Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Optimal Therapy Report

CADTH

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Second-Line Therapy for Patients With Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis

August 2010

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders and policy-makers make well-informed decisions and thereby improve the quality of health care services.

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EXECUTIVE SUMMARY

The Issue

Type 2 diabetes mellitus is a progressive disease that is usually treated using a stepwise approach, beginning with lifestyle modification followed by the addition of one or more oral antidiabetes drugs and eventual treatment with exogenous insulin. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone. Existing guidelines recommend several options for second-line therapy when metformin alone is no longer effective. There is a lack of specific recommendations regarding which agents are optimal as second-line therapy. Given the increasing prevalence of type 2 diabetes, there is a need to evaluate the evidence related to the clinical and cost-effectiveness of second-line drugs in order to facilitate their optimal use.

Objective

1) To conduct a systematic review of the clinical evidence pertaining to second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.
2) To conduct a cost-effectiveness analysis of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy based on the results of the systematic review.

Methods

Clinical: Active and placebo-controlled randomized controlled trials (RCTs) of antihyperglycemic agents used in patients with type 2 diabetes inadequately controlled or intolerant to metformin monotherapy were identified through electronic databases, grey literature, reference lists, conference abstracts, and stakeholder consultation. Outcomes of interest included glycosylated hemoglobin (A1C), hypoglycemia, long-term complications of diabetes, mortality, quality of life, and serious adverse effects. Mixed treatment comparison (MTC) and pairwise meta-analyses were conducted to pool trial results, when appropriate. Numerous sensitivity analyses were performed to examine robustness of meta-analytic results.

Economic: The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model was used to forecast diabetes-related complications and cost-consequences from the perspective of a Canadian ministry of health, and estimate incremental cost utility ratios (ICURs) for each class of second-line antidiabetes drugs. Treatment effect estimates were obtained from the systematic review of clinical evidence. Other inputs for the model were derived from published and unpublished sources. Numerous sensitivity analyses were performed to examine robustness of results to variation in model inputs and assumptions.

Results

Clinical: Evidence for eight classes of second-line antidiabetes therapies in adults with type 2 diabetes inadequately controlled with metformin monotherapy was identified. The methodological quality of the evidence was generally low. All agents achieved statistically significant reductions in A1C, and there were no statistically significant differences

between drug classes. Events of severe hypoglycemia were very rare for all agents; however, the insulins and insulin secretagogues were associated with a higher risk for overall hypoglycemia than the other agents. A modest increase in body weight was observed with most second-line therapies, the exceptions being dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) analogues. There was little evidence regarding the effect of second-line antidiabetes drugs on the long-term complications of diabetes or mortality.

Economic: Sulfonylureas were the most cost-effective second-line therapy in patients inadequately controlled on metformin, due primarily to their lower cost compared with insulin and newer agents. Cost-effectiveness results were robust to variations in model inputs and assumptions.

Conclusion

Sulfonylureas are equally efficacious as other agents when used as second-line treatment after inadequate control with metformin monotherapy, and represent the most cost-effective treatment option.

ABBREVIATIONS

A1C	glycosylated hemoglobin
BMI	body mass index
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DDD	defined daily dose
DPP-4	dipeptidyl peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MTC	mixed treatment comparison
N	total number of patients
NPH	neutral protamine Hagedorn
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
TZDs	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study

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1 INTRODUCTION

In March 2004, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — launched the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) as a service to federal, provincial, and territorial jurisdictions and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of CADTH, through COMPUS, is to optimize drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH goals are achieved through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps between clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the COMPUS Advisory Committee (CAC), which includes representatives from the federal, provincial, and territorial Health Ministries and related health organizations
- the COMPUS Expert Review Committee (CERC) members, whose members are listed previously in this document (the mandate of CERC is advisory in nature and is to provide recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal drug prescribing and use in Canada)
- stakeholder feedback.

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal therapy for one or more specific topics. For topics in the area of diabetes management, including insulin analogue therapy, blood glucose test strips, and second-line therapy for patients with type 2 diabetes in whom metformin monotherapy has failed, four endocrinologists/diabetes specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists or have other relevant qualifications, with expertise in one or more areas such as but not limited to family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members including Public Members are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

CAC has identified the management of diabetes as being a priority area for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

Within diabetes management, second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy was identified by CAC as a priority topic.

The treatment of patients with type 2 diabetes usually begins with lifestyle modifications and treatment with oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone.[1-5] Recent utilization data indicate that approximately 60% of patients with type 2 diabetes initiating pharmacotherapy in Canada are started on metformin monotherapy.[6] As type 2 diabetes is a progressive disease, glycemic levels are likely to worsen over time. Most patients eventually require two or more oral antidiabetes drugs, or the addition of an insulin regimen, to achieve or maintain target blood glucose levels.[7,8] Existing guidelines and consensus documents[1-3,9-15] vary regarding recommendations for second-line treatment after glycemic control cannot be achieved with metformin alone. Some recommend that a sulfonylurea be added to metformin.[3,11,12,15] Others, however, do not identify a single drug class or agent as being preferred; instead, a stepwise approach to add agents from various classes is often recommended.[1,2,9,10,13,14] Little or no evidence is cited in relation to recommendations regarding second-line therapy in any of the guidelines.

Canadians spent approximately $17.10 per capita on oral antidiabetes drugs in 2007, for a total of $563 million.[16] The average cost per oral antidiabetes drug prescription in publicly funded drug plans in Canada nearly doubled over the course of a decade, from $11.31 in 1998 to $20.77 in 2007.[6] The increase in costs may have at least partly been due to the introduction of more costly antidiabetes drugs to the market. For example, the thiazolidinediones (TZDs) — rosiglitazone and pioglitazone — represented only 9.4% of all prescriptions for antidiabetes drugs in 2008, yet they accounted for 33% of total expenditures.[17] Given the large, growing population of patients with type 2 diabetes in Canada, suboptimal use of second-line antidiabetes drugs is likely to have a detrimental effect on both health outcomes and the cost-effective use of drugs. Therefore, there is a need for clear recommendations based on clinical and cost-effectiveness evidence to guide second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy.

2.1 Diabetes Mellitus

Diabetes is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin.[18] Type 1 diabetes occurs in approximately 10% of patients with diabetes, and it results when little or no insulin is produced by the body.[19] Type 2 diabetes is a metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[19] When inadequately managed, diabetes is likely to result in poor glycemic control.[18] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, and lower limb amputation).[20,21]

It is estimated that 1.9 million Canadian men and women aged 20 years and older had been diagnosed with diabetes in 2005-2006, representing 6.2% of all men and 5.5% of all women. In addition, it is believed that a large number of Canadians have diabetes but have not been diagnosed.[22]

2.1.1 Technology description — second-line antidiabetes drugs

Eleven classes of antidiabetes drugs are available as second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, basal insulins, bolus insulins, biphasic insulins, weight-loss agents, and amylin analogues. These second-line antidiabetes drugs are presented in Table 1.

Table 1: Drugs Included in the Therapeutic Review

Generic Name	Dosage	Admin.	Relevant Indications
Sulfonylureas			
Gliclazide/ Gliclazide MR	Range: 80-320 mg DDD: 160 mg Range for MR: 30-120 mg	Oral	Control of hyperglycemia in gliclazide-responsive type 2 diabetes which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.[23,24]
Glimepiride	Range: 1-8 mg DDD: 2 mg	Oral	Indicated for use as follows: an adjunct to proper dietary management, exercise, and weight reduction to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise alone; in combination with metformin when diet and exercise and glimepride or metformin alone do not result in adequate glycemic control; in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent alone.[25]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Indications**
Glyburide	Range: 2.5-20 mg DDD: 10 mg	Oral	Indicated as an adjunct to proper dietary management, exercise, and weight reduction to lower blood glucose in adult patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise alone or when insulin therapy is not required.[26]
Chlorpropamide	Range: 100-500 mg DDD: 375 mg	Oral	In mild, stable type 2 diabetes to control hyperglycemia responsive to the drug. It should not be used in those patients who are prone to ketosis or who can be controlled by dietary management and exercise alone or for whom insulin therapy is more appropriate.[27]
Glipizide	Range: 5-40 mg DDD: 10 mg	Oral	Not approved in Canada.
Tolbutamide	Range: 500-3,000 mg DDD: 1,500 mg	Oral	To control hyperglycemia in tolbutamide-responsive type 2 diabetes which cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.[28]
Thiazolidinediones			
Pioglitazone	Range: 15-45 mg DDD: 30 mg	Oral	Indicated as monotherapy in patients not controlled by diet and exercise alone, to decrease insulin resistance and blood glucose levels in patients with type 2 diabetes. Also indicated for use in combination with a sulfonylurea or metformin when diet and exercise plus the single agent do not result in adequate glycemic control.[29]
Rosiglitazone	Range: 4-8 mg DDD: 6 mg	Oral	Indicated for use as an adjunct to diet and exercise in patients with type 2 diabetes as follows: as monotherapy in patients not controlled by diet and exercise alone and for whom metformin is inappropriate because of contraindications or intolerance; in combination with metformin when diet and exercise plus metformin do not result in adequate glycemic control; in combination with a sulfonylurea in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus sulfonylurea or rosiglitazone monotherapy do not result in adequate glycemic control.[30]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Indications**
Meglitinides			
Nateglinide	Range: 60-120 mg DDD: 360 mg	Oral	Indicated as monotherapy to lower the blood sugar in patients with type 2 diabetes who are not controlled satisfactorily by diet and exercise alone. Also indicated in combination with metformin in patients not controlled satisfactorily on diet, exercise, or metformin alone.[31]
Repaglinide	Range: 0.5-16 mg DDD: 4 mg	Oral	Indicated in patients with type 2 diabetes whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. Indicated in combination therapy with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus metformin monotherapy. Indicated in combination with rosiglitazone in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus rosiglitazone or repaglinide monotherapy do not result in adequate glycemic control.[32]
Alpha-glucosidase inhibitors			
Acarbose	Range: 150-300 mg DDD: 300 mg	Oral	Indicated for use as follows: as an adjunct to prescribed diet for the management of blood glucose levels in patients with type 2 diabetes who are inadequately controlled by diet alone; in combination with either a sulfonylurea, metformin, or insulin to improve glycemic control in patients with type 2 diabetes who are inadequately controlled on diet, exercise, and either a sulfonylurea, metformin, or insulin alone.[33]
Miglitol	Range: 75-300 mg DDD: 300 mg	Oral	Not approved in Canada.
DPP-4 inhibitors			
Sitagliptin	Range: 100 mg DDD: 100 mg	Oral	Indicated in combination with metformin in adult patients with type 2 diabetes inadequately controlled with metformin monotherapy.[34]
Vildagliptin	Range: 100 mg DDD: 100 mg	Oral	Not approved in Canada.
Saxagliptin	Range: 5 mg DDD: N/A	Oral	Indicated in patients with type 2 diabetes to improve glycemic control, in combination with metformin or a sulfonylurea when metformin or the sulfonylurea are used alone, with diet and exercise; does not provide adequate glycemic control.[35]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Indications**
GLP-1 analogues			
Exenatide	Range: 10-20 µg DDD: 15 µg	SC	Not approved in Canada.
Liraglutide	Range: 1.2-1.8 mg DDD: N/A	SC	Not approved in Canada.
Rapid-acting insulin analogues			
Insulin aspart	Dosage is individualized	SC	Patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin aspart should normally be used in regimens, together with an intermediate- or long-acting insulin.[36]
Insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes mellitus.[37]
Insulin glulisine	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes where treatment with insulin is required.[38]
Short-acting human insulin			
Regular human insulin	Dosage is individualized	SC	For the treatment of insulin-requiring diabetic patients.
Intermediate-acting insulin			
Insulin NPH	Dosage is individualized	SC	For the treatment of insulin-requiring diabetic patients.
Long-acting insulin analogues			
Insulin detemir	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes who require a basal insulin for the control of hyperglycemia; and the treatment of type 2 diabetes in combination with OADs (metformin, sulfonylureas, or a TZD) in adult patients who are not in adequate metabolic control on OADs alone.[39]
Insulin glargine	Dosage is individualized	SC	Indicated for once-daily subcutaneous administration in the treatment of patients (> 17 years of age) with type 2 diabetes who require basal insulin for the control of hyperglycemia.[40]
Insulin NPL	Dosage is individualized	SC	Not approved in Canada.
Premixed insulins			
Premixed regular NPH	Dosage is individualized	SC	For the treatment of insulin-requiring diabetic patients.
Biphasic insulin aspart	Dosage is individualized	SC	Indicated for the treatment of adult patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.[41]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Indications**
Biphasic insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes mellitus.[37]
Weight-loss agents			
Orlistat	Range: 360 mg DDD: 360 mg	Oral	Orlistat, when used in conjunction with a mildly hypocaloric diet, is indicated for: obesity management including weight loss and weight maintenance; reducing the risk of weight regain in obese patients after prior weight loss. These indications apply to obese patients with a BMI ≥ 30 kg/m2 or a BMI ≥ 27 kg/m2 in the presence of other risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia, excess visceral fat). Can be used in combination with antidiabetic drugs (sulphonylureas, metformin, insulin) to improve blood glucose control in overweight or obese type 2 diabetes patients who are inadequately controlled on diet, exercise, and one or more of a sulphonylurea, metformin, or insulin.[42]
Sibutramine	Range: 10-15 mg DDD: 10 mg	Oral	Indicated as adjunctive therapy within a weight management program for: obese patients with an initial BMI of 30 kg/m^2 or higher; obese patients with an initial BMI of 27 kg/m2 or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).[43]
Amylin analogues			
Pramlintide	Range: 60-120 µg	SC	Not approved in Canada.

BMI = body mass index; DDD = World Health Organization Defined Daily Dose; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagadorn; NPL = neutral protamine lispro; OADs = oral antidiabetes drugs; SC = subcutaneous; TZD = thiazolidinediones.

3 OBJECTIVES

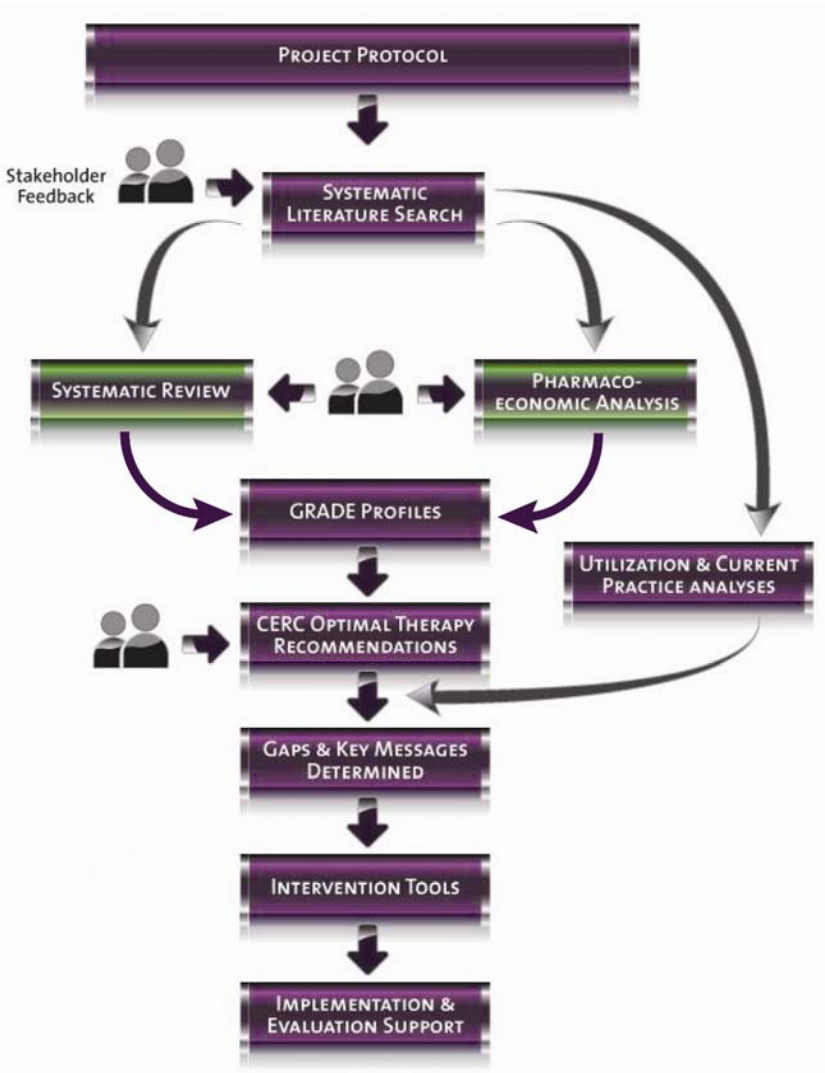
The objectives of this report were to:

- Identify and appraise the clinical evidence pertaining to use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.
- Conduct a cost-effectiveness analysis of second-line antidiabetes drugs in Canada.

The clinical and cost-effectiveness evidence generated in this review are used to develop optimal therapy recommendations.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The CAC provides advice and guidance throughout the process, from topic identification through to supporting intervention and evaluation tools. CERC, as described in Section 1.0, provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.



To identify and promote the implementation of evidence-based and cost-effective optimal therapy in the prescribing of second-line therapies, CADTH follows the process outlined in the flow chart to the right.

This report represents the draft systematic review and pharmacoeconomic analysis for stakeholder feedback (green boxes in flow chart) toward the development of optimal therapy recommendations for the prescribing and use of second-line therapy for patients with type 2 diabetes inadequately controlled with metformin monotherapy.

5 RESEARCH QUESTIONS

The following research questions were posed in this systematic review and cost-effectiveness analysis:

1. What is the comparative efficacy and safety of second-line antidiabetes drugs in patients with type 2 diabetes inadequately controlled on metformin monotherapy?
2. What is the cost-effectiveness of second-line antidiabetes agents in the management of patients with type 2 diabetes inadequately controlled on metformin monotherapy?

The populations of interest for this review were adults and children with type 2 diabetes inadequately controlled or intolerant to metformin monotherapy, and requiring a second antidiabetes drug. Inadequate control was defined as any of the following: glycosylated haemoglobin (A1C) > 6.5%; fasting plasma glucose > 7 mmol/L; or two-hour post-prandial glucose >10 mmol/L (see section 5.1 of the project protocol).[44] Clinical effects for all classes of second-line antidiabetes drugs approved for use by Health Canada, the Food and Drug Administration (FDA), or the European Medicines Agency were assessed. These included sulfonylureas, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, insulins and insulin analogues, alpha-glucosidase inhibitors, and weight-loss agents. GLP-1 analogues were not included in the cost-effectiveness analysis as these agents are not approved for use in Canada. A complete list of agents that were assessed is provided in the project protocol.[44] Outcomes of interest included A1C, hypoglycemia, body weight, body mass index (BMI), health-related quality of life (HRQoL), patient satisfaction with diabetes care and treatment, severe adverse events, long-term complications, and mortality. A complete list of outcomes is available in the project protocol.[44] Only published randomized, controlled trials were considered for inclusion in the review.

Outcomes of interest in the cost-effectiveness analysis included drug costs, costs for blood glucose test strips, total costs and quality-adjusted life years incurred over the average patients' lifetime, incremental cost utility ratios (ICURs), net monetary benefit, probability that a treatment strategy is most cost-effective, and mean rank in terms of cost-effectiveness.

6 CLINICAL REVIEW

6.1 Methods

This systematic review and meta-analysis was conducted according to a protocol prepared a priori.[44] Any changes were documented in protocol addenda[45] and prepared prior to conducting the affected analyses.

6.1.1 Literature search strategy

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, PubMed, and the Cochrane Central Register of Controlled Trials. The search strategy was comprised of both controlled vocabularies, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were type 2 diabetes mellitus, antidiabetes agents, and metformin. Methodological filters were applied to limit retrieval to randomized controlled trials (see Appendix 1 for detailed search strategies). The search was restricted to English language clinical articles published from 1980 to May 2009. Monthly Ovid AutoAlerts were active from June 2009 to October 2009 to identify studies published after May 2009.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies and professional associations. Google and other internet search engines were also searched. These searches were supplemented by hand-searching the bibliographies and abstracts of key papers and conference proceedings, and through elicitation of stakeholder feedback.

6.1.2 Systematic review and meta-analysis

a) Selection criteria

Active and placebo-controlled randomized controlled trials (RCTs) were selected for inclusion if they were published in English, reported relevant outcomes, and involved patients inadequately controlled on metformin monotherapy. All study populations were included where patients received second-line agents as add-ons to or switches from metformin monotherapy regardless of treatment history prior to metformin monotherapy. This included studies that employed a metformin monotherapy run-in period prior to the addition of second-line agents. Studies were excluded if:

- more than 15% of the patients used a drug other than metformin monotherapy at baseline, and no results were reported for the subgroup of metformin users
- initial therapy consisted of a combination of metformin with another antidiabetes drug
- second-line antidiabetes drugs added to metformin monotherapy were compared with switching to second-line therapy (i.e., discontinuation of metformin monotherapy)
- switch from metformin to another antidiabetes drug(s) was compared with switch to placebo or no therapy (i.e., no active comparator)
- treatment duration was less than four weeks.

Study selection was conducted independently by two reviewers, with a third reviewer used to resolve disputes.

b) Data extraction and quality assessment

Data extraction and quality assessment of RCTs were conducted independently by two reviewers, with a third reviewer used to resolve disputes. Quality assessment of RCTs was performed using the SIGN 50 instrument[46] for internal validity.

c) Data synthesis and analysis

WinBUGS[47] (MRC Biostatistics Unit, Cambridge, UK) was used for mixed treatment comparison (MTC) meta-analyses according to the routine developed at the Universities of Bristol and Leicester.[48] Metformin monotherapy was the reference group for all MTC analyses. Posterior densities for unknown parameters were estimated using Markov Chain Monte Carlo methods. Basic parameters were assigned non-informative or vague prior distributions. Point estimates and 95% credible intervals were used to summarize all findings. The probability of a drug class being optimal was estimated for each outcome based on the proportion of Markov Chain Monte Carlo simulations in which its relative measure of effect was best. We also calculated the mean rank for each drug class. We assessed consistency between direct and indirect evidence by comparing direct estimates obtained from pairwise meta-analysis with estimates from the MTC meta-analysis. As well, we formally tested for inconsistency using a function[49] that assesses each closed loop of the network according to the method of Bucher.[50] Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic[51] were assessed to ensure model convergence. Two chains were fit into WinBUGS for each analysis, each employing ≥ 20,000 iterations, with a burn-in of ≥ 20,000 iterations.

Frequentist pairwise meta-analysis was performed using R — a language and software environment for statistical computing. A random-effects model was used for the reference case in all pairwise and MTC meta-analyses. For pairwise meta-analyses, a frequentist approach was used rather than Bayesian statistics, since clinicians and policy-makers are more familiar with interpretation of the former.

Since weight-loss agents (i.e., orlistat and sibutramine) are primarily used to lower body weight rather than to treat hyperglycemia, it was determined through clinical expert opinion that the MTC analysis should be limited to therapeutic agents whose primary indication is lowering of blood glucose. Weight-loss agents were excluded from the MTC analysis, and only the results of direct comparisons are presented.

Following careful assessment of patient and trial characteristics, three different evidence networks were constructed for our various MTC analyses. The reference case analysis is based on a *drug class level* network in which moderate to high fixed dose and titrated dose studies were pooled into a single node, and low fixed dose studies were excluded. Low doses were defined as those being below the World Health Organization Defined Daily Dose (DDD). To account for differences in dosing across studies and avoid exclusion of the low-dose data, a *dose-stratified* MTC model was constructed in which each class of agent was stratified into three separate nodes representing distinct dosing strategies in the evidence network:

- individually titrated dosing
- moderate to high fixed doses (i.e., dosing ≥ DDD)
- low fixed doses (i.e., dosing < DDD).

The third model was an *individual agent* network that separated the TZD and sulfonylurea classes into their respective individual agents. Specifically, the TZD class was split into pioglitazone and rosiglitazone, and the sulfonylurea class into glyburide, gliclazide, glipizide, and glimepiride.

The *dose-stratified* and *individual agent* MTC models limited the ability to conduct sensitivity analyses as the probability that removal of studies will break the network increases with the number of nodes. Furthermore, the complexity of these models may also have hindered clinical interpretation of the results as there is an exponential increase in the number of effect estimates that must be considered as the number of nodes increases. Comparison of effect estimates from the two models with the simplified class-level model indicated similar results and adequate model fit in all three cases. Based on these results, the class-level model was chosen as the reference case for all subsequent analyses of clinical effectiveness. The reference case cost-effectiveness analysis was also performed using the results of the class-level model, although some results from the dose-stratified model were used to inform certain sensitivity analyses. Results of the dose-stratified and individual-agent models are also presented for comparative purpose (see appendices 15-20).

Sensitivity analyses were conducted by removing studies:

- of poor methodological quality
- employing a cross-over design
- of less than one year's duration (and less than three months' duration for the A1C outcome)
- where patients used less than 1,500 mg/day of metformin at baseline
- that tested agents currently not available in Canada.

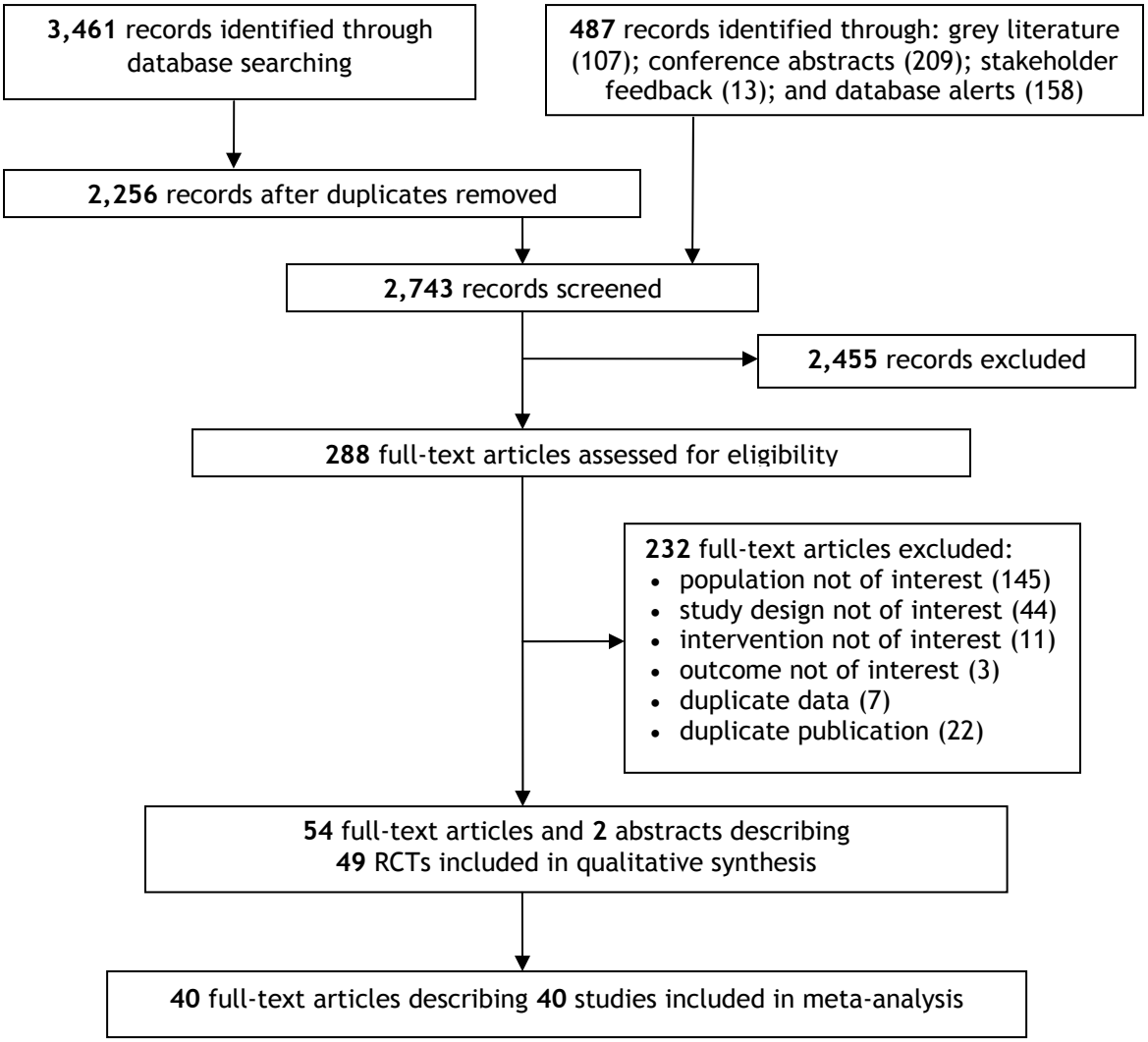
For outcomes subjected to MTC analysis, meta-regression analyses were performed to account for differences in baseline A1C, duration of diabetes, and baseline BMI (for the body weight outcome only).

6.2 Results

6.2.1 Selection of primary studies

Figure 1 illustrates the selection process used to identify primary studies of second-line drugs in patients inadequately controlled on metformin monotherapy. After removal of duplicates, a total of 2,743 citations were identified in the literature search. Of these, 2,455 citations were excluded, based on titles and/or abstracts. These consisted mainly of reviews, study designs other than randomized controlled clinical trials, and studies in which comparators were not of interest. Full-text articles of the remaining 288 citations were assessed, and 56 articles representing 49 unique RCTs were included in the systematic review. In several instances, data from the same clinical trial were presented in multiple full-text articles (see Appendix 9 for a list of companion papers). The publication with the longest duration of follow-up was used when analyzing data from such trials. Complete lists of included and excluded studies are presented in Appendices 2 and 3, respectively.

Figure 1: PRISMA Diagram of Study Selection Results



6.2.2 Study characteristics

The CADTH systematic review included 49 unique RCTs (reported in 54 full-text articles) [52-105] and two conference abstracts[106,107] that compared either one second-line drug with another, both in combination with metformin; or a second-line drug with placebo, both in combination with metformin (table 2). Sample size ranged from 13[104] to 2,789.[68] The threshold baseline A1C for inclusion in trials was typically in the range of 7.0% to 10%; however, some studies employed a threshold as low as 6.5% or as high as 11.5%. The mean baseline A1C of trial subjects ranged from 6.6%[108] to 10%[72] (weighted mean [SD] = 8.0% [0.9]). The baseline duration of diabetes ranged from 1.8 to 10.3 years (weighted mean [SD] = 6.1 [5.1] years). There were differences in the duration and dosage of metformin monotherapy prior to the addition of second-line drugs (see Appendices 4 and 5 for trial and patient characteristics). For the non-insulin drug classes, placebo-controlled trials were the most common: sulfonylureas,[63,83,90] meglitinides,[84,87] TZDs,[66,69,72,78,82,101] DPP-4 inhibitors,[58,59,61,65,73,95] alpha-glucosidase inhibitors;[74,92,98,99,103] and GLP-1 analogues.[64,70,89,90,93] The most common active comparison was sulfonylureas compared with TZDs (seven RCTs).[62,71,75,77,91,102,104] The majority of studies (89%) were sponsored by the pharmaceutical industry.

