hypoglycemia events per patient-year (SE)[b]									
Weeks 0-4	2.12 (0.35)	1.04 (0.24)	3.78 (0.57)	3.41 (0.55)	3.91 (0.58)	0.87 (0.27)	0.79 (0.46)	0.46 (0.46)	0.42 (0.19)
Weeks 26-52	0.43 (0.07)	0.52 (0.08)	0.74 (0.12)	0.79 (0.12)	0.64 (0.12)	0.45 (0.09)	---	---	---
Weeks 0-29	---	---	---	---	---	---	1.10 (0.25)	0.42 (0.09)	0.30 (0.06)
Treatment-emergent adverse events (%)[c]									
Total nausea	46.5	21.9	47.0	47.0	59.0	12.0	95.1	48.5	36.1
Severe nausea	6.2	1.7	8.5	6.8	5.8	1.3	7.3	4.0	0.7
Total vomiting	11.5	8.0	9.8	11.0	12.0	6.5	17.1	11.9	6.1
Severe vomiting	2.1	0.4	1.8	0.6	1.2	0.6	2.4	5.9	0.7
Total anorexia[d]	17.7	2.1	18.0	11.0	16.0	2.6	14.6	6.9	2.0
Severe anorexia	2.5	0.0	1.2	1.9	0.6	0.0	---	---	---
Total sinusitis	---	---	---	---	---	---	22.0	12.9	8.8

Abbreviations: TID, 3 times daily; QID, 4 times daily.
[a] All doses are reported as mcg/meal. 30/60, 30 or 60-mcg arms.
[b] Severe hypoglycemia event rates are calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation.
[c] Treatment-emergent adverse events with occurrences ≥10% for totals and the incidence in the pramlintide arm is at least twice that of placebo arm.
[d] The Edelman, 2006 study reported "total reduced appetite" instead of "total anorexia."

Detailed Assessment of Pramlintide in Type 2 Diabetes: Harms

Pramlintide-plus-insulin and placebo-plus-insulin groups had similar rates of withdrawal due to all causes and withdrawal due to adverse events (see Evidence Table 7). There was no evidence of cardiac, hepatic, renal, or drug-related idiosyncratic adverse events in patients in any treatment arm of the 4 randomized controlled trials identified for this review and no deaths were reported. Adverse effects are summarized in Table 48.

Hypoglycemia

Pramlintide-plus-insulin and placebo-plus-insulin groups experienced similar rates of mild-to-moderate hypoglycemia,[24, 26] but pramlintide-treated patients experienced more episodes of severe hypoglycemia. Severe hypoglycemia occurred most with pramlintide 120 mcg during the

first 4 weeks of therapy (0.9 events/patient-year compared with 0.3 events/patient-year with placebo).[25] The incidence of severe symptoms declined with continued use of pramlintide, and rates were similar to placebo for weeks 4-26 and 26-52.[25] Compared with RAIA, pramlintide had a lower incidence of hypoglycemia.[22] All trials predefined the term "severe hypoglycemia" to mean: those requiring either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

Nausea

The incidence of mild-to-moderate and severe nausea was significantly higher with pramlintide 75, 90, 120, and 150 mcg than with placebo plus insulin. Two trials reported data showing that most events occurred within the first 4 weeks of treatment.[22, 25] When metformin use was stratified in 1 trial, its addition to pramlintide plus insulin appeared to have no significant effect on nausea compared with the larger study population.[25] These trials did not report vomiting or anorexia.

Headache

In one trial, higher rates of headache were reported with pramlintide (15% and 17%) than with placebo (8%).[25] In another trial[26] rate of headache was similar among treatment groups, ranging from 13.2% in the placebo-plus-insulin group to 19.1% with pramlintide 75 mcg 3 times a day plus insulin. None of the studies provided enough information to determine whether there were any correlations between the incidence of headaches and hypoglycemic events.

Other adverse events

No trials reported any treatment-emergent adverse events occurring with a frequency of more than 2% to 5%. Overall adverse events occurring with a frequency of ≥10% with a minimum 5 percentage point difference between pramlintide- and placebo-treated patients comprised sinusitis, retinal disorder, inflicted injury, and injection site reactions (Table 48).[25, 26] Higher incidence of retinal disorder was reported with pramlintide 150 mcg than with lower pramlintide doses and placebo.[26] The authors performed detailed medical reviews of these patients with reported retinal disorder and concluded that the increased incidence was likely attributable to preexisting conditions that were not documented at the time of screening.

One post-hock analysis specifically looked at markers of cardiovascular risks.[23]. After 16 weeks, it was found that pramlintide treated patients had favorable decreases in triglycerides when compared to placebo treated patients (Table 48). No significant changes from baseline in LDL, HDL, or total cholesterol were seen.

Table 48. Adverse effects reported in placebo and active-control trials of pramlintide in type 2 diabetes

	Ratner 2002[26]			Hollander 2003[25]			Riddle 2007[24], Wysham 2008[23]		Riddle 2009[22]	
	75 TID[a]	150 TID	Placebo	90 BID	120 BID	Placebo	60/120 BID-TID	Placebo	120 TID	RAIA
Mean number of severe hypoglycemia events per patient-year (SD)b										
Weeks 0-4	---	---	---	0.1 (0.08)	0.9 (0.3)	0.3 (0.20)	---	---	--	--
Weeks 26-52	---	---	---	0.0 (0.02)	0.1 (0.05)	0.2 (0.06)	---	---	--	--
Weeks 0-52	---	---	---	0.1 (0.03)	0.3 (0.05)	0.3 (0.05)	---	---	--	--
Treatment-emergent adverse effects[c] (%)										
Total hypoglycemia	67.6	64.6	70.6	---	---	---	43.8	47.2	55	82
Severe hypoglycemia	2.2	2.8	1.5	---	---	---	0.95	0.0	0	0
Total nausea	26.5	22.9	16.9	18	16	3	31.4	10.4	21	0
Severe nausea	0.7	2.8	1.5				---	---	--	--
Nausea during weeks 0-4				31	30	14	---	---	--	--
Total headaches	19.1	16.0	13.2	15	17	8	---	---	--	--
Total sinusitis	18.4	9.7	8.1	---	---	---	---	---	--	--
Total retinal disorder	5.9	10.4	5.1	---	---	---	---	---	--	--
Mean change in lipid concentrations (mg/dL)										
Total cholesterol	--	--	--	--	--	--	--	--	--	--
LDL	--	--	--	--	--	--	−2.3	−3.0	--	--
HDL	--	--	--	--	--	--	−0.4	−0.9	--	--
Triglycerides	--	--	--	--	--	--	+10	−19	--	--

Abbreviations: BID, twice daily; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TID, 3 times daily.

[a] Doses are expressed in mcg.

[b] Severe hypoglycemia event rates are calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation.

[c] Treatment-emergent adverse events with occurrences ≥10% for totals and a 5% higher incidence in the pramlintide arm than placebo arm.

Summary of Findings for DPP-IV Inhibitors: Harms

Sitagliptin compared with saxagliptin

- We found no head-to-head evidence.

Summary of Findings for Sitagliptin: Harms

- The most commonly reported adverse events across treatment groups were hypoglycemia, nausea, vomiting, diarrhea, and abdominal pain.
- The rates for total withdrawal were slightly lower with sitagliptin than with placebo (pooled relative risk 0.63 95% CI 0.52 to 0.76) and rates of withdrawal due to adverse events were not significantly different between sitagliptin and placebo (pooled relative risk 0.88, 95% CI 0.54 to 1.43, moderate strength of evidence).
- Hypoglycemia was generally more frequent with glipizide than with sitagliptin (17.1-34.1% compared with 1.6-5.3%) and was more common when sitagliptin was used in combination with other hypoglycemic agents than when used as monotherapy (moderate strength of evidence).
- Hypoglycemia was not significantly different in subjects taking sitagliptin 100 mg and those taking placebo (pooled relative risk 1.26, 95% CI 0.49 to 3.25, low strength of evidence).
- Rates of gastrointestinal side effects were higher with metformin than with sitagliptin (moderate strength of evidence).
- Gastrointestinal side effects were not significantly different between sitagliptin and placebo treated subjects (nausea pooled relative risk 1.4, 95% CI 0.5 to 3.96; vomiting pooled relative risk 0.77, 95% CI 0.20 to 2.88, low strength of evidence).
- Upper respiratory infections and urinary tract infections were not significantly different between patients taking placebo and those taking sitagliptin (pooled relative risk 1.06, 95% CI 0.66, 1.7, low strength of evidence)
- Subjects treated with sitagliptin had similar changes or greater improvements in triglycerides than subjects treated with placebo (low strength of evidence); changes in other lipid parameters were not significantly different between sitagliptin and placebo (moderate strength of evidence).

Detailed Assessment of Sitagliptin: Harms

In 7 trials with data suitable for meta-analysis, total withdrawals were slightly lower among patients randomized to sitagliptin monotherapy than patients receiving only placebo (relative risk for total withdrawals 0.63, 95% CI 0.52 to 0.76); there was no significant difference for withdrawals due to adverse events (relative risk for withdrawal due to adverse events 0.88, 95% CI 0.54 to 1.43). Patients on sitagliptin monotherapy had lower rates of total withdrawal relative to patients on glipizide, who experienced more hypoglycemic events and higher rates of total withdrawal relative to patients on metformin. The rate of total withdrawals was also higher in patients whose add-on therapy was sitagliptin than in patients using monotherapy with metformin, pioglitazone, or glimepiride.

The most commonly reported adverse events were hypoglycemia, abdominal pain, nausea, vomiting, and diarrhea.

A total of 20 deaths were reported in 4 trials over 24-104 weeks. None was considered to be related to any study intervention; 8 were sudden cardiac deaths or myocardial infarctions, 2 were secondary to trauma, 1 was related to sepsis, 6 were due to cancer, 1 suicide, 1 was related to chronic obstructive pulmonary disease and interstitial lung disease, and 1 cause of death was unknown.

Rare adverse events

Sixteen randomized controlled trials reported adverse events. In those trials adverse events occurring in at least 4% of study subjects included: upper respiratory tract infections, headache, influenza, nasopharyngitis, and urinary tract infection. Incidence of adverse effects between sitagliptin and active comparator agents is summarized in Tables 49-50, and incidence of adverse effects between sitagliptin and placebo is summarized in Tables 52-53. Pooled relative risk for upper respiratory and urinary tract infections showed no significant difference between sitagliptin and placebo (relative risk 1.06, 95% CI 0.66 to 1.69) (Table 51).[42, 43, 45] Four studies[34, 42, 47, 49] reported small increases (≤10% from baseline) in mean white blood cell count, mainly an increase in absolute neutrophil count, in regimens with sitagliptin compared to regimens without. These increases appeared early and remained stable throughout the duration of the studies. No other trials provided data on changes in white blood cell count with sitagliptin. Edema was only reported for 1 study and the incidence was 5% in the rosiglitazone group and 1% in both placebo and sitagliptin groups.[36]

Hypoglycemia

In general, hypoglycemia was more common in patients treated with comparator agents as opposed to sitagliptin. Pioglitazone was the only comparator that had lower incidence of hypoglycemia. Patients taking sitagliptin in addition to glimepiride experienced more hypoglycemia than those taking glimepiride alone. Similarly, patients taking sitagliptin in addition to insulin and metformin experienced more hypoglycemia than those taking insulin and metformin alone.

There was no statistically significant difference in the overall risk of mild to moderate hypoglycemia between sitagliptin and placebo (pooled relative risk 1.26, 95% CI 0.48 to 3.25) (Table 51).[30, 31, 42-46] The rate of mild-to-moderate hypoglycemia increased slightly when sitagliptin was added to glimepiride (7.6% compared with 2.8%) or pioglitazone (1.1% compared with 0%).

Abdominal pain, nausea, vomiting, and diarrhea

Compared with metformin monotherapy, sitagliptin was associated with lower incidence of abdominal pain, nausea, vomiting, and diarrhea (Tables 49-50). Combination therapy of sitagliptin plus glimepiride, metformin, or pioglitazone had <6% incidence of abdominal pain, nausea, vomiting, and diarrhea; these results were not significantly different from their comparisons (Tables 49-50).

There were no statistically significant differences between sitagliptin monotherapy and placebo in the risk of nausea (pooled relative risk 1.4, 95% CI 0.49 to 3.96) (Table 51). [31, 42, 43, 45] and vomiting (pooled relative risk 0.76, 95% CI 0.20 to 2.87) (Table 51).[31, 42, 43] However, based on the elevated relative risks, there appears to be a trend for greater risk of experiencing abdominal pain, and nausea with sitagliptin monotherapy compared with placebo.

Lipids

Six publications reported changes in lipid parameters in patients taking sitagliptin compared to placebo, rosiglitazone, pioglitazone, glipizide, and metformin (Tables 54-56).[30, 32, 36, 46-48] The data for the remaining 9 publications was received from the manufacturer. In 12 trials, patients taking sitagliptin had either less elevation or greater reduction in triglycerides than those in the comparator groups. Changes in all other lipid parameters were less significant and more variable across studies. The results of our meta-analyses comparing sitagliptin with placebo for lipid parameters are summarized in Table 51. For these analyses, we assumed a pre-post correlation of 0.5 and conducted sensitivity analyses using correlations of 0.3 and 0.7. There was no statistically significant difference for total cholesterol, HDL, or LDL in our main analyses or any of the related sensitivity analyses (Appendix E). For triglycerides, the main analysis favored sitagliptin (WMD -9.97, 95% CI -19.4 to -0.49), but sensitivity analyses found no statistically significant difference between sitagliptin and placebo.

Table 49. Adverse events of sitagliptin compared with oral hypoglycemic agents

	Scott, 2007[30]		Goldstein, 2006[31]			Williams-Herman, 2009[32]			Williams-Herman, 2010[33]			Scott, 2008[36]		Chan, 2008[37]		Nauck, 2007[34]	
Adverse event	**S100**	**Glip**	**S100**	**M1**	**M2**	**S100**	**M1**	**M2**	**S100**	**M1**	**M2**	**S100**	**Rosi**	**S25/50**	**Glip**	**S/ MET**	**Glip/ MET**
	Treatment- emergent adverse events (%)																
Hypoglycemia	1.64[a]	17.1	0.6	0.6	1.1	1	1	1	1.1	1.6	2,2	1	1	4.6	23.1	4.9	32.0
Nausea	NR	NR	1.1	2.8	8.2	1	3	10	1.1	3.3	10.4	1	1	--	--	2.6	2.7
Vomiting	NR	NR	0.0	0.0	1.1	1	0	3	0.6	0	4.4	1	1	--	--	0.9	1.5
Diarrhea	NR	NR	2.8	5.0	10.4	4	7	12	4.5	7.7	12.6	3	3	10.8	15.4	5.8	5.5
Abdominal pain	NR	NR	3.4	2.8	5.0	5	4	6	5	3.8	6.6	0	1			2.7	2.1
	Rarer adverse events occurring with ≥4% incidence																
Nasopharyngitis	---	---				---	---	---	--	--	--	4.3	3.4	9.2	3.8	10.5	7.5
Upper respiratory tract infection	---	---				---	---	---	--	--	--	4.3	4.6	7.7	19.2	---	---
Influenza	---	---				---	---	---	--	--	--	--	--	--	--	---	---
Headaches	---	---				---	---	---	--	--	--	--	--	--	--	---	---
Urinary tract infections	---	---				---	---	---	--	--	--	--	--	10.8	11.5	5.4	2.7

Abbreviations: glim, glimepiride; glip, glipizide 5-20 mg/d; Glip/MET, glipizide added to metformin; M1, metformin 1000 mg/d; M2, metformin 2000 mg/d; MET, metformin; NR, not reported; pio, pioglitazone; S100, sitagliptin 100 mg daily; S/Glim, sitagliptin added to glimepiride; S/MET, sitagliptin added to metformin.

[a] Note: this trial also included treatment arms: glimepiride plus metformin, glimepiride plus metformin plus sitagliptin.

Table 50. Adverse events of sitagliptin compared with oral hypoglycemic agents (continued)

	Seck, 2010[35a]		Vilsboll, 2010[51]		Aschner, 2010[38]	
Adverse event	**S/ MET**	**Glip/ MET**	**S/insulin+ MET**	**P/insulin +MET**	**S100**	**M2**
Treatment- emergent adverse events (%)						
Hypoglycemia	5.3	34.1	16	8	1.7	3.3
Nausea	--	--	--	--	1.1	3.1
Vomiting	--	--	--	--	0.4	1.3
Diarrhea	--	--	--	--	3.6	10.9
Abdominal pain	--	--	--	--	2.1	3.8
Rarer adverse events occurring with ≥4% incidence						
Nasopharyngitis	12.1	10.4	3.1	2.5	1.9	3.3
Upper respiratory tract infection	12.4	13.5	3.1	3.4	0.9	2.1
Influenza	---	---	4	3.8	2.3	2.1
Headaches	---	---	--	--	3.2	3.3
Urinary tract infections	7.5	4.3	2.8	1.9	0.6	2.5

[a] Seck, 2010 is an extension of Nauck, 2007

Table 51. Meta-analysis comparing adverse events of sitagliptin 100 mg to placebo

						Heterogeneity
Outcome	**N**	**Measure**	**Estimate**	**95% CI**	***P* value**	**I^2**
Total	7[a]	RR	0.632	0.523, 0.763	<0.001	0%
Due to adverse event	7[a]	RR	0.88	0.544, 1.432	0.614	0%
Hypoglycemia	7[a]	RR	1.26	0.488, 3.25	0.63	0%
Infections	3[b]	RR	1.06	0.663, 1.694	0.808	0%
Nausea	4[c]	RR	1.40	0.497, 3.962	0.52	0%
Vomiting	3[d]	RR	0.765	0.203, 2.879	0.692	0%
Total cholesterol	3[e]	WMD	2.03	-5.6, 9.6	0.601	54.9%
HDL	7[f]	WMD	0.003	-1.38, 1.38	0.997	57.8%
LDL	7[f]	WMD	0.13	-2.62, 2.88	0.927	1.4%
Triglycerides	7[f]	WMD	-9.97	-19.4, -0.49	0.039	5.7%

[a] Studies included in analysis: Aschner (2006), Nonaka (2007), Raz(2006), Mohan (2009), Hanefeld(2007), Scott(2007), Goldstein(2007).
[b] Studies included in analysis: Aschner (2006), Raz (2006), Mohan (2009).
[c] Studies included in analysis: Aschner (2006), Raz (2006), Mohan (2009), Goldstein (2007).
[d] Studies included in analysis: Aschner (2006), Raz (2006), Goldstein (2007).
[e] Studies included in analysis: Charbonnel (2006), Hanefeld (2007), Scott (2007)
[f] Studies included in analysis: Charbonnel (2006), Hanefeld (2007), Scott (2007), Aschner (2006), Raz (2006), Goldstein (2007), Mohan (2009)

Table 52. Adverse events of sitagliptin compared with placebo[a]

	Aschner, 2006[42]		Raz, 2006[43]		Nonaka, 2008[44]		Raz, 2008[50]		Rosenstock, 2006[48]		Charbonnel, 2006[47]		Hermansen, 2007[49]	
Adverse event	**S100**	**PBO**	**S100**	**PBO**	**P/Pio**	**S/MET**	**P/MET**	**S/Glim**	**S/ Pio**	**P/Pio**	**S/ MET**	**P/MET**	**S/Glim**	**P/Glim**
Hypoglycemia	1.3	0.8	1.5	0	0	0	0	1.0	1.1	0.0	1.3	2.1	7.6	2.8
Nausea	2.1	1.2	1	0	--	--	2.1	2.1	1.1	0.0	1.3	0.8	0.0	0.0
Vomiting	1.3	1.2	0	0.9	--	--	0	1.1	0.6	0.6	1.1	0.8	0.9	0.0
Diarrhea	4.6	2.4	3.9	3.6	--	--	6.3	5.3	1.7	1.1	2.6	2.5	1.9	1.9
Gastritis	--	--	--	--	--	--	2.1	3.2	--	--	--	--	--	--
Abdominal pain	2.1	1.6	2.0	2.7	--	--	2.1	0	3.4	0.0	2.2	3.8	2.8	0.0
Gastrointestinal (overall)	16.4	11.5	--	--	21.3	17.1	10.4	7.4	--	--	--	--	--	--
Nasopharyngitis	--	--	--	--	--	--	7.3	7.4	4.0	3.9	4.1	3.4	---	---
Upper respiratory tract infection	--	--	--	--	--	--	0	3.2	6.3	3.4	7.3	9.3	---	---
Influenza	--	--	--	--	--	--	1.0	3.2	4.0	2.8	4.3	5.5	---	---
Headaches	--	--	--	--	--	--	4.2	4.3	5.7	3.9	---	---	---	---
Urinary tract infections	--	--	--	--	--	--	4.2	3.2	---	---	---	---	---	---

Abbreviations: Glim, glimepiride; Glip, glipizide 5-20 mg/d; Glip/MET, glipizide added to metformin; M1, metformin 1000 mg/d; M2, metformin 2000 mg/d; MET, metformin; NR, not reported; Pio, pioglitazone; S100, sitagliptin 100 mg daily; S/Glim, sitagliptin added to glimepiride; S/MET, sitagliptin added to metformin; S/Pio, sitagliptin added to pioglitazone.

[a] Data are presented as percentages.

Table 53. Adverse events of sitagliptin compared with placebo (continued)[a]

	Mohan, 2009[45]		Hanefeld, 2007[46]				
Adverse event	**S100**	**PBO**	**S25**	**S50**	**S100**	**S50BID**	**PBO**
Hypoglycemia	0	0	0.9	0.9	1.8	0.9	0
Nausea	--	--	--	--	--	--	--
Vomiting	--	--	--	--	--	--	--
Diarrhea	--	--	--	--	--	--	--
Gastritis	--	--	--	--	--	--	--
Abdominal pain	--	--	--	--	--	--	--
Gastrointestinal (overall)	5.1	0.6	11.8	9.1	9.1	8.1	13.5
Nasopharyngitis	--	--	6.3-9.1	1.8	--	--	--
Upper respiratory tract infection	2.8	2.8		--	--	--	--
Influenza	--	--	--	--	--	--	--
Headaches	--	--	--	--	--	--	--
Urinary tract infections	--	--	--	--	--	--	--

Abbreviations: BID, twice daily; PBO, placebo; S100, sitagliptin 100 mg daily.
[a] Data are presented as percentages.

Table 54. Changes in lipid parameters (mean change from baseline, mg/dL)

	Hanefeld, 2007[46]		Scott, 2008[36]			Charbonnel, 2006[47]		Mohan, 2009[45a]	
	S100	PBO	S100/MET	Rosi/MET	PBO	S100	PBO	S100	PBO
Total cholesterol	+6.1	-3.0	+8.1	+26.2	+17.4	+1.93	+5.4	NR	NR
HDL	+2.4	+0.2	+0.6	+3.5	+1.8	+1.16	+0.77	+0.3	+0.1
LDL	+4.9	-3.7	+9.8	+20.4	+12.8	+1.93	+1.93	+5.3	+4.3
TG	-5.6	+1.7	-14.5	-1.8	+20.1	-7.08	+19.46	-10	+10.6

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PBO, placebo; pio, pioglitazone; Rosi/MET, rosiglitazone added to metformin; S100/MET, sitagliptin added to metformin; S/Pio, sitagliptin added to pioglitazone; TG, triglyceride.
[a] Data received from manufacturer

Table 55. Changes in lipid parameters (mean change from baseline, mg/dL) (continued)

	Scott, 2007[30]			Goldstein, 2007[31a]					Williams-Herman, 2009[32]					Williams-Herman, 2010 [33b]				
	S100	PBO	Glip	S100	M1	M2	S/M1	S/M2	PBO	S100	M1	M2	S/M1	S/M2	S100	M1	M2	S/M1	S/M2
Total cholesterol	4.3	1.5	0.77	NR	NR	NR	NR	NR	NR	+0.5	0	-0.2	-6.6	-8.8	+1.4	-6.1	-0.6	-6.8	-4.7
HDL	1.5	0	0.79	+0.5	+1.4	+2.3	+1.2	+1.8	+1.3	+0.1	+2.4	+3.1	+1.7	+2.7	+2.8	+3.4	+3.5	+1.8	+3.1
LDL	2.7	-1.15	-0.77	+1.6	-3.2	-3.6	-3.7	-5.4	+4.8	-1.6	-3.0	-4.8	-5.0	-8.5	+5.6	-5.9	-3.8	-8.4	-7.1
TG	0	15.9	2.65	+7	-0.2	+9.2	-13.4	-20.5	+0.3	+15[a]	+6.0[a]	+24.0[a]	-8.0[a]	-15[a]	+3.0	-11.0	+18	+5.5	+1.5

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; M1, metformin 1000 mg/d; M2, metformin 2000 mg/d; TG, triglycerides.
[a] Reported as median change from baseline.
[b] Data received from manufacturer.

Table 56. Changes in lipid parameters (mean change from baseline, mg/dL) (continued)

Study	Aschner, 2006[42a]		Raz, 2006[43a]		Nauck, 2007[34a]		Chan, 2008[37a]		Hermansen, 2007[49a]	
Intervention	**S100**	**PBO**	**S100**	**PBO**	**S100**	**Glip**	**S25/50**	**PBO/Glip**	**S100**	**PBO/Pio**
Total cholesterol	NR	NR	NR	NR	NR	NR	-4.2	-7.2	NR	NR
HDL	+1.4	+0.6	0	+5.2	+1.1	0	0	+1.3	-1	-0.9
LDL	+3.1	0	+1.7	+4.8	+5.8	+3.1	-3.8	+6.8	+4.8	-3.1
TG	-6.5	-2.7	-0.3	-5.8	-3.9	-4.9	-14.7	+9.1	+3.7	+9.2

Study	Rosenstock, 2006[48]		Raz, 2008[50a]		Aschner, 2010[38b]		Vilsboll, 2010[51a]	
Intervention	**S/Pio**	**PBO/Pio**	**S100/Met**	**PBO/Met**	**S100**	**M2**	**S100+ insulin/Met**	**PBO+insulin/Met**
Total Cholesterol	+1.7	+2.7	NR	NR	+7.3	+0.9	NR	NR
HDL	+0.1	-0.6	-0.4	+0.9	+2.4	+2.8	+0.5	+0.4
LDL	+1.2	+1.6	+2.7	+7.4	+6.4	-2.4	+0.1	+1.1
TG	+-1.1	+12.1	-5.1	+13	-2.0	0	-8.0	-1.0

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; M2, metformin 2000mg/day; PBO, placebo; PBO/pio, placebo added to pioglitazone; PBO/Met, placebo added to metformin; S100, sitagliptin 100mg; S100/MET, sitagliptin added to metformin; S/Pio, sitagliptin added to pioglitazone; S100 + insulin/Met, sitagliptin 100mg added to insulin and metformin; PBO + insulin/Met, placebo added to insulin and metformin; TG, triglyceride.
[a] Data received from manufacturer

Summary of Findings for Saxagliptin: Harms

- The most commonly reported adverse effects were nasopharyngitis, upper respiratory infections, headache, and urinary tract infections.
- Rates for total withdrawal were lower with saxagliptin 2.5 and 5 mg compared with placebo used as monotherapy or as add-on therapy (2.5 mg relative risk 0.66, 95% CI 0.57 to 0.79; 5 mg relative risk 0.79, 95% CI 0.66 to 0.95, moderate strength of evidence).
- Rates of withdrawal due to adverse events were not significantly different with saxagliptin 2.5 mg used as monotherapy or as add-on therapy compared with placebo (pooled relative risk 0.85, 95% CI 0.29 to 2.53), however rates were higher in patients taking saxagliptin 5 mg than for those taking placebo (pooled relative risk 2.09, 95% CI 1.07 to 4.10, moderate strength of evidence).
- The incidence of hypoglycemia was not significantly different with saxagliptin 2.5 mg or 5 mg used as monotherapy or as add-on therapy compared with placebo (2.5 mg: pooled relative risk 2.01, 95% CI 0.63 to 6.39; 5 mg: pooled relative risk 1.04, 95% CI 0.28 to 3.81, low strength of evidence).
- There were no significant differences in infections between saxagliptin and placebo (low strength of evidence).

Detailed Assessment for Saxagliptin: Harms

In the 5 identified placebo-controlled trials (see Key Question 1 saxagliptin section for study characteristics), total withdrawals were higher in the placebo groups compared to either the saxagliptin 2.5 mg or 5 mg/day groups. Withdrawals due to adverse effects were similar between placebo and saxagliptin 2.5 mg/day, however higher in saxagliptin 5 mg/day. Similar rates of withdrawal due to adverse effects were seen regardless of saxagliptin being used as add-on therapy or monotherapy. Results of our meta-analyses are summarized in Table 57 and results from individual saxagliptin trials for adverse events are summarized in Table 58 and in Evidence Table 8.

The most common adverse effects seen were headache, upper respiratory infections, nasopharyngitis, and urinary tract infections. Gastrointestinal adverse effects were rarely reported and were most commonly seen when saxagliptin was used in combination with metformin.

Hypoglycemia

Hypoglycemia was reported in all 5 trials. The incidence of confirmed hypoglycemia (≤50 mg/dL) was low ranging from 0 to 2.4% in saxagliptin treated patients, with 2 trials reporting zero incidence in both saxagliptin and placebo treated patients.[53, 54] The trials that reported any confirmed hypoglycemia were those using saxagliptin in combination with either glyburide, metformin, or a TZD.[55-57] Overall, there was no difference in the incidence of confirmed hypoglycemia in saxagliptin 2.5 mg/day (pooled relative risk 2.01, 95% CI 0.63 to 6.39) or saxagliptin 5 mg/day (pooled relative risk 1.04, 95% CI 0.28 to 3.81) compared to placebo.

Infections

Infection related adverse events were reported in all 5 trials. Pooled relative risk showed no significant difference between saxagliptin 2.5 mg daily and placebo in incidence of upper respiratory tract infections (relative risk 0.95, 95% CI 0.65 to 1.37), nasopharyngitis (relative risk 0.86, 95% CI 0.58 to 1.27), or urinary tract infections (relative risk 1.16, 95% CI 0.81 to 1.68). Similarly, no difference was seen between saxagliptin 5 mg daily and placebo in incidence of upper respiratory tract infections (relative risk 0.99, 95% CI 0.69 to 1.42), nasopharyngitis (relative risk 0.84, 95% CI 0.57 to 1.24), or urinary tract infections (relative risk 1.2, 95% 0.84 to 1.73). Three of the 5 studies reported small numerical decreases in absolute lymphocyte counts in higher dose of saxagliptin (≥10 mg daily), however minimal to no decrease in either saxagliptin 2.5 mg or 5 mg daily.[53-55]

Lipids

Changes in lipid parameters were only reported in 1 trial.[56] When compared to placebo in addition to a TZD, there was a numerically greater increase in LDL cholesterol in subjects treated with saxagliptin in addition to a TZD (compared with a small decrease in LDL cholesterol with placebo), however there were no statistical comparisons reported. In addition, placebo-treated subjects total cholesterol decreased more than saxagliptin 2.5-treated subjects (−4.3 compared with −3.1, respectively); subjects treated with saxagliptin 5 demonstrated a small increase (+0.8). There was a greater numerical reduction seen in triglycerides in patients receiving saxagliptin as add-on therapy compared to placebo (*P*=NR) (Table 59).

Table 57. Meta-Analysis results comparing saxagliptin to placebo as both monotherapy and add-on therapy

							Heterogeneity
Dose	**Outcome**	**N**[a]	**Measure**	**Estimate**	**95% CI**	***P* value**	**I^2**
2.5 mg daily	Total	5	RR	0.666	0.565, 0.785	<0.001	0%
	Due to AE	5	RR	0.849	0.285, 2.529	0.769	22.6
5 mg daily	Total	5	RR	0.788	0.657, 0.945	0.01	22.3
	Due to AE	5	RR	2.091	1.067, 4.098	0.032	0%
2.5 mg daily	Hypoglycemia	5	RR	2.006	0.629, 6.393	0.239	0%
	Upper respiratory Infection	5	RR	0.945	0.651, 1.371	0.764	0%
	Nasopharyngitis	5	RR	0.857	0.577, 1.271	0.442	0%
	Urinary tract infection	5	RR	1.163	0.805, 1.679	0.421	0%
5 mg daily	Hypoglycemia	5	RR	1.036	0.282, 3.811	0.957	0%
	Upper respiratory Infection	5	RR	0.986	0.686, 1.418	0.94	0%

							Heterogeneity
Dose	**Outcome**	**N**[a]	**Measure**	**Estimate**	**95% CI**	***P* value**	**I^2**
	Nasopharyngitis	5	RR	0.843	0.574, 1.238	0.384	0%
	Urinary tract infection	5	RR	1.203	0.835, 1.732	0.321	0%

Abbreviations: AE, adverse event.
[a] Studies included in analysis: Rosenstock(2008), Rosenstock(2009), DeFronzo(2009), Hollander(2009), Chacra(2009).

Table 58. Adverse events in trials of saxagliptin

	Chacra, 2009			Rosenstock, 2008			DeFronzo, 2009			Rosenstock, 2009			Hollander, 2009		
Adverse event	**S2.5/Gly**	**S5/Gly**	**PBO/Gly**	**S2.5**	**S5**	**PBO**	**S2.5/Met**	**S5/Met**	**PBO/Met**	**S2.5**	**S5**	**PBO**	**S2.5/TZD**	**S5/TZD**	**PBO/TZD**
Treatment- emergent adverse events (%)															
Hypoglycemia (confirmed)	2.4	0.8	0.7	0	0	0	0.5	0.5	0.6	0	0	0	0.5	0	0
Nausea	--	--	--	1.8	4.3	7.5	--	--	--	--	--	--	--	--	--
Diarrhea	5.6	4.0	5.2	--	--	--	9.9	5.8	11.2	6.9	0.9	3.2	--	--	--
Rarer adverse events occurring with ≥4% incidence															
Nasopharyngitis	5.6	5.9	6.7	0	4.3	7.5	9.4	6.8	7.8	5.9	5.7	3.2	3.1	4.8	6.0
Upper respiratory tract infection	4.4	6.3	6.7	10.9	6.4	6.0	6.8	4.7	5.0	6.9	8.5	11.6	7.7	9.1	7.1
Influenza	5.2	4.0	6.0	--	--	--	6.3	6.3	7.3	3.9	3.8	1.1	--	--	--
Headaches	7.7	7.5	5.6	--	--	--	9.4	5.8	7.3	3.9	9.4	7.4	4.6	5.4	3.8
Urinary tract infections	5.7	10.7	8.2	10.9	4.3	7.5	5.2	5.2	4.5	7.8	8.5	4.2	3.6	6.5	6.5

Abbreviations: S2.5/5, sitagliptin 2.5/5 mg; Gly, glyburide; PBO, placebo; Met, metformin; TZD, thiazolidinedione.

Table 59. Changes in lipid parameters (mean change from baseline, mg/dL)

	Hollander, 2009		
	S2.5/TZD	**S5/TZD**	**PBO/TZD**
Total cholesterol	−3.1	+0.8	−4.3
HDL	−1.2	0	−0.4
LDL	+1.2	+4.3	−1.2
TG	−13.3	−27.4	−12.4

Abbreviations: S2.5/5, sitagliptin 2.5/5 mg; PBO, placebo; TZD, thiazolidinedione; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

Summary of Findings for GLP-1 Agonists: Harms

Exenatide compared with liraglutide

- In the 1 head-to-head randomized-control trial, withdrawal rates were similar between groups. The incidence of nausea was similar between the groups initially, but was more persistent over time in the exenatide group. The proportion of patients who reported minor hypoglycemia was less in the liraglutide group than the exenatide group (26% compared with 34%, 1.93 compared with 2.60 events per patient per year, rate ratio 0.55, CI 0.34 to 0.88; *P*=0.0131). There was no significant difference in change in total cholesterol, LDL cholesterol, or HDL cholesterol between the exenatide and the liraglutide treatment arms. Reduction in triglycerides was significantly greater in the liraglutide group than the exenatide group (−15.8 mg/dL (3.9) compared with −8.9 mg/dL (3.9) estimated treatment difference −6.9 mg/dL, CI −14.3 to 0.0; *P*=0.0485) (low strength of evidence).

Exenatide

- The longest duration of an included study was 52 weeks.
- In the active-control trials of exenatide compared to insulin, total withdrawals and withdrawals due to adverse events were higher in the exenatide groups than the insulin groups (moderate strength of evidence).
- Nausea and vomiting were the most frequent adverse events among exenatide-treated patients, and rates of these symptoms were significantly higher in the exenatide group than insulin and placebo groups. Nausea declined after the first 8 weeks of therapy (moderate strength of evidence).
- Studies of exenatide did not report an association with pancreatitis, although the US Food and Drug Administration has received reports of acute pancreatitis in patients who received exenatide. A majority of affected patients (90%) in those reports had other risk factors for pancreatitis.
- Rates of hypoglycemia were similar between insulin and exenatide groups (moderate strength of evidence).
- In the one trial comparing exenatide to glibenclamide, total withdrawals were higher in the glibenclamide group due to higher rates of hypoglycemia (low strength of evidence).
- There was no significant difference in total withdrawals between exenatide 5 mcg or 10 mcg daily and placebo (moderate strength of evidence).
- Withdrawal rates due to adverse events were higher with exenatide 10 mcg twice a day than with placebo (relative risk 3.18, CI 1.70 to 5.93); there was not a statistically significant difference between treatment groups at the 5 mcg twice daily dosing (relative risk 1.76, CI 0.98 to 3.19) (moderate strength of evidence).
- Nausea, vomiting, and diarrhea rates were significantly higher in subjects treated with exenatide (either dose) compared with those treated with placebo (moderate strength of evidence).
- The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg twice a day compared with placebo in all 4 studies of patients on background sulfonylurea therapy (moderate strength of evidence).

- There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups (low strength of evidence).
- There was no significant difference in lipid profiles between patients on exenatide compared with placebo in the 1 study that examined this outcome (low strength of evidence).

Liraglutide

- The longest duration of an included study was 52 weeks.
- Total withdrawal rates were similar between liraglutide- and glimepiride-treated subjects, but withdrawals due to adverse events were slightly higher for liraglutide than glimepiride (low strength of evidence).
- Rates of gastrointestinal side effects were higher with liraglutide than glimepiride (high strength of evidence).
- Hypoglycemia rates were lower with liraglutide than glimepiride (moderate strength of evidence).
- Pancreatitis: In clinical trials, there were more cases of pancreatitis among those treated with liraglutide than among those treated with other medications or placebo. Studies comparing liraglutide with glimepiride could not exclude a weak association between treatment with liraglutide and the development of pancreatitis (1 case compared with 1 case in LEAD-2 study; 2 cases compared with 0 in LEAD-3); there were no reports of pancreatitis in the active-control trial with insulin glargine; only 1 of the included placebo-controlled trials reported any cases of pancreatitis (1 case compared with 1 case) (insufficient strength of evidence).
- Rates of gastrointestinal side effects were higher with liraglutide than with insulin glargine (1 study) (low strength of evidence).
- Rates of minor hypoglycemia were similar between liraglutide and insulin glargine (1 study), but more patients treated with liraglutide had major hypoglycemic events (5 compared with 0) (low strength of evidence).
- In the active-control trial comparing liraglutide to rosiglitazone, the incidence of serious adverse events was similar between treatment arms.[84] Nausea was more common in the liraglutide groups compared to rosiglitazone (low strength of evidence).
- In the active-control trial comparing liraglutide to sitagliptin, the incidence of serious adverse events was similar between treatment arms.[41] Gastrointestinal complaints, particularly nausea, were more common in the liraglutide arms of the study than in the sitagliptin arm (low strength of evidence).
- Total withdrawal rates were lower for liraglutide (0.6 mg daily, 1.2 mg daily, and 1.8 mg daily) than placebo (relative risk range 0.37 to 0.62) (moderate strength of evidence).
- There was no significant difference in the risk of withdrawal due to adverse events with liraglutide 0.6 mg, 1.2 mg, or 1.8 mg daily compared with placebo (moderate strength of evidence).
- The incidence of hypoglycemia was elevated with liraglutide 1.8 mg daily compared with placebo (relative risk 1.66, CI 1.18 to 2.34). Rates of hypoglycemia were not significantly different between liraglutide 0.6 mg daily and liraglutide 1.2 mg daily, and placebo (moderate strength of evidence).

- The rates of gastrointestinal side effects were higher in the liraglutide-treated groups than in the placebo group. The risk increased with higher doses (relative risk 1.76 for 0.6 mg; relative risk 2.33 for 1.2 mg; relative risk 3.14 for 1.8 mg), but generally waned over time (high strength of evidence).
- In the 2 studies that examined lipid parameters in liraglutide compared to placebo, liraglutide improved triglycerides compared to placebo in both studies, and improved LDL cholesterol levels compared with placebo in 1 study (low strength of evidence).
- One study compared lipid parameters in liraglutide-treated and sitagliptin-treated subjects and found no significant difference with the exception of a slightly larger decrease in total cholesterol with liraglutide 1.8 mg (-6.6 mg/dL versus -0.8 mg/dL, P=0.0332) (low strength of evidence).

Detailed Assessment of GLP-1 Agonists: Harms

Characteristics of trials included in this section were described in the Key Question 1 section for GLP-1 agonists. In this section, we focus on the results of those trials related to harms. For observational studies, we provide a table summarizing study characteristics (Table 61).

Detailed Assessment of Exenatide Compared with Liraglutide: Harms

In the one 26-week randomized-controlled trial (N=464) of liraglutide compared with exenatide, withdrawal rates were not significantly different between groups.[61] In the liraglutide arm of the study, 14% of participants withdrew from the study, and 10% withdrew due to adverse events. In the exenatide arm of the study, 19% of participants withdrew from the study, and 13% withdrew due to adverse events.

Overall, participants in the liraglutide group reported fewer adverse events than in the exenatide group (74.9% compared with 78.9%), but reported more serious and severe adverse events (12.3% compared with 7.3%) Only 1 serious or severe adverse event was judged to be related to study medication (severe hypoglycemia in the exenatide group).

The incidence of nausea was similar between the groups initially, but was more persistent over time in the exenatide group. Otherwise, the distribution of adverse events was similar between the study arms.

There were 2 major episodes of hypoglycemia in patients in the exenatide arm of the study who were also on a sulfonylurea. No major episodes of hypoglycemia occurred in the liraglutide arm of the study. The proportion of patients who reported minor hypoglycemia was significantly less in the liraglutide group than the exenatide group (26% compared with 34%, rate ratio 0.55, CI 0.34 to 0.88; P=0.0131).

There was no significant difference in change in total cholesterol, LDL cholesterol, or HDL cholesterol between the exenatide and the liraglutide treatment arms. Reduction in triglycerides was significantly greater in the liraglutide group than the exenatide group (−15.8 mg/dL (3.9) compared with −8.9 mg/dL (3.9) estimated treatment difference −6.9 mg/dL, CI −14.3 to 0.0; P=0.0485)

Detailed Assessment of Exenatide: Harms

Active-control trials

Adverse effects

Total withdrawals in the exenatide group ranged from 12.0% to 21.3% and in the comparison group from 0% to 10.1% in the 4 active-control trials comparing exenatide to insulin.[62-65] Withdrawals due to adverse events for the exenatide group ranged from 8% to 15% and were less than 1% in the comparison groups. Nausea and vomiting were the most frequent adverse events among exenatide-treated subjects, and rates of these symptoms were significantly higher in the exenatide group than in groups using insulin glargine[62, 63] or other insulin routines,[65,64] with rates of nausea ranging from 33% to 57% in the exenatide groups compared with <1 to 9% with the comparison group receiving insulin.

Overall hypoglycemia rates were similar between groups treated with insulin and with exenatide. [62-64] Hypoglycemia was particularly common when exenatide (39%) or insulin (38%) was combined with sulfonylurea and/or metformin;[65] 79% of hypoglycemia cases were associated with sulfonylurea. In a study comparing exenatide and titrated insulin glargine,[62] the overall rate of hypoglycemia with exenatide (14.7%) was not statistically different than that with insulin glargine (25.2%). In subgroup analysis of this study, however, the rate of hypoglycemia in patients who received metformin and exenatide was 2.6% as compared with 17.4% in those receiving insulin glargine (P=0.010), whereas the rates of hypoglycemia in patients taking sulfonylureas was similar with exenatide (30.0%) and insulin glargine (34.5%).

In the one trial comparing exenatide to glibenclamide, total withdrawals were higher in the glibenclamide group due to higher rates of hypoglycemia.(total withdrawals exenatide 6%, total withdrawals glibenclamide 12%; hypoglycemia exenatide 0%, glibenclamide 5%).[66]

In the one trial comparing exenatide to rosiglitazone, total withdrawals were similar between the treatment arms (exenatide 27%, rosiglitazone 24%).[67] Nausea, vomiting, and diarrhea were more frequently reported in the exenatide arm than in the rosiglitazone arm of the study (nausea: exenatide 47%, rosiglitazone 4%; vomiting: exenatide 22%, rosiglitazone 0%; diarrhea exenatide 7%, rosiglitazone 4%). Symptomatic hypoglycemia occurred in 4% of participants in the exenatide arm of the study, and none of the participants in the rosiglitazone arm of the study.

Placebo-control trials

Adverse effects

The placebo-controlled trials were sufficiently homogenous to obtain pooled estimates for adverse effects. Studies were only included for each meta-analysis if they reported sufficient information for the adverse effect under study. For example, only studies that reported numbers of subjects with the adverse effect of headache were included in the meta-analysis for that adverse effect. Results of our meta-analyses are summarized below in Table 60.

Based on pooled estimates across the placebo-controlled trials, there was no significant difference in withdrawals from the study between placebo and exenatide 5 mcg twice daily (relative risk 0.77, 95% CI 0.56 to 1.058, P=0.106) or exenatide 10 mcg twice daily (relative risk 1.14, 95% CI 0.83 to 1.56, P=0.415). Among the 9 included placebo-controlled trials of exenatide 10 mcg daily, withdrawals due to adverse events were greater with exenatide 10 mcg twice daily than with placebo. There was no statistically significant difference in withdrawals due to adverse events between exenatide 5 mcg twice daily and placebo (Table 60).

Nausea, vomiting, and diarrhea were significantly more frequent with treatment at both dosages of exenatide than in the placebo group (Table 60). There was considerable statistical heterogeneity in the meta-analysis for nausea for exenatide 10 mcg bid (I^2=76%) due to variation among studies in the magnitude of the effect, but all studies consistently did report more nausea among those treated with exenatide compared to placebo. Nausea declined after 8 weeks of treatment, although the statistical significance of the trend was not reported.[69-72, 74] There was no correlation between change in body weight and duration[70, 71] or severity[79] of nausea. When the incidence of nausea remained stable, body weight continued to decrease.[197]

Hypoglycemia was more frequent in the exenatide study groups than in the placebo study groups in all 4 studies in which participants were on background sulfonylurea therapy.[69, 71, 73, 74] The risk of hypoglycemia was not increased compared with placebo when all subjects received a thiazolidinedione or metformin[70, 72, 77] or no background therapy.[73]

There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies. Serious adverse events were rare, and reported to be unrelated to the study drug. In 1 study[72] 2 treatment-group patients had serious adverse events (chest pain and allergic alveolitis) which did not necessitate study withdrawal. Kadowaki et al. reported 1 serious adverse event (tendon rupture) in the exenatide 2.5 mcg arm of the study. Gao et al. reported serious adverse events among 3 patients in the exenatide arm of the study (chronic cholecystitis, Bartholin's cyst, and hypoglycemia) and 4 patients in the placebo arm of the study. Only hypoglycemia was judged to be related to the study drug.

None of these studies included in this report noted cases of acute pancreatitis, however, from the date of the drug's approval through December 2006, the US Food and Drug Administration received 30 domestic reports of acute pancreatitis in patients who received exenatide.[198] Median age of patients was 60 years and daily doses ranged from 10-20 mcg. The median time to onset of the symptoms was 34 days (range 4 to 300 days). Median amylase value was 384 IU/L and median lipase value 545 IU/L. Seventy percent of patients required hospitalization. A majority of affected patients (90%) had other risk factors for pancreatitis, including alcohol use or hypertriglyceridemia.

Moretto was the only study reporting changes in lipid profiles among participants. In this 24-week study of exenatide monotherapy, changes in fasting total cholesterol, HDL cholesterol, and LDL cholesterol from baseline to end point were not significantly different with exenatide 5 mcg and 10 mcg treatment compared with placebo.[73]

Table 60. Placebo-control trials of exenatide: Summary of meta-analyses

Exenatide dosage	Outcome	N					Heterogeneity	
			Measure	Estimate	95% CI	*P* value	I2	p
10 mcg BID	Total WDs	9[a]	RR	1.14	(0.83; 1.56)	0.415	64%	0.005
	WDs due to AE	9[a]	RR	3.18	(1.70; 5.93)	<0.001	39%	0.106
5 mcg BID	Total WDs	5[b]	RR	0.77	(0.56; 1.06)	0.106	37%	0.174
	WDs due to AE	5[b]	RR	1.76	(0.98; 3.19)	0.058	0%	0.557
10 mcg BID	Hypoglycemia, any	8[c]	RR	2.96	(1.81; 4.84)	<0.001	63%	0.009
	Nausea	9[a]	RR	3.43	(2.20; 5.34)	<0.001	76%	<0.001
	Vomiting	8[d]	RR	4.28	(2.38; 7.72)	<0.001	38%	0.128
	Diarrhea	7[e]	RR	2.29	(1.60; 3.27)	<0.001	0%	0.913
	Upper respiratory tract infection	4[f]	RR	0.87	(0.63; 1.21)	0.414	0%	0.672
	Headache	5[g]	RR	1.23	(0.78; 1.92)	0.373	0%	0.859
5 mcg BID	Hypoglycemia, any	5[b]	RR	2.27	(1.20; 4.27)	0.011	52%	0.081
	Nausea	5[b]	RR	2.42	(1.47; 4.16)	0.001	65%	0.001
	Vomiting	5[b]	RR	3.55	(2.16; 5.83)	<0.001	0%	0.912
	Diarrhea	5[b]	RR	1.74	(1.13; 2.67)	0.011	0%	0.433
	Upper respiratory tract infection	3[h]	RR	0.79	(0.44; 1.39)	0.411	41%	0.184
	Headache	3[i]	RR	1.81	(1.10; 2.97)	0.019	0%	0.593

Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; RR, relative risk; WD, withdrawal; WMD, weighted mean difference.

[a] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009), Gill (2010), Apovian (2010).

[b] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Moretto (2008), Kadowaki (2009).

[c] Studies included in analysis: Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009), Gill (2010).

[d] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009), Apovian (2010).

[e] Studies included in analysis: Buse (2004), DeFronzo (2005), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009), Kadowaki (2009).

[f] Studies included in the analysis: DeFronzo (2005), Kendall (2005), Moretto (2008), Gao (2009).

[g] Studies included in analysis: Buse (2004), Kendall (2005), Zinman (2007), Moretto (2008), Gao (2009).

[h] Studies included in analysis: DeFronzo (2005), Kendall (2005), Moretto (2008).

[i] Studies included in analysis: Buse (2004), Kendall (2005), Moretto (2008).

Observational studies

We examined adverse events in cohort studies of exenatide and identified 6 single-arm open-label extension studies,[78-80, 197, 199, 200] 1 single-arm retrospective cohort[201] study, and 1 2-arm retrospective cohort study[202] (Table 61). All of the open label extension studies assessed exenatide 10 mcg twice daily. In these studies, investigators included only subjects who had previously completed a prior study and several studies[79, 80, 197] excluded patients who had received placebo.

An open-label extension study of 3 of the placebo-controlled primary trials[69-71] included in this report was published in multiple publications with overlapping or identical populations.[78-80, 197, 200] These publications represented a pooled synthesis of patients continuing in an open-label extension beyond the original 30-week trial comparing exenatide 5 mcg or 10 mcg twice daily to placebo. Subjects from both the placebo and treatment groups were invited to continue on 10 mcg twice daily along with their existing metformin and/or sulfonylurea regimens for a 2-year[78] and then 3-year[200] period. Mild-to-moderate nausea was the most frequently reported adverse event, and 3% of subjects withdrew over the extension period (30 weeks to 2 years) because of nausea. Eight percent of subjects continued to complain of nausea after 2-years of follow-up. Hypoglycemia (of any severity) occurred at a rate of 1 case in 1010 person-years of exenatide treatment. There were no cardiovascular, pulmonary, hepatic, or renal effects attributed to treatment.

Adverse events in subjects completing 3-year follow-up of the open label extension of these 3 placebo-controlled trials[200] included mild-to-moderate nausea (59%) (5% of subjects withdrew due to nausea over the 3 years), and hypoglycemia (40%) with 2 of 527 subjects withdrawing because of hypoglycemia. This study population was a select group: only approximately half (46%) of subjects originally enrolled in the 3 primary trials enrolled in the open-label extension. Of subjects enrolled, only 54% completed the 2-year follow-up and 41% the 3-year follow-up.

An unrelated open-label, extension study[199] ("Study B") of a 28-day trial reported that nausea and vomiting were the most common adverse effects with exenatide 10 mcg twice daily for 26 weeks, but incidence rates were not reported. Approximately ¾ of subjects also received metformin; the other ¼ received diet and exercise only. A retrospective chart review[201] of 200 patients who had used exenatide noted that 13% discontinued treatment due to side effects, including nausea (8%), urticaria (2%), and hypoglycemia (0.5%).

One fair quality observational study examined hypoglycemia in patients newly initiated on exenatide or insulin glargine.[202] This study found that the probability of a hypoglycemic events was significantly lower for exenatide than for insulin glargine (total adjusted annualized hypoglycemia event rate for insulin glargine 0.117 +/- 0.007 compared with exenatide 0.065 +/- 0.011, $P<0.001$) Of note, background use of a sulfonylurea was higher in the insulin glargine group, although this was accounted for in the multivariate analysis.

Table 61. Characteristics of exenatide observational studies in adults with type 2 diabetes

Author, Year Country	Sample size (N) Follow-up (weeks)	Age (years) (SD)[a] % Male[a] % White[a] % Hispanic[a] Diabetes duration (years)[a]	Baseline HbA1c (%)[a] Weight (kg)[a] BMI (kg/m^2)[a]	Intervention	Combination therapy	Primary trial citations
Blonde, 2006 US	974 (551-ITT) 82	55(10) 61 74 12 7(6)	8.4(1.0) 98(20) 34(6)	10 mcg BID	MET +/- SU	Buse, 2004 DeFronzo, 2005 Kendall, 2005
Buse, 2007 US	974 (521-ITT) 104	55(10) 59 74 12 8(6)	8.4(1.1) 99(20) 34(6)	10 mcg BID	NR	Buse, 2004 DeFronzo, 2005 Kendall, 2005
King, 2006 US	200 12	NR	NR	NR	None or various (TZD, SU, MET, insulin)	NA
Nelson, 2007 US	127 30	52(11) 44 76 6 3.9(4.5)	7.5(0.7) 100(19) 35(6)	10 mcg BID	MET or diet/exercise (“Study B”)	NA
Ratner, 2006 US	150 (92 completers) 82	54(10) 69 86 1 5(5)	8.1(1.0) 102(21) 34(6)	10 mcg BID	MET	DeFronzo, 2005
Riddle, 2006 US	518 (222 completers) 82	57(10) 61 75 12 8(6)	8.4(1.0) 99(21) 34(6)	10 mcg BID	SU	Buse, 2004 Kendall, 2005
Fabunmi, 2009 US	6300 52	53-56 46-59 NR NR NR	7.7-9.5 NR NR	Exenatide any dose	MET, SU, TZD, or combination	NA

Abbreviations: BID, twice daily; ITT, intention-to-treat population; MET, metformin; NR, not reported; SU, sulfonylurea; TZD, thiazolidinedione.
[a] Data presented are mean (standard deviation).

Systematic reviews

Three systematic reviews of exenatide met our inclusion criteria and were rated either fair or good qaulity.[28, 81, 82] Amori and colleagues[28] published a systematic review of published and unpublished English-language studies of US Food and Drug Administration-approved and unapproved DPP-4 inhibitors (sitagliptin and vildagliptin) and GLP-1 agonists including exenatide. Severe hypoglycemia was rare (5/2781 patients who used exenatide) and occurred only when combined with sulfonylurea use. The risk ratio for mild to moderate hypoglycemia with exenatide compared with placebo was 2.3 (95% CI 1.1 to 4.9). Dose-dependent nausea and vomiting were the most frequently reported adverse events with exenatide (risk ratio nausea compared with any other treatment 2.9 (95% CI 2.0 to 4.2). Withdrawal rates due to gastrointestinal effects were higher with exenatide (4%) than with placebo.

A second systematic review, published by Pinelli and colleagues in 2008, also compared exenatide to placebo and insulin in terms of adverse events.[81] In a meta-analysis of the 5 included studies on exenatide, the pooled odds ratios for nausea was 9.02 (95% CI 3.66 to 22.23), for vomiting was 4.56 (95% CI 3.13 to 6.65), and for diarrhea was 2.96 (95% CI 2.05 to 4.26), The risk of hypoglycemia was not significantly greater in the pooled analysis of exenatide versus comparators (pooled odds ratio 3.53; 95% CI 0.92 to 13.61).

Another systematic review of GLP-1 receptor agonists, including exenatide and liraglutide, was also included.[82] This study combined trials of both exenatide and liraglutide into one meta-analysis and found, similar to our results, an increased risk of gastrointestinal side effects with exenatide and liraglutide. Monami et al. found that exenatide increased the risk of hypoglycemia compared to placebo, but only when exenatide was combined with a sulfonylurea. This is similar to the findings of our meta-analyses.

Detailed Assessment of Liraglutide: Harms

Active-control trials

Among the 3 studies comparing liraglutide to glimepiride, total withdrawals in the liraglutide group ranged from 7% to 35% compared with 0% to 39% in the glimepiride group. [58-60] Withdrawals due to adverse events for the liraglutide group ranged from 5% to 12% and were 0% to 6% in the comparison glimepiride group. Nausea, vomiting, and diarrhea were frequent adverse events among liraglutide-treated subjects. Rates of these symptoms were higher in the liraglutide group than in groups using glimepiride. In the LEAD-2 study, 35% to 44% of participants on liraglutide reported nausea, vomiting, or diarrhea, compared to 17% of participants on glimepiride. Vomiting was reported in 5% to 7% of participants on liraglutide, compared to 1% on glimepiride. Diarrhea was reported in 8% to 15% of participants on liraglutide, compared to 4% on glimepiride. There was a trend toward increase side gastrointestinal side effects with the increased dose of liraglutide.[59] In the LEAD-3 study, 27% to 29% of participants on liraglutide reported nausea, compared to 8% of participants on glimepiride. Vomiting was reported in 9% to 12% in the liraglutide group, compared to 4% in the glimepiride group. Diarrhea was reported in 16% to19% in the liraglutide group, compared to 9% in the glimepiride group.[60] The majority of the symptoms of nausea occurred in the first weeks of therapy. In both the LEAD-2 and the LEAD-3 study groups, by week 4 less than 10% of subjects in the liraglutide groups reported nausea.

Overall hypoglycemia rates were lower in the liraglutide groups than in the glimepiride group.[58-60] Minor hypoglycemia occurred in 3% to 12% of the participants in the liraglutide

groups, and 15% to 24% of the participants in the glimepiride groups. There were no reports of major hypoglycemic events in any of the participants in these studies.

Two participants in the LEAD-2 study developed pancreatitis; 1 was in the liraglutide 1.2 mg arm and 1 was in the glimepiride arm. Two participants in the LEAD-3 study developed pancreatitis; both were in the liraglutide arms of the study. A weak association between development of pancreatitis and treatment with liraglutide could not be excluded.[59, 60]

In the 1 active-control trial comparing liraglutide 1.8 mg daily to open-label insulin glargine, rates of adverse events were higher in the liraglutide arm than the insulin glargine arm. This was in large part secondary to a higher incidence of nausea, dyspepsia, vomiting, and diarrhea in the liraglutide arm of the study (nausea: liraglutide 14% compared with insulin glargine 1%; dyspepsia: liraglutide 7% compared with insulin glargine 2%; vomiting: liraglutide 7% compared with insulin glargine 0.4%; diarrhea: liraglutide 10% compared with insulin glargine 1%.) The incidence of gastrointestinal symptoms was highest in the early weeks of the study and waned over time.[83] Rates of minor hypoglycemia were similar between the 2 groups (liraglutide 27.4% compared with insulin glargine 28.9%). Five patients in the liraglutide arm (2.2%) did report major hypoglycemic events in this study, compared to no patients with major hypoglycemic events in the insulin glargine arm of the study. There were no reports of pancreatitis in this study.

In the active-control trial comparing liraglutide to rosiglitazone, the incidence of serious adverse events was similar between treatment arms (rosiglitazone 3%, liraglutide 3-5%).[84] Nausea was more common in the liraglutide groups compared to rosiglitazone, although the occurrence of nausea decreased over time in the liraglutide treatment arms. Minor hypoglycemia was experienced by 4.3% of participants in the rosiglitazone arm, and by 5.2% to 9.2% of participants in the liraglutide arms of the study. One participant in the liraglutide 0.6 mg arm developed pancreatitis. No other cases of pancreatitis were reported in the study.

In the active-control trial comparing liraglutide to sitagliptin, the incidence of serious adverse events was similar between treatment arms (3% to 4%).[41] Gastrointestinal complaints, particularly nausea, was more common in the liraglutide arms of the study than in the sitagliptin arm (incidence of nausea: liraglutide 21-27%, sitagliptin 5%). The median duration of nausea was 8 days with liraglutide 1.8 mg, and 13 days with liraglutide 1.2 mg.

This study also compared changes in fasting lipid profile over the course of the study between the liraglutide and the sitagliptin study arms, and found no significant difference between the two drugs in terms of fasting lipid profile changes with the exception of a slightly larger decrease in total cholesterol with liraglutide 1.8 mg compared to sitagliptin (-6.6 mg/dL versus -0.8 mg/dL, P=0.0332).[41] None of the other active-control trials measured changes in lipid profile with liraglutide.

Placebo-controlled trials

Based on pooled estimates across the placebo-controlled trials included in this systematic review for the 3 dosing ranges of liraglutide (0.6 mg to 0.65 mg daily, 1.2 mg to 1.25 mg daily, and 1.8 mg to 1.9 mg daily) there was significantly lower risk of withdrawal in the liraglutide arms than the placebo arms, for all of the doses of liraglutide (Table 62). Withdrawals due to adverse events, however, were not significantly different between liraglutide and placebo for all 3 dosing ranges.

Gastrointestinal side effects were more frequent with liraglutide than with placebo at all of the liraglutide dosages included in this review (Table 62). There was an increasing risk of

gastrointestinal side effects at higher doses of liraglutide (pooled effect liraglutide 0.6 mg once daily relative risk 1.76, 95% CI 1.16 to 2.67, *P*=0.0196; liraglutide 1.2 mg once daily relative risk 2.33, 95% CI 1.78 to 3.04, *P*<0.001; liraglutide 1.8 mg once daily relative risk 3.14, 95% CI 2.49 to 3.94, *P*<0.001). In general, the gastrointestinal side effects were mild in severity, and decreased over time.[59, 86]

There was no significant difference in the risk of hypoglycemia between liraglutide 0.6 mg daily or liraglutide 1.2 mg daily, and placebo (Table 62). There was an increased risk of hypoglycemia with liraglutide 1.8 mg daily compared with placebo (pooled effect liraglutide 1.8 mg once daily relative risk 1.66, 95% CI 1.18 to 2.34, *P*=0.004) Russell-Jones et al was the only study reporting any major hypoglycemic events.[83] In this study, 5 patients in the liraglutide 1.8 mg daily arm and none in the placebo arm reported a major hypoglycemic event. Only 1 of these events required medical assistance.

There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies. Serious adverse events were rare. Nauck et al reported 1 case of pancreatitis in the liraglutide 1.2 mg arm of the study and 1 case of pancreatitis in the glimepiride arm of the study which required study withdrawal. Other than these cases, there were no reports of pancreatitis in the included studies.

Two studies evaluated lipid parameters. Vilsboll et al found no significant difference between liraglutide and placebo in changes in total cholesterol, LDL cholesterol, or HDL cholesterol, but did find that liraglutide significantly reduced triglyceride levels compared to placebo (liraglutide 1.90 mg compared with placebo: −22%, 95% CI −35 to −6, *P*=0.0110; liraglutide 1.25 mg compared with placebo: −15%, 95% CI −30 to 2, *P*=0.0854; liraglutide 0.65 mg compared with placebo: −19%, 95% CI −33 to −2, *P*=0.0304).[87] Zinman et al found no significant difference in total cholesterol or HDL cholesterol, but found a significant reduction in LDL cholesterol and triglyceride levels in participants treated with liraglutide 1.2 mg daily compared to placebo (reduction in LDL liraglutide 1.2 mg daily compared with placebo −10.81 mg/dL compared with −3.86 mg/dL, *P*<0.05; reduction in triglycerides liraglutide 1.2 mg daily compared with placebo −33.62 mg/dL compared with −11.5, *P*<0.05) . There was no significant difference for any of the lipid parameters tested for liraglutide 1.8 mg compared with placebo.[86]

Liraglutide causes dose-dependent and treatment-duration dependent thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors in humans, but because of the association in rats and mice prescribing information for liraglutide indicates that liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or with a history of Multiple Endocrine Neoplasia syndrome type 2.

Table 62. Liraglutide compared with placebo: Summary of meta-analyses

Liraglutide dosage	Outcome	N	Measure	Estimate	95% CI	*P* value	Heterogeneity I^2	Heterogeneity P
0.6 mg to 0.65 mg daily	Total WDs	4[a]	RR	0.37	(0.28; 0.50)	<0.001	0%	0.720
	WDs Due to AE	4[a]	RR	0.70	(0.23; 2.18)	0.537	38%	0.185
1.2 mg to 1.25 mg daily	Total WDs	4[b]	RR	0.46	(0.37; 0.58)	<0.001	0%	0.759
	WDs Due to AE	4[b]	RR	1.69	(0.51; 5.57)	0.387	71%	0.016
1.8 mg to 1.9 mg daily	Total WDs	5[c]	RR	0.62	(0.45; 0.85)	0.003	56%	0.058
	WDs Due to AE	5[c]	RR	2.59	(0.84; 7.95)	0.097	73%	0.005
0.6 mg daily	Hypoglycemia, minor	3[d]	RR	1.28	(0.55; 3.00)	0.563	0%	0.660
	Gastrointestinal	2[e]	RR	1.76	(1.16, 2.67)	0.0196	19%	0.266
1.2 mg daily	Hypoglycemia, minor	3[f]	RR	1.78	(0.91; 3.47)	0.094	22%	0.279
	Gastrointestinal	2[g]	RR	2.33	(1.78; 3.04)	<0.001	0%	0.980
1.8 mg daily	Hypoglycemia, minor	3[h]	RR	1.66	(1.18; 2.34)	0.004	0%	0.685
	Gastrointestinal	3[i]	RR	3.14	(2.49; 3.94)	<0.001	0%	0.808

Abbreviations: AE, adverse event; CI, confidence interval; RR, relative risk; WD, withdrawal.
[a] Studies included in analysis: Vilsboll (2007), Seino (2008), Nauck (2009), Marre (2009).
[b] Studies included in analysis: Vilsboll (2007), Nauck (2009), Zinman (2009), Marre (2009).
[c] Studies included in analysis: Vilsboll (2007), Nauck (2009), Russell-Jones (2009), Zinman (2009), Marre (2009).
[d] Studies included in analysis: Seino (2008), Nauck (2009), Marre (2009).
[e] Studies included in analysis: Seino (2008), Nauck (2009).
[f] Studies included in analysis: Nauck (2009), Zinman (2009), Marre (2009).
[g] Studies included in analysis: Nauck (2009), Zinman (2009).
[h] Studies included in analysis: Nauck (2009), Russell-Jones (2009), Zinman (2009), Marre (2009).
[i] Studies included in analysis: Nauck (2009), Russell-Jones (2009), Zinman (2009), Marre (2009).