The population of interest for this systematic review was patients with type 2 diabetes treated with metformin monotherapy as first-line therapy under routine clinical care who either:

- demonstrated inadequate glycemic control after an adequate trial of metformin and required additional or alternative antidiabetes therapy; or
- experienced intolerable adverse effects or developed contraindications to metformin and required alternative therapy.

Metformin monotherapy was not necessarily first-line therapy in most studies. Only a single RCT[62] reported inclusion criteria that were likely to limit inclusion to patients receiving metformin monotherapy as initial antidiabetes therapy. The most common scenario in trials was that patients were treated with metformin monotherapy under routine clinical care, and required to have abstained from use of other antidiabetes drugs for a certain period (usually the past three months) before screening.[52-60,63-65,67,68,70,71,73-77,79,81-84,86,87,90-93,96-107] However, treatment history prior to this period was unspecified. In the second scenario, patients using a variety of oral antidiabetes drugs underwent a run-in period with metformin monotherapy upon trial entry, and were randomized to add-on therapy if glycemic control was inadequate at the end of the run-in period.[61,66,69,72,78,80,88,89,94,95] No studies assessed the effects of switching from metformin to another antidiabetes drug due to intolerable adverse effects, development of contraindications, or inadequate glycemic control.

There was insufficient evidence to conduct the sub-group analyses specified in the project protocol (e.g., patients ≥ 65 years old, First Nations people, and ethnic minorities), nor was there any evidence for children (< 18 years of age) with type 2 diabetes inadequately controlled with metformin monotherapy. Regarding the interventions of interest, there were no RCTs that investigated the use of bolus insulins, although a small number of studies assessed basal and biphasic insulins. There was no evidence available for any of the following outcomes of interest: patient satisfaction with diabetes care; diabetes-specific, health-related quality of life; retinopathy; nephropathy; hyperosmolar hyperglycemic nonketotic coma; upper extremity fractures; and pancreatitis.

Table 2: Summary of Trial Characteristics		
Trial Characteristics	**Categories**	**Number of Included Studies**
Publication status	Full texts	54[52-105]
	Abstracts	2[106,107]
	Unique RCTs	49[52-55,57-75,77-84,86-93,95,96,99-105,109]
Country	Multinational	25[52,53,57,58,60-62,65,68,70,73,75,77,81,83,84,86,88-90,92,95,100,101,103]
	Single country	24[54,55,59,63,64,66,67,69,71,72,74,78-80,82,87,91,93,94,97-99,102,104]
Study design	Parallel RCTs	46[52,54,55,57,58,60-75,77-84,86-95,97-103]
	Crossover RCTs	3[53,59,104]
Sponsors	Industry	43[53-55,57-71,73-75,77,78,80,82-84,86-90,92-95,97-103]
	Public funding	2[52,91]
	Not reported	4[72,79,81,104]
Treated with antidiabetes drugs other than metformin prior to the study?	Yes	10[61,66,69,72,78,80,88,89,94,95]
	No	2[62]
	Uncertain	38[52-55,57-60,63-65,67,68,70,71,73-75,77,79,81-84,86,87,90-93,97-104]
Intervention comparison	Head-to-head	17[53,60,62,68,71,75,77,79-81,88,91,94,97,100,102,104]
	Placebo control	29[52,54,55,57-59,61,63-67,69,70,72-74,78,82-84,86,87,92,93,95,98,99,103]
	Both	3[89,90,101]
Publication year		Range: 1995[98] to 2009[55,57,57,60,65,68,70,73,77,78,90,91]
Randomized sample size		Range: 13[104] to 2789[68]
Duration of study treatment (months)		1[93] to 66[77]

RCTs = randomized controlled trials

Table 3: Summary of Patient Characteristics	
Patient Characteristics	**Range From All Included Studies**
Mean age (years)	48.0[86] to 63.6[91]
Gender (% male)	21[91] to 74[92]
Mean duration of diabetes (years)	1.8[86] to 10.3[72]
Mean duration of stable metformin therapy prior to the study (months)	1[72,80,94] to 44.3[57]
Mean metformin dose at baseline (mg/day)	500 or 750[78] to 2,550[63]
Mean A1C at baseline (%)	6.6[63] to 10[69]

A1C = glycosylated hemoglobin

6.2.3 Study quality

The methodological quality of the 49 included RCTs[52-55,57-75,77-84,86-93,95,96,99-105,109] was assessed using the SIGN-50 instrument. The majority of RCTs (62%) included in this review were assessed as being of "poor" methodological quality. The primary reasons for downgrading study quality were failure to describe an adequate method for allocation concealment, failure to use an intention-to-treat analysis, use of an open-label design, and unequal treatment between trial arms. The most common forms of unequal treatment between trial arms were fixed dosing of one second-line drug versus titrated dosing of another, or maximal dosing of

one drug versus sub-maximal dosing of another (see Appendix 6 for study-level risk of bias evaluations).

6.2.4 Data synthesis

MTC and pairwise meta-analyses were conducted for A1C, body weight, and overall hypoglycemia. In the case of severe hypoglycemia, MTC analysis could not be conducted because of the zero event rates observed in many studies. MTC analysis was also not performed for severe adverse events because of a lack of clear definitions for this outcome. Only pairwise direct comparisons were conducted for the remaining outcomes because of the small number of studies available.

Table 4: Overview of Evidence and Analyses Performed

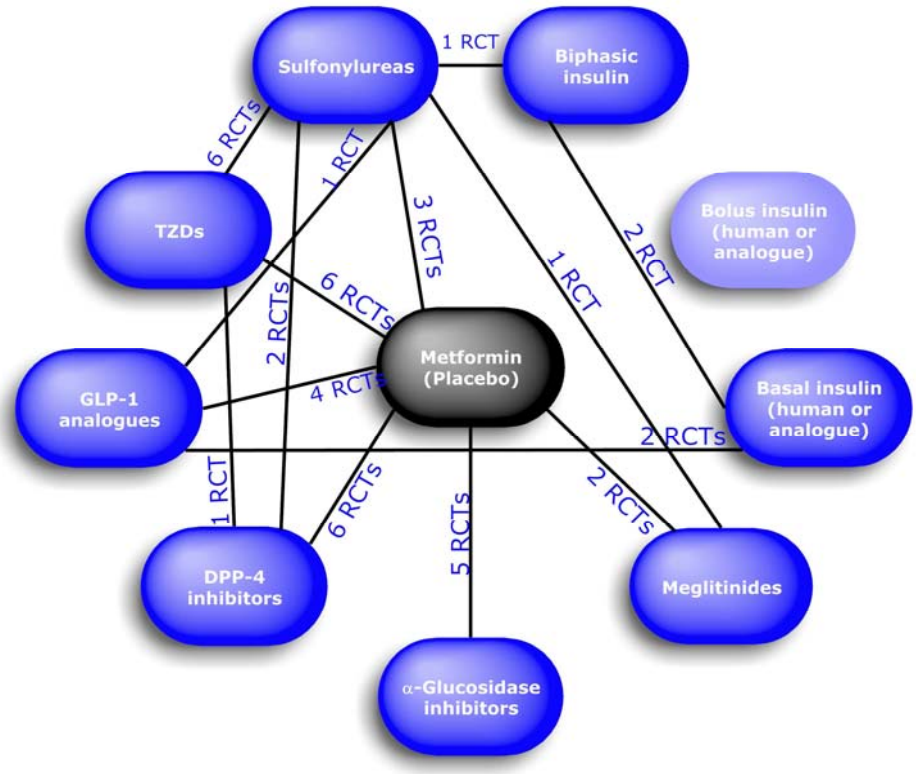
Outcome	No. of Treatment Strategies	No. of Pairwise Comparisons	No. of Studies and Patients	Type of Analysis Conducted
Hemoglobin A1C	9	14	40 RCTs (N = 17,795)	MTC and pairwise
Body weight	9	14	30 RCTs (N = 15,265)	MTC and pairwise
Overall hypoglycemia	9	14	34 RCTs (N = 16,704)	MTC and pairwise
Severe hypoglycemia	9	12	24 RCTs (N = 8,650)	Pairwise
Nocturnal hypoglycemia	7	5	6 RCTs (N = 805)	Pairwise
Body mass index	3	3	4 RCTs (N = 839)	Pairwise
Severe adverse events	9	10	22 RCTs (N = 11,933)	Pairwise
Congestive heart failure	5	4	4 RCTs (N = 4,147)	Pairwise
Ischemic heart disease	6	6	6 RCTs (N = 2,896)	Pairwise
All-Cause Mortality	7	8	11 RCTs (N = 9,108)	Pairwise
Macular edema	2	1	1 RCT (N = 2,222)	Pairwise
Neuropathy	2	1	1 RCT (N = 190)	Pairwise
Peripheral vascular disease	2	1	1 RCT (N = 2,789)	Pairwise
Stroke/TIA	3	2	2 RCTs (N = 3,364)	Pairwise
HRQoL				
IWQOL-Lite	2	1	1 RCT (N = 366)	Pairwise
SF-36: physical	2	1	1 RCT (N = 185)	Pairwise
SF-36: mental	2	1	1 RCT (N = 185)	Pairwise
DTSQ				
Overall	2	1	1 RCT (N = 187)	Pairwise
Perceived hypoglycemia	3	3	1 RCT (N = 457)	Pairwise
Perceived hyperglycemia	2	1	1 RCT (N = 727)	Pairwise

A1C = glycolsylated hemoglobin; DTSQ = diabetes treatment satisfaction questionnaire; HRQoL = health-related quality of life; IWQoL = impact of weight on quality of life-lite; MTC = mixed treatment comparisons (meta-analysis); N = total sample size; RCT = randomized controlled trial; TIA = transient ischemic attack.

a) Hemoglobin A1C

There were 40 RCTs[53,55,57,58,60-66,68,69,71-74,77,78,80-84,87-95,97-99,101-104] (N = 17,795) that reported change from baseline in A1C. Evidence was available for all drug classes with the exception of bolus insulin. The MTC evidence network for A1C highlights the number of RCTs available for each pairwise comparison (Figure 2). TZDs and DPP-4 inhibitors were most frequently studied in placebo-controlled trials (six RCTs each), while the most common active comparison was TZDs versus sulfonylureas.[62,71,77,91,102,104]

Figure 2: MTC Evidence Network for Hemoglobin A1C*



A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCTs = randomized controlled trials;TZDs = thiazolidinediones.
*All treatment nodes represent combination therapy with metformin.

A summary of the results of the MTC and direct pairwise meta-analyses is shown in Table 5. Based on qualitative assessment, the results of the direct pairwise estimates and MTC estimates are similar in both direction and magnitude. All eight classes of second-line agents resulted in a statistically significant reduction in A1C relative to metformin monotherapy: estimates of effect ranged from a high of -0.97% (95% Confidence Interval [CI]: -1.33, -0.62) for biphasic insulins to -0.64% (95% CI: -0.92, -0.38) for meglitinides (see Appendix 12 for full results and Appendix 21 for forest plots). The magnitude of A1C reduction was similar across classes and there were no statistically significant differences between the various active comparators.

A large number of sensitivity analyses, meta-regression analyses, and alternative modelling were conducted to explore the results of the reference case MTC meta-analysis for A1C (see Appendix 24). There were no statistically significant differences in the MTC estimates of effect after removing studies with any of the following criteria: poor quality, crossover

design, less than one year in duration, patients using less than 1,500 mg/day of metformin at baseline, and use of agents not available in Canada. Meta-regressions, performed to account for differences in baseline A1C and duration of diabetes, also yielded results that were consistent with the reference case analysis. The reference case analysis was conducted using a random effects model; therefore, these results were also compared against those obtained using a fixed effects model and found to be nearly identical.

In addition to grouping second-line agents by drug class, an additional MTC evidence network was constructed that separated the TZD and sulfonylurea classes into their respective individual agents. Specifically, the TZD class was split into pioglitazone and rosiglitazone, and the sulfonylurea class into glyburide, gliclazide, glipizide, and glimepiride. All the agents resulted in a statistically significant reduction in A1C relative to placebo; however, there were no statistically significant differences between any of the individual agents relative to one another (results presented in Appendix 18).

One small RCT[54] (N = 69) reported a statistically significant reduction in A1C in patients treated with orlistat relative to placebo (-0.93% [95% CI: -1.58%, -0.28%]). Another trial (N = 194) reported no statistically significant difference in patients treated with sibutramine versus placebo.[86]

b) Hypoglycemia

Overall hypoglycemia

Thirty-four RCTs[53,55,57-66,68,69,71-73,77,78,80-84,87-89,94,95,97,99,101-104] (N = 16,704) reported the number of patients experiencing at least one episode of overall hypoglycemia. There was variability in the clinical definitions of this outcome across RCTs (definitions of hypoglycemia are presented in appendices 30-32). The most common differences were the specific blood glucose threshold for hypoglycemia (range ≤ 2.8 to ≤ 3.9 mmol/L), and whether or not patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose. Results from the MTC meta-analysis and direct pairwise meta-analyses are shown in Table 5 (see Appendix 14 for detailed results and Appendix 21 for forest plots). There was good alignment between the direct and indirect comparisons. Relative to metformin monotherapy, basal insulin, and biphasic insulin, sulfonylureas and meglitinides were associated with a statistically significant increase in the odds of hypoglycemia (range: 5.2-11.0). No statistically significant differences were detected between these agents. In contrast, there was no statistically significant difference in the odds of hypoglycemia with TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 analogues relative to metformin alone. Meta-regression analyses for baseline A1C and trial duration generated similar results, as did removal of crossover studies in a sensitivity analysis or the use of a fixed-effects model (see Appendix 26). Other planned sensitivity analyses could not be conducted due to the lack of sufficient connectivity in the network.

Severe hypoglycemia

Twenty-four RCTs (N = 8,650)[53,57,58,60,61,63,64,66,68-73,80,81,83-85,87,89,94,102,103] were identified that reported the number of patients with at least one episode of severe hypoglycemia. Events of severe hypoglycemia were rare for all drug-classes including the insulins and insulin secretagogues (i.e., meglitinides and sulfonylureas). Overall, there were no events reported in 44 out of 50 treatment arms, and only a single study[68] reported more than two events. Results from MTC meta-analysis were not reported for this outcome as the rarity of events prevented model convergence. Treatment with sulfonylureas[63,83,89] (N = 501) or GLP-1 analogues[70,89,103] (N = 389) was not statistically significantly different from metformin alone

regarding the number of patients with severe hypoglycemia. One RCT[68] (N = 2,789) reported a statistically significant increase in severe hypoglycemia with sulfonylureas in comparison with DPP-4 inhibitors (Odds Ratio [OR] [95% CI] = 21.20 [1.24, 362.1]). There was no statistically significant difference between treatment with GLP-1 analogues or basal insulin treatment[53,60] (OR [95% CI] = 0.32 [0.01, 8.22]; N = 145). Given the very low occurrence of severe hypoglycemia across all trials and the consequent limitations in study power, the interpretability of these results is very limited (see Appendix 27).

Nocturnal hypoglycemia

Six RCTs (N = 805)[72,80,84,87,103,107] were identified that reported the number of patients with at least one episode of nocturnal hypoglycaemia; however, most of these trials reported zero events in all treatment arms. RCTs comparing metformin alone with meglitinides,[84,87] TZDs,[72] or alpha- glucosidase inhibitors[103] reported no events. One RCT[80] (N = 140) reported a non-statistically significant difference in the occurrence of nocturnal hypoglycemia with biphasic insulins in comparison with basal insulin (OR [95% CI] = 0.79 [0.34, 1.84]). Another RCT[107] (N = 76) reported no statistically significant difference between the GLP-1 analogue exenatide and insulin detemir. Given the very low occurrence of nocturnal hypoglycemia across all trials, the power to detect any differences between agents was extremely limited (see Appendix 27).

c) Body weight and body mass index

Thirty RCTs (N = 15,265)[53,55,57,58,60,62-64,66,68,71-73,77,78,80,81,83,84,87-89,91,92,94,97,99,101-103] reported change from baseline in body weight. A summary of MTC results and direct pairwise meta-analyses is shown in Table 5 (see Appendix 13 for detailed results and Appendix 21 for forest plots). Similar to the MTC results for A1C and overall hypoglycemia, there was good alignment between the direct pairwise and MTC estimates. Treatment with sulfonylureas, meglitinides, TZDs, and biphasic insulin all resulted in a statistically significant increase in body weight compared with metformin alone (range: 1.80-2.96 kg). There were no statistically significant differences amongst these classes. The only drug class that was associated with a statistically significantly reduction in body weight versus metformin alone was GLP-1 analogues (mean difference [95% CI] = -1.79 kg [-3.43, -0.14]). Results of head-to-head comparisons demonstrated significantly less weight gain with DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues in comparison with TZDs, basal insulin (glargine), sulfonylureas, and meglitinides. GLP-1 analogues and alpha-glucosidase inhibitors demonstrated the highest probabilities of having the most favourable effects on body weight.

A meta-regression analysis to adjust for differences in baseline BMI, a sensitivity analysis with removal of crossover studies, and a fixed-effects model all generated results that were similar to the reference case analysis of body weight (see Appendix 25). Other planned sensitivity analyses could not be conducted due to the lack of sufficient connectivity in the network.

Two studies comparing orlistat[54] and sibutramine[86] against placebo reported statistically significant reductions in body weight of -5.1 kg (95% CI: -6.86, -3.33) and -4.0 kg (95% CI: -5.79, -2.21), respectively.

Four RCTs (N = 839) reported change in BMI from baseline.[63,69,91,102] An MTC meta-analysis was not conducted for this outcome, as there were was only evidence for three treatment strategies. Pairwise meta-analysis demonstrated a non-statistically significant increase in BMI for patients treated with TZDs in comparison with sulfonylureas (mean difference [95% CI] = -

0.11 kg/m^2 [-0.47, 0.25]). In comparison with placebo, treatment with either TZDs (mean difference [95% CI] = 3.1 kg/m^2 [1.81, 4.39]) or sulfonylureas (mean difference [95% CI] = 0.46 kg/m^2 [0.17, 0.75]) resulted in statistically significant increases in BMI; however, the magnitude of the increase was much greater with TZDs. One RCT[86] compared sibutramine with placebo and reported a statistically significant reduction in BMI (mean difference = -1.9 kg/m^2 [-2.49, -1.31]).

Table 5: Summary of Direct and MTC Meta-analyses: Results for A1C, Overall Hypoglycemia, and Body Weight

Hemoglobin A1C (change from baseline, %)		
Treatment versus metformin monotherapy	**Direct estimates WMD (95% CI)**	**MTC estimates (95% CrI)**
Sulfonylureas	-0.80 (-1.00, -0.59)	-0.79 (-0.95, -0.63)
Meglitinides	-0.71 (-1.24, -0.18)	-0.64 (-0.93, -0.37)
TZDs	-0.96 (-1.18, -0.75)	-0.82 (-1.00, -0.66)
DPP-4 inhibitors	-0.78 (-0.96, -0.60)	-0.80 (-0.95, -0.65)
alpha-glucosidase inhibitors	-0.74 (-0.94, -0.53)	-0.74 (-0.98, -0.50)
GLP-1 analogues	-0.75 (-0.96, -0.53)	-0.82 (-1.05, -0.59)
Basal insulin	——	-0.82 (-1.16, -0.47)
Biphasic insulin	——	-0.97 (-1.33, -0.61)
Overall hypoglycemia (OR)		
Treatment versus metformin monotherapy	**Direct estimates WMD (95% CI)**	**MTC estimates median OR (95% CrI)**
Sulfonylureas	4.64 (1.27, 16.97)	8.22 (4.52, 16.63)
Meglitinides	6.59 (1.53, 28.29)	8.59 (3.47, 25.20)
TZDs	1.56 (0.56, 4.33)	1.10 (0.54, 2.27)
DPP-4 inhibitors	1.07 (0.59, 1.93)	1.05 (0.56, 2.21)
alpha-glucosidase inhibitors	0.49 (0.04, 5.55)	0.39 (0.01, 6.67)
GLP-1 analogues	1.00 (0.31, 3.20)	1.12 (0.33, 3.90)
Basal insulin	——	5.20 (1.48, 21.46)
Biphasic insulin	——	11.01 (3.48, 40.43)
Body weight (change from baseline, kg)		
Treatment versus metformin monotherapy	**Direct estimates WMD (95% CI)**	**MTC estimates (95% CrI)**
Sulfonylureas	1.79 (1.29, 2.28)	2.01 (1.09, 2.94)
Meglitinides	2.01 (-0.31, 4.32)	1.80 (0.35, 3.29)
TZDs	2.30 (1.93, 2.66)	2.59 (1.66, 3.51)
DPP-4 inhibitors	0.70 (0.20, 1.21)	0.57 (-0.45, 1.60)
alpha-glucosidase inhibitors	-0.90 (-1.92, 0.13)	-0.92 (-2.35, 0.51)
GLP-1 analogues	-1.58 (-3.53, 0.37)	-1.79 (-3.43, -0.14)
Basal insulin	——	1.56 (-0.46, 3.63)
Biphasic insulin	——	2.96 (0.96, 5.00)

A1C = glycosylated hemoglobnin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MD = mean difference; MTC = mixed treatment comparison; OR = odds ratio; TZDs = thiazolidinediones; WMD = weighted mean difference.

d) Patient-reported outcomes

Patient-reported outcomes such as health-related quality of life and diabetes treatment satisfaction were rarely reported in RCTs. Furthermore, there was a lack of consistency in the tools used to measure changes in these outcomes, and in the presentation of results. One RCT[82] comparing TZDs with placebo reported no statistically significant differences in either the physical or mental components of the SF-36 questionnaire. This study also reported no difference in scores on the Diabetes Treatment Satisfaction Questionnaire (DTSQ). A three-arm RCT[106] comparing sulfonylurea (glimepiride), GLP-1 analogue (liraglutide), and metformin alone reported statistically significant improvements in the "perceived frequency hyperglycemia" sub-scores of the DTSQ favouring liraglutide over metformin alone and glimepiride. No RCTs reported data related to diabetes-specific, health-related quality of life or patient satisfaction with diabetes care.

e) Long-term complications

Results for long-term complications are shown in Table 6. The majority of RCTs included in this review were inadequately powered to detect statistically significant differences in the occurrence of long-term complications of diabetes. In pairwise meta-analyses, no statistically significant differences between treatments were observed for any of the following long-term outcomes: congestive heart failure[56,62,68,103] (N = 4,147), ischemic heart disease[57,85,88,95,97,103] (N = 2,896), all-cause mortality[55,65,68,69,73,74,81,85,88,95,97] (N = 9,108), neuropathy[95] (N = 190), peripheral vascular disease[68] (N = 2,789), and stroke[57,68] (N = 3,364).

The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial was the only included RCT in which macrovascular complications were specified as the primary outcome of interest.[77] This large RCT involved patients inadequately controlled on metformin (N = 2,228) or sulfonylurea (N = 2,230) monotherapy. Data were not presented for the subgroup of subjects inadequately controlled on metformin monotherapy for most outcomes. No events of macular edema were observed in either treatment arm (N = 2,222).

Table 6: Summary of Findings for Long-Term Complications of Diabetes

Comparison	No. of Trials/Total N	OR (95% CI)
Ischemic heart disease		
TZDs vs. sulfonylureas	1 RCT[85] (N = 630)	2.97 (0.12, 73.22)
Alpha-glucosidase inhibitors vs. placebo	1 RCT[103] (N = 153)	0.32 (0.01, 7.89)
Meglitinides vs. sulfonylureas	1 RCT[97] (N = 213)	5.56 (0.27, 100)
DPP-4 inhibitors vs. sulfonylureas	1 RCT[88] (N = 1,135)	7.14 (0.37, 100)
DPP-4 inhibitors vs. placebo	1 RCT[95] (N = 190)	3.10 (0.12, 76.97)
DPP-4 inhibitors vs. TZDs	1 RCT[57] (N = 575)	1.05 (0.07, 16.93)
Congestive heart failure		
TZDs vs. sulfonylureas	1 RCT[62] (N = 630)	2.49 (0.48, 12.94)
DPP-4 inhibitors vs. sulfonylureas	1 RCT[68] (N = 2,789)	1.00 (0.14, 7.09)
DPP-4 inhibitors vs. TZDs	1 RCT[56] (N = 575)	*No events*
Alpha-glucosidase inhibitors vs. placebo	1 RCT[103] (N = 153)	0.32 (0.01, 7.89)
Macular edema		
TZDs vs. sulfonylureas	1 RCT[77] (N = 2,222)	*No events*

Table 6: Summary of Findings for Long-Term Complications of Diabetes		
Comparison	**No. of Trials/Total N**	**OR (95% CI)**
All-Cause Mortality		
TZD vs. sulfonylureas	1 RCT[85] (N = 630)	0.20 (0.01, 4.10)
DPP-4 inhibitors vs. placebo	3 RCTs[65,73,95] (N= 1,117)	0.22 (0.02, 2.16)
DPP-4 inhibitors vs. sulfonylureas	2 RCTs[68,88] (N = 3,924)	0.59 (0.14, 2.50)
TZD vs. placebo	1 RCT[69] (N = 223)	*No events*
Alpha-glucosidase inhibitors vs. Placebo	1 RCT[74] (N = 152)	*No events*
Meglitinides vs. sulfonylureas	1 RCT[97] (N = 213)	*No events*
BiAsp 30 vs. sulfonylureas	1 RCT[81] (N = 222)	3.20 (0.13, 79.29)
TZD vs. DPP-4 inhibitors	1 RCT[55] (N = 2,627)	6.05 (0.25, 148.75)
Neuropathy		
DPP-4 inhibitors vs. placebo	1 RCT[95] (N = 190)	2.00 (0.36, 11.19)
Peripheral vascular disease		
Sulfonylureas vs. DPP-4 inhibitors	1 RCT[68] (N = 2,789)	0.33 (0.01, 8.17)
Stroke/transient ischemic attack		
Sulfonylureas vs. DPP-4 inhibitors	1 RCT[68] (N = 2,789)	0.07 (0.00, 1.16)
TZDs vs. DPP-4 inhibitors	1 RCT[57] (N = 575)	3.18 (0.33, 30.79)

BiAsp 30 = biphasic insulin aspart 30/70; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4;GLP-1 = glucagon-like peptide-1; OR = odds ratio; N = total sample size; RCT = randomized controlled trial; TZDs = thiazolidinediones; vs. = versus.

f) Outcomes related to safety

Twenty-three RCTs (N = 11,933)[55,57,58,60,61,63,65,68,69,72,73,78,82,83,88,91,92,94,95,97,101-103] were identified that reported total severe adverse events. It should be noted that very few studies defined which adverse events were classified as "severe." Due to the heterogeneity associated with a lack of clear definitions, and the relatively high proportion of treatment arms (18%) with no events, an MTC meta-analysis was not performed for this outcome. Pairwise meta-analysis of three RCTs[55,57,101] (N = 3383) demonstrated a statistically significant increase in the number of severe adverse events for patients treated with TZDs in comparison with DPP-4 inhibitors (OR [95% CI] = 1.71 [1.06, 2.77]). No statistically significant differences were observed for the other nine pairwise comparisons, although statistical power was very limited (see Appendix 27 for detailed results). There was no evidence available from the included RCTs regarding the occurrence of pancreatitis, upper extremity fractures, or hyperosmolar hyperglycemic nonketotic coma.

7 ECONOMIC ANALYSIS

7.1 Methods

7.1.1 Cost-effectiveness analysis

This cost-effectiveness analysis was conducted according to a protocol[44] prepared a priori. Any changes were documented in protocol addenda[45] prepared prior to conducting the affected analyses.

An incremental cost-utility analysis was performed that compared alternative second-line therapies in adults with type 2 diabetes inadequately controlled with metformin

monotherapy. The United Kingdom Prospective Diabetes Study (UKPDS) model was used to forecast long-term diabetes-related complications, corresponding quality-adjusted life-years (QALYs), and cost consequences. Clinical effect estimates (i.e., A1C, body weight) for the UKPDS model were derived from the random-effects MTC meta-analysis reported in section 6. Patient characteristics, costs and utility decrements were derived from published sources. A detailed summary of model inputs and assumptions is presented in Appendix 33.

Modelling changes in treatment sequences over time is challenging with any model, including the UKPDS Outcomes Model. There is uncertainty over which treatment patients will add on or switch to after inadequate control on second-line therapy. When patients use multiple treatments over time, it is difficult to assess whether benefits conferred are attributable to the treatment of interest or to subsequent treatments. Due to these considerations, it was assumed in the reference case that patients remained on their respective second-line therapy over their expected lifetime, without adding or switching to subsequent agents. This approach is not reflective of clinical practice given the progressive nature of diabetes; however, it enabled CADTH to estimate costs and consequences which are solely attributable to each second-line treatment. The effect of this assumption was tested on the results through sensitivity analyses whereby patients were assumed to add on insulin as third-line therapy after a pre-defined period.

Patients using insulin secretagogues (i.e., sulfonylureas and meglitinides) and insulin have an increased risk of overall and severe hypoglycemia relative to those using other oral antidiabetes drugs. However, the UKPDS Outcomes Model does not directly incorporate the costs and consequences associated with hypoglycemia. Because hypoglycemia impacts health-related quality of life and, in some instances (e.g., severe hypoglycemia), may result in health care resource use, it was necessary to capture any benefits conferred by second-line drugs associated with a lower risk of hypoglycemia. To do so, two submodels were developed that incorporated the increased risk of overall and severe hypoglycemia among patients using insulin and insulin secretagogues. Additional details regarding the submodels are presented in Appendix 34.

7.1.2 Price of treatments

Unit costs for drugs were obtained from the Ontario Public Drug Programs, when available.[110] Otherwise, prices were obtained from other public drug programs in Canada.[111-114] For the reference case cost-effectiveness analysis, the price of the lowest cost alternative was applied for each drug class (e.g., price of generic glyburide for sulfonylureas, generic pioglitazone for TZDs), plus a 10% markup and $7.00 pharmacy fee per 90-day supply. Maximal doses were assumed for metformin, and defined daily doses (DDD) specified by the World Health Organization for second-line agents. Insulin doses were based upon a patient sample from British Columbia (observational data). We also ran analyses using insulin doses reported in RCTs.[115-118]

Patients using certain second-line antidiabetes drugs (e.g., insulin secretagogues and insulin) typically use more blood glucose test strips than those using other agents. For the economic analysis, average daily utilization of blood glucose test strips for each agent was derived from a recent utilization study in Ontario.[119] A cost of $0.72 per test strip was applied, plus a pharmacy fee of $7.00 per 100 test strips. No markup was applied because test strips are not eligible for markup in the Ontario Public Drug Programs.

Table 7: Agents, Doses, and Costs Incorporated in the Reference Case Economic Analysis of Second-Line Antidiabetes Therapies After Inadequate Control With Metformin Alone					
Class	**Agent/Class**	**Unit Dose**	**Cost Per Unit**	**Mean Daily Dose**	**Mean Test Strip Use Per Day**
Metformin	Apo-metformin	500 mg	$0.0965	2 g	0.94
Sulfonylurea	Apo-glyburide	5 mg	$0.0683	10 mg	1.16
	Apo-gliclazide	80 mg	$0.1863	160 mg	
	Glimepiride	1 mg	$0.49	2 mg	
Meglitinides	Repaglinide	2 mg	$0.3213	4 mg	
TZD	Apo-pioglitazone	30 mg	$2.2017	30 mg	0.94
	Rosiglitazone	2 mg	$1.4925	6 mg	
DPP-4 inhibitors	Sitagliptin	100 mg	$2.55	100 mg	
Alpha-glucosidase inhibitors	Acarbose	100 mg	$0.3584	300 mg	
Basal insulin	Basal human insulin	Humulin N vial 10 mL, 100 units/mL — $20.00; Humulin N cartridge 5 mL x 3 mL, 100 units/mL — $39.88; 65:35 cartridge vial ratio		0.75 U per kg per day (observational data) 0.35 U per kg per day (RCTs)	2.08
	Long-acting insulin analogue	Lantus vial 10 mL, 100 units/mL — $86.87; Lantus cartridge 5 mL x 3 mL, 100 units/mL — $86.87; 65:35 cartridge vial ratio		0.53 U per kg per day (observational data) 0.42 U per kg per day (RCTs)	
Biphasic insulin	Biphasic human insulin	Humulin 30/70 vial 10 mL, 100 units/mL — $20.00; Humulin 30/70 cartridge 5 mL x 3 mL, 100 units/mL— $39.26; 65:35 cartridge vial ratio		1.50 U per kg per day (observational data) 0.53 U per kg per day (RCTs)	
	Biphasic insulin analogue	NovoMix 30 penfill (cartridge) 5 mL x 3 mL, 100 units/mL — $51.87		1.20 U per kg per day (observational data) 0.76 U per kg per day (RCTs)	

DPP-4 = dipeptidyl peptidase-4; RCT = randomized controlled trial; TZD = thiazolidinedione; U = units.

7.2 Results

7.2.1 Price of treatments

Older generation sulfonylureas (glyburide, gliclazide) have the lowest daily cost among active treatments, even after the additional cost of blood glucose test strips is applied (Table 8).

The daily cost of the newer sulfonylurea glimepiride is higher than older sulfonylureas, similar in cost to meglitinides and alpha-glucosidase inhibitors, and less than newer oral agents (e.g, TZDs and DPP-4 inhibitors) and insulins. Using insulin doses from clinical practice, the cost of insulin NPH was similar to that of generic pioglitazone and lowest cost DPP-4 inhibitors. Generic pioglitazone, DPP-4 inhibitors, and insulin NPH were less expensive than rosiglitazone, long-acting insulin analogues, biphasic human insulin, or biphasic insulin analogues (Table 7). However, when we applied insulin doses from RCTs, the cost of insulin NPH decreased. Insulin NPH was more expensive than older oral drugs and less expensive than newer oral agents and other insulins.

Table 8: Average Daily Cost of Treatments With and Without the Additional Cost of Blood Glucose Test Strips, Stratified By Source of Insulin Dose

Treatment	Insulin Dose From Canadian Clinical Practice*		Insulin Dose from RCTs†	
	Daily Treatment Cost Without Test Strips‡	Daily Treatment Cost With Test Strips§	Daily Treatment Cost Without Test Strips	Daily Treatment Cost With Test Strips
Glyburide	$0.23	$1.14	$0.23	$1.14
Gliclazide	$0.49	$1.40	$0.49	$1.40
Glimepiride	$0.62	$1.53	$0.62	$1.53
Repaglinide	$0.78	$1.70	$0.78	$1.70
Acarbose	$1.26	$2.00	$1.26	$2.00
Insulin NPH	$1.95	$3.60	$1.08	$2.72
Pioglitazone¶	$2.50	$3.41	$2.50	$3.41
Rosiglitazone	$5.00	$5.92	$5.00	$5.92
Biphasic human insulin	$3.81	$5.45	$1.88	$3.52
DPP-4 inhibitors	$2.88	$3.80	$2.88	$3.80
Long-acting insulin analogues	$3.04	$4.69	$2.04	$3.68
Biphasic insulin analogues	$4.34	$5.98	$1.88	$3.51

DPP-4 = dipeptidyl peptidase-4;RCT= randomized controlled trial.
***** Insulin doses obtained from patient sample in British Columbia (Dr. Marshall Dahl, University of British Columbia: unpublished data, 2008). This dataset reported insulin doses of 0.53, 0.75, 1.2, and 1.5 U/kg for long-acting insulin analogues, insulin NPH, biphasic insulin analogues, and biphasic human insulin, respectively.
† Insulin doses obtained from RCTs[115-118] included in the systematic review,which reported insulin doses of 0.35, 0.42, 0.53, and 0.76 U/kg for long-acting insulin analogues, insulin NPH, biphasic insulin analogues, and biphasic human insulin, respectively.
‡ The cost of the lowest cost alternative was applied for each drug class, plus a 10% markup and $7.00 pharmacy fee per 90-day supply. It was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.[120]
§ Patients using insulin were assumed to use 2.1 test strips per day while those using oral drugs in combination with sulfonylureas used 1.16 test strips per day, based on data from the Ontario Drug Benefit Program.[119]
¶ Based on the cost of 30 mg generic pioglitazone in Saskatchewan,[114] Alberta,[111] and Non-Insured Health Benefits Program (NIHB);[121] In Ontario, generic pioglitazone costs less ($1.57) under the Ministry's Exceptional Access Program.[110]

The clinical benefits from the systematic review, when analyzed using the UKPDS Outcomes Model, translated into small differences (absolute ≤ 1%) in 40-year cumulative incidence rates between active comparators (Table 9). However, the absolute risk differences increased when compared with metformin monotherapy, particularly for myocardial infarction, stroke, amputation, and blindness.

Table 9: Cumulative Incidence of Long-Term Diabetes-Related Complications Over a 40-Year Period, Reference Case Analysis								
	Met	**SU**	**Meg**	**TZDs**	**DPP-4**	**AGI**	**Basl**	**Bipl**
IHD	11.2%	10.8%	11.0%	10.7%	10.8%	10.9%	10.8%	10.9%
MI	28.1%	27.3%	27.5%	27.2%	27.3%	27.3%	27.3%	27.5%
CHF	11.2%	11.2%	11.3%	11.1%*	10.8%	10.3%	11.2%	11.3%
Stroke	12.4%	12.0%	12.1%	12.1%	12.0%	11.9%	12.1%	12.1%
Amputation	6.8%	5.9%	6.2%	5.8%	5.9%	6.0%	5.7%	5.7%
Blindness	6.6%	6.0%	6.2%	5.9%	6.2%	6.1%	6.0%	6.1%
Renal Failure	3.2%	3.3%	3.3%	3.2%	3.3%	3.2%	3.4%	3.2%

AGI = alpha-glucosidase inhibitors; Basl = basal insulin; Bipl = biphasic insulin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; IHD = ischemic heart disease; Meg = meglitinides; Met = metformin; MI = myocardial infarction; SU = sulfonylurea; TZDs = thiazolidinediones.
*The reference case assumes that TZDs are not associated with an increased risk of CHF despite evidence from the RECORD trial. We explore the impact of this assumption through sensitivity analysis (see Table 12).

Total lifetime costs and QALYs, as well as incremental cost-effectiveness results from the reference case analysis, are presented in Table 10. The price of the lowest cost alternative was applied for each drug class. It was assumed that patients used the average DDD from the World Health Organization for each treatment. The doses for insulin products was obtained from a patient sample in British Columbia.[122] Among active treatments, sulfonylureas were associated with the lowest total lifetime costs ($40,669), while use of biphasic insulin incurred the highest lifetime costs ($52,367). There were very small differences in QALYs gained between active treatments (Range: 8.7682 with meglitinides to 8.7807 in TZDs). As such, cost-effectiveness estimates were largely driven by the difference in prices across treatments. Sulfonylureas were associated with the most favourable cost-effectiveness estimate, with an incremental cost of $12,757 per QALY gained relative to metformin monotherapy. Other active treatments were associated with unfavourable cost-effectiveness estimates (i.e., they were dominated or demonstrated very high ICURs) when compared with the next least costly treatment.

Table 10: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results From the Reference Case Analysis			
Treatment	**Average Costs Incurred Over Lifetime**	**Average QALYs Gained Over Lifetime**	**Incremental Cost-Effectiveness Results**
Metformin	$39,924	8.7194	N/A
Sulfonylurea	$40,669	8.7777	$12,757 per QALY (relative to metformin)
Meglitinides	$42,269	8.7682	Meglitinides dominated by sulfonylureas
Alpha-glucosidase inhibitors	$42,797	8.7800	$939,479 per QALY (relative to sulfonylureas)
TZD	$46,202	8.7807	$4,621,828 per QALY (relative to alpha-glucosidase inhibitors)
DPP-4 inhibitors	$47,191	8.7795	DPP-4 inhibitors dominated by TZD
Basal insulin	$47,348	8.7686	Basal insulin dominated by TZD
Biphasic insulin	$52,367	8.7761	Biphasic insulin dominated by TZD

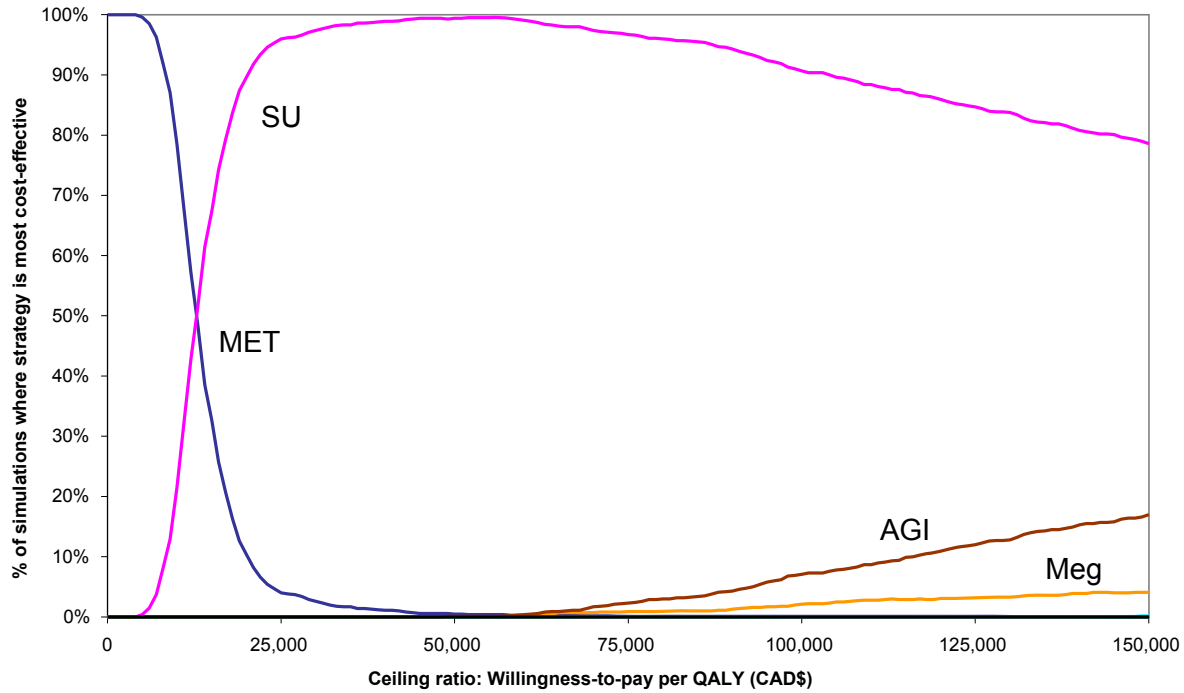
DPP-4 = dipeptidyl peptidase-4; N/A = not applicable; QALYs = quality-adjusted life-years; TZD = thiazolidinedione.

Net-benefit, rank, and mean rank across a range of willingness-to-pay thresholds are presented in Table 11. Sulfonylureas demonstrated the highest net benefit among active treatments and the lowest mean rank across all willingness-to-pay thresholds considered. The cost-effectiveness acceptability curve (Figure 3) shows that sulfonylureas had the highest probability of being most cost-effective beyond willingness-to-pay thresholds of ~$12,000 per QALY.

Table 11: Net-Benefit, Rank, and Mean Rank for Reference-Case Analysis Across a Range of Willingness-to-Pay Thresholds									
Treatment	**Net Monetary Benefit At:**			**Rank At:**			**Mean Rank At:**		
	20K per QALY	**50K per QALY**	**100K per QALY**	**20K per QALY**	**50K per QALY**	**100K per QALY**	**20K per QALY**	**50K per QALY**	**100K per QALY**
Metformin	$134,463	$396,045	$832,014	2	4	4	1.90	3.13	4.65
Sulfonylureas	$134,886	$398,218	$837,106	1	1	1	1.10	1.01	1.11
Meglitinides	$133,096	$396,143	$834,555	3	3	3	3.12	2.96	2.73
AGI	$132,803	$396,204	$835,204	4	2	2	3.88	2.90	2.07
TZD	$129,412	$392,835	$831,872	5	5	5	5.00	5.04	4.72
DPP-4 inhibitors	$128,398	$391,782	$830,755	6	6	6	6.00	6.07	5.75
Basal insulin	$128,024	$391,082	$829,513	7	7	7	7.00	6.89	6.74
Biphasic insulin	$123,156	$386,440	$825,246	8	8	8	8.00	8.00	8.00

AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; K = thousand; QALY = quality-adjusted life-year; TZDs = thiazolidinediones.

Figure 3: Cost-Effectiveness Acceptability Curve for the Reference Case Analysis



AGI= alpha-glucosidase inhibitor; CAD = Canadian; QALY = quality-adjusted life-year; SU = sulfonylurea; Meg = meglitinides; MET= metformin.

Results were robust to changes in clinical effect estimates, time to insulin initiation, price of treatments, dose of treatments, time horizon, discount rates, use of test strips, impact of hypoglycemia on HRQoL, event rates of hypoglycemia (overall and severe), inclusion of adverse events, and resource use and HRQoL impact of diabetes-related complications (Table 12). In all instances, sulfonylureas were the most cost-effective strategy if decision-makers were willing to pay $50,000 per QALY gained. More detailed results from sensitivity analyses are presented in Appendix 35.

Table 12: Summary of Results From Sensitivity Analyses*

Analysis	Met	SU	Meg	AGI	TZD	DPP-4	Basl	Bipl
Reference Case	**4**	**1**	**3**	**2**	**5**	**6**	**7**	**8**
Effect estimates from direct pairwise meta-analyses (rather than MTC meta-analysis)	4	1	2	3	5	6	7	8
Effect estimates from moderate to high dose nodes in dose-stratified MTC meta-analysis (rather than class-level MTC)	3	1	4	2	5	6	7	8
Effect estimates from titrated nodes in dose-stratified MTC meta-analysis (rather than class-level MTC)	4	1	2	3	5	6	7	8
Gliclazide price and gliclazide-effect estimates from agent-level MTC meta-analysis applied in SU arm (rather than glyburide price and class-level SU effects)	4	1	3	2	5	6	7	8

Table 12: Summary of Results From Sensitivity Analyses*								
Analysis	**Met**	**SU**	**Meg**	**AGI**	**TZD**	**DPP-4**	**Basl**	**Bipl**
Glimepiride price and glimepiride effect-estimates from agent-level MTC meta-analysis applied in SU arm (rather than glyburide price and class-level SU effects)	4	1	3	2	5	6	7	8
Glyburide price and glyburide effect-estimates from agent-level MTC meta-analysis applied in SU arm (rather than class-level SU effects)	4	1	3	2	5	6	7	8
All patients in model assumed to add-on insulin when A1C ≥ 9% (rather than stay on same therapy over lifetime)	6	1	2	3	4	7	5	8
Price of most-expensive agent within class applied (rather than lowest cost alternative)	4	1	3	4	7	5	6	8
Management cost for all long-term diabetes-related complications increased by 25%	4	1	3	2	5	6	7	8
Gliclazide price and class-effect estimates applied in SU arm (rather than glyburide price)	4	1	3	2	5	6	7	8
Glimepiride price and class-effect estimates applied in SU arm (rather than glyburide price)	4	1	3	2	5	6	7	8
Price of blood glucose test strips reduced by 50%	4	1	2	3	5	7	6	8
Price/dose of insulin products reduced by 10%	4	1	3	2	5	6	7	8
Insulin dose for basal human insulin and biphasic human insulin from RCTs[115-118] (rather than doses from BC dataset (Dr. Marshall Dahl, University of British Columbia: unpublished data, 2008))	**4**	**1**	**3**	**2**	**6**	**8**	**5**	**7**
No test strip use among non-users of insulin or insulin secretagogues	3	1	4	2	5	6	7	8
Assume improvement in HRQoL resulting from weight loss (NICE obesity guidelines[123] and Macran 2004[124])	3	1	4	6	5	2	7	8
Disutilities for diabetes-related complications obtained from group of patients with type 2 diabetes[125] (rather than general population[126])	4	1	3	2	5	6	7	8
Larger decrement in HRQoL associated with severe hypoglycemia (from Currie et al.[127] rather than NICE[15])	3	1	4	2	5	6	7	8
Larger decrement in HRQoL associated with mild to moderate hypoglycemia (from Levy et al.[128] rather than CADTH IA Report)	3	1	4	5	6	2	7	8
Higher baseline rate of mild to moderate hypoglycemia (Ferrannini et al.[68] rather	4	1	3	2	5	6	7	8

Table 12: Summary of Results From Sensitivity Analyses*								
Analysis	**Met**	**SU**	**Meg**	**AGI**	**TZD**	**DPP-4**	**Basl**	**Bipl**
than RECORD trial[77])								
Event rates for severe hypoglycemia derived from another large observational study (Bodmer et al.[108] rather than Leese et al[129])	3	1	2	5	4	6	7	8
No HRQoL decrement for fear of severe hypoglycemia (-0.00150274[130] rather than decrement of -0.01[15])	4	1	3	2	5	6	7	8
Increased risk of CHF and fractures in patients using TZDs (estimates from RECORD trial[77])	4	1	3	2	8	5	6	7
Model incorporates reduced HRQoL associated with increased gastrointestinal symptoms among patients using AGI[92,126,131]	3	1	2	5	4	6	7	8
Discount rate of 0% (rather than 5%)	4	1	3	2	5	6	7	8
Discount rate of 3% (rather than 5%)	4	1	3	2	5	6	7	8
Time horizon of 10 years (rather than 40 years)	2	1	3	4	5	6	7	8
Time horizon of 25 years (rather than 40 years)	2	1	3	4	5	6	7	8

A1C = glycosylated hemoglobin; AGI = alpha glucosidase inhibitor; Basl = basal insulin; BC = British Columbia; Bipl = biphasic insulin; CHF = congestive heart failure; DP-4 = dipeptidyl peptidase-4; HRQoL = health-related quality of life; IA = insulin analogue; Meg = meglitinides; Met = metformin; MTC = mixed treatment comparison; NICE = National Institute for Health and Clinical Excellence; OADs = oral antidiabetes drugs; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione.
*The treatment strategy with the highest net-benefit (i.e., most cost-effective) at a willingness-to-pay threshold of $50,000 per QALY is assigned a value of one. The treatment strategy with the lowest net-benefit (i.e., least cost-effective) at willingness-to-pay threshold of $50,000 per QALY is assigned a value of eight.

8 GRADE EVIDENCE PROFILES

Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating quality of evidence for each outcome of interest,[132] evidence quality ranged from "low" to "very low' for all outcomes assessed in this review (Table 13). The primary reasons for these ratings were methodological limitations (e.g., unclear allocation concealment, non–intention-to-treat analysis), imprecision of estimates, and indirectness. The population of interest in this review consisted of patients who were inadequately controlled with first-line metformin monotherapy and required a second-line drug. However, the study populations in most included trials consisted of patients who had received various antidiabetes drugs prior to use of metformin monotherapy. The evidence was therefore considered indirect across all outcomes as the applicability of study results to the population of interest may be somewhat limited. A1C is a surrogate outcome for clinically relevant complications of diabetes; hence, it received an additional deduction for indirectness. Evidence quality for long-term complications was reduced given that these events were very rarely reported and few trials were adequately powered to detect meaningful differences. Publication bias could not be formally assessed in this review due to a limited number of RCTs for each pairwise comparison.

Table 13: Summary of Quality of Evidence in GRADE Profiles		
Outcomes		**Overall Quality of Evidence**
Hemoglobin A1C		Very low
Hypoglycemia	Overall	Very low
	Severe	Low to very low
	Nocturnal	Low to very low
Body weight		Very low
Body mass index		Low to very low
Patient-reported outcomes	HRQoL generic	Very low
	HRQoL DM-specific	No evidence
	Patient satisfaction with DM tx	Very low
	Patient satisfaction with DM care	No evidence
Long-term complications	Congestive heart failure	Low to very low
	Ischemic heart disease	Low to very low
	Stroke/transient ischemic attack	Very low
	Peripheral vascular disease	Very low
	Retinopathy	No evidence
	Nephropathy	No evidence
	Neuropathy	Very low
	All-Cause Mortality	Low to very low
Other	HHNC	No evidence
	Severe adverse events	Low to very low
	Pancreatitis	No evidence
	Macular edema	Very low
	Upper extremity fractures	No evidence

DM = diabetes; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HHNC = hyperosmolar hyperglycemic nonketotic coma; HRQoL = health-related quality of life; mellitus; tx = treatment.

9 DISCUSSION

9.1 Summary of Main Findings

a) Summary of clinical findings

In this systematic review, 49 RCTs[52-107] were identified that reported the effects of eight classes of second-line therapies added to metformin in adults with type 2 diabetes inadequately controlled on metformin monotherapy. Whenever possible, MTC meta-analyses were conducted to facilitate a unified approach to comparing across classes that incorporated both direct and indirect evidence.

There was insufficient evidence regarding comparative efficacy of clinically important long-term complications of diabetes or mortality. All studies that did report diabetes-related complications, including the largest study,[77] found no statistically significant differences between any of the drug classes compared. Regarding glycemic control, MTC meta-analyses demonstrated that each of the eight drug classes resulted in statistically significant reductions in A1C relative to placebo; however, no statistically significant differences were found between any of the active treatments. Sulfonylureas, meglitinides, TZDs, and biphasic insulin were all associated with statistically significant increases in body weight relative to placebo. DPP-4 inhibitors and alpha-glucosidase inhibitors were found to be weight-neutral,

and GLP-1 analogues were associated with statistically significant reduced body weight. Both the insulins and insulin secretagogues demonstrated a statistically significant increase in overall hypoglycemia relative to placebo, whereas the TZDs, DPP-4 inhibitors, GLP-1 analogues, and alpha-glucosidase inhibitors did not. Events of severe hypoglycemia were very rare for all drug classes, including the insulins and insulin secretagogues.

b) Summary of economic findings

The prices of older oral antidiabetes drugs (e.g., sulfonylureas, meglitinides, alpha-glucosidase inhibitors) were found to be much lower than newer classes of drugs (e.g., TZDs, DPP4-inhibitors) and insulins (basal insulin, biphasic, or mixed insulin), even after consideration of the additional cost associated with increased use of test strips among patients using insulin and insulin secretagogues. The CADTH cost-effectiveness analysis, based on the results of the MTC meta-analysis, indicated that sulfonylureas were the most cost-effective second-line therapy in patients inadequately controlled on metformin monotherapy, despite higher rates of overall and severe hypoglycemia relative to other oral antidiabetes drugs. Favourable cost-effectiveness results for sulfonylureas are attributable to:

- low price relative to other classes of drugs, especially newer agents and insulin
- minimal differences in glycemic control between active drug classes
- low absolute risk of severe hypoglycemia requiring health care resource use in patients using sulfonylureas.

A multitude of sensitivity analyses were performed to examine robustness of results to variation in model inputs and assumptions. In all instances, sulfonylureas were the most cost-effective strategy, a result that was largely driven by the very low cost of these agents relative to other agents.

9.2 Strengths and Weaknesses of Review

This systematic review was conducted according to a protocol specified in advance, using standard approaches for identification of evidence, data abstraction, quality assessment, and analysis.[44] Unlike previous systematic reviews of therapies for type 2 diabetes,[133-135] this review included every drug class available for the treatment of type 2 diabetes after inadequate control with metformin alone. There were serious methodological limitations of the only previous review that has attempted to specifically address comparative efficacy after inadequate control with metformin.[4] In addition, previous reviews and meta-analyses have conducted pairwise comparisons rather than MTC meta-analyses to estimate the relative efficacy of active treatments. By conducting an MTC meta-analysis, both direct and indirect estimates of effect are captured and results are reported in a manner that is practical for health care professionals and decision-makers. Results from MTC meta-analyses were highly consistent with those from direct pairwise comparisons across all outcomes, a finding that further validates the analysis. A large number of sensitivity analyses and meta-regression analyses were reported to explore methodological heterogeneity. The consistency of these results, with the reference case analysis, demonstrate the robustness of the CADTH findings.

The cost-effectiveness analysis was conducted using the well-validated UKPDS Outcomes Model.[136] The ability of the UKPDS Outcomes Model to forecast long-term diabetes-related complications in patients with type 2 diabetes has been validated against published clinical and epidemiological studies. Cost-effectiveness results were found to be robust to variations in numerous model inputs and assumptions through detailed sensitivity analyses.

Despite the aforementioned strengths, limitations related to the available evidence warrant discussion. First, the population of interest for the systematic review consisted of patients inadequately controlled with first-line metformin monotherapy who required a second-line agent. However, most identified trials included patients who might have received various antidiabetes agents prior to the use of metformin monotherapy. The relative treatment effects we report are likely transferable to patients treated with initial metformin monotherapy, as the reference case results were robust to adjustment (through meta-regression) for differences across studies in duration of diabetes and baseline A1C. These are likely more important predictors of efficacy than treatment history per se.

Second, there was relatively little evidence for the effect of second-line agents on long-term diabetes-related complications. Hemoglobin A1C, a surrogate outcome, was the primary outcome reported in the majority of included RCTs. The validity of surrogate outcomes, particularly A1C, in forecasting cardiovascular end points in patients with type 2 diabetes has been debated.[137,138]

Third, inclusion of insulin in the MTC meta-analysis may be viewed with scepticism as it is not commonly considered in clinical practice as second-line therapy after metformin, and because trials of insulin may have enrolled patients with more advanced or severe disease than trials of oral agents. However, we believed it important to quantify the effects of insulin relative to other antihyperglycemic agents so that patients and clinicians can make informed choices regarding all available treatment options. Furthermore, scrutiny of subject characteristics revealed no major differences between insulin trials and trials of other agents. Meta-regression analyses to adjust for differences in baseline A1C and duration of diabetes produced results that were similar to the reference case; therefore, any differences in these parameters between insulin and non-insulin studies were of little consequence.
Fourth, we did not assess non-serious adverse effects that can impact the tolerability of antihyperglycemic agents. For example, acarbose is commonly associated with gastrointestinal adverse effects that may limit its usefulness.[92]

Certain limitations of the cost-effectiveness study are also noteworthy. The cost-effectiveness analysis is limited by the strength of the available clinical evidence. A majority of RCTs were assessed as being of "poor" methodological quality and were less than one year in duration. Longer, high-quality studies are required to evaluate the comparative efficacy of second-line agents over the long term in terms of clinically relevant end points. Because of the paucity of data on long-term outcomes, surrogate end points (e.g., A1C) were used to forecast the occurrence of long-term diabetes- related complications. The validity of surrogate outcomes, particularly A1C, in forecasting cardiovascular end points in patients with type 2 diabetes has been debated.[137,138] Moreover, the UKPDS Outcomes Model is based upon data from patients who used older classes of drugs (e.g, metformin, sulfonylureas, insulin). It is unclear whether or not equations derived from patients using older classes of drugs can be applied across newer classes of drugs (e.g., TZDs, DPP-4 inhibitors). One may therefore be more comfortable with estimates of long-term, diabetes-related complications for insulins than for estimates of diabetes-related complications in newer, less established agents.

The UKPDS model does not explicitly incorporate a number of morbidities (e.g., peripheral neuropathy, ulceration) related to diabetes.[136] Furthermore, some complications are represented as a single end point (e.g., blindness, end-stage renal disease) in the model rather than intermediate states (e.g., retinopathy, nephropathy) that may themselves be

associated with reduced health-related quality of life. Use of the UKPDS model may result in slight overestimation of incremental cost effectiveness ratios, as a reduced incidence of these outcomes and the resulting benefits for health-related quality of life and reduced treatment costs are not captured. However, the impact of this factor on cost-effectiveness estimates is likely modest, as the CADTH meta-analysis reported modest differences between active comparators in terms of glycemic control.

Modelling changes in treatment sequences over time is challenging with any model, including the UKPDS Outcomes Model.[136] There is uncertainty over which treatment patients will add on or switch to after inadequate control on second-line therapy. Furthermore, when patients use multiple treatments over time, it is difficult to assess whether benefits conferred are attributable to the treatment of interest or to subsequent treatments. Because of these considerations, it was assumed in the primary economic analysis that patients remained on their respective second-line therapy over their expected lifetime, without adding or switching to subsequent agents. This approach is not reflective of clinical practice given the progressive nature of diabetes; nevertheless, the effect of this assumption was tested through sensitivity analyses, whereby patients were assumed to either add on insulin as third-line therapy after a pre-defined period (A1C ≥ 9.0%). However, to conduct these sensitivity analyses within the UKPDS model, the weight and hypoglycemia inputs had to be front-loaded (i.e., applied in year 1) because, unlike A1C, these parameters could not be modified over time. Results from these sensitivity analyses should therefore be interpreted with caution as some elements of the results are not discounted appropriately. In future, if the UKPDS Outcomes Model is updated to enable more seamless integration of changes in treatment sequences over time, reanalysis of these sensitivity analyses may be warranted.

Modelling the increased risk of congestive heart failure in the UKPDS model is challenging as there is no risk multiplier. The risk of congestive heart failure was therefore applied in a sensitivity analysis whereby the risk was artificially increased among patients using TZDs by increasing the body weight by 30 kg among this patient population. However, the impact of this approach should be minimal; congestive heart failure is the only submodel in the UKPDS Outcomes Model that is influenced by BMI and therefore the only outcome that is affected by increased BMI.[136]

There is uncertainty regarding the disutility associated with insulin use,[139-141] weight gain,[123,124] and hypoglycemia.[142] Further research is needed that explores the impact of insulin use, weight gain, and hypoglycemia. In the absence of good data for these inputs, conservative estimates were used for the base case. Finally, the primary analysis does not include the potential risks of newer agents such as DPP-4 inhibitors which have largely unknown safety profiles due to limited clinical experience. The cost-effectiveness results for newer agents presented here may therefore prove to be optimistic should serious side effects be identified in the future.