II. Thiazolidinediones (TZDs)

Summary of Findings for TZDs: Harms

- In September 2010, the US Food and Drug Administration restricted access for rosiglitazone and combination products that contain rosiglitazone due to an increased risk of cardiovascular adverse events.
- We found no evidence of increased all-cause mortality or cardiovascular mortality with pioglitazone; some studies suggest reduced risk of all-cause and cardiovascular mortality with pioglitazone (low strength of evidence).
- Evidence from systematic reviews, randomized controlled trials, and observational studies indicate that both pioglitazone and rosiglitazone increase the risk of heart failure (odds ratios range from 1.32 to 2.18 in various meta-analyses, high strength of evidence).
- Evidence from systematic reviews, randomized controlled trials, and observational studies indicate that both pioglitazone and rosiglitazone increase the risk of edema (odds ratios range from 2.26 to 4.62 in various meta-analyses, high strength of evidence).
- The risk of hypoglycemia is reduced with TZDs when compared with sulfonylureas; the risk is similar to the risk with metformin (high strength of evidence).
- Both TZDs resulted in a similar weight increase. The increase is similar to that with sulfonylureas (moderate strength of evidence).
- Risk of fractures is increased among patients exposed to TZDs (odds ratio 1.45, 95% CI 1.18 to 1.79, from meta-analysis of 10 randomized controlled trials involving 13,715 participants, moderate strength of evidence). This risk appears to be increased among women (odds ratio 2.23, 95% CI 1.65 to 3.10) but not among men (odds ratio 1.00, 95% CI 0.73 to 1.39). These findings are consistent with the results of the ADOPT trial.
- Adverse events occurring with pioglitazone and rosiglitazone were similar in head-to-head trials (low strength of evidence).

Detailed Assessment of TZDs: Harms

Restricted access for rosiglitazone

In September 2010, the US Food and Drug Administration announced that GlaxoSmithKline must develop a restricted access program for its drug, rosiglitazone (Avandia®) and combination products that contain rosiglitazone (Avandaryl®, and Avandamet®). These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with Avandia. The restrictions limit the use of rosiglitazone to patients with type 2 diabetes who cannot control their glucose levels with other medications and cannot take pioglitazone. Doctors will have to document their patients' eligibility and patients will have to review information and acknowledge that they understand the risks. Patients who are currently using rosiglitazone and benefiting from it may continue using the medication if they choose.[203]

The US Food and Drug Administration also ordered GSK to convene an independent group of scientists to review key aspects of the company's RECORD trial, which studied the cardiovascular safety of Avandia compared to standard diabetes drugs. During the course of the US Food and Drug Administration's review of the RECORD study, important questions arose about potential bias in the identification of cardiovascular events. In addition, the US Food and

Drug Administration halted the GSK's TIDE trial, comparing Avandia to Actos and to standard diabetes drugs.[203]

Systematic reviews of active-control and placebo-controlled trials of TZDs

A number of systematic reviews examined adverse effects in the previous Drug Effectiveness Review Project TZDs reports[89, 106, 109, 111-116, 119-123] (See Evidence Table 1 for 2008 TZD Report). We identified 8 new systematic reviews meeting inclusion criteria for this report (Table 63 and Evidence Tables 17 and 18).[81, 204-210] Five were assessed as good quality [81, 204, 207, 208, 210] and 3 were fair quality.[205, 206, 209] One review focused on fractures,[204] 1 focused on cardiovascular outcomes,[210], 1 on the risk of myocardial infarction and other major adverse cardiac events,[209] and 1 on myocardial infarction and chronic heart failure.[206] Mannucci et al[205] reported all-cause mortality in addition to adverse cardiovascular events, and both Pinelli et al and Phung et al reported efficacy and safety outcomes.[81, 207]

Table 63. Recent systematic reviews reporting adverse events with thiazolidinediones

Author, Year Quality	Comparison	Main meta-analysis results for harms	
		Outcome	Result[a]
Loke, 2009[204] Good	TZD use vs. active and placebo controls	Fractures	OR 1.45, (1.18-1.79) *P*<0.001
Mannucci, 2008[205] Fair	Pioglitazone vs. active controls, placebo controls, and no treatment	Cardiovascular deaths	RR 0.35 (0.14–0.85)[b]
		Non-fatal coronary events	RR 0.82 (0.55–1.23)[b]
		Non-fatal heart failure	RR 1.32 (0.88–1.98)[b]
Monami, 2008[206] Fair	Rosiglitazone vs. any other treatment	Myocardial infarction	M-H OR 1.18 (0.91–1.53)
		CHF	M-H OR 1.59 (1.11–2.28)
Nagajothi, 2008[209]	Pioglitazone vs. placebo or another oral agent	Myocardial infarction	RR 0.86 (0.69 to 1.07)
		Stroke	RR 0.79 (0.61 to 1.02)
		Revascularization	RR 0.40 (0.13 to 1.23)
Phung, 2010[207]	TZDs, added to metformin, vs. placebo or other noninsulin antidiabetic drugs	Weight gain	WMD 2.3 kg (1.7 to 2.9)
		Overall hypoglycemia	RR 2.04 (0.5 to 8.23)
Pinelli, 2008[81] Good	TZD vs. active controls or Placebo	Nonsevere hypoglycemia	OR 1.59, (0.76-3.32)
		Weight gain	1.51 kg, (–0.12-3.15)
Selvin, 2008[210] Good	Rosiglitazone vs. placebo or another oral agent	Cardiovascular morbidity and mortality	OR 1.68 (0.92 to 3.06)

Abbreviations: CHF, chronic heart failure; MI, myocardial infarction; M-H, Mantel-Haenszel; OR, odds ratio; RCT, randomized control trial; RR, relative risk; TZD, thiazolidinediones; WMD, weighted mean difference.
[a] Results are: Effect size, 95% confidence interval, and *P* value.
[b] These results are from analyses that exclude the PROACTIVE trial data.
[c] The systematic reviews listed in this table are new since the 2008 TZD report.

Mortality

Few reviews examined mortality (total or cardiovascular).[89, 115, 121, 122] Eurich and colleagues[115] examined the use of various antidiabetic agents in patients with heart failure and diabetes and identified 3409 thiazolidinedione-treated subjects. Pooled odds ratios for thiazolidinediones compared with other hypoglycemic agents for all-cause mortality was 0.83 (95% CI 0.71 to 0.97, *P*=0.02) when 4 studies of varying designs (3 were observational studies) were pooled (I^2 = 52%, *P*=0.10). Pioglitazone and rosiglitazone were combined in the studies contributing to these pooled effects. These authors note that the finding of lower all-cause mortality with thiazolidinediones should be interpreted with caution, as 3 of the 4 studies contributing to this estimate were observational in design, and subjects receiving these drugs may have been at lower risk for heart failure due to the commonly perceived risk of using them among persons with higher risk of cardiovascular events and congestive heart failure.

In contrast to Eurich and colleagues,[115] Singh, Loke, and Furberg[122] found no difference in all-cause mortality when they examined only rosiglitazone. In 4 trials, the relative risk for all-cause mortality was 0.99 (95%, 0.80 to 1.23; *P*=0.92). Cardiovascular mortality rates were similar to all-cause rates (relative risk 0.90 [95% CI 0.63 to 1.26], *P*=0.53).

The Singh, Loke, and Furberg[122] review differed from that of Eurich and colleagues[115] as the former review included subjects with either type 2 diabetes or prediabetes, included randomized controlled trials only, and was not restricted to subjects with heart failure. Both of the reviews included active drug and placebo comparisons, and only the randomized controlled trial by Dargie[171] was included in both the reviews.

In a systematic review of thiazolidinedione use in subjects who underwent coronary stent implantation, at 6-month follow-up mortality rate was 2/259, a death in each the control and rosiglitazone arms.[121] Bolen and colleagues[89] did not identify sufficient studies examining mortality to permit calculation of a pooled estimate.

Mannucci et al[205] included 94 published and unpublished randomized control trials with over 20,000 subjects with type 2 diabetes to assess whether pioglitazone is associated with increased cardiovascular risk. They found a reduced risk of all-cause mortality (odds ratio 0.30, 95% CI 0.14 to 0.63; *P*<0.05) in an analysis of trials that reported at least 1 death and excluded the PROACTIVE study.[177] PROACTIVE was excluded because it enrolled subjects at very high cardiovascular risk and was considered to not be representative of subjects receiving pioglitazone in the actual world. When all studies, including the PROACTIVE study, were included in the analysis, there was no significant reduction in mortality associated with pioglitazone. An analysis of studies comparing pioglitazone to rosiglitazone showed no significant difference in all-cause mortality between the 2 drugs.

The study by Mannucci and colleagues [205] reported a statistically significant reduced risk of cardiovascular death with pioglitazone use when all studies that reported cause of death were analyzed (relative risk 0.35, 95% CI 0.14 to 0.85). When the authors considered only studies that reported at least 1 cardiovascular death, the results were not statistically significant (Mantel-Haenszel odds ratio 0.49, 95% CI 0.21 to 1.15 [*P*=0.10]).

Cardiovascular morbidity

Several reviews examined the effects of thiazolidinediones on cardiovascular events; 3 focused on rosiglitazone, [119, 122, 206], 1 focused on pioglitazone,[205] and another on both thiazolidinediones.[89] Richter and colleagues only identified data from ADOPT[147] (discussed below). Singh, Loke, and Furburg[122] identified 3 randomized controlled trials in type 2

diabetes,[147, 158, 171] all of which were included in this update. Pooled estimates were obtained for these 3 randomized controlled trials and the DREAM trial of persons with prediabetes.[211] These studies compared various drugs at a variety of follow-up intervals, although statistical tests for heterogeneity were not significant by usual criteria. The relative risk for myocardial infarction of rosiglitazone compared with other drugs was 1.42 (95% CI 1.06 to 1.91); as noted above, the relative risk for cardiovascular mortality was not increased.

Bolen[89] stratified studies by the drug used for comparison and did not obtain pooled estimates because of clinical and methodological diversity. Three randomized controlled trials comparing thiazolidinediones and metformin and 2 randomized controlled trials comparing thiazolidinediones and sulfonylureas reported similar rates of nonfatal myocardial infarction or coronary heart disease between the thiazolidinedione and the comparison drug. Five short-duration, placebo-controlled studies also found similar rates of cardiovascular disease events and the PROACTIVE placebo-controlled trial also demonstrated no significant difference.[177] Three randomized controlled trials examining restenosis rates noted fewer cardiovascular disease events with thiazolidinediones than with placebo in patients at high risk.

Mannucci and colleagues[205] reported no statistically significant difference in the risk of non-fatal coronary events associated with pioglitazone use based on an analysis of 40 randomized control trials (8,248 patients) of pioglitazone compared with any other treatment (relative risk 0.82, 95% CI 0.55 to 1.23). When limited to studies that reported at least 1 non-fatal coronary event, the results still did not meet statistical significance. These analyses did not include the PROACTIVE study.[177] When PROACTIVE was included in the analysis, the results reached statistical significance in favor of pioglitazone (results shown in graph only).

In a meta-analysis of 86 trials (30,003 patients) of rosiglitazone compared with any other treatment, Monami and colleagues [206] examined the association of the risk of chronic heart failure (discussed below) and the risk of myocardial infarction with specific baseline characteristics such as HbA1c, body mass index, lipid levels, duration of diabetes, and insulin use. They aimed to identify moderators of the effect of rosiglitazone on the risk of myocardial infarction and chronic heart failure in type 2 diabetic patients. The authors used data from the studies that reported at least 1 myocardial infarction to calculate a Mantel-Haenszel (M-H) odds ratio for myocardial infarction. The observed increased risk of myocardial infarction with rosiglitazone use was not statistically significant (M-H odds ratio 1.18, 0.91 to 1.53). Trials enrolling patients with a higher HbA1c at baseline reported a lower risk of myocardial infarction. This correlation remained significant after adjusting for duration of the trials (r −0.24, P=0.03). Other significant correlations after adjusting for trial duration included lower triglycerides, higher body mass index, and more patients treated with insulin were associated with a higher risk of myocardial infarction.

Congestive heart failure

In a review of persons with diabetes or prediabetes using rosiglitazone,[122] the relative risk of heart failure for rosiglitazone compared with various other antidiabetic drugs was 2.09 (1.52 - 2.88), corresponding to a number needed to harm of 383 per year if baseline risk was 0.24% per year (low risk, from the ADOPT trial).[147]

Singh and colleagues[123] also examined onset of congestive heart failure in both pioglitazone and rosiglitazone compared with placebo in 3 randomized controlled trials with subjects with either type 2 diabetes or prediabetes. The odds ratio for all heart failure adverse events was 2.10 (95% CI 1.08 to 4.08). Four observational studies produced an odds ratio1.55

(95% CI 1.33 to 1.80). These authors also examined case reports, including 162 case subjects with 99 analyzable cases. Among these cases, the median time to onset of congestive heart failure was 24 weeks, although failure could occur early and did not appear to relate to dosage. Heart failure was not limited to the elderly; 26% of cases were in subjects less than 60 years of age.

Hospital admission for heart failure was elevated with thiazolidinediones compared with other treatments (pooled odds ratio 1.13 [95% CI 1.04 to 1.22], *P*=0.004; 4 studies, including 3 of observational design).[115]

In a Cochrane review of placebo-controlled trials of rosiglitazone,[119] the authors identified data only from the ADOPT trial.[147]

In a review of oral hypoglycemic agents, Bolen and colleagues[89] noted that the risk for congestive heart failure was higher with thiazolidinediones as either monotherapy or combination therapy than with metformin or sulfonylureas, with a range of 0.8% to 3.6% for thiazolidinediones and 0 to 2.6% for nonthiazolidinediones.

In a systematic review of thiazolidinediones use in diabetes and prediabetes,[116] Lago, Singh, and Nesto noted an increased risk of congestive heart failure compared with controls (placebo-controlled and active-control trials): relative risk 1.72 (95% CI 1.21 to 2.42). For placebo-controlled trials only, the relative risk was 1.97 (95% CI 0.94 to 4.13). When examined separately, the relative risk for pioglitazone was 1.32 (95% CI 1.04 to 1.68); for rosiglitazone the relative risk was 2.18 (95% CI 1.44 to 3.32). The overall event rate for congestive heart failure with thiazolidinediones was 2.3% and with the comparison drugs 1.4%. The number needed to harm for congestive heart failure was 107 over the 29.7-month follow-up (number needed to harm ranged across studies from 35 to 491). Although the risk of heart failure was increased, the risk of cardiovascular death was not significant: relative risk 0.93 (95% CI 0.67 to 1.29); placebo-controlled trials only: relative risk 1.08 (95% CI 0.66 to 1.76); pioglitazone only: relative risk 1.01 (95% CI 0.51 to 2.09); rosiglitazone only: relative risk 0.91 (95% CI 0.63 to 1.3).

An analysis of 40 randomized control trials of pioglitazone use in 10,171 patients with type 2 diabetes by Mannucci et al[205] showed no statistically significant increase in the risk of non-fatal heart failure (relative risk 1.32, 95% CI 0.88 to 1.98). When PROACTIVE[177] was included in the analysis, an increased risk of non-fatal heart failure with the use of pioglitazone became statistically significant (results reported in graph only).

Monami and colleagues [206] found an increased risk of chronic heart failure for rosiglitazone compared with other treatments (M-H odds ratio 1.59, 95% CI 1.11 to 2.28) in an analysis of randomized control trials that reported at least 1 occurrence of chronic heart failure. The risk ratio for chronic heart failure in rosiglitazone-treated patients was lower in trials enrolling subjects with higher HbA1c. This correlation did not remain statistically significant after controlling for the duration of the trials. Correlations between duration of diabetes and higher triglycerides with a lower risk of chronic heart failure were statistically significant after adjusting for duration of trials.

Edema

Bolen and colleagues[89] noted that the risk for edema was higher with thiazolidinediones than metformin or second generation sulfonylureas. Although few cases were considered serious, withdrawals secondary to edema were common. Both pioglitazone and rosiglitazone were associated with higher rates of edema than placebo; the between-group difference (in favor of placebo) was 0% to 3.4% for pioglitazone and 2.5% to 17% for rosiglitazone.

In a Cochrane review of pioglitazone,[120] the authors pooled data on all available randomized controlled trials regardless of comparisons and noted a relative risk of edema of 2.86 (95% CI 1.14 to 3.18). Richter and colleagues did a similar review of rosiglitazone[119] and noted an odds ratio for edema of 4.62 (95% CI 2.28 to 9.38).

Berlie and colleagues[114] examined the risk of edema in a systematic review and the odds ratio for pioglitazone and rosiglitazone combined (from comparisons with various drugs) was 2.26 (95% CI 2.02 to 2.53, $P<0.00001$). These authors attempted to compare the rates with rosiglitazone and pioglitazone and found the rates higher with rosiglitazone (odds ratio 3.75 [95% CI 2.70 to 5.20]) compared with pioglitazone (odds ratio 2.42 [95% CI 1.90 to 3.08]).

Hypoglycemia

Hypoglycemia was fairly uncommon with both thiazolidinediones. The combination of insulin and a thiazolidinedione increased rates of hypoglycemia.[89, 120, 212] Hypoglycemia rates with thiazolidinediones were lower than rates with sulfonylureas.[89, 119, 120] Thiazolidinediones cause less hypoglycemia than second generation sulfonylureas, with risk differences ranging between 0.3 and 0.25 (overall risk difference 0.09, 95% CI 0.03 to 0.25). Rates with metformin were similar to those with thiazolidinediones (obtained from indirect comparisons).[89]

Pinelli and colleagues[81] conducted a systematic review to compare the efficacy and safety of adding TZDs or exenatide to oral agents. They conducted a meta-analysis of 17 randomized control trials comparing a TZD with placebo or active control. Four of these studies reported results for hypoglycemic events. The risk of experiencing nonsevere hypoglycemia with TZD use compared with other treatments was not statistically significant (odds ratio 1.59, 95% CI 0.76 to 3.32). Severe hypoglycemia was rare in all of the trials.

Phung[207] conducted a systematic review with meta-analysis to compare the addition of various noninsulin antidiabetic drugs to ongoing metformin. They found that there was no statistically significant increased risk of hypoglycemia with TZDs (RR 2.04, 95% CI 0.5 to 8.23).

Elevated serum aminotransferase levels

Bolen and colleagues[89] found that rates of significant increases in serum aminotransferase levels (> 1.5 to 2 times normal) were low (<1%) and were similar to rates with metformin and second generation sulfonylureas. Other systematic reviews reached similar conclusions.[106, 111, 213]

Weight change

Thiazolidinediones caused similar weight gain compared with sulfonylureas either as mono- or combined therapy. Metformin consistently caused weight loss compared with thiazolidinediones and other oral agents.[89] These authors identified 2 head-to-head randomized controlled trials and noted similar increases in weight with pioglitazone and rosiglitazone.

The review by Pinelli and colleagues[81] assessed weight change with TZD use. Data from 5 studies with sufficient data on change in weight from baseline, showed that TZD use was associated with a statistically nonsignificant increase in weight (weighted mean difference 1.51 kg, 95% CI –0.12 to 3.15). When 3 trials comparing a TZD to an insulin secretagogue or muraglitazar were removed from the analysis, TZDs were associated with a statistically significant increase in body weight (weighted mean difference 2.19 kg, 95% CI 1.24 to 3.14).

The review by Phung and colleagues[207] comparing the addition of various noninsulin antidiabetic drugs to ongoing metformin found that TZDs, sulfonylureas, and glinides were

associated with weight gain (WMD 2.3 kg, 95% CI 1.7 to 2.9 for TZDs compared with placebo), whereas GLP-1 analogs, alpha-glucosidase inhibitors, and DPP-IV inhibitors were associated with weight loss or no weight change.

Fractures

One systematic review that analyzed data on the occurrence of fractures among patients using TZDs met our inclusion criteria.[204] It reported a statistically significant increased risk of fracture among patients who were exposed to rosiglitazone and pioglitazone (odds ratio 1.45, 95% CI 1.18 to 1.79). The analysis was based on 10 randomized controlled trials involving 13,715 participants. The authors reported a significantly increased risk of fractures among women (odds ratio 2.23, 95% CI 1.65 to 3.10) but not among men (odds ratio 1.00, 95% CI 0.73 to 1.39) (data from 5 trials). The review concluded that long-term use of TZDs doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk among men.

Other reviews

In addition to the systematic reviews identified for the previous Drug Effectiveness Review Project TZDs report, 2 reviews were described (See Evidence Table 1 for 2008 TZD Report) in the previous Drug Effectiveness Review Project TZDs report that were not systematic and therefore did not fulfill inclusion criteria for the previous report.[214, 215] We found 1 additional review[216] that used the same dataset from the review by Nissen et al.

Nissen and Wolski[215] examined the cardiovascular morbidity and mortality associated with rosiglitazone in a meta-analysis of 42 trials which included data from the Food and Drug Administration Web site, a clinical trials registry maintained by GlaxoSmithKline, and a search of the published literature. This paper was not determined to be a systematic review and therefore did not fulfill inclusion criteria. Evidence of a comprehensive literature search and data synthesis was not provided in the publication. Two large trials (DREAM and ADOPT) were the only included trials from the published literature. The authors noted an odds ratio for myocardial infarction of 1.43 (95% CI 1.03 to 1.98) and for death from cardiovascular causes of 1.64 (95% CI 0.98 to 2.74).

Diamond and colleagues[216] reanalyzed the 42 trials included in the review by Nissen and Wolski to demonstrate variation in results from using various meta-analytic approaches.

Lincoff and colleagues[214] examined the effect of pioglitazone on ischemic cardiovascular disease complications in diabetes using a database of individual patient data from Takeda Pharmaceuticals, the manufacturers of pioglitazone. The primary composite endpoint (death, nonfatal myocardial infarction, and nonfatal stroke) was decreased with pioglitazone as mono- or combination therapy with a variety of antidiabetic drugs (hazard ratio 0.82 [95% CI 0.72 to 0.94; *P*=0.005]). For placebo-controlled trials the hazard ratio was 0.09 (95% CI 0.01 to 0.84). The risk of serious heart failure was increased with pioglitazone (hazard ratio 1.41 [95% CI 1.14 to 1.76; *P*=0.002]).

One additional review by Padwal and colleagues[217] examined various drugs in the prevention of diabetes and included several studies on troglitazone, but none on pioglitazone or rosiglitazone.

Direct evidence: Pioglitazone compared with rosiglitazone head-to-head trials

Eight head-to-head efficacy trials with adverse event data were identified.[92, 93 90, 99-102] In one,[92] 719 patients with both type 2 diabetes and dyslipidemia were randomized to treatment with

pioglitazone 30 mg daily for 12 weeks followed by 45 mg for an additional 12 weeks, or rosiglitazone 4 mg daily followed by 8 mg for the same intervals. There were no differences between the drugs in adverse events including weight change (2.0 ±0.2 kg for pioglitazone compared with 1.6 ±0.2 kg for rosiglitazone, *P*=0.164), liver function tests, creatine phosphokinase level, blood pressure and heart rate, hemoglobin and hematocrit, hypoglycemic episodes, edema, or congestive heart failure. Data on the incidence of specific adverse events were not reported. Total withdrawals (19.0% for pioglitazone compared with 21.9% for rosiglitazone) and withdrawals due to adverse events (2.7% for both drugs) were similar.

A second study included patients who were switched to pioglitazone or rosiglitazone from troglitazone.[93] There was no information reported about adverse events in this study, with the exception of a similar weight gain in both groups (data not reported).

In a head-to-head trial in patients with type 2 diabetes and metabolic syndrome,[90] there was no significant difference in the increase in body mass index after 12 months of treatment with pioglitazone 15 mg (1.2 kg/m^2) or rosiglitazone 4 mg (1.5 kg/m^2), with both groups receiving glimepiride. Of the 87 patients (96%) who completed the study, 6.7% of subjects in the pioglitazone group and 11.9% in the rosiglitazone group had mild to moderate adverse events (transient headache and flatulence), with none resulting in withdrawal. There were no significant differences between treatment groups in serum alanine (ALT) or aspartate (AST) aminotransferase at 12-month follow-up. In 1 subject in the pioglitazone group (N=45) ALT and AST increased to 1.5 times the upper limit of normal but returned to normal range after 15 days. With rosiglitazone (N=42) 2 subjects increased AST.

One of the head-to-head studies identified for the updated report (2008) presented both tolerability and adverse events data. Derosa and colleagues[94-96, 142] noted among study completers (93% completion rate) that the rate of any side effect was 8.3% in the pioglitazone group and 10.4% in the rosiglitazone group (between-group *P* value >0.05), with both groups also taking metformin. These adverse events were transient headache and flatulence (metformin was new to some of the study subjects).[98] In this trial, there were no significant differences between treatment groups in ALT or AST at 12-month follow-up. In 2 subjects in the pioglitazone group (N=48) ALT and AST increased to 1.5 times the upper limit of normal, but regressed to normal range after 15 days. With rosiglitazone (N=48) in 3 subjects AST and ALT increased to 2.0 times the upper limit of normal and also regressed. No other adverse events were reported in this study. Hematocrit decreased significantly in both treatment groups (*P*<0.05): Change with pioglitazone was −2.3 umol/L and with rosiglitazone was −2.4umol/L.

The detailed adverse event results for the other 4 can be found in Evidence Table 10.[99-102] Briefly, all 4 of these were small studies (Numbers of 12, 35, 50, and 60) ranging from 12 to 20 weeks and were not designed to assess harms. Three of them reported slightly greater improvements in some lipid measures with pioglitazone than with rosiglitazone.[99, 101, 102]

Indirect evidence

For this report, we did not update the comparisons of pioglitazone or rosiglitazone compared with placebo. This information was included in the 2008 Drug Effectiveness Review Project drug class review on TZDs. We briefly summarize the findings of that report here.[18]

Overall withdrawals

Nine placebo-controlled trials of pioglitazone[160, 163-165, 177, 180, 218-220] and 16 of rosiglitazone[166, 167, 169-172, 176, 221-232] reported overall withdrawal rates. Treatment group withdrawal rates ranged from

7% to 33% in pioglitazone trials and 0 to 28% in rosiglitazone trials. Pooled risk differences showed trends for lower overall withdrawals in treatment groups than placebo groups for both pioglitazone (−1.0%; 95% CI −3.0% to 1.0%) and rosiglitazone (−5.0%; 95% CI −10.0 to 0.0). There was significant heterogeneity among rosiglitazone trials.

Withdrawals due to adverse events

The previous Drug Effectiveness Review Project TZDs report[18] found that the proportion of patients who withdrew due to adverse events was similar for the 2 drugs: 4.7% in pioglitazone trials and 5.3% in rosiglitazone trials. Pooled risk differences showed no differences from placebo in either pioglitazone (0%; 95% CI −2 to 2) or rosiglitazone (−1%; 95% CI −3 to 0) trials. The proportion of withdrawals due to adverse events in the placebo groups differed between these groups of studies (4.4% in pioglitazone studies compared with 6.8% in rosiglitazone studies), so the pooled risk differences were not directly comparable.

Specific adverse events reported in placebo-controlled trials

The previous Drug Effectiveness Review Project TZDs[18] indicated that the quality of reporting of adverse events in randomized controlled trials designed to measure efficacy was fair to poor. Most studies did not prespecify which events were evaluated and did not report details about ascertainment methods. In most cases, there was no difference from placebo in the number of patients reporting an adverse event. The most frequently reported adverse events were edema, hypoglycemia, and weight gain.

Edema

The incidence of edema reported in 16 placebo-controlled trials ranged from 0% to 27%. The incidence of edema was significantly greater with both pioglitazone and rosiglitazone than placebo. The pooled risk difference was significantly greater than placebo in pioglitazone trials (4%, 95% CI 2 to 7). Rosiglitazone was also associated with an increased risk of edema. The pooled risk difference in 7 placebo-controlled trials[170, 176, 221, 227, 232-234] was 8% (95% CI 3 to 13). There was significant heterogeneity among the rosiglitazone trials, due to a higher incidence of edema in 2 of the trials (23% and 24%).[176, 232] The incidence in the other 5 trials ranged from 3% to 8%, with differences from placebo ranging from 2% to 6%.

Hypoglycemia

The incidence of hypoglycemic episodes was reported in 11 placebo-controlled efficacy trials. The incidence ranged from 0 to 37.5% in 7 studies of pioglitazone and from 5.2% to 52.5% in 4 studies of rosiglitazone. The pooled risk difference between treatment and placebo was not significantly different for either drug, however.

The trials of rosiglitazone examined combination therapy with sulfonylureas[176, 233, 235] or triple therapy with sulfonylurea and metformin.[170] In pioglitazone trials, 3 used monotherapy,[163, 236, 237] 1 used combination therapy with sulfonylureas,[164] and 3 used combination therapy with insulin.[165, 218, 238] Pooled risk differences were not significantly different from placebo in pioglitazone trials using monotherapy (1%, 95% CI −1 to 2), combination therapy with sulfonylureas (1%, 95% CI −1 to 2), or insulin (7%, 95% CI −4 to 19). The highest rates of hypoglycemic events in pioglitazone studies were noted where pioglitazone was combined with insulin.[165, 218]

Weight gain

Twenty-six placebo-controlled trials provided information about weight gain in patients taking pioglitazone or rosiglitazone. A pooled estimate was not calculated for all of those studies to make indirect comparisons because of differences in the methods of measuring the outcome (for example, body mass index, change in weight, or patients gaining >5% of body weight) and limited reporting of results (for example, means were reported without a measure of dispersion). Trials with several doses found increased weight gain associated with higher doses.

Only 4 trials provided sufficient information to calculate a weighted mean difference. The pooled estimates for these trials were very similar for pioglitazone (3.69 kg, 95% CI 2.48 to 4.89)[224, 231] and rosiglitazone (3.50 kg, 95% CI 2.25 to 4.75),[220, 239] indicating that the drugs cause a similar amount of weight gain. This evidence is consistent with the findings of no difference between the drugs in weight gain reported in head-to-head trials.[90, 92, 93]

A 2004 meta-analysis[112] found similar results in an analysis of 11 trials. Within 6 months of initiating therapy, the average weight gain was 2.7 kg (95% CI 1.8 to 3.7 kg), and drug grouping was not a predictor of heterogeneity (P>0.10).

The range of weight gain reported in active control trials found patients taking pioglitazone or rosiglitazone gained more weight than those taking a sulfonylurea or metformin.

Liver function abnormalities

The first thiazolidinedione approved for use in the United States, troglitazone, was withdrawn from the United States market in 2000 due to concerns about liver damage. Elevations in ALT (>3 times the upper limit of normal) were rare in efficacy trials of pioglitazone and rosiglitazone, with either no cases or reported incidences of less than 1%.

Risk of fracture

Based on data from ADOPT, in February 2007 GlaxoSmithKline issued a safety warning regarding increased risk of fractures associated with use of rosiglitazone. An analysis of these data[240] found significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide (9.3% compared with 5.1% and 3.5% respectively). The incidence in women was 2.74 per 100 patient-years with rosiglitazone, 1.54 per 100 patient-years with metformin, and 1.29 per 100 patient-years with glyburide. The majority of these fractures were in the upper arm (humerus), hand, or foot. The observed incidence of fractures for male patients in ADOPT was similar among the 3 treatment groups.

At GlaxoSmithKline's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial, which compared rosiglitazone in combination with either metformin or sulfonylurea to combination therapy with metformin and sulfonylurea. The results of the preliminary analysis were reported to GSK as being consistent with the observations from ADOPT.

Heart failure and other cardiac adverse events

The product label states that rosiglitazone is not indicated in combination with insulin based on an increased incidence of cardiac failure and other cardiovascular adverse events observed in patients on insulin plus rosiglitazone compared with patients using insulin plus placebo.[241] Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were for the most part taking rosiglitazone 8 mg daily.

Two placebo-controlled trials of pioglitazone added to insulin reported incidences of congestive heart failure of 12.5%[218] and 1%.[238]

The pioglitazone product label[242] cites a 24-week postmarketing study comparing pioglitazone with glyburide in patients with New York Heart Association class II and III heart failure. Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on pioglitazone compared with 4.7% of patients on glyburide. This adverse event associated with pioglitazone was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

In the PROACTIVE trial,[177] rates of any report of congestive heart failure were increased with pioglitazone compared with placebo ($P<0.0001$), but rates of fatal heart failure were not different between groups ($P=0.634$)

Adverse events reported in active-control trials

Overall withdrawals, withdrawals due to adverse events, and specific adverse events reported in active-control trials are shown in Evidence Table 10.

Observational studies of adverse events

Direct evidence comparing pioglitazone with rosiglitazone: Harms

Overview

The previous Drug Effectiveness Review Project TZDs report[18] included 12 observational studies that compared adverse events in patients taking pioglitazone with those in patients taking rosiglitazone. Five of these were designed to assess specific adverse events; in the others, adverse events were reported but were not the primary outcome. In this update, we did not include additional observational studies aiming to assess the risk of cardiovascular adverse events or fractures for people taking TZDs because it was felt that sufficient, and stronger, evidence from systematic reviews was already available. We did include 2 additional observational studies in this section of the report for the current update.[243, 244] The main results of these studies related to this key question are summarized in Table 65 and Evidence Table 21.

Lower extremity and pulmonary edema

The prevalence of edema was the primary outcome in a retrospective chart review of 99 patients receiving thiazolidinediones in combination with insulin.[245] The prevalence of edema was 12.7% for patients taking rosiglitazone 4 mg and 5.1% in those taking rosiglitazone 8 mg. Among patients taking pioglitazone, there was an increase in edema with increasing dose (1.3% with 15 mg and 6.3% with 30 mg). There was 1 case of pulmonary edema in a patient taking rosiglitazone.

In a retrospective chart review,[246] pulmonary edema was noted in 2 patients (1.9%) taking pioglitazone and 3 taking rosiglitazone (3.1%). Four of these had existing congestive heart failure treated with diuretics. Another study[247] reported edema in patients with documented heart failure. Fluid retention was seen with the use of both pioglitazone (15.6%) and rosiglitazone (14.3%) across all dosages. Two patients (11%) had physical signs of pulmonary edema, but the study does not report which drug the patients were taking.

Macular edema

The manufacturer of rosiglitazone issued a warning letter in December 2005 regarding post-marketing reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone.[248] The incidence is not reported, but the warning letter states that reports were very rare. In the majority of these cases, the patients also reported concurrent peripheral edema. We identified no reports of macular edema in placebo-controlled trials or observational studies. Abnormal vision was reported in 2.3% of patients in 1 trial of rosiglitazone in combination with sulfonylureas,[232] but this was lower than the rate in the placebo group (5.4%).

Heart failure

A retrospective cohort study used claims data to assess the risk of developing heart failure in patients taking pioglitazone (N=1347) or rosiglitazone (1882) for up to 40 months.[249] Compared with a control group of patients who did not take thiazolidinediones, the hazard ratio for pioglitazone was 1.92 (95% CI 1.24 to 2.97), and for rosiglitazone 2.27 (95% CI 1.65 to 3.13). There was no significant difference in the risk of developing heart failure between these 2 drugs (P=0.091).

A retrospective database study designed to assess the prevalence of edema found no documentation of new-onset heart failure or exacerbations of existing heart failure in patients initiating thiazolidinediones therapy plus insulin.[245] The study authors caution, however, that documentation of heart failure was poor and that the data may be unreliable.

Weight gain

Seven comparative observational studies reported weight gain in follow-up periods ranging from 8 weeks to 1 year (Table 64).[244, 246, 250-255] There was no difference in the amount of weight gain in patients taking pioglitazone compared with rosiglitazone in any study.

Table 64. Range of weight gain reported in comparative observational studies

Study[a]	Duration	Weight gain with pioglitazone (kg)	Weight gain with rosiglitazone (kg)
King 2000[255]	16 weeks	0.5	2.6
LaCivita 2002[251]	6 months (range 3-11 months)	1.6	1.5
Boyle 2002[250]	18 weeks	2.0	1.6
Olansky 2003[252]	12 weeks or longer	2.0	1.6
Harmel 2002[254]	25-27 weeks	2.2	1.6
Hussein 2004[246]	8 weeks or longer	2.3	2.9
Gegick 2004[253]	1 year	4.1	3.0
Miyazaki 2008[244]	3 months	2.7	2.9

[a] There was no significant difference between drugs in any study.

Evidence comparing pioglitazone or rosiglitazone to active controls: Harms

Ten observational studies reported adverse events associated with thiazolidinediones compared with other active drugs (Table 65, Evidence Table 21).[243, 256-264] The adverse events they

examined included mortality, coronary heart disease events, heart failure, cancer or adenoma incidence, edema, weight gain and progression to insulin use. Because these studies did not report results separately for pioglitazone and rosiglitazone or they included only 1 of the thiazolidinediones, they do not provide information about the comparative safety of the thiazolidinediones. They do provide information about thiazolidinediones as a class compared with other antidiabetic agents.

In 2 studies, thiazolidinediones were not associated with increased mortality compared with other oral hypoglycemic agents.[258, 261] In 1 study, pioglitazone was associated with reduced all-cause mortality compared with other oral antidiabetic medications.[243] In older patients with heart failure thiazolidinediones, either alone or combined with metformin, were associated with a lower risk of death over a 15-month period compared with patients not treated with an insulin sensitizer.[261]

Two studies reported the incidence of coronary heart disease events (myocardial infarction or revascularization) with thiazolidinediones compared with metformin or sulfonylureas. A good-quality study using United States health insurance data found no increased risk of coronary heart disease events in patients initiating thiazolidinedione monotherapy compared with those initiating metformin plus sulfonylurea combination therapy.[257] The other found similar risks with rosiglitazone compared with sulfonylureas, metformin, or insulin, either alone or in combination.[262] Both studies also found no increased risk in the individual components of the composite outcome with thiazolidinedione use.

Table 65. Observational studies comparing adverse events associated with thiazolidinediones to adverse events associated with active controls

Author, Year Sample Size (Quality)	Comparison	Data source, Population description	Main outcomes	Main results
Kahler 2007[258] 39 721 (Fair)	TZD vs. SU monotherapy vs. metformin monotherapy vs. metformin + SU vs. no drugs	Veterans Health Administration data	All-cause mortality (15 months)	Adjusted odds ratio (95% CI) SU (reference): 1.00 TZDs: 1.04 (0.75 to 1.46) Metformin: 0.87 (0.68 to 1.10) Metformin + SU: 0.92 (0.82 to 1.05) No drugs: 0.90 (0.74 to 1.09)
Masoudi 2005[261] 16 417 (Good)	TZDs vs. metformin vs. no insulin sensitizer	Medicare Older patients with heart failure	All-cause mortality (1 year)	Adjusted hazard ratio (95% CI) TZDs: 0.87 (0.80 to 0.94) Metformin: 0.86 (0.78 to 0.97) SU: 0.99 (0.91 to 1.08) Insulin: 0.96 (0.88 to 1.05) TZD+metformin: 0.76 (0.58 to 0.99)
Johannes 2007[257] 25 140 (Good)	TZDs vs. metformin + SU	US health insurance claims data	Coronary heart disease events (myocardial infarction or coronary revascularization)	Adjusted hazard ratio (95% CI) TZDs: 1.02 (0.87 to 1.20) Metformin+SU (reference): 1.00
McAfee 2007[262] 26 931	Rosiglitazone vs. metformin vs. sulfonylurea	US health insurance claims data	Coronary heart disease events (myocardial	Adjusted hazard ratio (95% CI) Rosiglitazone vs. metformin: 1.07 (0.85 to 1.34)

Author, Year Sample Size (Quality)	Comparison	Data source, Population description	Main outcomes	Main results
(Good)		Patients with type 2 diabetes	infarction or coronary revascularization)	Rosiglitazone vs. SU: 0.82 (0.67 to 1.02) Rosiglitazone combined with insulin vs. other oral antidiabetics combined with insulin: 0.88 (0.59 to 1.32) Rosiglitazone therapy vs. all other non-rosiglitazone therapies: 0.93 (0.80 to 1.10)
Karter 2005[259] 23 440 (Fair)	Pioglitazone vs. SU vs. metformin vs. insulin	Kaiser Permanente Northern California Diabetes Registry	Hospital admission for heart failure (mean 10.2 months)	Adjusted hazard ratio (95% CI) Pioglitazone: 1.28 (0.85 to 1.92) Insulin: 1.56 (1.00 to 2.45) Metformin: 0.70 (0.49 to 0.99) SU (reference): 1.00
Hartung 2005[265] 1940 (Fair)	TZDs vs. SU vs. metformin vs. metformin + SU vs. insulin vs. insulin + TZD vs. alpha-glucosidase inhibitor	Oregon Medicaid Claims data	Hospital admission for heart failure (within 60 days)	Adjusted odds ratio (95% CI) TZDs: 1.37 (0.98 to 1.92 SU: 0.95 (0.73 to 1.24) Metformin: 0.97 (0.72 to 1.30) Metformin+SU: 0.90 (0.60 to 1.34) Insulin: 1.25 (0.92 to 1.69) Insulin+TZDs: 1.35 (0.84 to 2.18) Alpha-glucosidase inhibitor: 0.82 (0.28 to 2.18)
Koro 2007 [260] 126 971 (Fair)	TZDs vs. other antidiabetic agents	US Integrated Healthcare Information Services database	Cancer incidence	Adjusted odds ratio (95% CI) TZDs (mono- or combination therapy) compared with other anti-diabetic agents Breast cancer: 0.89 (0.68 to 1.15) Colon cancer: 1.03 (0.84 to 1.32) Prostate cancer: 1.04 (0.83 to 1.31)
Hanefeld 2006[256] 500 (Poor)	Pioglitazone vs. glibenclamide	Primary care sites, Germany Patients with type 2 diabetes insufficiently controlled on metformin alone	Progression to insulin	Pioglitazone: 55/250 (22%) Glibenclamide: 138/250 (55%) *P*<0.001
Habib 2009[243] 19,717 (Good)	Rosiglitazone vs. pioglitazone	Vertically integrated HMO system (hospitals and	All-cause mortality	Adj. HR with propensity adjustment, each compared to no TZD use: Rosi = 0.87 (0.54-1.39);

Author, Year Sample Size (Quality)	Comparison	Data source, Population description	Main outcomes	Main results
		clinics)		Pio = 0.63 (0.45-0.87) NSD
	Any TZD vs. non-TZD OAD	Vertically integrated HMO system (hospitals and clinics)	All-cause mortality	Adj. HR with propensity adjustment = 0.69 (0.52 - 0.90)
	Rosiglitazone vs. non-TZD OAD			Adj. HR with propensity adjustment = 0.91 (0.57 - 1.48) (NS)
	Pioglitazone vs. non-TZD OAD			Adj. HR with propensity adjustment = 0.60 (0.42 - 0.96)
Miyazaki 2008[244] 56 (Fair)	Rosiglitazone vs. pioglitazone	Clinical research center cohort study; Previous treatment with insulin, metformin or TZD	Lipids	Mean change in LDL, mg/dL (SD): Rosiglitazone: +15 (5); Pioglitazone: +1 (4) Mean change in HDL, mg/dL (SD): Rosiglitazone: +4 (1) Pioglitazone: +2 (1) Mean change in triglycerides, mg/dL (SD): Rosiglitazone: −8 (8) Pioglitazone: −47 (7)
			Weight gain	Mean change in weight, kg (SD): Rosiglitazone: +2.9 (0.4) Pioglitazone: +2.7 (0.8)
Asche 2008[264] 5438 (Good)	Sulfonylurea vs. TZD	Primary care and specialty clinics. A variety of practice types including solo practitioner, community practitioners, community clinics, academic medical centers and large integrated delivery networks.	Hypoglycemia	SU: N=58 (2.6%) TZD: N=20 (2.2%)
			Weight gain >= 4.5 kg	SU: N=196 (8.8%) TZD: N=120 (13.5%)
			Edema	SU: NR TZD: N=39 (4.4%)
Lewis 2008[263] 3 studies: 4248	TZD vs. no TZD	Nested case-control; Kaiser Permanente database	Adenoma	Adjusted OR (95% CI) of any adenoma on first colonoscopy, TZDs vs. no TZDs:

Author, Year Sample Size (Quality)	Comparison	Data source, Population description	Main outcomes	Main results
9813 1825 (Fair)				Study 1: 0.73 (0.57-0.92) Study 2: 0.86 (0.65-1.14) Study 3: 0.75 (0.44-1.28)

Abbreviations: CI, confidence interval; SU, sulfonylurea; TZD, thiazolidinedione.

Hospital admission for congestive heart failure was the main outcome in a fair-quality cohort study that used data from a Kaiser Permanente diabetes registry.[259] Relative to patients initiating therapy with sulfonylureas, patients initiating therapy with thiazolidinediones were no more likely to experience a hospitalization for heart failure after an average of 10.2 months of follow-up. A case-control study based on Oregon Medicaid claims data, in contrast, found a trend suggesting increased risk of hospitalization for heart failure associated with exposure to thiazolidinediones within the previous 60 days.[265] Increased risk was also found with exposure to insulin and to the combination of insulin plus thiazolidinediones, but not for other oral antidiabetic agents.

A series of nested case-control studies found no difference in the incidence of breast, colon, or prostate cancer associated with exposure to thiazolidinediones compared with other oral diabetic medications or insulin.[260] A case-control study found a slightly higher odds of having an adenoma on first colonoscopy for subjects with type 2 diabetes exposed to TZDs compared with those not exposed to TZDs.[263]

A study conducted in 500 primary care patients in Germany found fewer patients progressed to insulin therapy when taking pioglitazone than when taking a sulfonylurea.[256] However, because this study did not control for confounders and did not clearly report its recruitment strategy and other methods, these results may have a high risk of bias.

The previous Drug Effectiveness Review Project TZDs report identified 43 additional uncontrolled studies of adverse events associated with individual thiazolidinediones.[266-303] The results of these studies were consistent with evidence from randomized controlled trials and comparative observational studies. Conclusions that can be drawn from this body of evidence are limited because the studies do not provide information about comparative harms.

III. Fixed-dose Combination Products (FDCPs) or Dual Therapy

Summary of findings for Fixed Dose Combination Products or Dual Therapy: Harms

Harms in children

- We did not find any evidence meeting inclusion/exclusion criteria for children.

Harms in adults

- We found no head-to-head trials that compared harms between any 2 FDCPs (insufficient strength of evidence).
- We found no studies that evaluated long-term harms beyond 15 months for any available FDCP (insufficient strength of evidence).

Avandamet® or dual therapy with metformin plus rosiglitazone

- Similar rates of withdrawals due to adverse events with Avandamet®/dual therapy groups and monotherapy groups (3 trials ranging from 24 to 32 weeks, low strength of evidence).
- Similar or slightly higher rates of hypoglycemia with Avandamet®/dual therapy groups compared with monotherapy groups (3 trials ranging from 24 to 32 weeks, low strength of evidence).
- Similar rates of adverse cardiovascular events with Avandamet®/dual therapy and monotherapy, but duration of studies may not have been sufficient to reliably assess adverse cardiovascular events (3 trials ranging from 24 to 32 weeks, low strength of evidence).
- Gastrointestinal adverse effects were the most frequently reported adverse events with Avandamet® and dual therapy with metformin plus rosiglitazone. Rates of gastrointestinal adverse effects with Avandamet® or dual therapy were high (28 to 47%), but were the same or slightly lower than those with metformin monotherapy (moderate strength of evidence).
- Higher rates of edema with Avandamet® or dual therapy than with metformin monotherapy (moderate strength of evidence).
- In 2 included trials of Avandamet®, subjects receiving Avandamet® reported virtually no change in weight from baseline (0.0 kg to 0.01 kg) compared with slight weight gain with rosiglitazone monotherapy, and slight weight gain (1.9 kg) or weight loss (−2.9 kg) with metformin monotherapy (moderate strength of evidence).

Avandaryl® or dual therapy with rosiglitazone and glimepiride

- Few definitive conclusions about comparative harms for Avandaryl® or dual therapy with rosiglitazone and glimepiride can be drawn from direct evidence. The 2 included trials were a 28 week trial (N=874) comparing 2 dosages of Avandaryl® with glimepiride monotherapy and rosiglitazone monotherapy, and a 20 week trial (N=40) comparing concurrent use of rosiglitazone and glimepiride with rosiglitazone monotherapy.
- Rates of hypoglycemia were greater with Avandaryl® or dual therapy than with monotherapy (moderate strength of evidence).
- Weight gain was slightly greater with Avandaryl® or dual therapy than with monotherapy (moderate strength of evidence).

Actoplus Met® or dual therapy with pioglitazone and metformin

- Evidence was limited to one large trial (N=600) comparing Actoplus Met® with component monotherapies and a 15 month trial comparing dual therapy with pioglitazone and metformin to monotherapy with either that reported very little harms information.
- Overall incidence of adverse events, including serious adverse events, was similar across treatment groups (low strength of evidence).

- Headache was reported more frequently with Actoplus Met® than with either component monotherapy (low strength of evidence).
- Patients on Actoplus Met® gained less weight than patients on pioglitazone alone but gained more weight than patients on metformin alone (low strength of evidence).
- Patients on Actoplus Met® experienced lower rates of edema than patients on pioglitazone alone but higher rates of edema than patients on metformin alone (low strength of evidence).
- Diarrhea, hypoglycemia, and gastrointestinal events were reported most frequently in patients on metformin monotherapy and least frequently in patients on pioglitazone alone, with patients on Actoplus Met® reporting rates in between those for metformin and pioglitazone (low strength of evidence).

Janumet® or dual therapy with sitagliptin and metformin

- No studies including Janumet® were found that met inclusion criteria. Evidence was limited to 1 trial (N=1,091, with outcomes reported at 24 and 54 weeks) including dual therapy with sitagliptin and metformin.[31, 32]
- Gastrointestinal adverse effects were commonly reported (15% to −31% across all treatment arms) and were similar between sitagliptin 100 plus metformin 2000 and metformin 2000 monotherapy at 24 weeks (24.7 compared with 25.3%) and at 54 weeks (29 compared with 31%). Rates were slightly higher for sitagliptin 100 plus metformin 1000 compared with sitagliptin 100 monotherapy or with metformin 1000 monotherapy at 24 weeks (17.9 compared with 15.1 compared with 15.9%, respectively) and at 54 weeks (26 compared with 20 compared with 20%) (low strength of evidence).
- Weight loss for subjects treated with sitagliptin plus metformin (−0.7 to −1.7 kg) was similar to that for subjects treated with metformin monotherapy (−1.0 to −1.5 kg) (low strength of evidence).
- The combination of sitagliptin plus metformin resulted in slightly greater improvements in total cholesterol (at 24 weeks: −3.2 to −7.1; at 54 weeks: −6.6 to −8.8 mg/dL) compared with metformin or sitagliptin monotherapy (at 24 weeks: −1.5 to +2.7; at 54 weeks: −0.2 to +0.5 mg/dL) (low strength of evidence).

Detailed assessment for FDCPs and Dual Therapy: Harms

We identified studies that have been conducted specifically using fixed-dose combination tablets comprised of rosiglitazone/metformin (Avandamet®),[183, 185], rosiglitazone/glimepiride (Avandaryl®),[186] and pioglitazone/metformin (Actoplus Met®).[139] Two of these were new since the 2007 Drug Effectiveness Review Project report on FDCPs.[139, 183] We found no head-to-head studies comparing FDCPs.

We also included studies using dual therapy of rosiglitazone plus metformin,[184] rosiglitazone plus glimepiride,[187] pioglitazone plus metformin,[188] and sitagliptin plus metformin.[31, 32] All of these were new for this report.

No studies were identified that used the fixed-dose combination tablets comprised of pioglitazone/glimepiride (Duetact®) [189] or sitagliptin/metformin (Janumet®).[190] The safety of Duetact® and Janumet® have been established based on trials using the co-administration of their separate components.

More detailed descriptions and summary tables for the studies in this section are provided in the corresponding section of Key Question 1 (Detailed assessment for FDCPs and Dual Therapy) related to efficacy. Details of included studies are found in Tables 37, 39, 41, and 43 and in Evidence Tables 5, 11. Throughout this section, meta-analyses were not performed due to an insufficient number of studies or heterogeneity of study populations, interventions, outcomes, and designs.

Avandamet® and dual therapy with metformin and rosiglitazone

Three randomized controlled trials including either Avandamet® or dual therapy with metformin and rosiglitazone met inclusion criteria. No comparative cohort studies, case-control studies or systematic reviews were identified reporting harms. Table 66 summarizes adverse events of Avandamet® (metformin + rosiglitazone) and rosiglitazone/metformin dual therapy in adults with type 2 diabetes.

Head-to-head trials

We found no head-to-head trials of Avandamet® or dual therapy with metformin and rosiglitazone comparing them with other FDCPs that met inclusion criteria.

Trials comparing Avandamet® or dual therapy with component monotherapy

Three fair-quality trials compared Avandamet® or dual therapy with metformin and rosiglitazone to monotherapy with metformin or rosiglitazone. Two trials compared Avandamet® with metformin monotherapy; 1 of them also compared Avandamet® with rosiglitazone monotherapy. The dual therapy trial compared concurrent use of metformin and rosiglitazone with metformin monotherapy. Study duration ranged from 24 to 32 weeks.

Mortality and withdrawals

One death occurred in the dual therapy arm of 1 trial; no other deaths during or shortly after treatment were reported. Rates of withdrawal due to adverse events ranged from 1% to 7.3% for Avandamet®/ dual therapy groups and from 2% to 9.6% in monotherapy groups. In the Avandamet®/ dual therapy groups, rates of withdrawal due to adverse events were consistently slightly numerically lower than or equal to those in the monotherapy arms.

Across trials, 1 rosiglitazone-treated patient and 2 dual therapy patients withdrew due to edema. One patient on metformin was withdrawn due to hypoglycemia. Gastrointestinal symptoms led 11 Avandamet® and 7 metformin-treated patients to withdraw from studies. One metformin and 2 dual therapy patients withdrew due to cardiovascular events; 1 dual therapy patient experienced abnormal liver function values and withdrew.

Only 1 trial reported the total rate of adverse events: 62% of patients on Avandamet® and 59% of those on metformin monotherapy. In the 2 Avandamet® trials, rates of serious adverse events were equivalent between the Avandamet® (3% to 4%) and monotherapy arms (3% to 4%). Other adverse events were mild to moderate in intensity.

Hypoglycemia

In both Avandamet® trials, subjects on Avandamet® reported slightly higher rates of hypoglycemia (7% to 12%) compared with metformin monotherapy (4% to 9%) or rosiglitazone monotherapy (8%). Most hypoglycemic symptoms were reported as mild or moderate and the

majority required no intervention or minor dietary intervention. Finger stick glucose values indicated that confirmed hypoglycemia (glucose <50 mg/dL) was rare across arms.

Cardiovascular events
Adverse cardiovascular events were somewhat rare in these trials. In 2 of the 3, patients on Avandamet® or dual therapy reported higher rates of cardiovascular events (2% and 1.3%) compared with those on metformin monotherapy (0% and 0.8%). In the third trial, 1% of patients on Avandamet® reported such events, compared with 3% in each monotherapy arm. Across trials, cardiac ischemia occurred in 5 patients on Avandamet®, 5 patients on dual therapy, 2 patients on rosiglitazone, and 5 patients on metformin.

Gastrointestinal events
In all 3 studies, gastrointestinal events were the most commonly reported across treatment groups, ranging from 28% to 51%. Rates with Avandamet® or dual therapy were the same or slightly lower than those with metformin monotherapy. More patients on Avandamet® reported nausea/vomiting (16%) and dyspepsia (10%), compared with patients on metformin (13% and 8%, respectively) or rosiglitazone (8% and 9%). Metformin was associated with the highest incidence of diarrhea (21% compared with 14% with Avandamet® and 7% with rosiglitazone).

Edema
In 2 of the 3 trials, patients on Avandamet® or dual therapy reported higher rates of edema (2% and 4.7%) compared with those on metformin monotherapy (0% and 1.3%). In the third trial, 7% of patients on rosiglitazone monotherapy reported edema, compared with 6% on Avandamet® and 3% on metformin monotherapy.

Weight change
In the 2 Avandamet® trials, patients receiving Avandamet® reported virtually no change in weight from baseline (0.0 kg to 0.01 kg). Rosiglitazone monotherapy was associated with a slight weight gain, and metformin monotherapy was associated with slight weight gain in 1 trial (1.9 kg) and weight loss (2.9 kg) in the other. In the dual therapy trial, patients on metformin lost a mean 1.78 kg and patients on dual therapy gained 1.79 kg from baseline.

Total cholesterol
Across all 3 trials, metformin monotherapy was consistently associated with a decrease in total cholesterol. Avandamet® had mixed results for total cholesterol; 1 trial reported a slight decrease while the other reported an increase.

Other adverse events
Headache was reported in 1 trial, with incidence being roughly equivalent across treatment arms. Of the patients in the dual therapy arm of that trial, 1.6% reported anemia, compared with no such reports by patients on metformin monotherapy.

Table 66. Adverse events of Avandamet® (metformin + rosiglitazone) and rosiglitazone/metformin dual therapy in adults with type 2 diabetes

	Rosenstock 2006[185]			Stewart 2006[183]		Weissman 2005[a184]	
	Avandamet	Metformin	Rosiglitazone	Avandamet	Metformin	Dual therapy	Metformin
Withdrawals due to adverse events (%)	1	2	5	5	5	28 (7.3)	37 (9.6)
Rate of severe adverse events (%)	3	3	3	4	4	NR	NR
Overall adverse events, N (%)	NR	NR	NR	NR (62)	NR (59)	NR	NR
Cardiovascular	1	3	3	4 (2)	0 (0)	5 (1.3)	3 (0.8)
Hypoglycemia Reported Confirmed[b]	 NR (12) 1 (0.6)	 NR (9) 2 (1.3)	 NR (8) 0 (0)	 17 (7) NR	 10 (4) NR	 4 (NR) NR	 4 (NR) NR
Gastro-intestinal	NR (47)	NR (51)	NR (37)	NR (33)	NR (33)	100 (27.9)	136 (38.7)
Nausea/ vomiting	25 (16)	20 (13)[c]	13 (8)[c]	NR	NR	NR	NR
Diarrhea	22 (14)[c]	32 (21)[c]	11 (7)[c]	NR (8)	NR (18)	NR	NR
Dyspepsia	15 (10)[c]	12 (8)[c]	14 (9)[c]	NR	NR	NR	NR
Headache	17 (11)[c]	18 (12)[c]	16 (10)[c]	NR	NR	NR	NR
Edema	NR (6)	NR (3)	NR (7)	6 (2)	0 (0)	18 (4.7)	5 (1.3)
Liver function test abnormalities	NR	NR	NR	NR	NR	1 (NR)	0 (0)
Weight change (kg), mean (SD)	0.0 (5.3)	−2.9 (4.4)	1.5 (5.9)	0.01 (0.3)	1.9 (0.3)	1.79 (4.15)	−1.78 (3.5)
Total cholesterol, mean change from baseline (SD)	−4.3 (NR)	18.2 (NR)	10.4 (NR)	10.42 mg/dL (NR)	−11.58 mg/dL (NR)	20.5 mg/dL (NR)	−2.2 mg/dL (NR)
Anemia	NR	NR	NR	NR	NR	6 (1.6)	0 (0)

Abbreviations: CI, confidence interval; NR, not reported; SEM, standard error of the mean.
[a] Goldstein et al, 2006 [194] analyzed a subset of this trial; that study is not included in this section in order to avoid duplication of data.
[b] Defined as finger stick glucose <50 mg/dL.
[c] Adverse event reported by >=10% of patients.

Avandaryl® and dual therapy with rosiglitazone and glimepiride

Two randomized controlled trials including either Avandaryl® or dual therapy with rosiglitazone and glimepiride met inclusion criteria. No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Head-to-head trials

We found no head-to-head trials of Avandaryl® or dual therapy with rosiglitazone and glimepiride comparing them with other FDCPs that met inclusion criteria.

Trials comparing Avandaryl® or dual therapy with rosiglitazone and glimepiride

Two fair- or good-quality trials (2 articles) compared Avandaryl® or dual therapy with rosiglitazone and glimepiride to active treatment arms. Study durations were 28[186] and 20 weeks.[187]

One good-quality trial (N=874) compared 2 dosages of Avandaryl® with glimepiride monotherapy and with rosiglitazone monotherapy.[186] One fair-quality dual therapy trial (N=40) compared concurrent use of rosiglitazone and glimepiride with rosiglitazone monotherapy.[187] Table 67 summarizes adverse effects of Avandaryl® (rosiglitazone + glimepiride) and rosiglitazone/glimepiride dual therapy in adults with type 2 diabetes.

Mortality and withdrawals

No deaths occurred in either trial. Rates of withdrawal in the Avandaryl® trial due to adverse events ranged from 1.4% (Avandaryl® 8 mg/4 mg) to 4.3% (rosiglitazone). In the 2 Avandaryl® arms, a total of 10 patients withdrew due to adverse events: 7 on the lower dose and 3 on the higher dose. Six patients on glimepiride and 10 patients on rosiglitazone withdrew due to adverse events. Roughly 50% of patients in each arm of the Avandaryl® trial reported at least 1 adverse event (excluding hypoglycemia), with the majority being mild to moderate. No serious adverse events were noted in the dual therapy trial, and the overall number of events was not reported.

Hypoglycemia

In the Avandaryl® (4 mg/4 mg) trial, over 19% of patients across arms reported a hypoglycemic episode. Of patients receiving Avandaryl®, 29% (4 mg/4 mg) and 22.5% (8 mg/4 mg) reported hypoglycemia. Similarly, 21.6% of patients on glimepiride reported such symptoms. Only 5.2% of those in the rosiglitazone monotherapy arm reported them. After finger stick glucose was tested, between 3.6% and 5.5% of patients on Avandaryl or glimepiride had confirmed hypoglycemia (blood glucose <50 mg/dL), compared with 0.4% of patients in the rosiglitazone arm.

In the small dual therapy trial, patients receiving the 2 drugs reported a total of 59 episodes of hypoglycemia; rosiglitazone monotherapy-treated patients reported only 4 episodes in total.

Cardiovascular events

Two patients in the Avandaryl® trial reported congestive heart failure: 1 in the glimepiride group and 1 in the higher-dose Avandaryl®. No cardiovascular events were reported in the dual therapy study.

Gastrointestinal events

None were reported in either trial.

Edema

Edema reports were fairly consistent across arms of the Avandaryl® trial and ranged from 2.3% (glimepiride group) to 3.2% (higher-dose Avandaryl). No episodes of edema were reported in the dual therapy study.

Weight change
Patients in all arms of the Avandaryl® trial gained weight. Glimepiride-treated patients gained a mean 1.1 kg; patients on rosiglitazone gained 1.0 kg. There appeared to be a dose-repose association between the 2 Avandaryl® arms: patients on lower-dose Avandaryl® gained 2.0 kg, and those on the higher dose gained 3.4 kg. 1 lower-dose Avandaryl® patient withdrew due to weight gain. In the dual therapy v rosiglitazone trial, all patients gained weight: 5.1 kg and 2.4 kg, respectively, with the difference between arms being statistically insignificant.

Total cholesterol
In the Avandaryl trial, mean total cholesterol increase was significant in the rosiglitazone and Avandaryl arms. The largest increase was in the rosiglitazone arm (21.8 mg/dL); more modest but still significant increases were found in the lower- and higher-dose Avandaryl® arms (8.7 mg/dL and 14.4 mg/dL, respectively). There was no significant difference in cholesterol levels between dual therapy and rosiglitazone.

Other adverse events
Headache and nasopharyngitis were reported in roughly 4% of patients in each arm of the Avandaryl® trial. 1.8% of patients in the higher-dose Avandaryl® arm and 2.2% in the rosiglitazone arm experienced anemia, compared with <1% in the glimepiride and lower-dose Avandaryl® arms.

Table 67. Adverse effects of Avandaryl® (rosiglitazone + glimepiride) and rosiglitazone/glimepiride dual therapy in adults with type 2 diabetes

	Chou 2008[186]				McCluskey 2004[187]	
	Avandaryl 4 mg/4 mg	Avandaryl 8 mg/4 mg	Glimepiride	Rosiglitazone	Dual therapy	Rosiglitazone
Withdrawals due to adverse events (%)	3.1	1.4	2.6	4.3	0	0
Cardiovascular	NR (0.4)	NR (0.5)	NR (1.3)	NR (0.9)		
Hypoglycemia Reported Confirmed[b]	 221 (29) 13 (3.6)	 159 (22.5) 18 (5.5)	 128 (21.6) 11 (4.1)	 18 (5.2) 1 (0.4)	 59[a] (NR) NR	 4[a] (NR) NR
Edema		NR (3.2)	NR (2.3)			
Weight change (kg), mean (SD)	2.0 (NR)	3.4 (NR)	1.1 (NR)	1.0 (NR)	5.1 (NR)	2.4 (NR)
Total cholesterol, mean change from baseline	8.7 mg/dL	14.4 mg/dL	−1.1 mg/dL	21.8 mg/dL	−3.3 mg/dL (3.1)	1.4 mg/dL (4.3)
Anemia	NR (0.9)	NR (1.8)	0 (0)	NR (2.2)		

Abbreviations: CI, confidence interval; NR, not reported; SD, standard deviation; SEM, standard error of the mean.
[a] Numbers represent episodes of hypoglycemia, rather than subjects.
[b] Defined by report of hypoglycemic symptoms with finger stick glucose <50 mg/dL.

Actoplus Met® and dual therapy with pioglitazone and metformin

We found one active-control trials of Actoplus Met® compared with monotherapies of its components that met inclusion criteria. This 24-week RCT (N=600) compared Actoplus Met® (30 mg/1,700 mg daily) with pioglitazone alone (30 mg daily) and metformin alone (1,700 mg daily).[139] Overall incidences of adverse events were similar across treatment arms: 50.7%, 52.1% and 53.1% for the Actoplus Met®, pioglitazone monotherapy, and metformin monotherapy arms, respectively. Reports of severe adverse events were also similarly distributed among the arms: 1.0% for Actoplus Met®, 1.6% for pioglitazone monotherapy, and 1.4% for metformin monotherapy.

A 15 month trial (N=271) compared dual therapy with pioglitazone and metformin to monotherapy with each component (3 month run-in/titration phase, 12 month full-dose treatment and follow-up phase). Very little harms information was reported in this trial.[188] Table 68 summarizes adverse effects of Avandaryl® (rosiglitazone + glimepiride) and rosiglitazone/glimepiride dual therapy in adults with type 2 diabetes.

Mortality and withdrawals

Fewer withdrawals from the FDCP study due to adverse events occurred in the Actoplus Met® and pioglitazone alone arms compared with the metformin alone arm (3.0%, 3.2%, and 4.8%, respectively). There were no deaths during the FDCP trial.