9.3 Generalizability of Findings

The results of the CADTH MTC meta-analyses for A1C, hypoglycemia, and body weight are consistent with previous systematic reviews and meta-analyses that have assessed the comparative efficacy of antidiabetes drugs without a restricted focus on the second-line setting.[133,134,143,144] Also consistent with other systematic reviews on oral antidiabetes drugs,[133,145] a lack of conclusive evidence data was encountered regarding long-term, diabetes-related complications. CADTH results are similar to those of Monami et al. (2008),[4]

who also evaluated comparative efficacy after inadequate control with metformin monotherapy. In particular, both reviews found that treatment with insulin does not result in a greater reduction in A1C over other agents.

The available RCTs typically included patients with various treatment histories such that metformin monotherapy was not usually first-line therapy for most subjects. Two possible limitations arise from this aspect of the available evidence:

- Heterogeneity in treatment histories across studies may reduce the internal validity of MTC meta-analysis, since a high degree of trial similarity is required when conducting indirect comparisons.
- The applicability of findings to clinical practice may be compromised, as the population of interest consists of patients inadequately controlled with first-line metformin monotherapy.

Regarding the internal validity of the MTC meta-analysis, subject characteristics such as baseline A1C, duration of diabetes, and age were found to be quite similar across studies. The stability of MTC results when differences in the first two parameters were adjusted for through meta-regression, and the remarkable consistency between direct pairwise and MTC estimates, both attest to the validity of the MTC analysis. The consequences for external validity, if any, are more difficult to assess. It is conceivable that patients inadequately controlled after first-line metformin monotherapy have a shorter duration of diabetes than those enrolled in trials (mean diabetes duration was about 10 years); hence, drug efficacy may differ.

Insulins are infrequently used as a therapeutic option for patients with type 2 diabetes inadequately controlled on metformin alone, and are reserved instead for more advanced disease that is resistant to a number of oral agents. Nevertheless, CADTH included them in its analysis, as various guidelines, including those from the Canadian Diabetes Association,[1] cite insulin therapy as a possible option if normoglycemia is not achieved with metformin alone. The possibility that the insulin trials differed from trials of other agents in terms of the subjects enrolled was considered, particularly with respect to the extent of disease progression. Comparison of subject characteristics such as baseline A1C and duration of diabetes revealed a high degree of similarity; inclusion of insulin trials in the MTC meta-analysis was deemed appropriate. There was close alignment between the direct and indirect estimates involving insulins.

Within the limitations of modelling long-term outcomes using surrogate indicators, the results of CADTH's cost effectiveness analysis are generalizable to patients with type 2 diabetes in Canada. This reasoning is based on the use of Canadian cost data, Canadian data on utilization (such as of blood glucose test strips) and clinical characteristics of patients with diabetes, and validation of inputs by Canadian diabetes experts. One of the assumptions in CADTH's reference case cost-effectiveness analysis was that patients were assumed to remain on second-line therapy over the duration of their lives. Although such a strategy was required in order to ascribe the cost-effectiveness results to the second-line therapies in question, it is acknowledged that it does not reflect clinical practice whereby patients require changes in treatment regimen over time due to disease progression. Sensitivity analyses were performed in which the time horizon was varied and changed in treatment regimen over time. These results were similar to the reference case; hence, the assumption of static drug therapy over a lifetime does not limit the applicability of our results to clinical practice.

Long-term studies such as the UKPDS have convincingly demonstrated a progressive time-dependant increase in the A1C levels of patients with type 2 diabetes.[8,146] This gradual loss of glycemic control is primarily attributable to a corresponding decrease in pancreatic beta-cell function. There is speculation that newer agents such as the incretins (i.e., DPP-4 inhibitors and GLP-1 analogues) and TZDs can offer the benefit of prolonged glycemic control by slowing the decline of beta-cell function; however, the evidence is limited and inconclusive. A recent systematic-review of DPP-4 inhibitors reported that no definite conclusions can be made regarding their effects on beta-cell function.[143] In contrast, A Diabetes Outcome Progression Trial (ADOPT) reported a statistically significant difference in the number of patients experiencing monotherapy failure favouring TZDs over sulfonylureas and metformin.[147] The progressive nature of type 2 diabetes means that many patients will eventually require insulin therapy to maintain glycemic control. In this context, oral agents that are capable of longer periods of sustained glycemic control could delay the onset of insulin initiation, which may be desirable for some patients and could result in cost savings due to the expense of insulin therapy. Further long-terms studies are needed that explore differences in glycemic durability between agents over time, especially for the newer more expensive oral antidiabetes drugs.

Outcomes of interest for this review were determined a priori based on a systematic assessment by an expert review committee. Several outcomes such as fasting blood glucose, post-prandial blood glucose, and systolic blood pressure were excluded in this process. The primary reasons for excluding the additional glycemic control parameters were inconsistent methods of reporting and assessing (e.g., laboratory versus patient measured). Systolic blood pressure is an outcome that is rarely reported in clinical trials for diabetes and, therefore, is not particularly useful in assessing relative efficacy across the nine different classes of available agents. Nevertheless, the exclusion of these outcomes should be noted as a limitation of this systematic review.

9.4 Knowledge Gaps

Similar to Bolen et al. (2007)[133] and Selvin et al. (2008),[145] a general lack of evidence was encountered regarding the effect of second-line antidiabetes drugs on clinically important, long-term complications of diabetes (e.g., blindness, myocardial infarctions, end-stage renal disease). The length of follow-up in the majority of included studies was less than one year, and only a single study (comparing a sulfonylurea with a TZD) was adequately powered to detect differences in long-term complications.[77] Similarly, data on severe hypoglycemia requiring health care utilization were sparse. Longer-term studies of adequate duration are needed to establish if any of the available second-line agents demonstrate clinically significant advantages for preventing long-term, diabetes-related complications or severe hypoglycemia. Possible differences in quality of life between agents also require more rigourous study given the sparse reporting of this outcome and inconsistencies in the instruments used. Any effects on quality of life of hypoglycemia are of particular relevance given the increase in hypoglycemia risk associated with sulfonylureas. Finally, possible benefits of a particular class regarding delay in the onset of insulin initiation may be a desirable outcome because of the high costs of insulin and poor acceptance by some patients. No evidence was found regarding the relative durability of effect of second-line medications.

Each class of antidiabetes therapy is associated with risks that partially offset its benefits. Among the older agents, the insulins and insulin secretagogues carry an increased risk of hypoglycemia and weight gain. TZDs have been shown to increase the risk of congestive heart

failure, fractures, and weight gain.[77,147-152] The long-term safety profile of newer agents (e.g., DPP-4 inhibitors and GLP-1 analogues) is still largely unknown because of a lack of clinical experience in their use. In particular, the association between pancreatitis and incretin agents (i.e., DPP-4 inhibitors and GLP-1 analogues) requires further study in light of post-market reports of acute pancreatitis in patients treated with sitagliptin, and conflicting evidence from other sources.[153-155]

There was no evidence regarding the comparative efficacy of second-line agents in children with type 2 diabetes or the following subgroups of interest: First Nations people, ethnic minorities, ≥ 65 years of age, or seniors ≥ 75 years of age. There was also no evidence for patients requiring a switch to second-line therapy due to metformin intolerance or contraindication. Studies in First Nations and the elderly are especially pertinent given the high prevalence of diabetes in these populations.

10 CONCLUSION

In this systematic review and MTC meta-analysis of all available RCT evidence related to the second-line use of antidiabetes therapies after inadequate control with metformin monotherapy, all drug classes added to metformin achieved statistically signficant reductions in A1C. No statistically significant differences were observed between classes. Events of severe hypoglycemia were very rare for all agents; however, the insulins and insulin secretagogues were associated with a statistically significant increase in overall hypoglycemia relative to the other classes. Increased body weight was observed with the majority of second-line therapies, the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues. Further studies of adequate size and duration are required to assess comparative efficacy of long-term complications of diabetes, quality of life, and initiation of insulin.

Sulfonylureas were associated with the most favourable cost-effectiveness results. This finding was primarily driven by the low cost of sulfonylureas relative to other drugs, marginal differences in glycemic control and long-term complications between sulfonylureas and other agents, and the low absolute risk of severe hypoglycemic episodes requiring health care resource use.

Given the increasing prevalence of type 2 diabetes, the optimal use of antidiabetes therapies is of paramount importance. Although individualization of therapy is required for all patients, the addition of a sulfonylurea to metformin is as similarly efficacious as the addition of other antidiabetes drugs, and represents the most cost-effective use of health care resources. Widespread use of newer, more expensive antidiabetes drugs or insulin as second-line therapy in patients with type 2 diabetes would result in significant expenditure of funds without significant improvements in patient health. These funds could otherwise be used for more cost-effective interventions for the treatment of type 2 diabetes.

11 GLOSSARY

A1C: A glycosylated form of hemoglobin, formed by the attachment of sugars to the hemoglobin molecule when glucose levels are elevated. A1C levels increase with the average concentration of glucose in the blood.

Bayesian analysis: A statistical analysis conducted according to Bayesian principles. It involves incorporation of existing information regarding the likelihood of an event (i.e., "priors") to estimate the likelihood based on additional information (i.e., "posteriors").

Closed network: A type of network in which all elements are connected to one another.

Coherence: Presence of agreement between direct and indirect evidence. Coherence can be assessed by informally comparing estimated effects from the direct pairwise, head-to-head evidence and MTC evidence or by using available statistical techniques.

Confidence interval: The interval in which a population parameter lies, based on a random sample of the population. The most commonly reported confidence interval is the 95% confidence interval.

Congestive heart failure: A condition in which abnormal cardiac structure or function is responsible for the inability of the heart to fill with or eject blood at a rate to meet the requirements of the metabolizing tissues.

Convergence: The approach toward a fixed or equilibrium value. In WinBUGS, we can assess whether the estimates have converged using a variety of diagnostic tests (e.g., Gelman-Rubin diagnostic, examining Monte Carlo error, trace plots).

Cost-effectiveness acceptability curve: A graphical approach to conveying uncertainty of cost-effectiveness results. A cost-effectiveness acceptability curve presents the probability that a particular intervention is most cost-effective (e.g., highest net-monetary benefit) relative to all other treatments, across a range of decision-makers' willingness-to-pay thresholds.

Cost-utility analysis: A form of economic analysis that is widely used in pharmacoeconomics and health technology assessment.The purpose of cost-utility analysis is to estimate the ratio between the cost of a health technology and the benefit it produces in quality-adjusted life-years (QALYs) gained by the beneficiaries.

Credible interval: In Bayesian statistics, an interval in which the actual value of a parameter of interest lies with a defined probability.

Deviance information criterion (DIC): A measure of model comparison and accuracy. Smaller DIC values with a difference greater than two indicate a better-fitting model.

Effectiveness: The extent to which an intervention, procedure, regimen, or service produces the intended outcomes when deployed under routine ("real world") circumstances.

Fixed-effects meta-analysis: Methods of fixed effects meta-analysis are based on the mathematical assumption that a single common (or "fixed") effect underlies every study in the meta-analysis. In other words, if we were doing a meta-analysis of odds ratios, we would assume that every study is estimating the same odds ratio. Under this assumption, if every study were infinitely large, every study would yield an identical result. This is the same as assuming there is no (statistical) heterogeneity among the studies.

Gelman-Rubin diagnostic: The Gelman-Rubin diagnostic involves checking convergence of a chain using two or more samples generated in parallel. An R statistic is calculated and values of R close to 1 indicate convergence.

Health-related quality of life: A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values, and perceived levels of satisfaction and general well-being regarding either specific health conditions or life as a whole from the perspective of the individual.

Heterogeneity: Variation in treatment effects between RCTs within a pairwise contrast. Heterogeneity is likely to occur if trials have been undertaken on different patient groups, and/or different settings, and/or methodological differences in the design and conduct of the trials.

Hyperglycemia: A qualitative term used to describe blood glucose that is above the normal range.

Hypoglycemia: A qualitative term used to describe blood glucose that is below the normal range. Definitions vary across studies, although one or more of the following is usually required to define a hypoglycemic event: autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake, and/or a plasma glucose level below a specific value (threshold is usually between 3.4 mmol/L to 4.0 mmol/L).

Inconsistency: Variation in treatment effects between trials, between a pairwise contrast. A key assumption of MTC meta-analysis is that trials within and between pairwise contrasts are similar enough to combine. However, if trials have been compared in different conditions (e.g., populations, settings, and/or methodological differences), then this may lead to misleading results. Similar to traditional meta-analysis, it is important to consider whether or not the RCTs are similar enough to "pool."

Incretin agents: Therapeutics that promote glycemic control through potentiation of the incretin system. GLP-1 analogues and DPP-4 inhibitors are examples of incretin agents.

Ischemic heart disease: Heart disease, due to inadequate blood perfusion of the myocardium, which causes an imbalance between oxygen supply and demand.

Meta-analysis: Statistical synthesis of the results of individual studies that examine the same question to produce a single estimate of effect.

Mixed treatment comparison meta-analysis: A Bayesian approach that combines direct and indirect evidence in a single analysis, thus enabling simultaneous comparison of multiple treatment interventions.

Monte Carlo error: Measure the variation of the mean of the parameter of interest due to a simulation. If Monte Carlo errors are low (< 5%) in comparison to the corresponding posterior standard deviations, then the estimated posterior mean was estimated with high precision.

Nocturnal hypoglycemia: Hypoglycemic events that occur at night, usually from midnight to 6:00 a.m.

Non-informative or vague prior distributions: A distribution that will not influence the posterior distribution.

Overall hypoglycemia: Overall hypoglycemia is defined by either symptoms or signs of hypoglycemia and/or blood glucose less than 4 mmol/L.

Posterior distribution: A distribution that embodies both the prior distribution and the observed data information.

Posterior mean residual deviance: A method of accessing goodness of fit of a model. A model with adequate model fit would have a mean posterior residual deviance less than or equal to the number of unconstrained data points.

Prior distribution: A distribution that expresses information available to the researcher before any "data" are involved in the statistical analysis.

Quality-adjusted life-year: A health outcome measure that combines both quantity (mortality) and quality of life (morbidity). This measure enables comparisons across diseases and programs.

Random-effects meta-analysis: A random effects analysis makes the assumption that individual studies are estimating different treatment effects. In order to make some sense of the different effects they assume, they have a distribution with some central value and some degree of variability.

Randomized controlled trial: A prospective experimental study designed to test the efficacy of an intervention in which patients are randomly allocated to either a treatment group or to the control group.

Severe hypoglycemia: An event with characteristic hypoglycemic symptoms requiring the assistance of another person.

Standard deviation: A measure of the variability or spread of the data.

Systematic review: A summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Transient ischemic attack: Episodes of stroke symptoms that last only briefly.

Type 2 diabetes mellitus: Diabetes characterized by insulin resistance and varying degrees of insulin deficiency, especially as the diabetes progresses.

Utility: A utility is a quantitative expression for an individual's health state. The conventional utility scale has a utility of 0 for dead and 1 for perfect health. States worse than death can have negative values.

APPENDIX 1: LITERATURE SEARCH STRATEGY FOR ANTIDIABETES DRUGS USED IN THE MANAGEMENT OF TYPE 2 DIABETES

OVERVIEW	
Interface:	OVID
Databases:	BIOSIS Previews <1985 to 2009 Week 21>; Embase <1980 to 2009 Week 18>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 4, 2009>; Ovid MEDLINE(R) <1950 to April Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	May 4, 2009
Alerts:	Monthly search updates began June 2009 and ran to April 2010.
Study Types:	randomized controlled trials
Limits:	Publication years 1980-present English

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

Line No.	Searches
MEDLINE / BIOSIS	
1	Hypoglycemic drugs/
2	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
3	Thiazolidinediones/
4	(glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab.
5	(122320-73-4 or 155141-29-0).rn.
6	Dipeptidyl-Peptidase IV Inhibitors/
7	(Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.
8	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9	(dpp adj IV adj inhibitor*).ti,ab.
10	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
11	DPP-4 inhibitors.ti,ab.
12	dipeptidyl peptidase-4 inhibitors.ti,ab.
13	exp Sulfonylurea Compounds/
14	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
15	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
16	alpha-Glucosidases/ai [Antagonists & Inhibitors]
17	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
18	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
19	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
20	acarbose/ [mesh]
21	Lipase/ai [Antagonists & Inhibitors]
22	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
23	(96829-58-2 or 106650-56-0).rn.
24	(lipase adj inhibit*).ti,ab.
25	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
26	(135062-02-1 or 105816-04-4).rn.
27	Amyloid/
28	(Pramlintide or symlin).ti,ab.
29	(amylin adj analog*).ti,ab.
30	151126-32-8.rn.
31	exp insulin/
32	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
33	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.

Line No.	Searches
MEDLINE / BIOSIS	
34	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
35	(nph insulin or humulin or novolin).ti,ab.
36	11061-68-0.rn.
37	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
38	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
39	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
40	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
41	or/1-40
42	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
43	exp Diabetes Mellitus, Type 2/
44	(Mody or niddm or t2dm).ti,ab.
45	diabetes mellitus/
46	or/42-45
47	41 and 46
48	Randomized Controlled Trial.pt.
49	Randomized Controlled Trials as Topic/
50	Randomized Controlled Trial/
51	Randomization/
52	Random Allocation/
53	Double-Blind Method/
54	Double Blind Procedure/
55	Double-Blind Studies/
56	Single-Blind Method/
57	Single Blind Procedure/
58	Single-Blind Studies/
59	Placebos/
60	Placebo/
61	(random* or sham or placebo*).ti,ab,hw.
62	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
63	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
64	or/48-63
65	Metformin/
66	Metformin.ti,ab.
67	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
68	(657-24-9 or 1115-70-4).rn.
69	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
70	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
71	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or

Line No.	Searches
MEDLINE / BIOSIS	
	Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
72	or/65-71
73	47 and 64 and 72
74	limit 73 to yr="1980 -Current"
75	limit 74 to english language

Line No.	Searches
EMBASE	
1	*Diabetes Mellitus/
2	*Maturity Onset Diabetes Mellitus/
3	*Non Insulin Dependent Diabetes Mellitus/
4	*Lipoatrophic Diabetes Mellitus/
5	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
6	(Mody or niddm or t2dm).ti,ab.
7	or/1-6
8	Metformin/
9	Metformin.ti,ab.
10	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
11	(657-24-9 or 1115-70-4).rn.
12	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
13	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
14	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
15	or/8-14
16	Antidiabetic agent/
17	Oral Antidiabetic agent/
18	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
19	exp *glitazone derivative/
20	(glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab.
21	(122320-73-4 or 155141-29-0).rn.

Line No.	Searches
EMBASE	
22	exp *Dipeptidyl Peptidase IV Inhibitor/
23	(Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.
24	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
25	(dpp adj IV adj inhibitor*).ti,ab.
26	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
27	DPP-4 inhibitors.ti,ab.
28	dipeptidyl peptidase-4 inhibitors.ti,ab.
29	exp *sulfonylurea derivative/
30	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
31	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
32	exp *"Alpha Glucosidase Inhibitor"/
33	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
34	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
35	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
36	Lipase inhibitor/
37	*Tetrahydrolipstatin/
38	*Sibutramine/
39	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
40	(96829-58-2 or 106650-56-0).rn.
41	(lipase adj inhibit*).ti,ab.
42	*Meglitinide/
43	*Repaglinide/
44	*Nateglinide/
45	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
46	(135062-02-1 or 105816-04-4).rn.
47	*Pramlintide/
48	(Pramlintide or symlin).ti,ab.
49	(amylin adj analog*).ti,ab.
50	151126-32-8.rn.
51	*biphasic insulin/ or *human insulin/ or *insulin/ or *insulin aspart/ or *insulin detemir/ or *insulin glargine/ or *insulin glulisine/ or *insulin lispro/ or *isophane insulin/ or *long acting insulin/ or *monocomponent insulin/ or *neutral insulin/ or *recombinant human insulin/ or *synthetic insulin/
52	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
53	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
54	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.

Line No.	Searches
EMBASE	
55	(nph insulin or humulin or novolin).ti,ab.
56	11061-68-0.rn.
57	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
58	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
59	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
60	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
61	or/16-60
62	7 and 15 and 61
63	Randomized Controlled Trial.pt.
64	Randomized Controlled Trials as Topic/
65	Randomized Controlled Trial/
66	Randomization/
67	Random Allocation/
68	Double-Blind Method/
69	Double Blind Procedure/
70	Double-Blind Studies/
71	Single-Blind Method/
72	Single Blind Procedure/
73	Single-Blind Studies/
74	Placebos/
75	Placebo/
76	(random* or sham or placebo*).ti,ab,hw.
77	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
78	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
79	or/63-78
80	62 and 79
81	limit 80 to english language

Line No.	Searches
Cochrane Central Register of Controlled Trials	
1	Hypoglycemic drugs/
2	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
3	Thiazolidinediones/
4	(glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab.
5	[(122320-73-4 or 155141-29-0).rn.]
6	Dipeptidyl-Peptidase IV Inhibitors/
7	(Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.

Line No.	Searches
Cochrane Central Register of Controlled Trials	
8	[(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.]
9	(dpp adj IV adj inhibitor*).ti,ab.
10	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
11	DPP-4 inhibitors.ti,ab.
12	dipeptidyl peptidase-4 inhibitors.ti,ab.
13	exp Sulfonylurea Compounds/
14	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
15	[(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.]
16	alpha-Glucosidases/ai [Antagonists & Inhibitors]
17	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
18	[(56180-94-0 or 72432-03-2 or 83480-29-9).rn.]
19	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
20	acarbose/ [mesh]
21	Lipase/ai [Antagonists & Inhibitors]
22	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
23	[(96829-58-2 or 106650-56-0).rn.]
24	(lipase adj inhibit*).ti,ab.
25	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
26	[(135062-02-1 or 105816-04-4).rn.]
27	Amyloid/
28	(Pramlintide or symlin).ti,ab.
29	(amylin adj analog*).ti,ab.
30	[151126-32-8.rn.]
31	exp insulin/
32	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
33	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
34	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
35	(nph insulin or humulin or novolin).ti,ab.
36	[11061-68-0.rn.]
37	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
38	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
39	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
40	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
41	or/1-40
42	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend*

Line No.	Searches
Cochrane Central Register of Controlled Trials	
	or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
43	exp Diabetes Mellitus, Type 2/
44	(Mody or niddm or t2dm).ti,ab.
45	or/42-44
46	41 and 45
47	Metformin/
48	Metformin.ti,ab.
49	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
50	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
51	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
52	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
53	or/47-52
54	46 and 53
55	limit 54 to yr="1980 -Current"
56	limit 55 to randomized controlled trial

SUPPLEMENTAL SEARCH, SAXAGLIPTIN

OVERVIEW	
Interface:	OVID
Databases:	EMBASE <1980 to 2009 Week 31>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 5, 2009>; Ovid MEDLINE(R) <1950 to July Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	August 5, 2009
Alerts:	Monthly search updates began August 5, 2009 and ran to April 2010.
Study Types:	No limits
Limits:	Publication years 1980-present English

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

Line No.	Searches
MEDLINE	
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	or/1-2
4	from 3 keep 1-19
5	limit 4 to (english language and yr="1980 -Current")

Line No.	Searches
EMBASE	
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	saxagliptin/
4	or/1-3
5	limit 4 to english language

Line No.	Searches
Cochrane Central Register of Controlled Trials	
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	[(361442-04-811 or 945667-22-111).rn.]
3	saxagliptin/
4	or/1-3

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library, Issue 4	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types. Syntax adjusted for Cochrane Library databases.

Grey Literature and Hand-Searches

Dates for Search:	May 2009
Keywords:	metformin, second-line therapy, oral antidiabetes agents, antidiabetic agents, type 2 diabetes. All keywords associated with each included drug
Limits:	Publication years 1980 to present

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

Agencies and Institutes

Institute of Health Economics
http://www.ihe.ca/

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS)
http://www.aetmis.gouv.qc.ca/site/en_publications_liste.phtml
Canadian Agency for Drugs and Technologies in Health
http://www.cadth.ca/index.php/en/hta/reports-publications

Ontario Ministry of Health and Long Term Care: Health Technology Reviews
http://www.health.gov.on.ca/english/providers/program/ohtac/tech/techlist_mn.html

Institute for Clinical Evaluative Sciences (ICES): Ontario
http://www.ices.on.ca/

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/publications/publications_by_subject/

Therapeutics Initiative, Evidence-Based Drug Therapy: The University of British Columbia
http://www.ti.ubc.ca

Health Quality Council: Saskatchewan.
http://www.hqc.sk.ca/

INAHTA — International Network of Agencies for Health Technology Assessment
http://www.inahta.org

NPS RADAR — National Prescribing Service Ltd.
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

Centre for Reviews and Dissemination
www.york.ac.uk/inst/crd/crddatabases.htm

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA).
http://www.hta.ac.uk/

NICE NHS National Institute for Health and Clinical Excellence
http://www.nice.org.uk

AHRQ Agency for Healthcare Research and Quality
http://www.ahrq.gov/clinic/techix.htm

AHRQ: Effective Health Care Program, Reports
http://effectivehealthcare.ahrq.gov/index.cfm

ECRI Institute
http://www.ecri.org/

Evidence-Based Information on Prescription Drugs for Consumers and Health Care Providers
http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml#Prescription_Drugs

DERP Drug Effectiveness Review Project: Oregon Health & Science University
http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/products.cfm

United States Department of Veterans Affairs, Drug Class Reviews
http://www.pbm.va.gov/DrugClassReviews.aspx

Saskatoon Health Region, RxFiles
http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx

U.S. National Institutes of Health Clinical Trials Database
http://clinicaltrials.gov/ct/gui

Current Controlled Trials Ltd.
http://www.controlled-trials.com/

National Research Register. U.K. Dept. of Health
http://www.update-software.com/national/

World Health Organization — International Clinical Trials Registry Platform Search Portal
http://www.who.int/trialsearch

Conferences/Societies/Organizations/Associations

Canadian Diabetes Association (CDA)
http://www.diabetes.ca

European Society of Endocrinology (ESE)
http://www.euro-endo.org/

Society for Endocrinology
http://www.endocrinology.org/

European Society for Paediatric Endocrinology (ESPE)
http://www.eurospe.org/

The Endocrine Society (US)
http://www.endo-society.org/

American Association of Clinical Endocrinologists Annual Meeting and Clinical Congress (AACE)
http://www.aace.com

American Diabetes Association (ADA) Scientific Sessions
http://www.diabetes.org/home.jsp

EASD European Association for the Study of Diabetes
http://www.easd.org/

Association of British Clinical Diabetologists
www.diabetologists.org.uk

PCDE Primary Care Diabetes Europe
http://www.pcdeurope.org

International Diabetes Federation
www.idf.org/home

Search Engines

Google
http://www.google.ca/

APPENDIX 2: LIST OF INCLUDED STUDIES

AUTHOR	YEAR	CITATION
AHREN et al.[52]	2004	Diabetes Care 2004;27(12):2874-80
BARNETT et al.[53]	2007	Clin Ther 2007;29(11):2333-48
BERNE et al.[54]	2005	Diabet Med 2005;22(5):612-8
BLONDE et al.[55]	2009	Diabetes Obes Metab 2009;
BOLLI et al.[56]	2008	Diabetes Obes Metab 2008;10(1):82-90
BOLLI et al.[57]	2009	Diabetes Obes Metab 2009;11(6):589-95
BOSI et al.[58]	2007	Diabetes Care 2007;30(4):890-5
BRAZG et al.[59]	2007	Diabetes Obes Metab 2007;9(2):186-93
BUNCK et al.[60]	2009	Diabetes Care 2009;32(5):762-8
CHARBONNEL et al.[61]	2006	Diabetes Care 2006;29(12):2638-43
CHARBONNEL et al.[62]	2005	Diabetologia 2005;48(6):1093-104
CHARPENTIER et al.[63]	2001	Diabet Med 2001;18(10):828-34
DEFRONZO et al.[64]	2005	Diabetes Care 2005;28(5):1092-100
DEFRONZO et al.[65]	2009	Diabetes Care. 2009 Sep;32(9):1649-55
EINHORN et al.[66]	2000	Clin Ther 2000;22(12):1395-409
FEINGLOS et al.[67]	2005	Diabetes Res Clin Pract 2005;68(2):167-75
FERRANNINI et al.[68]	2009	Diabetes Obes Metab 2009;11(2):157-66
FONSECA et al.[69]	2000	JAMA 2000;283(13):1695-702
FRID et al.[106]	2008	Diabetes 2008;57(Suppl 1):A574-A575, JUN
GAO et al.[70]	2009	Diabetes Res Clin Pract 2009;83(1):69-76
GARBER et al.[71]	2006	Diabetes Obes Metab 2006;8(2):156-63
GOMEZ-PEREZ et al.[72]	2002	Diabetes Metab Res Rev 2002;18(2):127-34
GOODMAN et al.[73]	2009	Horm Metab Res 2009;
HALIMI et al.[74]	2000	Diabetes Res Clin Pract 2000;50(1):49-56
HAMANN et al.[75]	2008	Exp Clin Endocrinol Diabetes 2008;116(1):6-13
HOME et al.[76]	2007	Diabet Med 2007;24(6):626-34
HOME et al.[77]	2009	Lancet 2009;
KAKU[78]	2009	Curr Med Res Opin 2009;25(5):1111-9
KHANOLKAR et al.[79]	2008	Atherosclerosis 2008;197(2):718-24
KILO et al.[80]	2003	J Diabetes Complicat 2003;17(6):307-13
KVAPIL et al.[81]	2006	Diabetes Obes Metab 2006;8(1):39-48
LEITER et al.[82]	2005	Can J Diabetes 2005;29(4):384-92
MARRE et al.[83]	2002	Diabet Med 2002;19(8):673-80
MARRE et al.[84]	2002	Diabetes Obes Metab 2002;4(3):177-86
MATTHEWS et al.[85]	2005	Diabetes Metab Res Rev 2005;21(2):167-74
MCNULTY et al.[86]	2003	Diabetes Care 2003;26(1):125-31
MOSES et al.[87]	1999	Diabetes Care 1999;22(1):119-24
NAUCK et al.[88]	2007	Diabetes Obes Metab 2007;9(2):194-205
NAUCK et al.[89]	2006	Exp Clin Endocrinol Diabetes 2006;114(8):417-23
NAUCK et al.[90]	2009	Diabetes Care 2009;32(1):84-90
PAPATHANASSIOU et al.[91]	2009	Atherosclerosis 2009;205(1):221-6
PHILLIPS et al.[92]	2003	Diabetes Care 2003;26(2):269-73
POON et al.[93]	2005	Diabetes Technol Ther 2005;7(3):467-77
RASKIN et al.[94]	2007	Eur J Intern Med 2007;18(1):56-62
RAZ et al.[95]	2008	Curr Med Res Opin 2008;24(2):537-50

AUTHOR	YEAR	CITATION
RISTIC et al.[96]	2006	Diabet Med 2006;23(7):757-62
RISTIC et al.[97]	2007	Diabetes Obes Metab 2007;9(4):506-11
RODGER et al.[98]	1995	Clin Invest Med 1995;18(4):318-24
ROSENSTOCK et al.[99]	1998	Diabetes Care 1998;21(12):2050-5
SCHERNTHANER et al.[100]	2004	Eur J Clin Invest 2004;34(8):535-42
SCOTT et al.[101]	2008	Diabetes Obes Metab 2008;10(10):959-69
TRAUTMANN et al.[107]	2007	Diabetes 2007;56(Suppl 1):A45, JUN
UMPIERREZ et al.[102]	2006	Curr Med Res Opin 2006;22(4):751-9
VAN GAAL et al.[103]	2001	Diabetes Obes Metab 2001;3(5):326-31
VON BIBRA et al.[104]	2008	Diab Vasc Dis Res 2008;5(4):310-8
WOLEVER et al.[105]	1997	Int J Obes Relat Metab Disord 1997;21(9):756-63

APPENDIX 3: LIST OF EXCLUDED STUDIES

AUTHOR	YEAR	EXCLUSION REASON
ALBA et al.[156]	2008	Study design not of interest
BALU et al.[157]	2007	Study design not of interest
RASKIN et al.[109]	2005	Companion
USHAKOVA et al.[158]	2007	Population not of interest
SHARMA et al.[159]	2008	Population not of interest
OLSSON et al.[160]	2002	Population not of interest
BAO et al.[161]	2008	Study design not of interest
BOSI et al.[162]	2006	Duplicate
BOSI et al.[163]	2007	Population not of interest
BRANDLE et al.[164]	2008	Study design not of interest
BRODOWS et al.[165]	2008	Duplicate
BROOK et al.[166]	2008	Study design not of interest
MOSES[167]	1999	Decided not to include during data extraction
JOSSE[168]	1995	Duplicate
CHIASSON et al.[169]	1994	Duplicate
BUNCK et al.[170]	2008	Duplicate
BUNCK et al.[171]	2008	Outcome not of interest
BUNCK et al.[172]	2008	Outcome not of interest
CHAN et al.[173]	2007	Study design not of interest
CHAPMAN et al.[174]	2008	Study design not of interest
CHOE et al.[175]	2006	Population not of interest
CORNER et al.[176]	2008	Duplicate
DE MATTIA et al.[177]	2007	Study design not of interest
DEFRONZO et al.[178]	2007	Intervention not of interest
BETTERIDGE and VERGES[179]	2005	Duplicate data
AHREN et al.[180]	2005	Duplicate data
GARCIA-SORIA et al.[181]	2008	Intervention not of interest
GOKE et al.[182]	2007	Intervention not of interest
ROGER et al.[183]	1999	Intervention not of interest
O'BRIEN et al.[184]	2007	Intervention not of interest
TESTA et al.[185]	2004	Intervention not of interest
NAUCK et al.[186]	2009	Intervention not of interest
DEJAGER et al.[187]	2006	Population not of interest
DORNHORST et al.[188]	2006	Study design not of interest
EVANGELISTA et al.[189]	2007	Population not of interest
FOOS et al.[190]	2006	Study design not of interest
REBOUSSIN et al.[191]	2004	Not stated
DHINDSA et al.[192]	2001	Outcome not of interest
FORDAN et al.[193]	2008	Population not of interest
GALLWITZ[194]	2009	Study design not of interest
DORKHAN et al.[195]	2009	Population not of interest
D'ALESSIO et al.[196]	2009	Population not of interest
DEROSA et al.[197]	2009	Population not of interest
DORKHAN et al.[198]	2008	Population not of interest
COMASCHI et al.[199]	2008	Population not of interest

AUTHOR	YEAR	EXCLUSION REASON
PAPA et al.[200]	2008	Population not of interest
KLONOFF et al.[201]	2008	Population not of interest
CHIEN et al.[202]	2007	Population not of interest
KELLY et al.[203]	2007	Population not of interest
DEROSA et al.[204]	2007	Population not of interest
LABROUSSE-LHERMINE et al.[205]	2007	Population not of interest
PALA et al.[206]	2007	Population not of interest
COMASCHI et al.[207]	2007	Population not of interest
NELSON et al.[208]	2007	Population not of interest
HOME et al.[209]	2007	Population not of interest
DAVIES et al.[210]	2007	Population not of interest
DEROSA et al.[211]	2007	Population not of interest
KIM et al.[212]	2007	Population not of interest
REYNOLDS et al.[213]	2007	Population not of interest
JACOB et al.[214]	2007	Population not of interest
DEROSA et al.[215]	2007	Population not of interest
DEROSA et al.[216]	2005	Population not of interest
BAKRIS et al.[217]	2006	Population not of interest
KUO et al.[218]	2006	Population not of interest
DEROSA et al.[219]	2006	Population not of interest
DEROSA et al.[220]	2006	Population not of interest
BAILEY et al.[221]	2005	Population not of interest
DEROSA et al.[222]	2005	Population not of interest
FEINGLOS et al.[223]	2005	Population not of interest
WANG et al.[224]	2005	Population not of interest
DEROSA et al.[216]	2005	Population not of interest
DEROSA et al.[225]	2005	Population not of interest
DOUEK et al.[226]	2005	Population not of interest
MALONE et al.[227]	2005	Population not of interest
BRUNETTI et al.[228]	2004	Population not of interest
MALONE et al.[229]	2004	Population not of interest
DEROSA et al.[230]	2004	Population not of interest
GOUDSWAARD et al.[117]	2004	Population not of interest
RASKIN et al.[231]	2004	Population not of interest
JOVANOVIC et al.[232]	2004	Population not of interest
FURLONG et al.[233]	2003	Population not of interest
MALONE et al.[234]	2003	Population not of interest
ALTUNTAS et al.[235]	2003	Population not of interest
FINEMAN et al.[236]	2003	Population not of interest
RASKIN et al.[237]	2003	Population not of interest
MILES et al.[238]	2002	Population not of interest
GOKCEL et al.[239]	2001	Population not of interest
RASKIN et al.[240]	2000	Population not of interest
HOLMAN et al.[241]	1999	Population not of interest
LAM et al.[242]	1998	Population not of interest
SOTANIEMI et al.[243]	1990	Population not of interest
PEREZ et al.[244]	2006	Population not of interest

AUTHOR	YEAR	EXCLUSION REASON
GOTTSCHALK et al.[245]	2005	Population not of interest
BELCHER et al.[246]	2003	Population not of interest
MAHER et al.[247]	2003	Population not of interest
ALJABRI et al.[248]	2003	Population not of interest
DAVIS et al.[249]	2001	Population not of interest
HOLMAN et al.[250]	1996	Population not of interest
LI et al.[251]	2009	Population not of interest
GARBER et al.[252]	2009	Population not of interest
KING[253]	2009	Population not of interest
BRETZEL et al.[254]	2008	Population not of interest
ROSENSTOCK et al.[255]	2008	Population not of interest
HOULDEN et al.[256]	2007	Population not of interest
TAN et al.[257]	2007	Population not of interest
ERDMANN et al.[258]	2007	Population not of interest
ASCHNER et al.[259]	2006	Population not of interest
BOYE et al.[260]	2006	Population not of interest
JACOBER et al.[261]	2006	Population not of interest
HERMANSEN et al.[262]	2006	Population not of interest
DORMANDY et al.[263]	2005	Population not of interest
DEROSA et al.[264]	2004	Population not of interest
DROUIN et al.[265]	2004	Population not of interest
TAN et al.[266]	2004	Population not of interest
MENEILLY et al.[267]	2003	Population not of interest
ROSSKAMP[268]	2003	Population not of interest
MASSI et al.[269]	2003	Population not of interest
GOKE[270]	2002	Population not of interest
FINER et al.[271]	2000	Population not of interest
DEROSA et al.[272]	2009	Population not of interest
ZINMAN et al.[273]	2009	Population not of interest
GARBER et al.[274]	2006	Population not of interest
GARBER et al.[275]	2007	Study design not of interest
GARBER et al.[276]	2007	Study design not of interest
GARBER et al.[277]	2006	Study design not of interest
GOLDBERG et al.[278]	2007	Intervention not of interest
GOLUBOVIC et al.[279]	2006	Population not of interest
GOODMAN et al.[280]	2008	Duplicate
HALIMI et al.[281]	2006	Population not of interest
HEDDAEUS et al.[282]	2006	Study design not of interest
HENRIKSEN et al.[283]	2008	Population not of interest
HENRY et al.[284]	2006	Population not of interest
HERMAN et al.[285]	2007	Study design not of interest
HERMANSEN et al.[286]	2008	Population not of interest
HSIA[287]	2008	Population not of interest
ISRAEL et al.[288]	2008	Population not of interest
IVANYI et al.[289]	2007	Population not of interest
JENDLE et al.[290]	2008	Duplicate
JENDLE et al.[291]	2008	Study design not of interest

AUTHOR	YEAR	EXCLUSION REASON
KADOWAKI et al.[292]	2008	Population not of interest
KARASIK et al.[293]	2006	Duplicate
KAWAI et al.[294]	2007	Study design not of interest
KENDALL et al.[295]	2008	Study design not of interest
KIM et al.[296]	2006	Duplicate
KURASHVILI et al.[297]	2008	Population not of interest
KURASHVILI et al.[298]	2006	Duplicate
LUND et al.[299]	2006	Population not of interest
MAGGS et al.[300]	2006	Population not of interest
MARKOLF et al.[301]	2006	Study design not of interest
MATTHEWS et al.[302]	2008	Population not of interest
MATTHEWS et al.[303]	2008	Study design not of interest
MEININGER et al.[304]	2006	Common data pool
MENEGHINI et al.[305]	2006	Population not of interest
NAIKER et al.[306]	2006	Population not of interest
NATHWANI et al.[307]	2006	Population not of interest
NAUCK et al.[308]	2008	Common data pool
NAUCK et al.[309]	2006	Population not of interest
OSTER et al.[310]	2006	Population not of interest
OVALLE et al.[311]	2007	Study design not of interest
DEFRONZO et al.[312]	2008	Study design not of interest
SCHWARTZ et al.[313]	2008	Study design not of interest
BLONDE et al.[314]	2006	Study design not of interest
RATNER et al.[315]	2006	Study design not of interest
RAJAGOPALAN et al.[316]	2005	Study design not of interest
MALONE[317]	2005	Study design not of interest
GOLDSTEIN et al.[318]	2007	Study design not of interest
LOFTHOUSE[319]	2006	Study design not of interest
PAISEY et al.[320]	2008	Population not of interest
PEREZ et al.[244]	2006	Population not of interest
PFÜTZNER et al.[321]	2009	Intervention not of interest
PIRAGS[322]	2009	Study design not of interest
QI et al.[323]	2008	Population not of interest
RASKIN et al.[324]	2006	Population not of interest
RASKIN et al.[325]	2006	Population not of interest
RHEE et al.[326]	2008	Population not of interest
RIJZEWIJK et al.[327]	2008	Population not of interest
RIJZEWIJK et al.[328]	2008	Population not of interest
ROBBINS et al.[329]	2006	Population not of interest
ROBBINS et al.[330]	2006	Population not of interest
RUSSELL-JONES et al.[331]	2008	Study design not of interest
SCHEEN et al.[332]	2006	Intervention not of interest
SCHMITZ et al.[333]	2008	Study design not of interest
SCHOENDORF et al.[334]	2008	Study design not of interest
SCHÖNDORF et al.[335]	2008	Study design not of interest
SHARMA et al.[159]	2008	Population not of interest
SPANHEIMER et al.[336]	2006	Population not of interest

AUTHOR	YEAR	EXCLUSION REASON
TAN et al.[337]	2006	Population not of interest
TAN et al.[338]	2006	Population not of interest
TAYLOR et al.[339]	2006	Study design not of interest
VAAG et al.[340]	2008	Study design not of interest
VON BIBRA et al.[341]	2007	Population not of interest
WAJCBERG et al.[342]	2006	Study design not of interest
WANG[343]	2007	Study design not of interest
WILLIAMS-HERMAN et al.[344]	2008	Population not of interest
WILLIAMS-HERMAN and XU[345]	2007	Study design not of interest
WINTLE et al.[346]	2006	Study design not of interest
WOLFFENBUTTEL et al.[347]	2008	Population not of interest
WU et al.[348]	2008	Population not of interest
ZINMAN et al.[349]	2006	Population not of interest
ZINMAN et al.[350]	2006	Population not of interest
TANKOVA et al.[351]	2003	Study design not of interest
LIGTHELM[352]	2009	Study design not of interest

APPENDIX 4: STUDY CHARACTERISTICS OF INCLUDED STUDIES

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
*†Barnett et al., 2007[53]	Australia; Greece; Hungary; Italy; Mexico; Poland	Eli Lilly and Company	• Exenatide (10 µg b.i.d.) • Insulin Glargine q.d.	4	≥ 1500	3 months	A1C ≥ 7.1%	76
Blonde et al., 2009[55]	USA	Novartis	• Vildagliptin (100 mg); • Pioglitazone or Rosiglitazone)	3	1452 ± 500 (SD)‡	≥ 4 weeks	A1C 7%-10%	2,664
Bolli et al., 2009[57]	Multinational	Novartis	• Vildagliptin (100 mg/day) • Pioglitazone (30 mg/day)	12	2020 ± 453 (SD)‡	43 ± 3 (SD) months‡	A1C 7.5%-11%	576
Bosi et al., 2007[58]	Multinational	Novartis	• Vildagliptin (50 mg/day) • Vildagliptin (100 mg/day)	6	2101 ± 320 (SD)‡	18 ± 23 (SD) months‡	A1C > 7%	367
*Brazg et al., 2007[59]	USA	Merck & Co., Inc. Whitehouse Station, NJ	• Sitagliptin (50 mg b.i.d.); • Placebo	1	≥ 1500	≥ 6 weeks	A1C ≥ 6.5%; FPG 126-240 mg/dL	28
Bunck et al., 2009[60]	Sweden; Finland; Netherlands	Amylin Pharmaceuticals; Eli Lilly and Company	• Exenatide (5 µg b.i.d. for 4 weeks; 10 µg b.i.d.; titrated up to 20 µg b.i.d.); • Glargine (titrated)	12	2168 ± 773 (SD)‡	2 months	A1C ≥ 6.5%	69
†Charbonnel et al.,2005[62]	Multinational	Takeda Europe R&D and Eli Lilly and Company	• Pioglitazone (15-45 mg/day); • Gliclazide (80-320 mg/day)	24 months	≥ 50% of maximum recommended or maximum tolerated dose	≥ 3 months	A1C - 7.5%-11%	630
Charbonnel et al., 2006[61]	France; Israel;	Sponsored by Merck Research	• Sitagliptin (100 mg/day)	6	≥ 1500	Up to 19 weeks for those	A1C ≥ 7	701

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
	USA	Laboratories	• Placebo			patients not treated by metformin mono- therapy before the trial		
Charpentier et al., 2001[63]	France	Grant from Hoechst Marion Roussel	• Glimepiride (1mg-6 mg/day) • Glimepiride + Metformin • Metformin only	5	2550	≥ 4 weeks	FBG 7.8-13.9 mmol/L	372
Defronzo et al., 2005[64]	USA	Amylin pharmaceuticals; Eli Lilly and Company	• Exenatide (5 µg/b.i.d.) • Exenatide (10 µg/b.i.d.) • Placebo	7.5	≥ 1500	3 months	A1C - 7.1%-11%	226
DeFronzo et al., 2009[65]	USA; Brazil	Bristol-Myers Squibb; AstraZeneca	• Saxagliptin (2.5 mg) • Saxagliptin (5 mg) • Saxagliptin (10 mg) • Placebo	6	1,500-2,550	≥ 8 weeks	A1C > 7.0%	562
Einhorn et al., 2000[66]	USA	Takeda Pharmaceuticals North America	• Pioglitazone (30 mg/day) • Placebo	4.25	Stable dose	≥ 30 days	At the end of run-in with Met-mono therapy, A1C ≥ 8% were eligible	328
Feinglos et al., 2005[67]	USA	Pfizer Inc	• Glipizide (2.5 mg/day) • Placebo	4	1511 ‡	≥ 3 months	A1C 7.0%-8.5%	61
†Ferrannini et al., 2009[68]	Multinational	Novartis	• Vildagliptin (100 mg/day) • Glimepiride (mean 4.5 mg/day)	12	1897 ± 410 (SD)‡	≥ 4 weeks	A1C 6.5-8.5%	2789
Fonseca et al., 2000[69]	USA	SmithKline Beecham Pharmaceuticals	• Rosiglitazone (4 mg/day) • Rosiglitazone	6.5	≤ 2500	> 4 weeks	FPG >7.7 mmol/L	348

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
			(8 mg/day) • Metformin (2,500 mg/day)					
§Frid et al., 2008[106]	Sweden; Germany; Denmark; USA; UK	NR	• Glimepiride • Liraglutide 0.6 mg/day • Liraglutide 1.2 mg/day • Liraglutide 1.8 mg/day • Placebo	6.5	NR	NR	NR	NR
†Gao et al., 2009[70]	China; India; Korea; Taiwan	Amylin Pharmaceuticals; Eli Lilly and Company	• Exenatide (4 µg x 4 weeks; 10 µg for 12 weeks) • Placebo	4	1,000 – 3,000	≥ 3 months	A1C ≥ 7%	91
Garber et al., 2006[71]	USA	Authors from Bristol-Myers Squibb Pharmaceutical Research Insitiute, USA	• Glyburide (5 mg-10 mg) • Rosiglitazone (4 mg/day)	6	1821	≥ 8 weeks	A1C > 7.0%	318
Gomez-Perez et al., 2002[72]	Mexico	NR; Three out of 7 authors are from GlaxoSmithKline	• Rosiglitazone (4 mg/day) • Rosiglitazone (8 mg/day) • Placebo	6	2,500 during 4-week titration phase	4-week titration phase	FPG ≥ 140 mg/dL	116
Goodman et al., 2009[73]	Multinational	Novartis	• Vildagliptin (100 mg/day AM) • Vildagliptin (100 mg/day PM) • Placebo	6	1,896 ± 391 (SD)‡	≥ 3 months	A1C ≥ 7.5%	370
Halimi et al., 2000[74]	France	Authors from Bayer	• Acarbose (1,700 or 2,550 mg/day) • Placebo	6	1,770-2,550	≥ 2 months	A1C > 7%	152

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
†Hamann et al., 2008[75]	Multinational	Authors from GlaxoSmithKline	• Sulfonylurea (Glyburide or Gliclazide 80 mg/day) • Rosiglitazone (4 mg/day) • Both arms titrated drugs as study progressed	12	1,500-2,000 (forced titration)	≥ 8 weeks prior to screening, then 4 weeks forced titration	A1C > 7%	596
†Home et al., 2009[77]	UK; Denmark; Spain; German; France	GlaxoSmithKline plc, United Kingdom	• Sulfonylurea (titrated) • Rosiglitazone (titrated)	66	≥1500	≥ 8 weeks	A1C > 7%	2222
Kaku et al., 2009[78]	Japan	Takeda Pharmaceutical Company, Ltd.	• Pioglitazone (titrated from 15 mg-30 mg/day for 12 and further 16 weeks, respectively) • Placebo	7	500 or 750	3 months	A1C ≥ 6.5%	169
Khanolkar et al., 2008[79]	United Kingdom	NR	• Rosiglitazone (4 mg/day) • Gliclazide (80 mg/day)	6	≤ 2,000	> 4 weeks	A1C > 6.5%	25
Kilo et al., 2003[80]	USA	Novo Nordisk Pharmaceuticals	• Biphasic insulin aspart (1x daily 10 min. before dinner) • Biphasic human insulin (1x daily 30 min. before dinner) • NPH insulin (at 10 p.m.)	3	500-2500	4 weeks	FBG 90-126 mg/dL	140
Kvapil et al., 2006[81]	Multinational	NR	• Biphasic insulin aspart (b.i.d.) • Biphasic insulin	4	1,660 (range 500-3,500)	≥ 1 month	A1C > 7%	230

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
			aspart (b.i.d.) with metformin • Glyburide (titrated)					
†Leiter et al., 2005[82]	Canada	GlaxoSmithKline	• Rosiglitazone (4mg-8 mg/day) • Metformin	8	≤1,700	≥3 months	FPG > 7.0 mmol/L	236
Marre et al., 2002[83]	Multinational	Merck Lipha	• Glyburide (5 mg) • Glyburide (2.5 mg) + metformin • Glyburide (5 mg) + metformin • metformin	4	≥ 1,500	≥ 2 months	FPG ≥ 7 mmol/L	411
Marre et al., 2002[84]	Multinational	Novartis AG	• Nateglinide 60 mg a.c. • Nateglinide 120 mg a.c. • Placebo a.c.	6	2,000	≥ 4 weeks	A1C ≥ 6.8%	467
Matthews et al., 2005[85]	Multinational	Takeda Euro R&D; Eli Lilly and Co.	• Pioglitazone (15 mg q.d.) • Gliclazide (80 mg q.d.)	12	50% of maximum recommended or maximum tolerated dose	≥ 3 months	A1C ≥ 7.5%	630
McNulty et al., 2003[86]	Multinational	Abbott Laboratories	• Sibutramine (15 mg/day) • Sibutramine (20 mg/day) • Placebo	12	1,250 (mean)	0.6 years (range: 0.1-2.9)	Fasting serum glucose > 7.0 mmol/L	194
Moses et al., 1999[87]	Australia	Novo Nordisk Pharmaceuticals	• Rapaglinide (0.5 mg-4.0 mg titration) • Placebo	4.5	1,800 ± 700 (SD)	4 ± 3 (SD) years ‡	A1C > 7.1%	27
† Nauck et al., 2007[88]	Germany; USA	Merck & Co., USA. One person	• Sitagliptin (100 mg/day)	12	≥ 1,500	≥ 2 weeks	A1C ≥ 6.5% and ≤ 10%	1,172

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
		from the Merck & Co. contributed in writing the manuscript	• Glipizide (5 mg/day)					
†Nauck et al., 2009[90]	Multinational	Novo Nordisk	• Glimepiride (4 mg/day) + placebo (injection) • Placebo (tablets) + placebo (injection) • Liraglutide (either 0.6, 1.2 or 1.8 mg/day injections)	6.5	1,500-2,000 (forced titration)	≥3 weeks (forced titration)	A1C > 7%	366
Nauck et al., 2006[89]	German; Poland; Demark	Novo Nordik A/S	• Liraglutide (0.5 mg–2 mg) • Metformin • Liraglutide (0.5 mg–2 mg q.d.) • Metformin • Glimepiride (2 mg-4 mg)	1.25	≤ 2,000	≥ 2 weeks. (overall, 2 weeks to ≥ 3 months. Metformin monotherapy run- in for 2 weeks for those patients with multiple OADs at screening)	FPG ≥ 9 mmol/L	36
Papathanassiou et al., 2009[91]	Greece	University of Ioannina	• Glimepiride (4 mg q.d.) • Pioglitazone (30 mg q.d.)	6	NR	≥ 6 months of metformin	A1C > 6.5%	14
Phillips et al., 2003[92]	Australia; New Zealand	Bayer AG	• Acarbose (titrated up to 100 mg b.i.d.) • Placebo	6	1,700 (500-4,000) (min-max)	≥ 3 months	A1C > 7%	83
†Poon et al., 2005[93]	USA	Amylin Pharmaceuticals	• Exenatide (2.5 µg b.i.d.) • Exenatide	1	Unspecified	NR	A1C ≥ 6.8%	71

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
			(5.0 µg b.i.d.) • Exenatide (7.5 µg b.i.d.) • Exenatide (10.0 µg b.i.d.) • Placebo					
Raskin et al., 2007[94]	USA	Novo Nordisk	• BiAsp 30 (titrated) • Insulin glargine (titrated)	7	1,500-2,550 during 4 week run-in period	4 week run-in period	A1C > 8.0%	157
Raz et al., 2008[95]	Israel; USA	Merck & Co., Inc. Whitehouse Station, NJ, USA	• Sitagliptin (100 mg/day) • Placebo	7.5	1,500	1.5 months	A1C ≥ 8% ≤ 11%; FBG ≥ 7.2mmol/L ≤ 15.6 mmol/L	190
Ristic et al., 2006[96]	Multinational	Novartis Pharma	• Gliclazide (80 mg-240 mg/day) • Nateglinide (60 mg-180 mg TID)	6	1,000	≥ 3 months	A1C 6.8-9.0%	262
Ristic et al., 2007[97]	Switzerland	Norvatis, Basel	• Gliclazide (80, 160, 240 mg/day) • Nateglinide (60, 120, 180 mg a.c.)	12	1,000	≥ 2 months	A1C > 6.8%	NR
†Rodger et al., 1995[98]	Canada	Bayer Canada, Inc.	• Acarbose (titrated from 50 mg – 200 mg a.c.) • Placebo	12	NR	NR	A1C > 7%	83
Rosenstock et al., 1998[99]	USA	Bayer Corporation	• Acarbose (25-50 mg t.i.d.); • Placebo	6	2,000-2,500	≥ 56 days	A1C > 7%	84
†Schernthaner et al., 2004[100]	10 European countries	Grant from Servier, France	• Gliclazide MR 30 mg -120 mg daily); • Glimepiride (1 mg -6 mg daily) alone or	6.75	NR	≥ 3 months(for metformin use but not specific to stable metformin therapy)	A1C 6.9%-11.5%	219

Author, Year	Country	Sponsor	Interventions/ Comparators (in combination with Metformin)	Treatment Duration (months)	Metformin Monotherapy Prior to Studies		Criteria for Defining Metformin Monotherapy Failure	Sample Size
					Dose at Baseline (mg/day)	Duration with Stable Dose		
			in combination with current treatment					
Scott et al., 2008[101]	Multinational	Merck & Co.	• Rosiglitazone (8 mg/day); • Sitagliptin (100 mg/day); • Placebo	4.5	≥ 1,500	≥ 10 weeks	A1C > 7%	273
*†[5]Trautmann et al., 2007[107]	USA; Australia; United Kingdom	NR	• Exenatide (5 µg b.i.d. x 4 weeks, then 10 µg b.i.d. x 12 weeks); • Glargine	4	NR	NR	NR	NR
Umpierrez et al., 2006[102]	USA	Sanofi-aventis	• Glimepiride (2 mg-8 mg/day) • Pioglitazone (30 mg-45 mg/day)	6	1,000-2,500 or 500-2,000 for extended release	2 months	Inadequate control on metformin, A1C ≥ 7.5%; FBG ≥ 7 mmol/L	210
Van Gaal et al., 2001[103]	Belgium; Israel; Austria; Czech Republic	Bayer and Sanofi-Synthélabo	• Miglitol (4 weeks x 25 mg t.i.d.; 12 weeks x 50 mg t.i.d.; 16 weeks x 100 mg t.i.d.) • Placebo	8	Unspecified stable dose	> 3 months	A1C ≥ 7.5	153
*Von Bibra et al., 2008[104]	Germany	NR	• Glimepiride (3 mg/day) • Rosiglitazone (8 mg/day)	4	1,600 ± 500 (SD)	NR	A1C 6.5-9.0%	13
†Wolever et al., 1997[105]	Canada	Bayer Canada, Inc.	• Acarbose (50 mg-200 mg t.i.d.) • Placebo	12	NR	NR	A1C > 7%	83

A1C = glycosylated haemoglobin; a.c.= taken with meals; b.i.d. = twice daily; FBG = fasting blood glucose; FPG = fasting plasma glucose; min = minutes; NR = not reported; OADs = oral antidiabetes drugs; q.d. = once daily; SD = standard deviation; t.i.d. = three times daily. * Crossover study; † Subgroup data; ‡ Pooled values for all treatment arms; § Abstract

APPENDIX 5: PATIENT CHARACTERISTICS OF INCLUDED STUDIES

Author, Year	Avg. Age (Years)	% Male	Avg. Duration of DM (Years)	Avg. Baseline A1C (%)
*†Barnett et al., 2007[53]	54.9	NA	7.46	8.95
Blonde et al., 2009[55]	55.6	52	5.13	7.98
Bolli et al., 2009[57]	56.6	63	6.4	8.40
Bosi et al., 2007[58]	54.2	43	6.26	8.35
* Brazg et al., 2007[59]	55.9	35.7	6.6	7.7
Bunck et al., 2009[60]	58.4	65	4.89	7.5
†Charbonnel et al., 2005[62]	56.5	50.0	5.65	8.62
Charbonnel et al., 2006[61]	54.5	57	6.2	7.98
Charpentier, 2001[63]	56.2	59	5.76	6.55
DeFronzo et al., 2005[64]	53.0	60	5.9	8.23
DeFronzo et al., 2009[65]	54.6	50	6.53	8.08
Einhorn et al., 2000[66]	55.6	57	NR	9.81
Feinglos et al., 2005[67]	58.0	47	5.6	NA
†Ferrannini et al., 2009[68]	57.5	53	5.73	7.31
Fonseca et al., 2000[69]	58.2	68	7.69	8.8
‡ Frid et al., 2008[106]	56.7	NR	8	8.38
† Gao et al., 2009[70]	54.5	NR	8	8.3
Garber et al., 2006[71]	56.0	60	5.5	8.4
Gomez-Perez et al., 2002[72]	53.1	24	10.29	10
Goodman et al., 2009[73]	54.8	58	NR	8.57
Halimi et al., 2000[74]	55.0	55	9.25	8.55
†Hamann et al., 2008[75]	58.9	NR	6.35	8
†Home et al., 2007[76]	57.1	51	6.2	7.8
†Home et al., 2009[77]	57.1	51	6.2	7.8
Kaku et al., 2009[78]	52.5	61	5.06	7.56
Khanolkar et al., 2008[79]	57.5	NR	NR	NA
Kilo et al., 2003[80]	55.9	52	9.83	9.43
Kvapil et al., 2006[81]	57.2	50	7.39	9.35
†Leiter et al., 2005[82]	58.7	62	5.43	7.5
Marre et al., 2002[83]	58.7	52	6.15	7.87