Hypoglycemia

In the FDCP trial, rates of hypoglycemia (defined as fasting plasma glucose <60 mg/dL) were low in all treatment arms: 1.0%, 0.5%, and 1.4% in the Actoplus Met®, pioglitazone alone, and metformin alone arms, respectively. In the dual therapy study, 3 patients in the dual therapy arm withdrew due to hypoglycemia (defined as above).

Cardiovascular events

There were no episodes of congestive heart failure during the FDCP trial. Three patients in the monotherapy arms (2 on pioglitazone and 1 on metformin) showed clinically significant worsening ECG results from baseline to end of follow-up. One pioglitazone patient was found to have coronary artery disease and myocardial infarction; the other was diagnosed with arterial branch block. The metformin patient was determined to have myocardial ischemia.

Gastrointestinal events

Diarrhea and gastrointestinal events were reported less frequently in patients taking Actoplus Met® (9.0% and 17.9%, respectively) compared with patients on metformin alone (15.3% and 25.8%, respectively) but more often than in patients on pioglitazone alone (2.6% and 105%,m respectively). In the dual therapy trial, 5 patients in the metformin arm withdrew due to gastrointestinal events.

Edema

Incidence of peripheral edema in the FDCP trial was highest for pioglitazone alone (4.2%), lowest for metformin alone (1.4%) and in between for patients on Actoplus Met® (3.0%).

Weight change
In the FDCP trial, patients on Actoplus Met® reported less weight gain (0.69 kg)from baseline than patients on pioglitazone alone (1.64 kg) but greater weight gain than patients on metformin alone (-1.28 kg). In the dual therapy study, 3 pioglitazone monotherapy patients withdrew from the study due to excessive weight gain. While weight change itself was not reported for this trial, dual therapy and metformin were associated with significant decreases in body mass index, compared to an increase in the pioglitazone group.

Total cholesterol
Neither the FDCP trial nor the dual therapy trial reported outcomes related to cholesterol.

Other adverse events
In the FDCP trial, headache was reported more frequently with than Actoplus Met® (5.5%) than with pioglitazone (2.6%) or metformin (4.8%) monotherapy. In the same trial, bone fractures occurred in 1 metformin monotherapy patient (traffic accident) and 1 patient on Actoplus Met® (unspecified cause).

Table 68. Adverse events of Actoplus Met® or pioglitazone plus metformin dual therapy in adults with type 2 diabetes

	Perez 2009[139]			Derosa 2009[a 188]		
	Actoplus Met®	**Pio**	**Met**	**Pio + Met**	**Pio**	**Met**
Overall incidence of AEs (%)	50.7	52.1	53.1	NR	NR	NR
Incidence of serious AEs (%)	1.0	1.6	1.4	NR	NR	NR
Withdrawals due to AE (%)	3.0	3.2	4.8	3.1	1.6	3.2
Gastrointestinal events (%)	17.9	10.5	25.8	NR	NR	NR
Hypoglycemia (%)	1.0	0.5	1.4	NR	NR	NR
Weight gain (kg)	0.69	1.64	-1.28	-0.3 [b]	0.4 [b]	-0.3 [b]
Headache (%)	5.5	2.6	4.8	NR	NR	NR
Diarrhea (%)	9.0	2.6	15.3	NR	NR	NR
Pharyngitis (%)	4.0	2.6	3.3	NR	NR	NR
Urinary tract infection (%)	3.0	2.6	4.3	NR	NR	NR
Back pain (%)	2.0	4.2	2.9	NR	NR	NR
Peripheral edema (%)	3.0	4.2	1.4	NR	NR	NR
Nasopharyngitis (%)	4.0	1.6	2.4	NR	NR	NR
Bronchitis (%)	2.5	3.7	1.4	NR	NR	NR
Abdominal pain (%)	2.0	1.6	3.3	NR	NR	NR
Dizziness (%)	3.0	1.6	1.9	NR	NR	NR
Insomnia (%)	3.0	1.1	1.0	NR	NR	NR
Fracture (%)	0.5	0.0	0.5	NR	NR	NR
Cardiac events (%)	0.0	1.1	0.5	NR	NR	NR

Abbreviations: AE, adverse event; CI, confidence interval; Met, metformin; NR, not reported; Pio, pioglitazone; SD, standard deviation.

[a] Data reported are from the full-dose 12 month treatment and follow-up period.
[b] Reported as change in BMI (kg/m^2) (SD) from baseline

Janumet® and dual therapy with sitagliptin and metformin

No studies including Janumet® were found that met inclusion criteria. One randomized controlled trial including dual therapy with sitagliptin and metformin met inclusion criteria. This trial resulted in 3 publications; one reporting results after 24 weeks[31] (N=1,091), one reporting results after 54 weeks,[32] and the other after a total of 104 weeks[33] No comparative cohort studies, case-control studies or systematic reviews were identified reporting long-term benefits.

Table 69 summarizes adverse events of metformin/sitagliptin dual therapy in adults with type 2 diabetes. Incidences of adverse events were generally similar between treatment arms over the 104-week study period. One patient in the higher-dose dual therapy group died of an electrical shock during the continuation phase, and 1 patient withdrew from the lower-dose metformin monotherapy arm due to esophageal carcinoma and died during the study period. Withdrawals due to adverse events were low (1.1% to 2.8% during the first 24 weeks and 2% to 4% during the entire study period) and were similar across treatment arms. There was slightly more variation in the incidence of severe adverse events between groups. At 24 weeks, fewer patients in the higher-dose dual therapy arm reported serious events (0.5%) than patients receiving sitagliptin monotherapy (5.0%), lower-dose metformin monotherapy (2.2%), higher-dose metformin monotherapy (1.1%) and lower-dose dual therapy (3.2%). After 104 weeks, sitagliptin monotherapy was associated with the highest rate of serious adverse events (7.3%), and lower-dose metformin monotherapy with the lowest rate (3.8%). Incidence of severe events in both dual therapy arms was 6% and 6.3% at the end of the study.(Table 69)

After 104 weeks, fewer sitagliptin monotherapy patients reported adverse events (60.3%), compared with the other treatment arms, including a high of 75.3% in the higher-dose sitagliptin-metformin combination arm. Seventy-one percent of patient in the lower-dose combination arm reported adverse effects.

Hypoglycemic events were rare across treatment groups at 24, 54 and 104 weeks and were of mild or moderate severity. At both points of measurement, more higher-dose dual therapy patients reported hypoglycemia (2.2%, 3%, and 4.9% at 24, 54 and 104 weeks, respectively). After 104 weeks, rates of hypoglycemia across the 3 monotherapy arms ranged from 1.1 to 2.2% with the lowest reported in the sitagliptin monotherapy arm

Gastrointestinal events were reported with similar frequency across treatment arms, with the higher-dose metformin monotherapy patients reporting the highest rates at both measurement points (25.3% at 24 weeks, 31% at 54 weeks, and 33% at 104 weeks). Patients in either dual therapy arm reported adverse gastrointestinal events more frequently than patients on sitagliptin monotherapy or lower-dose metformin. Nausea / vomiting and abdominal pain were reported most frequently in the higher-dose metformin monotherapy group, and diarrhea was reported most frequently by higher-dose dual therapy patients.

After 104 weeks, there was no change in weight from baseline for the sitagliptin monotherapy patients. Body weight decreased by small but statistically significant amounts in the other arms, ranging from 0.7 kg in the lower-dose dual therapy group to 1.7 kg in the higher-dose dual therapy arm.

The only arm in which total cholesterol changed significantly from baseline was higher-dose dual therapy; total cholesterol decreased by 3.0 mg/dL on average.

Table 69. Adverse events of metformin/sitagliptin dual therapy in adults with type 2 diabetes

	Goldstein 2007[31]					Williams-Herman, 2009[32a]					Williams-Herman, 2010[33a]				
	Sita 100	**Met 1,000**	**Met 2,000**	**Sita 100 + Met 1,000**	**Sita 100 + Met 2,000**	**Sita 100**	**Met 1,000**	**Met 2,000**	**Sita 100 + Met 1,000**	**Sita 100 + Met 2,000**	**Sita 100**	**Met 1,000**	**Met 2,000**	**Sita 100 + Met 1,000**	**Sita 100 + Met 2,000**
Withdrawals due to adverse events (%)	2.8	2.2	2.7	2.6	1.1	3	3	4	3	2					
Rate of severe adverse events (%)	5.0	2.2	1.1	3.2	0.5	7	3	2	4	4					
Overall adverse events, N (%)[b]	96 (53.6)	101 (55.5)	113 (62.1)	110 (57.9)	105 (57.7)	105 (59)	114 (63)	129 (71)	130 (68)	126 (69)					
Hypo-glycemia[c]	1 (0.6)	1 (0.5)	2 (1.1)	2 (1.1)	4 (2.2)	2 (1)	2 (1)	2 (1)	4 (2)	5 (3)	2 (1.1)	3 (1.6)	4 (2.2)	5 (2.6)	9 (4.9)
Gastro-intestinal	27 (15.1)	29 (15.9)	46 (25.3)	34 (17.9)	45 (24.7)	36 (20)	37 (20)	57 (31)	50 (26)	53 (29)	37 (20.7)	38 (20.9)	60 (33)	56 (29.5)	60 (33)
Nausea/ vomiting	2 (1.1)	5 (2.7)	17 (9.3)	10 (5.3)	16 (8.8)	3 (2)	6 (3)	24 (13)	14 (7)	18 (10)	3	6	26	14	21
Diarrhea	5 (2.8)	9 (4.9)	19 (10.4)	12 (6.3)	16 (8.8)	7 (4)	13 (7)	22 (12)	17 (9)	23 (13)	8 (4.5)	14 (7.7)	23 (12.6)	19 (10.0)	25 (13.7)
Abdominal pain	6 (3.4)	5 (2.7)	15 (8.2)	8 (4.2)	10 (5.5)	8 (5)	7 (4)	10 (6)	5 (3)	7 (4)	9 (5.0)	7 (3.8)	12 (6.6)	7 (3.7)	9 (4.9)
Weight change (kg), mean (SD)						0 kg	−1.0 kg	−1.5 kg	−0.7 kg	−1.7 kg	+0.5 kg	−0.8 kg	-.24 kg	0 kg	−1.2 kg
Total cholesterol, mean change from baseline	2.7 mg/dL	−1.5 mg/dL	0.6 mg/dL	−3.2 mg/dL	−7.1 mg/dL	0.5 mg/dL	0 mg/dL	−0.2 mg/dL	−6.6 mg/dL	−8.8 mg/dL	+1.4	−6.1	−0.6	−6.8	−4.7

Abbreviations: Met, metformin; Sita, sitagliptin 100 mg.

[a] Williams-Herman et al, 2009 is a 30-week extension of Goldstein et al, 2007. Williams-Herman et al, 2010 is an extension of Goldstein et al, 2007.

[b] N (%) with 1 or more adverse events.

[c] Assessed and classified by study investigators based on patient-reported symptoms and finger stick glucose values.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications differ in efficacy/effectiveness or frequency of adverse events?

I. Newer Drugs for the Treatment of Diabetes Mellitus: Amylin Agonists, DPP-4 Inhibitors, and GLP-1 agonists

Summary of Findings for Newer Drugs

- We found insufficient evidence to draw any firm conclusions about whether there are subgroups of patients based on demographics, comorbidities, or other medications for which newer diabetes medications differ in efficacy/effectiveness or frequency of adverse events.
- The evidence that was found is generally hypothesis-generating, using post hoc pooled analyses or post hoc subgroup analyses in an exploratory manner.

Detailed Assessment for Newer Drugs

Pramlintide for type 1 diabetes

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, or baseline HbA1c in individual studies.

One randomized controlled trial conducted subgroup analyses that were not all prespecified, and 1 post hoc pooled-analyses was identified.[21, 304] Results from these hypothesis-generating analyses should be used with caution. Further prospective research with larger sample sizes will need to be conducted to verify these findings.

Baseline body mass index

Pramlintide appeared to inhibit weight gain in patients with baseline body mass index ≤ 23 kg/m^2 while producing mild weight loss for patients with body mass index > 23 kg/m^2 (baseline to week 26).[21] Data at 52-week follow-up were not reported.

Baseline HbA1c < 8%

Data from 3 studies that included patients with baseline HbA1c between 7% and 8.5% receiving pramlintide 30 mcg or 60 mcg were pooled and reported in a separate publication.[304] Two of the 3 studies were identified and included in our review.[19, 21] The third study was in abstract form and was excluded. The pooled publication reported results up to 26 weeks. In this subgroup, the pooled change in HbA1c was −0.3% and the change in weight was −1.6 kg (both placebo-corrected; both P<0.0009). There was no overall increased risk in hypoglycemia. The improvement in HbA1c in this pooled subgroup analysis was similar to the change in HbA1c noted for all subjects (across a range of HbA1c) in the original studies. Thus, it appears that patients with good but not optimal baseline HbA1c of 7% to 8.5% experienced similar degrees of HbA1c reduction as the populations included in the original trials, with no increased risk of hypoglycemia at 26 weeks.

Age, sex, total daily insulin dose, and prior use of oral hypoglycemic agents

None of the randomized controlled trials conducted subgroup analyses evaluating whether pramlintide had differential effects in these populations.

Race and ethnicity

A post hoc analysis[305] of two 52-week trials[25, 26] pooled subjects of various ethnic groups. Black and Hispanic patients tended to have higher baseline HbA1c (9.2% to 9.7%) than white patients (8.9% to 9.1%). Pramlintide produced larger reductions in HbA1c and weight from baseline in black patients (0.7%, 4.1 kg) than white patients (0.5%, 2.4 kg) and Hispanic patients (0.3%, 2.3 kg). Changes in total daily insulin requirement and baseline oral hyperglycemic use were not different among the different races and ethnicities.

Nausea and weight loss and effects of weight on HbA1c

Weight loss experienced with pramlintide 90 or 120 mcg appeared to be independent of nausea, as weight loss was similar in patients never experiencing nausea (90 or 150 mcg, −1.1 to −1.5 kg) and patients experiencing nausea at any time (90 or 150 mcg, −0.3 to −2.0 kg).[25] In addition, improvements in HbA1c observed with pramlintide appeared to be independent of weight lost or gained during the trial (subjects who gained weight, change in HbA1c −0.29% to −0.53%; subjects who lost weight, change in HbA1c −0.22% to −0.58%).

A pooled analysis[306] of overweight and obese patients also evaluated whether weight loss associated with pramlintide 120 mcg was influenced by nausea. Like the other, this post hoc subgroup analysis suggested that weight loss was independent of nausea (change in weight in group reporting "never nausea," −1.3 kg; "nausea at any time," −1.9 kg). None of the studies explored to see if there were any correlations between anorexia and weight loss.

Overweight and obese patients

A post hoc analysis[306] pooled data from 2 randomized controlled trials comparing pramlintide 120 mcg with placebo when both were added to insulin. At 26-week follow-up overweight and obese (body mass index > 25 kg/m^2) patients receiving pramlintide showed greater reductions in HbA1c and weight than similar patients receiving placebo. Approximately 2% of overweight and obese patients on pramlintide plus insulin achieved weight loss of ≥10% change from baseline compared with 0% in those on placebo plus insulin. Markedly obese patients (baseline body mass index 35-40 kg/m^2 and >40 kg/m^2) had the greatest weight loss (−2.4 kg and −3.2 kg, respectively).

Baseline HbA1c

When patients were stratified by baseline HbA1c,[24] at 16 weeks patients with baseline HbA1c > 8.5% who received pramlintide plus insulin glargine showed larger improvements in HbA1c, fasting plasma glucose, and postprandial glucose than patients receiving placebo plus glargine (pramlintide change in HbA1c −1.19%, fasting plasma glucose −44.4 mg/dL, postprandial glucose −23 mg/dL, and weight −1.0 kg compared with placebo plus glargine HbA1c −0.69%, fasting plasma glucose −18.4 mg/dL, postprandial glucose +3.2 mg/dL, weight +1.1 kg). Among subjects with lower baseline HbA1c (≤ 8.5%), improvements in HbA1c (−0.36%) and weight (−2.0 kg) were also larger in pramlintide-treated patients than those who took placebo plus glargine. Overall, reductions in HbA1c were greatest in those with baseline HbA1c >8.5%.

Another post hoc analysis[307] pooled data from 2 trials at 26-week follow-up and examined patients with baseline HbA1c of 7.0% to 8.5%. Pramlintide plus insulin was better than placebo plus insulin for HbA1c (placebo-corrected change in HbA1c −0.43, $P<0.0009$) and weight (placebo-corrected change in weight −2.0 kg, $P<0.0003$).

Sitagliptin

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, baseline HbA1c, or other characteristics at the study level. Subgroup data not available in publications were supplemented by data provided by the manufacturer. The results from this section should be considered with caution until larger prospective trials evaluating these populations verify the findings.

Age, sex, race, body mass index, and prior use of oral hypoglycemic agents

Four published trials[36, 43, 44, 46, 50, 51] reported no significant differences in changes in HbA1c based on subgroups defined by age, sex, race, and body mass index. Data on file from 3 additional trials [42, 48, 49, 308] also showed similar findings.

Data on file from 2 trials [45, 47, 308] showed a significant interaction between treatment effect and race for those on sitagliptin monotherapy and placebo. In one study,[47] Hispanic patients experienced the largest decline in HbA1c (placebo-corrected difference in HbA1c from baseline: −1.04%, 95% CI −1.38 to −0.70) followed by White patients (placebo-corrected difference: in HbA1c from baseline: −0.69%, 95% CI −0.84 to 0.55), and Other patients (placebo-corrected difference in HbA1c from baseline: −0.44%, 95% CI, −0.82 to −0.07). In another study,[45] the greatest HbA1c reduction was seen in Indian (placebo corrected change -1.4%, 95%CI -1.7 to -1.0) and Korean patients (placebo corrected change -1.4%, 95% CI -1.9 to -0.8).

Of 7 studies [30, 31, 44-47, 49, 308] that stratified groups by prior oral hypoglycemic agent use, only 1 trial [31, 308] showed a large numerical difference in treatment effect. Patients who were not taking an oral hypoglycemic agent prior to this trial experienced greater decline in HbA1c across all treatment arms compared with patients who were using oral agents before enrolling into the study. For instance, the change in HbA1c from baseline for "no prior oral agent use" for sitagliptin compared with placebo was −1.11% compared with −0.13% compared with −0.26% compared with +0.52% for those "treated with prior oral agents." Between-group difference calculations were not conducted.

Baseline HbA1c

Subgroup information stratified by baseline HbA1c was found in 14 trials. Some data were available from published studies[31, 34, 36, 38, 42-46, 48-51] and additional information from 6 trials (Scott 2007, Charbonnel 2006, Nauck, 2006, Scott 2008, Vilsboll 2010, and Aschner 2010) were obtained from data on file.[38, 45, 51, 308]

Four trials [43, 44, 47, 49, 51] found no significant differences in the change in baseline HbA1c among those in the following subgroups: <7.5%, <8%, 8-8.9%, >7.5%, ≥8.5%, and ≥9%. One trial[42] showed significant interaction ($P<0.001$) in the change in HbA1c stratified by baseline HbA1c <8% and ≥9%. In patients with baseline HbA1c ≥9%, placebo-corrected reductions of −1.52% were observed for sitagliptin 100 mg/d compared with about −0.6% decrease in those with baseline HbA1c <8%. Data from Goldstein, et al.[308] also showed consistent findings for sitagliptin 100 mg/d compared with placebo. For this study, interaction analyses were not

conducted (change in HbA1c from baseline for those with HbA1c <8%: sitagliptin, −0.37% compared with placebo, +0.15% compared with those with HbA1c ≥9%: sitagliptin, −0.88% compared with placebo, +0.08%). In another trial, greater reduction was seen with sitagliptin 50mg twice daily (placebo corrected change -1.15%, 95% CI -2.27 to -0.03) and sitagliptin 100mg daily (placebo corrected change -1.18%, 95% CI -2.26 to -0.09 for patients with HbA1c >9% at baseline. Similarly, in patients with HbA1c ≥10% there HbA1c reduction than in the entire cohort with average HbA1c of 8.7%(-1.4% as compared to -1.0%).[45] Compared to metformin, the greatest HbA1c reduction was see in patients with baseline HbA1c ≥8%, however there was no difference between sitagliptin and metformin (0.12%, 95% CI -0.07 to 0.3).[38]

Duration of diabetes

Two trials [43, 51] reported a potential interaction between median baseline duration of diabetes and HbA1c effects in patients randomized to sitagliptin 100 mg compared with placebo. One trial [43] reported patients with diabetes of ≤ 3 years' duration had significantly greater reductions in HbA1c than patients who had diabetes for > 3 years (placebo-corrected mean change HbA1c for ≤ 3years −0.90%, 95% CI −1.21 to −0.60 compared with mean change HbA1c for > 3years −0.28%, 95% CI −0.59 to +0.20). Another trial [51] reported greater HbA1c reduction for patients having diabetes for >12 years as compared to <12 years (-0.64% compared to -0.5%).

Saxagliptin

Age, sex, race, body mass index, and prior use of oral hypoglycemic agents

One published study reported consistent HbA1c reduction across subgroups defined by age, sex, race, and body mass index.[55]

Baseline HbA1c

Three published studies reported results stratified by baseline HbA1c.[54-56] All three studies reported statistically significant interaction for treatment effect with higher baseline HbA1c. Two studies did not report the HbA1c cut off that was statistically significant,[55, 56] however one study reported the HbA1c reduction for saxagliptin groups for baseline HbA1c ≥9% ranged from -0.84 to -1.25% compared to +0.13% for placebo (P<0.05).[54]

Duration of diabetes

One published study reported HbA1c lowering effects to be consistent across a subgroup of patients defined by duration of diabetes, however the duration was not specified.[55]

Exenatide

Two publications examined subgroups based on demographic characteristics. A pooled analysis[78] of 3 placebo-controlled trials reported that reductions in HbA1c were not related to age and that hypoglycemia was not more frequent in subjects ≥ 65 years of age. No primary study examined the efficacy or effectiveness of exenatide in subgroups defined by age or other characteristics.

Another study aiming to evaluate the efficacy and safety of sitagliptin as an add-on to metformin therapy (compared with adding placebo to metformin) in patients with moderately severe (HbA1c ≥ 8.0% and ≤ 11.0%) type 2 diabetes mellitus (T2DM) randomized 190 subjects for 30 weeks of treatment.[50] Post hoc subgroup analyses were conducted for change in HbA1c for the following groups: differences by age (≤55 compared with >55), body mass index (≤30.1

compared with >30.1), sex, duration of diabetes, (≤6 years compared with >6), and previous metformin or metformin-based combination therapy. The study found that treatment effects were consistent across subgroups.

Liraglutide

We found no studies of liraglutide meeting inclusion criteria that examined differences in efficacy/effectiveness or adverse events for subgroups.

II. Thiazolidinediones (TZDs)

Summary of Findings for Thiazolidinediones (TZDs)

- We found insufficient evidence to draw any firm conclusions about whether there are subgroups of patients based on most demographic characteristics, comorbidities, or other medications for which newer diabetes medications differ in efficacy/effectiveness or frequency of adverse events.
- The evidence that was found is generally hypothesis-generating, using post hoc pooled analyses or post hoc subgroup analyses in an exploratory manner.
- Some studies reported that the risk of fractures is increased with TZD use in women, but not in men.[204, 309] On analysis of data from ADOPT found hazard ratios comparing rosiglitazone with metformin and glyburide were 1.81 (95% CI 1.17 to 2.80) and 2.13 (1.30 to 3.51), respectively.[309] A systematic review and meta-analysis reported an increased risk among women (OR 2.23, 95% CI 1.65 to 3.10), but not in men (OR 1.00, 95% CI 0.73, 1.39).[204]

Detailed Assessment for Thiazolidinediones (TZDs)

Studies examining subgroups based on demographic characteristics or comorbidities are summarized in Table 70. Most studies were conducted in the United States or in Western Europe and examined white populations. Some studies included minority populations but did not present subgroup analyses on these populations.[310] Thus, there are very limited data on the comparative effectiveness of pioglitazone and rosiglitazone among persons with various demographic characteristics and no conclusions can be drawn as to which drug is more efficacious or effective, or associated with fewer side effects in population subgroups.

Most of the studies identified in this review examined persons with type 2 diabetes without significant comorbidities such as coronary heart disease, heart failure, or renal insufficiency. Thus there is a paucity of data on the interaction of TZDs and micro- and macrovascular diseases that are highly prevalent among persons with diabetes, and no conclusions can be drawn on the comparative effectiveness of the 2 drugs under review among populations with significant comorbidities.

Subgroups based on demographic characteristics

Kreider and colleagues[311] pooled the results of 8 randomized controlled trials examining monotherapy with rosiglitazone and examined subgroups of age less than and greater than 70 years. They found no differences between the 2 age groups for HbA1c and found rosiglitazone

well tolerated in both age groups. The percentage of persons with at least 1 adverse event was comparable between the rosiglitazone and placebo groups, and between persons older and younger than 70 years. The incidence of anemia was higher in older patients taking rosiglitazone than in younger patients taking the drug and treatment patients had higher rates of anemia than patients in the placebo group. Weight gain was higher in the under-seventy group (2.14 kg) than the over-seventy group (1.66 kg) and the placebo groups (<70 years, −0.41 kg; >70 years, −1.34 kg).

Several studies examined racial or ethnic minorities. King compared Mexican Americans with non-Hispanic persons in a retrospective cohort study and found that HbA1c and weight changed to a similar degree in both populations. Jun and colleagues[312] examined 100% Hispanics, and pioglitazone produced a decrease in HbA1c of 2.0% at 6 months. Twelve Chinese persons with nephropathy and type 2 diabetes were exposed to rosiglitazone over 15.5 months with improved HbA1c, a nonsignificant increase in weight, and no adverse events.[313] Pioglitazone was as effective as glimepiride among 244 Mexican patients.[314]

Barnett and colleages[235] examined the use of rosiglitazone in an Indian and Pakistani population in the United Kingdom and noted results and adverse events comparable to other placebo-controlled trials discussed above. Vongthavaravat et al.[315] examined a mixed Asian and white population and their results were also consistent with findings in largely white populations in other studies of rosiglitazone.

In the updated Drug Effectiveness Review Project TZDs report (2008), several additional studies of rosiglitazone provided data on subgroups based on demographic data.[143, 147, 170, 176] In a combination therapy, double-blind study (N=365) both groups received combination tablets of glyburide/metformin. The addition of rosiglitazone achieved greater reduction in HbA1c than the addition of placebo (between-group difference −1.0%, $P<0.001$). An improvement in HbA1c was demonstrated across age, sex, and racial subgroups.[170]

In a study of older adults with type 2 diabetes,[176] HbA1c improved with rosiglitazone plus glipizide 10 mg twice a day compared with glipizide alone at 2-year follow-up (between-group change in HbA1c −0.79%, $P<0.0001$).

In a double-blind study (N=318) in subjects who had failed to achieve adequate control on metformin,[143] metformin 1000 mg/glibenclamide 5 mg was compared with metformin 1500−2000 mg plus rosiglitazone 4 mg daily. Reduction in HbA1c was greater in the glibenclamide group at 24 weeks follow-up as noted above. This larger decrease in HbA1c occurred in the glibenclamide group across strata defined by sex, race, age, baseline HbA1c, or entry metformin dose.

In ADOPT,[147] rosiglitazone was more effective than glyburide in all subgroups for the primary outcome of monotherapy failure: age ≤ 50 years, between 50 and 59 years, and ≥ 60 years; males and females; body mass index ≤ 30 kg/m^2, between 30 and 35 kg/m^2, and ≥ 35 kg/m^2; baseline fasting plasma glucose ≤ 140 mg/dL and > 140 mg/dL; and waist circumference ≤ 99 cm, >99 – 110 cm, and > 110 cm.

An analysis using data from 1,840 women and 2,511 men randomly assigned in ADOPT to rosiglitazone, metformin, or glyburide examined time to first fracture, rates of occurrence, and sites of fractures.[309] In men, fracture rates did not differ between treatment groups. In women, the study identified an increased risk of fractures with rosiglitazone. The cumulative incidence of fractures at 5 years was 15.1% (95% CI 11.2 to 19.1) with rosiglitazone, 7.3% (4.4 to 10.1) with metformin, and 7.7% (3.7 to 11.7) with glyburide. Thus, in women, the hazard ratios comparing

rosiglitazone with metformin and glyburide were 1.81 (1.17 to 2.80) and 2.13 (1.30 to 3.51), respectively.

A systematic review and meta-analysis of 10 randomized controlled trials and 2 observational studies found similar results, concluding that long-term TZD use doubles the risk of fractures among women with type 2 diabetes, without significant increase in risk of fractures among men with type 2 diabetes.[204] The risk of fractures overall in the 10 randomized controlled trials was increased with TZDs (odds ratio 1.45, 95% CI 1.18 to 1.79). Five randomized controlled trials showed an increased risk among women (odds ratio 2.23, 95% CI 1.65 to 3.10), but not in men (odds ratio 1.00, 95% CI 0.73, 1.39).

Comorbidities and other population characteristics

Patients with impaired renal function were examined in several studies. Agrawal and colleagues[233] examined patients with renal impairment (creatinine clearance 30-80 mL/min) and found that rosiglitazone had similar effects on HbA1c in patients with and without renal impairment. In a retrospective chart review[316] of patients on dialysis with end stage renal disease, rosiglitazone was associated with weight gain and a decrease in hematocrit at 3-month follow-up compared with pioglitazone. Data for pioglitazone, however, were not presented, limiting conclusions that can be drawn.

In a fair-quality study pooling 2 randomized controlled trials that compared rosiglitazone plus metformin combined therapy with metformin monotherapy, Jones and colleagues[317] examined subgroups with body mass index < 25 kg/m^2, 25-30 kg/m^2, and >30 kg/m^2. They noted greater improvement in HbA1c with rosiglitazone 4 or 8 mg daily plus metformin than with metformin monotherapy (P=0.025). Safety profiles were similar in all 3 subgroups. Weight gain was noted in the obese group (body mass index > 30 kg/m^2) receiving metformin plus rosiglitazone (2.5 kg), while weight loss of 0.9 kg was found in obese patients on metformin alone. Weight change was not reported for the other body mass index subgroups.

Patients with diagnosed coronary artery disease were examined in 3 studies which were described above in Key Question 2, as these were the only studies that reported cardiovascular outcomes. Wang and colleagues[168] examined 70 Chinese with coronary artery disease and type 2 diabetes and noted significant improvement in HbA1c with rosiglitazone with change in weight similar to the no-treatment control group. The primary and composite endpoint of coronary events (including death) was significantly decreased in the rosiglitazone group (P value reported as both <0.05 and <0.01). Wang and colleagues[230] also examined Chinese persons with metabolic syndrome and found that fasting plasma glucose did not improve significantly in either the rosiglitazone or the placebo group (HbA1c was not presented).

In a poor-quality study, Choi and colleagues[178] compared treatment with rosiglitazone plus conventional antidiabetic therapy among patients undergoing coronary catheterization to conventional treatment. At 6-month follow-up there were no significant differences in glycemic control or lipid concentrations between the 2 groups. The rate of restenosis and the stenosis diameter were less in the rosiglitazone group (between-group P=0.03).

Thirty-one postmenopausal women were examined in a poor-quality, placebo-controlled trial of rosiglitazone 4 mg daily.[166] Results were similar to other placebo-controlled trials and no adverse events were reported.

No studies explicitly examined populations with a history of hypoglycemic episodes. Nor were studies identified that examined the effect of concomitant medications on the comparative effectiveness of pioglitazone and rosiglitazone. Most studies permitted the use of a variety of

antihypertensive, cardiac, and cholesterol-lowering medications among participants. Subgroup or other stratified analyses were not performed to allow examination of drug-drug interactions with the thiazolidinediones.

In the updated Drug Effectiveness Review Project TZDs report, new data on the use of thiazolidinediones in persons with comorbidities was identified, particularly with cardiovascular disease. Since the publication of the large PROACTIVE study[177] (discussed above) which compared pioglitazone with placebo, several additional subgroup analyses have been published, including of subjects with prior myocardial infarction[318] or stroke.[319] In the subgroup of patients with a previous myocardial infarction at baseline[318] (N=2445) pioglitazone had a significant beneficial effect on fatal and nonfatal myocardial infarction (28% risk reduction, *P*=0.045) and acute coronary syndrome (37% risk reduction, *P*=0.035). There were no significant differences between groups for cardiovascular death or nonfatal myocardial infarction, or stroke, although event rates in the pioglitazone group were consistently lower than with placebo. Rates of heart failure requiring hospitalization or fatal heart failure were not significantly different between the pioglitazone and placebo groups, but heart failure occurred in a greater proportion of patients in the myocardial infarction subgroup (11.6%) than in subjects without prior myocardial infarction (7.0%, *P*<0.0001). The change in HbA1c was −0.8% (interquartile range −1.6% to −0.1%) in the pioglitazone group and −0.4% (interquartile range −1.1% to 0.3%) in the placebo group (between-group *P*<0.0001).

In another prespecified subgroup analysis of the PROACTIVE trial, pioglitazone was examined in subjects with (N=984) and without (N=4254) a prior stroke.[319] In subjects with prior stroke, there was a trend (although not statistically significant) towards benefit with pioglitazone for the primary composite endpoint (all-cause death, nonfatal myocardial infarction, acute coronary syndrome, and cardiac interventions, stroke, amputation above the ankle, or revascularization) (hazard ratio 0.78, 95% CI 0.60 to 1.02). Also in the group with prior stroke, pioglitazone reduced fatal or nonfatal stroke (hazard ratio 0.53, 95% CI 0.34 to 0.85). In the subgroup without prior stroke, pioglitazone did not reduce the risk of first stroke.

Several other smaller recent trials also examined comorbidity subgroups with pioglitazone. In a small, open-label study in subjects with overt diabetic nephropathy (mean creatinine 2.6 mg/dL and 2.4 mg/dL in the pioglitazone and glipizide groups, respectively), HbA1c decreased more with pioglitazone (change −0.1 [standard deviation 1.2]) than with glipizide (change −0.4 [standard deviation 1.8]) (between-group *P* value 0.52).[125] A small, placebo-controlled pioglitazone monotherapy study in persons newly diagnosed with type 2 diabetes and coronary heart disease found was no significant difference between groups in change in HbA1c.[320]

In a small randomized controlled trial (N=47) patients with impaired glucose tolerance or type 2 diabetes in addition to nonalcoholic steatohepatitis received either pioglitazone 45 mg daily or placebo, in addition to a weight loss intervention.[180] Glycemic control improved with pioglitazone compared with placebo (*P*<0.001), with a decrease in weight and body mass index with pioglitazone compared with placebo (*P*=0.003 and 0.005, respectively). Liver aminotransferase levels normalized with pioglitazone, and plasma aspartate and alanine aminotransferase levels, along with hepatic fat content, all decreased with pioglitazone compared with placebo (*P*<0.05). Histologic changes in the liver also improved significantly with pioglitazone. In this fair-quality trial, patients were not stratified with respect to type 2 diabetes or impaired glucose tolerance status.

In another small study, patients with acute coronary syndrome received pioglitazone or no additional treatment starting 2 weeks after percutaneous, bare metal stent placement.[181] Determined from quantitative angiography at 6 months, the late luminal loss was less in the pioglitazone group than in the control group (P=0.0008) and the restenosis rate was decreased (between-group P=0.0052). Major cardiac events (myocardial infarction or revascularization of the target lesion) were significantly decreased in the pioglitazone group at 6 months compared with the control group (7.7% compared with 60.7%, P<0.0001). No deaths occurred in either group.

Several studies in the updated report examined rosiglitazone with comorbidities. In a very small (N=16), poor-quality randomized controlled trial, subjects with coronary stent implantation were randomized to rosiglitazone 4-8 mg daily or placebo for 6 months. Rosiglitazone did not reduce in-stent restenosis. There were no differences in cardiac events between the groups.[174] Lautamaki and colleagues noted a decrease in HbA1c compared with placebo in a study of combination therapy in patients with coronary artery disease (P<0.0001 compared with placebo).[172]

Table 70. Studies examining subgroups based on demographic characteristics or comorbidities

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
Pioglitazone								
Jun JK 2003 Fair, for case series	USA Single center	Time series retrospective chart review	Hispanic 100%	SU 50% Insulin 52% Metformin 70%	54.6 (8.5) yr 83% female	10.4% (1.7%) 78.9 (21.4) kg 32.0 (8.1) kg/m^2	6-month follow-up HbA1c: −2.0% (*P*<0.0001)	8 patients (5.6%) withdrew secondary to significant peripheral edema; 1 patient had exacerbation of congestive heart failure, 1 reported myalgias
King AB 2003 Fair (for cohort study)	USA Single center	Cohort with comparison group Retrospective chart review	98 non-Hispanic Caucasians and 81 Mexican-Americans	SU 55% Insulin 0% Metformin 21%	Hispanics: 52.7 (15.2) yr Non-Hispanics: 61.2 (12.8) yr % female NR	Hispanics: 8.2% (1.9%) non-Hispanics: 8.0% (1.9%) Hispanics: 89.2 (NR) kg Non-Hispanics: 99.6 (NR) kg	HbA1c at 3-m follow-up Hispanic: −1.2(1.8) Non-Hispanic: 1.1(1.4)	No AEs presented Weight gain: Hispanics 1.41 kg, Caucasians 1.64 kg (*P*=0.54)
Rajagopalan R., 2004 NA (based on 5 other studies, 1 of fair quality; data not available in 4)	Countries NR Multicenter trials	5 RCTs, 1 published (Rosenblatt 2001), others unpublished by Takeda Pharmaceuticals	NR	2 placebo-controlled Pio monotherapy trials; 1trial each of Pio combined with metformin, sulfonylurea, or insulin	Two subgroups examined: <65 and ≥65 years; mean age and % female NR	< and >65 years reported as ranges for the 5 studies combined HbA1c: 9.8% to 10.9%; 8.9% to 10.3% BMI, weight NR	Mean decrease from baseline in HbA1c 0.53 to 1.94%; older group had similar response to younger group; both groups also benefits to a comparable degree for lipid levels	Adverse cardiovascular events and hypoglycemia were similar in the younger and older age groups treated with Pioglitazone monotherapy and with Pioglitazone combined with metformin. Hypoglycemia was 2-fold higher in the older-aged group using Pioglitazone combined with a sulfonylurea or

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
								insulin.
Tan M 2004 (glimepiride study) Fair	Mexico Multicenter	RCT, AC, DB	Hispanic 99%, white 1%	None	55.3 (NR) yr 51% female	NR 74.4 (NR) kg	HbA1c at 1-year follow-up Pio: −0.8% Glimepiride: −0.7% Between-group *P* value = 0.64	Incidence of treatment-emergent and severe AEs was similar in the 2 groups
Agrawal, A 2003 Fair, based on secondary data	UK Multicenter	RCT, PC, DB, secondary data from 3 RCTs examined subgroup with decreased renal function (creatinine clearance 30-80 ml/min)	NR	Added to various SU	61.6 (NR) yr 38% female	9.15% (NR) 28.8 (NR) kg/m^2	HbA1c at 6m: Between-group change −1.1% for both renal impaired and nonimpaired patients	% AEs was similar for patients in both treatment groups when comparing those with renal impairment and those without, including incidence of hypoglycemia; edema more common in patients with normal renal function in both treatment groups (no statistics)
Barnett, A 2003 Fair	UK Multicenter	RCT, PC, DB	Indian: 60%; Pakistani: 27%; Bangladeshi: 9.5%; Sri Lankan: 3%; Mauritian: less than 1%	Added to SU	54.2 (NR) yr 22% female	9.13% (NR) 26.6 (NR) kg/m^2	HbA1c at 26 weeks Rosi: −1.16, Placebo 0.26 (*P*<0.001)	Treatment-emergent AEs in 70% Rosi and 75% with placebo; withdrawals for AEs: Rosi 5%, placebo 10% Weight (kg): Rosi 3.9, placebo −0.1 (*P*<0.001)
Chan NN 2004 (Observational	USA Single	Cohort, single	Chinese	Monotherapy	65 (8.3) yr 58% female	8.6% (NR)	HbA1c at 15.5m: −1.1 (*P*=0.01)	LFT: no significant increase in ALT

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
study)	center	group				71.7 (NR) kg		Hematocrit: NSD weight gain 2.2 kg (P=0.08)
Choi D 2004 (Observational study)	Korea Single center	RCT	Korean	Combined therapy with a variety of hypoglycemic agents used by both groups (SU, metformin, α-glucosidase inhibitor, or insulin); % son each drug not specified	59.9 (9.3) yr 30%	7.72% (1.13%) 68.1 (11.0) kg 24.8 (3.35) kg/m^2	6 months: Intervention change: −0.61 (1.15) Control change: −0.75 (1.07)	"No patient had significant side effects, such as an elevation in the liver enzyme levels."
Honisett, S 2003 Poor	Australia NR	RCT, PC, DB	NR	80% continued their use of metformin, SU, or both	NR 100% female	NR NR	HbA1c change at 12 weeks: −1.2%, P=0.001	No AEs were reported to the investigators
Jones, T 2003 Fair	USA NR	RCT, PC, open-label	NR	Added to metformin	59.9 (NR) yr 32% female	8.83% (NR) 28.2 kg/m2	BMI<25: Rosi 8 mg+metformin −0.3; metformin alone 0.3 BMI 25-30: Rosi 8 mg+ metformin: −0.7; metformin alone 0.1 BMI >30: Rosi: 8 mg+ metformin −1.0; metformin alone 0.2 Data from graphs, exact values NR rosi vs. metformin P<0.025 for all 3 groups	AE profile not different between normal weight, overweight, and obese
Kreider M 2002 NA (based on 8	USA Multicenter	Secondary data: 8 studies,	% White: <70years: 79%	Monotherapy, elderly	<70 years: 56 >70 years: 73 37% female	<70 years: Rosi: 8.8% (1.5%);	HbA1c at 26 weeks <70 years:	Hypoglycemic episodes occurred in <1% on ROSI in

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
other studies, primary data not available)		either PC or AC, DB	>70years: 91%			placebo 9.0% (1.7%) >70 years: rosi: 8.6% (1.4%); placebo 8.9% (1.5%) BMI: <70 years: Rosi: 29.8 (4.1) kg/m^2; placebo 29.8 (4.2) kg/m^2 >70 years: Rosi: 28.3 (3.9) kg/m^2; placebo 28.4 (4.1) kg/m^2	Rosi 4 mg daily: −0.2; 8 mg daily −0.5; placebo 0.8 >70 years: Rosi 4 mg daily: −0.1; 8 mg daily: −0.4; placebo 1.0 NSD between the 2 age groups	either age group; 2 patients <70y in Rosi group discontinued treatment because of hypoglycemia
Vongthavaravat V., 2002 Fair	Various Asia and South America Multicenter	RCT, no-treatment control, open-label	White (38.3%); Black (3.0%); Asian (57.5%); Other (1.2%)	Added to SU	56.0 (NR) yr 56% female	NR 68.9 kg 27.1 kg/m^2	HbA1c change at 26 weeks:Rosi+SU: −1.1(95% CI −1.37 to −0.89); SU control: 0.1(−0.1 to 0.2)	Hypoglycemia (%)Rosi+SU: 11.6; SU control: 1.2 (*P*<0.001) Serious AE (%): Rosi+SU: 2.4; SU control: 5.3
Wang G., 2005 Fair	China Single center	RCT, no-treatment control, open-label	Chinese (assumed)	Monotherapy	61.2 (8.6) yr 18% female	7.33% (0.17%) 25.6 (2.7) kg/m^2	Change in HbA1c reported graphically only (difficult to interpret) Rosi: decreased at 6m compared to control group (*P*<0.05)	Weight gain: NSD from baseline level and from control group (data not provided)

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
Wang, T 2004 (Metabolic syndrome only) Fair	Taiwan Multicenter	RCT, PC, open-label	Chinese (assumed)	Monotherapy	59.5 (NR) y 42% female	NR 25.4 (NR) kg/m^2	HbA1c NR FPG: NSD within or between groups (*P*>0.05)	AEs reported as none
Manley HJ 2003 Fair (Cohort study)	USA Single Center	Retro-spective cohort	NR	Combined therapy, various	64.8 (11.5) yr Range: 46-85 yr 35% female	8.6% (2.2%) NR	Comparison of rosi to pio: interdialytic weight change Rosi: 3.6 kg at baseline and 3.97 at 3m follow-up (*P*=0.0032); hematocrit: Rosi 34.89 at baseline and 34.0 at follow-up; data not provided for pio, but difference between pio and rosi for these 2 variables was reported as significant, but NR direction of pio effects compared to rosi	No data provided on AEs
Kahn, 2008[309] Fair	Multiple Countries Multicenter	Analysis of data from ADOPT	NR	Monotherapy	Mean age of women taking rosiglitazone: 56.1 (10.2) Mean age of women taking metformin: 56.7 (10.0) Mean age of women taking	NR for Overall	NR	Estimated HRs (95% CI) for risk of fracture with rosiglitazone vs. metformin and glyburide were 1.57 (1.13–2.17; *P* =0.0073) and 1.61 (1.14 –2.28; *P*= 0.0069) For men, no

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Mean age (SD) Gender	Baseline HbA1c (SD) Weight (SD) or BMI (SD)	HbA1c outcomes	Adverse events and tolerability
					glyburide: 56.3 (10.7) Mean age of men taking rosiglitazone: 56.4 (9.9) Mean age of women taking metformin: 57.0 (9.9) Mean age of women taking glyburide: 56.6 (9.8)			difference among the groups. For women, With the Cox proportional hazards model, estimated HR (95% CI) for risk of fracture with rosiglitazone vs. metformin was 1.81 (1.17–2.80; *P* =0.008) and for rosiglitazone vs. glyburide was 2.13 (1.30 – 3.51; *P*= 0.0029).

Abbreviations: AE, adverse event; DB, double blind; MI, myocardial infarction; NR, not recorded; NSD, no significant difference; NYHA, New York Heart Association; PC, placebo-controlled; pio, pioglitazone; RCT, randomized controlled trial; rosi, rosiglitazone; SU, sulfonylurea.

SUMMARY

Strength of Evidence (SOE)

Most of the evidence was limited to adult populations. Most of the included studies evaluated intermediate outcomes, such as HbA1c or weight. Very few studies reported health outcomes and few studies were longer than 6 months. For the amylin agonists, DPP-IV inhibitors, and GLP-1 agonists, we found no studies that focused on health outcomes as primary outcomes. Some studies of these drug classes reported some health outcomes such as all-cause mortality or number of people with macrovascular disease among secondary outcomes or adverse events, but overall evidence was generally insufficient to determine how medications in these classes compare with other treatments for their impact on health outcomes. Here we summarize some of the main comparative findings for the most commonly reported outcomes and the related strength of evidence (SOE). A more detailed summary of findings is presented in Table 71.

For the newer diabetes drugs (pramlintide, sitagliptin, saxagliptin, exenatide, and liraglutide), all of the included medications were efficacious for reducing HbA1c compared with placebo. For reduction in HbA1c, pramlintide was similar to rapid acting insulin analog when added to insulin glargine or detemir (low SOE); sitagliptin monotherapy was less efficacious than metformin or glipizide monotherapy (low SOE); sitagliptin was not significantly different than rosiglitazone when either was added to metformin (moderate SOE); and there was no comparative evidence for saxagliptin (insufficient SOE). One head-to-head trial comparing exenatide with liraglutide reported a slightly greater reduction in HbA1c with liraglutide (between group difference −0.33%, 95% CI -0.47 to -0.18, low SOE). For reduction in HbA1c, exenatide was similar to glibenclamide (low SOE), rosiglitazone (low SOE), and insulin (with both groups also receiving oral diabetes agents, moderate SOE). Liraglutide-treated subjects had greater reductions in HbA1c than subjects treated with glargine (low SOE), rosiglitazone (low SOE), or sitagliptin (low SOE), and similar or greater reductions than those treated with glimepiride (insufficient SOE).

For weight, pramlintide, exenatide, and liraglutide (doses of 1.2 or greater) appear to cause weight loss compared with placebo. Sitagliptin and saxagliptin are likely weight neutral. Most studies evaluating weight change were 6 months or less and it is uncertain whether weight loss is sustained long-term. Rates of hypoglycemia were lower with sitagliptin than with glipizide (moderate SOE), with liraglutide than exenatide (low SOE), and with liraglutide than glimepiride (high SOE). Hypoglycemia rates were similar to placebo for sitagliptin and saxagliptin (low SOE) and were similar between exenatide and insulin (moderate SOE). Rates of gastrointestinal side effects were higher with exenatide and liraglutide than with comparators.

For the TZDs, the available evidence indicates that pioglitazone and rosiglitazone are not statistically significantly different in their ability to reduce HbA1c (moderate SOE). Further, there were no significant differences in ability to reduce HbA1c between either TZD and sulfonylureas or metformin (moderate to high SOE). Both TZDs increase the risk of heart failure (high SOE), edema (high SOE), and fractures in women (moderate SOE). The risk of hypoglycemia is reduced with TZDs when compared with sulfonylureas; the risk is similar to the risk with metformin (high SOE). Both TZDs cause a similar degree of weight gain to that caused by sulfonylureas (moderate SOE). Although rosiglitazone now has restricted access due to an increased risk of cardiovascular adverse events, we found no evidence of increased all-cause

mortality or cardiovascular mortality with pioglitazone; some studies suggest reduced risk of all-cause and cardiovascular mortality with pioglitazone (low SOE).

For the FDCPs, we found no head to head trials that compared HbA1c control between any 2 FDCPs (insufficient SOE). Therapy with Avandamet®, Avandaryl®, Actoplus Met®, or dual therapy with metformin and sitagliptin produced statistically significantly greater reductions in HbA1c compared to monotherapy with any of their respective components.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to applicability of the results (addressed below) and those relating to methodology within the scope of this review. Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do: Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that not proven does not mean proven not; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

Applicability

The applicability of the results are limited by the scope of the Key Questions and inclusion criteria and by the applicability of the studies included. Many studies included narrowly defined populations of patients. Minorities, older patients, and the most seriously ill patients were often underrepresented.

Pramlintide: Applicability to General Populations with Type 1 Diabetes

The methods for recruiting study subjects were not reported in the included trials of pramlintide, and subjects likely represent a highly selected population: Primarily white, middle-aged men and

women with mean baseline HbA1c ranging from 8.1% to 9.0% and diabetes of 16 to 21 years duration. None of the patients had significant cardiovascular or renal disease or problems with gastrointestinal motility. Data regarding baseline comorbidities, disease severity, and existing microvascular disease such as retinopathy or neuropathy were not reported. The population included highly motivated subjects who were willing to add 2 to 4 injections to their daily regimen and who rigorously self-monitored blood glucose over the course of the study. Study settings were not reported, but they were likely to have been outpatient clinics.

Pramlintide: Applicability to General Populations with Type 2 Diabetes

No included trial evaluated the effects of pramlintide in patients whose type 2 diabetes was inadequately managed on combination prandial and basal insulin therapy with or without oral agents. Two studies evaluated pramlintide in patients using fixed-dose insulin. One trial used flexible dosing for insulin glargine only and 1 compared pramlintide with flexible rapid acting insulin analog (RAIA; lispro, aspart, or glulisine) in addition to flexible basal insulin (glargine or detemir).[22] Hence, results have limited applicability to the broader population using more commonly prescribed insulin regimens.

US Food and Drug Administration-approved dosage of pramlintide for type 2 diabetes includes initial therapy of 60 mcg/meal and maintenance therapy of 120 mcg/meal. Three trials examined the 120 mcg dosage.[22, 24, 25] The third included trial was a dose-ranging study that did not use a 120 mcg dose but did include a 75 mcg dose which may be used in clinical practice.[26]

Overall, patients included in these 3 trials represent a highly selected population: mainly white, middle-aged men and women with mean baseline HbA1c between 8.2% and 9.3% and diabetes of 11-13 years' duration. None of the patients had significant pulmonary, cardiovascular, renal, neurologic, or hematologic diseases or problems with gastrointestinal motility. The study populations probably included highly motivated subjects who desired to achieve optimal glycemic control through the additional 2-4 injections added to their usual regimens of insulin and oral hypoglycemic agent over 16-52 weeks of participation in a trial. Study setting also was not reported in any of the included trials; subjects likely were evaluated in outpatient clinics.

Sitagliptin and Saxagliptin: Applicability to General Diabetes Populations

Patients enrolled in the sitagliptin and saxagliptin trials represented a highly selected population: primarily white, middle-aged, obese adults with moderately elevated baseline HbA1c (< 9%) and diabetes for less than 10 years. These populations were further selected during long dose-stabilization and run-in periods, where only persons with > 75% adherence to placebo went on to randomization. Moreover, these trials did not provide much baseline information on comorbidities and other characteristics and laboratory values that would enable inference about the applicability of study findings to general diabetic populations. The available data appear to be limited to persons with diabetes without related comorbidities and who are highly motivated.

Exenatide: Applicability to General Diabetes Populations

The studies identified for this review are rather homogeneous, relatively small, and may be rather selected, thus applicability to broader diabetes populations may be limited. Study subjects were

homogeneous across studies for age, sex, and baseline HbA1c in both the placebo- and active-control trials. Significant comorbidities were excluded in placebo-controlled studies reporting that characteristic[69-71] and comorbidities were not mentioned in 3 of the 4 active-control trials.[62, 64, 65]

Most studies reported only the number of subjects randomized, and randomization occurred in all placebo-controlled trials after a run-in of injected placebo. In other words, the number of potential study subjects who did not tolerate twice daily injections and who were therefore not included in the study was usually not reported. Open label extension studies were of highly selected populations who completed the primary study and who volunteered to continue (or start if on placebo) exenatide.

Liraglutide: Applicability to General Diabetes Populations

The studies identified for this review are rather homogeneous, relatively small, and may be rather selected, thus applicability to broader diabetes populations may be limited. Study subjects were homogeneous across studies for age, sex, duration of diabetes, and baseline HbA1c in both the placebo- and active-control trials. Significant comorbidities were excluded in the placebo-controlled studies reporting that characteristic.

Studies Currently Being Conducted

We identified no trials in progress that would meet inclusion criteria for this review that would potentially change conclusions.

Table 71. Summary of the evidence by key question

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
Amylin agonists: Pramlintide for Type 1 diabetes	Insufficient	*Evidence in children* No data on children were reported, although people as young as 16 years were eligible for study enrollment in 2 included trials (% of children enrolled was not reported)[19, 20]
	Low	*Evidence in adults* HbA1c was either slightly improved or no different with the addition of pramlintide 30 or 60 mcg/meal to a flexible-dose insulin regimen compared with placebo plus flexible-dose insulin regimen over 29 weeks[20] (between-group difference: 0.0%) and 52 weeks[19] (between-group difference: 0.27%, *P* value, not reported) of treatment.
	Low	Greater reduction in HbA1c when pramlintide 60 mcg 3 or 4 times a day was added to fixed-dose insulin therapy (decreased from baseline by 0.29% to 0.34%, P<0.01) than when placebo was added to fixed-dose insulin (, with no significant effect in the placebo group (decrease by 0.04%, not statistically significant) at 52 weeks[21]
	Moderate	Slight weight loss with pramlintide in addition to insulin (range: −0.4 to −1.3 kg) compared with slight weight gain with placebo plus insulin in a fixed- or flexible-dose setting (range: +0.8 to +1.2 kg) over 29 and 52 weeks.

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
Amylin agonists: Pramlintide for Type 2 diabetes	Insufficient	*Evidence in children* Children and adolescents ≤ 18 years were not enrolled in any of the included studies
	Insufficient	*Evidence in adults* No included studies focused on health outcomes as the primary outcomes. One study reported some health outcomes among the adverse events.
	Moderate	Greater reduction in HbA1c with pramlintide doses from 75 mcg to 120 mcg given 2 or 3 times daily added to fixed- or stable doses of insulin compared with placebo and insulin (range 0.13% to 0.4% at 52 weeks)
	Moderate	Greater reduction in weight with pramlintide doses from 75 mcg to 120 mcg given 2 or 3 times daily added to fixed- or stable doses of insulin compared with placebo and insulin (range 1.1 kg to 1.85 kg, placebo-corrected differences at 52 weeks).
	Low	No statistically significant difference for reduction in HbA1c between the addition of pramlintide 120 mcg at meals to glargine or detemir compared with rapid acting insulin analog at 24 weeks (1.1% vs. 1.3%, *P*=0.46).
	Low	No change in weight reported with the addition of pramlintide 120 mcg at meals to glargine or detemir, compared with a 4.7 kg weight gain with rapid acting insulin analog at 24 weeks (+4.7 kg between group difference, *P*<0.0001)
DPP-IV inhibitors: Sitagliptin vs. Saxagliptin	Insufficient	*Sitagliptin vs. Saxagliptin* We found no head-to-head studies of sitagliptin and saxagliptin meeting inclusion criteria.
DPP-IV inhibitors: Sitagliptin	Insufficient	*Sitagliptin: Evidence in children* Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness or efficacy.
	Insufficient	*Sitagliptin: Evidence in adults* All studies focused on intermediate outcomes with none focusing on health outcomes as primary outcomes. Some studies reported some health outcomes such as all-cause mortality or number of people with macrovascular disease among secondary outcomes or adverse events.
	Insufficient	No studies provided data on efficacy/effectiveness for follow up beyond 2 years.
	Low (for both comparisons)	Sitagliptin monotherapy resulted in slightly less HbA1c reduction than either metformin monotherapy over 54 weeks (between group difference −0.16 for metformin 1000 and −0.47 for metformin 2000 mg/d) or glipizide monotherapy over 12 weeks (between group difference −0.22%).
	Low	Sitagliptin monotherapy resulted in slight weight gain, compared with slight weight loss for those treated with metformin monotherapy over 54 weeks (between group difference −1.6 to −2.1 at 54 weeks).
	Low	Sitagliptin monotherapy resulted in slightly less weight gain compared with glipizide monotherapy over 12 weeks (+0.4 kg vs. +0.9 kg).
	Moderate	Greater reduction in HbA1c with sitagliptin 100 mg/d monotherapy than with placebo (WMD −0.79%, 95% CI −0.93% to −0.66%) in patients inadequately controlled on diet and exercise over 12-24 weeks.

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
	Moderate	Less weight loss with sitagliptin 100 mg/d monotherapy than with placebo (WMD 0.66, 95% CI 0.43 to 0.89).
	Low	Studies comparing add-on of sitagliptin to other hypoglycemic agents (metformin, pioglitazone, or glimepiride) found sitagliptin-treated subjects to have either more weight gain, less weight loss, or similar changes in weight compared to placebo-treated subjects.
	Moderate	Overall, in patients with inadequate glycemic control on 1 (metformin, pioglitazone, or glimepiride) or 2 hypoglycemic agents, the addition of sitagliptin resulted in greater reduction in HbA1c than the addition of placebo (between group difference −0.5 to −1.0)
	Moderate	No significant difference in reduction in HbA1c between rosiglitazone and sitagliptin when added to metformin therapy in two randomized controlled trials.
DPP-IV inhibitors: Saxagliptin		*Saxagliptin: Evidence in children*
	Insufficient	We found no studies including children and adolescents ≤ 18 years
		Saxagliptin: Evidence in adults
	Insufficient	All studies focused on intermediate outcomes with none focusing on health outcomes as primary outcomes. Some studies reported some health outcomes such as all-cause mortality or cardiac death among secondary outcomes or adverse events.
	Insufficient	No studies provided data on efficacy or effectiveness for follow up beyond 24 weeks.
	Insufficient	We found no active-control studies meeting inclusion/exclusion criteria for saxagliptin.
	Moderate	Greater reduction in HbA1c with saxagliptin monotherapy compared to placebo (between group difference −0.45 to −0.65%); reduction was greater with saxagliptin 5 mg than with saxagliptin 2.5 mg.
	Low for each comparison; Moderate overall for saxagliptin add-on therapy vs. placebo add-on	Saxagliptin added on to either metformin, a thiazolidinedione, or glyburide resulted in greater HbA1c reduction than placebo added on to metformin, a thiazolidinedione, or glyburide (between group difference ranges were −0.72 to −0.82%, −0.36 to −0.64, and −0.62 to −0.72, respectively; 1 study was identified for each comparison).
	Moderate	Weight loss was greater with placebo than with saxagliptin monotherapy and greater weight loss was seen with saxagliptin 2.5 mg than with 5 mg. (between group difference −0.09 to −0.2 kg for placebo compared with saxagliptin 2.5; −0.8 to −1.3 kg compared with saxagliptin 5).
GLP-1 agonists: Exenatide vs. Liraglutide		*Exenatide vs. Liraglutide*
	Low	In the 1 included head-to-head trial (N=464), liraglutide 1.8 mg once daily reduced mean HbA1c more than exenatide 10 mcg twice daily (−1.12% vs. −0.79%; estimated treatment difference −0.33; 95% CI −0.47 to −0.18)
	Low	Exenatide and liraglutide resulted in similar weight loss (−2.87 vs. −3.24 kg, respectively; estimated treatment difference −0.38 kg; 95% CI −0.99 to 0.23)

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
GLP-1 agonists: Exenatide		*Exenatide: Evidence in children*
	Insufficient	No included study examined children or adolescents with type 2 diabetes.
		Exenatide: Evidence in adults
	Insufficient	Except for one study reporting quality of life, no included studies examined the impact of treatment with exenatide on health outcomes (such as MI, death, stroke, or renal failure).
	Moderate	Four active-control trials compared exenatide to insulin, with both groups also receiving oral diabetes agents, and all found no difference between groups for reduction in HbA1c (range for exenatide 10 mcg twice daily −1.0% to −1.4%; range for insulin −0.9% to −1.4%). In 1 of the trials, the substitution of exenatide for insulin did not improve HbA1c compared to continuing insulin.
	Moderate	Active-control studies demonstrated significant weight loss in exenatide groups compared to weight gain with insulin (treatment difference range 4.1 kg to 5.4 kg).
	Low	One active-control trial found no significant difference in improvement in HbA1c between exenatide and glibenclamide (-1.5% compared with -1.8%, *P*>0.05.) Weight loss in the exenatide arm of the study was significantly greater than in the glibenclamide arm of the study (change with exenatide -8.0 kg, change with glibenclamide +4.3 kg, *P*<0.001).
	Low	One trial comparing exenatide to rosiglitazone with all participants on background metformin therapy, found no significant difference in improvement in HbA1c (-0.9% vs. -1.0%, P=0.720), but greater weight loss in the exenatide arm of the study (-2.8 kg vs. +1.5, P<0.001).
	Moderate overall; High for 5mcg vs. placebo and for 10mcg vs. placebo	Greater reduction in HbA1c with exenatide than with placebo, both when added to various oral agents and as monotherapy. For exenatide 5 mcg twice daily vs. placebo (5 studies) WMD –0.72, 95% CI –0.99 to –0.45. For exenatide 10 mcg twice daily vs. placebo (8 studies) WMD –0.90, 95% CI –1.08 to –0.73.
	Low	For change in weight, pooled analysis (5 studies) found no statistically significant difference between exenatide 5 mcg twice daily and placebo (weighted mean difference −0.61 kg, 95% CI −1.28 to 0.06). However, statistical heterogeneity was high for the pooled analysis (I^2=74%), and a sensitivity analysis removing a single study resulted in significant weight loss for exenatide 5mcg compared to placebo (weighted mean difference −0.87, 95% CI −1.35 to −0.40, *P*<0.001, I^2=33%)
	High	For change in weight, pooled analyses (9 studies) found that exenatide 10 mcg twice daily resulted in significant weight loss compared to placebo (WMD –1.25 kg, 95% CI –1.60 to –0.90)
	Low	Quality of life was examined in only 1 study of exenatide 10 mcg twice a day. No significant differences were seen between exenatide and insulin glargine.
GLP-1 agonists: Liraglutide		*Liraglutide: Evidence in children*
	Insufficient	No included study examined children or adolescents with type 2 diabetes.
		Liraglutide: Evidence in adults

Key Question 1. What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?		
Drugs	**Strength of evidence[a]**	**Conclusion**
	Insufficient	No included studies focused on health outcomes as the primary outcomes. Some studies reported a health outcome among other secondary outcomes or in the adverse events section.
	Insufficient	Three active-control trials comparing liraglutide to glimepiride demonstrated improvement in HbA1c in both treatment groups. Results indicate either no significant difference between treatment groups (2 trials) with liraglutide 0.6 mg daily and glimepiride 1 to 4 mg daily[58] and between liraglutide 1.2 mg and 1.8 mg daily and glimepiride 4 mg daily[59] or greater improvement in HbA1c with liraglutide (1.2 mg and 1.8 mg daily) than with glimepiride 8 mg daily.[60]
	Moderate	Two studies of liraglutide 1.2 mg and 1.8 mg found significant weight loss with liraglutide compared to weight gain with glimepiride.
	Low	Greater reduction in HbA1c in 1 good quality active-control trial comparing liraglutide 1.8 mg daily to open-label insulin glargine (−1.33% vs. −1.09%; *P*=0.0015)
	Low	Greater weight loss with liraglutide compared with insulin glargine in the same study (treatment difference −3.43 kg; *P*<0.0001)
	Low	One trial comparing the addition of rosiglitazone with the addition of liraglutide (to ongoing glimepiride treatment) reported greater reduction in HbA1c with liraglutide (−1.1 compared with −0.4%, P<0.0001) and greater weight gain in the rosiglitazone arm (change in weight: liraglutide 0.6mg +0.7kg; liraglutide 1.2mg +0.3 kg; liraglutide 1.8mg -0.2 kg; rosiglitazone 4 mg +2.1 kg; P<0.0001 for all doses of liraglutide compared to rosiglitazone).
	Low	Greater reduction in HbA1c with liraglutide 1.2 mg and 1.8 mg daily than with sitagliptin 100 mg daily in one trial (-1.24% to -1.5% compared with -0.6%; P<0.0001).
	Low	Greater weight loss with liraglutide 1.2 mg and 1.8 mg daily than with sitagliptin in the same study (-2.86 kg to -3.38 kg compared with -0.96 kg; P<0.0001).
	Moderate	Greater reduction in HbA1c with liraglutide than with placebo, both when added to various oral agents and as monotherapy (liraglutide 0.6 to 0.65 mg daily WMD −1.10, 95% CI –1.45 to –0.75; liraglutide 1.2 to 1.25 mg daily WMD −1.28, 95% CI –1.56 to –1.00; liraglutide 1.8 to 1.9 mg daily WMD −1.26, 95% CI −1.50 to −1.03).
	Moderate	When compared with placebo, liraglutide 1.8 mg to 1.9 mg daily produced a significant decrease in weight (liraglutide 1.8 mg to 1.9 mg WMD −1.43 kg, 95% CI –2.33 to –0.53).
	Moderate	There was no statistically significant weight loss for liraglutide 0.6 to 0.65 mg compared with placebo.
	Low	Liraglutide 1.2 to 1.25 mg resulted in significant weight loss compared to placebo in all studies except for in the 1 included study in which all participants were on background sulfonylurea therapy.
TZDs: Pioglitazone vs. Rosiglitazone	Moderate	Meta-analysis of 8 head-to-head RCTs found no statistically significant difference between pioglitazone and rosiglitazone for their ability to improve glycemic control (for change in HbA1c, WMD −0.09, 95% CI −0.23, 0.05). Prior systematic reviews found both drugs appear to have similar effects on HbA1c, producing a decrease of approximately 1%, similar to the change

Key Question 1. What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?		
Drugs	**Strength of evidence[a]**	**Conclusion**
		produced with other oral agents (including metformin, glibenclamide, or glimepiride). Effect of both pioglitazone and rosiglitazone appears to be similar when used in either monotherapy or combination therapy.
	Insufficient	None of the included head-to-head trials reported comparative efficacy/effectiveness of health outcomes or utilization outcomes.
TZDs:		*Evidence in children*
Pioglitazone	Insufficient	No data on children were reported.
		Evidence in adults
	Moderate	Overall, no significant difference in reduction in HbA1c between pioglitazone and sulfonylureas.
	High	No significant difference in 7 trials for reduction in HbA1c between pioglitazone and metformin.
TZDs:		*Evidence in children*
Rosiglitazone	Insufficient	No data on children were reported.
		Evidence in adults
	Moderate	No significant difference in reduction in HbA1c between rosiglitazone and sulfonylureas.
	Moderate	No significant difference in reduction in HbA1c between rosiglitazone and metformin.
	Low	One trial comparing the addition of rosiglitazone with the addition of liraglutide (to ongoing glimepiride treatment) reported greater reduction in HbA1c with liraglutide (−1.1 vs. −0.4%, *P*<0.0001)
	Low	One trial comparing the addition of exenatide with the addition of rosiglitazone (to ongoing metformin), found no significant difference in improvement in HbA1c (-0.9% vs. -1.0%, P=0.720).
	Low	Thiazolidinedione plus metformin compared with a second-generation sulfonylurea plus metformin (4 randomized controlled trials) did not show a consistent effect favoring 1 of the combinations, nor did an RCT comparing thiazolidinediones with repaglinide.
	Moderate	No significant difference in reduction in HbA1c between rosiglitazone and sitagliptin in two randomized controlled trials.
FDCPs and		*Evidence in children*
Dual Therapy:	Insufficient	We did not find any evidence
Avandamet®		
Actoplus Met®		*Evidence in adults*
Avandaryl®	Insufficient	We found no studies that focused on health outcomes as the primary outcomes for any available FDCP. Two studies reported health outcomes among other secondary outcomes or in the adverse events section.
Duetact®		
Janumet®		
Metformin + Rosiglitazone	Insufficient	We found no head-to-head trials that compared HbA1c control between any 2 FDCPs
Metformin + Pioglitazone		
Glimepiride + Rosiglitazone	Insufficient	We found no trials that evaluated the following FDCPs: Duetact®, Janumet®
Glimepiride + Pioglitazone	Moderate	Greater reduction in HbA1c with Avandamet® or dual therapy with metformin and rosiglitazone than with component monotherapy in trials of 24 to 32 weeks (treatment difference range 0.13% to 0.7%)
Metformin +		

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
Sitagliptin		
	Moderate	Greater reduction in HbA1c with Avandaryl® or dual therapy with rosiglitazone and glimepiride than with component monotherapy in trials from 20 to 28 weeks (treatment difference range 0.6% to 0.8%)
	Moderate	Greater reduction in HbA1c with Actoplus Met® or dual therapy with pioglitazone and metformin than with component monotherapy in trials from 24 weeks to 15 months (treatment difference range 0.2% to 0.9%)
	Moderate	Greater reduction in HbA1c with dual therapy with metformin and sitagliptin than with component monotherapy in a 24 week trial with additional 30 and 52 week extensions (range 0.4% to 1.2%)

Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
Amylin agonists: Pramlintide for Type 1 diabetes		*Evidence in children*
	Insufficient	No data on children were reported, although people as young as 16 years were eligible for study enrollment in 2 included trials.[19, 20]
		Evidence in adults
	Moderate	Greater withdrawals due to adverse effects for pramlintide-treated subjects than for insulin-treated subjects (ranges across trials were 5% to 20% vs. 2% to 8%, respectively).
	Moderate	Gastrointestinal adverse events including nausea, vomiting, anorexia, and reduced appetite were more commonly reported with the use of pramlintide plus insulin than with placebo plus insulin.
	Moderate	Severe hypoglycemia occurred more frequently with pramlintide plus insulin during the first 4 weeks of treatment compared with placebo plus insulin. Rates of severe hypoglycemia declined once pramlintide doses stabilized but continued to remain slightly higher than with placebo plus insulin at up to 52 weeks of follow-up.
Amylin agonists: Pramlintide for Type 2 diabetes		*Evidence in children*
	Insufficient	Children and adolescents ≤ 18 years were not included in any of the published studies on efficacy or effectiveness.
		Evidence in adults
	Moderate	The most commonly reported adverse event was nausea, which occurred more frequently with pramlintide plus insulin than with placebo plus insulin especially during the first 4 weeks of treatment, but declined thereafter.
	Moderate	Severe hypoglycemia occurred more frequently with pramlintide compared with placebo.
	Low	Hypoglycemia occurred less frequently in subjects taking pramlintide than those taking rapid acting insulin analogs (RAIA) in one 24 week study.
DPP-IV inhibitors: Sitagliptin vs. Saxagliptin	Insufficient	We found no head-to-head studies of sitagliptin and saxagliptin meeting inclusion criteria.

Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
DPP-IV inhibitors: Sitagliptin	Not graded	The most commonly reported adverse events across treatment groups were hypoglycemia, nausea, vomiting, diarrhea, and abdominal pain.
	Moderate	The rates of withdrawal due to adverse events were not significantly different between sitagliptin and placebo (pooled RR 0.88, 95% CI 0.54 to 1.43).
	Moderate	Hypoglycemia was generally more frequent with glipizide than with sitagliptin (17.1-34.1% compared with 1.6-5.3%) and was more common when sitagliptin was used in combination with other hypoglycemic agents than when used as monotherapy.
	Low	Hypoglycemia was not significantly different in subjects taking sitagliptin 100 mg and those taking placebo (pooled RR 1.26, 95% CI 0.49 to 3.25).
	Moderate	Rates of gastrointestinal side effects were higher with metformin than with sitagliptin.
	Low	Gastrointestinal side effects were not significantly different between sitagliptin and placebo treated subjects (nausea pooled RR 1.4, 95% CI 0.5 to 3.96; vomiting pooled RR 0.77, 95% CI 0.20 to 2.88).
	Low	Upper respiratory infections and urinary tract infections were not significantly different between patients taking placebo and those taking sitagliptin (pooled RR 1.06, 95% CI 0.66, 1.7)
	Low; Moderate	Subjects treated with sitagliptin had similar changes or greater improvements in triglycerides than subjects treated with placebo; changes in other lipid parameters were not significantly different between sitagliptin and placebo.
DPP-IV inhibitors: Saxagliptin	Not graded	The most commonly reported adverse effects were nasopharyngitis, upper respiratory infections, headache, and urinary tract infections.
	Moderate	Rates for total withdrawal were lower with saxagliptin 2.5 and 5 mg compared with placebo used as monotherapy or as add-on therapy (2.5 mg RR 0.66, 95% CI 0.57 to 0.79; 5 mg RR 0.79, 95%CI 0.66 to 0.95).
	Moderate	Rates of withdrawal due to adverse events were not significantly different with saxagliptin 2.5 mg used as monotherapy or as add-on therapy compared with placebo (pooled RR 0.85, 95% CI 0.29 to 2.53), however rates were higher in patients taking saxagliptin 5 mg than for those taking placebo (pooled RR 2.09, 95% CI 1.07 to 4.10).
	Low	The incidence of hypoglycemia was not significantly different with saxagliptin 2.5 mg or 5 mg used as monotherapy or as add-on therapy compared with placebo (2.5 mg: pooled RR 2.01, 95% CI 0.63 to 6.39; 5 mg: pooled RR 1.036, 95% CI 0.28 to 3.811).
	Low	There were no significant differences in infections between saxagliptin and placebo.
GLP-1 agonists: Exenatide vs. Liraglutide	Low	In the 1 head-to-head randomized-control trial, withdrawal rates were not significantly different between groups. The incidence of nausea was similar between the groups initially, but was more persistent over time in the exenatide group. The proportion of patients who reported minor hypoglycemia was significantly less in the liraglutide group than the exenatide group (26% vs. 34%, rate ratio 0.55, CI 0.34 to 0.88; *P*=0.0131). There was no significant difference in change in total cholesterol, LDL cholesterol, or HDL cholesterol between the

Key Question 2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?		
Drugs	**Strength of evidence[a]**	**Conclusion**
		exenatide and the liraglutide treatment arms. Reduction in triglycerides was significantly greater in the liraglutide group than the exenatide group (−15.8 mg/dL (3.9) vs. −8.9 mg/dL (3.9) estimated treatment difference −6.9 mg/dL, CI −14.3 to 0.0; *P*=0.0485)
GLP-1 agonists: Exenatide	Moderate	In the active-control trials, total withdrawals and withdrawals due to adverse events were higher in the exenatide groups than the insulin groups.
	Moderate	Nausea and vomiting were the most frequent adverse events among exenatide-treated patients, and rates of these symptoms were significantly higher in the exenatide group than insulin and placebo groups. Nausea declined after the first 8 weeks of therapy.
	Moderate	Rates of hypoglycemia were similar between insulin and exenatide groups.
	Low	In the one trial comparing exenatide to glibenclamide, total withdrawals were higher in the glibenclamide group due to higher rates of hypoglycemia.
	Moderate	There was no significant difference in total withdrawals between exenatide 5 mcg or 10 mcg daily and placebo.
	Moderate	Withdrawal rates due to adverse events were higher with exenatide 10 mcg twice a day than with placebo (RR 3.18, CI 1.70 to 5.93); there was not a statistically significant difference between treatment groups at the 5 mcg twice daily dosing (RR 1.76, CI 0.98 to 3.19)
	Moderate	Nausea, vomiting, and diarrhea rates were significantly higher in subjects treated with exenatide (either dose) compared with those treated with placebo.
	Moderate	The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg twice a day compared with placebo in all 4 studies of patients on background sulfonylurea therapy.
	Low	There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups.
	Low	There was no significant difference in lipid profiles between patients on exenatide vs. placebo in the 1 study that examined this outcome.
GLP-1 agonists: Liraglutide	Low	Total withdrawal rates were similar between liraglutide- and glimepiride-treated subjects, but withdrawals due to adverse events were slightly higher for liraglutide than glimepiride.
	High	Rates of gastrointestinal side effects were higher with liraglutide than glimepiride.
	Moderate	Hypoglycemia rates were lower with liraglutide than glimepiride.
	Insufficient	Pancreatitis: studies comparing liraglutide with glimepiride could not exclude a weak association between treatment with liraglutide and the development of pancreatitis (1 case vs. 1 case in LEAD-2 study; 2 cases vs. 0 in LEAD-3); there were no reports of pancreatitis in the active-control trial with insulin glargine; only 1 of the included placebo-controlled trials reported any cases of pancreatitis (1 case vs. 1 case).
	Low	Rates of gastrointestinal side effects were higher with liraglutide than with insulin glargine (1 study).

Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
	Low	Rates of minor hypoglycemia were similar between liraglutide and insulin glargine (1 study), but more patients treated with liraglutide had major hypoglycemic events (5 vs. 0)
	Low	In the active-control trial comparing liraglutide to rosiglitazone, the incidence of serious adverse events was similar between treatment arms. Nausea was more common in the liraglutide groups compared to rosiglitazone.
	Low	In the active-control trial comparing liraglutide to sitagliptin, the incidence of serious adverse events was similar between treatment arms. Gastrointestinal complaints, particularly nausea, were more common in the liraglutide arms of the study than in the sitagliptin arm.
	Moderate	Total withdrawal rates were lower for liraglutide (0.6 mg daily, 1.2 mg daily, and 1.8 mg daily) than placebo (RR range 0.37 to 0.62).
	Moderate	There was no difference in the risk of withdrawal due to adverse events with liraglutide 0.6 mg daily, 1.2 mg, or 1.8 mg daily vs. placebo.
	Moderate	The incidence of hypoglycemia was elevated with liraglutide 1.8 mg daily compared with placebo (RR 1.66, CI 1.18 to 2.34). Rates of hypoglycemia were not significantly different between liraglutide 0.6 mg daily or liraglutide 1.2 mg daily, and placebo.
	High	The rates of gastrointestinal side effects were higher in the liraglutide-treated groups than in the placebo group. The risk increased with higher doses (RR 1.76 for 0.6 mg; RR 2.33 for 1.2 mg; RR 3.14 for 1.8 mg), but generally waned over time.
	Low	In the 2 studies that examined lipid parameters, liraglutide improved triglycerides compared to placebo in both studies, and improved LDL levels compared to placebo in 1 study.
	Low	One study compared lipid parameters in liraglutide-treated and sitagliptin-treated subjects and found no significant difference with the exception of a slightly larger decrease in total cholesterol with liraglutide 1.8 mg (-6.6 mg/dL versus -0.8 mg/dL, P=0.0332).
TZDs: Pioglitazone Rosiglitazone	Not graded	In September 2010, the US Food and Drug Administration restricted access for rosiglitazone and combination products that contain rosiglitazone due to an increased risk of cardiovascular adverse events.
	Low	We found no evidence of increased all-cause mortality or cardiovascular mortality with pioglitazone; some studies suggest reduced risk of all-cause and cardiovascular mortality with pioglitazone.
	High	Evidence from systematic reviews, RCTs, and observational studies indicate that both pioglitazone and rosiglitazone increase the risk of heart failure (odds ratios range from 1.32 to 2.18 in various meta-analyses).
	High	Evidence from systematic reviews, RCTs, and observational studies indicate that both pioglitazone and rosiglitazone increase the risk of edema (odds ratios range from 2.26 to 4.62 in various meta-analyses).
	High	The risk of hypoglycemia is reduced with TZDs when compared with sulfonylureas; the risk is similar to the risk with metformin.

Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?

Drugs	Strength of evidence[a]	Conclusion
	Moderate	Both TZDs resulted in a similar weight increase. The increase is similar to that with sulfonylureas.
	Moderate	Risk of fractures is increased among patients exposed to TZDs (OR 1.45, 95% CI 1.18 to 1.79, from meta-analysis of 10 RCTs involving 13,715 participants). This risk appears to be increased among women (OR 2.23, 95% CI 1.65 to 3.10) but not among men (OR 1.00, 95% CI 0.73 to 1.39). These findings are consistent with the results of the ADOPT trial.
	Low	Adverse events occurring with pioglitazone and rosiglitazone were similar in head-to-head trials.
FDCPs and Dual Therapy: Avandamet® Actoplus Met® Avandaryl® Duetact® Janumet® Metformin + Rosiglitazone Metformin + Pioglitazone Glimepiride + Rosiglitazone Glimepiride + Pioglitazone Metformin + Sitagliptin	Insufficient	*Harms in children* We did not find any evidence meeting inclusion/exclusion criteria on children
	Insufficient	*Harms in adults* We found no head-to-head trials that compared harms between any 2 FDCPs.
	Insufficient	We found no studies that evaluated long-term harms beyond 15 months for any available FDCP.
	Low	*Avandamet® or dual therapy with metformin plus rosiglitazone* Similar rates of withdrawals due to adverse events with Avandamet®/dual therapy groups and monotherapy groups (3 trials ranging from 24 to 32 weeks).
	Low	Similar or slightly higher rates of hypoglycemia with Avandamet®/dual therapy groups and monotherapy groups (3 trials ranging from 24 to 32 weeks).
	Low	Similar rates of adverse cardiovascular events with Avandamet®/dual therapy and monotherapy, but duration of studies may not have been sufficient to reliably assess adverse cardiovascular events (3 trials ranging from 24 to 32 weeks).
Avandamet® or dual therapy with metformin plus rosiglitazone	Moderate	Gastrointestinal adverse effects were the most frequently reported adverse events with Avandamet® and dual therapy with metformin plus rosiglitazone. Rates of gastrointestinal adverse effects with Avandamet® or dual therapy were high (28 to 47%), but were the same or slightly lower than those with metformin monotherapy.
	Moderate	Higher rates of edema with Avandamet® or dual therapy than with metformin monotherapy.
	Moderate	In 2 included trials of Avandamet®, subjects receiving Avandamet® reported virtually no change in weight from baseline (0.0 kg to 0.01 kg) compared with slight weight gain with rosiglitazone monotherapy, and slight weight gain (1.9 kg) or weight loss (−2.9 kg) with metformin monotherapy.
Avandaryl® or dual therapy with rosiglitazone and glimepiride	Not graded	*Avandaryl® or dual therapy with rosiglitazone and glimepiride* Few definitive conclusions about comparative harms for Avandaryl® or dual therapy with rosiglitazone and glimepiride can be drawn from direct evidence. The 2 included trials were a 28 week trial (N=874) comparing 2 dosages of Avandaryl® with glimepiride monotherapy and rosiglitazone monotherapy, and a 20 week trial (N=40) comparing concurrent use of rosiglitazone and glimepiride with rosiglitazone monotherapy.
	Moderate	Rates of hypoglycemia were greater with Avandaryl® or dual therapy than with monotherapy.

Key Question 2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and drug combinations (administered as fixed dose combination products or dual therapy) for children and adults with diabetes mellitus?		
Drugs	**Strength of evidence[a]**	**Conclusion**
	Moderate	Weight gain was slightly greater with Avandaryl® or dual therapy than with monotherapy.
Actoplus Met® or dual therapy with pioglitazone and metformin	Not graded	*Actoplus Met® or dual therapy with pioglitazone and metformin* Evidence was limited to one large trial (N=600) comparing Actoplus Met® with component monotherapies and a 15 month trial comparing dual therapy with pioglitazone and metformin to monotherapy with either that reported very little harms information.
	Low	Overall incidences of adverse events were similar across treatment arms: 50.7%, 52.1% and 53.1% for the Actoplus Met®, pioglitazone monotherapy, and metformin monotherapy arms, respectively. Reports of severe adverse events were also similarly distributed among the arms: 1.0% for Actoplus Met®, 1.6% for pioglitazone monotherapy, and 1.4% for metformin monotherapy. Fewer withdrawals due to adverse events occurred in the Actoplus Met® and pioglitazone alone arms compared with the metformin alone arm (3.0%, 3.2%, and 4.8%, respectively).
	Low	Headache was reported more frequently with Actoplus Met® than with either component monotherapy.
	Low	Patients on Actoplus Met® gained less weight than patients on pioglitazone alone but gained more weight than patients on metformin alone.
	Low	Patients on Actoplus Met® experienced lower rates of edema than patients on pioglitazone alone but higher rates of edema than patients on metformin alone.
	Low	Diarrhea, hypoglycemia, and gastrointestinal events were reported most frequently in patients on metformin monotherapy and least frequently in patients on pioglitazone alone, with patients on Actoplus Met® reporting rates in between those for metformin and pioglitazone.
Janumet® or dual therapy with sitagliptin and metformin	Not graded	*Janumet® or dual therapy with sitagliptin and metformin* No studies including Janumet® were found that met inclusion criteria. Evidence was limited to 1 trial ((N=1,091, with outcomes reported at 24 and 54 weeks) including dual therapy with sitagliptin and metformin.[31, 32]
	Low	Gastrointestinal adverse effects were commonly reported (15−31% across all treatment arms) and were similar between sitagliptin 100 plus metformin 2000 and metformin 2000 monotherapy at 24 weeks (24.7 vs. 25.3%) and at 54 weeks (29 vs. 31%). Rates were slightly higher for sitagliptin 100 plus metformin 1000 compared with sitagliptin 100 monotherapy or with metformin 1000 monotherapy at 24 weeks (17.9 vs. 15.1 vs. 15.9%, respectively) and at 54 weeks (26 vs. 20 vs. 20%).
	Low	Weight loss for subjects treated with sitagliptin plus metformin (−0.7 to −1.7 kg) was similar to that for subjects treated with metformin monotherapy (−1.0 to −1.5 kg).
	Low	The combination of sitagliptin plus metformin resulted in slightly greater improvements in total cholesterol (at 24 weeks: −3.2 to −7.1; at 54 weeks: −6.6 to −8.8 mg/dL) compared with metformin or sitagliptin monotherapy (at 24 weeks: −1.5 to +2.7; at 54 weeks: −0.2 to +0.5 mg/dL)

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications differ in efficacy/effectiveness or frequency of adverse events?		
Drugs	**Strength of evidence[a]**	**Conclusion**
Amylin agonists: Pramlintide DPP-IV inhibitors: Sitagliptin Saxagliptin GLP-1 agonists: Exenatide Liraglutide	Insufficient	We found insufficient evidence to draw any firm conclusions about whether there are subgroups of patients based on demographics, comorbidities, or other medications for which newer diabetes medications differ from each other in efficacy/effectiveness or frequency of adverse events. The evidence that was found is generally hypothesis-generating, using post hoc pooled analyses or post hoc subgroup analyses in an exploratory manner.
TZDs: Pioglitazone Rosiglitazone	Insufficient	We found insufficient evidence to draw any firm conclusions about whether there are subgroups of patients based on most demographic characteristics, comorbidities, or other medications for which newer diabetes medications differ in efficacy/effectiveness or frequency of adverse events. The evidence that was found is generally hypothesis-generating, using post hoc pooled analyses or post hoc subgroup analyses in an exploratory manner.
	Moderate	Some studies reported that the risk of fractures is increased with TZD use in women, but not in men.[204, 309] On analysis of data from ADOPT found hazard ratios comparing rosiglitazone with metformin and glyburide were 1.81 (95% CI 1.17 to 2.80) and 2.13 (1.30 to 3.51), respectively.[309] A systematic review and meta-analysis reported an increased risk among women (OR 2.23, 95% CI 1.65 to 3.10), but not in men (OR 1.00, 95% CI 0.73, 1.39).[204]
FDCPs and Dual Therapy	Insufficient	We found no studies meeting inclusion/exclusion criteria that provided evidence to determine whether there are subgroups of patients based on demographics, comorbidities, or other medications for which newer diabetes medications differ from each other in efficacy/effectiveness or frequency of adverse events

Abbreviations: FDCP, fixed-dose combination product; HbA1c, OR, odds ratio; RCT, randomized controlled trial; RR, relative risk, SE, standard error; TZD, thiazolidinedione; WMD, weighted mean difference.

[a] See Appendix F for full strength of evidence tables for each comparison, for outcomes of greatest importance, or those reported enough to assess the strength of evidence.

CONCLUSIONS

All of the included medications were efficacious for reducing HbA1c and none of the newer medications appear to cause weight gain. Little data was available to evaluate the long-term effectiveness of the newer medications compared with more established treatments, limiting our ability to determine how to best incorporate newer medications into clinical practice.

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Appendix A. Boxed warnings for included drugs

Trade name	Active ingredient(s)	Boxed warnings
Symlin®	Pramlintide Acetate	SYMLIN is used with insulin and has been associated with an increased risk of insulin induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.
Januvia®	Sitagliptin Phosphate	No boxed warning
Onglyza®	Saxagliptin Hydrochloride	No boxed warning
Byetta®	Exenatide	No boxed warning
Victoza®	Liraglutide Recombinant	Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumor

Trade name	Active ingredient(s)	Boxed warnings
Avandia®	Rosiglitazone Maleate	Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction must be considered. Not recommended in patients with symptomatic heart failure. Initiation of Avandia™ in patients with established NYHA Class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration 6 months: 14,237 total patients), most of which compared Avandia™ to placebo, showed Avandia™ to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing Avandia™ to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Trade name	Active ingredient(s)	Boxed warnings
Avandamet®	Metformin Hydrochloride Rosiglitazone Maleate	*Rosiglitazone maleate*: Congestive Heart Failure and Myocardial Ischemia Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of AVANDAMET, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDAMET must be considered. AVANDAMET is not recommended in patients with symptomatic heart failure. Initiation of AVANDAMET in patients with established NYHA Class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. *Metformin hydrochloride:* Lactic Acidosis Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, discontinue AVANDAMET and hospitalize the patient immediately.

Trade name	Active ingredient(s)	Boxed warnings
Avandaryl®	Rosiglitazone Maleate Glimepiride	Congestive Heart Failure and Myocardial Ischemia Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of AVANDARYL, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDARYL must be considered. AVANDARYL is not recommended in patients with symptomatic heart failure. Initiation of AVANDARYL in patients with established NYHA Class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.
Actos®	Pioglitazone Hydrochloride	Congestive Heart Failure Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients (see WARNINGS). After initiation of ACTOS, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered. ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated (see CONTRAINDICATIONS and WARNINGS).

Trade name	Active ingredient(s)	Boxed warnings
Actoplus Met®	Metformin Hydrochloride Pioglitazone Hydrochloride	Congestive Heart Failure Thiazolidinediones, including pioglitazone, which is a component of ACTOPLUS MET and ACTOPLUS MET XR, cause or exacerbate congestive heart failure in some patients (see WARNINGS, *Pioglitazone*). After initiation of ACTOPLUS MET or ACTOPLUS MET XR, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOPLUS MET or ACTOPLUS MET XR must be considered. ACTOPLUS MET and ACTOPLUS MET XR are not recommended in patients with symptomatic heart failure. Initiation of ACTOPLUS MET or ACTOPLUS MET XR in patients with established NYHA Class III or IV heart failure is contraindicated (see CONTRAINDICATIONS and WARNINGS, *Pioglitazone*). Lactic Acidosis Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, ACTOPLUS MET or ACTOPLUS MET XR should be discontinued and the patient hospitalized immediately (see WARNINGS, *Metformin Hydrochloride*).
Duetact®	Glimepiride Pioglitazone Hydrochloride	Thiazolidinediones, including pioglitazone, which is a component of DUETACT, cause or exacerbate congestive heart failure in some patients (see WARNINGS, Pioglitazone hydrochloride). After initiation of DUETACT, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation of DUETACT must be considered. DUETACT is not recommended in patients with symptomatic heart failure. Initiation of DUETACT in patients with established NYHA Class III or IV heart failure is contraindicated

Trade name	Active ingredient(s)	Boxed warnings
Janumet®	Metformin Hydrochloride Sitagliptin Phosphate	Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, JANUMET[1] should be discontinued and the patient hospitalized immediately.
Kombiglyze[a]	Saxagliptin hydrochloride Metformin hydrochloride	Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, saxagliptin hydrochloride/ metformin hydrochloride extended-release combination should be discontinued and the patient hospitalized immediately.

[a] Kombiglyze was not included in this review because it wasn't yet approved when the inclusion/exclusion criteria were finalized

Appendix B. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see External Validity

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond.

The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See External Validity.

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See Adverse Event

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See Blinding

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable

outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around

the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

> *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
>
> *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
>
> *Continuous:* taking values on a continuum (e.g. HbA1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started

Appendix C. Search strategies

New Diabetes Drugs: Pramlintide, Exenatide, Sitagliptin, Saxagliptin PubMed December 18, 2009

Search	Most Recent Queries	Result
#2	Search pramlintide	222
#3	Search amylin	1769
#4	Search Symlin	224
#7	Search 196078-30-5[rn]	0
#10	Search #2 OR #3 OR #4 OR #7	1858
#11	Search ("2008/01/01"[Entrez Date] : "3000"[Entrez Date]) AND (#10) Limits: Humans, English	150
#12	Search exenatide	692
#13	Search Byetta	695
#14	Search exendin-4	805
#15	Search glp-1	3691
#16	Search 141732-76-5[rn]	550
#17	Search #12 OR #13 OR #14 OR #15 OR #16	3982
#18	Search ("2008/01/01"[Entrez Date] : "3000"[Entrez Date]) AND (#17) Limits: Humans, English	541
#21	Search sitagliptin	268
#22	Search januvia	269
#23	Search dipeptidyl peptidase	3908
#24	Search cd26 inhibitor	391
#25	Search gliptins	982
#26	Search 790712-60-6[rn]	0
#27	Search #21 OR #22 OR #23 OR #24 OR #25 OR #26	4080
#28	Search ("2008/01/01"[Entrez Date] : "3000"[Entrez Date]) AND (#27) Limits: Humans, English	404
#32	Search Onglyza	39

#33	Search saxagliptin	39
#34	Search 361442-04-8 [rn]	0
#35	Search #32 OR #33 OR #34	39
#36	Search #35 Limits: Humans, English	25
#37	Search #11 OR #18 OR #28 OR #36 Limits: Humans, English	921
#39	Search "diabetes mellitus, type 2"[MeSH Terms] Limits: Humans, English	45028
#40	Search #37 AND #39 Limits: Humans, English	395
#41	Search **"diabetes mellitus"[MeSH Terms]** Limits: **Humans, English**	152458
#42	Search **#37 AND #41** Limits: **Humans, English** Sort by: **Author**	464

TZD Search January 11, 2010

Search	Most Recent Queries	Result
#2	Search **thiazolidinediones**	7171
#3	Search **pioglitazone**	2314
#5	Search **rosiglitazone**	3266
#7	Search **#2 OR #3 OR #5**	8067
#9	Search **"Diabetes Mellitus, Type 2"[Mesh]**	56495
#10	Search **#7 AND #9**	2484
#11	Search **("2007/08/01"[Entrez Date] : "3000"[Entrez Date]) AND (#10)** Limits: **English**	612
#12	Search **#11** Limits: **Humans, English**	568
#13	Search **#11** Limits: **Editorial, Letter, Case Reports**	83
#14	Search **#12 NOT #13** Sort by: **Author**	485
#15	Search **"thiazolidinediones"[MeSH Terms]**	6290
#16	Search **"pioglitazone"[Substance Name]**	1661
#17	Search **"rosiglitazone"[Substance Name]**	2328
#18	Search **#15 OR #16 OR #17**	6290

#19	Search **#9 AND #18**	2110
#20	Search **("2007/08/01"[Entrez Date] : "3000"[Entrez Date]) AND (#19)** Limits: **Humans, English**	480
#21	Search **#20** Limits: **Editorial, Letter, Case Reports**	82
#23	Search **#20 NOT #21** Sort by: **Author**	398
#24	Search **#14 NOT #23** Sort by: **Author**	87

Cochrane: 187 – 104 =83
IPA: 193 (31 internal) 162 – 35 = 127

Fixed Dose Combination Product Search January 11, 2010

Search	Most Recent Queries	Result
#1	Search **Avandamet**	20
#3	Search **metformin**	5829
#4	Search **rosiglitazone**	3266
#6	Search **#3 AND #4**	472
#7	Search **#1 OR #6**	472
#8	Search **pioglitazone**	2314
#10	Search **#3 AND #8**	395
#11	Search **Actoplus Met**	2
#13	Search **#10 OR #11**	395
#14	Search **glimepiride**	547
#16	Search **#14 AND #4**	69
#17	Search **Avandaryl**	1
#18	Search **#16 OR #7**	496
#19	Search **#14 AND #8**	75
#20	Search **Duetact**	2
#21	Search **#19 OR #20**	75
#22	Search **sitagliptin**	274

#24	Search **#22 AND #3**	82
#25	Search **Janumet**	4
#26	Search **#24 OR #25**	82
#27	Search **#7 OR #13 OR #18 OR #21 OR #26**	821
#28	Search **("2007/01/01"[Entrez Date] : "3000"[Entrez Date]) AND (#27)** Limits: **Humans, English**	295
#32	Search **"Diabetes Mellitus, Type 2"[Mesh]** Limits: **Humans, English**	45298
#33	Search **#28 AND #32** Limits: **Humans, English**	233
#39	Search **#33** Limits: **Editorial, Letter, Case Reports**	18
#40	Search **#33 NOT #39** Sort by: **Author**	215

TZD + Insulin Search February 4, 2010

Search	Most Recent Queries	Result
#20	Search **"pioglitazone "[Substance Name]**	1663
#21	Search **"rosiglitazone "[Substance Name]**	2332
#22	Search **"Insulin"[Mesh]**	135651
#23	Search **#20 AND #22**	329
#24	Search **#21 AND #22**	383
#25	Search **#23 OR #24**	674
#26	Search **#25** Limits: **Humans, English**	362
#27	Search **#26** Limits: **Humans, Editorial, Letter, Case Reports, English**	25
#28	Search **#26 NOT #27** Sort by: **PublicationDate**	337
#30	Search **("Insulin/administration and dosage"[Mesh] OR "Insulin/adverse effects"[Mesh] OR**	96222

	"Insulin/analogs and derivatives"[Mesh] OR "Insulin/analysis"[Mesh] OR "Insulin/diagnostic use"[Mesh] OR "Insulin/pharmacology"[Mesh] OR "Insulin/poisoning"[Mesh] OR "Insulin/therapeutic use"[Mesh] OR "Insulin/therapy"[Mesh] OR "Insulin/toxicity"[Mesh]))	
#31	Search **#20 AND #30**	265
#32	Search **#21 AND #30**	301
#33	Search **#31 OR #32**	537
#34	Search **#33** Limits: **Humans, English**	302
#35	Search **#34** Limits: **Editorial, Letter, Case Reports**	20
#36	Search **#34 NOT #35**	282

Cochrane: 51 -39 dups =12
IPA: 314 -97 dups = 217

Liraglutide Search March 22, 2010

Search	Most Recent Queries	Result
#1	Search **"liraglutide "[Substance Name]**	107
#2	Search **liraglutide**	184
#3	Search **Victoza**	3
#4	Search **204656-20-2[rn]**	0
#5	Search **#1 OR #2 OR #3 OR #4**	184
#6	Search **"diabetes mellitus, type 2"[MeSH Terms]**	57536
#7	Search **"Diabetes Mellitus/drug therapy"[Mesh]**	39859
#8	Search **#6 OR #7**	83622
#9	Search **#5 AND #8**	112
#10	Search **#9** Limits: **Humans, English**	100
#11	Search **#10** Limits: **Editorial, Letter, Case Reports**	4
#12	Search **#10 NOT #11** Sort by: **PublicationDate**	96

Cochrane: 7 (22-15 duplicates)
EMBASE: 99 (103-4 duplicate)
IPA: 26 (50-24 duplicates)

"Diabetes Mellitus/drug therapy"[Mesh], with date limits March 23, 2010

Search	Most Recent Queries	Result
#1	Search **pramlintide**	231
#2	Search **amylin**	1810
#3	Search **Symlin**	233
#4	Search **196078-30-5[rn]**	0
#5	Search **#1 OR #2 OR #3 OR #4**	1903
#6	Search **#5** Limits: **Humans, English**	1193
#7	Search **(#6) AND "2008/01/01"[Entrez Date] : "2009/12/18"[Entrez Date]**	173
#8	Search **exenatide**	741
#9	Search **Byetta**	744
#10	Search **exendin-4**	862
#11	Search **glp-1**	3839
#12	Search **141732-76-5[rn]**	581
#13	Search **#8 OR #9 OR #10 OR #11 OR #12**	4149
#14	Search **#13** Limits: **Humans, English**	2122
#15	Search **(#14) AND "2008/01/01"[Entrez Date] : "2009/12/18"[Entrez Date]**	628
#16	Search **sitagliptin**	292
#17	Search **januvia**	293
#18	Search **dipeptidyl peptidase**	3986
#19	Search **cd26 inhibitor**	402
#20	Search **gliptins**	1036
#21	Search **790712-60-6[rn]**	0
#22	Search **#16 OR #17 OR #18 OR #19 OR #20 OR #21**	4168
#23	Search **#22** Limits: **Humans, English**	2191
#24	Search **(#23) AND "2008/01/01"[Entrez Date] : "2009/12/18"[Entrez Date]**	455
#25	Search **Onglyza**	45
#26	Search **saxagliptin**	45
#27	Search **361442-04-8 [rn]**	0
#28	Search **#25 OR #26 OR #27**	45
#29	Search **#28** Limits: **Humans, English**	38
#30	Search **#7 OR #15 OR #24 OR #29**	1063
#31	Search **"diabetes mellitus, type 2"[MeSH Terms]**	57550
#32	Search **#30 AND #31**	452
#33	Search **"Diabetes Mellitus/drug therapy"[Mesh]**	39866
#34	Search **#30 AND #33**	390
#36	Search **#34 AND #32**	353
#37	Search **#34 NOT #36**	37

Diabetes medications update search July 28, 2010

Search	Most Recent Queries	Result
#1	Search pramlintide	235
#2	Search amylin	1849
#3	Search Symlin	237
#4	Search 196078-30-5[rn]	0
#5	Search #1 OR #2 OR #3 OR #4	1945

#6	Search #5 Limits: Humans, English	1233
#7	Search exenatide	823
#8	Search Byetta	826
#9	Search exendin-4	952
#10	Search glp-1	4093
#11	Search 141732-76-5[rn]	640
#12	Search #7 OR #8 OR #9 OR #10 OR #11	4430
#13	Search #12 Limits: Humans, English	2277
#14	Search sitagliptin	344
#15	Search januvia	345
#16	Search dipeptidyl peptidase	4121
#17	Search cd26 inhibitor	411
#18	Search gliptins	1100
#19	Search 790712-60-6[rn]	0
#20	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19	4327
#21	Search #20 Limits: Humans, English	2274
#22	Search Onglyza	63
#23	Search saxagliptin	63
#24	Search 361442-04-8[rn]	0
#25	Search #22 OR #23 OR #24	63
#26	Search #25 Limits: Humans, English	45
#27	Search #6 OR #13 OR #21 OR #26	5203
#28	Search ((#27) AND "2009/9/1"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	384
#29	Search liraglutide	217
#30	Search Victoza	217
#31	Search 204656-20-2[rn]	0
#32	Search #29 OR #30 OR #31	217
#33	Search #32 Limits: Humans, English	142
#34	Search ((#33) AND "2010/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	19
#35	Search Search "rosiglitazone-metformin combination"[Substance Name] OR "rosiglitazone-metformin combination"[All Fields] OR "avandamet"[All Fields]	22
#36	Search ACTOplus met	2
#37	Search Avandaryl	1
#38	Search Duetact	2
#39	Search "janumet"[Substance Name] OR "janumet"[All Fields]	5
#40	Search #35 OR #36 OR #37 OR #38 OR #39	32
#41	Search #40 Limits: Humans, English	26
#42	Search ((#41) AND "2007/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	15
#43	Search "2,4-thiazolidinedione"[Substance Name] OR "2,4-thiazolidinedione"[All Fields] OR "thiazolidinedione"[All Fields] OR "thiazolidinediones"[MeSH Terms] OR "thiazolidinediones"[All Fields]	7968
#44	Search 2295-31-0[rn]	453
#45	Search #43 OR #44	7968
#46	Search #45 Limits: Humans, English	4910
#47	Search "pioglitazone"[Substance Name] OR "pioglitazone"[All Fields]	2486
#48	Search Actos	2493

#49	Search 112529-15-4[rn]	1770
#50	Search 111025-46-8[rn]	1770
#51	Search #47 OR #48 OR #49 OR #50	2493
#52	Search #51 Limits: Humans, English	1451
#53	Search "rosiglitazone"[Substance Name] OR "rosiglitazone"[All Fields]	3537
#54	Search Avandia	3542
#55	Search 155141-29-0[rn]	0
#56	Search 122320-73-4[rn]	2531
#57	Search #53 OR #54 OR #55 OR #56	3542
#58	Search #57 Limits: Humans, English	2036
#59	Search #46 OR #52 OR #58	5248
#60	Search ((#59) AND "2007/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	2102
#61	Search #28 OR #34 OR #42 OR #60	2457
#62	Search "diabetes mellitus, type 2"[MeSH Terms]	59427
#63	Search #61 AND #62	1033
#64	Search "Diabetes Mellitus/drug therapy"[Mesh]	40923
#65	Search #61 AND #64	1001
#66	Search #63 OR #65	1157
#67	Search #66 Limits: Editorial, Letter, Case Reports	159
#68	Search #66 NOT #67	995

PubMed: 995
Cochrane: 39 (259 before duplicates removed)
IPA: 18 (59 before duplicates removed)

Appendix D. Excluded studies and studies of poor quality

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. The list does not include the publications excluded for wrong publication type (e.g. letter, editorial, non-systematic reviews, case reports, case series). See previous reports on newer diabetes medications, TZDs, and fixed dose combination products on the Drug Effectiveness Review Project website for studies excluded previously.

2 = Ineligible drug or already included in a previous Drug Effectiveness Review Project report of diabetes medications

3 = Ineligible comparison or no comparison

4 = Ineligible outcome

5 = Ineligible study design (including duration too short)

7 = Ineligible population

UNR = Full text not available

P = Poor quality rating

Excluded References	Exclude Code
Abe M, Kikuchi F, Kaizu K, Matsumoto K. Combination therapy of pioglitazone with voglibose improves glycemic control safely and rapidly in Japanese type 2-diabetic patients on hemodialysis. Clin Nephrol 2007;68(5):287-94.	3
Abe M, Kikuchi F, Okada K, Kaizu K, Matsumoto K. Efficacy of pioglitazone on type 2 diabetic patients with hemodialysis. Diabetes Res Clin Pract 2008;80(3):432-8.	3
Abe M, Okada K, Kikuchi F, Matsumoto K. Clinical investigation of the effects of pioglitazone on the improvement of insulin resistance and blood pressure in type 2-diabetic patients undergoing hemodialysis. Clin Nephrol 2008;70(3):220-8.	3
Aguilar D, Bozkurt B, Pritchett A, Petersen NJ, Deswal A. The impact of thiazolidinedione use on outcomes in ambulatory patients with diabetes mellitus and heart failure. J Am Coll Cardiol 2007;50(1):32-6.	3
Albertini JP, McMorn SO, Chen H, Mather RA, Valensi P. Effect of rosiglitazone on factors related to endothelial dysfunction in patients with type 2 diabetes mellitus. Atherosclerosis 2007;195(1):e159-66.	3
Alvarez Guisasola F, Mavros P, Nocea G, Alemao E, Alexander CM, Yin D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008;10 Suppl 1:8-15.	5
Alvarez Guisasola F, Tofe Povedano S, Krishnarajah G, Lyu R, Mavros P, Yin D. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. Diabetes Obes Metab 2008;10 Suppl 1:25-32.	5
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Appendix E. Meta-analyses

Sitagliptin Meta-Analyses

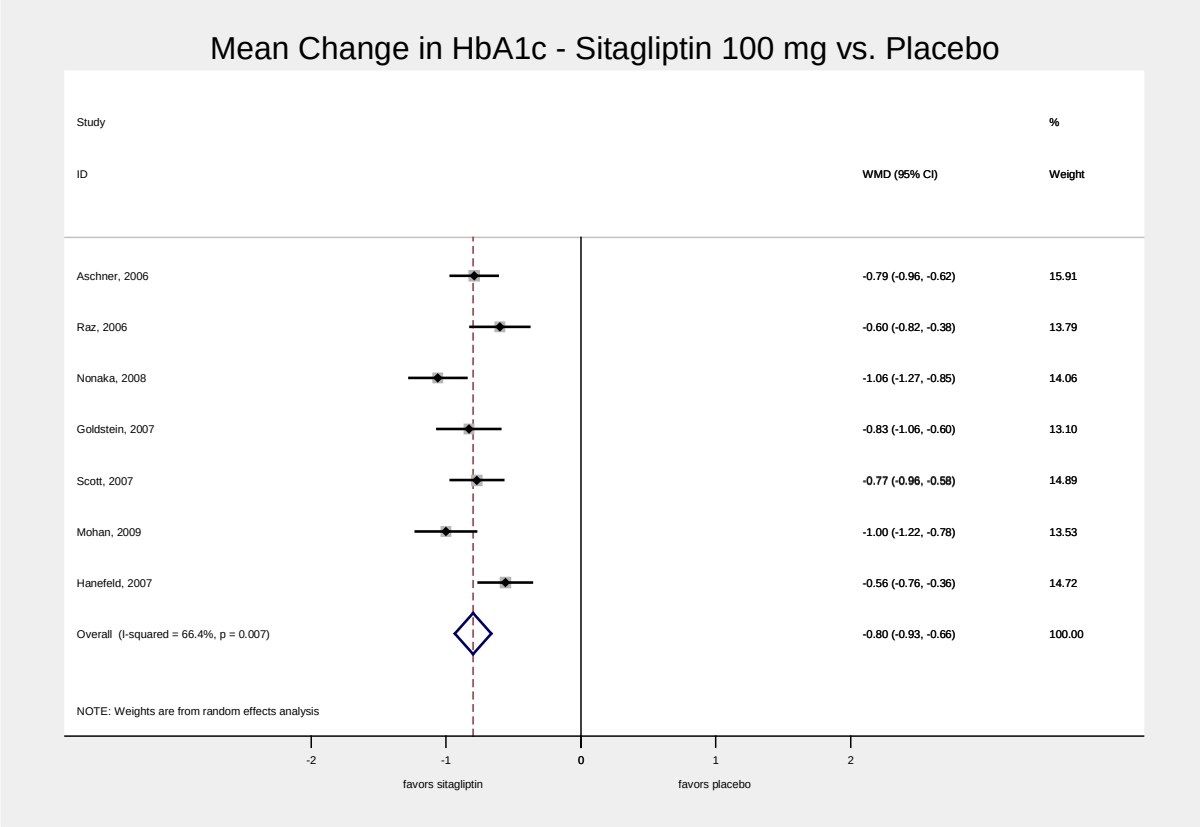
Note: Chan, 2008 was not included in the sitagliptin analyses because the study used 25mg and 50 mg doses.

1) Sitagliptin 100 mg v Placebo – Mean Change in HbA1c

Study Statistics

Study	WMD	[95% Conf. Interval]	% Weight
Aschner, 2006	−0.790	−0.963 −0.617	15.91
Raz, 2006	−0.600	−0.818 −0.382	13.79
Nonaka, 2008	−1.060	−1.272 −0.848	14.06
Goldstein, 2007	−0.830	−1.063 −0.597	13.10
Scott, 2007	−0.770	−0.964 −0.576	14.89
Mohan, 2009	−1.000	−1.224 −0.776	13.53
Hanefeld, 2007	−0.560	−0.758 −0.362	14.72
D+L pooled WMD	−0.799	−0.933 −0.664	100.00

Heterogeneity chi-squared = 7.86 (d.f. = 6) *P*=0.007; I-squared (variation in WMD attributable to heterogeneity) = 66.4%; Estimate of between-study variance Tau-squared = 0.0217; Test of WMD=0 : z= 11.65 *P*=0.000

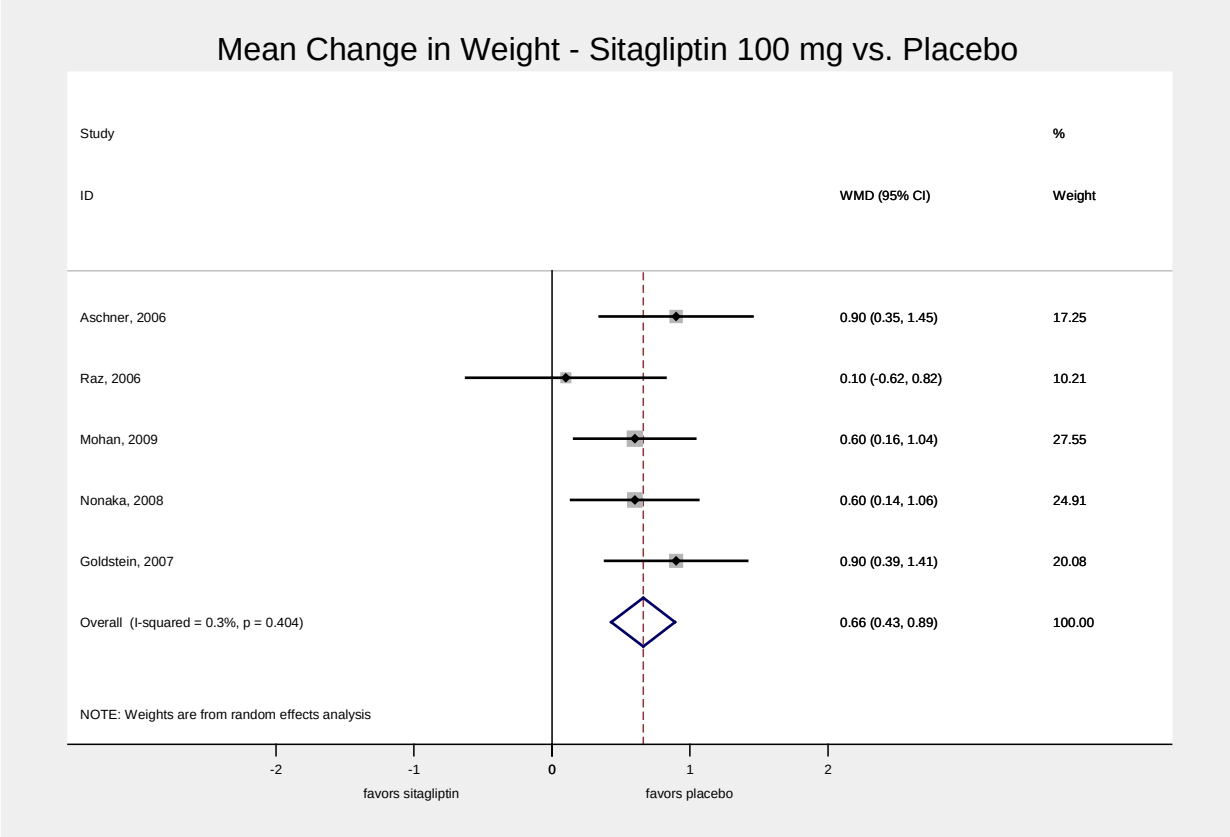


2) Sitagliptin 100 mg v Placebo – Mean Change in Weight

Study Statistics

Study	WMD	[95% Conf. Interval]	% Weight
Aschner, 2006	0.900	0.346 1.454	17.25
Raz, 2006	0.100	−0.621 0.821	10.21
Mohan, 2009	0.600	0.162 1.038	27.55
Nonaka, 2008	0.600	0.139 1.061	24.91
Goldstein, 2007	0.900	0.386 1.414	20.08
D+L pooled WMD	0.661	0.430 0.892	100.00

Heterogeneity chi-squared = 4.01 (d.f. = 4) *P*=0.404; I-squared (variation in WMD attributable to heterogeneity) = 0.3%; Estimate of between-study variance Tau-squared = 0.0002; Test of WMD=0 : z= 5.62 *P*=0.000

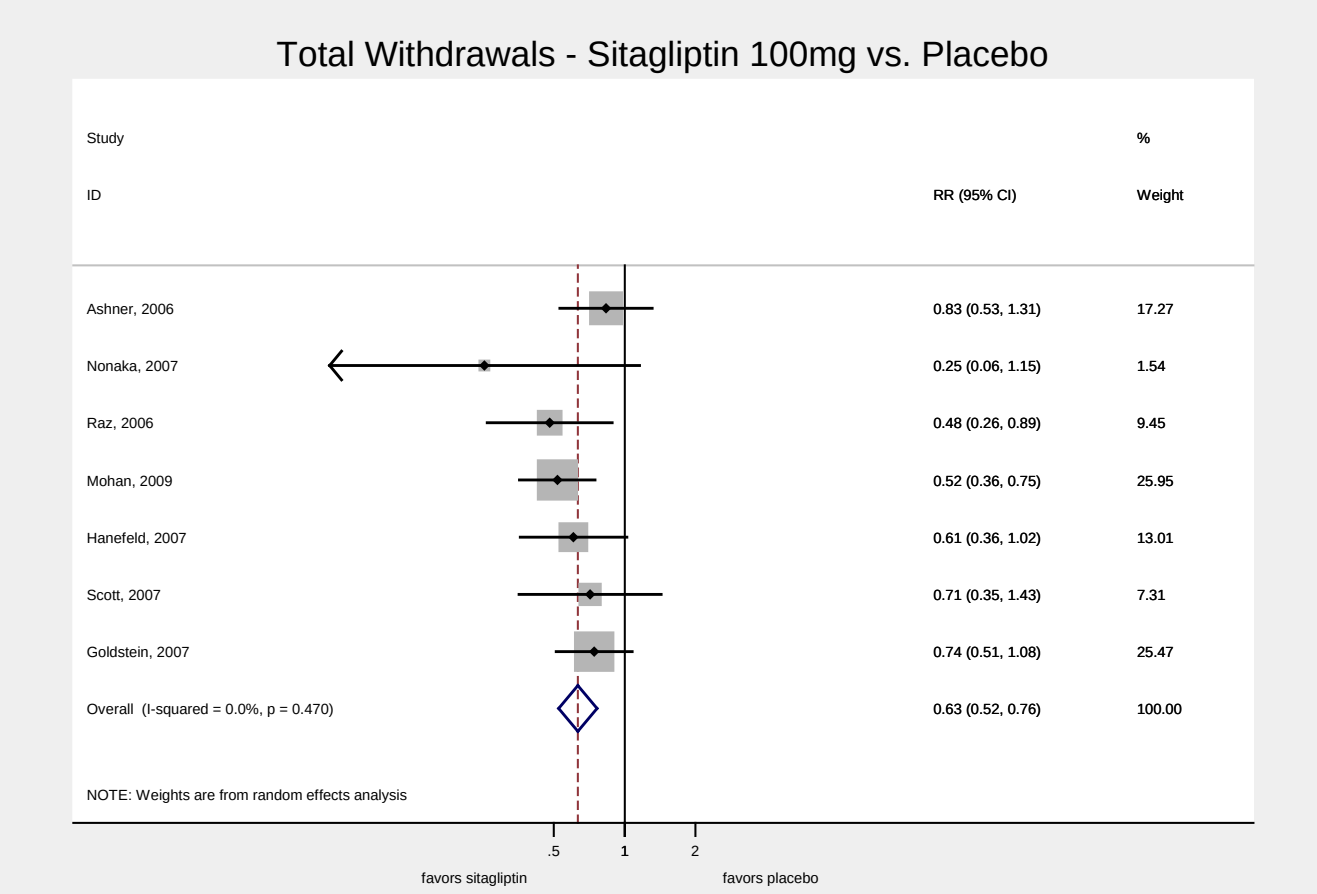


3) Sitagliptin 100 mg v Placebo – Total Withdrawals

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	0.833	0.530 1.310	17.27
Nonaka, 2007	0.253	0.056 1.154	1.54
Raz, 2006	0.480	0.260 0.885	9.45
Mohan, 2009	0.517	0.357 0.748	25.95
Hanefeld, 2007	0.605	0.359 1.020	13.01
Scott, 2007	0.712	0.355 1.427	7.31
Goldstein, 2007	0.742	0.511 1.078	25.47
D+L pooled RR	0.632	0.523 0.763	100.00

Heterogeneity chi-squared = 5.60 (d.f. = 6) *P*=0.470; I-squared (variation in RR attributable to heterogeneity) = 0.0%; Estimate of between-study variance Tau-squared = 0.0000; Test of RR=1 : z= 4.78 *P*=0.000

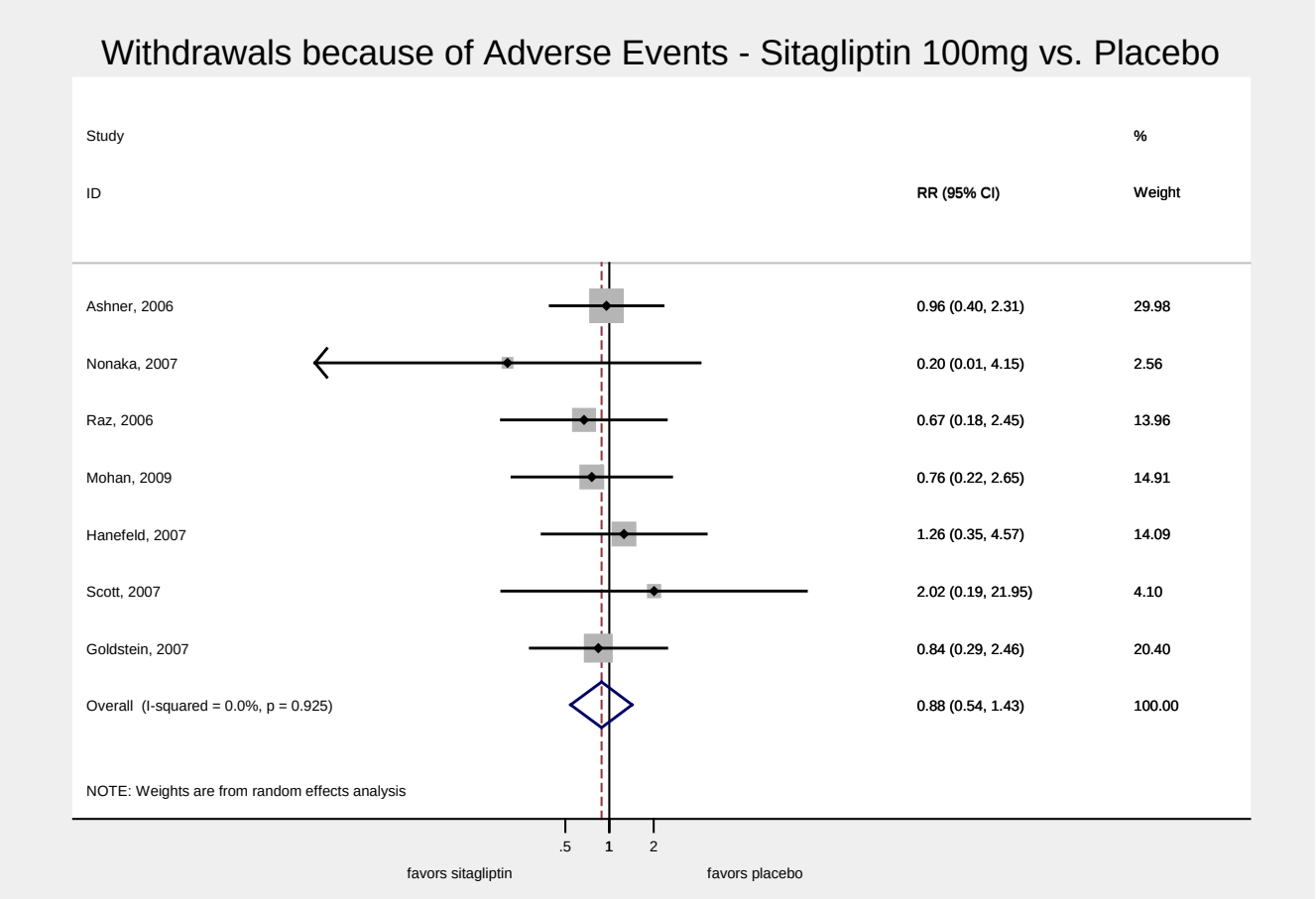


4) Sitagliptin 100 mg v Placebo – Withdrawals because of Adverse Events

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	0.957	0.396 2.313	29.98
Nonaka, 2007	0.203	0.010 4.151	2.56
Raz, 2006	0.671	0.184 2.447	13.96
Mohan, 2009	0.759	0.217 2.653	14.91
Hanefeld, 2007	1.261	0.348 4.573	14.09
Scott, 2007	2.016	0.185 21.950	4.10
Goldstein, 2007	0.843	0.289 2.458	20.40
D+L pooled RR	0.883	0.544 1.432	100.00

Heterogeneity chi-squared = 1.94 (d.f. = 6) *P*=0.925
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.50 *P*=0.614

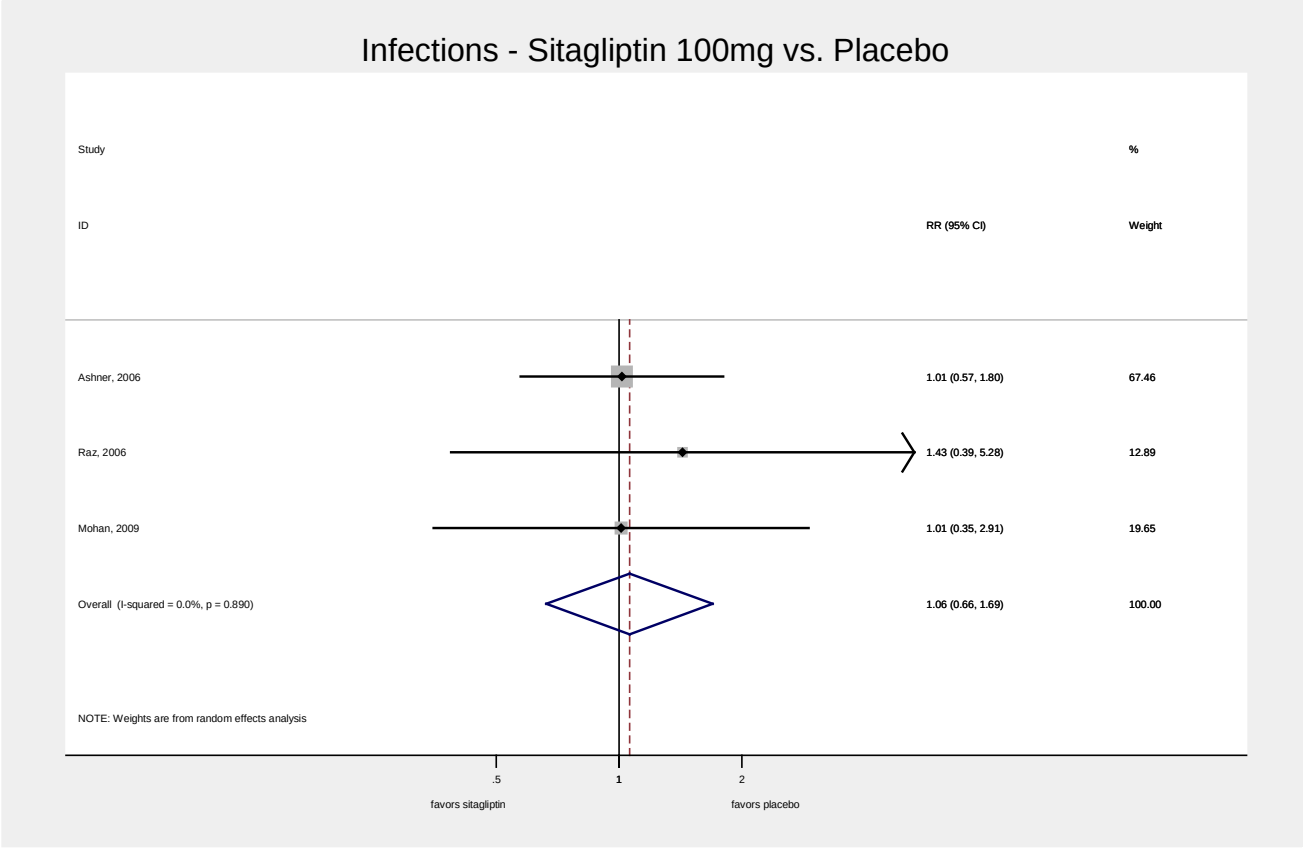


5) Sitagliptin 100 mg v Placebo – Infection

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	1.015	0.573 1.796	67.46
Raz, 2006	1.431	0.387 5.285	12.89
Mohan, 2009	1.011	0.351 2.914	19.65
D+L pooled RR	1.060	0.663 1.694	100.00

Heterogeneity chi-squared = 0.23 (d.f. = 2) *P*=0.890
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.24 *P*=0.808

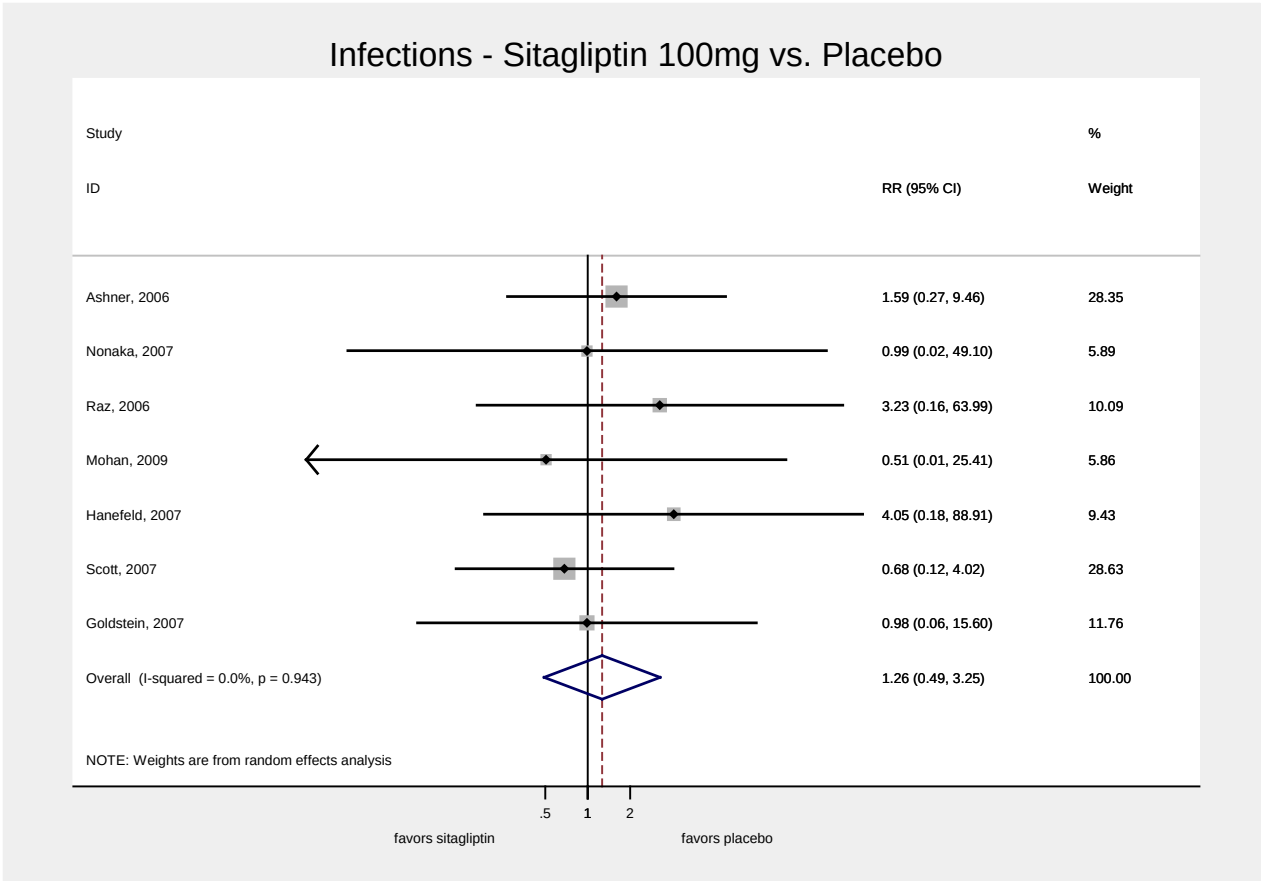


6) Sitagliptin 100 mg v Placebo – Hypoglycemia

Study statistics (0.5 added to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	1.595	0.269 9.459	28.35
Nonaka, 2007	0.987	0.020 49.100	5.89
Raz, 2006	3.234	0.163 63.989	10.09
Mohan, 2009	0.506	0.010 25.415	5.86
Hanefeld, 2007	4.055	0.185 88.908	9.43
Scott, 2007	0.683	0.116 4.017	28.63
Goldstein, 2007	0.983	0.062 15.597	11.76
D+L pooled RR	1.260	0.488 3.250	100.00

Heterogeneity chi-squared = 1.73 (d.f. = 6) *P*=0.943
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.48 *P*=0.633