Author, Year	Avg. Age (Years)	% Male	Avg. Duration of DM (Years)	Avg. Baseline A1C (%)
Marre et al., 2002[84]	57.2	58	6.84	8.14
Matthews et al., 2005[85]	56.5	NR	5.65	8.62
McNulty et al., 2003[86]	49.3	44	2	NA
Moses et al., 1999[87]	57.5	65	6.95	8.45
†Nauck et al., 2007[88]	56.7	62	6.35	7.5
†Nauck et al., 2009[90]	56.7	57	7.56	8.38
Nauck et al., 2006[89]	57.2	57	8.23	9.43
Papathanassiou et al., 2009[91]	63.1	21	5.3	7.55
Phillips et al., 2003[92]	60.5	74	5.7	7.91
†Poon et al., 2005[93]	53.7	46	4	7.47
Raskin et al., 2007[94]	51.9	53	9.2	9.9
Raz et al., 2008[95]	54.8	46	7.86	9.2
Ristic et al., 2006[96]	61.8	NR	6.93	NA
Ristic et al., 2007[97]	61.8	53	6.93	7.6
†Rodger et al., 1995[98]	57.4	64	8.8	7.85
Rosenstock et al., 1998[99]	56.6	54	7.5	8.32
†Schernthaner et al., 2004[100]	NR	NR	NR	NA
Scott et al., 2008[101]	55.1	59	4.97	7.72
*†‡Trautmann et al., 2007[107]	54.9	NR	7.46	8.95
Umpierrez et al., 2006[102]	53.7	55	5.42	8.35
Van Gaal et al., 2001[103]	57.9	45	NR	8.45
* Von Bibra et al., 2008[104]	59.0	67	3	6.8
†Wolever et al., 1997[105]	57.4	NR	8.8	7.85

* Crossover study
† Subgroup data
‡ Abstract

APPENDIX 6: QUALITY ASSESSMENT OF STUDIES

Study	Appropriate and Clearly Focused Question	Randomized Assignment	Adequate Concealment	Blinding of Subjects and Investigators	Groups are Similar at Baseline	Only Difference Between Groups is Treatment Under Investigation	Standard, Valid and Reliable Measurement of Outcome(S)	Drop Out Rate is Acceptable (<20%) And is Comparable Between the Groups	ITT Analysis Performed	Comparable Results for Multi Study Sites	Overall QA
Ahren et al.[52]	AA	NR	NAd	NR	AA	AA	AA	No	WC	NAd	Good(+)
Barnett et al.[53]	AA	AA	AA	NAd	AA	AA	AA	Yes	AA	NAd	Good(+)
Berne et al.[54]	AA	AA	NAd	AA	PA	AA	WC	Yes	AA	NAd	Good(+)
Blonde et al.[55]	WC	WC	AA	NAd	WC	PA	AA	Yes	PA	NAd	Poor (-)
Bolli et al.[56]	AA	NR	NAd	NR	AA	AA	AA	Yes	NAd	NAd	Poor (-)
Bolli et al.[57]	WC	WC	WC	AA	WC	WC	WC	No	PA	NAd	Poor (-)
Bosi et al.[58]	AA	NR	NAd	NR	AA	AA	AA	No	PA	NAd	Poor (-)
Brazg et al.[59]	AA	NR	NAd	AA	PA	AA	PA	Yes	NAd	NAd	Poor (-)
Bunck et al.[60]	WC	AA	NAd	NAd	AA	AA	AA	Yes	WC	NAd	Poor (-)
Charbonnel et al.[61]	AA	NR	NAd	AA	AA	PA	AA	No	PA	NAd	Poor (-)
Charbonnel et al.[62]	AA	NR	NAd	AA	AA	AA	AA	No	AA	NAd	Good(+)
Charpentier et al.[63]	AA	AA	AA	AA	AA	AA	AA	Yes	AA	NAd	Good(+)
DeFronzo et al.[65]	WC	WC	WC	AA	AA	AA	PA	No	AA	NAd	Good(+)
DeFronzo et al.[64]	AA	NR	NAd	AA	AA	AA	AA	Yes	WC	NAd	Good(+)
Einhorn et al.[66]	WC	NR	NAd	NR	AA	WC	WC	No	AA	NAd	Poor (-)
Feinglos et al.[67]	AA	NR	NAd	NR	AA	WC	WC	Yes	WC	NAd	Poor (-)
Ferrannini[68]	WC	NR	NAd	AA	WC	PA	WC	Yes	PA	NAd	Poor (-)
Fonseca[69]	WC	WC	AA	AA	AA	WC	WC	Yes	AA	NAd	Good(+)
Gao et al.[70]	AA	AA	NAd	AA	AA	AA	PA	No	PA	NR	Poor (-)
Garber et al.[71]	AA	NR	NAd	WC	WC	WC	AA	Yes	PA	NAd	Good(+)
Gomez-Perez et al.[72]	AA	NR	NAd	AA	AA	WC	WC	No	PA	NAd	Poor (-)
Goodman et al.[73]	AA	NR	NAd	NR	AA	AA	AA	No	PA	NAd	Poor (-)
Halimi et al.[74]	AA	NR	NAd	AA	AA	WC	WC	No	PA	NAd	Poor (-)
Hamann et al.[75]	AA	AA	AA	NR	AA	AA	AA	No	AA	NAd	Good(+)
Home et al.[77]	AA	WC	AA	NAd	AA	PA	AA	NR	AA	NAd	Poor (-)
Home et al.[76]	AA	WC	AA	NAd	AA	PA	AA	No	AA	NAd	Poor (-)
Kaku[78]	AA	NR	NAd	AA	AA	WC	AA	Yes	AA	NAd	Poor (-)

Study	Appropriate and Clearly Focused Question	Randomized Assignment	Adequate Concealment	Blinding of Subjects and Investigators	Groups are Similar at Baseline	Only Difference Between Groups is Treatment Under Investigation	Standard, Valid and Reliable Measurement of Outcome(S)	Drop Out Rate is Acceptable (<20%) And is Comparable Between the Groups	ITT Analysis Performed	Comparable Results for Multi Study Sites	Overall QA
Khanolkar et al.[79]	AA	NR	NAd	AA	AA	AA	PA	Yes	AA	NAd	Good(+)
Kilo et al.[80]	AA	NR	NAd	NAd	AA	AA	AA	Yes	PA	NAd	Poor (-)
Kvapil et al.[81]	AA	AA	AA	NAd	AA	AA	AA	Yes	PA	NAd	Good(+)
Leiter et al.[82]	AA	NR	NAd	NAd	AA	AA	PA	Yes	PA	NAd	Poor (-)
Marre et al.[83]	AA	NR	NAd	AA	AA	AA	AA	Yes	WC	NAd	Good(+)
Marre et al.[84]	AA	WC	AA	WC	WC	WC	WC	Yes	WC	NAd	Good(+)
Matthews et al.[85]	AA	NR	NAd	AA	AA	PA	NR	Yes	PA	NAd	Poor (-)
McNulty et al.[86]	AA	NR	NAd	AA	AA	PA	PA	No	AA	NAd	Poor (-)
Moses et al.[87]	AA	NR	NAd	AA	AA	AA	AA	No	AA	NAd	Good(+)
Nauck et al.[88]	WC	NR	NAd	AA	WC	WC	AA	No	PA	NAd	Poor (-)
Nauck et al.[89]	AA	NR	NAd	NAd	AA	AA	AA	No	AA	NAd	Poor (-)
Nauck et al.[90]	AA	AA	AA	AA	PA	PA	AA	No	PA	NAd	Poor (-)
Papathanassiou et al.[91]	AA	PA	NAd	NAd	WC	AA	AA	Yes	WC	N/A	Poor (-)
Phillips et al.[92]	AA	NR	NAd	WC	WC	WC	WC	Yes	AA	NAd	Good(+)
Poon et al.[93]	WC	NR	NAd	WC	AA	WC	PA	Yes	AA	NAd	Poor (-)
Raskin[109]	WC	NR	AA	NAd	WC	WC	AA	No	WC	NAd	Poor (-)
Raskin et al.[94]	WC	NR	AA	NAd	AA	WC	AA	No	WC	NAd	Poor (-)
Raz et al.[95]	WC	WC	NAd	NR	AA	PA	AA	Yes	AA	NAd	Poor (-)
Ristic et al.[96]	WC	WC	AA	WC	WC	AA	AA	Yes	AA	NAd	Good(+)
Ristic et al.[97]	WC	WC	WC	WC	AA	WC	WC	No	AA	NAd	Good(+)
Rodger et al.[98]	AA	NR	NAd	AA	PA	AA	PA	NR	PA	NAd	Good(+)
Rosenstock et al.[99]	AA	NR	NAd	AA	WC	WC	WC	Yes	PA	NAd	Poor (-)
Schernthaner et al.[100]	AA	AA	NAd	WC	NAd	WC	WC	Yes	PA	NAd	Poor (-)
Scott et al.[101]	AA	NR	NAd	AA	AA	AA	AA	Yes	PA	NAd	Poor (-)
Umpierrez et al.[102]	WC	NR	NAd	NAd	AA	AA	AA	Yes	AA	NAd	Poor (-)
Van Gaal et al.[103]	WC	AA	NAd	AA	WC	AA	AA	No	AA	NAd	Good(+)
Von Bibra et al.[104]	WC	NR	NAd	AA	PA	AA	WC	Yes	PA	NAp	Poor (-)
Wolever et al.[105]	AA	NR	NAd	AA	PA	AA	AA	NR	PA	NAd	Poor (-)

AA = adequately addressed; NAd = not addressed; NAp = not applicable; NR = not reported; PA = poorly addressed; QA = quality assessment; WC =well-covered.

APPENDIX 7: SUMMARY OF EXISTING SYSTEMATIC REVIEWS

Where possible, the Canadian Agency of Drugs and Technolgies in Health (CADTH) builds on existing applicable Canadian and international initiatives and research. Therefore, the first stage in the research process was to conduct a literature search for existing systematic reviews that have examined the use of oral antidiabetes agents in diabetes mellitus.

Several major databases (MEDLINE, CINAHL, Embase, BIOSIS, and PsycINFO) were searched to identify systematic reviews, health technology assessments, and meta-analyses. Two reviewers independently selected systematic reviews for consideration based on predefined inclusion and exclusion criteria. The methodological quality of selected systematic reviews was assessed independently by two reviewers using the AMSTAR instrument.[353] Based on the scope and quality of each review, two reviewers determined whether the selected publications could be used as a basis for CADTH to develop recommendations for the optimal prescribing and use of second-line therapies for patients inadequately controlled on metformin monotherapy. Details regarding the search strategy, selection process, and quality assessment are provided in the project protocol.[44]

Summary of Systematic Reviews Regarding the Use of Second-Line Diabetes Therapies

Author and Year of Publication	Quality Score	No. of Studies Included	Key Results
Amori, et al. 2007[134]	7/11	29 RCTs	*Glycemic control:* • GLP-1 analogues vs. placebo: WMD –0.97% • (95% CI, –1.13%, –0.81%) • DPP-4 inhibitors vs. placebo: WMD –0.74% • (95% CI, –0.85%, –0.62%) • Incretins were non-inferior to other agents. *Body weight:* • GLP-1 analogues vs. placebo: -1.4 kg • GLP-1 analogues vs. insulin: -4.8 kg • DPP-4 inhibitors were weight neutral. *Adverse events:* • GLP-1 analogues had more GI side effects (risk ratio, 2.9 • [95% CI, 2.0-4.2] for nausea and 3.2 [95% CI, 2.5-4.4] for vomiting).
Belsey, et al. 2008[354]	5/11	6 RCTs	Note: this review combined studies with various active comparators, as well as placebo, into single meta-analyses (e.g., sulfonylureas vs. meglitinides is pooled with sulfonylurea vs. placebo). Given this high degree of methodological heterogeneity, the results should be interpreted with caution. *Glycemic control:* • Adding sulfonylureas to metformin therapy resulted in a pooled estimate for change in A1C from baseline of (WMD [95%CI]) -0.9% (0.7, 1.1). *Body weight:* • Mean weight change ranged from a gain of 2.5 kg relative to metformin + sitagliptin to a reduction of -0.1 kg for metformin + pioglitazone. *Hypoglycemia:* • The odds of experiencing a hypoglycemic event was significantly higher in sulfonylurea-treated patients

Summary of Systematic Reviews Regarding the Use of Second-Line Diabetes Therapies			
Author and Year of Publication	**Quality Score**	**No. of Studies Included**	**Key Results**
			than in those on comparator treatments OR [95% CI] 5.3 [1.7, 16.3]).
Black, et al. 2007[144]	9/11	15 RCTs	*Glycemic control:* • Repaglinide vs. placebo (decrease in A1C = 0.1 to 2.1%) • Repaglinide vs. metformin (similar efficacy in reducing A1C) • Nateglinide vs. placebo (decrease in A1C = 0.2 to 0.6%) • Nateglinide vs. metformin (decrease of A1C = 0.5% vs. 0.8%)
Bolen, et al. 2007[133]	10/11	216 controlled trials and cohort studies and 2 systematic reviews	*Glycemic control:* • TZD plus metformin vs. sulfonylurea plus metformin: 2 RCTs, results showed no consistent effect favouring one of the combination arms. • Metformin vs. metformin plus TZDs: four RCTs, greater improvement with combination 0.62%, (95% CI, 0.23, 1%). • Metformin vs. metformin plus sulfonylurea: 11 RCTs, results favours combination therapy, 1% (95% CI, 0.76, 1.34). *Body weight:* • TZD plus metformin vs. sulfonylurea plus metformin: 2 RCTs, results favoured combination of TZD plus metformin (range -1.5 to -1.4 kg). • Metformin vs. metformin plus TZD: 2 RCTs, combination caused mean weight gain 0.7 to 1.9 kg, while metformin caused weight loss. • Metformin vs. metformin plus sulfonylurea: 10 RCTs, favoured metformin monotherapy, -2.4 kg (95% CI, -3.6, 1.1). *Hypoglycemia:* • TZD plus metformin vs. sulfonylurea plus metformin: 1 RCT, more incidence of patient with hypoglycemia in those taking sulfonylurea plus metformin than TZD plus metformin. • Metformin vs. metformin plus TZD: 3 RCTs, no difference between groups. • Metformin vs. metformin plus sulfonylurea: 9 RCTs, less incidence of patient with hypoglycemia with metformin compared with metformin plus sulfonylurea, RR (95% CI), -0.14 (-0.21, -0.07).
Goudswaard, et al. 2004[355]	10/11	20 RCTs	*Glycemic control:* • Insulin-OAD combination therapy had statistically significant benefits on glycemic control over insulin monotherapy only when the latter was applied as a once-daily injection of NPH insulin. • Twice-daily insulin monotherapy (NPH or mixed insulin) provided superior glycemic control to insulin-OAD combination therapy regimens where insulin was administered as a single morning injection. • Regimens utilizing OADs with bedtime NPH insulin provided comparable glycemic control to insulin monotherapy (administered as twice daily, or multiple daily injections).

Summary of Systematic Reviews Regarding the Use of Second-Line Diabetes Therapies			
Author and Year of Publication	**Quality Score**	**No. of Studies Included**	**Key Results**
			Hypoglycemia: • Of the 14 studies (22 comparisons) reporting hypoglycemia, 13 demonstrated no significant difference in the frequency of symptomatic or biochemical hypoglycemia between insulin and combination therapy regimens. *Other outcomes:* • No significant differences in quality of life-related issues were detected. Combination therapy with bedtime NPH insulin resulted in statistically significantly less weight gain compared to insulin monotherapy, provided metformin was used. • Overall, insulin-OAD combination therapy was associated with a 43% relative reduction in total daily insulin requirement compared to insulin monotherapy.
Monami, et al. 2008[4]	2/11	27 RCTs	*Glycemic control:* • Relative to placebo, sulfonylureas, alpha-glucosidase inhibitors and TZDs reduced A1C (%) (WMD [95%CI]) by 0.85 (0.78, 0.94), 0.61 (0.55, 0.67), 0.42 (0.40, 0.44), respectively. • In direct comparisons, sulfonylureas induced a greater reduction in A1C (0.17 [0.16, 0.1]) than TZDs. There was no significant difference between sulfonylureas and insulin.
Richter, et al. 2008[143]	8/11	25 RCTs	*Glycemic control:* • Sitagliptin and vildagliptin therapy, in comparison with placebo, resulted in an A1C reduction of approximately 0.7% and 0.6%, respectively. • Data on comparisons with active comparators were limited but indicated no improved metabolic control following DPP-4 intervention in contrast to other hypoglycemic agents. *Body weight:* • Sitagliptin and vildagliptin therapy did not result in weight gain, but weight loss was more pronounced following placebo interventions. *Hypoglycemia* • Overall, sitagliptin and vildagliptin were well tolerated, no severe hypoglycemia was reported

A1C = glycosylated hemoglobin; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; NPH = neutral protamine Hagedorn; OADs = oral antidiabetes drugs; RCT = randomized controlled trial; RR = relative risk; TZD = thiazolidinedione; WMD = weighted mean difference.

Following our assessment of the seven systematic reviews that met our inclusion criteria, we determined that none were sufficient to appropriately address our research questions. The primary reasons for this can be summarized as follows:

- The time-effort requirements for adopting an existing review will be, at best, equivalent to conducting our own review.
- Multiple reviews would be required to address our population.

APPENDIX 8: INCLUSION AND EXCLUSION CRITERIA FOR RCTS

Author	Inclusion Criteria	Exclusion Criteria
Ahren et al.[52]	Male or infertile female patients aged ≥ 30 years diagnosed with type 2 diabetes ≥ six months before enrollment and treated with a stable dosage of metformin for ≥ three months were included. Pre-randomization A1C while on metformin monotherapy was required to be between 7.0 and 9.5% (inclusive), and baseline BMI was required to be between 20 and 35 kg/m^2 (inclusive).	Type 1 or secondary forms of diabetes, significant diabetes complications, clinically significant cardiovascular abnormalities, liver disease, acromegaly, asthma, major skin allergies, or major gastrointestinal surgery; fasting triglyceride levels > 5.1 mmol/L or FPG < 6.1 or ≥13.3 mmol/L; treated with any drugs considered possibly able to affect results or their interpretation.
Barnett et al.[53]	Type 2 diabetes, male and female, aged ≥ 30 years, Receiving treatments with either a stable dose for immediate- or extended-release metformin ≥ 1,500 mg/dL for 3 months, A1C ≥ 7.1% and ≤ 11.0%, BMI > 2.5 kg/m^2 and < 40 kg/m^2, body weight that has been stable (not varying by > 10%) for ≥ 3 months.	NR.
Berne et al.[54]	Male and female, type 2 diabetes, receiving treatment with metformin alone or metformin and sulfonylurea, 30 years to 75 years, BMI of 28 kg/m^2-40 kg/m^2, A1C 6.5%-10%.	Treatment with insulin, a recent myocardial infarction, other significant peripheral vascular, cardiac, respiratory, renal, neurological, gastrointestinal, or endocrine diseases or signs of fat-soluble vitamin deficiencies. Those taking drugs influencing appetite, resins, fish oil supplements, and retinoids; A1C > 10%.
Blonde et al.[55]	Type 2 diabetes, aged 18-80, inadequate glycemic control (A1C 7%-10%) on metformin mono with stable met dose ≥ four weeks, BMI 22-41 kg/m^2, FPG <270 mg/dL.	History of type 1 diabetes, diabetes from pancreatic injury or secondary form, history of myocardial infarction, coronary artery bypass surgery or unstable angina within six months, congestive heart failure needing pharmacological intervention, pregnant or lactating, liver disease, alanine or aspartase transaminase ≥ 2.5 times the upper normal limit, bilirubin >1.3 times upper normal limit, any contraindications and warnings according to metformin and the specific thiazolidinedione.
Bolli et al.[56]	Patients who were diagnosed with type 2 diabetes and had A1C of 7.5%–11.0% at the screening visit while receiving a stable dose of metformin ≥1500 mg/day. Male and female (non-fertile or of child-bearing potential using a medically approved birth control method) patients aged 18 years to 77 years, inclusive, BMI of 22 kg/m^2 –45 kg/m^2, inclusive, and with FPG of <15 mmol/L were eligible to participate.	Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous six months. Congestive heart failure (New York Heart Association Classes I–IV) and liver disease such as cirrhosis or chronic active hepatitis also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the ULN, direct bilirubin >1.3 times the ULN, serum creatinine levels ≥132 µmol/L (males) or µ125µmol/L (females), clinically significant abnormal

Author	Inclusion Criteria	Exclusion Criteria
		thyroid-stimulating hormone or fasting triglycerides >7.9 mmol/L.
Bolli et al.[57]	Patients who were diagnosed with type 2 diabetes and had A1C of 7.5%–11.0% at the screening visit while receiving a stable dose of metformin ≥1,500 mg/day. Male and female (non-fertile or of child-bearing potential using a medically approved birth control method) patients aged 18 years–77 years, inclusive, BMI of 22 kg/m^2–45 kg/m^2, inclusive, and with FPG of <15 mmol/L were eligible to participate.	Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetic complications, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. Congestive heart failure (New York Heart Association Classes I–IV) and liver disease such as cirrhosis or chronic active hepatitis also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the ULN, direct bilirubin >1.3 times the ULN, serum creatinine levels ≥ 132 µmol/L (males) or 125 µmol/L (females), clinically significant abnormal thyroid-stimulating hormone or fasting triglycerides >7.9 mmol/L.
Bosi et al.[58]	Type 2 diabetes who had been treated with metformin monotherapy for ≥ three months and who had been on a stable dose of ≥1,500 mg daily for ≥ four weeks before visit one. Participants were required to have A1C in the range of 7.5%–11.0% at the screening visit, and, if they were not at that time receiving their maximum-tolerated dose, they agreed to increase their metformin dose to 2,000 mg daily at visit one. Male and female patients (nonfertile or of child-bearing potential using a medically approved birth control method) aged 18 years–78 years, inclusive, with a BMI in the range of 22 kg/m^2–45 kg/m^2, inclusive, and with FPG <15 mmol/L were eligible to participate.	History of type 1 or secondary forms of diabetes, acute metabolic diabetes complications within the past 6 months, congestive heart failure requiring pharmacologic treatment, myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous six months. Liver disease such as cirrhosis or chronic active hepatitis also precluded participation, as did renal disease or renal dysfunction, as suggested by elevated serum creatinine levels ≥132 µmol/L for male and ≥123 µmol/L for female subjects.
Brazg et al.[59]	Male and female, 25 years-75 years of age, type 2 diabetes, inadequate glycemic control on metformin monotherapy at a stable doses of ≥ 1,500 mg/dL for ≥ six weeks, A1C ≥ 6.5% and < 10%, FPG ≤ 240 mg/dL.	History of type 1 diabetes, C-peptide levels ≤ 0.8 ng/dL, heptic transaminases or creatine phosphokinase more than twofold upper limit of normal, elevated serum creatine, BMI < 22 kg/m^2 or > 40 kg/m^2, any medically significant cardiovascular event within 6 months.
Bunck et al.[60]	Ages 30 years-75 years, A1C 6.5%-9.5%, BMI 25 kg/m^2-40 kg/m^2, metformin monotherapy for 2 months at a stable dose.	No OAD other than metformin within 3 months prior to screening, no changes in other agents known to affect ß-cell function were allowed during the study.
Charbonnel et al.[61]	Men and women (aged 18 years–78 years) with type 2 diabetes and inadequate glycemic control (defined by an A1C level ≥7% and ≤10%) while taking metformin monotherapy at a stable dose of at least 1,500 mg/day, either at entry into the study or after a metformin dose-stable run-in period, were eligible to be randomized. Patients who were not currently taking an OAD, were taking any OAD in monotherapy, or were taking metformin in combination with another OAD were potentially eligible to participate in the study if their A1C level met the screening criteria.	Patients were excluded if they had a history of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with the use of metformin, or a fasting plasma glucose (or a fasting fingerstick glucose) at, or just before, randomization >14.4 mmol/L (260 mg/dL).

Author	Inclusion Criteria	Exclusion Criteria
Charbonnel et al.[62]	Male and female patients with type 2 diabetes inadequately managed with metformin or sulfonylurea monotherapy (at ≥ 50% of the maximum recommended dose or at the maximum tolerated dose for ≥ three months), age 35 years–75 years; A1C 7.5%–11.0%; fasting C-peptide levels ≥0.50 mmol/L (1.5 ng/mL); and stable or worsening glycemic control for ≥ 3 months prior to screening.	Type 1 diabetes, ketoacidosis, symptomatic heart failure, acute malabsorption or chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years, substance abuse or myocardial infarction, transient ischemic attacks or stroke in the previous 6 months, or were pregnant. Patients previously treated with insulin, gliclazide, pioglitazone, or other sulphonylureas or TZDs were not eligible for entry into the pioglitazone vs. gliclazide addition to metformin study, and patients treated with insulin, metformin, pioglitazone, or other TZDs were not eligible for entry into the pioglitazone vs. metformin addition to sulfonylurea study.
Charpentier et al.[63]	Patients aged 35 years-70 years with type 2 diabetes inadequately controlled by metformin monotherapy for ≥ 4 weeks (FBG: 7.8-13.9 mmol/L), and with a serum creatinine < 110 µmol/L were recruited. Newly diagnosed patients (< 1 year) were included provided that BMI was ≥ 23.0 kg/m^2 for female patients or ≥ 25.0 kg/m^2 for male patients, without any evidence or history of spontaneous weight loss or ketonuria associated with glucosuria.	Secondary or insulin-dependent diabetes, any severe chronic disease, grade 3 overweight (BMI was ≥ 40.0 kg/m^2), history of major cardiovascular events in the last 6 months, allergy to sulfonylurea, or drugs or alcohol abuse. Treatment with any other antidiabetic drugs other than metformin chlorhydrate, or with miconazole, systemic corticosteroid or any other investigational treatment in the four weeks before entry to the study was prohibited. Dose of concomitant treatment with antihypertensive or lipid-lowering therapy required to remain constant.
DeFronzo et al.[64]	19 years–78 years of age with type 2 diabetes treated with metformin monotherapy, FPG <13.3 mmol/L (<240 mg/dL), BMI of 27 kg/m^2–45 kg/m^2, and A1C of 7.1%–11.0%. The metformin dose was ≥1,500 mg/day for 3 months before screening. Subjects were weight-stable (±10%) for 3 months before screening, with no clinically significant abnormal laboratory test values (> 25% outside normal laboratory values). Female subjects were postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study.	Use of sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, exogenous insulin therapy, weight-loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or evidence of clinically significant comorbid conditions for 3 months before screening.
DeFronzo et al.[65]	Men and women with type 2 diabetes; A1C ≥7.0% and ≤ 10.0%; stable dose of metformin (≥ 1,500 mg/day, but not > 2,550 mg/day) for at least 8 weeks prior to screening, fasting C-peptide concentration ≥1.0 ng/mL, aged 18 years-77 years, and BMI ≤40 kg/m^2.	Poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; use of any other any hyperglycemic medication (8 weeks prior) or insulin (one year prior); cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤ 40%; chronic or repeated intermittent corticosteroid treatment; history of alcohol or drug abuse within the previous year; treatment with potent systemic cytochrome P450 3A4 inhibitors or inducers; active liver disease and/or clinically significant abnormalities on screening tests of hepatic function; or an assessment of an immunocompromised

Author	Inclusion Criteria	Exclusion Criteria
		state. Pregnant or breast-feeding women were excluded.
Einhorn et al.[66]	Type 2 diabetes; stable dose of metformin for ≥ 30 days; BMI 25 kg/m^2-45 kg/m^2 at screening; A1C ≥ 8.0%; and fasting C-peptide level >1.0 ng/mL.	Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired liver function, impaired kidney function, or anemia were excluded. Patients with unstable cardiac conditions (e.g. New York Heart Association Class III or IV, congestive heart failure, history of myocardial infarction, or stroke) or cerebrovascular conditions within 6 months of study.
Feinglos et al.[67]	Male and female patients, aged between 30 years and 81 years with type 2 diabetes of at least 6 months duration, moderately (A1C 7.0%-8.5%), but inadequately controlled with metformin monotherapy at a dose of ≥ 1,000 mg/day, maintained for at least 3 months prior to screening, and with a BMI of 27 kg/m^2 -38 kg/m^2 were eligible for the study.	Exclusion criteria: use of any other oral glucose-lowering medication, including thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, or other sulfonylureas for the 12 weeks prior to screening; insulin use for longer than 1 week out of 12-week period; specific contraindications to sulfonylureas, sulfonamides, or biguinides; a history of cardiovascular dysfunction within the preceding 6 months of the study, significant gastrointestinal dysfunction, substance abuse or alcoholism; impaired liver function; and impaired renal function. Concomitant therapy with glucocorticoids (other than topical or inhaled) was not permitted, although other medications that affect glucose homeostasis were permitted if they had been administered in a stable dosage during the preceding 6 months.
Ferrannini et al.[68]	Male and female (non-fertile or using medically approved birth control), type 2 diabetes, received metformin for ≥ three months and on stable dose of ≥ 1,500 mg daily for a minimum of ≥ 4 weeks prior to visit 1, were aged 18-73, BMI 22 kg/m^2-45 kg/m^2.	History of type 1 or secondary forms of diabetes, experienced acute metabolic diabetes complications 6 months prior, acute infections that might affect blood glucose control in the 4 weeks prior to visit 1, serious cardiac conditions (history of torsades de pointes or ventricular tachycardia; percutaneous coronary intervention 3 months prior; myocardial infarction, coronary artery bypass surgery, unstable angina or stroke 6 months prior, congestive heart failure requiring pharmacological treatment; 2-or 3-atrioventricular block or prolonged QTc) or clinically significant liver or renal disease. Laboratory abnormalities such as alanine aminotransferase or aspartate aminotransferase > 3 times ULN, direct bilirubin > 1.3 times ULN, serum creatine levels ≥ 132 µmol/L in men or ≥ 123 µmol/L in women, clinically significant thryroid-stimulating hormone outside of normal range at screening; or fasting triglycerides > 7.9 mmol/L.
Fonseca et al.[69]	Persons between the ages of 40 and 80 years with type 2 diabetes as defined by the National Diabetes Data Group,12 with FPG concentrations	Patients were excluded if they had clinically significant renal or hepatic disease, angina, New York Heart Association Class III or IV

Author	Inclusion Criteria	Exclusion Criteria
	of between 7.8 mmol/L and 16.7 mmol/L (140 mg/dL and 300 mg/dL) at screening and during the placebo-maintenance period while taking 2.5 g/d of metformin were eligible. All patients demonstrated insulin secretory capacity as determined by a fasting C-peptide concentration of 0.27 nmol/L (0.8 ng/mL) or more at screening. Subjects were required to have a BMI, calculated as weight in kilograms divided by the square of height in meters, of 22 to 38 and a weight change of no more than 10% between screening and baseline. FPG >7.7 mmol/L at the end of 4 weeks-7 weeks metformin maintenance period.	cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical abnormality on electrocardiogram, abnormal laboratory test results (blood chemistry, hematology, or urinalysis), use of chronic insulin therapy, participated in any rosiglitazone-related study, or used any investigational drug (excluding metformin) within 30 days of study (or 5 half-lives of the investigational drug, if longer than 30 days). Anorectic agents were discontinued at least 30 days before screening.
Frid et al.[106]	Not reported.	Not reported.
Gao et al.[70]	Male and female, 21 years to 75 years, treated with a stable dose of one of the following for at least 3 months prior to screening: ≥1,000 mg/day immediate-release metformin; or metformin ≥1,000 mg/day and sulfonylurea or sulfonylurea /metformin combination therapy. A1C between 7.1% and 11.0%, inclusive. BMI >21 kg/m^2 and <35 kg/m^2.	Have participated in this study previously, or any other study using exenatide or GLP-1 analogues, an interventional, medical, surgical, or pharmaceutical study within 30 days of screening, have characteristics contraindicating metformin or sulfonylurea use, been treated with exogenous insulin for more than 1 week within the 3 months prior to screening, used drugs for weight loss within one month of screening.
Garber et al.[71]	Adults (aged 20 years-78 years) with established type 2 diabetes requiring oral therapy were eligible for enrollment. Before screening, patients were required to be on a stable dosage of metformin ≥ 1,500 mg/day for > 8 weeks, A1C levels 7%-12% and BMI 23 kg/m^2-45 kg/m^2. Only patients willing and able to perform self-monitoring of blood glucose were eligible. Women with child-bearing potential had to practice acceptable methods of birth control and to have negative pregnancy test results within 72 hours of study treatment.	Marked polyuria, and polydipsia with > 10% weight loss, the use of any hypoglycemic agent other than metformin within 8 weeks before screening, anemia (hemoglobin: < 12.5 g/dL in men and < 11.0 g/dL in women) and significant abnormal renal, cardiac or hepatic dysfunction or disease. Pregnant or nursing women and patients with known sensitivity to any study medication.
Gomez-Perez et al.[72]	Men and women of non-child-bearing potential with type 2 diabetes were eligible for the study providing they were 40-80 years of age, had a fasting C-peptide level ≥0.8 ng/mL at screening, and a fasting plasma glucose level ≥140 mg/dL and ≤300 mg/dL at weeks 0 and 2 of the metformin maintenance period, respectively.	Clinically significant renal or hepatic disease (serum creatinine >1.5 mg/dL for men or >1.4 mg/dL for women or alanine aminotransferase, aspartate aminotransferase, total bilirubin or alkaline phosphatase >2.5 the upper limit of the normal laboratory value), anemia (hemoglobin <11 g/dL for men or <10 g/dL for women), severe cardiac disease, left ventricular hypertrophy, and hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg). The use of insulin and oral antidiabetic drugs other than metformin was prohibited during the study, as was the use of warfarin and certain anti-obesity drugs.
Goodman et al.[73]	Type 2 diabetes, male and female (nonfertile or using appropriate birth control), baseline A1C of 7.5%-11%, receiving a stable dose of metformin ≥1500 mg/day for at least 3 months, aged 18-78, BMI of 22 kg/m^2 -40 kg/m^2 and a FPG <270 mg/dL (<15 mmol/l), and agreeing to stay on the same dose of metformin throughout the study.	Pregnant or lactating, history of type 2 diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes; acute metabolic diabetic complications, liver disease, significant renal dysfunction, treatment with OADs other than metformin within 3 months of study entry, chronic

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		insulin treatment within the past 6 months, any of the following laboratory abnormalities: alanine aminotransferase or aspartate aminotransferase > than 2 times the ULN, total bilirubin >than 2 times the ULN, serum creatinine levels ≥1.5 mg/dL (males) or 1.4 mg/dL (females) or a history of abnormal creatinine clearance.
Halimi et al.[74]	Men and non-pregnant women diagnosed with type 2 diabetes, defined according to WHO criteria, for at least 1 year before the start of the study. 30 years-70 years of age, body mass index ≥ 25.0 kg/m^2 and ≤35.0 kg/m^2, and have poor glycemic control (A1C = >7.0% and <11.0%) despite receiving metformin 850 mg/day for at least 2 months, serum creatinine level below 135 µmol/L, transaminases, alkaline phophatase and bilirubin liver function parameters less than twice the upper limit of normal, a γ-GT liver function test less than three times the upper limit of normal, and a fasting C-peptide value of ≥ 0.20 µg/L.	Nursing mothers, seeking to become pregnant, participated in a clinical study during the previous 30 days, any of the following clinically unstable conditions that could impact the patient's response to acarbose or metformin: cardiac, pulmonary, hepatic, renal, gastrointestinal, neurological, or psychiatric. Patients were also excluded if they were showing signs of type 1 or secondary diabetes, taking intestinal adsorbents, neomycin, preparations containing gastrointestinal enzymes or any antidiabetic drug other than metformin, or has taken one or more prohibited medications during the two months before the study.
Hamann et al.[75]	Overweight (BMI ≥ 25 kg/m^2) men and women with type 2 diabetes, A1C ≥7% and <10% having received metformin (≥ 850 mg/day) for ≥ eight weeks prior to screening.	Any oral antidiabetes drug other than metformin in the prior 12 weeks, insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin <11.0g/dL for men and <10.0 g/dL for women), renal or hepatic disease, known congestive heart failure, unstable or severe angina, history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or cerebrovascular accident within three months, left ventricular dysfunction within six months of screening, fasting C-peptide <0.5 nmol/L, systolic blood pressure >170 mmHg or dystolic blood pressure >100 mmHg while on antihypertensive medication.
Home et al.[76]	Type 2 diabetes, inadequately controlled on metformin or sulphonylureas, aged 40 years-75 years, BMI > 25.0 kg/m^2, A1C > 7.0%-9.0%	Using other glucose-lowering therapies; use of a combination of two or more oral glucose-lowering agents within 6 months; use of insulin, except for pregnancy, intercurrent illness, or stabilization; previous use of any PPARγ agonist. Hospitalization for a major CV event in the last 3 months; scheduled major CV intervention, or gangrene; diagnosed or receiving medication specifically for heart failure (except diuretics alone); systolic or diastolic blood pressure >180/105 mmHg, on therapy if used; fasting serum triglycerides >12.0 mmol/L; serum creatinine >130 µmol/L (>1.47 mg/dL); ALT, AST, total bilirubin, or alkaline phosphatase ≥2.5 times

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		the upper limit of normal; hemoglobin <11.0 g/dL for males or <10.0 g/dL for females or hemoglobinopathy interfering with valid A1C assay; contraindication/intolerance to metformin, glyburide, gliclazide, or glimepiride; pre-existing medical condition judged to preclude safe participation in the study; abuse of alcohol or drugs, or presence of any condition that may lead to poor adherence to study protocols; recent use of an investigational drug; pregnancy, breast-feeding, or planning pregnancy.
Home et al.[77]	Type 2 diabetes, inadequately controlled on metformin, aged 40 years–75 years, BMI > 25.0 kg/m^2, A1C > 7.0%–9.0%.	Using other glucose-lowering therapies; use of a combination of two or more oral glucose-lowering agents within 6 months; use of insulin, except for pregnancy, intercurrent illness, or stabilization; previous use of any PPARγ agonist. Hospitalization for a major cardiovascular event in the last 3 months, scheduled major cardiovascular intervention, or gangrene; diagnosed or receiving medication specifically for heart failure (except diuretics alone); systolic or diastolic blood pressure >180/105 mmHg, on therapy if used; fasting serum triglycerides >12.0 mmol/L; serum creatinine >130 µmol/L (>1.47 mg/dL); ALT, AST, total bilirubin, or alkaline phosphatase ≥2.5 times the upper limit of normal, hemoglobin <11.0 g/dL for males or <10.0 g/dL for females or hemoglobinopathy interfering with valid A1C assay; contraindication/intolerance to metformin, glyburide, gliclazide, or glimepiride; pre-existing medical condition judged to preclude safe participation in the study; abuse of alcohol or drugs, or presence of any condition that may lead to poor adherence to study protocols; recent use of an investigational drug; pregnancy, breast feeding, or planning pregnancy.
Kaku[78]	Type 2 diabetes, aged 20 years-65 years, metformin monotherapy.	Type 2 diabetes, impaired hepatic function, renal insufficiency, cardiac failure or other serious heart disease, cerebrovascular disease, cancer, severe lung, gastrointestinal, pancreatic, or hematological disorders; also history of lactic acidosis/ketoacidosis/diabetic coma (or pre-coma within the preceding 26 weeks), or with a history of drug dependency.
Khanolkar et al.[79]	Male and female, aged 36 years-71 years, A1C > 6.5%, on metformin monotherapy.	Smokers, history of overt cardiovascular disease/cardiac failure, microalbuminuria, on antiplatelet medications (aspirin/clopidogrel/dipyridamole) or non-steroidal anitinflammatory drugs, those with significantly abnormal liver function tests (baseline alanine transaminase > 2 times the

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		upper limit of normal), female patients of child-bearing age likely to get pregnant during or within 3 months after completion of the study.
Kilo et al.[80]	Men or woman, 18 yearsor older, with type 2 diabetes and body weight ≤ 100 kg and BMI ≤ 40 kg/m^2. The patients were naive to insulin treatment at the screen, patients had inadequate glycemic control (A1C ≥ 7.5%) on a regimen of ≥ 3 months of metformin as monotherapy or in combination with a sulfonylurea or repaglinide. At the end of run-in period: FBG > 126 mg/dL (FPG > 7.8mmol/L).	Significantly impaired hepatic (alanine aminotransferase or alkaline phosphatase ≥ 2 times the upper limit) or renal function (serum creatinine ≥ 1.4 mg/dL for women, ≥ 1.5 mg/dL for men) or significant cardiac (decompensated heart failure), New York Heart Association Class III or IV, unstable angina pectoris, or a myocardial infarction within 12 months.
Kvapil et al.[81]	Type 2 diabetes, ≥850 mg/day metformin for at least 1 month.	Patients with significant medical problems such as proliferative retinopathy, impaired hepatic or renal function, recurrent hypoglycemia, cardiac disease, anemia, or change in dose of medications known to interfere with glucose metabolism.
Leiter et al.[82]	Type 2 diabetes, aged 20-80 years, baseline FPG ≥7 mmol/l, A1C ≤9.5% treated with metformin for ≥ 3 months at stable dose ≤1700 mg/day.	Any clinical finding that would have precluded patients taking metformin and/or rosiglitazone (according to product monographs).
Marre et al.[83]	FPG ≥ 7 mmol/L (126 mg/dL) despite treatment with metformin monotherapy at a dose of ≥850 mg b.i.d. or ≥500 mg t.i.d., diet and exercise for the 2-month period immediately before enrollment. Additional inclusion criteria included age > 18 years and BMI < 40 kg/m^2. Premenopausal female patients were included subject to reliable contraception, a negative pregnancy test, or having undergone documented surgical sterilization.	Patients were excluded for renal disease or dysfunction (serum creatinine > 127 µmol/L) or if they suffered from hypoxic states, such as cardiovascular collapse, acute heart failure, myocardial infarction, or any condition characterized by hypoxemia (e.g., any severe respiratory disturbance or infection). Further exclusion criteria were hepatic dysfunction (serum glutamic-oxaloacetic transaminase or serum glutamic-pyruvic transaminase above twice the upper normal level), history of metabolic acidosis including diabetic ketoacidosis, known hypersensitivity to metformin or glyburide, a history of cancer of any type (excepting basocellular cancer that had been treated successfully at least 2 years prior to the study), pregnancy or lactation, excessive alcohol intake, major disease problems, drug addiction, or concomitant treatment with other anti-diabetic drugs.
Marre et al.[84]	Male and female, type 2 diabetes for at least 6 months, treated with metformin for ≥ 3 months at a dose of >1,500 mg/day for at least 4 weeks before study entry, ≥ 30 years, BMI 20-35 kg/m^2, A1C 6.8%-11%.	FPG ≥ 15 mmol/L at 4 or 2 weeks prior to study, patients with significant diabetic complications, such as gastroparesis or renal impairment (serum creatinine >120 µmol/L females or >133 µmol/L for males), patients who had significant changes in body weight during the run-in period (>5%), significant or unstable cardiac abnormalities, liver function abnormalities (cirrhosis, chronic hepatitis or persistent elevations in liver enzymes), or who were treated with antidiabetic agents other than metformin (including insulin) 3 months before the start of the study.

Author	Inclusion Criteria	Exclusion Criteria
Matthews et al.[85]	Male and female patients with type 2 diabetes, inadequately managed with metformin alone (at ≥50% of the maximum recommended dose or at the maximum tolerated dose for at least 3 months), were screened. Entry criteria included the following: age between 35 and 75 years, inclusive; HbA1c of ≥7.5% or ≤11.0%; fasting C-peptide of ≥1.5 ng/mL (0.50 nmol/L) and stable or worsening glycemic control for ≥3 months prior to screening.	Exclusions included patients with type 1 diabetes; ketoacidosis, myocardial infarction, transient ischemic attacks or stroke in the previous 6 months; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli; malignant disease in the previous 10 years; or substance abuse. Female patients had to be postmenopausal, sterilized or using satisfactory contraception, and pregnant or breast-feeding women were excluded. Previous treatment with insulin, gliclazide, pioglitazone, or other sulphonylureas or TZDs was not permitted.
McNulty et al.[86]	Type 2 diabetes (absence of ketonuria, rapid preceding weight loss, or need for insulin treatment), diabetes duration for greater than six months, BMI ≥27 kg/m^2, duration of metformin treatment of 3 months to 2 years, fasting serum glucose 7.0 mmol/L–15.0 mmol/L, and aged 25 years–70 years.	Current or previous evidence of ischemic heart disease, heart failure, or stroke; seated pulse rate >100 bpm; diastolic blood pressure >95 mmHg; total fasting serum cholesterol >7.8 mmol/L; fasting serum triglycerides >5.6 mmol/L; serum creatinine >120 µmol/L; serum liver enzymes or bilirubin levels that exceeded twice the upper limit of normal; weight change of >3 kg during the preceding 3 months; malignancy; and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) were anorectic agents, laxatives, ß-agonists (other than inhalers), cyproheptadine, phenothiazines, antidepressants, antiserotoninergics, barbiturates, antipsychotics, and oral corticosteroids. Antihypertensive and lipid-lowering drugs were permitted if treatment was stable for at least 3 months. Women were excluded if they were pregnant, lactating, or of child-bearing potential and not taking adequate contraceptive precautions.
Moses et al.[87]	Men or women with type 2 diabetes treated with metformin alone (1 g/day -3 g/day) for more than 6 months who had not achieved optimal glycemic control (A1C >7.1%). Additional inclusion criteria were aged 40-75 years and BMI ≥ 21 kg/m^2.	Clinically significant elevation in either serum creatinine or liver transaminases, vitamin B12 <150 pmol/L (associated with hemoglobin <130 g/L in men or 119 g/L in women), anemia, previous insulin treatment, unawareness of hypoglycemia, cardiac problems, uncontrolled hypertension, alcohol or drug abuse, a history of lactic acidosis, known contraindications to metformin, and an intention to become pregnant
Nauck et al.[88]	Patients with type 2 diabetes on a variety of different regimens at screening were allowed to participate. Men and women, aged 18 years-78 years, already on metformin monotherapy ≥ 1,500mg/day or switching to metformin monotherapy treatment titration and dose-stable period for at least 8 weeks (currently not on an OAD, or an OAD other than metformin monotherapy ≥ 1,500mg/day, or on metformin in	No oral antidiabetes drugs within 3 months, no changes in other agents known to affect β-cell function were allowed during the study. Type 2 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with the use of metformin, or FPG at or just prior to randomization > 15.0 mmol/L.

Author	Inclusion Criteria	Exclusion Criteria
	combination with another OAD), A1C ≥ 6.5% and ≤ 10%.	
Nauck et al.[89]	At screen: 1. Type 2 diabetes at least for 1 year, aged 18 years-70 years, at least 50% maximal dose of maximal dose of one or two OADs except TZD use in last 3 months, BMI 25-40 kg/m^2, A1C 8%-13%. 2. At run-in period on metformin treatment (1,000 mg b.i.d.) at least 2 weeks, FPG > 10 mmol/L.	Impaired liver function, renal function, cardiac failure New York Heart Association Class (III-IV), unstable angina pectoris, or myocardial infarction within the last year.
Nauck et al.[90]	Type 2 diabetes, aged 18 years–80 years, A1C between 7% and 11% (pre-study OAD monotherapy for ≥ 3 months) or between 7% and 10% (pre-study combination OAD therapy for ≥3 months), and BMI ≤ 40 kg/m^2.	Used insulin during the previous 3 months (except short-term treatment).
Papathan-assiou et al.[91]	Type 2 diabetes treated only with metformin for 6 months, A1C >6.5%, normal liver enzymes and renal function.	History of coronary artery, cerebrovascular, or peripheral vascular disease, chronic heart failure, liver or renal disease, anemia, thyroid dysfunction, new onset of medications within previous 8 weeks.
Phillips et al.[92]	Type 2 diabetes for at least 6 months insufficiently controlled by metformin (stable dose ≥ 3 months), aged ≥ 40 years, BMI of 25 kg/m^2-35 kg/m^2, A1C 7-10%, 80%-120% compliant during the run-in period.	Taken any antidiabetic medication other than metformin during the last 3 months, presence of significant diseases or conditions, including emotional disorders and substance abuse likely to alter the course of diabetes or the patient's ability to complete the study; presence of gastrointestinal diseases likely to be associated with abnormal gut mobility or altered absorption of nutrients; medication causing a significant change in gastrointestinal mobility and/or absorption; treatment with preparations containing digestive enzymes; conditions that might be aggravated by abnormally large amounts of gas in the intestine, including gastrocardiac syndrome, significant hernias, intestinal stenoses, and active ulcers; chronic pancreatitis; or concomitant medication affecting glucose homeostasis, such as glucocorticoids within 8 weeks before screening (ß-blockers, ACE-inhibitors, or thiazide diuretics could be continued if unchanged during the study and stable for 8 weeks before the study); uncontrolled thyroid function, transaminases elevated 3 times the upper limit of normal, or serum creatinine ≥2 mg/dL; infections likely to affect glucose metabolism; pregnant or lactating women; patients receiving any other investigational drug or participating in any other clinical study within 8 weeks before screening.
Poon et al.[93]	Male and female, type 2 diabetes, aged 18 years-65 years, treated with stable dose of metformin for ≥ 3 months before screening, A1C of 6.8%-9.0%, FPG of < 240 mg/dL, BMI of 27-45 kg/m^2, history of stable body weight (not varying > 10% for ≥ 3 months before screening), no clinically relevant abnormal laboratory test values, female subjects were postmenopausal,	Patients had received exogenous insulin therapy, OADs other than metformin, or prescription weight-loss agents within 3 months before screening; lipid-lowering agents that had not been stable for a minimum of 6 weeks before screening or antihypertension agents that had not been stable for a minimum of 4 weeks before the

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	surgically sterile, or using contraceptives before screening and continuing throughout the study.	screening; or if they had evidence of clinically significant comorbid conditions; those receiving chronic systemic glucocorticoid therapy or that had participated within the prior 3 months in an interventional medical, surgical, or pharmaceutical study.
Raskin et al.[94]	Aged 18 years–75 years and had a BMI ≤ 40 kg/m^2, body weight < 125 kg (275 lbs), and an A1C value ≥ 8%. All subjects were previously treated with metformin, at least 1,000 mg/day, as a single agent or in combination therapy for at least 3 months before the trial.	Women of child-bearing age were excluded if they were pregnant, breastfeeding, or not practicing contraception.
Raz et al.[95]	At screening: 1. Type 2 diabetes, aged 18 years-78 years, who were currently on metformin-monotherapy or any other single OAD, or metformin in combination with another OAD if A1C > 8% at the end of run-in period on metformin 1.5 g alone for more than 6 weeks; 2. At the end of run-in period, A1c 8.0 %-11%, FBG 7.2-15.6 mmol/L.	Patients treated with insulin within 8 weeks prior to screening, treated with TZDs or exenatide within 12 weeks; type 2 diabetes, BMI < 20 kg/m^2 or > 43 kg/m^2 or FPG (during run-in) consistently < 7.2 mmol/L or > 15.6 mmol/L; patients who were pregnant or breastfeeding.
Ristic et al.[96]	Type 2 diabetes for at least 6 months and had received metformin monotherapy for at least 3 months; the patients also had to be on a minimum metformin dose of 1,000 mg/day continuously for at least 2 months prior to study entry, but remain inadequately controlled by medication, diet, and physical exercise. Other inclusion criteria were a baseline A1C 6.8%–9.0%, and BMI 20 kg/m^2-35 kg/m^2.	Not reported.
Ristic et al.[97]	Type 2 diabetes diagnosed at least for 6 months; metformin monotherapy for at least 3 months; minimum dose of 1,000 mg/day for at least for 2 months; A1C 6.8-9%; BMI 20 kg/m^2-35 kg/m^2.	Not reported.
Rodger et al.[98]	Men or women with non–insulin-dependant diabetes for at least 6 months, at least 18 years of age, A1C > 7%, except for patients in the diet only group (>6.5%).	Patients with debilitating diseases, documented gastrointestinal disease, lactose intolerance, or patients receiving drugs that altered gastrointestinal motility and/or absorption, and any glucocorticoid therapy or lipid-lowering agents.
Rosenstock et al.[99]	Men and women 30 years of age with type 2 diabetes, inadequately controlled on diet plus 2,000 mg or 2,500 mg metformin daily, no other pharmacological therapy for type 2 diabetes was allowed for at least 56 days before screening, willing to follow a diet appropriate for people with diabetes, with at least 50% of calories derived from carbohydrates, required to have an A1C between 7% and 10%, stable body weight (within 3 kg) for at least 4 weeks before screening.	Significant diseases or conditions likely to alter the course of the diabetes or the patient's ability to complete the study; acute or chronic acidosis, persistent ketonuria, or a history of ketoacidosis (suggesting the need for insulin therapy); documented gastrointestinal diseases likely to be associated with abnormal gut motility, altered absorption of nutrients, chronic diarrheal states or chronic enteropathies; chronic liver or kidney disease; inadequately controlled hypertension (sitting blood pressure160/90 mmHg); a myocardial infarction within 2 months before screening; history of excessive alcohol consumption; serum creatinine levels 1.5 mg/dL for men and 1.4 mg/dL for women; aspartate aminotransferase or alanine aminotransferase elevated 1.8 times the normal level; low vitamin B12 levels;

Author	Inclusion Criteria	Exclusion Criteria
		hemoglobin 11 g/dL, or any hemoglobin variant. Patients were not allowed concomitant therapy with glucocorticoids, other investigational drugs (during the study or within 30 days before screening), medications to lower serum lipids or blood pressure (unless on a stable dose for at least 28 days before screening), or medications that might significantly alter gastrointestinal motility or absorption. Women of child-bearing age who were pregnant, who were unable or unwilling to use effective birth control measures, or who were nursing a child during the study were also excluded. Patients with known hypersensitivity to metformin or acarbose were not allowed in the study.
Schernthaner et al.[100]	Type 2 diabetes; treated with metformin at least for 3 months; A1c 6.9%-11.5%; aged >35 years old.	Currently using insulin, TZD, contraindication to the study drug, no effective contraceptive in women with child-bearing potential; elevated trasaminase, calculated creatine clearance <20ml/min (using Cockroft-Gault formula).
Scott et al.[101]	Men and women with type 2 diabetes (18 years-75 years of age) who were taking metformin monotherapy at a stable dose of ≥1,500 mg/day for at least 10 weeks prior to the screening visit and had inadequate glycemic control (A1C ≥7% and ≤11%).	Type 1 diabetes, insulin use within 8 weeks of the screening visit, any contraindications for use of TZDs or metformin, impaired renal function (creatinine clearance <60 ml/min), alanine aminotransferase or aspartate aminotransferase levels more than twofold the upper limit of normal or a fasting glucose value >270 mg/dL prior to randomization.
Trautmann et al.[107]	Not reported.	Not reported.
Umpierrez et al.[102]	Men and women aged 18 years-79 years with a diagnosis of type 2 diabetes for at least 6 months, and who were taking stable doses of metformin (1 g/day-2.5 g/day) or extended release metformin (0.5 g/day-2.0 g/day) as their only OADs for at least 2 months. All subjects were required to have BMI ≥ 24, and A1C 7.5%- 10%, a FPG 126 mg/dL-235 mg/dL (7-13 mmol/L) and C-peptide concentration ≥ 0.27 nmol/L during the stabilization period.	History of substance abuse, severe hypoglycemia, metabolic complications, or clinical significant abnormal baseline lab value including hematology, blood chemistry, or urinalysis.
Van Gaal et al.[103]	Type 2 diabetes for at least 1 year; aged 30 years-75 years; inadequately controlled by diet and metformin taken at a stable dose for at least 3 months; A1C ≥ 7.5- ≤10.5; BMI 23 kg/m^2-40 kg/m^2; stable body weight (<5% change) over the 3 months preceding enrollment.	Medical conditions affecting the underlying diabetes or interpretation of study results, any other serious medical conditions including hepatic or renal dysfunction, decompensated heart failure, serious hemopoietic disorders, or any gastrointestinal disorders or medications likely to affect gastrointestinal function. Use of any oral antidiabetes drug other than metformin within 30 days prior to enrollment, or of diuretic and glucocorticoids unless at a stable dose in the 3 months prior to enrollment, was also ground for exclusion.
Von Bibra et	Type 2 diabetes of relative short duration,	Atrial fibrillation, ischemic heart disease,

Author	Inclusion Criteria	Exclusion Criteria
al.[104]	taking metformin monotherapy, aged 35 years-75 years, BMI 25 kg/m^2-35 kg/m^2, no major complications of macrovascular disease, normal systolic left ventricular function by 2-dimensional echocardiography, blood pressure normal or < 140/85 mmHg if treated, cholesterol and triglyceride levels < 250 mg/dL (6.5 mmol/L and 2.8 mmol/L, respectively), no signs of microvascular complications and no albuminuria.	severe left ventricular hypertrophy, history or signs of heart failure, hepatic and/or renal insufficiency (creatine > 1.5 mg/dL).
Wolever et al.[105]	Men or women with non–insulin-dependant diabetes for at least 6 months, at least 18 years of age, A1C > 7%, except for patients in the diet-only group (>6.5%).	Patients with debilitating diseases, documented GI disease, lactose intolerance, or patients receiving drugs that altered GI motility and/or absorption, and any glucocorticoid therapy or lipid-lowering agents.

A1C = glycosylated hemoglobin; b.i.d. = twice daily; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; FPG = fasting plasma glucose; NR = not reported; OADs = oral antidiabetes drugs; RCTs = randomized controlled trials; t.i.d. = three times daily; TZD = thiazolidinedione; ULN = upper limit of normal.

APPENDIX 9: LIST OF RCTS REPORTED IN MULTIPLE PUBLICATIONS

Author	Year	Status	Companion Status
Sulfonylureas vs. Placebo			
NAUCK et al.[90]	2009	Full text	Companion of Frid et al.[106]
FRID et al.[106]	2008	Abstract	Companion of Nauck et al.[90]
Alpha glucosidase inhibitors vs. placebo			
WOLEVER et al.[105]	1997	Full text	Companion of Rodger et al.[98]
RODGER et al.[98]	1995	Full text	Companion of Wolever et al.[105]
Sulfonylureas vs. TZD			
HOME et al.[76]	2007	Full text	Companion of Home et al.[77]
HOME et al.[77]	2009	Full text	Companion of Home et al.[76]
CHARBONNEL et al.[62]	2005	Full text	Companion of Matthews et al.[85]
MATTHEWS et al.[85]	2005	Full text	Companion of Charbonnel et al.[62]
DPP-4 inhibitor vs. TZD			
BOLLI et al.[56]	2008	Full text	Companion of Bolli et al.[57]
BOLLI et al.[57]	2009	Full text	Companion of Bolli et al.[56]
Meglitinides vs. sulfonylureas			
RISTIC et al.[97]	2007	Full text	Companion of Ristic et al.[96]
RISTIC et al.[96]	2006	Full text	Companion of Ristic et al.[97]
Insulins vs. GLP-1 analogues			
BARNETT et al.[53]	2007	Full text	Companion of Trautmann et al.[107]
TRAUTMANN et al.[107]	2007	Abstract	Companion of Barnett et al.[53]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione; vs. = versus.