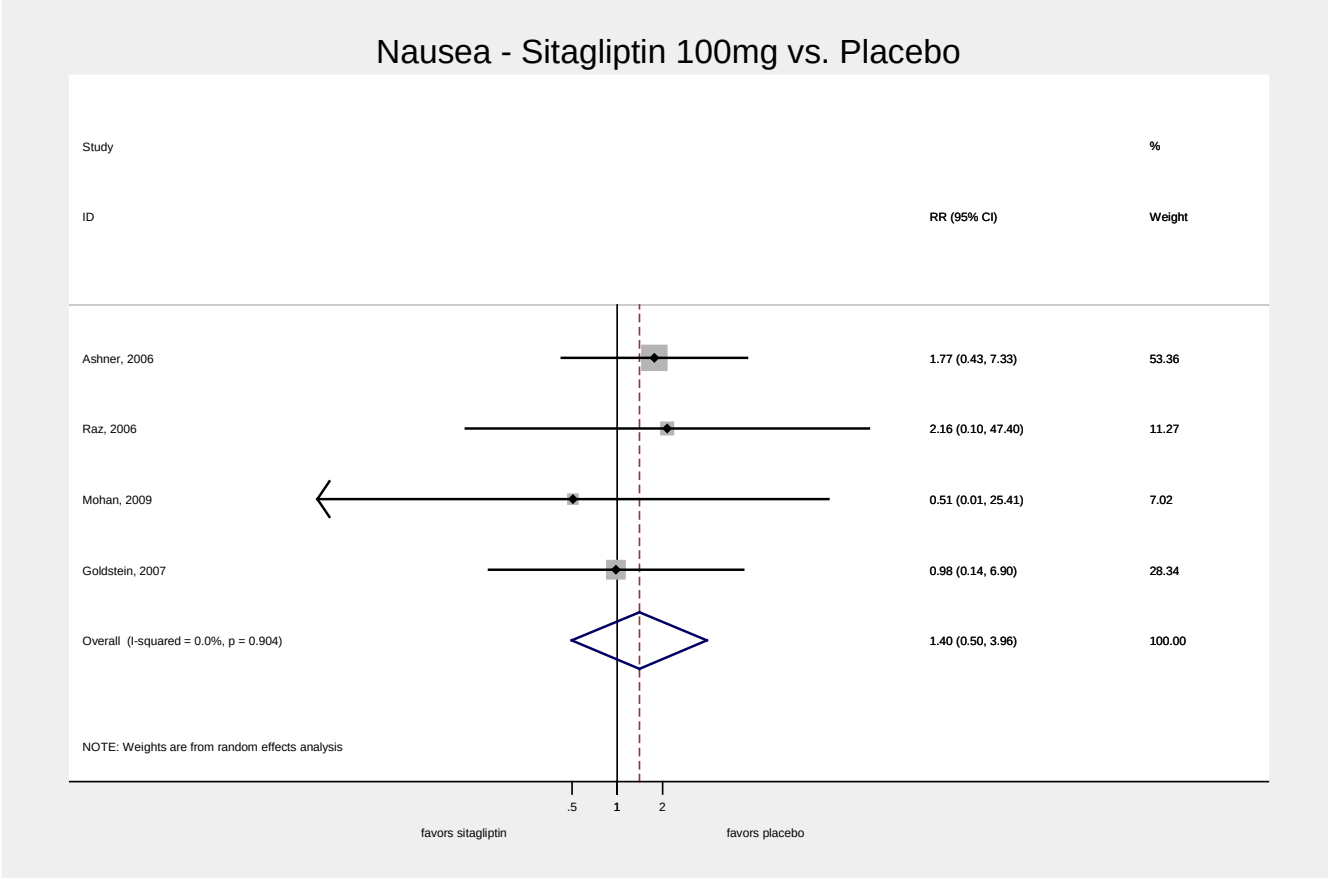


7) Sitagliptin 100 mg v Placebo – Nausea

Study statistics (0.5 added to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	1.772	0.428 7.332	53.36
Raz, 2006	2.156	0.098 47.400	11.27
Mohan, 2009	0.506	0.010 25.415	7.02
Goldstein, 2007	0.983	0.140 6.903	28.34
D+L pooled RR	1.404	0.497 3.962	100.00

Heterogeneity chi-squared = 0.57 (d.f. = 3) *P*=0.904
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.64 *P*=0.522

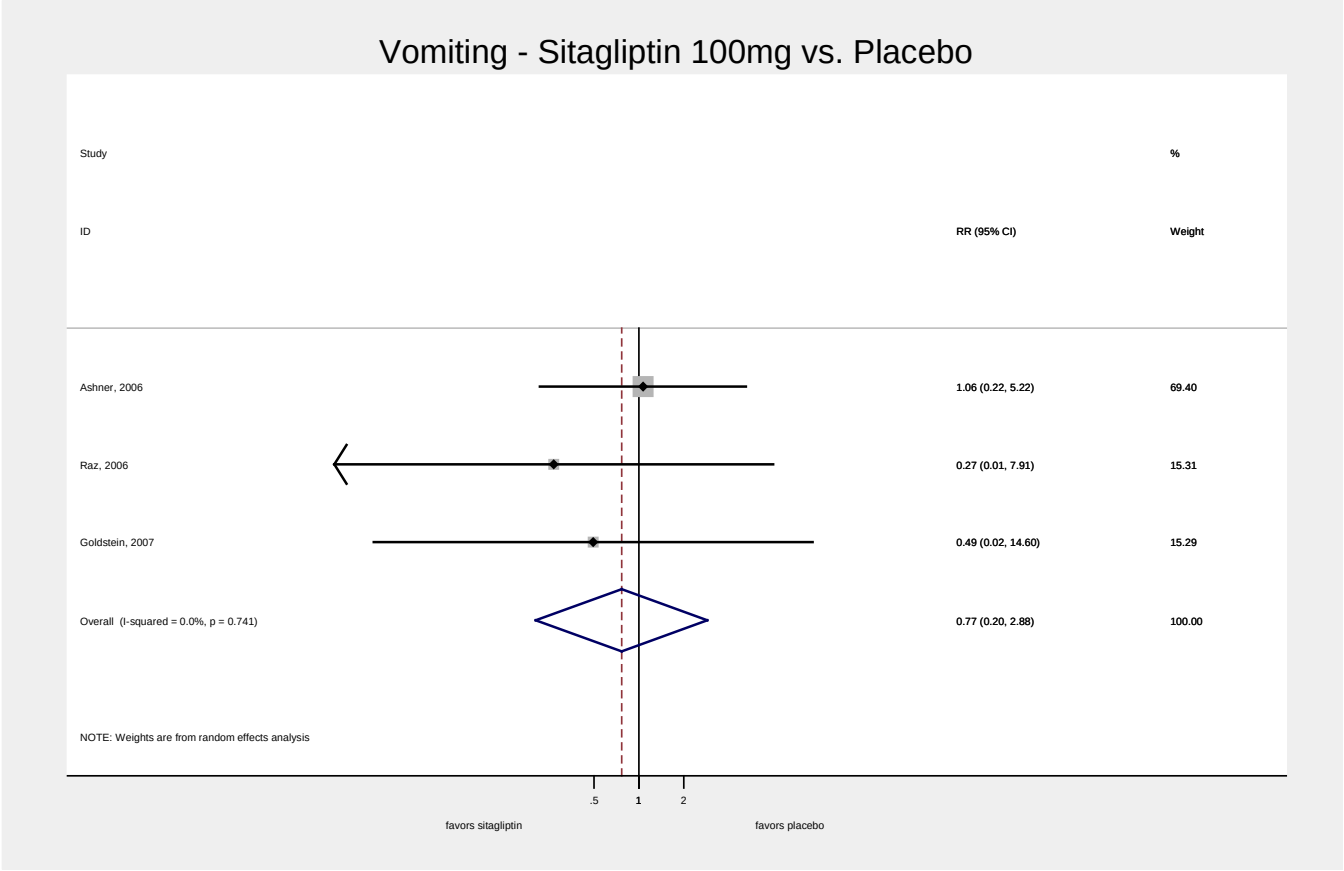


8) Sitagliptin 100 mg v Placebo – Vomiting

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Aschner, 2006	1.063	0.217 5.215	69.40
Raz, 2006	0.268	0.009 7.915	15.31
Goldstein, 2007	0.493	0.017 14.603	15.29
D+L pooled RR	0.765	0.203 2.879	100.00

Heterogeneity chi-squared = 0.60 (d.f. = 2) *P*=0.741
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.40 *P*=0.692



9) Sitagliptin 100 mg v Placebo – Change in Triglycerides

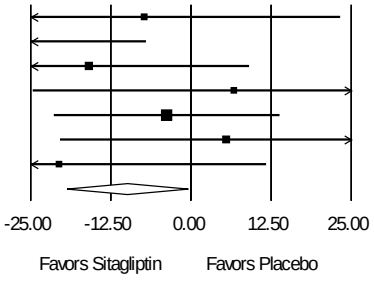
Pre-post correlation = 0.5
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
6.364	6	0.384	5.718

Sitagliptin vs. Placebo: Change in Triglycerides

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	-7.300	15.601	243.376	-37.876	23.276	-0.468	0.640
Charbonnel, 2006	-26.550	9.948	98.967	-46.048	-7.052	-2.669	0.008
Scott, 2007	-15.930	12.747	162.487	-40.914	9.054	-1.250	0.211
Goldstein, 2007	6.700	16.016	256.517	-24.691	38.091	0.418	0.676
Aschner, 2006	-3.800	8.982	80.673	-21.404	13.804	-0.423	0.672
Raz, 2006	5.500	13.230	175.037	-20.431	31.431	0.416	0.678
Mohan, 2009	-20.600	16.481	271.639	-52.903	11.703	-1.250	0.211
	-9.966	4.834	23.371	-19.441	-0.491	-2.061	0.039



9a. Sitagliptin 100 mg v Placebo – Change in Triglycerides

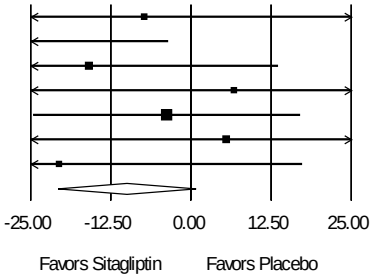
Pre-post correlation = 0.3
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
4.576	6	0.599	0.000

Sitagliptin vs. Placebo: Change in Triglycerides

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	-7.300	18.384	337.969	-43.332	28.732	-0.397	0.691
Charbonnel, 2006	-26.550	11.715	137.244	-49.511	-3.589	-2.266	0.023
Scott, 2007	-15.930	15.052	226.549	-45.430	13.570	-1.058	0.290
Goldstein, 2007	6.700	18.881	356.495	-30.306	43.706	0.355	0.723
Aschner, 2006	-3.800	10.626	112.907	-24.626	17.026	-0.358	0.721
Raz, 2006	5.500	15.653	245.026	-25.180	36.180	0.351	0.725
Mohan, 2009	-20.600	19.354	374.563	-58.532	17.332	-1.064	0.287
	-10.062	5.499	30.237	-20.840	0.715	-1.830	0.067



9b. Sitagliptin 100 mg v Placebo – Change in Triglycerides

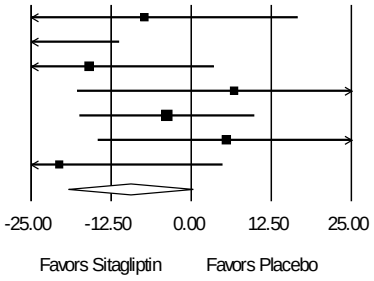
Pre-post correlation = 0.7
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
10.447	6	0.107	42.569

Sitagliptin vs. Placebo: Change in Triglycerides

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	-7.300	12.198	148.784	-31.207	16.607	-0.598	0.550
Charbonnel, 2006	-26.550	7.790	60.690	-41.819	-11.281	-3.408	0.001
Scott, 2007	-15.930	9.921	98.425	-35.375	3.515	-1.606	0.108
Goldstein, 2007	6.700	12.512	156.539	-17.822	31.222	0.536	0.592
Aschner, 2006	-3.800	6.960	48.439	-17.441	9.841	-0.546	0.585
Raz, 2006	5.500	10.249	105.049	-14.588	25.588	0.537	0.592
Mohan, 2009	-20.600	12.989	168.716	-46.058	4.858	-1.586	0.113
	-9.489	4.962	24.618	-19.214	0.235	-1.913	0.056

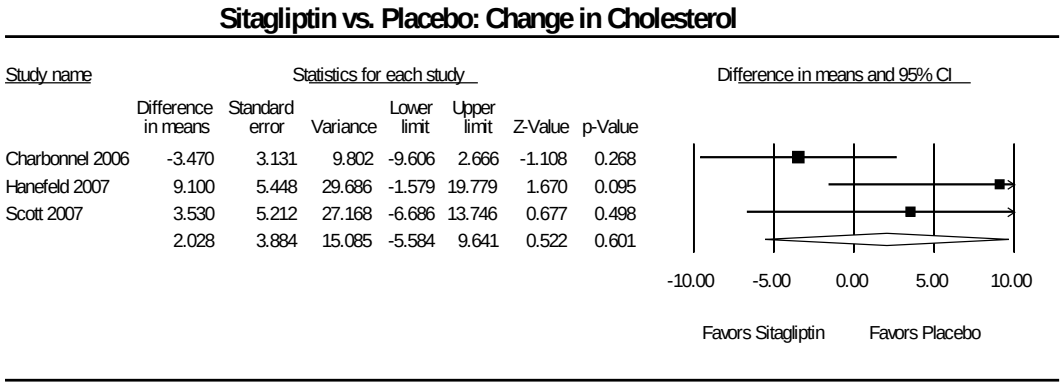


10. Sitagliptin 100 mg v Placebo – Change in Total Cholesterol

Pre-post correlation = 0.5
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
4.437	2	0.109	54.926



10a. Sitagliptin 100 mg v Placebo – Change in Total Cholesterol

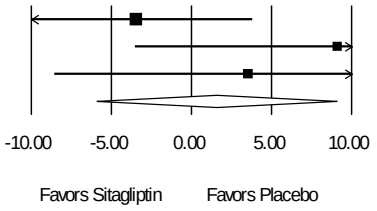
Pre-post correlation = 0.3
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
3.172	2	0.205	36.956

Sitagliptin vs. Placebo: Change in Cholesterol

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Charbonnel 2006	-3.470	3.704	13.716	-10.729	3.789	-0.937	0.349
Hanefeld 2007	9.100	6.442	41.505	-3.527	21.727	1.413	0.158
Scott 2007	3.530	6.167	38.034	-8.557	15.617	0.572	0.567
	1.565	3.829	14.665	-5.940	9.071	0.409	0.683



10b. Sitagliptin 100 mg v Placebo – Change in Total Cholesterol

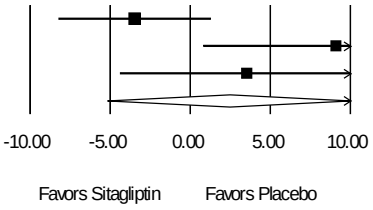
Pre-post correlation = 0.7
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
7.379	2	0.0025	72.896

Sitagliptin vs. Placebo: Change in Cholesterol

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Charbonnel 2006	-3.470	2.427	5.889	-8.226	1.286	-1.430	0.153
Hanefeld 2007	9.100	4.227	17.866	0.815	17.385	2.153	0.031
Scott 2007	3.530	4.037	16.301	-4.383	11.443	0.874	0.382
	2.457	3.905	15.253	-5.197	10.112	0.629	0.529



11. Sitagliptin 100 mg v Placebo – Change in HDL

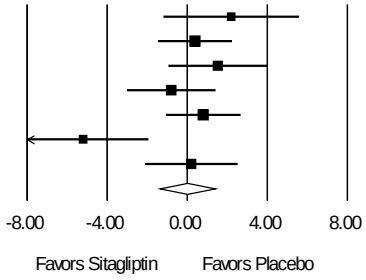
Pre-post correlation = 0.5
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
14.233	6	0.027	57.814

Sitagliptin vs. Placebo: Change in HDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	2.200	1.727	2.981	-1.184	5.584	1.274	0.203
Charbonnel, 2006	0.390	0.939	0.881	-1.450	2.230	0.415	0.678
Scott, 2007	1.530	1.258	1.584	-0.936	3.996	1.216	0.224
Goldstein, 2007	-0.800	1.126	1.269	-3.008	1.408	-0.710	0.478
Aschner, 2006	0.800	0.949	0.900	-1.059	2.659	0.843	0.399
Raz, 2006	-5.200	1.662	2.762	-8.457	-1.943	-3.129	0.002
Mohan, 2009	0.200	1.180	1.394	-2.114	2.514	0.169	0.865
	0.003	0.704	0.496	-1.377	1.383	0.004	0.997



11a. Sitagliptin 100 mg v Placebo – Change in HDL

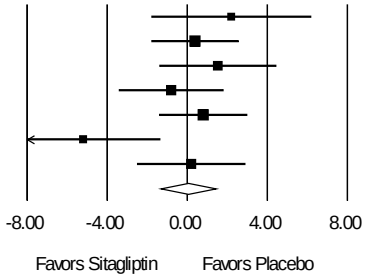
Pre-post correlation = 0.3
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
10.174	6	0.118	41.024

Sitagliptin vs. Placebo: Change in HDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	2.200	2.036	4.146	-1.791	6.191	1.080	0.280
Charbonnel, 2006	0.390	1.110	1.233	-1.786	2.566	0.351	0.725
Scott, 2007	1.530	1.489	2.216	-1.388	4.448	1.028	0.304
Goldstein, 2007	-0.800	1.332	1.775	-3.412	1.812	-0.600	0.548
Aschner, 2006	0.800	1.122	1.260	-1.400	3.000	0.713	0.476
Raz, 2006	-5.200	1.965	3.863	-9.052	-1.348	-2.646	0.008
Mohan, 2009	0.200	1.380	1.904	-2.505	2.905	0.145	0.885
	0.045	0.701	0.491	-1.328	1.419	0.065	0.949



11b. Sitagliptin 100 mg v Placebo – Change in HDL

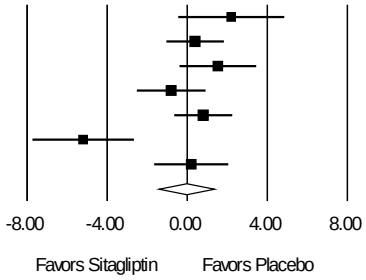
Pre-post correlation = 0.7
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
23.627	6	0.001	74.606

Sitagliptin vs. Placebo: Change in HDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	2.200	1.348	1.816	-0.441	4.841	1.632	0.103
Charbonnel, 2006	0.390	0.728	0.530	-1.037	1.817	0.536	0.592
Scott, 2007	1.530	0.975	0.951	-0.381	3.441	1.569	0.117
Goldstein, 2007	-0.800	0.873	0.762	-2.511	0.911	-0.916	0.360
Aschner, 2006	0.800	0.735	0.540	-0.641	2.241	1.088	0.276
Raz, 2006	-5.200	1.289	1.660	-7.726	-2.674	-4.035	0.000
Mohan, 2009	0.200	0.940	0.883	-1.642	2.042	0.213	0.831
	-0.046	0.706	0.498	-1.428	1.337	-0.065	0.949



12. Sitagliptin 100 mg v Placebo – Change in LDL

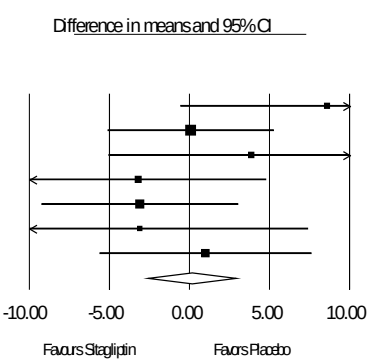
Pre-post correlation = 0.5
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
6.087	6	0.413	1.435

Sitagliptin vs. Placebo: Change in LDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	8.600	4.685	21.949	-0.582	17.782	1.836	0.066
Charbonnel, 2006	0.080	2.657	7.061	-5.128	5.288	0.030	0.976
Scott, 2007	3.860	4.556	20.755	-5.069	12.789	0.847	0.397
Goldstein, 2007	-3.200	4.085	16.690	-11.207	4.807	-0.783	0.433
Aschner, 2006	-3.100	3.144	9.886	-9.263	3.063	-0.986	0.324
Raz, 2006	-3.100	5.366	28.797	-13.618	7.418	-0.578	0.563
Mohan, 2009	1.000	3.384	11.453	-5.633	7.633	0.295	0.768
	0.129	1.402	1.964	-2.618	2.876	0.092	0.927



12a. Sitagliptin 100 mg v Placebo – Change in LDL

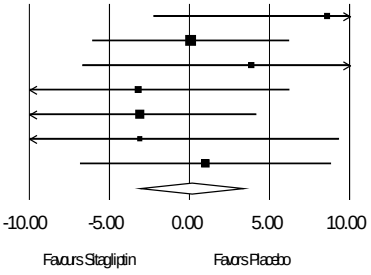
Pre-post correlation = 0.3
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
4.351	6	0.629	0.000

Sitagliptin vs. Placebo: Change in LDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	8.600	5.543	30.724	-2.264	19.464	1.552	0.121
Charbonnel, 2006	0.080	3.143	9.881	-6.081	6.241	0.025	0.980
Scott, 2007	3.860	5.390	29.048	-6.703	14.423	0.716	0.474
Goldstein, 2007	-3.200	4.825	23.285	-12.658	6.258	-0.663	0.507
Aschner, 2006	-3.100	3.719	13.831	-10.389	4.189	-0.834	0.405
Raz, 2006	-3.100	6.349	40.309	-15.544	9.344	-0.488	0.625
Mohan, 2009	1.000	4.003	16.024	-6.846	8.846	0.250	0.803
	0.121	1.643	2.698	-3.098	3.340	0.074	0.941



12b. Sitagliptin 100 mg v Placebo – Change in LDL

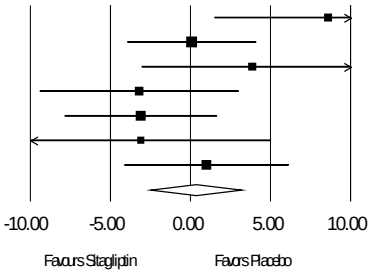
Pre-post correlation = 0.7
WMD, Random Effects Model

Study statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
10.131	6	0.119	40.776

Sitagliptin vs. Placebo: Change in LDL

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hanefeld, 2007	8.600	3.630	13.173	1.486	15.714	2.369	0.018
Charbonnel, 2006	0.080	2.059	4.240	-3.956	4.116	0.039	0.969
Scott, 2007	3.860	3.530	12.461	-3.059	10.779	1.093	0.274
Goldstein, 2007	-3.200	3.177	10.095	-9.427	3.027	-1.007	0.314
Aschner, 2006	-3.100	2.437	5.941	-7.877	1.677	-1.272	0.203
Raz, 2006	-3.100	4.157	17.284	-11.248	5.048	-0.746	0.456
Mohan, 2009	1.000	2.623	6.881	-4.141	6.141	0.381	0.703
	0.318	1.448	2.096	-2.519	3.156	0.220	0.826



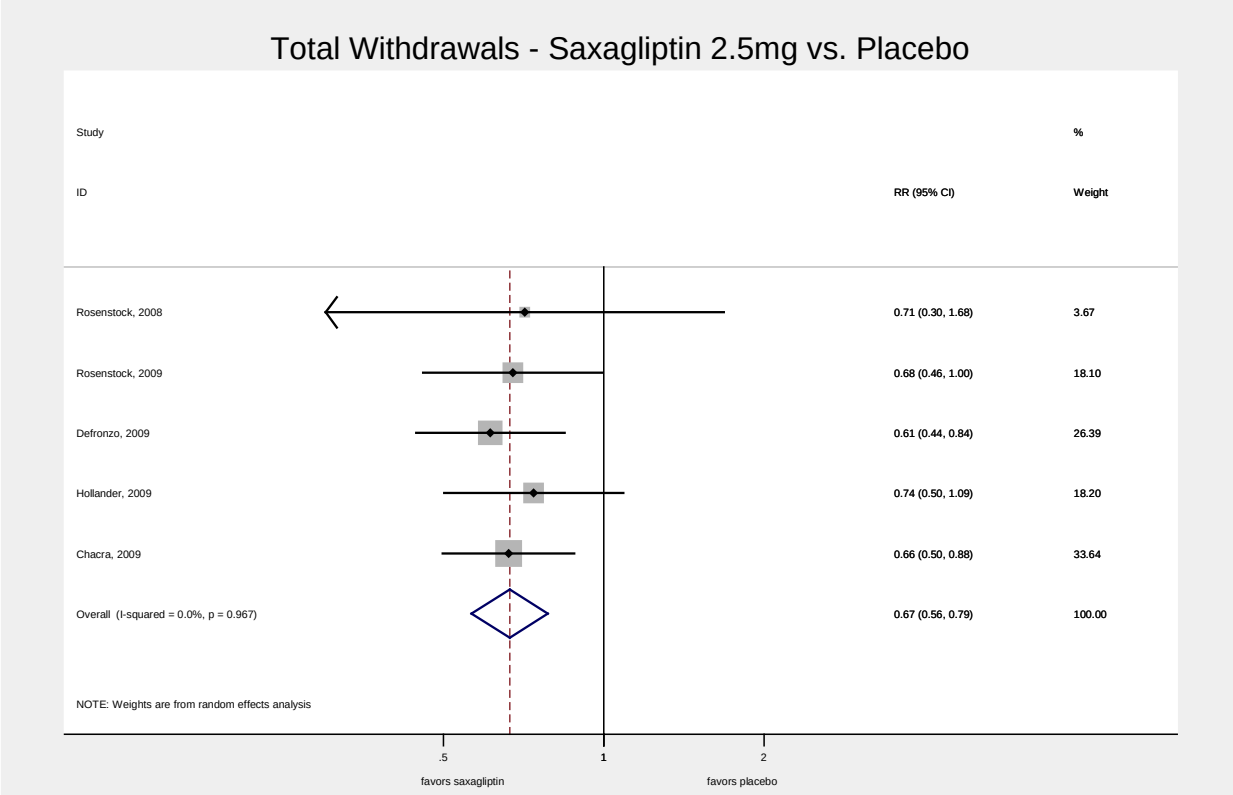
Saxagliptin Meta-Analyses

1) Saxagliptin 2.5 mg – Total Withdrawals

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	0.711	0.300 1.681	3.67
Rosenstock, 2009	0.675	0.458 0.995	18.10
Defronzo, 2009	0.612	0.444 0.844	26.39
Hollander, 2009	0.738	0.502 1.087	18.20
Chacra, 2009	0.663	0.498 0.881	33.64
D+L pooled RR	0.666	0.565 0.785	100.00

Heterogeneity chi-squared = 0.57 (d.f. = 4) *P*=0.967
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.83 *P*=0.000

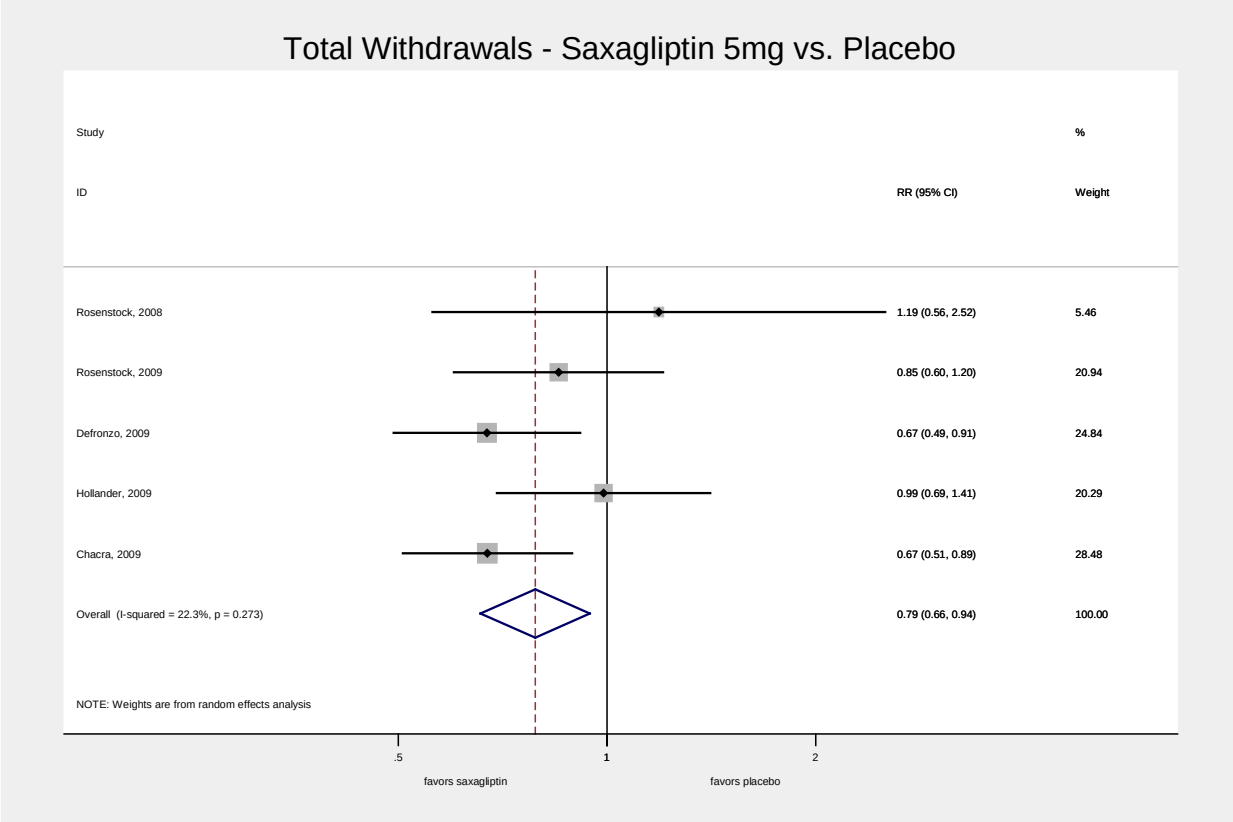


2) Saxagliptin 5 mg – Total Withdrawals

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.188	0.560 2.519	5.46
Rosenstock, 2009	0.851	0.602 1.205	20.94
Defronzo, 2009	0.671	0.493 0.915	24.84
Hollander, 2009	0.989	0.694 1.410	20.29
Chacra, 2009	0.673	0.508 0.891	28.48
D+L pooled RR	0.788	0.657 0.945	100.00

Heterogeneity chi-squared = 5.15 (d.f. = 4) *P*=0.273
I-squared (variation in RR attributable to heterogeneity) = 22.3%
Estimate of between-study variance Tau-squared = 0.0095
Test of RR=1 : z= 2.58 *P*=0.010

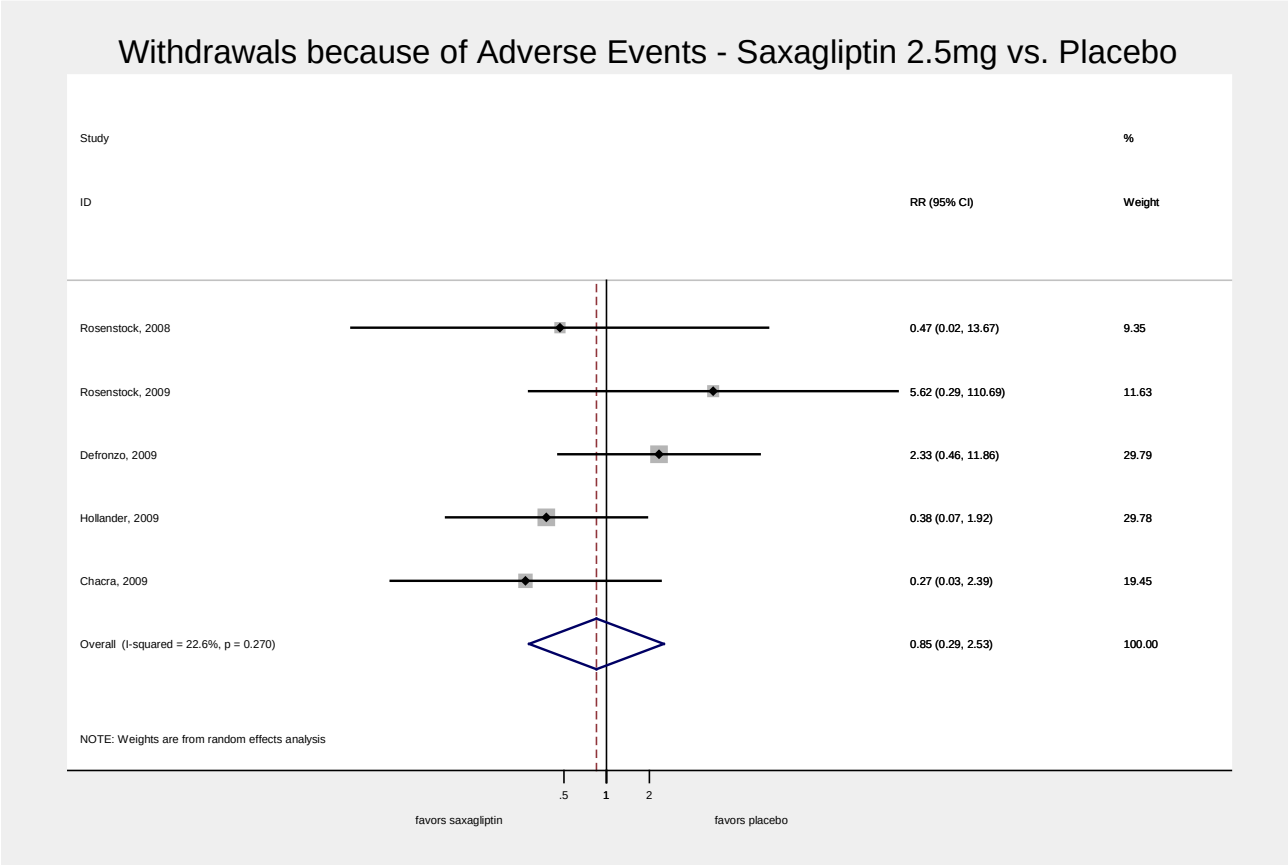


3) Saxagliptin 2.5 mg – Withdrawals because of Adverse Events

Study statistics (0.5 added to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	0.468	0.016 13.672	9.35
Rosenstock, 2009	5.618	0.285 110.694	11.63
Defronzo, 2009	2.331	0.458 11.862	29.79
Hollander, 2009	0.377	0.074 1.921	29.78
Chacra, 2009	0.269	0.030 2.392	19.45
D+L pooled RR	0.849	0.285 2.529	100.00

Heterogeneity chi-squared = 5.17 (d.f. = 4) *P*=0.270
I-squared (variation in RR attributable to heterogeneity) = 22.6%
Estimate of between-study variance Tau-squared = 0.3515
Test of RR=1 : z= 0.29 *P*=0.769

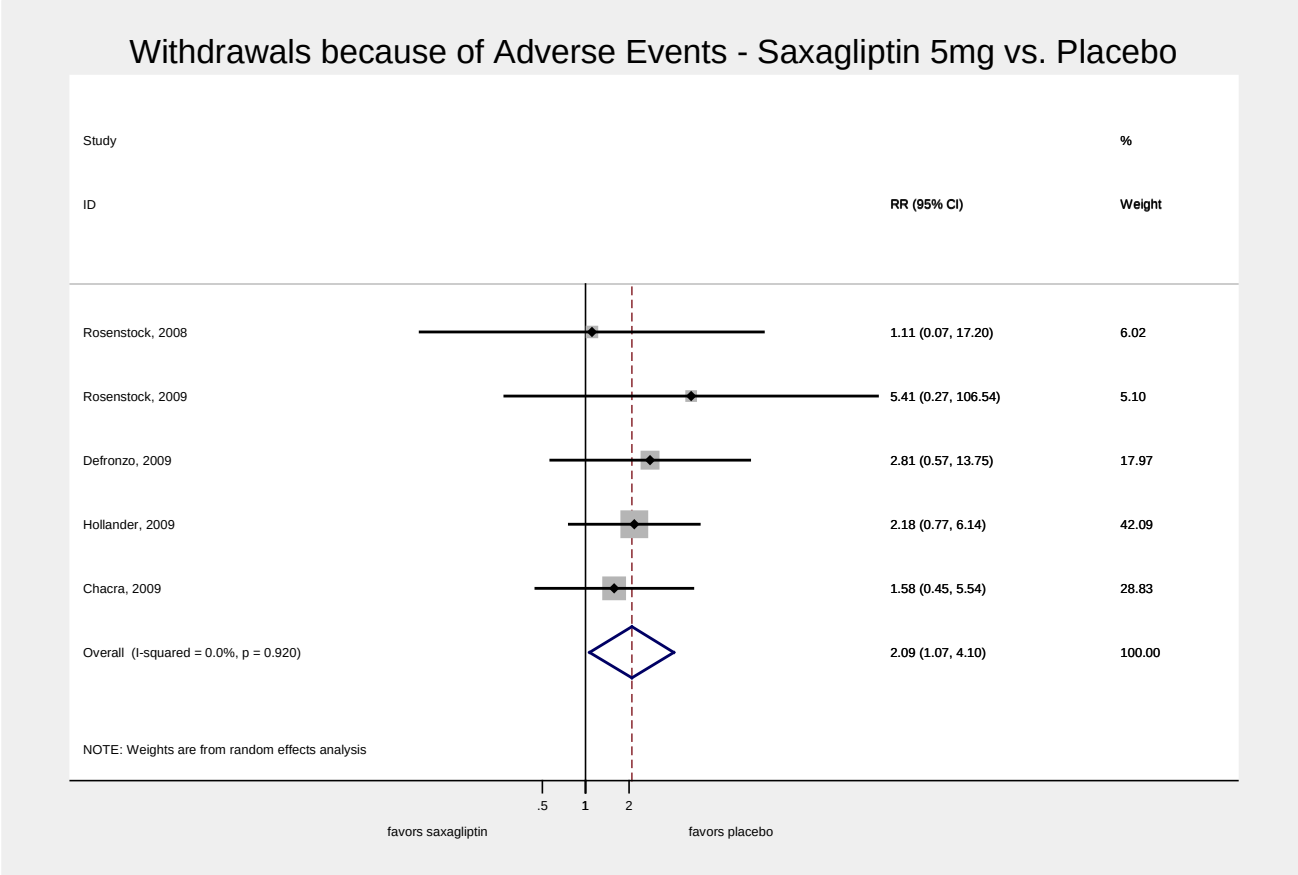


4) Saxagliptin 5 mg – Withdrawals because of Adverse Events

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.106	0.071 17.196	6.02
Rosenstock, 2009	5.406	0.274 106.542	5.10
Defronzo, 2009	2.812	0.575 13.749	17.97
Hollander, 2009	2.176	0.771 6.141	42.09
Chacra, 2009	1.583	0.452 5.544	28.83
D+L pooled RR	2.091	1.067 4.098	100.00

Heterogeneity chi-squared = 0.93 (d.f. = 4) *P*=0.920
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.15 *P*=0.032

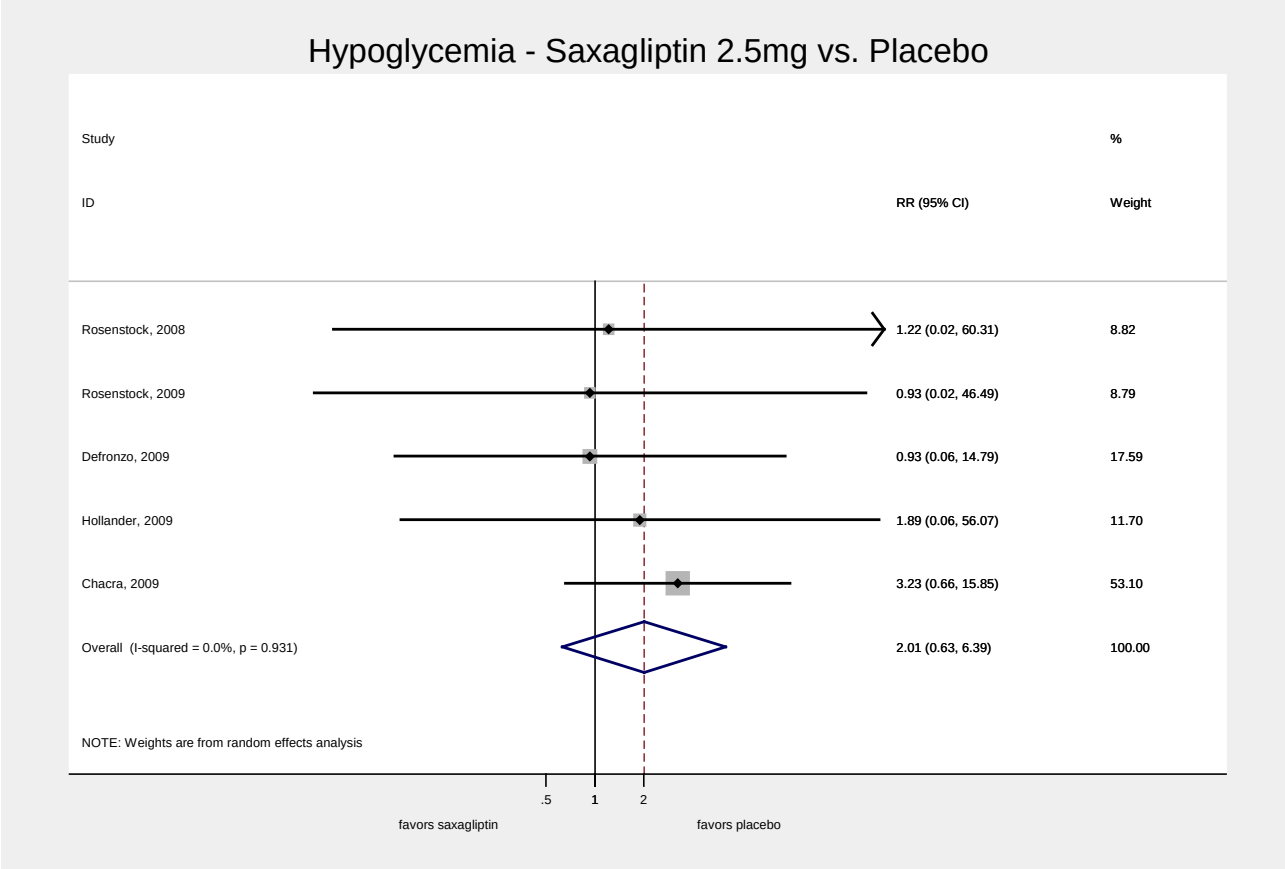


5) Saxagliptin 2.5 mg – Hypoglycemia

Study statistics (0.5 added to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.216	0.025 60.313	8.82
Rosenstock, 2009	0.932	0.019 46.491	8.79
Defronzo, 2009	0.932	0.059 14.794	17.59
Hollander, 2009	1.892	0.064 56.069	11.70
Chacra, 2009	3.230	0.658 15.853	53.10
D+L pooled RR	2.006	0.629 6.393	100.00

Heterogeneity chi-squared = 0.85 (d.f. = 4) *P*=0.931
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 1.18 *P*=0.239

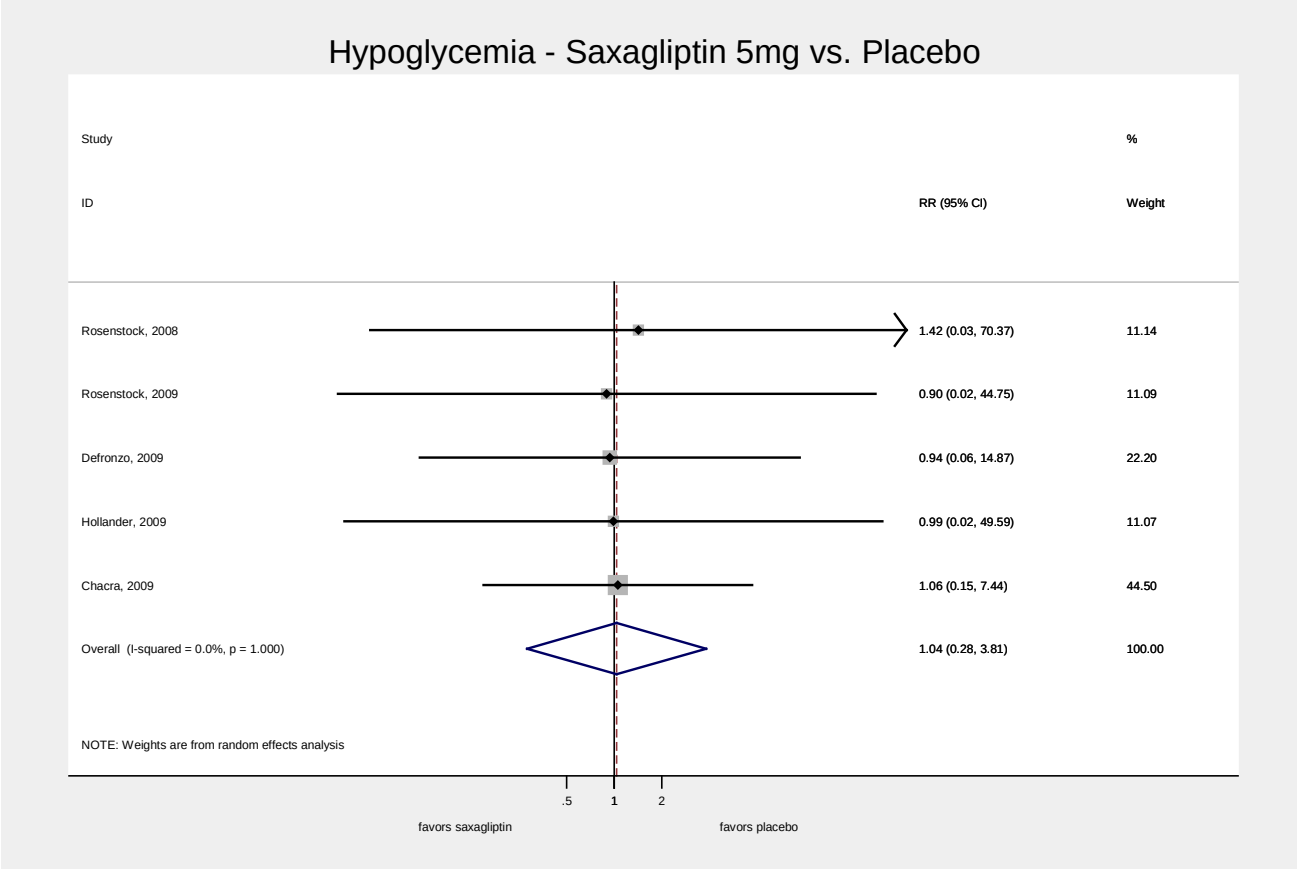


6) Saxagliptin 5 mg – Hypoglycemia

Study statistics (0.5 added to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.421	0.029 70.366	11.14
Rosenstock, 2009	0.897	0.018 44.753	11.09
Defronzo, 2009	0.937	0.059 14.871	22.20
Hollander, 2009	0.989	0.020 49.593	11.07
Chacra, 2009	1.055	0.150 7.435	44.50
D+L pooled RR	1.036	0.282 3.811	100.00

Heterogeneity chi-squared = 0.04 (d.f. = 4) *P*=1.000
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.05 *P*=0.957

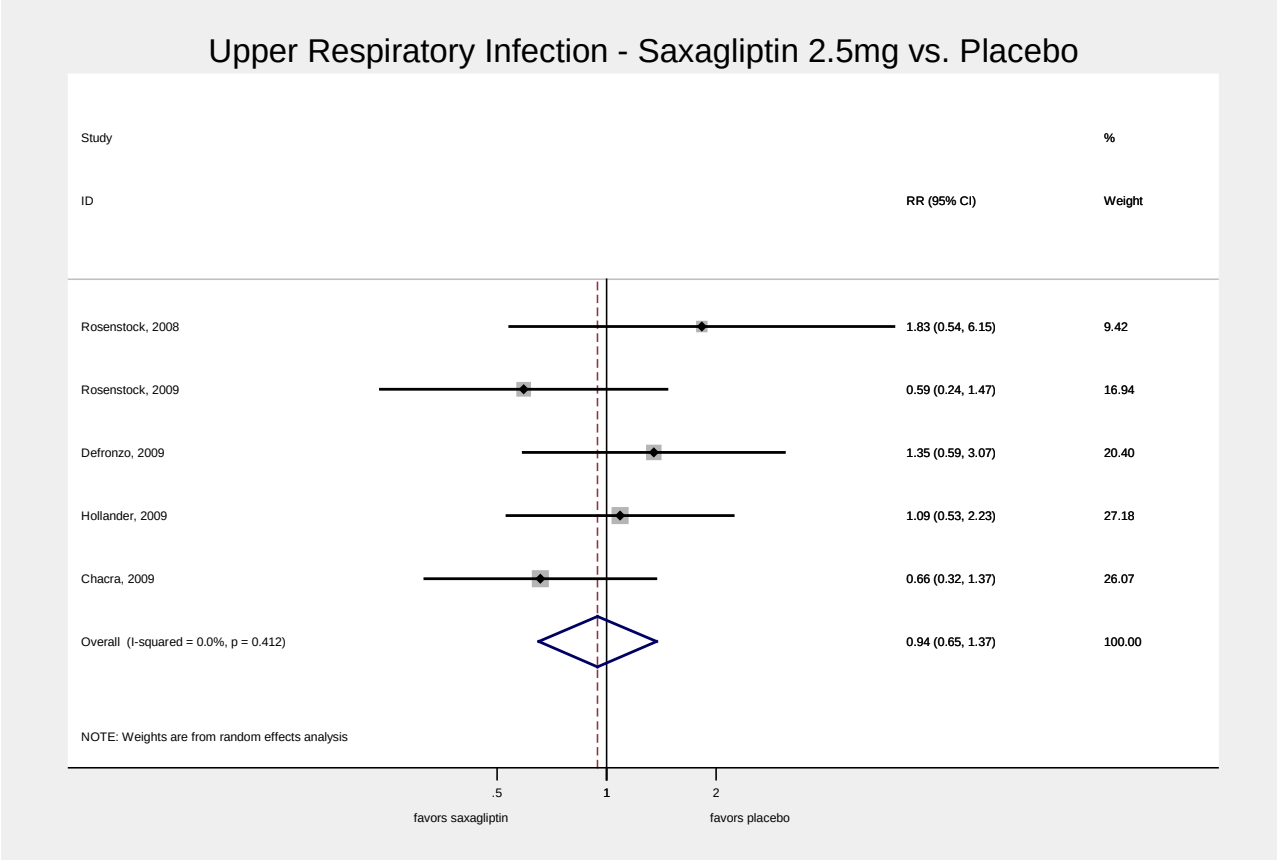


7) Saxagliptin 2.5 mg – Upper Respiratory Infection (URI)

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.827	0.543 6.151	9.42
Rosenstock, 2009	0.593	0.240 1.466	16.94
Defronzo, 2009	1.347	0.590 3.073	20.40
Hollander, 2009	1.089	0.533 2.225	27.18
Chacra, 2009	0.658	0.317 1.365	26.07
D+L pooled RR	0.945	0.651 1.371	100.00

Heterogeneity chi-squared = 3.96 (d.f. = 4) *P*=0.412
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.30 *P*=0.764

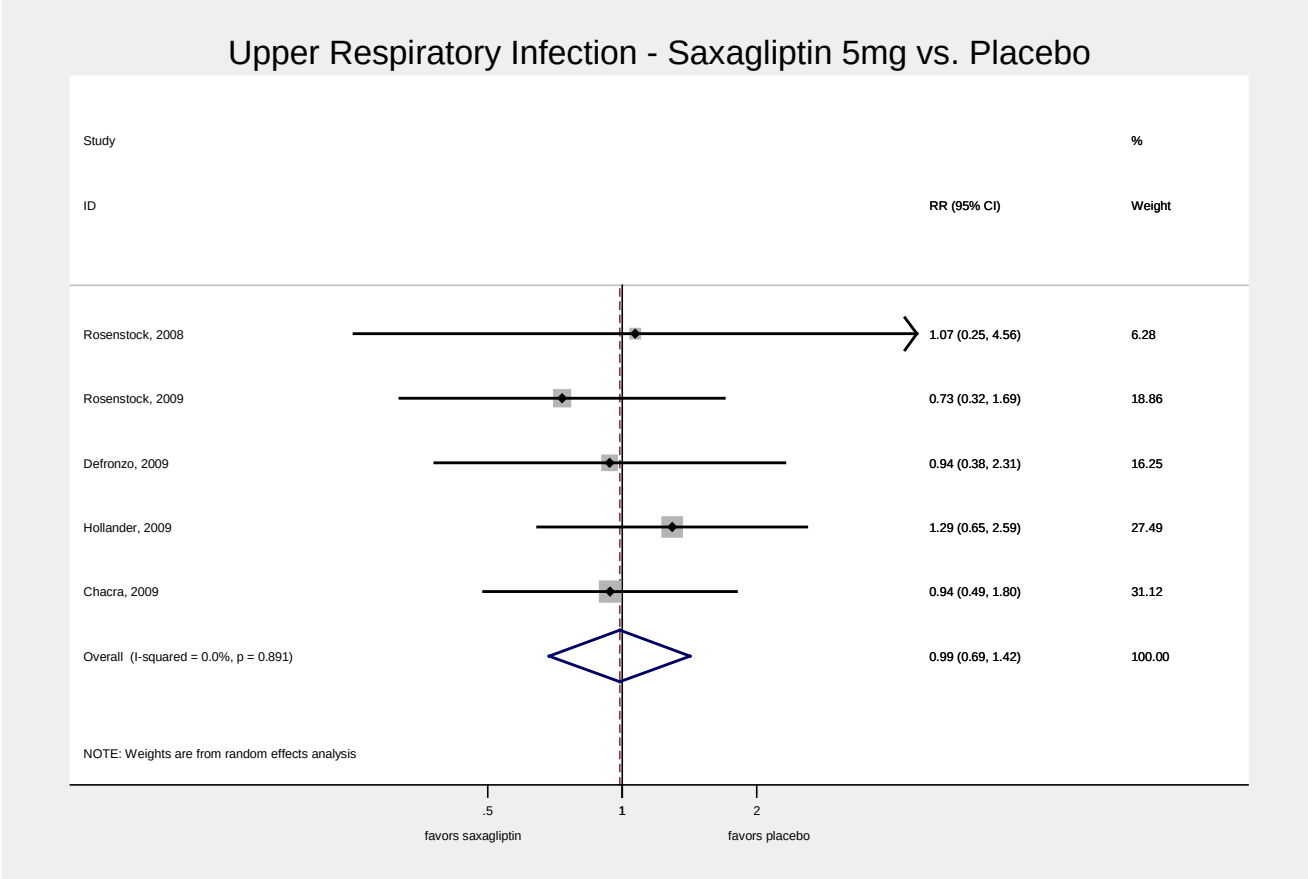


8) Saxagliptin 5 mg – Upper Respiratory Infection (URI)

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.069	0.251 4.557	6.28
Rosenstock, 2009	0.733	0.318 1.692	18.86
Defronzo, 2009	0.937	0.381 2.308	16.25
Hollander, 2009	1.294	0.647 2.586	27.49
Chacra, 2009	0.938	0.489 1.799	31.12
D+L pooled RR	0.986	0.686 1.418	100.00

Heterogeneity chi-squared = 1.12 (d.f. = 4) *P*=0.891
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.08 *P*=0.940

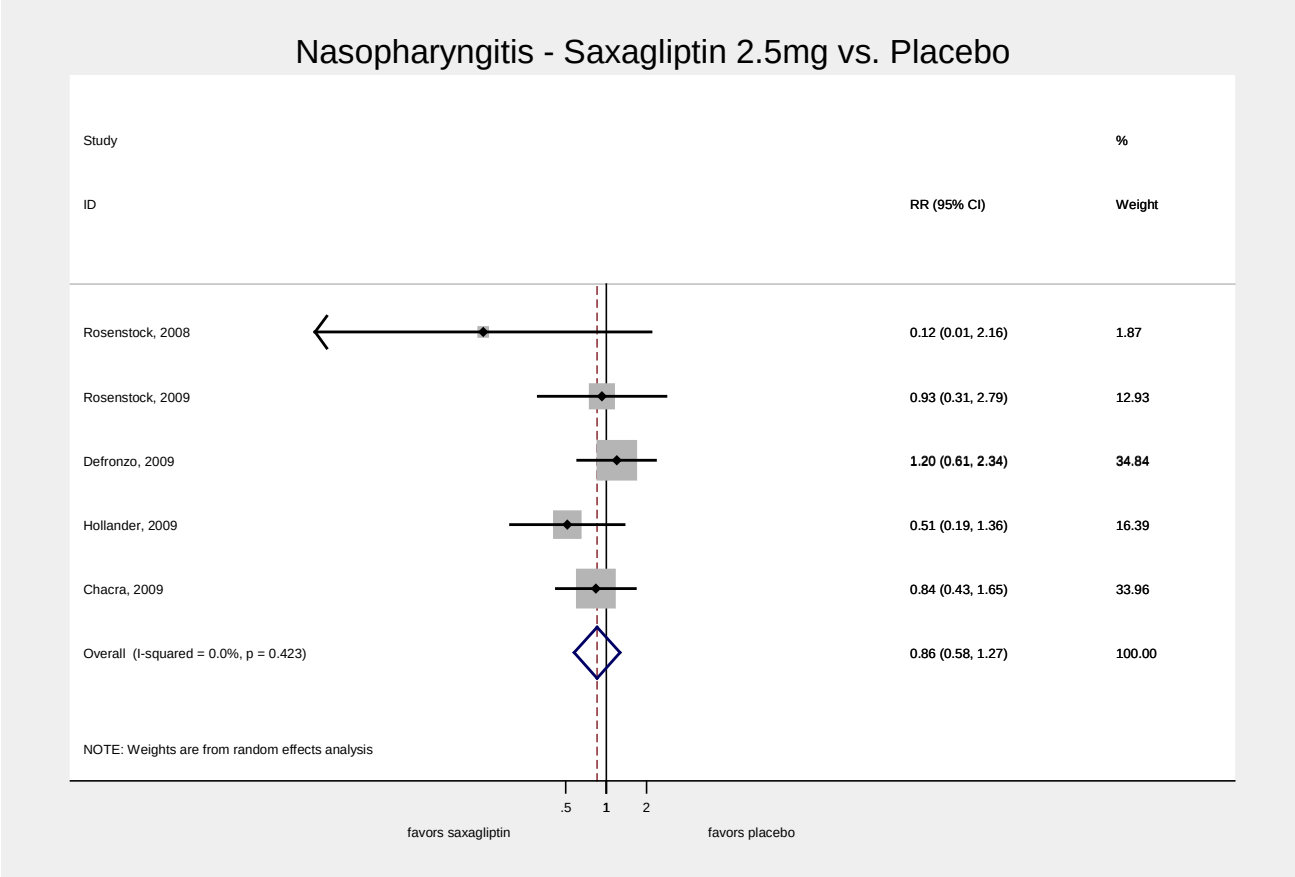


9) Saxagliptin 2.5 mg – Nasopharyngitis

Study statistics (added 0.5 to zero cells):

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	0.121	0.007 2.162	1.87
Rosenstock, 2009	0.931	0.311 2.788	12.93
Defronzo, 2009	1.199	0.615 2.338	34.84
Hollander, 2009	0.515	0.194 1.363	16.39
Chacra, 2009	0.837	0.426 1.647	33.96
D+L pooled RR	0.857	0.577 1.271	100.00

Heterogeneity chi-squared = 3.88 (d.f. = 4) *P*=0.423
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.77 *P*=0.442

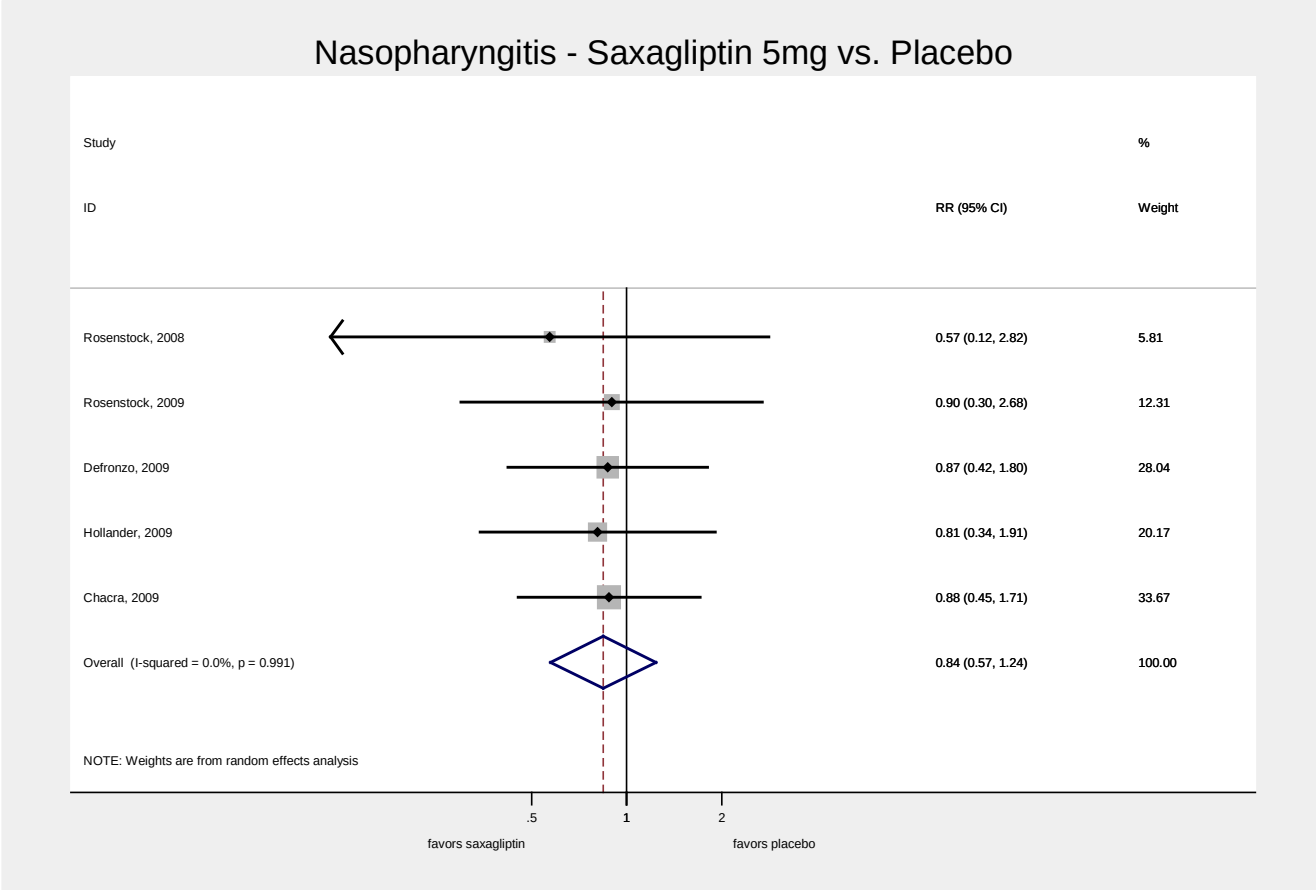


10) Saxagliptin 5 mg – Nasopharyngitis

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	0.570	0.115 2.815	5.81
Rosenstock, 2009	0.896	0.299 2.685	12.31
Defronzo, 2009	0.870	0.421 1.800	28.04
Hollander, 2009	0.809	0.344 1.907	20.17
Chacra, 2009	0.879	0.453 1.707	33.67
D+L pooled RR	0.843	0.574 1.238	100.00

Heterogeneity chi-squared = 0.27 (d.f. = 4) *P*=0.991
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.87 *P*=0.384

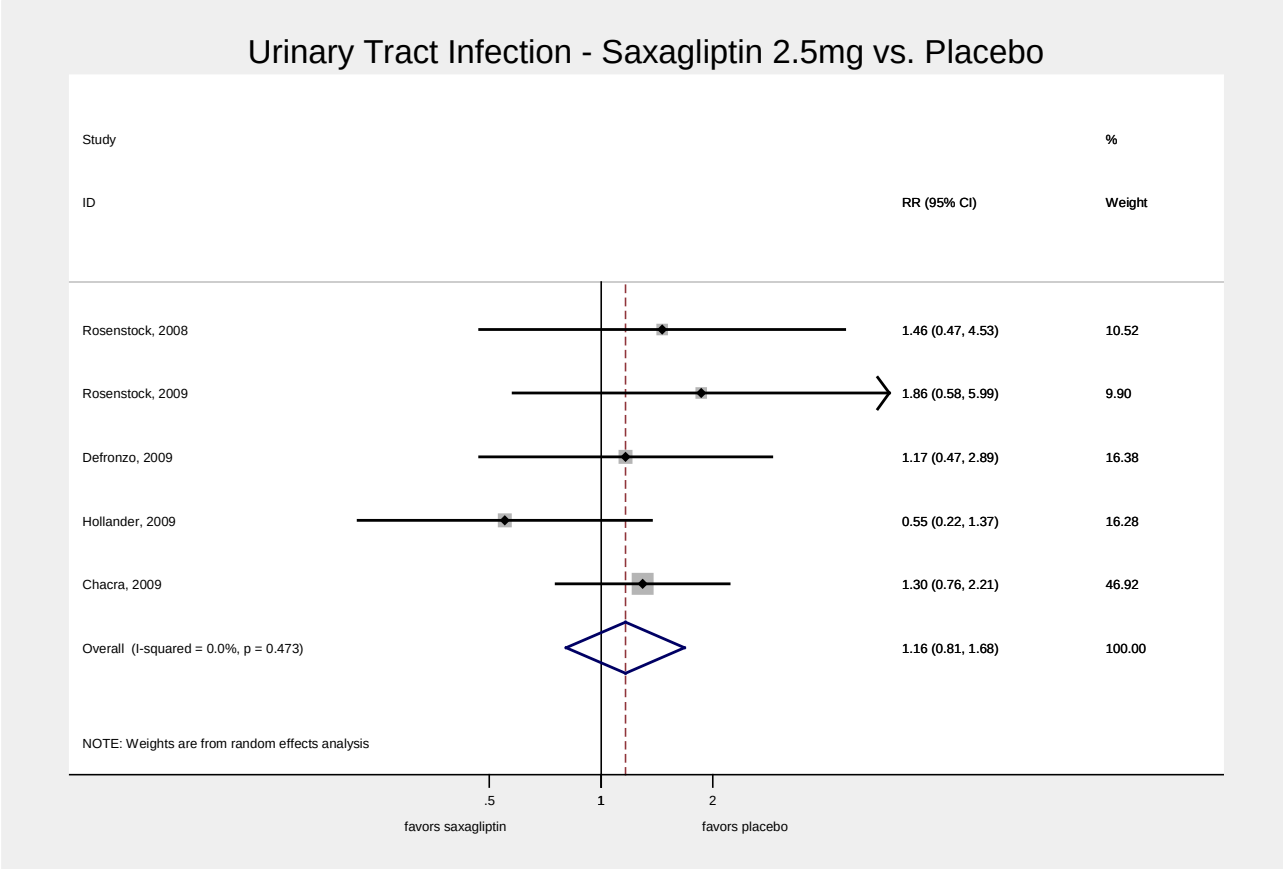


11) Saxagliptin 2.5 mg – Urinary Tract Infection (UTI)

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	1.462	0.471 4.534	10.52
Rosenstock, 2009	1.863	0.580 5.985	9.90
Defronzo, 2009	1.165	0.470 2.887	16.38
Hollander, 2009	0.550	0.222 1.368	16.28
Chacra, 2009	1.295	0.758 2.214	46.92
D+L pooled RR	1.163	0.805 1.679	100.00

Heterogeneity chi-squared = 3.53 (d.f. = 4) *P*=0.473
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.80 *P*=0.421

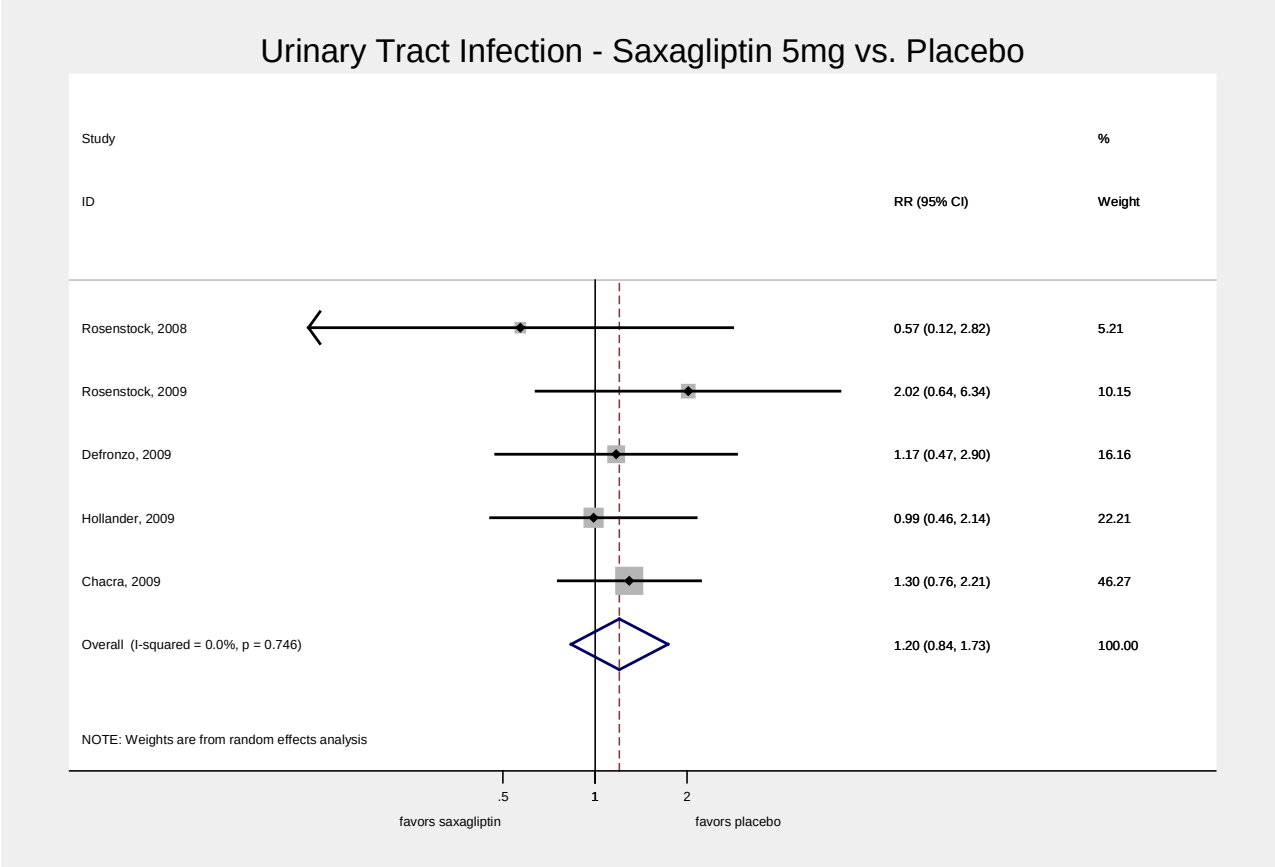


12) Saxagliptin 5 mg – Urinary Tract Infection (UTI)

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Rosenstock, 2008	0.570	0.115 2.815	5.21
Rosenstock, 2009	2.017	0.642 6.335	10.15
Defronzo, 2009	1.171	0.473 2.902	16.16
Hollander, 2009	0.989	0.456 2.145	22.21
Chacra, 2009	1.295	0.758 2.214	46.27
D+L pooled RR	1.203	0.835 1.732	100.00

Heterogeneity chi-squared = 1.94 (d.f. = 4) *P*=0.746
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.99 *P*=0.321



Exenatide Meta-Analyses

1) Total Withdrawals, Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	0.739	0.524 1.043	16.20
DeFronzo, 2005	0.833	0.489 1.420	12.71
Kendall, 2005	0.747	0.526 1.061	16.08
Zinman, 2007	2.025	1.189 3.449	12.72
Moretto, 2008	1.234	0.515 2.959	7.83
Gao, 2009	1.694	1.059 2.710	13.85
Kadowaki, 2009	6.486	0.819 51.366	2.05
Gill, 2010	1.857	0.517 6.673	4.62
Apovian, 2010	1.021	0.641 1.625	13.94
D+L pooled RR	1.139	0.833 1.557	100.00

Heterogeneity chi-squared = 22.11 (d.f. = 8) p = 0.005
I-squared (variation in RR attributable to heterogeneity) = 63.8%
Estimate of between-study variance Tau-squared = 0.1266
Test of RR=1 : z= 0.81 p = 0.415

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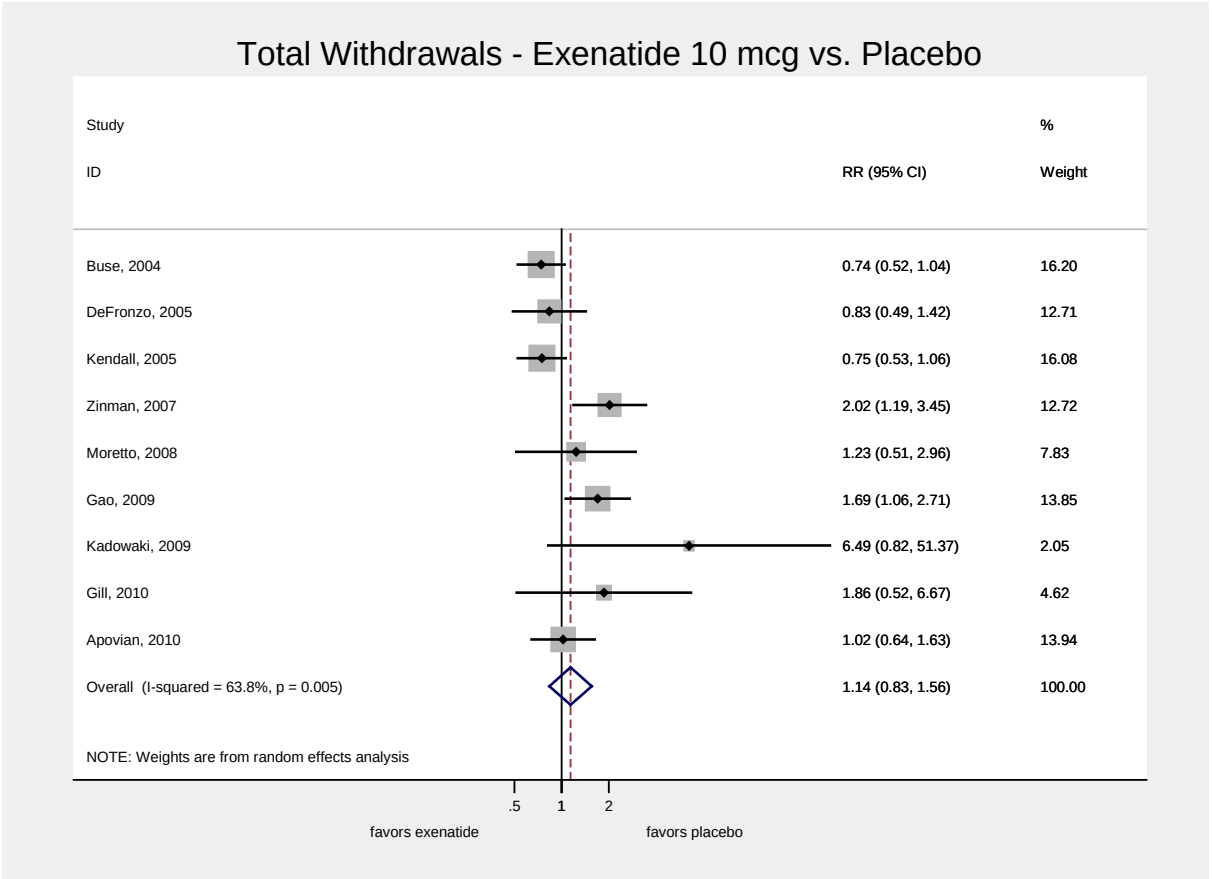
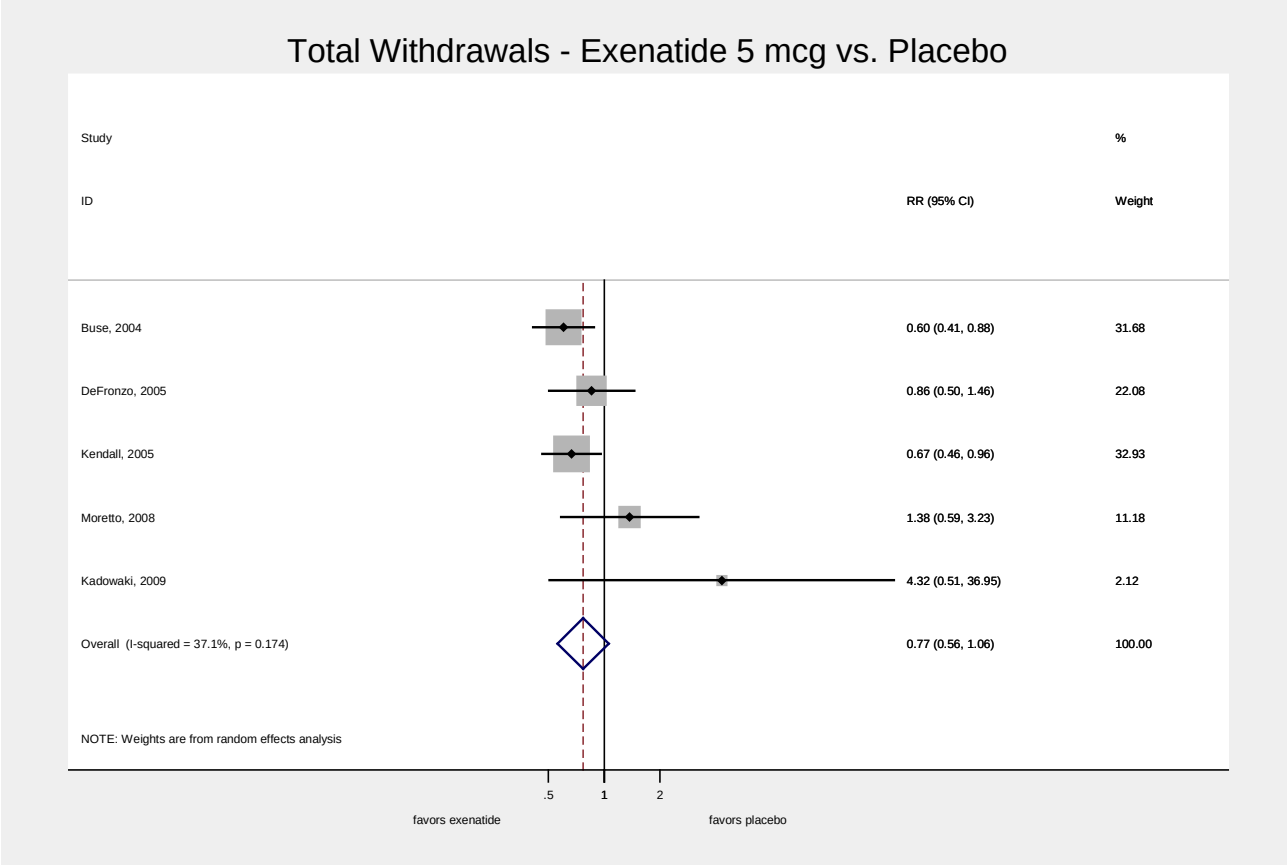


2) Total Withdrawals, Exenatide 5mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	0.602	0.412 0.881	31.68
DeFronzo, 2005	0.856	0.503 1.458	22.08
Kendall, 2005	0.666	0.463 0.959	32.93
Moretto, 2008	1.375	0.585 3.230	11.18
Kadowaki, 2009	4.324	0.506 36.947	2.12
D+L pooled RR	0.770	0.560 1.058	100.00

Heterogeneity chi-squared = 6.36 (d.f. = 4) *P*=0.174
I-squared (variation in RR attributable to heterogeneity) = 37.1%
Estimate of between-study variance Tau-squared = 0.0455
Test of RR=1 : z= 1.61 *P*=0.106

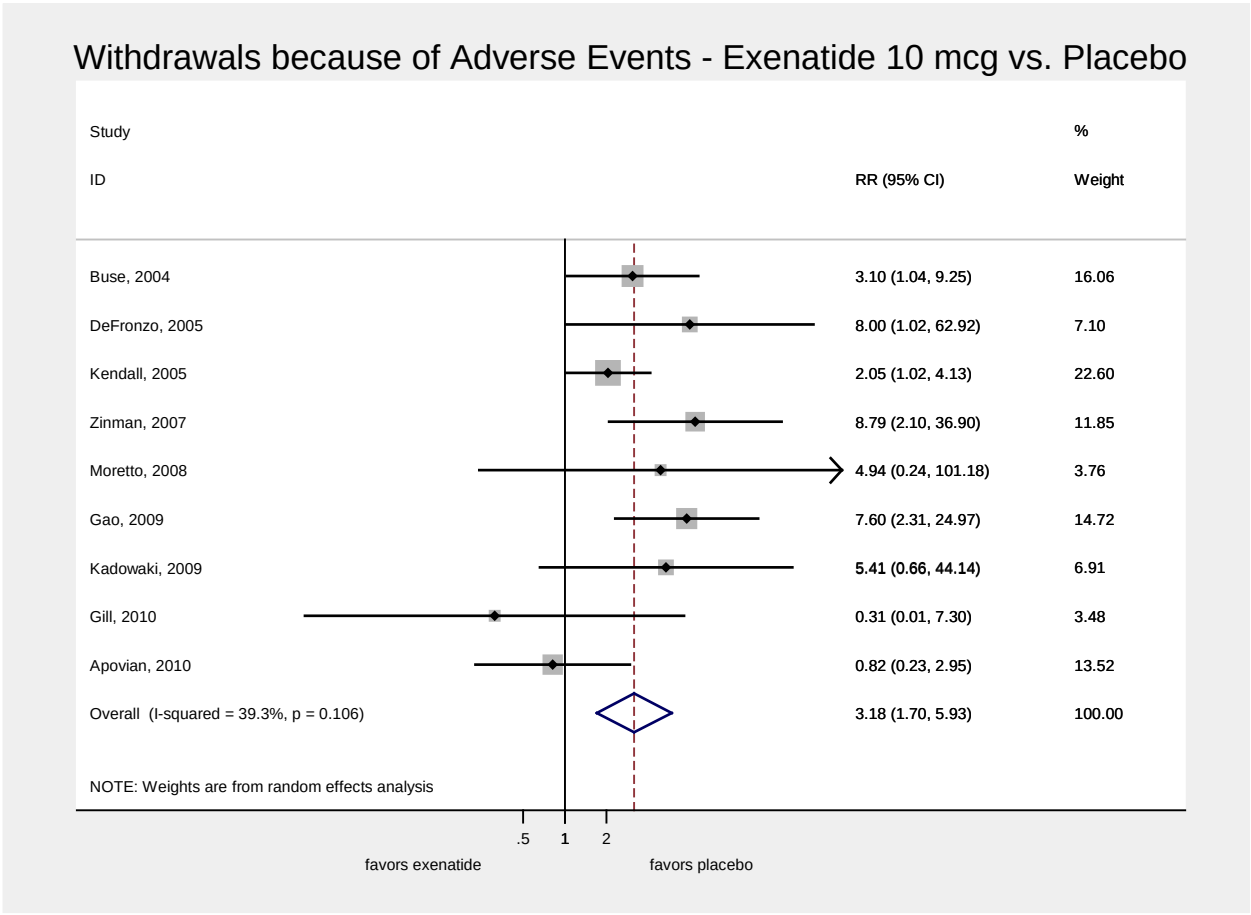


3) Withdrawals because of adverse events, Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	3.099	1.039 9.245	16.06
DeFronzo, 2005	8.000	1.017 62.921	7.10
Kendall, 2005	2.050	1.016 4.135	22.60
Zinman, 2007	8.793	2.096 36.899	11.85
Moretto, 2008	4.937	0.241 101.180	3.76
Gao, 2009	7.601	2.314 24.969	14.72
Kadowaki, 2009	5.405	0.662 44.140	6.91
Gill, 2010	0.310	0.013 7.296	3.48
Apovian, 2010	0.817	0.226 2.950	13.52
D+L pooled RR	3.178	1.702 5.933	100.00

Heterogeneity chi-squared = 13.18 (d.f. = 8) p = 0.106
I-squared (variation in RR attributable to heterogeneity) = 39.3%
Estimate of between-study variance Tau-squared = 0.3208
Test of RR=1 : z= 3.63 p = 0.000

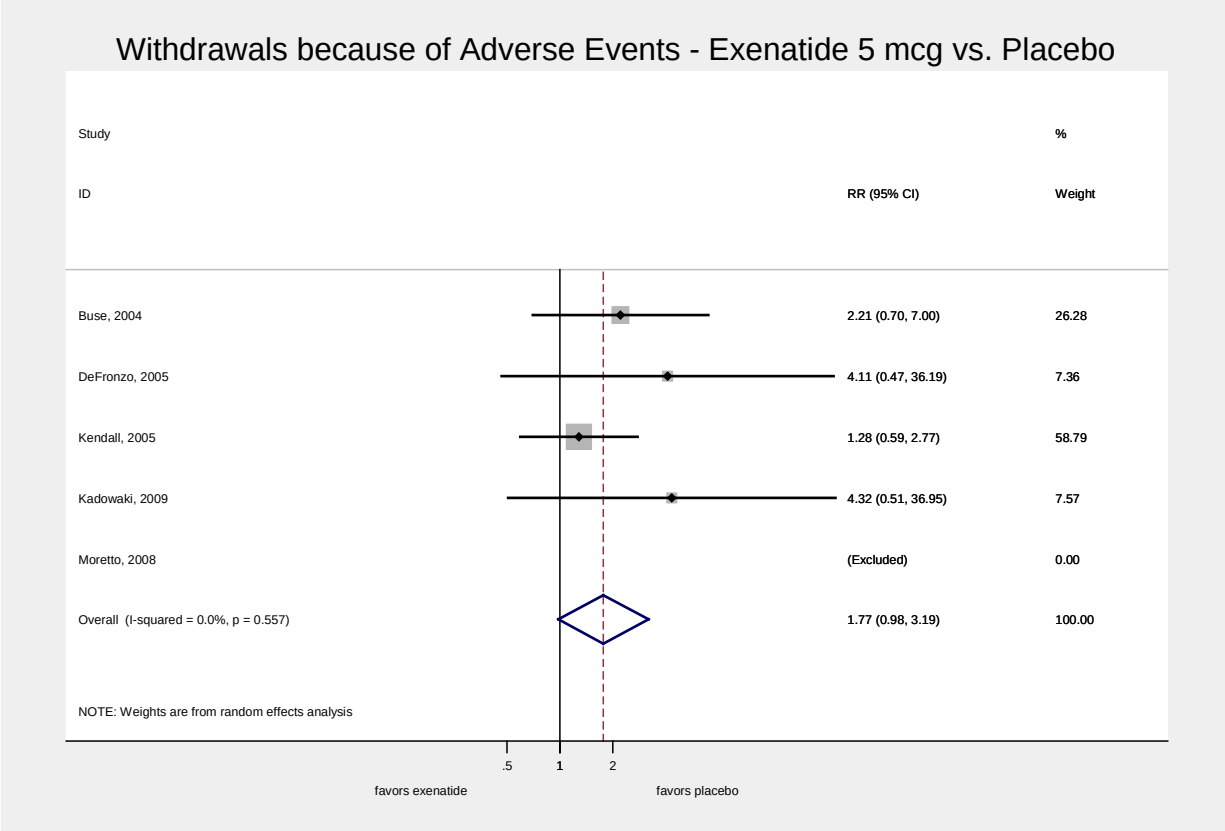


4) Withdrawals because of adverse events, Exenatide 5 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	2.214	0.700 7.001	26.28
DeFronzo, 2005	4.109	0.467 36.188	7.36
Kendall, 2005	1.283	0.594 2.770	58.79
Kadowaki, 2009	4.324	0.506 36.947	7.57
Moretto, 2008	(Excluded)		
D+L pooled RR	1.769	0.980 3.191	100.00

Heterogeneity chi-squared = 2.08 (d.f. = 3) *P*=0.557
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 1.89 *P*=0.058

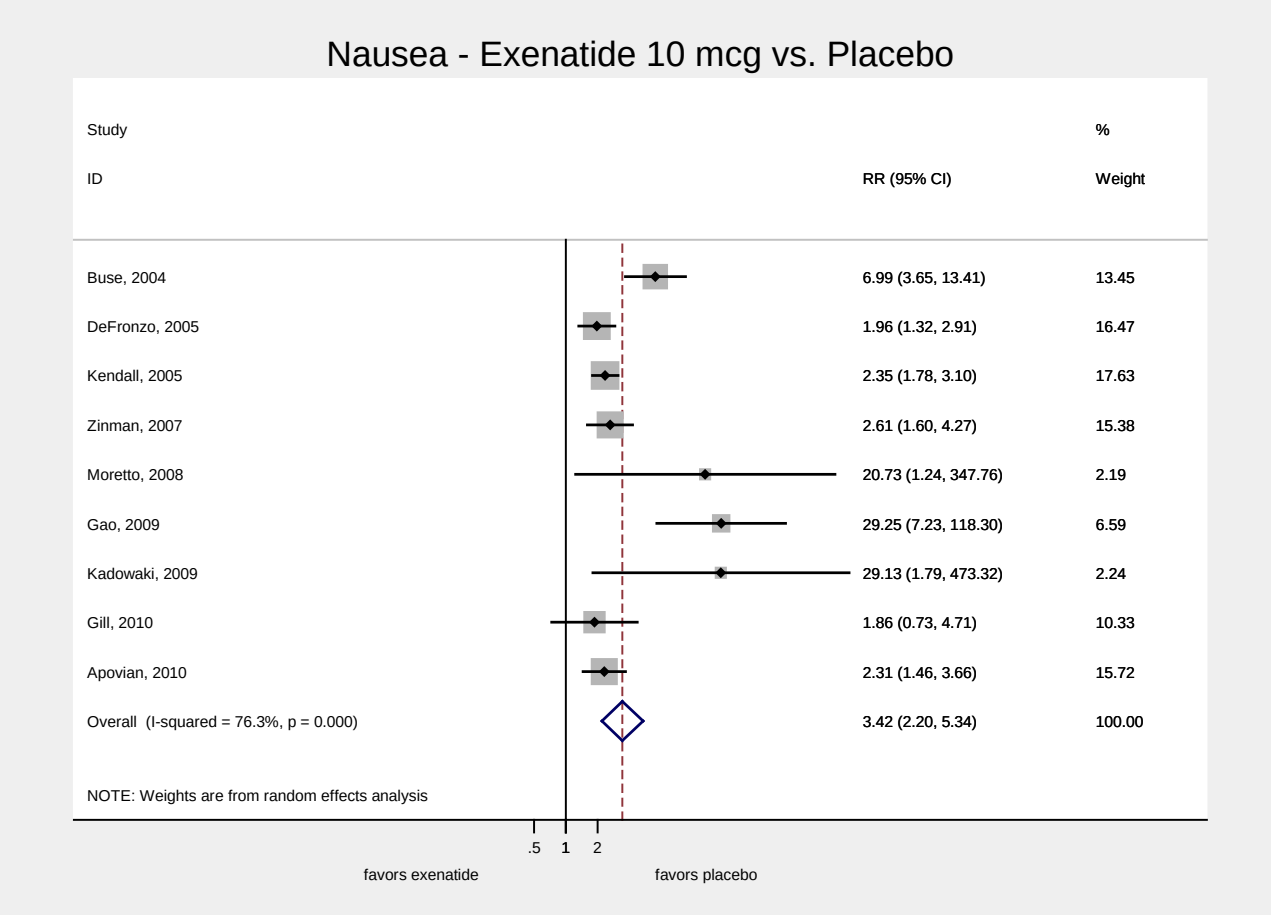


5) Nausea – Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	6.992	3.646 13.410	13.45
DeFronzo, 2005	1.962	1.323 2.908	16.47
Kendall, 2005	2.351	1.783 3.101	17.63
Zinman, 2007	2.614	1.601 4.265	15.38
Moretto, 2008	20.734	1.236 347.761	2.19
Gao, 2009	29.248	7.231 118.304	6.59
Kadowaki, 2009	29.132	1.793 473.322	2.24
Gill, 2010	1.857	0.732 4.714	10.33
Apovian, 2010	2.310	1.457 3.662	15.72
D+L pooled RR	3.425	2.196 5.340	100.00

Heterogeneity chi-squared = 33.79 (d.f. = 8) p = 0.000
I-squared (variation in RR attributable to heterogeneity) = 76.3%
Estimate of between-study variance Tau-squared = 0.2715
Test of RR=1 : z= 5.43 p = 0.000

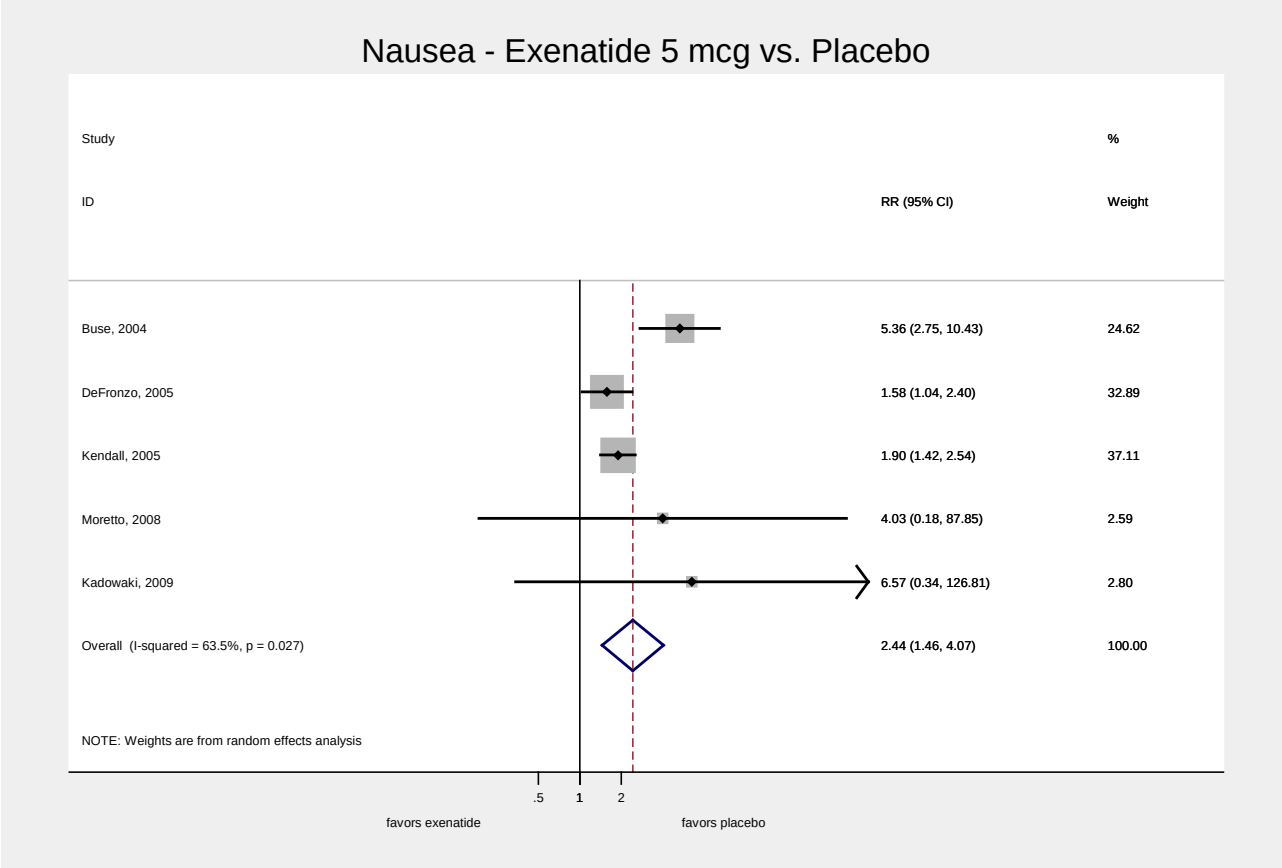


6) Nausea – Exenatide 5 mcg

Study Statistics (added 0.5 to the zero cells)

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	5.357	2.753 10.425	24.62
DeFronzo, 2005	1.580	1.040 2.401	32.89
Kendall, 2005	1.898	1.420 2.536	37.11
Moretto, 2008	4.026	0.184 87.852	2.59
Kadowaki, 2009	6.568	0.340 126.808	2.80
D+L pooled RR	2.436	1.459 4.066	100.00

Heterogeneity chi-squared = 10.96 (d.f. = 4) *P*=0.027
I-squared (variation in RR attributable to heterogeneity) = 63.5%
Estimate of between-study variance Tau-squared = 0.1624
Test of RR=1 : z= 3.40 *P*=0.001

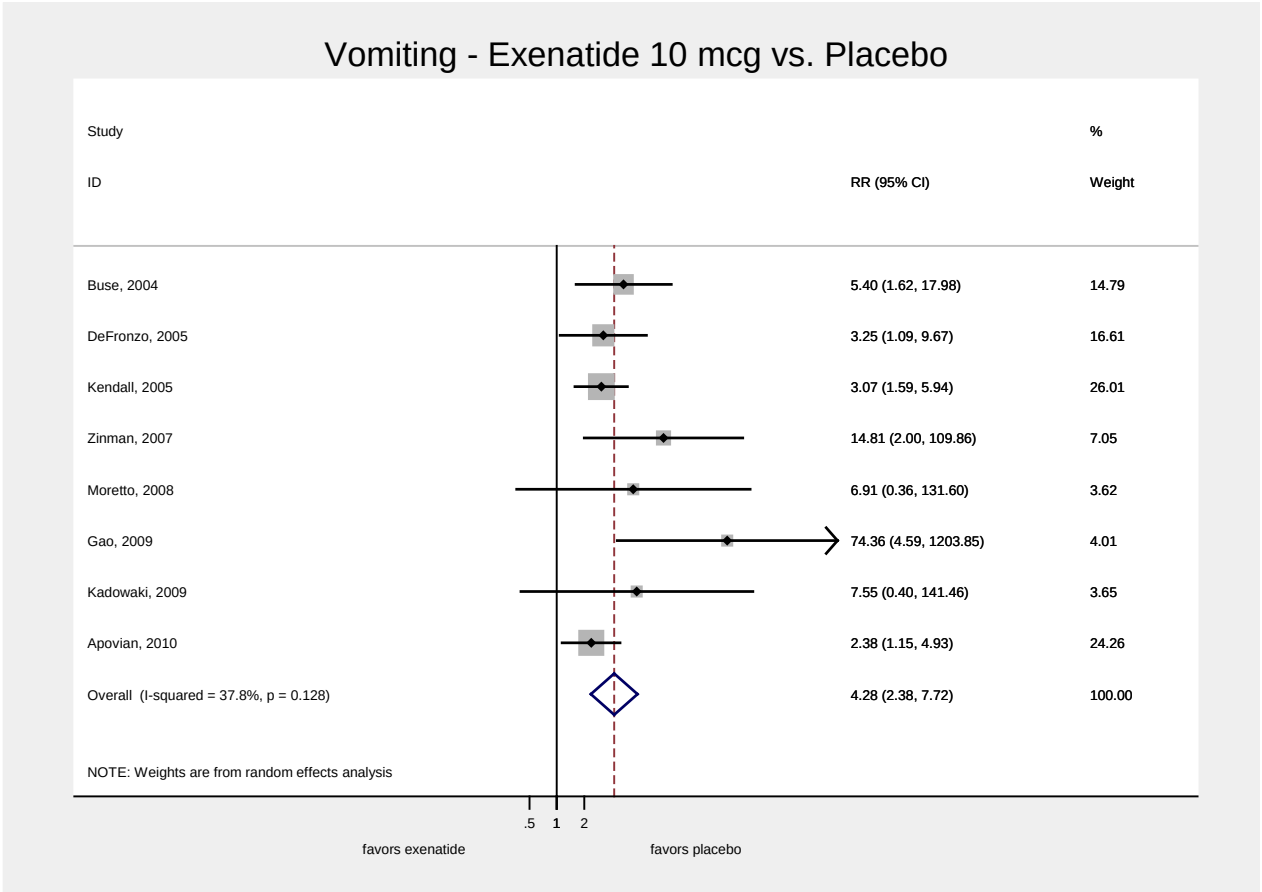


7) Vomiting – Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf.	Interval]	% Weight
Buse, 2004	5.403	1.624	17.980	14.79
DeFronzo, 2005	3.250	1.093	9.665	16.61
Kendall, 2005	3.075	1.591	5.942	26.01
Zinman, 2007	14.810	1.997	109.856	7.05
Moretto, 2008	6.911	0.363	131.604	3.62
Gao, 2009	74.362	4.593	1203.846	4.01
Kadowaki, 2009	7.553	0.403	141.462	3.65
Apovian, 2010	2.382	1.150	4.935	24.26
D+L pooled RR	4.282	2.377	7.715	100.00

Heterogeneity chi-squared = 11.25 (d.f. = 7) p = 0.128
I-squared (variation in RR attributable to heterogeneity) = 37.8%
Estimate of between-study variance Tau-squared = 0.2338
Test of RR=1 : z= 4.84 p = 0.000

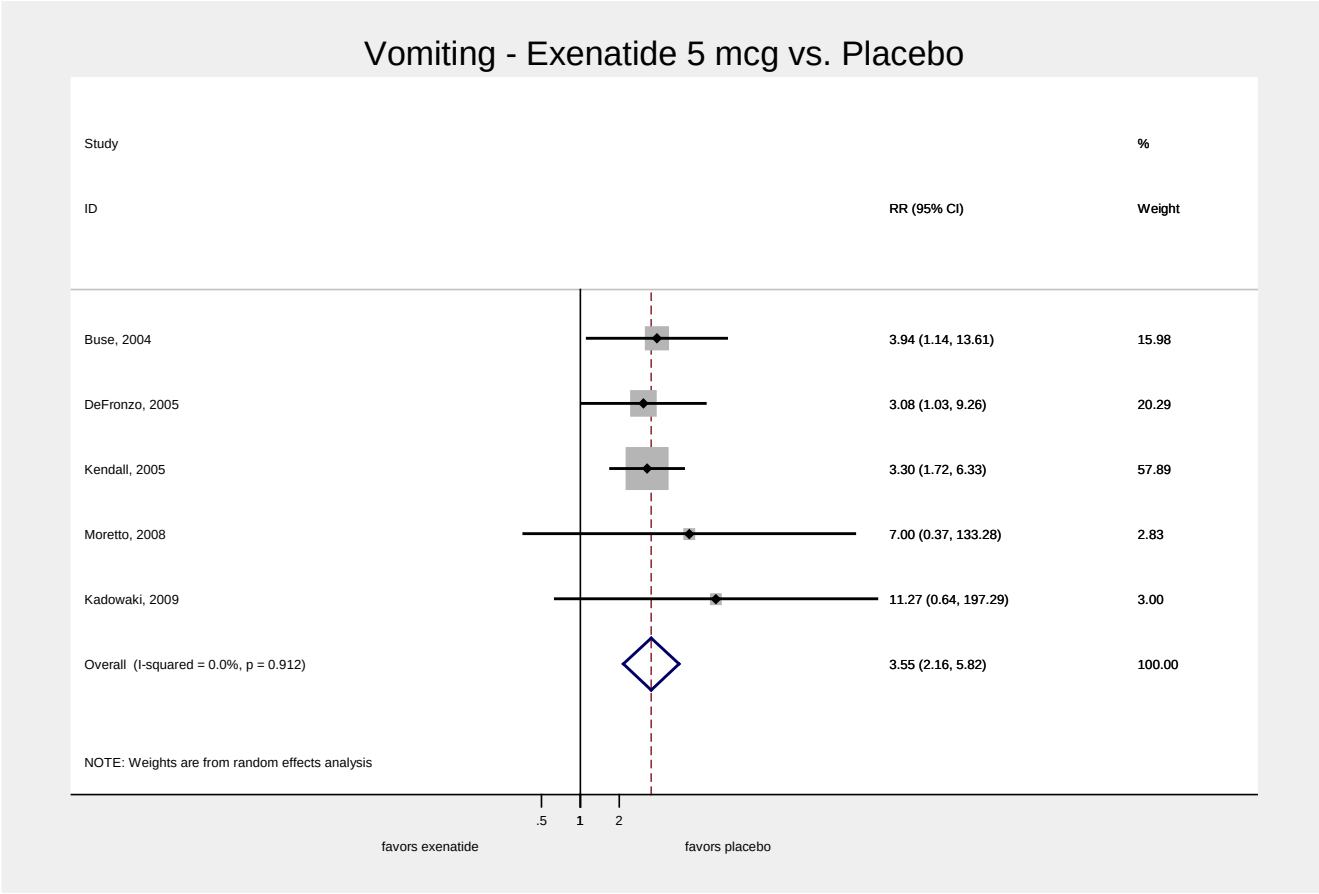


8) Vomiting – Exenatide 5 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	3.936	1.139 13.607	15.98
DeFronzo, 2005	3.082	1.025 9.265	20.29
Kendall, 2005	3.299	1.720 6.331	57.89
Moretto, 2008	7.000	0.368 133.277	2.83
Kadowaki, 2009	11.275	0.644 197.293	3.00
D+L pooled RR	3.548	2.161 5.825	100.00

Heterogeneity chi-squared = 0.98 (d.f. = 4) *P*=0.912
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 5.01 *P*=0.000

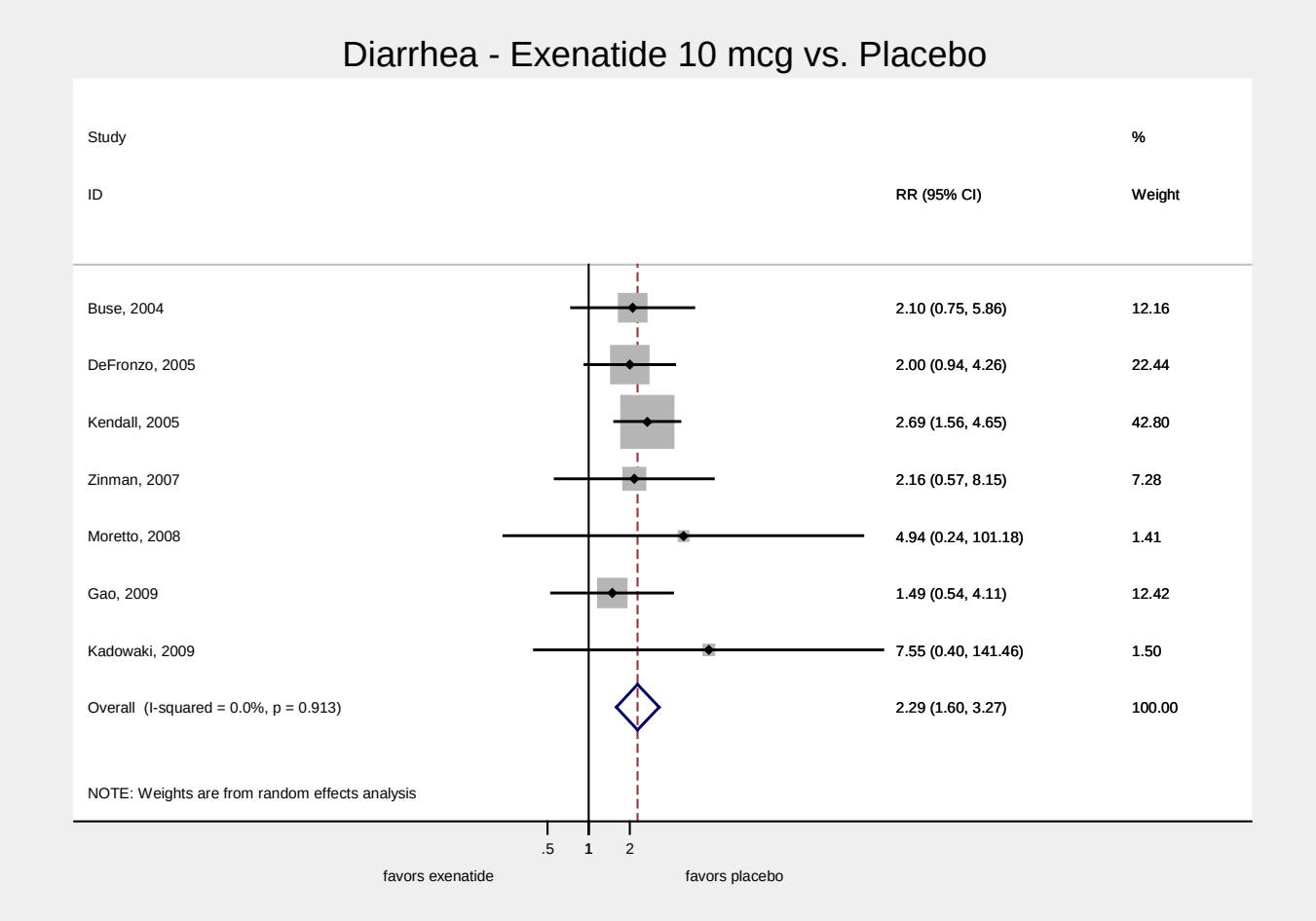


9) Diarrhea – Exenatide 10 mcg

Study statistics

Study	RR	[95% Conf.	Interval]	% Weight
Buse, 2004	2.098	0.750	5.863	12.16
DeFronzo, 2005	2.000	0.939	4.261	22.44
Kendall, 2005	2.690	1.556	4.653	42.80
Zinman, 2007	2.160	0.572	8.149	7.28
Moretto, 2008	4.937	0.241	101.180	1.41
Gao, 2009	1.487	0.538	4.111	12.42
Kadowaki, 2009	7.553	0.403	141.462	1.50
D+L pooled RR	2.287	1.598	3.273	100.00

Heterogeneity chi-squared = 2.08 (d.f. = 6) *P*=0.913
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.52 *P*=0.000

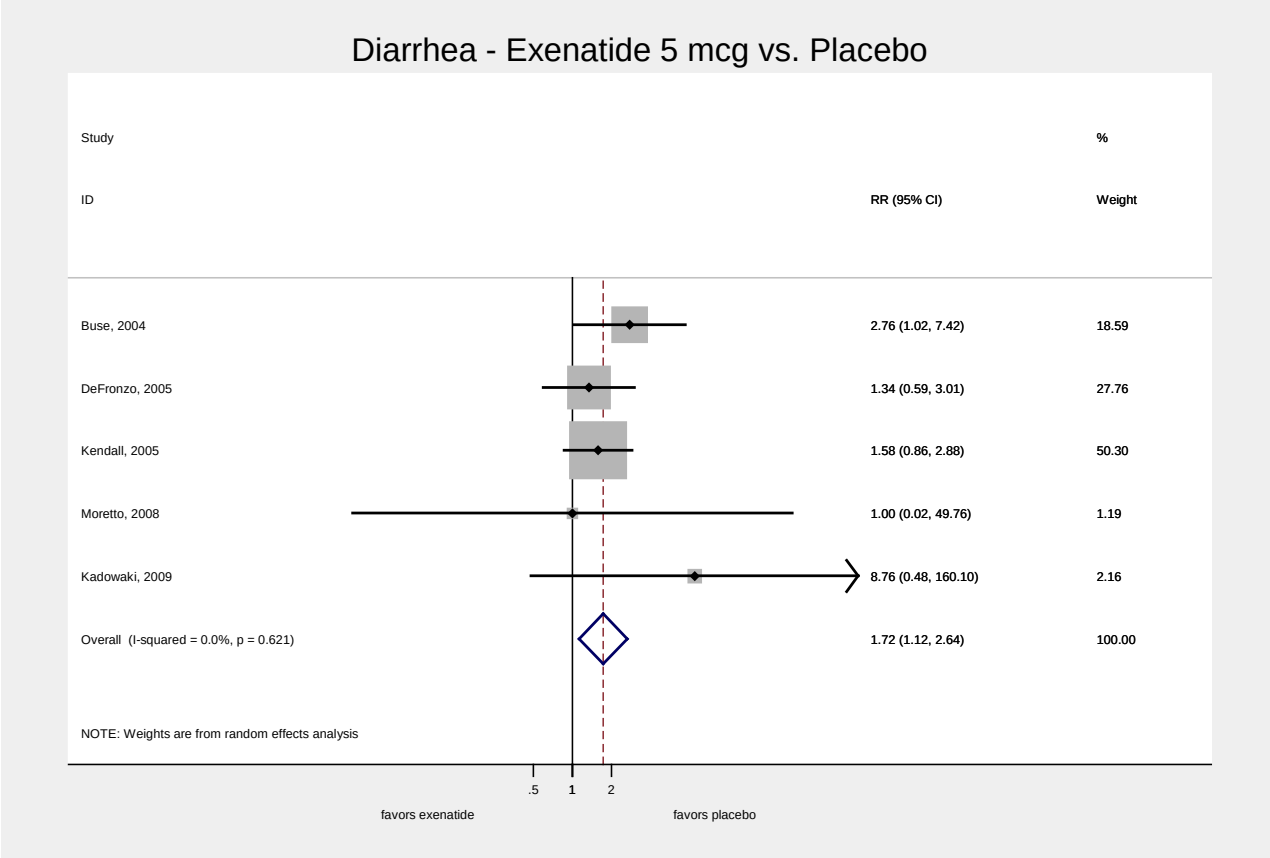


10) Diarrhea – Exenatide 5 mcg

Study statistics (adding 0.5 to the zero cells):

Study	RR	[95% Conf.	Interval]	% Weight
Buse, 2004	2.755	1.023	7.417	18.59
DeFronzo, 2005	1.338	0.595	3.009	27.76
Kendall, 2005	1.575	0.863	2.876	50.30
Moretto, 2008	1.000	0.020	49.763	1.19
Kadowaki, 2009	8.757	0.479	160.098	2.16
D+L pooled RR	1.724	1.125	2.642	100.00

Heterogeneity chi-squared = 2.63 (d.f. = 4) *P*=0.621
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.50 *P*=0.012

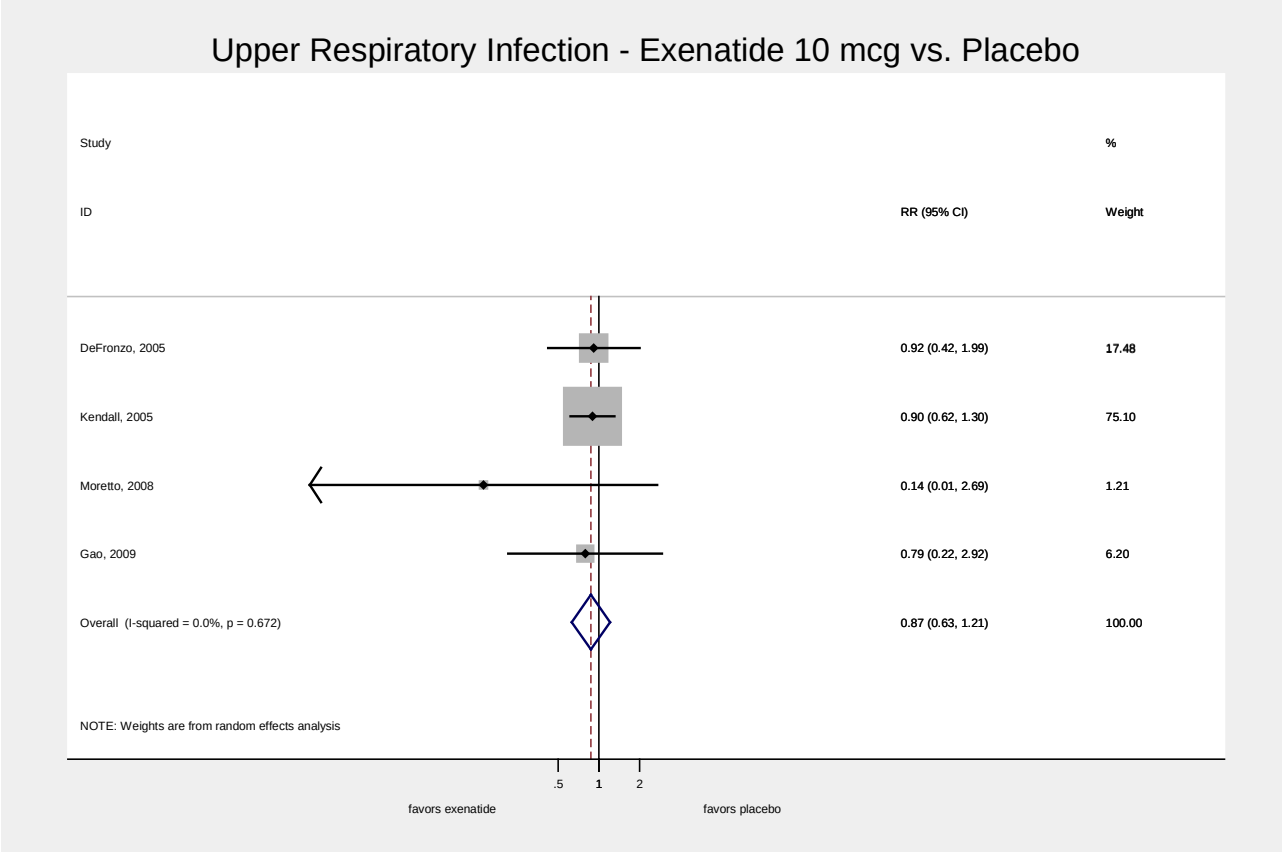


11) Upper Respiratory Infection – Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
DeFronzo, 2005	0.917	0.422 1.991	17.48
Kendall, 2005	0.897	0.617 1.304	75.10
Moretto, 2008	0.141	0.007 2.686	1.21
Gao, 2009	0.793	0.216 2.917	6.20
D+L pooled RR	0.874	0.632 1.208	100.00

Heterogeneity chi-squared = 1.55 (d.f. = 3) *P*=0.672
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.82 *P*=0.414

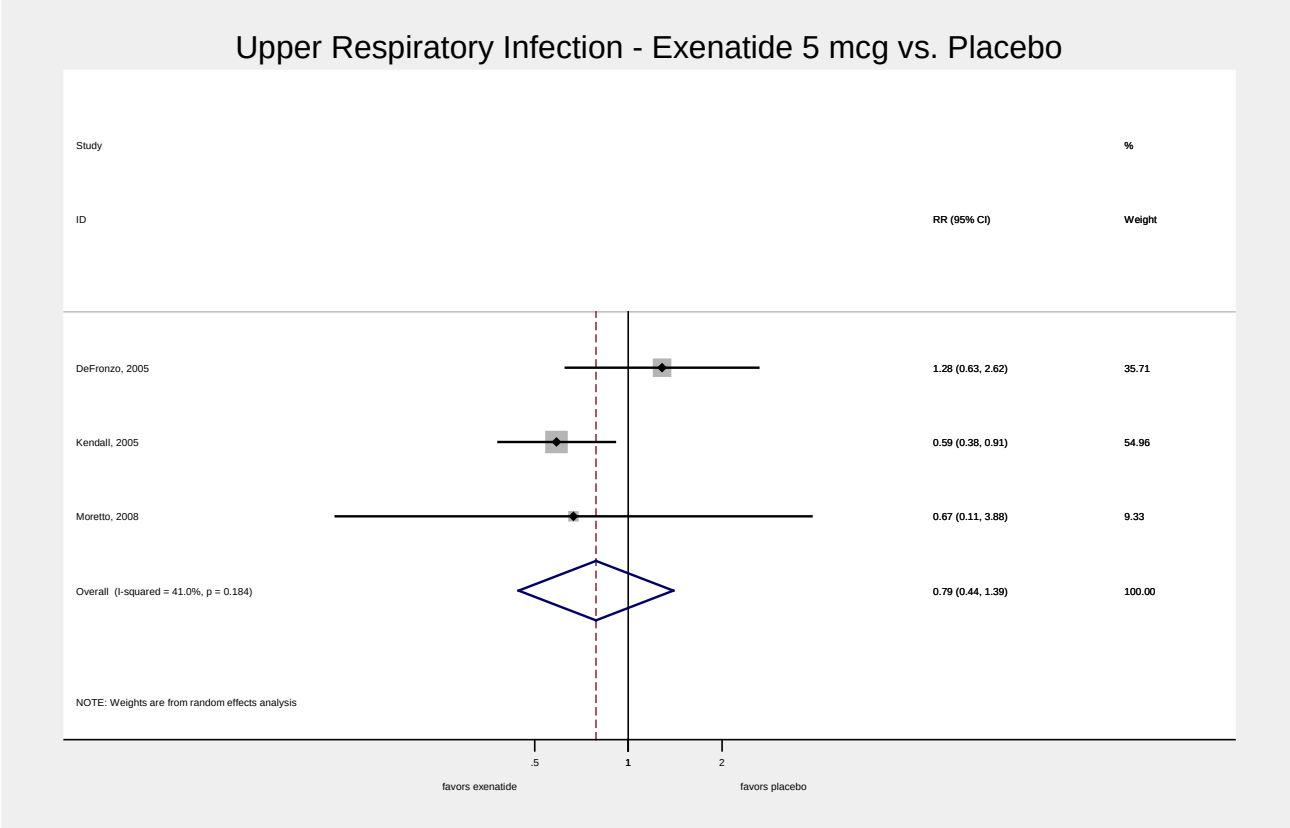


12) Upper Respiratory Infection – Exenatide 5 mcg

Study Statistics

Study	RR	[95% Conf.	Interval]	% Weight
DeFronzo, 2005	1.284	0.630	2.618	35.71
Kendall, 2005	0.588	0.382	0.905	54.96
Moretto, 2008	0.667	0.115	3.879	9.33
D+L pooled RR	0.786	0.444	1.394	100.00

Heterogeneity chi-squared = 3.39 (d.f. = 2) *P*=0.184
I-squared (variation in RR attributable to heterogeneity) = 41.0%
Estimate of between-study variance Tau-squared = 0.1068
Test of RR=1 : z= 0.82 *P*=0.411

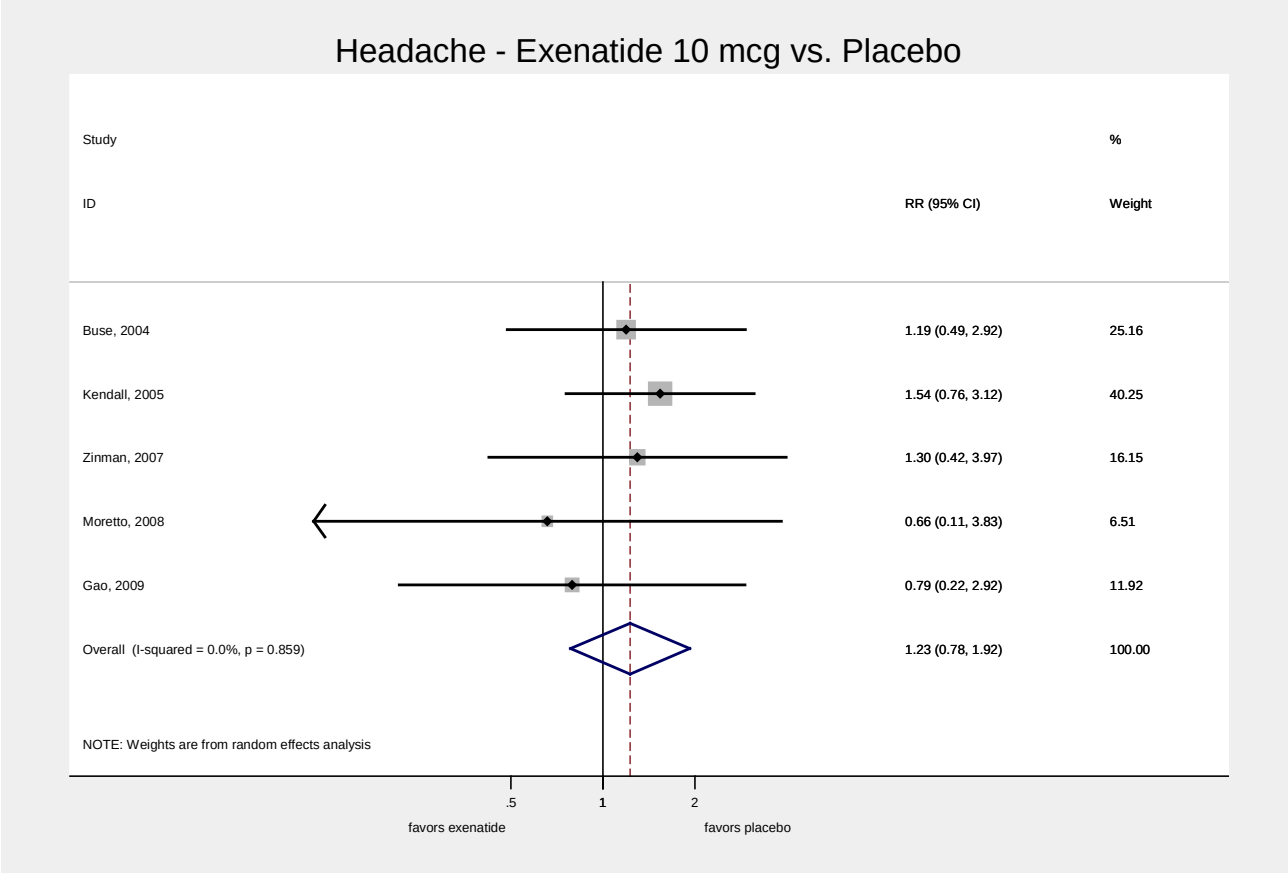


13) Headache – Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	1.192	0.486 2.921	25.16
Kendall, 2005	1.537	0.757 3.122	40.25
Zinman, 2007	1.296	0.423 3.966	16.15
Moretto, 2008	0.658	0.113 3.830	6.51
Gao, 2009	0.793	0.216 2.917	11.92
D+L pooled RR	1.227	0.782 1.923	100.00

Heterogeneity chi-squared = 1.31 (d.f. = 4) *P*=0.859
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.89 *P*=0.373

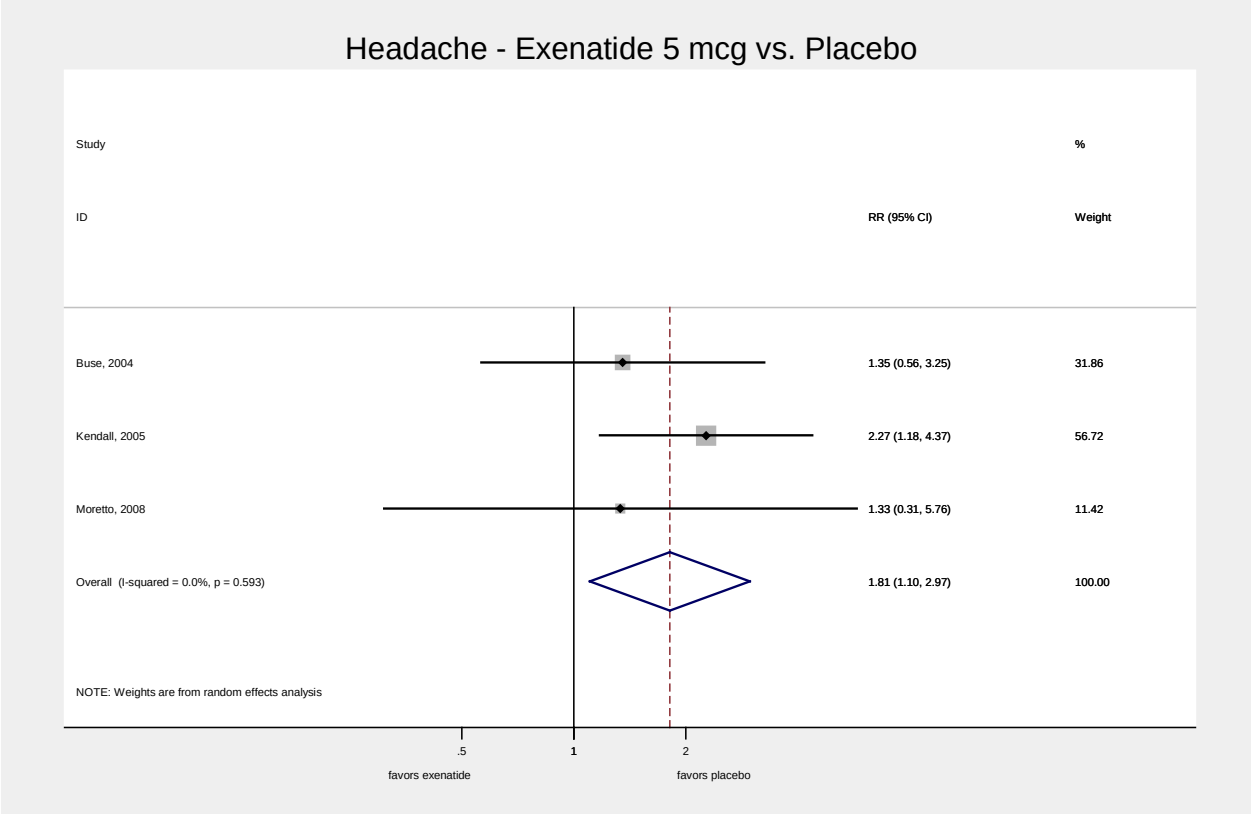


14) Headache – Exenatide 5 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	1.353	0.563 3.249	31.86
Kendall, 2005	2.268	1.176 4.374	56.72
Moretto, 2008	1.333	0.309 5.760	11.42
D+L pooled RR	1.811	1.104 2.969	100.00

Heterogeneity chi-squared = 1.05 (d.f. = 2) *P*=0.593
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.35 *P*=0.019

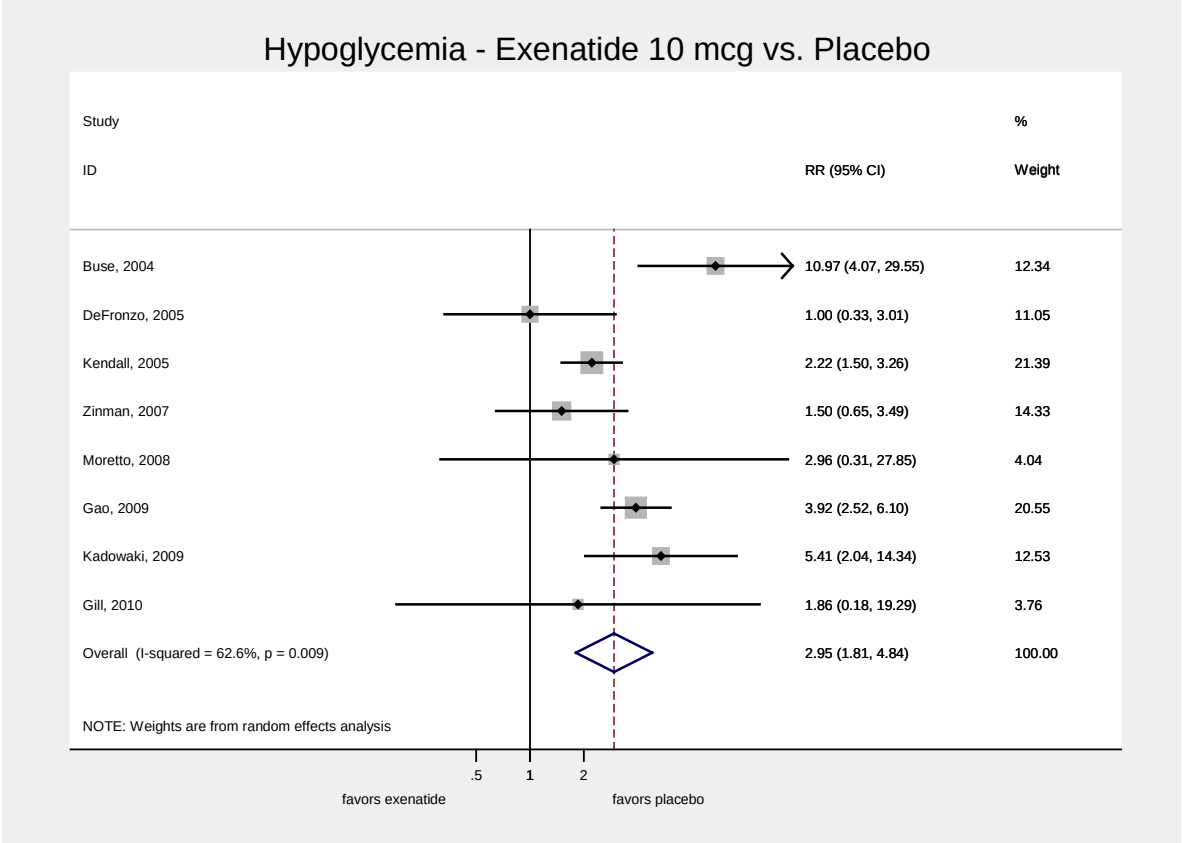


15) Hypoglycemia – Exenatide 10 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	10.965	4.069 29.551	12.34
DeFronzo, 2005	1.000	0.332 3.008	11.05
Kendall, 2005	2.215	1.504 3.262	21.39
Zinman, 2007	1.504	0.648 3.492	14.33
Moretto, 2008	2.962	0.315 27.851	4.04
Gao, 2009	3.919	2.516 6.103	20.55
Kadowaki, 2009	5.405	2.037 14.345	12.53
Gill, 2010	1.857	0.179 19.286	3.76
D+L pooled RR	2.955	1.805 4.837	100.00

Heterogeneity chi-squared = 18.70 (d.f. = 7) p = 0.009
I-squared (variation in RR attributable to heterogeneity) = 62.6%
Estimate of between-study variance Tau-squared = 0.2566
Test of RR=1 : z= 4.31 p = 0.000

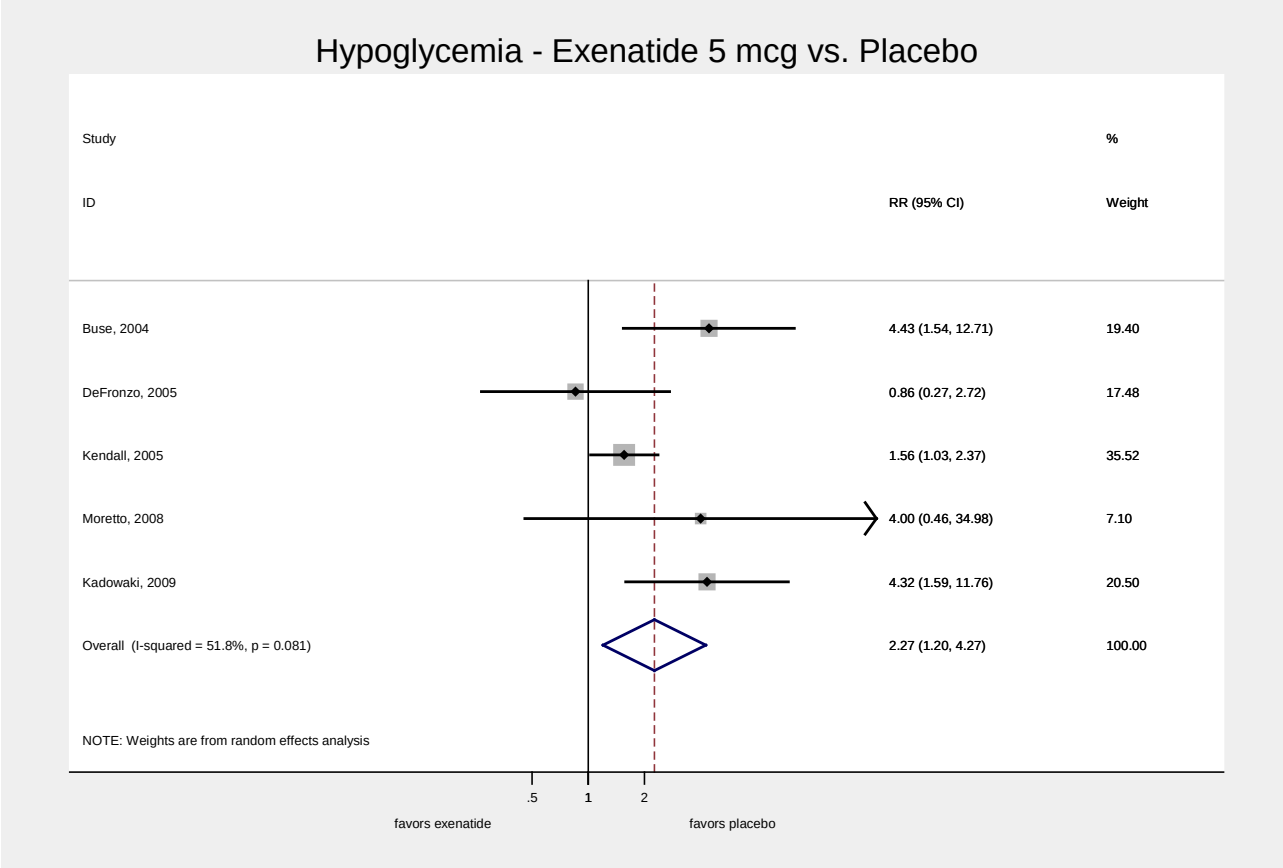


16) Hypoglycemia – Exenatide 5 mcg

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Buse, 2004	4.428	1.543 12.710	19.40
DeFronzo, 2005	0.856	0.269 2.724	17.48
Kendall, 2005	1.561	1.030 2.365	35.52
Moretto, 2008	4.000	0.457 34.978	7.10
Kadowaki, 2009	4.324	1.590 11.758	20.50
D+L pooled RR	2.267	1.203 4.272	100.00

Heterogeneity chi-squared = 8.30 (d.f. = 4) *P*=0.081
I-squared (variation in RR attributable to heterogeneity) = 51.8%
Estimate of between-study variance Tau-squared = 0.2494
Test of RR=1 : z= 2.53 *P*=0.011



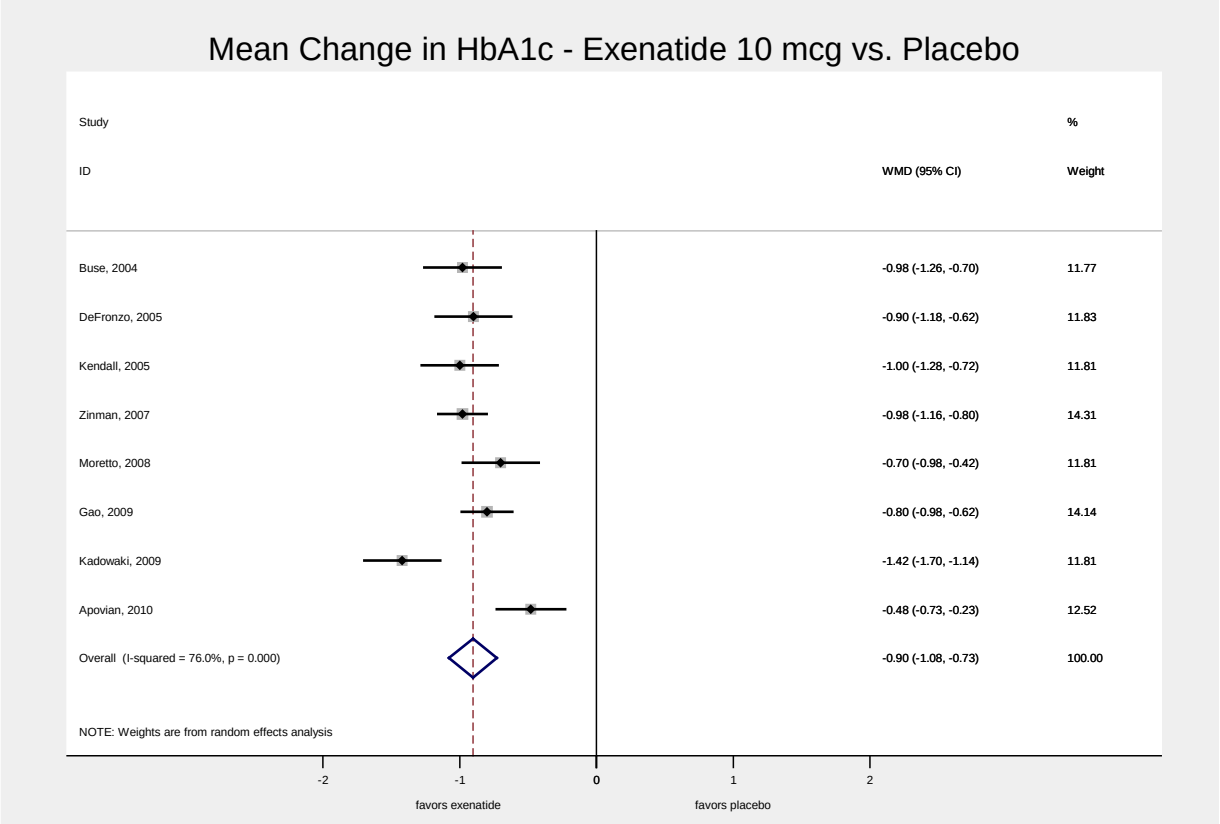
17) Mean Change in HbA1c - Exenatide 10 mcg

Study Statistics

(With Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	-0.980	-1.259 -0.701	11.77
DeFronzo, 2005	-0.900	-1.176 -0.624	11.83
Kendall, 2005	-1.000	-1.277 -0.723	11.81
Zinman, 2007	-0.980	-1.158 -0.802	14.31
Moretto, 2008	-0.700	-0.977 -0.423	11.81
Gao, 2009	-0.800	-0.985 -0.615	14.14
Kadowaki, 2009	-1.420	-1.697 -1.143	11.81
Apovian, 2010	-0.480	-0.729 -0.231	12.52
D+L pooled WMD	-0.904	-1.079 -0.729	100.00

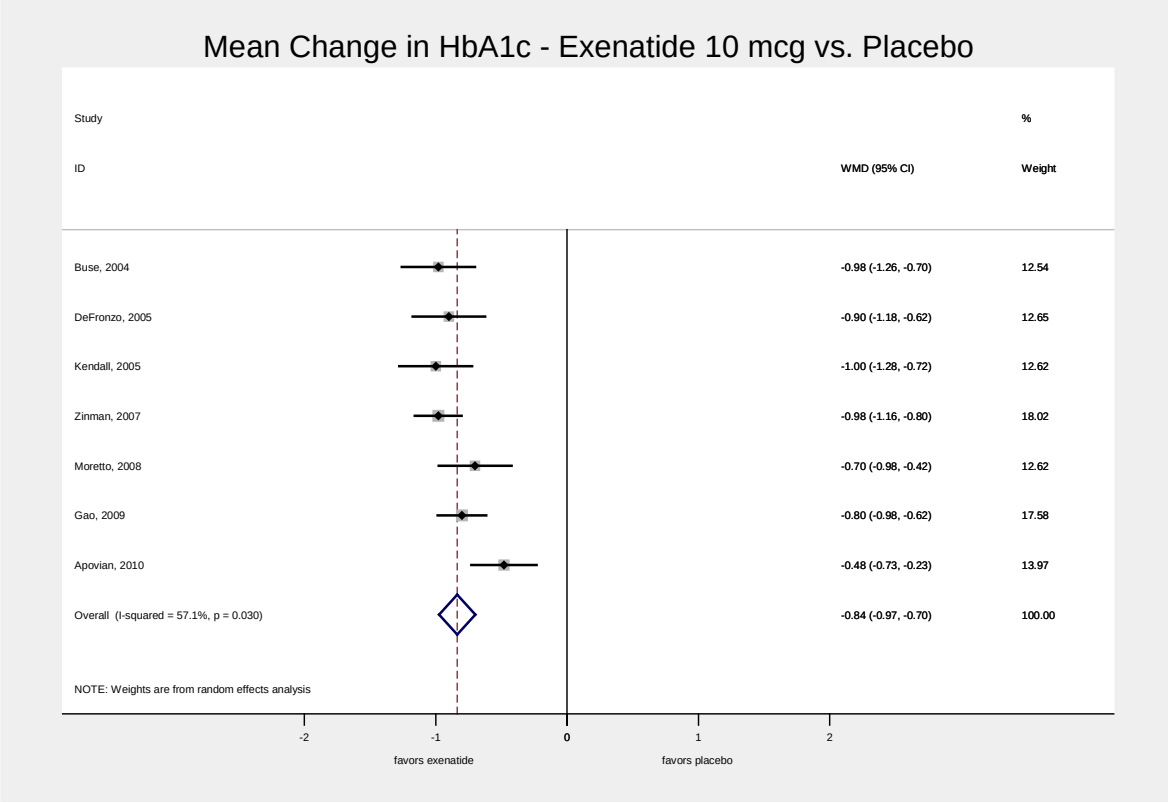
Heterogeneity chi-squared = 29.12 (d.f. = 7) p = 0.000
I-squared (variation in WMD attributable to heterogeneity) = 76.0%
Estimate of between-study variance Tau-squared = 0.0475
Test of WMD=0 : z= 10.12 p = 0.000



(Without Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	-0.980	-1.259 -0.701	12.54
DeFronzo, 2005	-0.900	-1.176 -0.624	12.65
Kendall, 2005	-1.000	-1.277 -0.723	12.62
Zinman, 2007	-0.980	-1.158 -0.802	18.02
Moretto, 2008	-0.700	-0.977 -0.423	12.62
Gao, 2009	-0.800	-0.985 -0.615	17.58
Apovian, 2010	-0.480	-0.729 -0.231	13.97
D+L pooled WMD	-0.836	-0.974 -0.698	100.00

Heterogeneity chi-squared = 13.97 (d.f. = 6) p = 0.030
I-squared (variation in WMD attributable to heterogeneity) = 57.1%
Estimate of between-study variance Tau-squared = 0.0193
Test of WMD=0 : z= 11.86 p = 0.000



18)

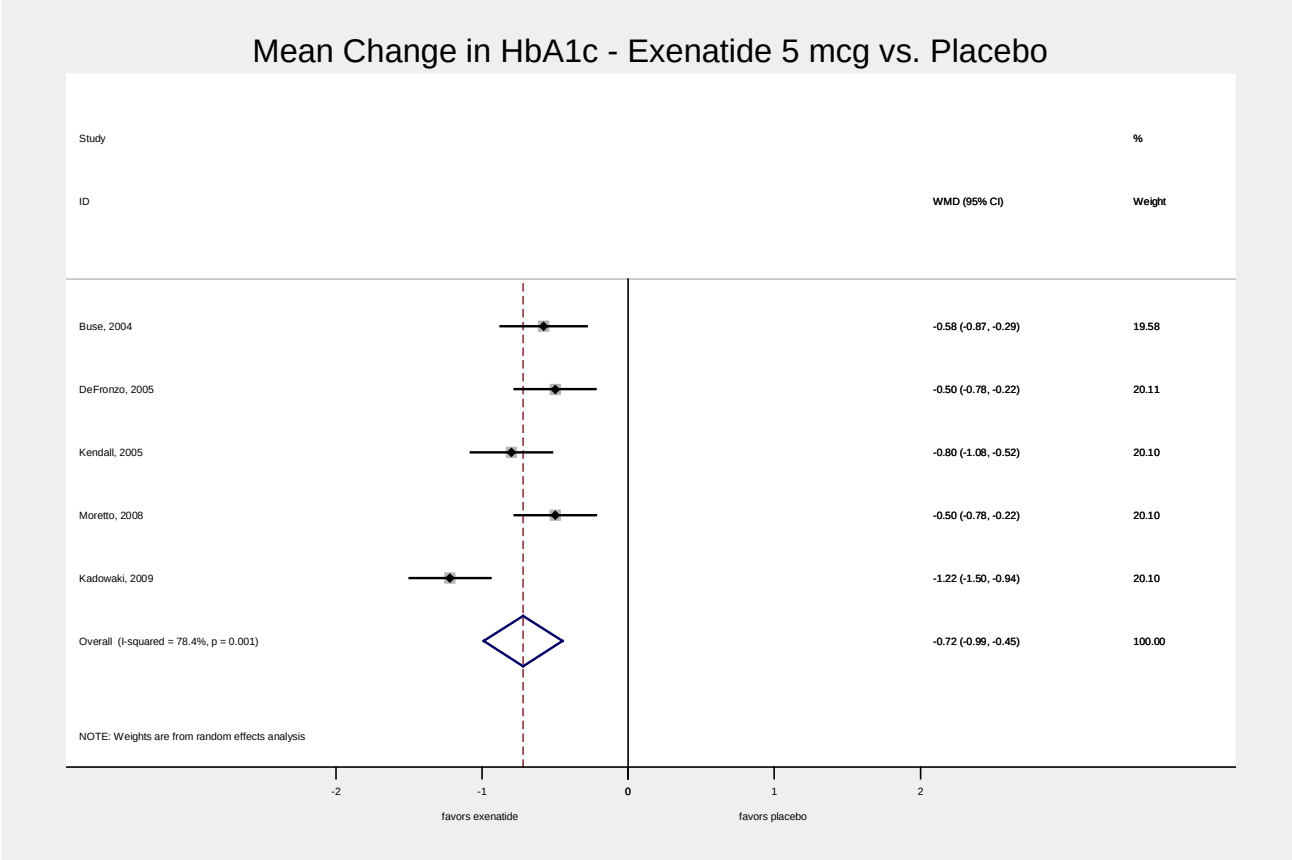
18) Mean Change in HbA1c - Exenatide 5 mcg

Study Statistics

(With Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	−0.580	−0.874 −0.286	19.58
DeFronzo, 2005	−0.500	−0.777 −0.223	20.11
Kendall, 2005	−0.800	−1.077 −0.523	20.10
Moretto, 2008	−0.500	−0.777 −0.223	20.10
Kadowaki, 2009	−1.220	−1.497 −0.943	20.10
D+L pooled WMD	−0.721	−0.991 −0.451	100.00

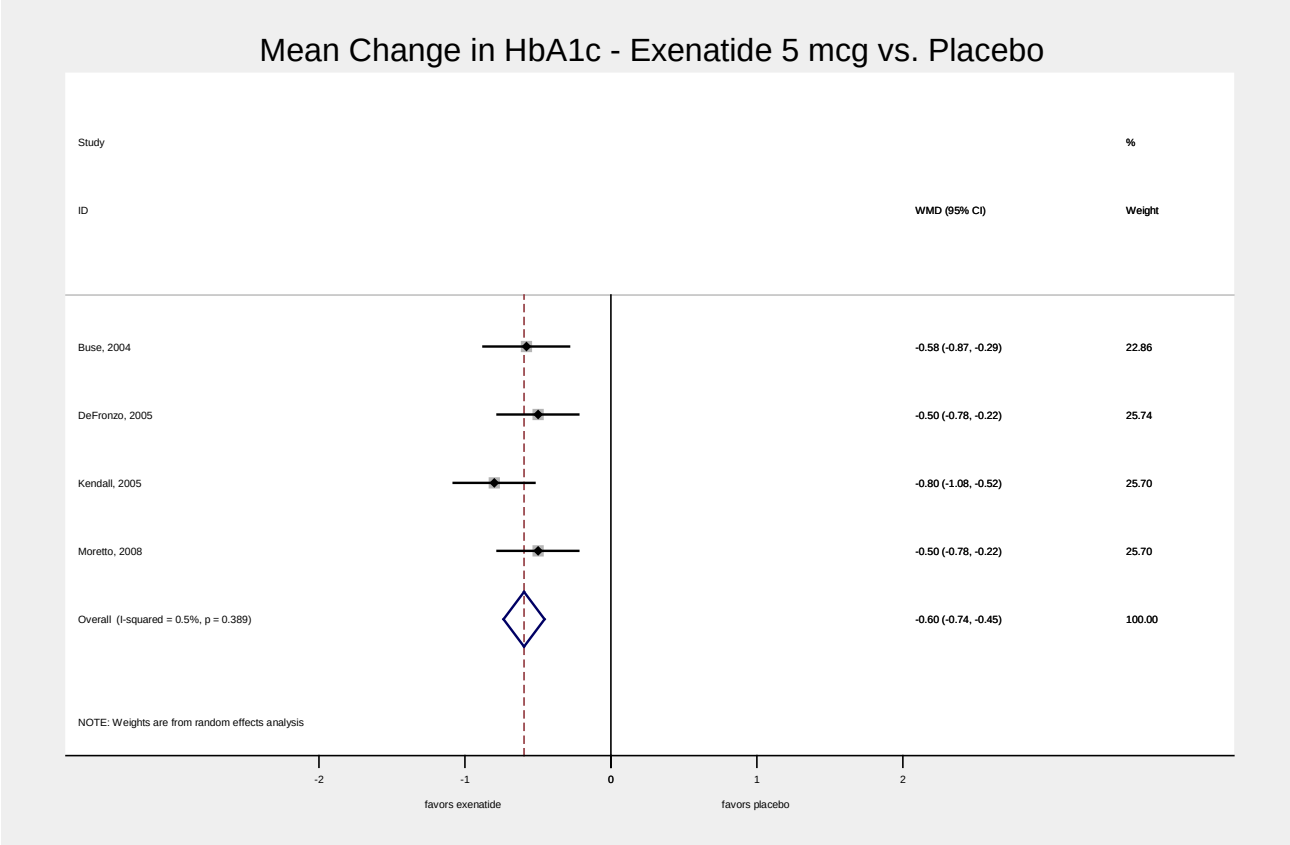
Heterogeneity chi-squared = 18.53 (d.f. = 4) *P*=0.001
I-squared (variation in WMD attributable to heterogeneity) = 78.4%
Estimate of between-study variance Tau-squared = 0.0743
Test of WMD=0 : z= 5.23 *P*=0.000



(Without Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	−0.580	−0.874 −0.286	22.86
DeFronzo, 2005	−0.500	−0.777 −0.223	25.74
Kendall, 2005	−0.800	−1.077 −0.523	25.70
Moretto, 2008	−0.500	−0.777 −0.223	25.70
D+L pooled WMD	−0.595	−0.736 −0.455	100.00

Heterogeneity chi-squared = 3.01 (d.f. = 3) *P*=0.389
I-squared (variation in WMD attributable to heterogeneity) = 0.5%
Estimate of between-study variance Tau-squared = 0.0001
Test of WMD=0 : z= 8.28 *P*=0.000



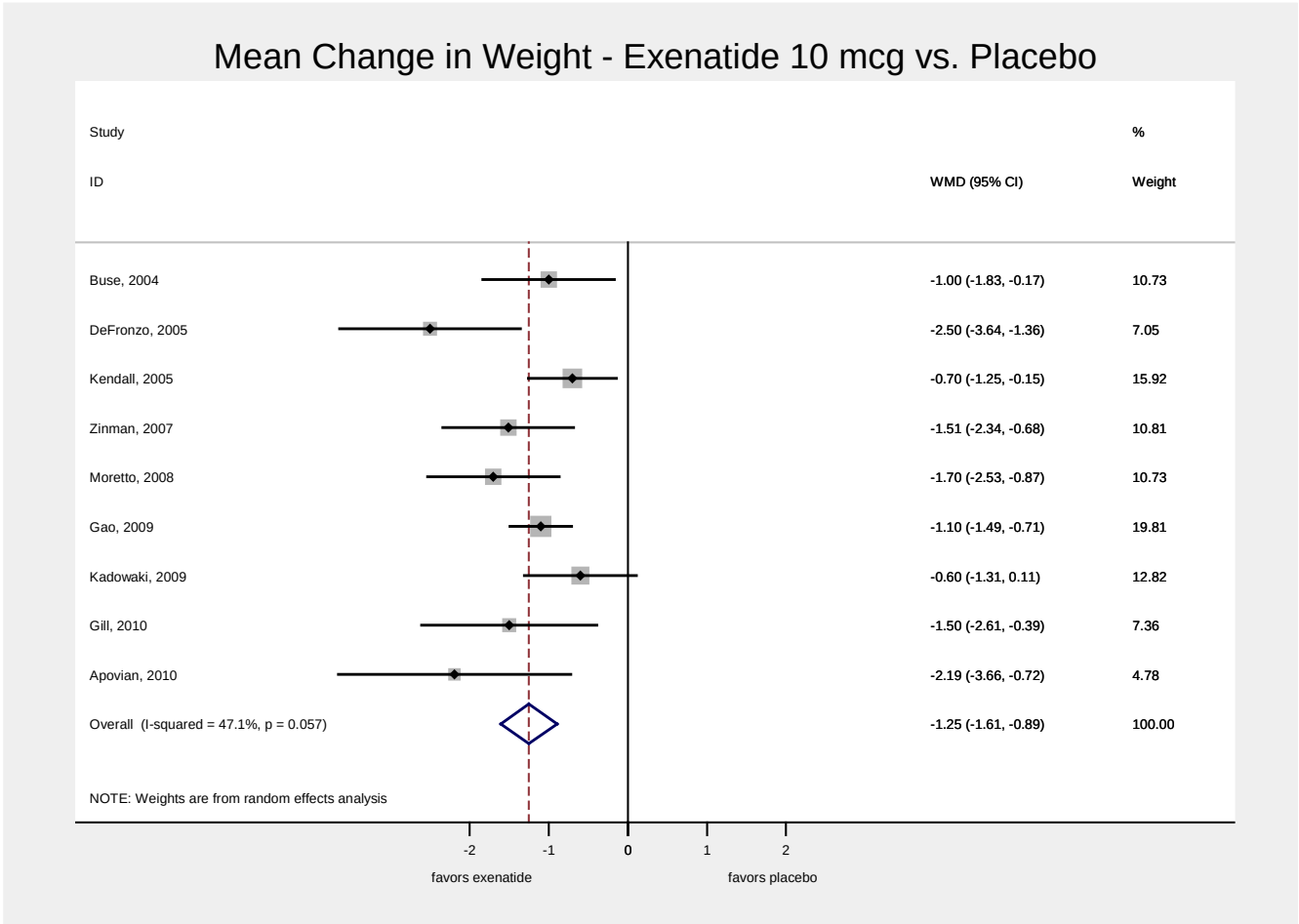
19) Mean Change in Weight - Exenatide 10 mcg

Study Statistics

(With Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	-1.000	-1.832 -0.168	10.73
DeFronzo, 2005	-2.500	-3.643 -1.357	7.05
Kendall, 2005	-0.700	-1.254 -0.146	15.92
Zinman, 2007	-1.510	-2.336 -0.684	10.81
Moretto, 2008	-1.700	-2.532 -0.868	10.73
Gao, 2009	-1.100	-1.489 -0.711	19.81
Kadowaki, 2009	-0.600	-1.307 0.107	12.82
Gill, 2010	-1.500	-2.609 -0.391	7.36
Apovian, 2010	-2.190	-3.659 -0.721	4.78
D+L pooled WMD	-1.250	-1.606 -0.895	100.00

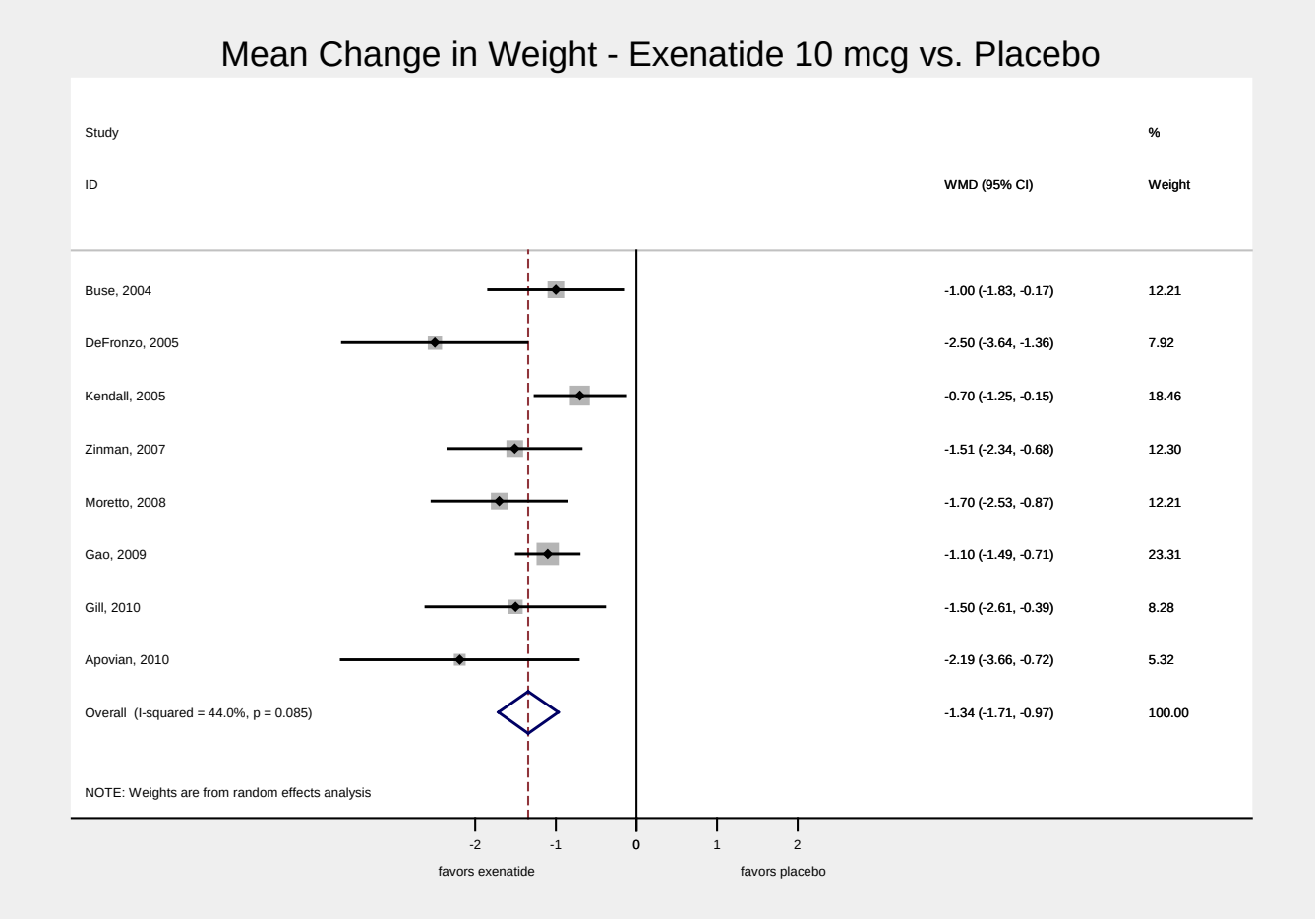
Heterogeneity chi-squared = 15.12 (d.f. = 8) p = 0.057
I-squared (variation in WMD attributable to heterogeneity) = 47.1%
Estimate of between-study variance Tau-squared = 0.1266
Test of WMD=0 : z= 6.89 p = 0.000



(Without Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	-1.000	-1.832 -0.168	12.21
DeFronzo, 2005	-2.500	-3.643 -1.357	7.92
Kendall, 2005	-0.700	-1.254 -0.146	18.46
Zinman, 2007	-1.510	-2.336 -0.684	12.30
Moretto, 2008	-1.700	-2.532 -0.868	12.21
Gao, 2009	-1.100	-1.489 -0.711	23.31
Gill, 2010	-1.500	-2.609 -0.391	8.28
Apovian, 2010	-2.190	-3.659 -0.721	5.32
D+L pooled WMD	-1.340	-1.712 -0.968	100.00

Heterogeneity chi-squared = 12.51 (d.f. = 7) p = 0.085
I-squared (variation in WMD attributable to heterogeneity) = 44.0%
Estimate of between-study variance Tau-squared = 0.1152
Test of WMD=0 : z= 7.06 p = 0.000



20) Mean Change in Weight - Exenatide 5 mcg

Study Statistics

(With Kadowaki)

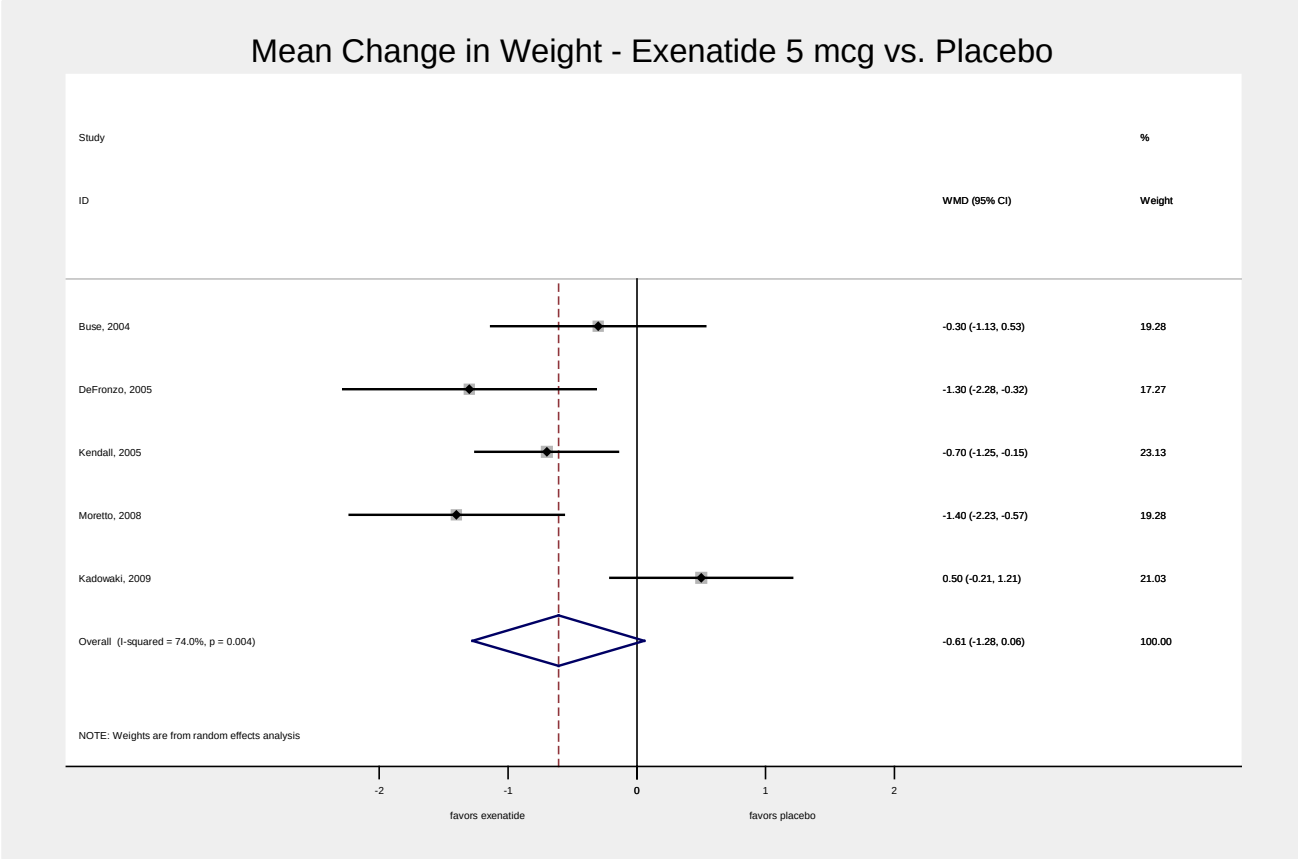
Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	−0.300	−1.132 0.532	19.28
DeFronzo, 2005	−1.300	−2.280 −0.320	17.27
Kendall, 2005	−0.700	−1.254 −0.146	23.13
Moretto, 2008	−1.400	−2.232 −0.568	19.28
Kadowaki, 2009	0.500	−0.207 1.207	21.03
D+L pooled WMD	−0.609	−1.276 0.058	100.00

Heterogeneity chi-squared = 15.37 (d.f. = 4) *P*=0.004

I-squared (variation in WMD attributable to heterogeneity) = 74.0%

Estimate of between-study variance Tau-squared = 0.4212

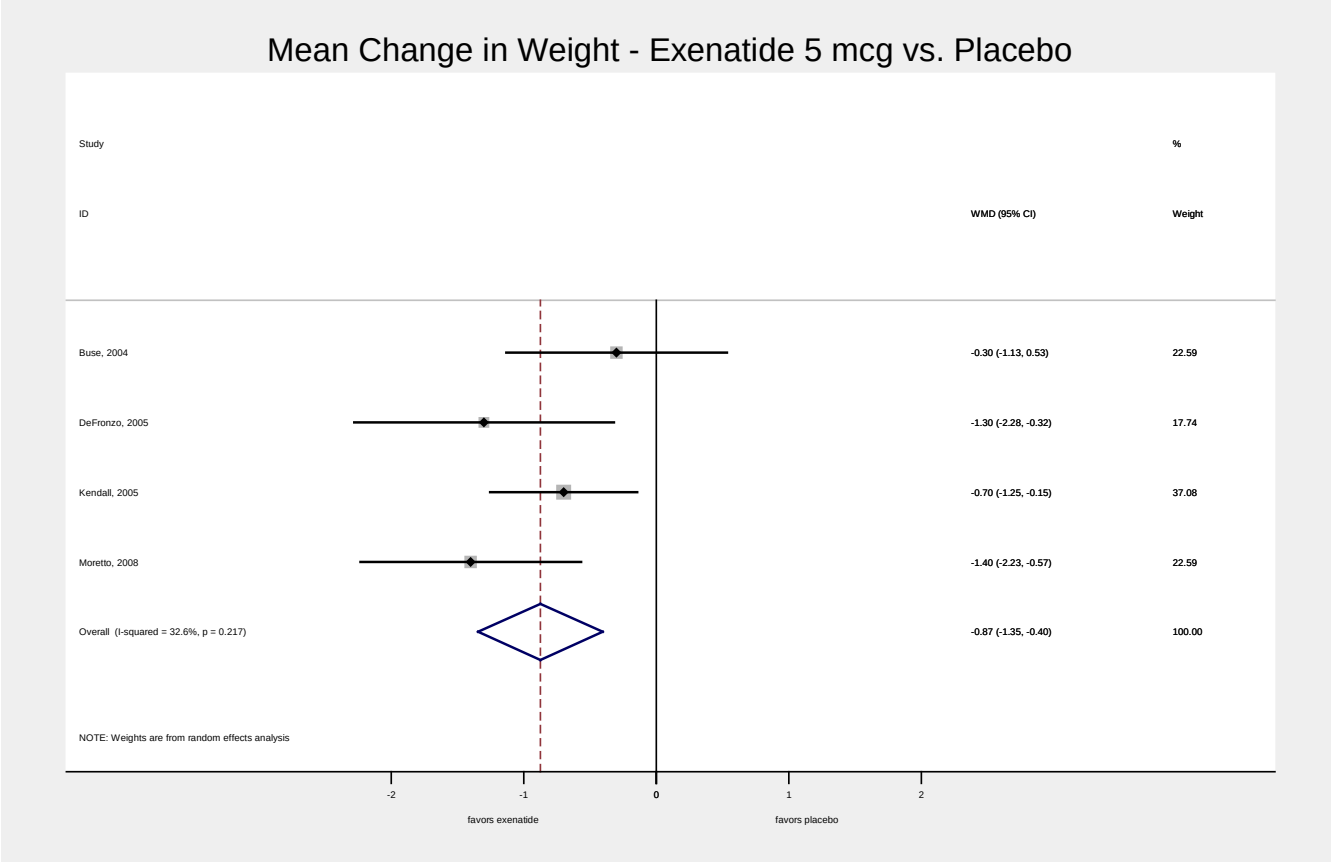
Test of WMD=0 : z= 1.79 *P*=0.074



(Without Kadowaki)

Study	WMD	[95% Conf. Interval]	% Weight
Buse, 2004	−0.300	−1.132 0.532	22.59
DeFronzo, 2005	−1.300	−2.280 −0.320	17.74
Kendall, 2005	−0.700	−1.254 −0.146	37.08
Moretto, 2008	−1.400	−2.232 −0.568	22.59
D+L pooled WMD	−0.874	−1.345 −0.403	100.00

Heterogeneity chi-squared = 4.45 (d.f. = 3) *P*=0.217
I-squared (variation in WMD attributable to heterogeneity) = 32.6%
Estimate of between-study variance Tau-squared = 0.0759
Test of WMD=0 : z= 3.64 *P*=0.000



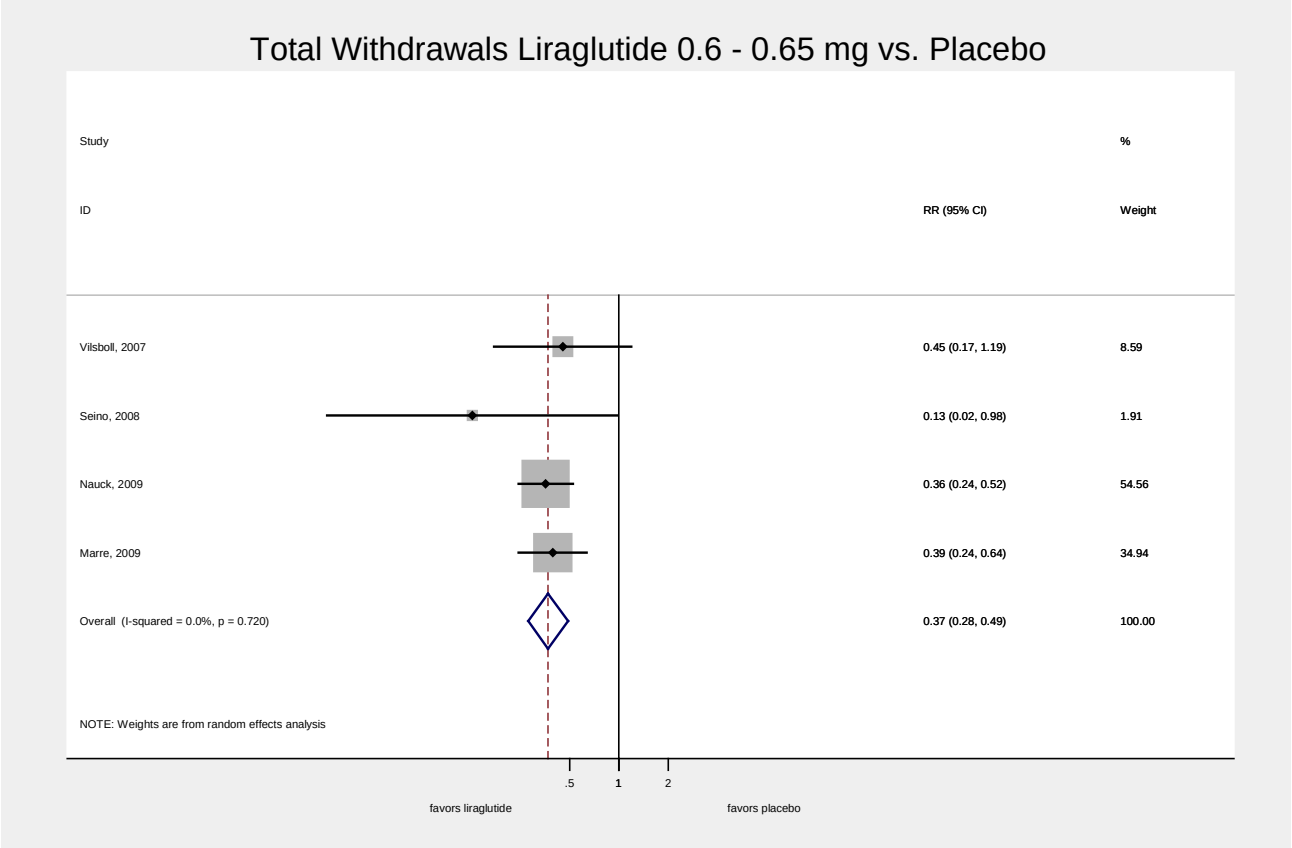
Liraglutide Meta-Analyses

1) Liraglutide 0.6 – 0.65 mg Compared with Placebo – Total Withdrawals

Study Statistics

Study	RR	[95% Conf.	Interval]	% Weight
Vilsboll, 2007	0.455	0.174	1.190	8.59
Seino, 2008	0.128	0.017	0.981	1.91
Nauck, 2009	0.357	0.244	0.523	54.56
Marre, 2009	0.395	0.245	0.636	34.94
D+L pooled RR	0.370	0.279	0.491	100.00

Heterogeneity chi-squared = 1.34 (d.f. = 3) p = 0.720
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 6.91 p = 0.000

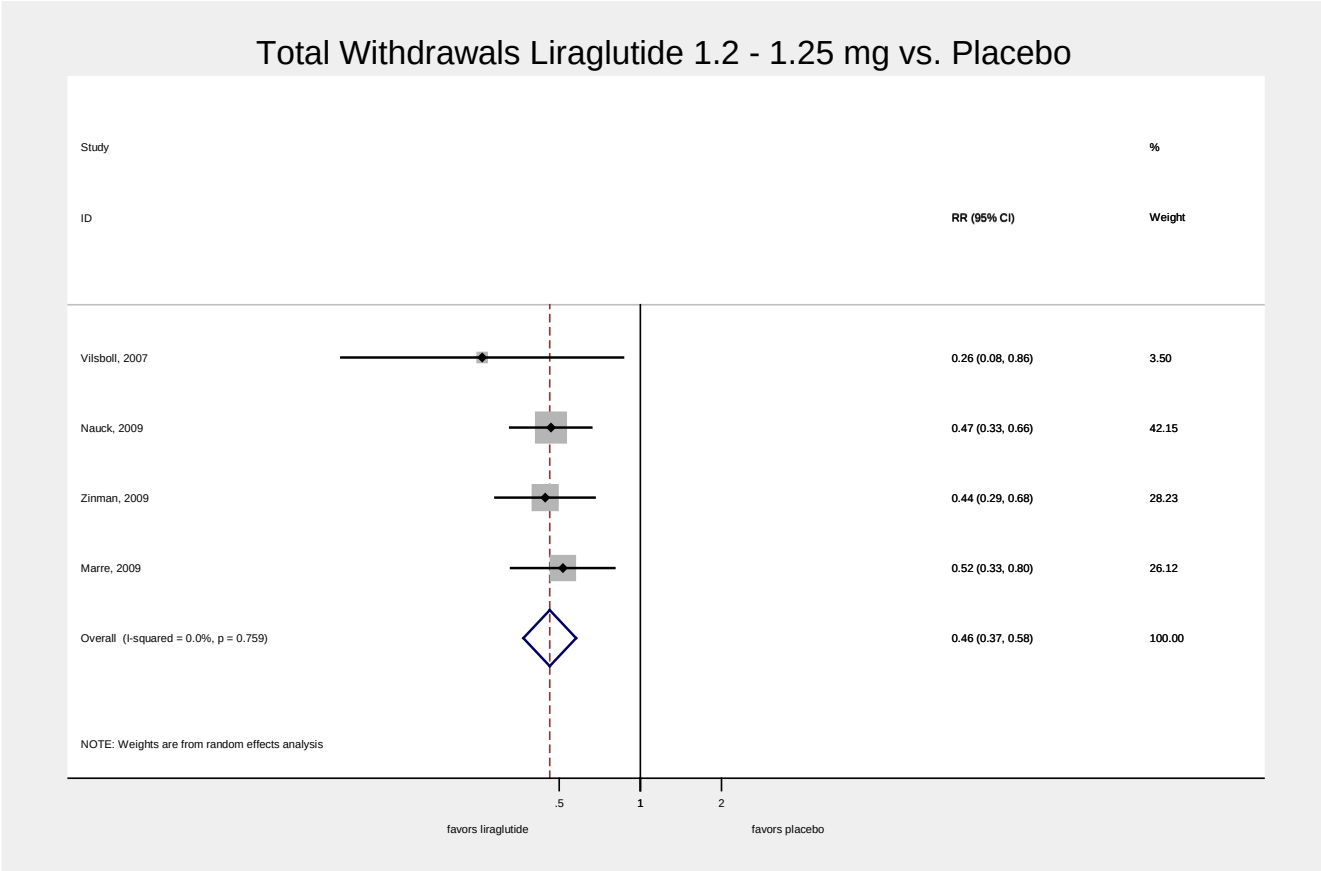


2) Liraglutide 1.2 – 1.25 mg Compared with Placebo – Total Withdrawals

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Vilsboll, 2007	0.260	0.078 0.863	3.50
Nauck, 2009	0.466	0.330 0.659	42.15
Zinman, 2009	0.444	0.291 0.678	28.23
Marre, 2009	0.516	0.332 0.801	26.12
D+L pooled RR	0.463	0.369 0.579	100.00

Heterogeneity chi-squared = 1.17 (d.f. = 3) p = 0.759
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 6.72 p = 0.000

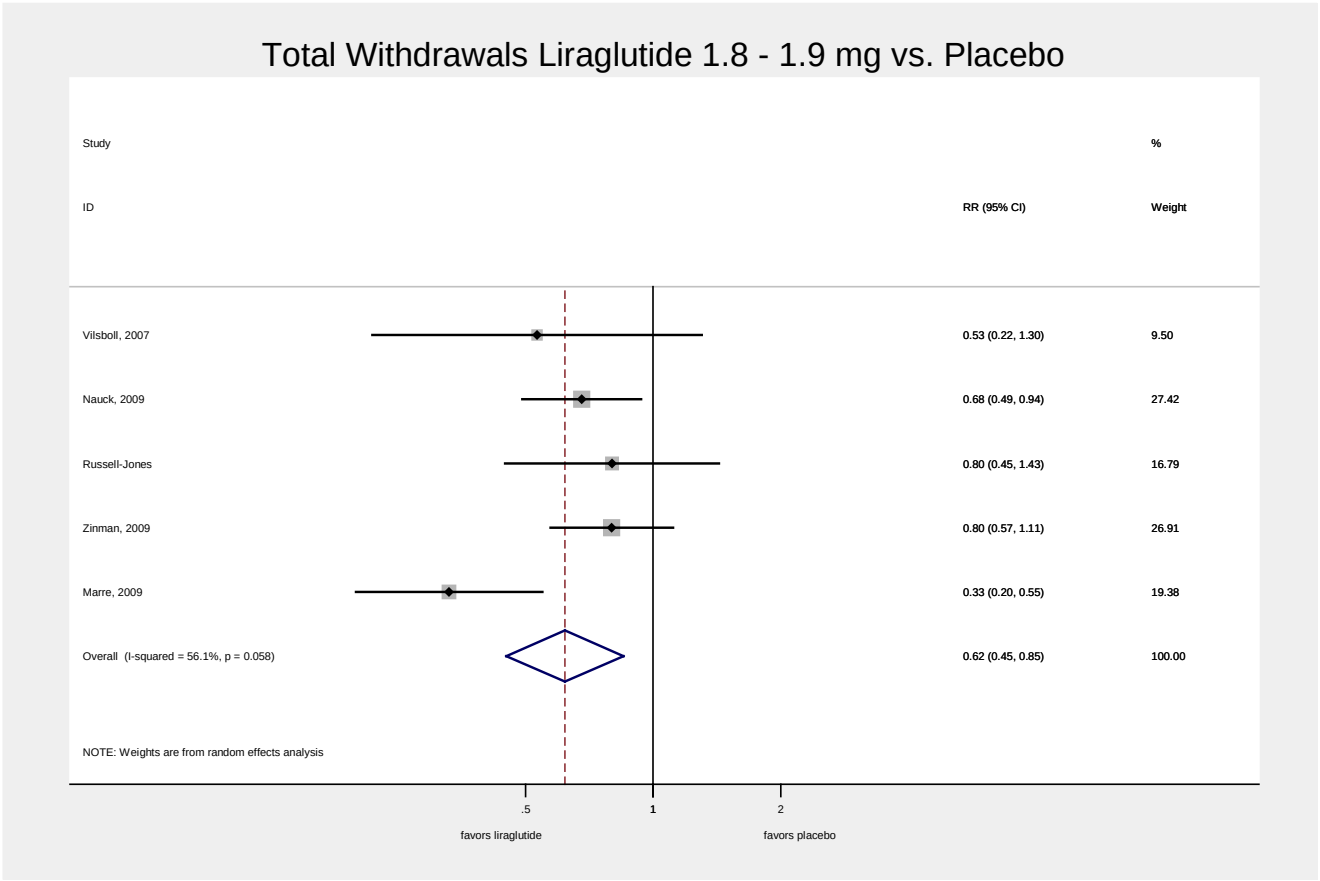


3) Liraglutide 1.8 – 1.9 mg Compared with Placebo – Total Withdrawals

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Vilsboll, 2007	0.532	0.218 1.301	9.50
Nauck, 2009	0.679	0.492 0.937	27.42
Russell-Jones	0.800	0.448 1.430	16.79
Zinman, 2009	0.799	0.573 1.114	26.91
Marre, 2009	0.330	0.199 0.548	19.38
D+L pooled RR	0.619	0.451 0.851	100.00

Heterogeneity chi-squared = 9.12 (d.f. = 4) p = 0.058
I-squared (variation in RR attributable to heterogeneity) = 56.1%
Estimate of between-study variance Tau-squared = 0.0690
Test of RR=1 : z= 2.95 p = 0.003

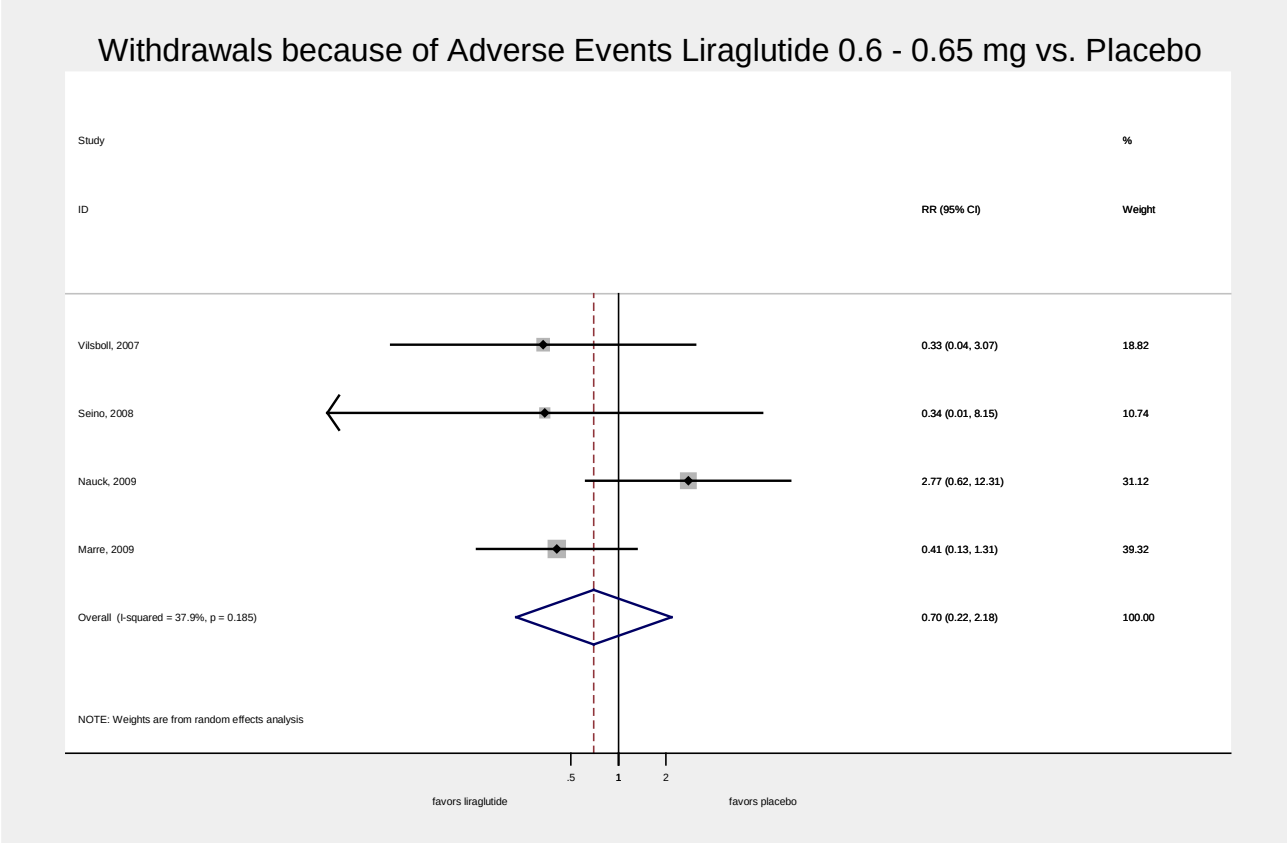


4) Liraglutide 0.6 – 0.65 mg Compared with Placebo – Withdrawals because of Adverse Events

Study Statistics

Study	RR	[95% Conf.	Interval]	% Weight
Vilsboll, 2007	0.333	0.036	3.070	18.82
Seino, 2008	0.341	0.014	8.146	10.74
Nauck, 2009	2.773	0.624	12.313	31.12
Marre, 2009	0.408	0.127	1.308	39.32
D+L pooled RR	0.699	0.225	2.176	100.00

Heterogeneity chi-squared = 4.83 (d.f. = 3) p = 0.185
I-squared (variation in RR attributable to heterogeneity) = 37.9%
Estimate of between-study variance Tau-squared = 0.4997
Test of RR=1 : z= 0.62 p = 0.537

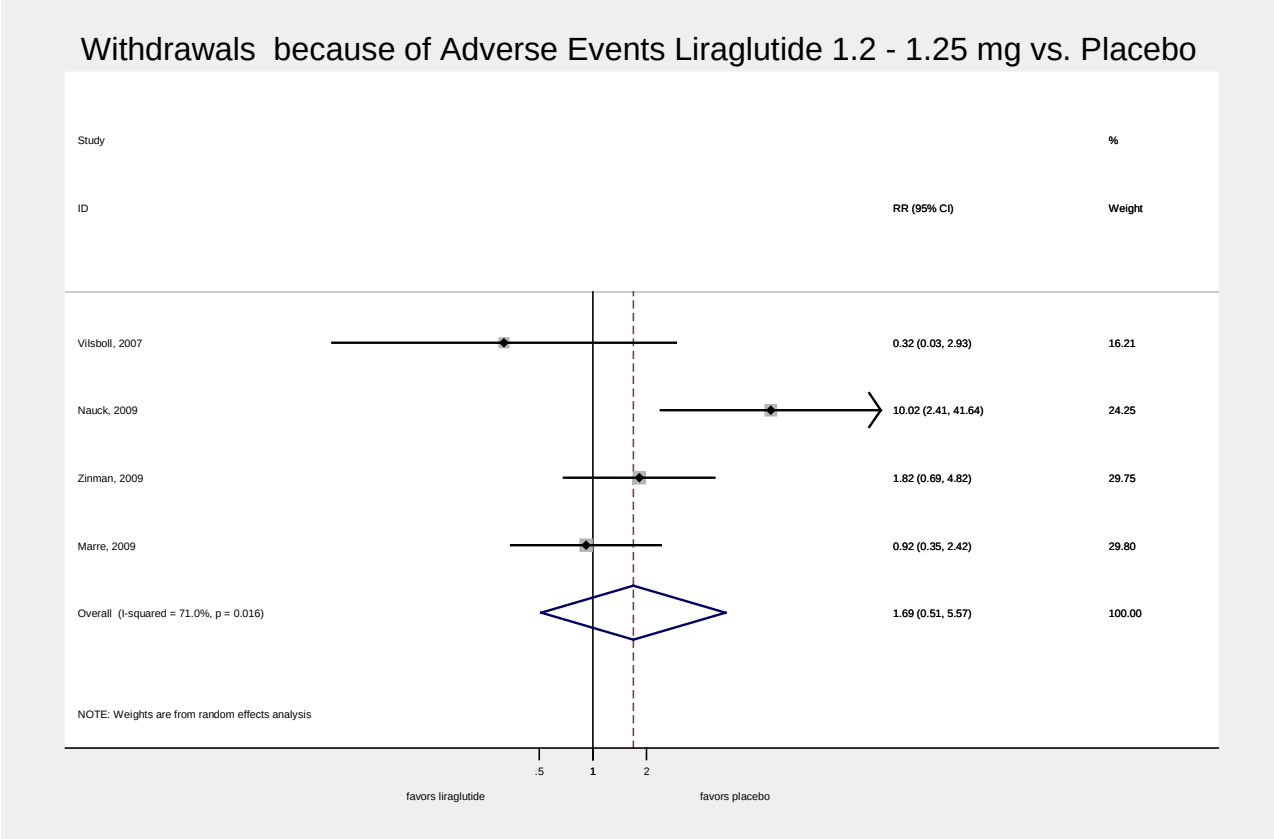


5) Liraglutide 1.2 – 1.25 mg Compared with Placebo – Withdrawals because of Adverse Events

Study Statistics

Study	RR	[95% Conf.	Interval]	% Weight
Vilsboll, 2007	0.317	0.034	2.927	16.21
Nauck, 2009	10.021	2.412	41.641	24.25
Zinman, 2009	1.823	0.689	4.822	29.75
Marre, 2009	0.917	0.348	2.416	29.80
D+L pooled RR	1.692	0.514	5.568	100.00

Heterogeneity chi-squared = 10.34 (d.f. = 3) p = 0.016
I-squared (variation in RR attributable to heterogeneity) = 71.0%
Estimate of between-study variance Tau-squared = 0.9958
Test of RR=1 : z= 0.86 p = 0.387

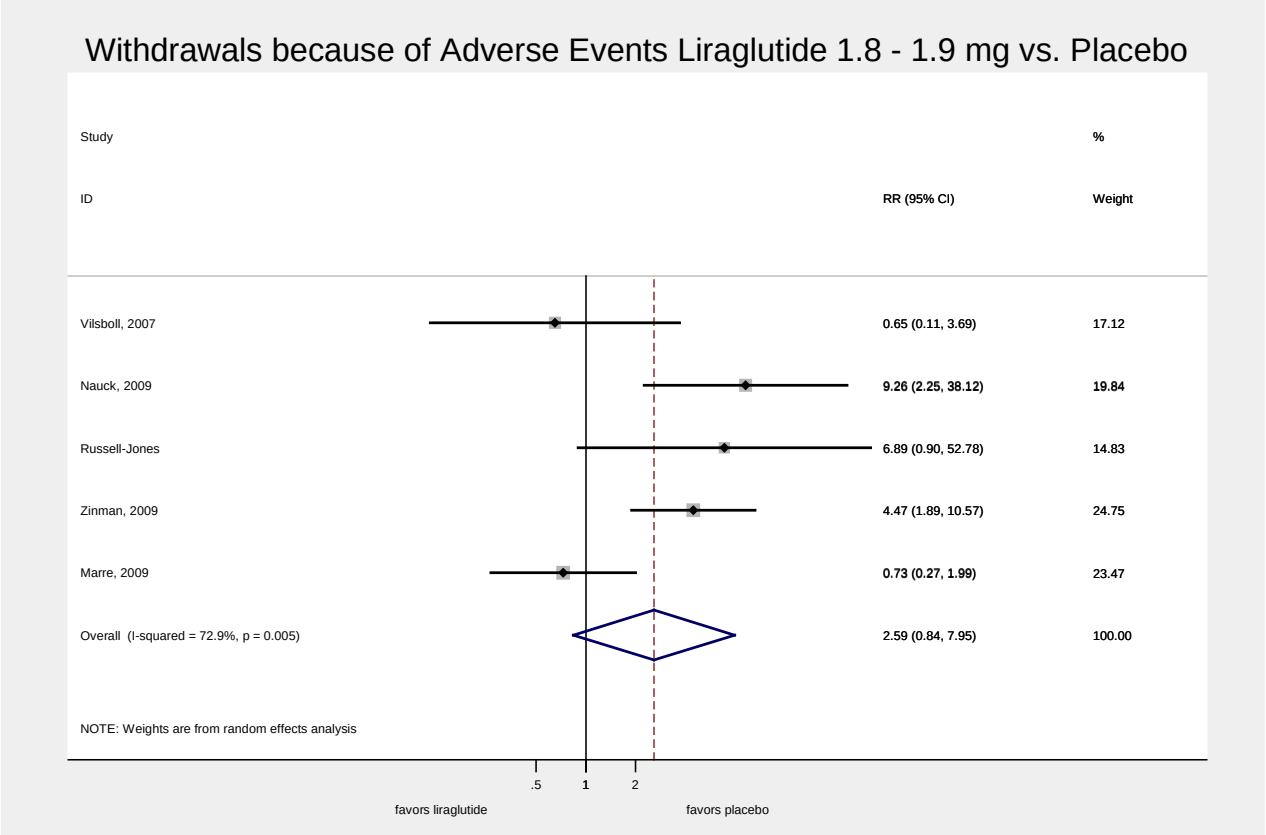


6) Liraglutide 1.8 – 1.9 mg Compared with Placebo – Withdrawals because of Adverse Events

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Vilsboll, 2007	0.650	0.115 3.688	17.12
Nauck, 2009	9.262	2.250 38.117	19.84
Russell-Jones	6.887	0.899 52.779	14.83
Zinman, 2009	4.475	1.894 10.572	24.75
Marre, 2009	0.728	0.265 1.995	23.47
D+L pooled RR	2.586	0.841 7.954	100.00

Heterogeneity chi-squared = 14.75 (d.f. = 4) p = 0.005
I-squared (variation in RR attributable to heterogeneity) = 72.9%
Estimate of between-study variance Tau-squared = 1.1353
Test of RR=1 : z= 1.66 p = 0.097

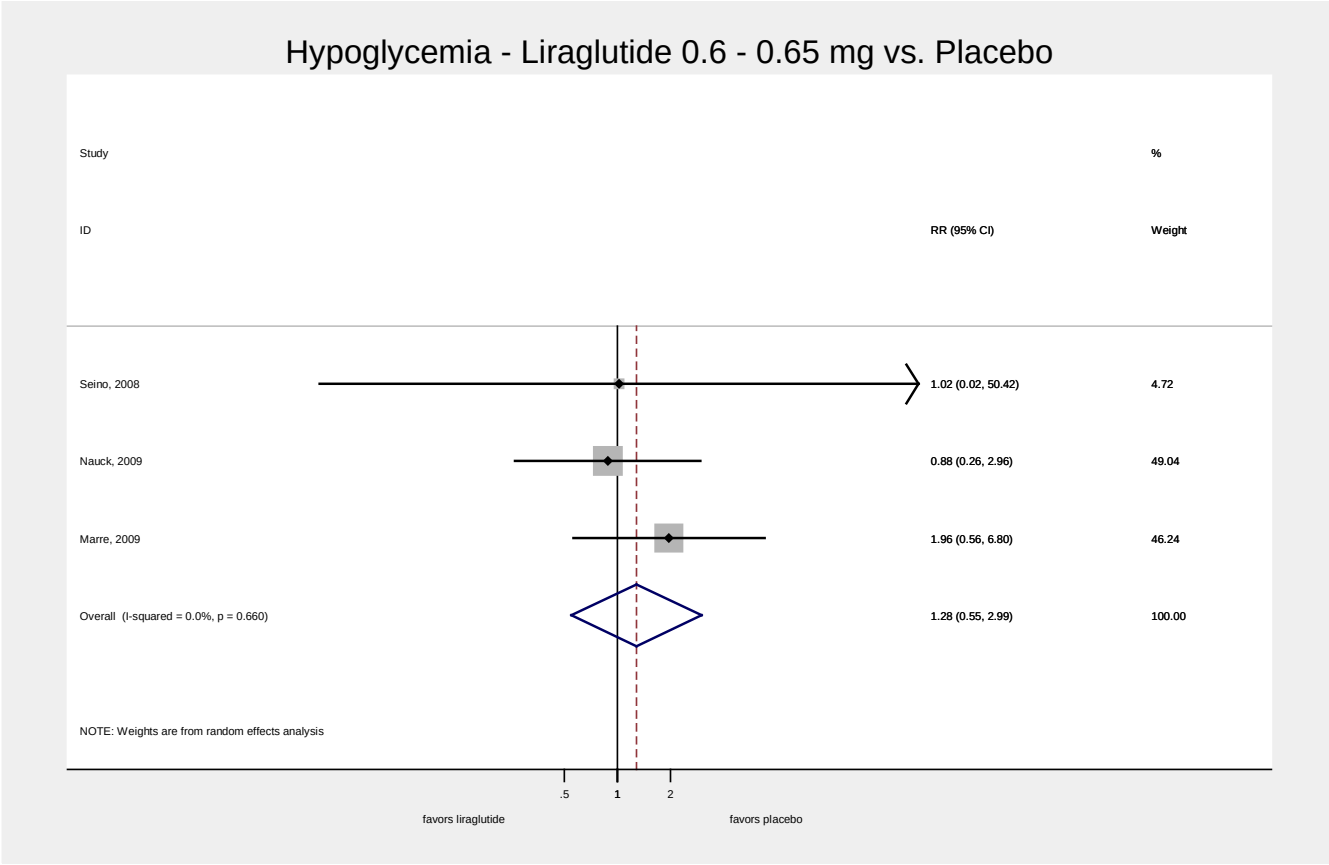


7) Liraglutide 0.6 – 0.65 Compared with Placebo – Hypoglycemia

Study statistics (added 0.5 to the zero cells)

Study	RR	[95% Conf. Interval]	% Weight
Seino, 2008	1.022	0.021 50.416	4.72
Nauck, 2009	0.882	0.263 2.956	49.04
Marre, 2009	1.957	0.563 6.798	46.24
D+L pooled RR	1.284	0.551 2.994	100.00

Heterogeneity chi-squared = 0.83 (d.f. = 2) p = 0.660
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.58 p = 0.563

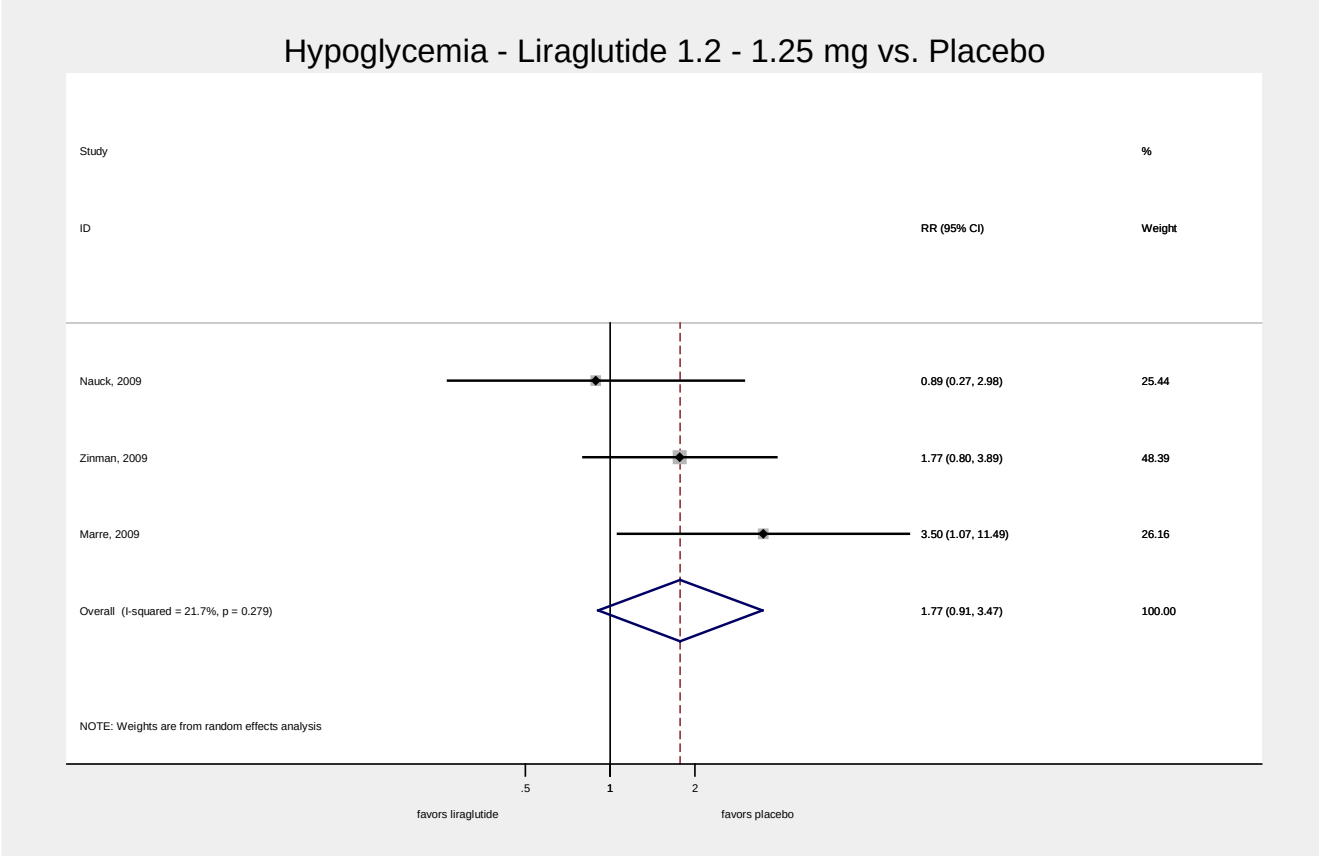


8) Liraglutide 1.2 – 1.25 mg Compared with Placebo – Hypoglycemia

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Nauck, 2009	0.890	0.266 2.980	25.44
Zinman, 2009	1.768	0.803 3.894	48.39
Marre, 2009	3.500	1.066 11.489	26.16
D+L pooled RR	1.775	0.908 3.470	100.00

Heterogeneity chi-squared = 2.55 (d.f. = 2) p = 0.279
I-squared (variation in RR attributable to heterogeneity) = 21.7%
Estimate of between-study variance Tau-squared = 0.0795
Test of RR=1 : z= 1.68 p = 0.094

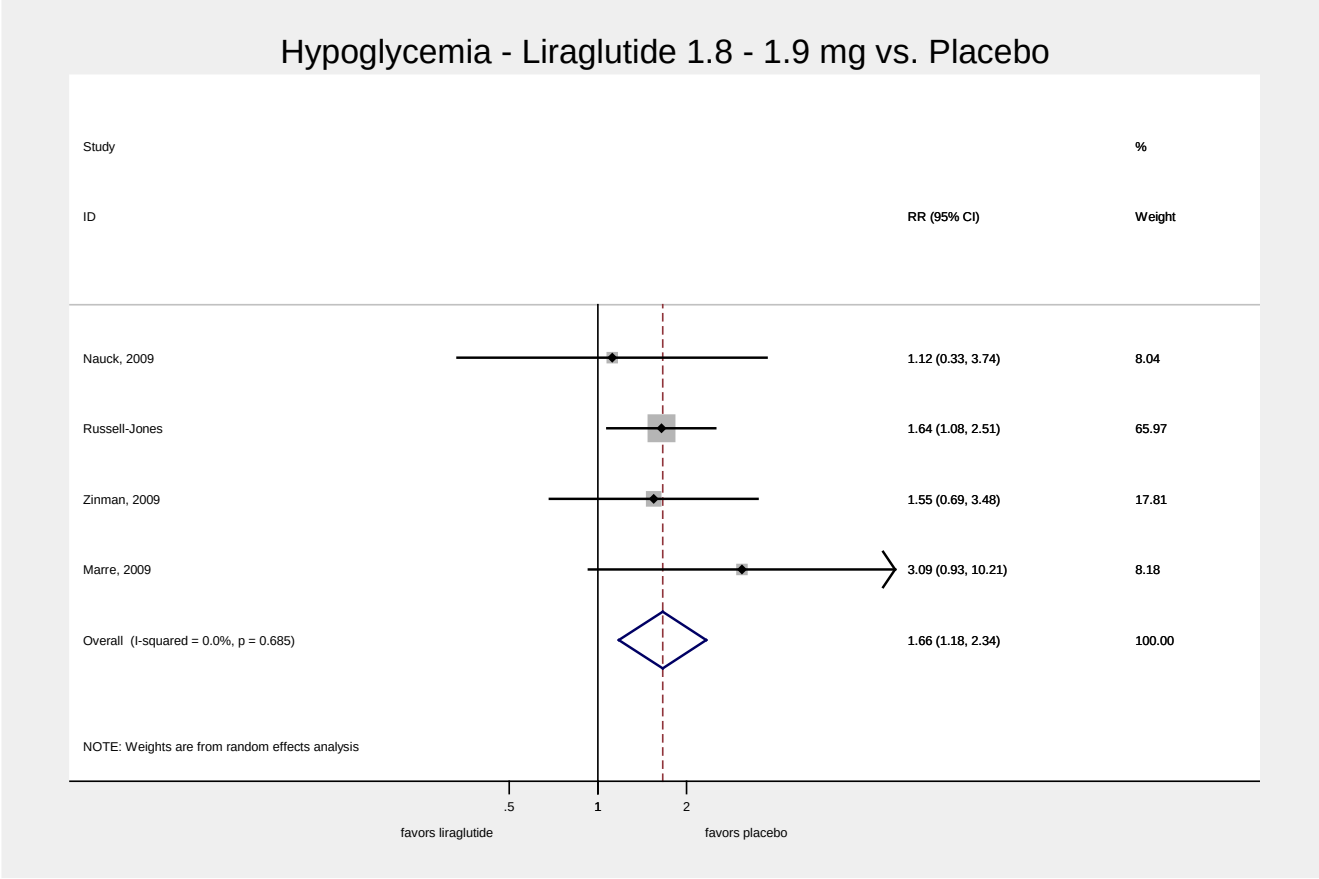


9) Liraglutide 1.8 – 1.9 Compared with Placebo – Hypoglycemia

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Nauck, 2009	1.118	0.334 3.738	8.04
Russell-Jones	1.643	1.078 2.505	65.97
Zinman, 2009	1.547	0.687 3.481	17.81
Marre, 2009	3.085	0.932 10.212	8.18
D+L pooled RR	1.660	1.178 2.337	100.00

Heterogeneity chi-squared = 1.49 (d.f. = 3) p = 0.685
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 2.90 p = 0.004

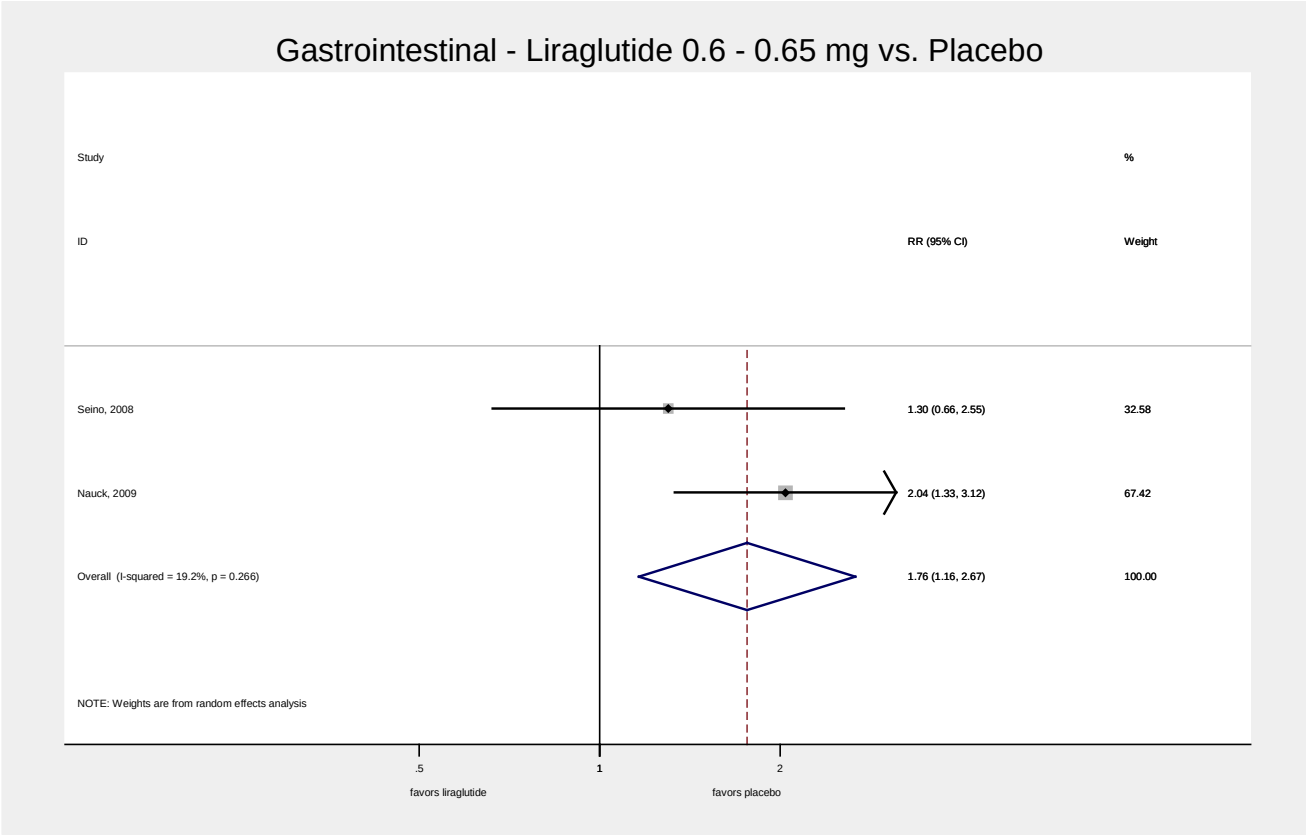


10) Liraglutide 0.6 – 0.65 mg Compared with Placebo – Gastrointestinal

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Seino, 2008	1.301	0.663 2.554	32.58
Nauck, 2009	2.041	1.334 3.122	67.42
D+L pooled RR	1.762	1.163 2.670	100.00

Heterogeneity chi-squared = 1.24 (d.f. = 1) *P*=0.266
I-squared (variation in RR attributable to heterogeneity) = 19.2%
Estimate of between-study variance Tau-squared = 0.0196
Test of RR=1 : z= 2.67 *P*=0.008

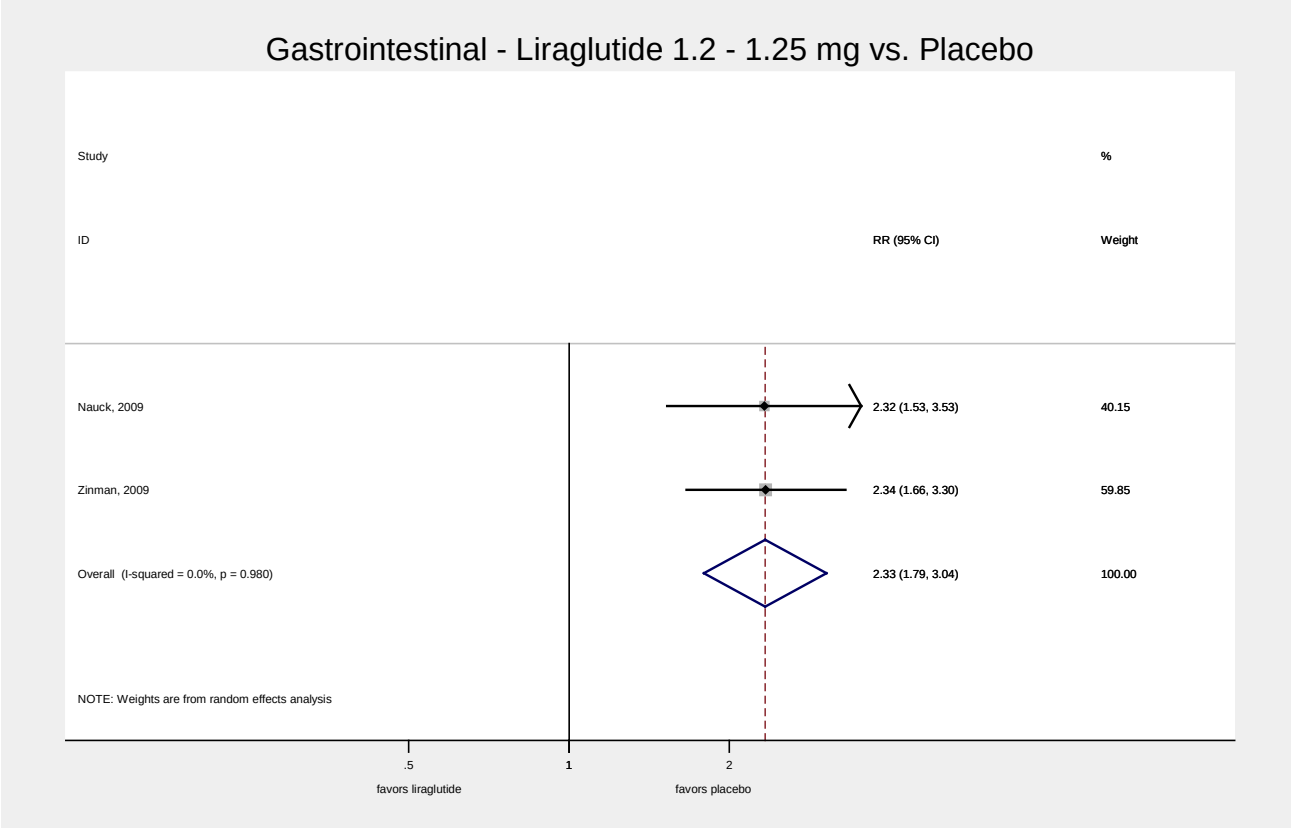


11) Liraglutide 1.2 – 1.25 mg Compared with Placebo – Gastrointestinal

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Nauck, 2009	2.324	1.529 3.533	40.15
Zinman, 2009	2.340	1.660 3.297	59.85
D+L pooled RR	2.333	1.789 3.043	100.00

Heterogeneity chi-squared = 0.00 (d.f. = 1) *P*=0.980
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 6.26 *P*=0.000

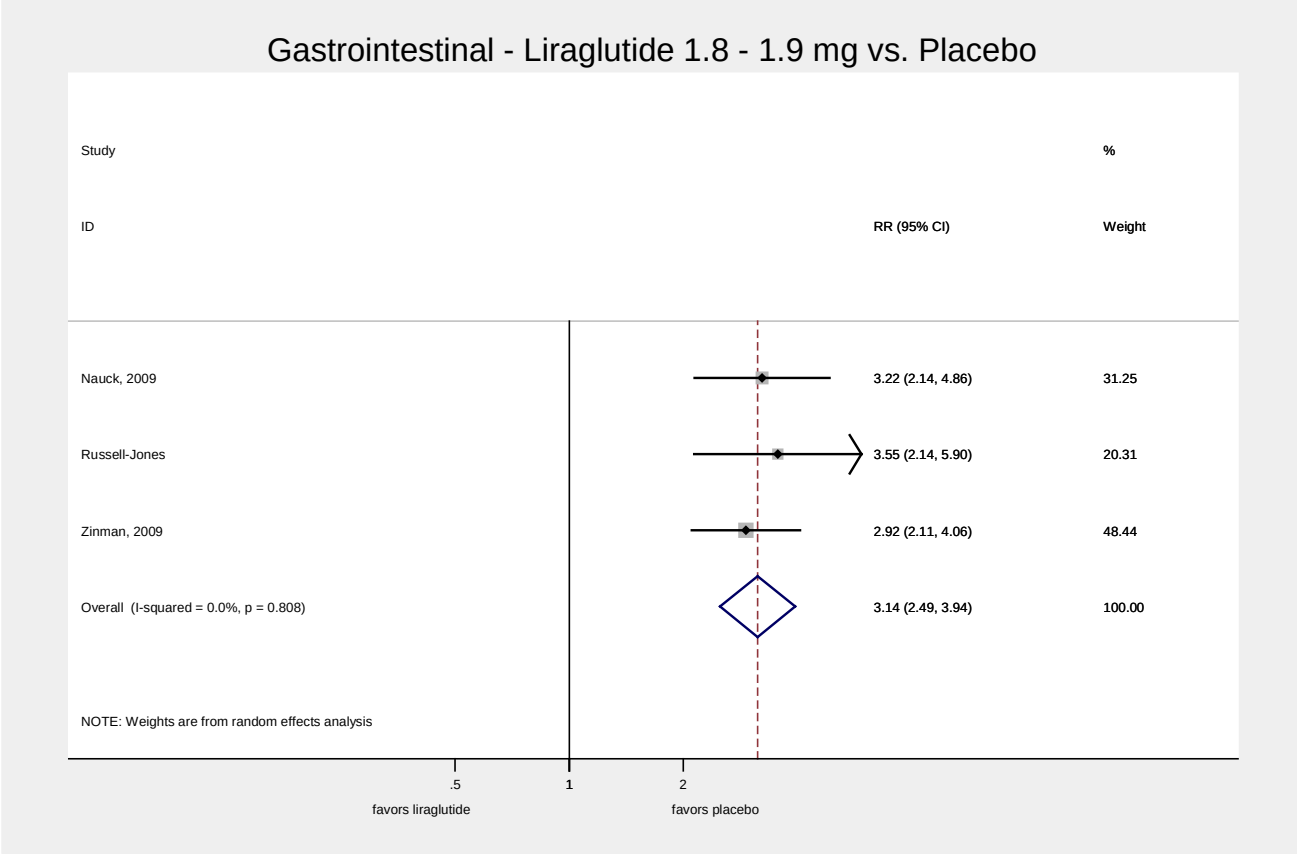


12) Liraglutide 1.8 – 1.9 mg Compared with Placebo – Gastrointestinal

Study Statistics

Study	RR	[95% Conf. Interval]	% Weight
Nauck, 2009	3.224	2.141 4.855	31.25
Russell-Jones	3.548	2.135 5.895	20.31
Zinman, 2009	2.925	2.105 4.063	48.44
D+L pooled RR	3.136	2.494 3.942	100.00

Heterogeneity chi-squared = 0.43 (d.f. = 2) *P*=0.808
I-squared (variation in RR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 9.79 *P*=0.000



13) Liraglutide 0.6 to 0.65 mg Compared with Placebo – Mean Change in Weight

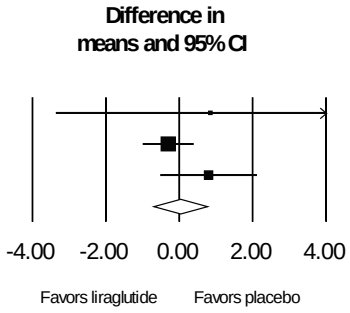
Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.280523	2	0.319735	12.30083

Note: The P value for the between group mean difference used in this analysis for the Marre, 2009 article was based on a two sample t-test using standard errors estimated from Figure 6 in the article. For the following studies included in this analysis, the SD of the change from baseline for each group was imputed from the baseline SD: Seino, 2008.

Liraglutide 0.6mg vs. Placebo: Mean Change in Weight

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Seino, 2008	0.850	2.149	4.620	-3.363	5.063	0.395	0.693
Nauck, 2009	-0.300	0.353	0.125	-0.992	0.392	-0.850	0.396
Marre, 2009	0.800	0.671	0.450	-0.515	2.115	1.192	0.233
	0.027	0.373	0.139	-0.705	0.759	0.072	0.942

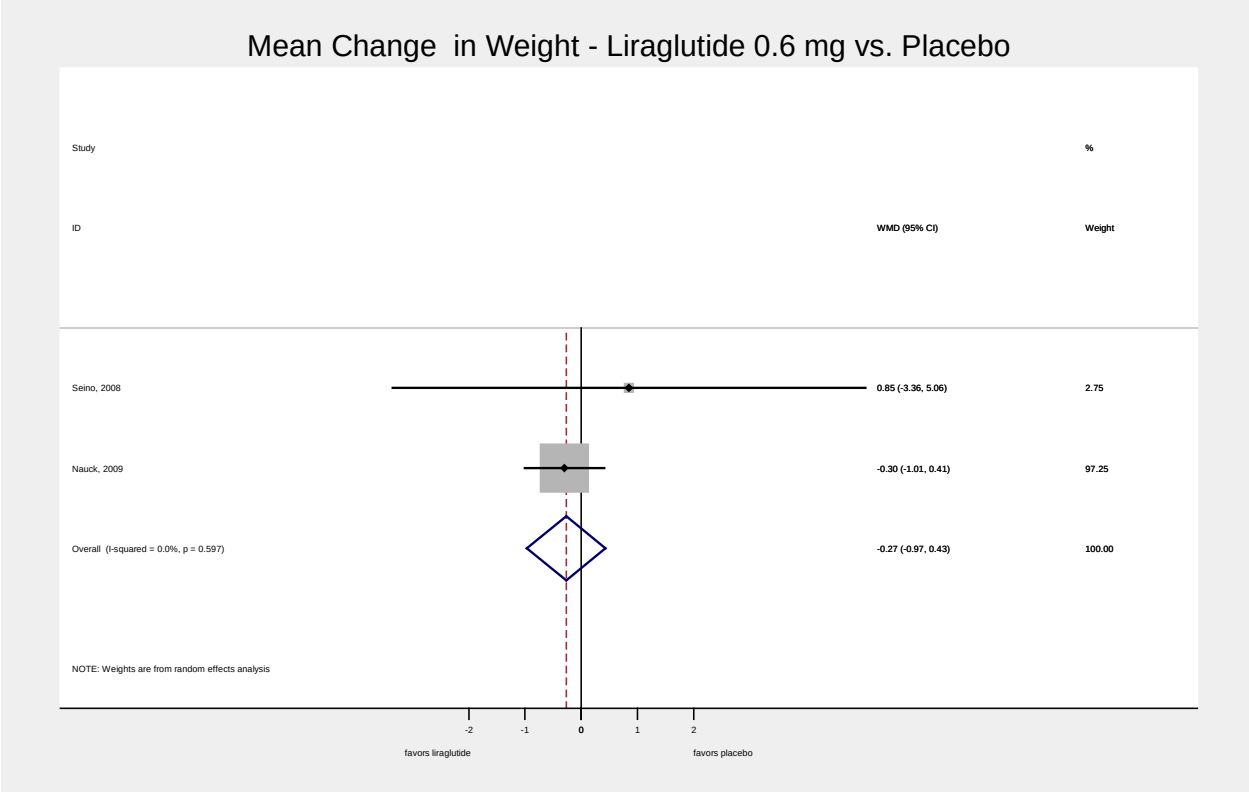


13a. Analysis without Marre, 2009 – Liragutide 0.6 – 0.65 mg vs. Placebo, Mean Change in Weight

Study Statistics

Study	WMD	[95% Conf. Interval]	% Weight
Seino, 2008	0.850	-3.356 5.056	2.75
Nauck, 2009	-0.300	-1.007 0.407	97.25
D+L pooled WMD	-0.268	-0.965 0.428	100.00

Heterogeneity chi-squared = 0.28 (d.f. = 1) p = 0.597
I-squared (variation in WMD attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.75 p = 0.450

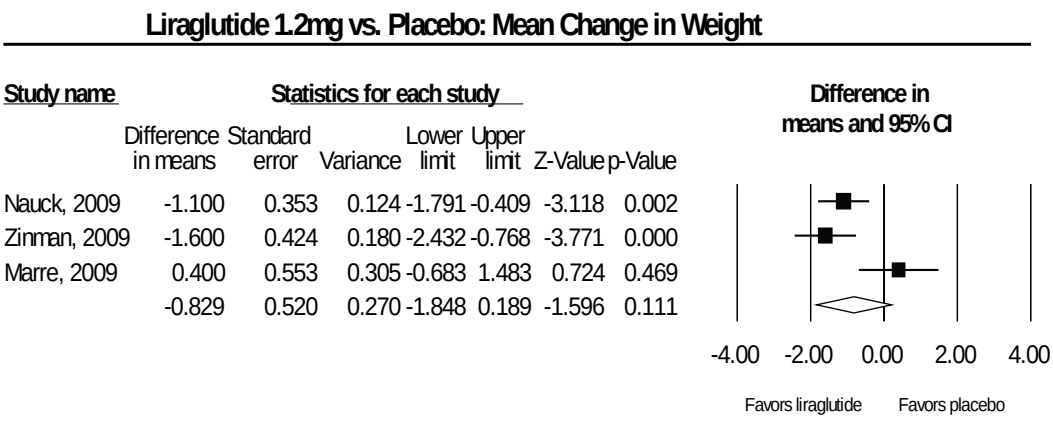


14) Liraglutide 1.2 to 1.25 mg Compared with Placebo – Mean Change in Weight

Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
8.488499	2	1.43E-02	76.43871

Note: The P value for the between group mean difference used in this analysis for the Marre, 2009 article was based on a two sample t-test using standard errors estimated from Figure 6 in the article.

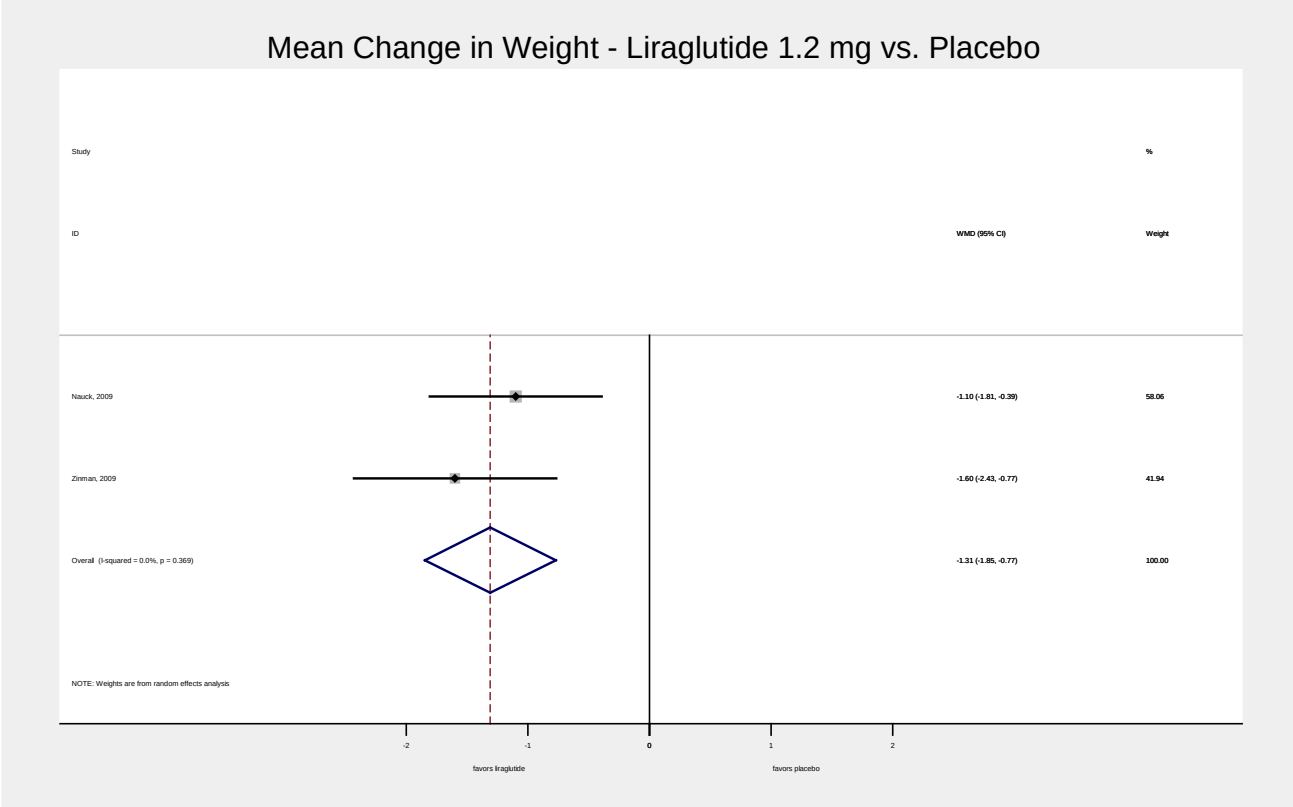


14a. Analysis without Marre, 2009 – Liraglutide 1.2 – 1.25 mg v Placebo, Mean Change in Weight

Study Statistics

Study	WMD	[95% Conf. Interval]	% Weight
Nauck, 2009	-1.100	-1.807 -0.393	58.06
Zinman, 2009	-1.600	-2.432 -0.768	41.94
D+L pooled WMD	-1.310	-1.848 -0.771	100.00

Heterogeneity chi-squared = 0.81 (d.f. = 1) p = 0.369
I-squared (variation in WMD attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 4.77 p = 0.000



15) Liraglutide 1.8 to 1.9 mg Compared with Placebo – Mean Change in Weight

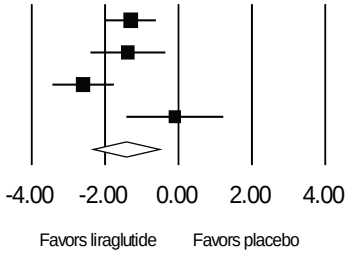
Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
11.41532	3	9.68E-03	73.71953

Note: The P value for the between group mean difference used in this analysis for the Marre, 2009 article was based on a two sample t-test using standard errors estimated from Figure 6 in the article.

Liraglutide 1.8mg vs. Placebo: Mean Change in Weight

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Nauck, 2009	-1.300	0.347	0.120	-1.979	-0.621	-3.752	0.000
Russell-Jones	-1.380	0.519	0.269	-2.397	-0.363	-2.660	0.008
Zinman, 2009	-2.600	0.424	0.180	-3.432	-1.768	-6.128	0.000
Marre, 2009	-0.100	0.671	0.451	-1.416	1.216	-0.149	0.882
	-1.428	0.460	0.212	-2.331	-0.526	-3.103	0.002

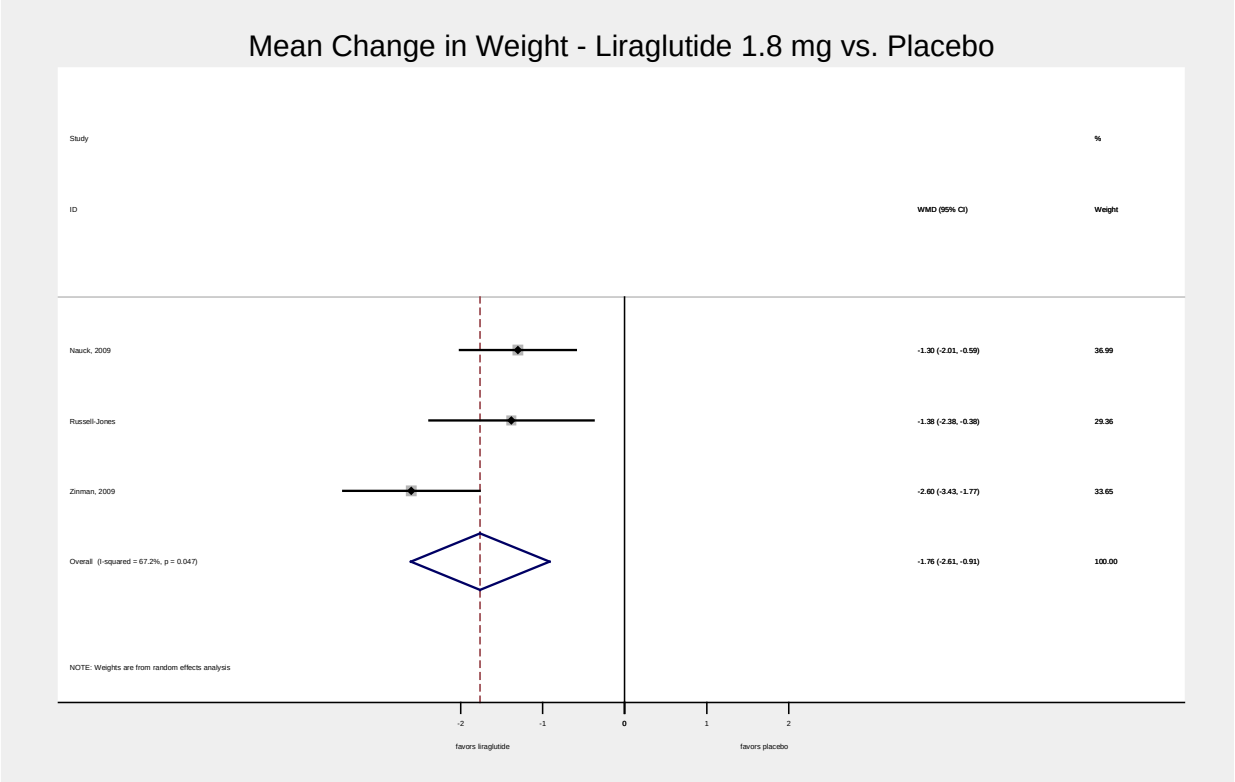


15a. Analysis without Marre, 2009 – Liraglutide 1.8 mg vs. Placebo, Mean Change in Weight

Study Statistics

Study	WMD	[95% Conf. Interval]	% Weight
Nauck, 2009	-1.300	-2.007 -0.593	36.99
Russell-Jones	-1.380	-2.381 -0.379	29.36
Zinman, 2009	-2.600	-3.432 -1.768	33.65
D+L pooled WMD	-1.761	-2.607 -0.915	100.00

Heterogeneity chi-squared = 6.09 (d.f. = 2) p = 0.047
I-squared (variation in WMD attributable to heterogeneity) = 67.2%
Estimate of between-study variance Tau-squared = 0.3740
Test of WMD=0 : z= 4.08 p = 0.000

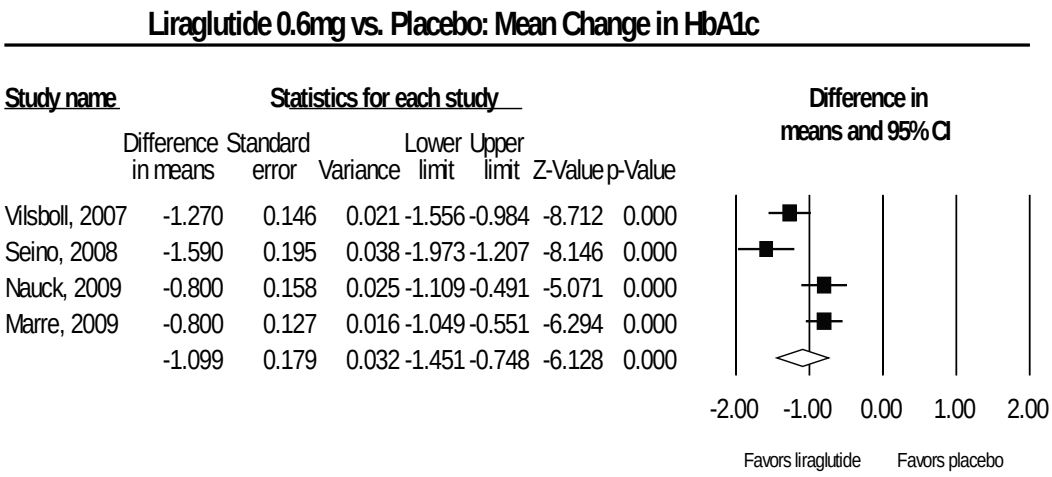


16) Liraglutide 0.6 to 0.65 mg Compared with Placebo – Mean Change in HbA1c

Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
16.30550712	3	9.82E-04	81.601308

Note: For the following studies included in this analysis, the SD of the change from baseline for each group was imputed from the baseline SD: Vilsboll, 2007 and Seino, 2008.



17) Liraglutide 1.2 to 1.25 mg Compared with Placebo – Mean Change in HbA1c

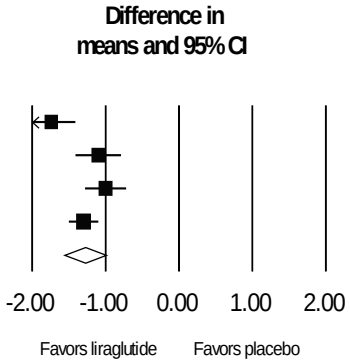
Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
12.88147242	3	4.90E-03	76.71074

Note: For the following studies included in this analysis, the SD of the change from baseline for each group was imputed from the baseline SD: Vilsboll, 2007.

Liraglutide 1.2mg vs. Placebo: Mean Change in HbA1c

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Vilsboll, 2007	-1.740	0.166	0.028	-2.066	-1.414	-10.461	0.000
Nauck, 2009	-1.100	0.157	0.025	-1.408	-0.792	-6.989	0.000
Zinman, 2009	-1.000	0.141	0.020	-1.277	-0.723	-7.071	0.000
Marre, 2009	-1.300	0.102	0.010	-1.499	-1.101	-12.785	0.000
	-1.278	0.144	0.021	-1.561	-0.996	-8.869	0.000

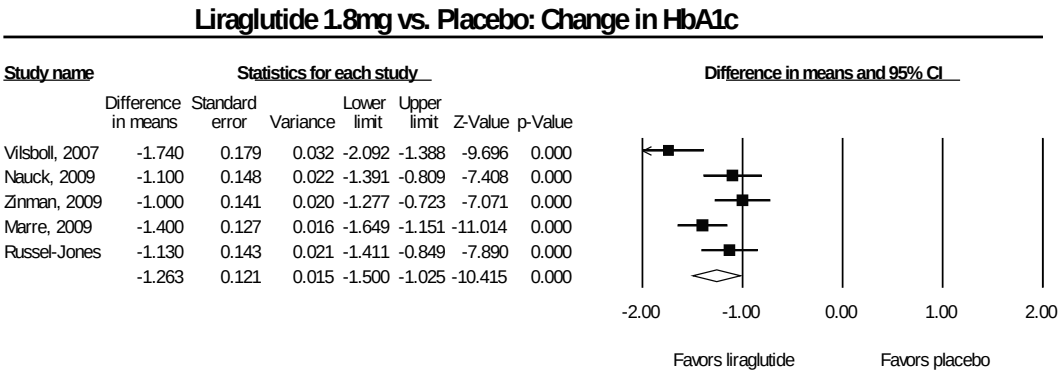


18) Liraglutide 1.8 to 1.9 mg Compared with Placebo – Mean Change in HbA1c

Study Statistics

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
13.69384976	4	8.34E-03	70.78981

Note: For the following studies included in this analysis, the SD of the change from baseline for each group was imputed from the baseline SD: Vilsboll, 2007.

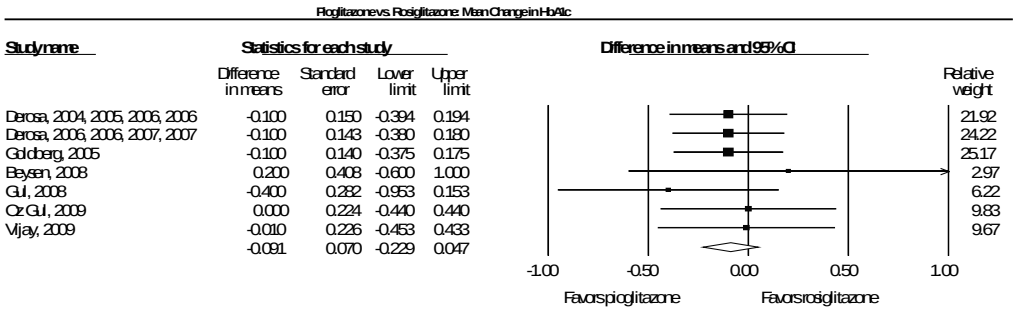


Pioglitazone compared with Rosiglitazone HbA1c Meta-analysis

1) Pioglitazone compared with rosiglitazone: mean change in HbA1c

Heterogeneity (random)			
Q-value	df (Q)	P-value	I-squared
2.0130901	6	0.9184908	0

Note: For the following studies included In this analysis, standard deviations of the mean change from baseline for each group were imputed using an average SD from similar sized trials and rounding up: Derosa (2004, 2005, 2006, and 2006), Derosa (2006, 2006, 2007, and 2007), Gul (2008), and Oz Gul (2009). Kahn, 2002 was not included in this analysis because of insufficient data.



Appendix F. Strength of evidence

Table F- 1. Pramlintide vs. Placebo in Type 1 diabetes

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c for studies adding pramlintide to flexible dose insulin regimens						
2; 776	Medium RCTs/Fair	Inconsistent	Indirect	Precise	Slight or no improvement with Pram (0% to −0.27% between group difference)	Low
HbA1c for studies adding pramlintide to fixed dose insulin regimens						
1; 651	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater improvement with Pram (between group difference −0.29 to −0.34%)	Low
Weight loss						
3; 1427	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with Pram (−0.4 kg to -1.3 kg) than placebo (+0.8 kg to +1.2 kg)	Moderate
Withdrawals due to adverse events						
3; 1427	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater with Pram	Moderate
GI adverse events (nausea, vomiting, anorexia, reduced appetite)						
3; 1427	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater incidence with Pram	Moderate
Severe hypoglycemia						
3;1427	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater incidence with Pram	Moderate

Table F- 2. Pramlintide compared with placebo in type 2 diabetes

	Domains pertaining to strength of evidence				Magnitude of effect[a]	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c for studies adding pramlintide to flexible dose insulin regimens						
1; 212	Medium RCT/Fair	Unknown/NA	Indirect	Imprecise	Slight or no improvement with Pram (0.36% between group difference, P and CI NR)	Low
HbA1c for studies adding pramlintide to fixed dose insulin regimens						
2; 1194	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater improvement with Pram (between group difference −0.13 to −0.4%)	Moderate
Weight change						
3; 1406	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with Pram (1.1 to 1.8 kg	Moderate

					more than placebo at 52 weeks)	
Severe hypoglycemia						
2; 749	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater frequency with pramlintide	Moderate
Nausea						
3; 1406	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater frequency with pramlintide (16-31.4% vs. 3-16.9%)	Moderate

[a]Outcomes/effect sizes are for approved doses only (up to 120 mcg for pramlintide)

Table F- 3. Pramlintide compared with rapid acting insulin analog in type 2 diabetes

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 113	Medium RCT/Fair	Unknown/NA	Indirect	Imprecise	No difference (−0.2 between group difference, *P*=0.46)	Low
Weight						
1; 113	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Weight gain seen with RAIA (+4.7 kg between group difference, *P*<0.0001)	Low
Severe Hypoglycemia						
1; 113	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater incidence in RAIA	Low

Table F- 4. Sitagliptin 100 mg monotherapy compared with placebo

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
7; 4333	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with sitagliptin (WMD −0.79, 95% CI −0.93 to −0.66)	Moderate
Weight change						
5;3035	Medium RCTs/Fair	inconsistent	Indirect	Precise	Less weight loss with sitagliptin than with placebo (WMD 0.66, 95% CI 0.43 to 0.89)	Moderate
Hypoglycemia						
7; 4333	Medium RCTs/Fair	Inconsistent	Indirect	Imprecise	No difference (RR 1.26, 95% CI 0.48 to 3.25)	Low
Withdrawals due to adverse events						
7; 4333	Medium RCTs/Fair	Inconsistent	Indirect	Imprecise	Pooled RR 0.88 (95%CI 0.54-1.43)	Moderate
GI adverse effects (nausea)						
4, 2883	Medium RCTs/Fair	Inconsistent	Indirect	Imprecise	Similar incidence seen, pooled RR 1.4 (95% CI	Low

					0.49-3.96)	
GI adverse effects (vomiting)						
3; 2353	Medium RCTs/Fair	Inconsistent	Indirect	Imprecise	Similar incidence seen, pooled RR 0.77 (95% CI 0.2-2.88)	Low
Infections (upper respiratory & urinary tract infections)						
3; 1792	Medium RCTs/Fair	Consistent	Indirect	Precise	Similar incidence seen, pooled RR 1.06 (95% CI 0.66-1.69	Low

Table F- 5. Sitagliptin monotherapy compared with active control

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c for studies comparing sitagliptin to metformin						
1;1091	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with metformin (−0.16 to −0.47% between group difference at 24 weeks, p NR)	Low
HbA1c for studies comparing sitagliptin to glipizide						
1; 743	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with glipizide (between group difference −0.22%)	Low
Weight change for studies comparing sitagliptin to metformin						
1;1091	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Reduction greater with metformin (between group difference −0.9 to −1.1 kg at 24 weeks; −1.6 to −2.1 at 54 weeks)	Low
Weight change for studies comparing sitagliptin to glipizide						
1; 743	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight gain with glipizide (between group difference +0.5)	Low
Hypoglycemia for studies comparing sitagliptin to glipizide						
1; 743	Medium RCT/Fair	Unknown/NA	Direct	Precise	Greater incidence with glipizide	Low*
GI side effects for studies comparing sitagliptin to metformin						
1; 1091	Medium RCT/Fair	Unknown/NA	Direct	Precise	Greater incidence with metformin	Low*

*when also considering indirect evidence from placebo-controlled studies, we determined the strength of evidence to be moderate

Table F- 6. Sitagliptin compared with active therapy, as add-on to active therapy

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c for studies comparing sitagliptin to glipizide (add on to metformin)						
1; 1172	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Similar reduction (between group difference −0.05%)	Low

HbA1c for studies comparing sitagliptin to rosiglitazone (add on to metformin)						
2; 442	Medium RCTs/Fair	Consistent	Indirect	Precise	No significant difference	Moderate
HbA1c for studies comparing sitagliptin to metformin (add on to pioglitazone)						
1; 151	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Similar reduction (between group difference 0.1 %, *P*=NR)	Low
Weight change for studies comparing sitagliptin to glipizide (add on to metformin)						
1; 1172	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight loss with sita (−1.5 kg) compared to weight gain with glipizide (+1.1 kg)	Low
Weight change for studies comparing sitagliptin to rosiglitazone (add on to metformin)						
1; 273	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight loss with sita (−0.4 kg) compared to weight gain with rosiglitazone (+1.5 kg)	Low
Weight change for studies comparing sitagliptin to metformin (add on to pioglitazone)						
1; 151	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight loss with metformin (-2,8 kg) compared with sitagliptin (-1.6 kg)	Low

Table F- 7. Sitagliptin compared with placebo, as add-on therapy to metformin

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
3; 1164	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with sitagliptin (between group difference −0.51 to −1.0)	Moderate
Weight change						
3; 1164	Medium RCTs/Fair	Inconsistent	Indirect	Precise	Similar change in weight between groups	Low

Table F- 8. Sitagliptin compared with placebo, as add-on therapy to pioglitazone

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 353	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater reduction with sitagliptin (between group difference −0.7)	Low
Weight change						
1; 353	Medium	Unknown/NA	Indirect	Precise	Greater weight gain	Low

	RCT/Fair				with sitagliptin (between group difference +0.3 kg)	

Table F- 9. Sitagliptin compared with placebo, as add-on therapy to glimepiride

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 441	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater reduction with sitagliptin (between group difference −0.57)	Low
Weight change						
1;441	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater weight gain with sitagliptin combination (between group difference +1.1 kg)	Low

Table F- 10. Sitagliptin compared with placebo, as add-on therapy to insulin ± metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 641	Medium RCT/Fair	Unknown/NA	Indirect	Precise	Greater reduction with sitagliptin (between group difference −0.6%)	Low
Weight change						
1;641	Medium RCT/Fair	Unknown/NA	Indirect	Precise	No difference (between group difference 0 kg)	Low

Table F- 11. Saxagliptin monotherapy compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
2; 741	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with saxagliptin (between group difference −0.45 to −0.65%)	Moderate
Weight change						
2; 741	Medium RCTs/Fair	Consistent	Indirect	Precise	Greater reduction with placebo (between group difference −0.09 to −1.3 kg)	Moderate

Table F- 12. Saxagliptin compared with placebo, as add-on therapy to metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 743	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction with saxagliptin (between group difference −0.72 to −0.82%)	Low
Weight change						
1; 743	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction with saxagliptin 2.5 mg, but not saxagliptin 5 mg, compared with placebo	Low

Table F- 13. Saxagliptin compared with placebo, as add-on therapy to glyburide

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 768	Medium RCT/Fair	Unknown	Indirect	Precise	Greater reduction seen with saxagliptin (between group difference −0.62 to −0.72)	Low
Weight change						
1; 768	Medium RCT/Fair	Unknown	Indirect	Precise	Greater weight gain seen with saxagliptin (between group difference +0.4 to +0.5 kg)	Low

Table F- 14. Saxagliptin compared with placebo, as add-on therapy to thiazolidinedione

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 565	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction seen with saxagliptin (between group difference −0.36 to −0.64)	Low
Weight change						
1; 565	Medium RCT/Fair	Unknown (single study)	Indirect	Precise	Greater weight gain seen with saxagliptin	Low

					(between group difference +0.4 to 0.5 kg)	

Table F- 15. Saxagliptin vs. placebo harms[a]

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
Total withdrawals						
5; 2817	Medium RCT/Fair	Consistent	Indirect	Precise	Lower rates with saxagliptin 2.5 mg (pooled RR 0.66, 95% CI 0.57−0.79) and saxagliptin 5 mg (pooled RR 0.79, 95% CI 0.66 to 0.95)	Moderate
Withdrawals due to adverse effects						
5; 2817	Medium RCT/Fair	Inconsistent	Indirect	Imprecise	Similar incidence seen with saxagliptin 2.5 mg compared to placebo (pooled RR 0.85, 95%CI 0.29-2.53) but higher withdrawal seen in saxagliptin 5 mg compared with placebo (pooled RR 2.09, 95% CI 1.07-4.10)	Moderate
Hypoglycemia						
5; 2817	Medium RCT/Fair	Inconsistent	Indirect	Imprecise	Similar incidence seen with saxagliptin 2.5 mg and 5 mg compared with placebo	Low
Infections (upper respiratory tract infection, nasopharyngitis, urinary tract infection)						
5; 2817	Medium RCT/Fair	Inconsistent	Indirect	Imprecise	Similar incidence see with saxaglipitin 2.5 mg and 5 mg compared with placebo	Low

[a] Includes monotherapy and add-on therapy

Table F- 16. Liraglutide compared with exenatide

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 464	Medium	Unknown	Indirect	Precise	Favors liraglutide;	Low

	1 RCT/Good				estimated treatment difference −0.33; 95% CI −0.47 to −0.18; *P*<0.0001	
Weight change						
1; 464	Medium 1 RCT/Good	Unknown	Indirect	Imprecise	No significant difference (treatment difference −0.38 kg; 95% CI −0.99 to 0.23; *P*=0.2235)	Low
Hypoglycemia						
1; 464	Medium 1 RCT/Good	Unknown	Direct	Imprecise	Less with liraglutide; rate ratio 0.55 for minor hypoglycemia, CI 0.34 to 0.88; *P*=0.0131	Low

Table F- 17. Exenatide compared with insulin

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
4; 1245	Medium 4 RCTs/Fair	Consistent	Indirect	Precise	No difference between groups for reduction	Moderate
Weight						
4; 1245	Medium 4 RCTs Fair	Consistent	Indirect	Imprecise	Greater weight loss with exenatide (treatment difference range 4.1 kg to 5.4 kg)	Moderate
Hypoglycemia						
4; 1245	Medium 4 RCTs/Fair	Consistent	Direct	Imprecise	Similar rates of hypoglycemia between exenatide and insulin	Moderate

Table F- 18. Exenatide compared with glibenclamide

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 128	Medium 1 RCT/Fair	Unknown	Indirect	Imprecise	No significant difference	Low
Weight						
1; 128	Medium 1 RCT/Fair	Unknown	Indirect	Imprecise	Weight loss with exenatide and weight gain with glibenclamide (treatment difference 12.3 kg, *P*<0.001)	Low

Table F- 19. Exenatide 5 mcg BID compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Precise	WMD –0.72 (–0.99 to –0.45)	Moderate
Weight						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Inconsistent	Indirect	Imprecise	WMD −0.61 kg (−1.28 to 0.06)[a]	Low
Hypoglycemia						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Imprecise	RR 2.27 (1.20 to 4.27)	Moderate
Nausea						
5; 1832	Low 1 RCT/Good 4 RCTs/Fair	Consistent	Indirect	Imprecise	RR 2.42 (1.47 to 4.16)	Moderate

[a]statistical heterogeneity was high for the pooled analysis (I^2=74%), and a sensitivity analysis removing a single study resulted in significiant weight loss for exenatide 5mcg compared to placebo (weighted mean difference −0.87, 95% CI −1.35 to −0.40, *P*<0.001, I^2=33%)

Table F- 20. Exenatide 10 mcg BID compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
8; 2727	Low 2 RCTs/Good 6 RCTs/Fair	Consistent	Indirect	Precise	WMD –0.90 (–1.08 to –0.73)	High
Weight						
9; 2781	Low 2 RCTs/Good 7 RCTs/Fair	Consistent	Indirect	Precise	WMD –1.25 kg, (–1.60 to –0.90)	High
Hypoglycemia						
8; 2587	Low 2 RCTs/Good 6 RCTs/Fair	Consistent	Indirect	Imprecise	RR 2.96 (1.81 to 4.84)	Moderate
Nausea						
9; 2781	Low 2 RCTs/Good 7 RCTs/Fair	Consistent	Indirect	Imprecise	RR 3.43 (2.20 to 5.34)	Moderate

Table F- 21. Liraglutide 0.6 mg compared with glimepiride

	Domains pertaining to strength of evidence	Magnitude of effect	Strength of

						evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
2; 1284	Medium 2 RCTs/Fair	Consistent	Indirect	Imprecise	Both studies with no significant difference between liraglutide and glimepiride	Low
Weight						
2; 1284	Medium 2 RCTs/Fair	Inconsistent	Indirect	Imprecise	One study found significant weight loss with liraglutide 0.6 mg compared to weight gain with glimepiride. The other study found no significant change in weight with liraglutide or glimepiride.	Insufficient

Table F- 22. Liraglutide 1.2 to 1.8 mg compared with glimepiride

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
2; 1837	Medium 3 RCTs/Fair	Inconsistent	Indirect	Imprecise	Studies with heterogenous results; either no difference between groups or slightly greater reduction in HbA1c with liraglutide	Insufficient
Weight						
2; 1837	Medium 2 RCTs/Fair	Consistent	Indirect	Imprecise	Both studies show that liraglutide 1.2 and 1.8 mg result in significantly greater weight loss than glimepiride.	Moderate

Table F- 23. Liraglutide compared with insulin glargine

	Domains pertaining to strength of evidence	**Magnitude of effect**	**Strength of evidence**

Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
HbA1c						
1; 581	Low 1 RCT/Good	Unknown	Indirect	Imprecise	Between group difference −0.24% (−0.08 to −0.39)	Low
Weight						
1; 581	Low 1 RCT/Good	Unknown	Indirect	Imprecise	Between group difference - 3.43 kg (−4.00 to −2.86)	Low

Table F- 24. Liraglutide compared with sitagliptin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
1; 665	Medium 1 RCT/Fair	Unknown	Indirect	Imprecise	Between group difference −0.64% to 0.9% (*P*<0.0001)	Low
Weight						
1; 665	Medium 1 RCT/Fair	Unknown	Indirect	Imprecise	Between group difference – 1.9 kg tp - 2.42 kg (*P*<0.0001)	Low

Table F- 25. Liraglutide 0.6 to 0.65 mg daily compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
4 2523	Medium 3 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD −1.10 (–1.45 to –0.75)	Moderate
Weight						
3; 2358	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD 0.27(−0.71 to 0.76)	Moderate
Hypoglycemia						
3; 2358	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 1.28 (0.55 to 3.00)	Moderate
Gastrointestinal side effects						
2; 1317	Medium 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 1.76 (0.28 to 2.84)	Moderate

Table F- 26. Liraglutide 1.2 to 1.25 mg daily compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
4; 2830	Medium 4 RCT/Fair	Consistent	Indirect	Imprecise	WMD −1.8 (CI –1.56 to –1.00)	Moderate
Weight						
3; 2665	Medium 3 RCT/Fair	Inconsistent	Indirect	Imprecise	WMD −0.83 kg (–1.85 to 0.19)	Low
Hypoglycemia						
3; 2665	Medium 3 RCT/Fair	Consistent	Indirect	Precise	RR 1.78 (0.91 to 3.47)	Moderate
Gastrointestinal side effects						
2; 1624	Medium 2 RCT/Fair	Consistent	Indirect	Precise	RR 2.33 (1.78 to 3.04)	Moderate

Table F- 27. Liraglutide 1.8 to 1.9 mg daily compared with placebo

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
5; 3411	Medium 4 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD −1.26, 95% CI −1.50 to −1.03, *P*<0.001	Moderate
Weight						
4; 3246	Medium 3 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	WMD −1.43 kg, 95% CI –2.33 to –0.53, *P*=0.002	Moderate
Hypoglycemia						
4; 3246	Medium 3 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 1.66 (1.18 to 2.34)	Moderate
Gastrointestinal side effects						
3; 2205	Medium 2 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	RR 3.14 (2.49 to 3.94)	Moderate

Table F- 28. Pioglitazone compared with rosiglitazone

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
8; 1209	Low RCTs/Fair	Consistent	Indirect	Precise	WMD −0.09, 95% CI −0.23, 0.05	Moderate
Weight change						
8; 1209	Medium RCTs/Fair Systematic reviews	Consistent	Indirect	Precise	Both TZDs resulted in a similar weight increase. The increase is similar to sulfonylureas	Moderate
Heart Failure						
Multiple systematic reviews, trials and observational studies	Low Systematic reviews RCTs	Consistent	Direct	Precise	Both pioglitazone and rosiglitazone increase the risk of heart failure (odds ratios range from 1.32 to 2.18 in various meta-analyses)	High
Edema						
Multiple systematic reviews, trials and observational studies	Low Systematic reviews RCTs	Consistent	Direct	Precise	Both pioglitazone and rosiglitazone increase the risk of edema (odds ratios range from 2.26 to 4.62 in various meta-analyses).	High
Fractures						
Including meta-analysis of 10 RCTs involving 13,715 participants	Systematic reviews RCTs	Consistent	Direct	Precise	Risk of fractures is increased among patients exposed to TZDs (OR 1.45, 95% CI 1.18 to 1.79); Risk appears to be increased among women (OR 2.23, 95% CI 1.65 to 3.10) but not among men (OR 1.00, 95% CI 0.73 to 1.39)	Moderate

Table F- 29. Pioglitazone compared with sulfonylureas (monotherapy or add-on)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
10; 1787	Medium RCTs/Fair	Consistent[a]	Indirect	Precise	No difference (7/10 trials found no difference, 2 favored pio and 1 favored glimepiride)	Moderate

Weight change						
10; 1787	Medium RCTs/Fair	Inconsistent	Indirect (intermediate outcome)	Precise	Pioglitazone and sulfonylureas result in similar weight gain	Moderate

[a] Most of the evidence was consistent, finding no difference; with a large number of studies it is consistent with random error to have a few studies finding a small difference in favor of one treatment or the other

Table F- 30. Pioglitazone compared with metformin (monotherapy or add-on)

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
7; 2106	Low 2 RCTs/Good 5 RCTs/Fair	Consistent	Indirect	Precise	No difference	High
Weight change						
5;1832 Multiple systematic reviews	Low	Consistent	Indirect (intermediate outcome)	Precise	Weight gain with pioglitazone compared with weight loss with metformin (between group difference around 2kg[a])	Moderate

[a]Bolen et al, 2007[89]

Table F- 31. Rosiglitazone compared with sulfonylureas

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
9; 7009	Low 1 RCT/Good 8 RCTs/Fair	Consistent[a]	Indirect	Precise	No difference (7 of 9 trials found no difference, 1 favored rosiglitazone and 1 favored the sulfonylurea group)	Moderate
Weight change						
9; 7009	Medium 1 RCT/Good 8 RCTs/Fair	Inconsistent	Indirect (intermediate outcome)	Precise	Rosiglitazone and sulfonylureas result in similar weight gain	Moderate

[a] Most of the evidence was consistent, finding no difference; with a large number of studies it is consistent with random error to have a few studies finding a small difference in favor of one treatment or the other

Table F- 32. Rosiglitazone compared with metformin

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
4; 8925	Medium RCTs/Fair	Consistent	Indirect	Precise	No difference (3 of 4 trials found no difference; 1 reported a very small difference favoring rosiglitazone, 0.13% between group difference)	Moderate
Weight change						
3;1182	Medium RCT/Fair	Inconsistent	Indirect (intermediate outcome)	Precise	Weight gain with rosiglitazone compared with weight loss with metformin	Moderate

Table F- 33. Avandamet® or dual therapy with metformin and rosiglitazone compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; # of subjects	**Risk of Bias; Design / Quality**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
3; 1,686	Medium 3 RCT/Fair	Consistent	Indirect	Imprecise	Greater reduction in HbA1c with Avandamet® or dual therapy than with monotherapy (treatment difference range 0.13% to 0.7%)	Moderate[a]
Weight						
2[b]; 977	Medium 2 RCTs/Fair	Consistent	Indirect	Precise	No weight change with Avandamet® (0.0 kg to 0.01 kg) compared with slight weight gain with rosiglitazone monotherapy, and slight weight gain (1.9 kg) or weight loss (−2.9 kg) with metformin monotherapy	Moderate
Edema						
3; 1,686	Medium 3 RCTs/Fair	Consistent	Indirect	Imprecise	Higher rates of edema with Avandamet® or dual therapy than with metformin monotherapy	Moderate

Gastrointestinal adverse effects						
3; 1,686	Medium 3 RCTs/Fair	Consistent	Direct	Imprecise	Rates of gastrointestinal adverse effects with Avandamet® or dual therapy were high (28 to 47%), but were the same or slightly lower than those with metformin monotherapy.	Moderate

[a] Rated moderate rather than high because of the study with point estimate of 0.13 for between group difference making it more likely that a pooled estimate of effect would change with additional studies (in contrast to the strength of evidence grade below for Avandaryl® or dual therapy where the range of effect sizes was within a more narrow range).
[b] This includes only the two trials of Avandamet® and not the one included trial of dual therapy.

Table F- 34. Avandaryl® or dual therapy with rosiglitazone and glimepiride compared with monotherapy

	Domains pertaining to strength of evidence				**Magnitude of effect**	**Strength of evidence**
Number of studies; # of subjects	**Risk of Bias; Design / Quality**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Imprecise	Greater reduction in HbA1c with Avandaryl® or dual therapy than with monotherapy (treatment difference range 0.6% to 0.8%)	Moderate
Weight						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Precise	Weight gain was slightly greater with Avandaryl® or dual therapy than with monotherapy	Moderate
Hypoglycemia						
2; 914	Low[a] 1 RCT/Fair 1 RCT/Good	Consistent	Indirect	Precise	Rates of hypoglycemia were greater with Avandaryl® or dual therapy than with monotherapy	Moderate

[a] Risk of bias rated low because the Good study has a low risk of bias and contributes 96% of the total sample N

Table F- 35. Actoplus Met® or dual therapy with pioglitazone and metformin compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
# of studies; # of subjects	**Risk of Bias; Design / Quality**	**Consistency**	**Directness**	**Precision**	**Summary Effect Size (95% Confidence Interval)**	**High, Moderate, Low, Insufficient**
HbA1c						
2; 871	Moderate 1 RCT/Good 1 RCT/Fair	Consistent	Indirect	Imprecise	Greater reduction in HbA1c with Actoplus Met® or dual therapy than with monotherapy (treatment difference range 0.2% to 0.9%)	Moderate
Weight/BMI						
2; 871	Moderate 1 RCT/Good 1 RCT/Fair	Inconsistent	Indirect	Imprecise	Both trials reported weight gain with pioglitazone monotherapy and weight loss with metformin monotherapy, but results for Actoplus Met® are mixed.	Low
Gastrointestinal events						
1; 600	Moderate 1 RCT/Fair	Unknown	Indirect	Precise	Rates of gastrointestinal events with Actoplus Met® fell between those reported for component monotherapies.	Low

Table F- 36. Dual therapy with metformin and sitagliptin compared with monotherapy

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
# of studies; # of subjects	Risk of Bias; Design / Quality	Consistency	Directness	Precision	Summary Effect Size (95% Confidence Interval)	High, Moderate, Low, Insufficient
HbA1c						
1; 1,091[a]	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Greater reduction in HbA1c with dual therapy than with monotherapy (range 0.4% to 1.2%)	Moderate
Weight						
1; 1,091[a]	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Similar weight loss of sitagliptin plus metformin (−0.7 to −1.7 kg) and metformin monotherapy (−1.0 to −1.5 kg).	Low
Gastrointestinal adverse effects						
1; 1,091[a]	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Similar between sitagliptin 100 plus metformin 2000 vs. metformin 2000 monotherapy (24 weeks: 24.7 vs. 25.3%; 54 weeks: 29 vs. 31%). Higher rates for sitagliptin 100 plus metformin 1000 vs. sitagliptin or metformin 1000 monotherapy (24 weeks: 17.9 vs. 15.1 vs. 15.9%; 54 weeks: 26 vs. 20 vs. 20%).	Low
Total cholesterol						
1; 1,091[a]	Medium 1 RCT/Fair	Unknown (single study)	Indirect	Precise	Combinations resulted in slightly greater improvements in total cholesterol (at 24 weeks: −3.2 to −7.1; at 54 weeks: -6.6 to −8.8 mg/dL) compared with metformin or sitagliptin monotherapy (at 24 weeks: −1.5 to +2.7; at 54 weeks: −0.2 to +0.5 mg/dL)	Low

[a] This includes data from 2 publications, one being a 30-week extension of the other. Number of subjects is from the initial study (not double-counting subjects)