APPENDIX 10: LIST OF EXCLUDED AND POOLED TREATMENT ARMS

Studies and/or treatment arms excluded from the reference case (dosing below DDD):

- Hamann et al. 2008[75] — whole study
- Feinglos et al. 2005[67] — whole study
- Poon et al. 2005[93] — 2.5 µg/b.i.d. and 5 µg/b.i.d. treatment arms
- Ahren et al. 2004[52] — whole study
- DeFronzo et al.[64] — 5 µg/b.i.d. treatment arm
- Bosi et al. 2007[58] — 50 mg/day treatment arm
- Fonseca et al. 2009[69] — 4 mg/day treatment arm
- Gomez-Perez et al. 2002[72] — 4 mg/day treatment
- Marre et al. 2002[84] — 60 mg/day treatment arm
- Marre et al. 2002[83] — 2.5 mg treatment arm
- Khanolkar et al. 2008[79] — whole study

Studies and/or treatment arms with excessive dosing:

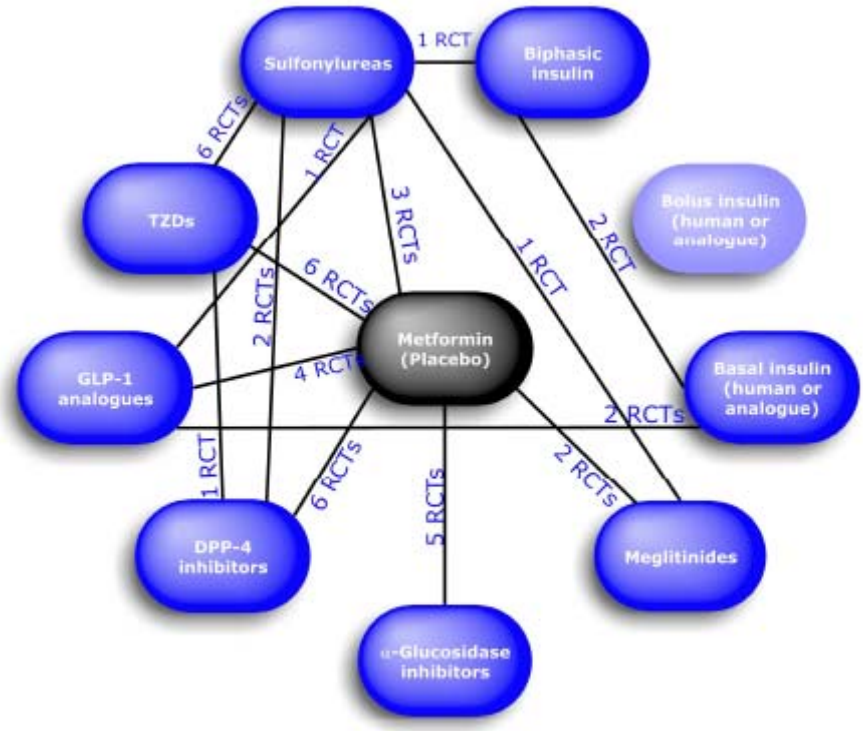
- DeFronzo et al. 2009[65] — 1 treatment arm (10 mg/day) excluded from all analyses
- McNulty et al.[86] — 1 treatment arm (20 mg/day) excluded from all analyses

Studies with pooled treatment arms:

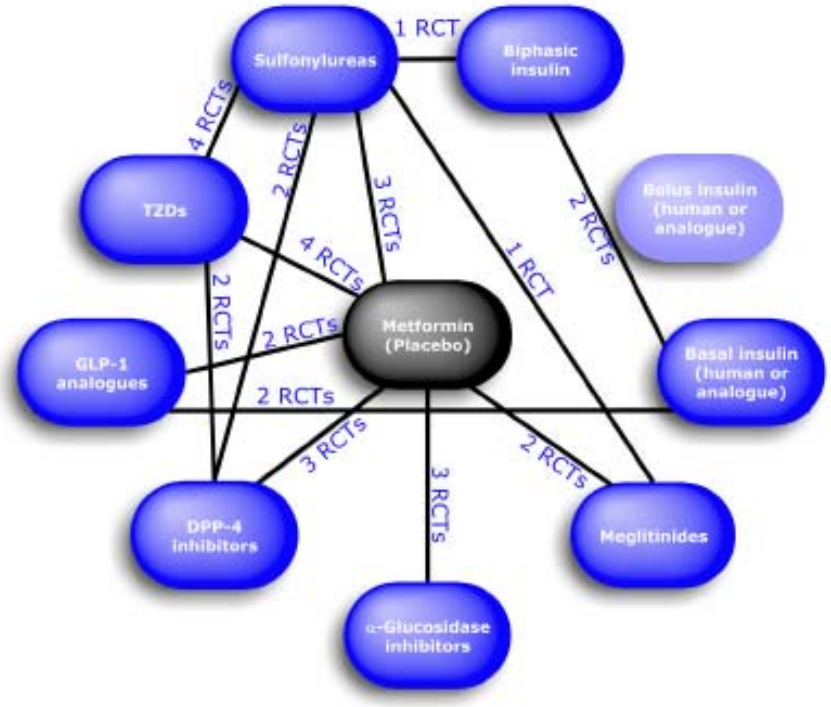
- Goodman et al.[73] — AM and PM arms were pooled for all analyses (pooled for A1C and BW)
- Poon et al. 2005[93] — 2.5 µg/b.i.d. and 5 µg/b.i.d. treatment arms were pooled for all low dose SA (pooled for A1C)
- Poon et al. 2005[93] — 7.5 µg/b.i.d. and 10 µg/b.i.d. were pooled for all analyses (pooled for A1C)
- DeFronzo et al. 2009[65]— 2.5 mg/day and 5 mg/day arms were pooled for all analyses (pooled for A1C)
- Nauck et al. 2009[90] — Pooled 1.2 mg/day and 1.8 mg/day
- Kilo et al. 2003[80] — Pooled for A1C and BW
- McNulty et al. 2003[86] — Pooled 15 mg/day and 20 mg/day arms

A1C = glycosylated hemoglobin; b.i.d. = twice daily; BW = body weight; DDD = defined daily dose;

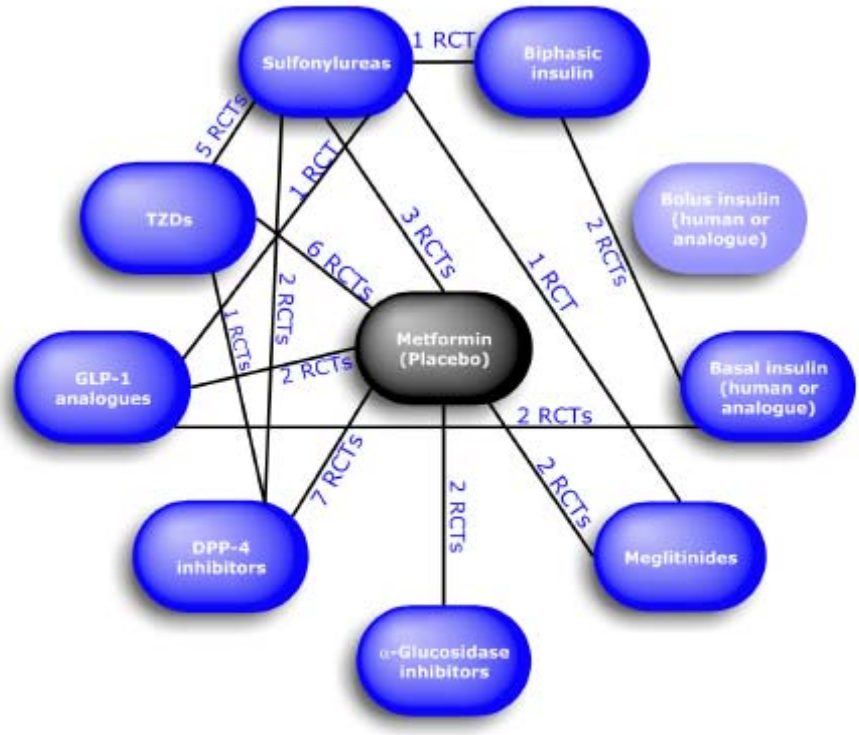
APPENDIX 11: MTC EVIDENCE NETWORK DIAGRAMS



Class Level MTC Evidence Network for Hemoglobin A1C



Class Level MTC Evidence Network for Body Weight



Class Level MTC Evidence Network for Overall Hypoglycemia

A1C = glycosylkated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCTs = randomized controlled trials; TZD = thiazolidinedione.

APPENDIX 12: FULL MTC RESULTS FOR A1C

This table presents the results of the MTC reference case and the pairwise meta-analyses of direct comparisons for A1C (40 RCTs; N = 17,795). All values represent the difference in the change in A1C% from baseline between two treatment arms. The MTC results are presented as the mean pooled estimate of effect (95% credible interval) and the direct comparisons as the mean difference for the change in A1C from baseline (95% confidence interval). The table also presents the MTC results in the form of the probability of achieving the largest reduction in A1C and the probability of achieving a reduction in A1C of ≥0.7% with each individual treatment. The "Rank" represents the average ranking for each treatment relative to the others over the 40,000 simulations. For example, a lower number indicates that a particular treatment had the largest reduction in A1C for the majority of simulations (relative to other treatments), while a higher number indicates that a treatment had the smallest reduction in A1C. The results in this table were derived from the Class Level MTC evidence network.

Full MTC Results for A1C								
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates* (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (≥ 0.7%)
Metformin monotherapy vs:								
Sulfonylureas	3[63,83,90]	945	0	-0.80 (-1.00, -0.59)	-0.80 (-0.96, -0.65)	1.8%	4.6	90.2%
Meglitinides	2[84,87]	366	61.9	-0.71 (-1.24, -0.18)	-0.64 (-0.92, -0.38)	1.5%	6.9	33.4%
TZDs	6[66,69,72,78,82,101]	1217	0	-0.96 (-1.18, -0.75)	-0.85 (-1.02, -0.69)	12.8%	3.3	96.5%
DPP-4 Inhibitors	6[58,61,65,73,95,101]	2376	60.2	-0.78 (-0.96, -0.60)	-0.77 (-0.92, -0.64)	1.4%	5.2	85.3%
Alpha-glucosidase inhibitors	5[74,92,98,99,103]	791	14.2	-0.74 (-0.94, -0.53)	-0.75 (-0.98, -0.51)	6.0%	5.5	64.4%
GLP-1 analogues	4[64,89,90,93]	973	17.9	-0.75 (-0.96, -0.53)	-0.82 (-1.05, -0.60)	8.2%	4.1	86.7%
Basal insulin	——	——	——	——	-0.82 (-1.16, -0.48)	7.9%	4.3	76.3%
Biphasic insulin	——	——	——	——	-0.97 (-1.33, -0.62)	60.4%	2.1	93.9%
Sulfonylurea vs:								
Meglitinides	1[97]	262	——	0.13 (-0.17, 0.43)	0.16 (-0.13, 0.44)	See above		0.0%
TZDs	6[62,71,77,91,102,104]	3421	81.2	-0.02 (-0.25, 0.21)	-0.05 (-0.19, 0.09)			0.0%
DPP-4 inhibitors	2[68,88]	3961	73.5	0.05 (-0.05, 0.14)	0.03 (-0.13, 0.17)			0.0%
Alpha-glucosidase inhibitors	——	——	——	——	0.05 (-0.23, 0.33)			0.0%

Full MTC Results for A1C								
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates* (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (≥ 0.7%)
GLP-1 analogues	1[90]	727	——	-0.13 (-1.27, 1.02)	-0.02 (-0.27, 0.22)			0.0%
Basal insulin	——	——	——	——	-0.02 (-0.36, 0.32)			0.0%
Biphasic insulin	1[81]	230	——	-0.20 (-0.49, 0.09)	-0.17 (-0.51, 0.16)			0.2%
Meglitinides vs:								
TZDs	——	——	——	——	-0.21 (-0.50, 0.10)	See above		0.1%
DPP-4 inhibitors	——	——	——	——	-0.13 (-0.42, 0.17)			0.0%
Alpha-glucosidase inhibitors	——	——	——	——	-0.10 (-0.46, 0.26)			0.1%
GLP-1 analogues	——	——	——	——	-0.18 (-0.52, 0.17)			0.2%
Basal insulin	——	——	——	——	-0.18 (-0.59, 0.25)			0.7%
Biphasic insulin	——	——	——	——	-0.33 (-0.76, 0.11)			4.4%
TZDs vs:								
DPP-4 inhibitors	2[55,57]	3166	0	-0.1 (-0.16, -0.04)	0.08 (-0.08, 0.23)	See above		0.0%
Alpha-glucosidase inhibitors	——	——	——	——	0.11 (-0.18, 0.39)			0.0%
GLP-1 analogues	——	——	——	——	0.03 (-0.23, 0.29)			0.0%
Basal insulin	——	——	——	——	0.03 (-0.32, 0.39)			0.0%
Biphasic insulin	——	——	——	——	-0.12 (-0.48, 0.23)			0.2%
DPP-4 inhibitors vs:								
Alpha-glucosidase inhibitors	——	——	——	——	0.03 (-0.24, 0.30)	See above		0.0%
GLP-1 analogues	——	——	——	——	-0.05 (-0.30, 0.21)			0.0%
Basal insulin	——	——	——	——	-0.05 (-0.39, 0.32)			0.0%
Biphasic insulin	——	——	——	——	-0.20 (-0.56, 0.16)			0.4%
Alpha-glucosidase inhibitors vs:								
GLP-1 analogues	——	——	——	——	-0.08 (-0.40, 0.25)	See above		0.0%
Basal insulin	——	——	——	——	-0.08 (-0.49, 0.34)			0.2%

Full MTC Results for A1C								
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates* (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (≥ 0.7%)
Biphasic insulin	——	——	——	——	-0.23 (-0.65, 0.20)			1.5%
GLP-1 analogues vs:								
Basal insulin	2[53,60]	107	0	0.01 (-0.25, 0.28)	0.00 (-0.29, 0.30)	See above		0.0%
Biphasic insulin	——	——	——	——	-0.15 (-0.50, 0.19)			0.2%
Basal insulin vs:								
Biphasic insulin	2[80,94]	297	51.9	-0.16 (-0.56, 0.25)	-0.15 (-0.45, 0.14)	See above		0.0%

A1C = glycosylated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCT = randomized controlled trial; TZDs = thiazolidinediones; vs = versus; WMD = weighted mean difference.

* Model fit parameters: DIC = 33.85, residual deviance = 19.06

APPENDIX 13: FULL MTC RESULTS FOR BODY WEIGHT

This table presents the results of the MTC reference case and the pairwise meta-analyses of direct comparisons for body weight (30 RCTs; N = 15,265). All values represent the difference in the change in body weight from baseline between two treatment arms. The MTC results are presented as the mean pooled estimate of effect (95% credible interval) and the direct comparisons as the mean difference for the change in body weight from baseline (95% confidence interval). The "Rank" represents the average ranking for each treatment relative to the others over the 40,000 simulations. For example, a lower number indicates that a particular treatment had the least weight gain (or greatest weight loss) for the majority of simulations (relative to other treatments), while a higher number indicates that a treatment had the largest weight gain. The table also presents the MTC results in the form of the probability of achieving the largest reduction in body weight with each individual treatment.

Full MTC Results for Body Weight (kg)							
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Weight Reduction	Rank
Metformin monotherapy vs:							
Sulfonylureas	3[63,83,89]	501	0	1.79 (1.29, 2.28)	2.01 (1.10, 2.93)	0.0%	6.5
Meglitinides	2[84,87]	366	88.7	2.01 (-0.31, 4.32)	1.80 (0.36, 3.28)	0.0%	6.2
TZDs	4[66,72,78,101]	752	0	2.30 (1.93, 2.66)	2.59 (1.67, 3.51)	0.0%	7.9
DPP-4 inhibitors	3[58,73,101]	923	19.4	0.70 (0.20, 1.21)	0.57 (-0.45, 1.61)	0.2%	4.1
Alpha-glucosidase inhibitors	3[92,99,103]	404	69.2	-0.90 (-1.92, 0.13)	-0.91 (-2.35, 0.53)	20.9%	2.0
GLP-1 analogues	2[64,89]	298	75.2	-1.58 (-3.53, 0.37)	-1.79 (-3.41, -0.15)	78.7%	1.2
Basal insulin	——	——	——	——	1.55 (-0.46, 3.61)	0.0%	5.7
Biphasic insulin	——	——	——	——	2.95 (0.95, 5.00)	0.0%	8.3
Sulfonylurea vs:							
Meglitinides	1[97]	262	——	-0.49 (-1.41, 0.43)	-0.21 (-1.76, 1.35)	See above	
TZDs	5[62,71,77,91,102]	3408	96.4	0.76 (-1.46, 2.99)	0.58 (-0.30, 1.45)		
DPP-4 inhibitors	2[68,88]	3961	78.0	-2.11 (-2.81, -1.42)	-1.44 (-2.47, -0.42)		
Alpha-glucosidase inhibitors	——	——	——	——	-2.92 (-4.64, -1.24)		
GLP-1 analogues	1[89]	72	——	-2.70 (4.29, -1.11)	-3.80 (-5.51, -2.09)		
Basal insulin	——	——	——	——	-0.46 (-2.47, 1.58)		

Full MTC Results for Body Weight (kg)							
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Weight Reduction	Rank
Biphasic insulin	1[81]	230	——	0.66 (-0.14, 1.46)	0.94 (-0.98, 2.88)		
Meglitinides vs:							
TZDs	——	——	——	——	0.79 (-0.87, 2.42)	See above	
DPP-4 inhibitors	——	——	——	——	-1.23 (-2.94, 0.48)		
Alpha-glucosidase inhibitors	——	——	——	——	-2.71 (-4.77, -0.68)		
GLP-1 analogues	——	——	——	——	-3.59 (-5.74, -1.45)		
Basal insulin	——	——	——	——	-0.25 (-2.69, 2.21)		
Biphasic insulin	——	——	——	——	1.15 (-1.25, 3.59)		
TZDs vs:							
DPP-4 inhibitors	3[55,57,101]	3421	83.2	-1.72 (-2.59, 0.84)	-2.02 (-3.02, -1.00)	See above	
Alpha-glucosidase inhibitors	——	——	——	——	-3.50 (-5.20, -1.81)		
GLP-1 analogues	——	——	——	——	-4.37 (-6.15, -2.60)		
Basal insulin	——	——	——	——	-1.03 (-3.13, 1.11)		
Biphasic insulin	——	——	——	——	0.37 (-1.68, 2.44)		
DPP-4 inhibitors vs:							
Alpha-glucosidase inhibitors	——	——	——	——	-1.48 (-3.25, 0.27)	See above	
GLP-1 analogues	——	——	——	——	-2.36 (-4.20, -0.51)		
Basal insulin	——	——	——	——	0.98 (-1.20, 3.18)		
Biphasic insulin	——	——	——	——	2.38 (0.27, 4.53)		
Alpha-glucosidase inhibitors vs:							
GLP-1 analogues	——	——	——	——	-0.87 (-3.03, 1.29)	See above	
Basal insulin	——	——	——	——	2.47 (-0.04, 4.99)		
Biphasic insulin	——	——	——	——	3.87 (1.41, 6.36)		
GLP-1 analogues vs:							
Basal insulin	2[53,60]	107	51.9	3.51 (1.79, 5.24)	3.34 (1.67, 5.01)	See above	
Biphasic insulin	——	——	——	——	4.74 (2.76, 6.73)		

Full MTC Results for Body Weight (kg)							
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Weight Reduction	Rank
Basal insulin vs:							
Biphasic insulin	2[80,94]	297	82.1	1.55 (-0.24, 3.35)	1.40 (-0.19, 3.01)	See above	

Model fit parameters: DIC = 90.36, residual deviance = 31.25
A1C = glycosylated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCTs = randomized controlled trials; SC = study characteristics; TC = trial characteristics; TZDs = thiazolidinediones; vs = versus; WMD = weighted mean difference.

APPENDIX 14: FULL MTC RESULTS FOR OVERALL HYPOGLCYEMIA

This table presents the results of the MTC reference case and the pairwise meta-analyses of direct comparisons for overall hypoglycemia (34 RCTs; N = 16,704). All values represent the difference in the change in overall hypoglycemia from baseline between two treatment arms. The MTC results are presented as the mean pooled odds ratio (95% credible interval) and the direct comparisons as the pooled odds ratio for overall hypoglycemia (95% confidence interval). The table also presents the MTC results in the form of the probability of achieving the least overall hypoglycemia with each individual treatment.

Full MTC Results for Overall Hypoglycemia									
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates OR (95% CI)	MTC Estimates			Probability of Least Hypoglycemia	Rank
					Mean OR	Median OR	(95% CrI)		
Metformin monotherapy vs:									
Sulfonylureas	3[63,83,89]	501	42	4.64 (1.27, 16.97)	8.8	8.2	(4.5, 16.6)	0.0%	7.5
Meglitinides	2[84,87]	366	31	6.59 (1.53, 28.29)	10.0	8.6	(3.5, 25.2)	0.0%	7.6
TZDs	6[66,69,72,78,82,101]	1210	0	1.56 (0.56, 4.33)	1.2	1.1	(0.5, 2.3)	6.2%	3.4
DPP-4 inhibitors	7[58,59,61,65,73,95,101]	2428	0	1.07 (0.59, 1.93)	1.1	1.0	(0.6, 2.2)	7.7%	3.2
Alpha-glucosidase inhibitors	2[99,103]	321	——	0.49 (0.04, 5.55)	1.1	0.4	(0.0, 6.7)	66.4%	2.1
GLP-1 analogues	1[64]	226	——	1.00 (0.31, 3.20)	1.4	1.1	(0.3, 3.9)	12.9%	3.4
Basal insulin	——	——	——	——	6.8	5.2	(1.5, 21.5)	0.0%	6.4
Biphasic insulin	——	——	——	——	13.8	11.0	(3.5, 40.4)	0.0%	8.3
Sulfonylurea vs:									
Meglitinides	1[97]	213	——	1.09 (0.52, 2.25)	1.2	1.0	(0.4, 2.9)	See above	
TZDs	5[62,71,77,102,104]	3397	69.9	0.16 (0.09, 0.28)	0.1	0.1	(0.1, 0.2)		
DPP-4 inhibitors	2[68,88]	3961	0	0.10 (0.07, 0.13)	0.1	0.1	(0.1, 0.2)		
Alpha-glucosidase inhibitors	——	——	——	——	0.1	0.0	(0.0, 0.9)		
GLP-1 analogues	1[89]	72	——	0.31 (0.03, 3.17)	0.2	0.1	(0.0, 0.5)		
Basal insulin	——	——	——	——	0.8	0.6	(0.2, 2.3)		

Full MTC Results for Overall Hypoglycemia									
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates OR (95% CI)	MTC Estimates			Probability of Least Hypoglycemia	Rank
					Mean OR	Median OR	(95% CrI)		
Biphasic insulin	1[81]	222	——	1.23 (0.69, 2.18)	1.6	1.3	(0.5, 4.2)		
Meglitinides vs:									
TZDs	——	——	——	——	0.1	0.1	(0.0, 0.4)	See above	
DPP-4 inhibitors	——	——	——	——	0.1	0.1	(0.0, 0.3)		
Alpha-glucosidase inhibitors	——	——	——	——	0.1	0.0	(0.0, 0.9)		
GLP-1 analogues	——	——	——	——	0.2	0.1	(0.0, 0.6)		
Basal insulin	——	——	——	——	0.8	0.6	(0.1, 2.8)		
Biphasic insulin	——	——	——	——	1.7	1.3	(0.3, 5.5)		
TZDs vs:									
DPP-4 inhibitors	3[55,57,101]	3383	0	1.79 (0.62, 5.14)	1.0	0.9	(0.5, 2.1)	See above	
Alpha-glucosidase inhibitors	——	——	——	——	1.1	0.4	(0.0, 6.7)		
GLP-1 analogues	——	——	——	——	1.3	1.0	(0.3, 3.8)		
Basal insulin	——	——	——	——	6.2	4.7	(1.3, 19.9)		
Biphasic insulin	——	——	——	——	12.5	10.0	(3.1, 36.5)		
DPP-4 Inhibitors vs:									
Alpha-glucosidase inhibitors	——	——	——	——	1.1	0.4	(0.0, 6.8)	See above	
GLP-1 analogues	——	——	——	——	1.3	1.1	(0.3, 3.9)		
Basal insulin	——	——	——	——	6.4	5.0	(1.3, 19.8)		
Biphasic insulin	——	——	——	——	12.9	10.6	(3.0, 36.7)		
Alpha-glucosidase inhibitors vs:									
GLP-1 analogues	——	——	——	——	23.4	2.9	(0.1, 130.5)	See above	
Basal insulin	——	——	——	——	111.0	13.7	(0.6, 638.9)		
Biphasic insulin	——	——	——	——	229.3	29.2	(1.3, 1317.0)		
GLP-1 analogues vs:									
Basal insulin	2[53,60]	107	0	4.58 (1.40, 15.03)	5.7	4.6	(1.5, 16.3)	See above	
Biphasic insulin	——	——	——	——	12.5	9.9	(2.8, 38.2)		

Full MTC Results for Overall Hypoglycemia									
	No. of Trials	No. of Patients	I^2 (%)	Direct Estimates OR (95% CI)	MTC Estimates			Probability of Least Hypoglycemia	Rank
					Mean OR	Median OR	(95% CrI)		
Basal insulin vs:									
Biphasic insulin	2[80,94]	297	32	2.23 (1.21, 4.09)	2.3	2.1	(0.9, 5.1)	See above	

Model fit parameters: DIC = 333.12, residual deviance = 64.63
Note: One small crossover RCT[104] (N = 12) comparing sulfonylureas and TZDs was not included in the MTC analysis. The combination of one of the treatment arms having zero events and the extremely small sample size created numerical difficulties, so the trial was excluded from the MTC. The trial was included in the direct pairwise comparisons.
A1C = glycosylated hemoglobin; CI = confidence interval; CrI = credible interval; OR = odds ratio; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; I^2 = ;
MTC = mixed treatment comparison; RCTs = randomized controlled trials; SC = study characteristics; TC = trial characteristics; TZDs = thiazolidinediones; vs = versus.

APPENDIX 15: FULL MTC RESULTS FOR A1C (DOSE-STRATIFIED MODEL)

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Metformin monotherapy vs:							
Sulfonylureas							
Titrated	2 RCTs[63,83]	429	-0.80 (-1.01, -0.59)	-0.81 (-1.00, -0.63)	0.2%	7.5	89.4%
Low dose	1 RCT[67]	122	-0.47 (-0.71, -0.23)	-0.63 (-0.97, -0.29)	0.5%	11.9	32.8%
Moderate/high dose	1 RCT[90]	130	-0.77 (-1.59, 0.05)	-0.80 (-1.26, -0.34)	9.8%	7.9	66.7%
Meglitinides							
Titrated	1 RCT[87]	54	-1.08 (-1.73, -0.43)	-0.79 (-1.19, -0.38)	6.3%	8.2	66.6%
Low dose	1 RCT[84]	307	-0.36 (-0.59, -0.13)	-0.36 (-0.76, 0.04)	0.1%	15.6	4.5%
Moderate/high dose	1 RCT[84]	312	-0.51 (-0.75, -0.27)	-0.51 (-0.91, -0.10)	0.4%	13.7	16.9%
TZDs							
Titrated	2 RCTs[78,82]	405	-0.92 (-1.17, -0.66)	-0.81 (-1.02, -0.60)	0.7%	7.6	85.4%
Low dose	2 RCTs[69,72]	198	-1.01 (-1.48, -0.54)	-0.70 (-1.08, -0.33)	2.5%	10.2	48.7%
Moderate/high dose	4 RCTs[66,69,72,101]	806	-1.06 (-1.47, -0.66)	-0.92 (-1.21, -0.65)	13.1%	4.8	94.1%
DPP-4 inhibitors							
Low dose	2 RCTs[52,58]	380	-0.70 (-0.86, -0.54)	-0.65 (-0.93, -0.37)	0.4%	11.4	36.9%
Moderate/high dose	6 RCTs[58,61,65,73,95,101]	2376	-0.78 (-0.96, -0.60)	-0.81 (-0.96, -0.67)	0.3%	7.4	93.5%
Alpha-glucosidase inhibitors							
Titrated	5 RCTs[74,92,98,99,103]	791	-0.74 (-0.94, -0.53)	-0.74 (-0.99, -0.50)	1.2%	9.2	64.4%
GLP-1 analogues							
Titrated	1 RCT[89]	72	-0.80 (-1.20, -0.40)	-0.95 (-1.31, -0.60)	14.9%	4.5	92.0%
Low dose	3 RCTs[64,90,93]	439	-0.45 (-0.67, -0.24)	-0.45 (-0.75, -0.15)	0.0%	15.0	5.0%
Moderate/high dose	3 RCTs[64,90,93]	542	-0.73 (-1.04, -0.42)	-0.73 (-1.04, -0.43)	2.2%	9.5	57.6%
Basal insulin	———	———	———	-0.92 (-1.33, -0.50)	8.1%	5.5	85.2%
Biphasic insulin	———	———	———	-1.04 (-1.43, -0.65)	39.3%	3.1	95.6%
Titrated sulfonylureas vs:							
Sulfonylureas					See above		
Low dose	———	———	———	0.19 (-0.20, 0.57)			0.0%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Moderate/high dose	–––	–––	–––	0.01 (-0.47, 0.49)			0.3%
Meglitinides							
Titrated	1 RCT[97]	262	0.13 (-0.43, 0.17)	0.03 (-0.36, 0.41)			0.0%
Low dose	–––	–––	–––	0.45 (0.02, 0.89)			0.0%
Moderate/high dose	–––	–––	–––	0.30 (-0.14, 0.75)			0.0%
TZDs							
Titrated	4 RCTs[62,71,77,102]	3380	0.01 (-0.28, 0.27)	0.01 (-0.16, 0.17)			0.0%
Low dose	–––	–––	–––	0.12 (-0.30, 0.52)			0.0%
Moderate/high dose	–––	–––	–––	-0.11 (-0.43, 0.20)			0.1%
DPP-4 inhibitors							
Low dose	–––	–––	–––	0.16 (-0.16, 0.49)			0.0%
Moderate/high dose	2 RCTs[68,88]	3961	0.05 (-0.14, 0.05)	0.00 (-0.17, 0.17)			0.0%
Alpha-glucosidase inhibitors							
Titrated	–––	–––	–––	0.07 (-0.23, 0.37)			0.0%
GLP-1 analogues							
Titrated	1 RCT[89]	72	-0.30 (-0.05, 0.65)	-0.14 (-0.48, 0.20)			0.1%
Low dose	–––	–––	–––	0.37 (0.01, 0.72)			0.0%
Moderate/high dose	–––	–––	–––	0.08 (-0.27, 0.44)			0.0%
Basal insulin	–––	–––	–––	-0.10 (-0.49, 0.29)			0.2%
Biphasic insulin	1 RCT[81]	230	-0.20 (-0.09, 0.49)	-0.23 (-0.59, 0.13)			0.6%
Low-dose sulfonylureas vs:							
Sulfonylureas					See above		
Moderate/high dose	–––	–––	–––	-0.18 (-0.74, 0.39)			3.5%
Meglitinides							
Titrated	–––	–––	–––	-0.16 (-0.69, 0.37)			2.3%
Low dose	–––	–––	–––	0.27 (-0.25, 0.80)			0.0%
Moderate/high dose	–––	–––	–––	0.12 (-0.41, 0.65)			0.2%
TZDs							
Titrated	–––	–––	–––	-0.18 (-0.57, 0.22)			0.5%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Low dose	2 RCTs[75,79]	645	0.06 (-0.22, 0.10)	-0.07 (-0.37, 0.22)			0.0%
Moderate/high dose	———	———	———	-0.30 (-0.74, 0.14)			3.5%
DPP-4 inhibitors							
Low dose	———	———	———	-0.03 (-0.46, 0.42)			0.1%
Moderate/high dose	———	———	———	-0.19 (-0.55, 0.19)			0.3%
Alpha-glucosidase inhibitors							
Titrated	———	———	———	-0.12 (-0.53, 0.30)			0.3%
GLP-1 analogues							
Titrated	———	———	———	-0.33 (-0.81, 0.17)			6.5%
Low dose	———	———	———	0.18 (-0.27, 0.63)			0.0%
Moderate/high dose	———	———	———	-0.10 (-0.55, 0.36)			0.5%
Basal insulin	———	———	———	-0.29 (-0.82, 0.25)			6.4%
Biphasic insulin	———	———	———	-0.41 (-0.92, 0.11)			13.1%
Moderate/high dose sulfonylureas vs:							
Meglitinides					See above		
Titrated	———	———	———	0.02 (-0.59, 0.62)			1.0%
Low dose	———	———	———	0.44 (-0.17, 1.05)			0.0%
Moderate/high dose	———	———	———	0.29 (-0.32, 0.91)			0.1%
TZDs							
Titrated	———	———	———	0.00 (-0.49, 0.49)			0.3%
Low dose	———	———	———	0.11 (-0.48, 0.68)			0.4%
Moderate/high dose	2 RCTs[91,104]	41	-0.10 (-0.29, 0.49)	-0.12 (-0.53, 0.29)			0.3%
DPP-4 inhibitors							
Low dose	———	———	———	0.15 (-0.39, 0.69)			0.1%
Moderate/high dose	———	———	———	-0.01 (-0.47, 0.46)			0.2%
Alpha-glucosidase inhibitors							
Titrated	———	———	———	0.06 (-0.46, 0.58)			0.2%
GLP-1 analogues							
Titrated	———	———	———	-0.15 (-0.72, 0.43)			3.0%
Low dose	1 RCT[90]	170	0.29 (-0.53, 1.11)	0.36 (-0.19, 0.90)			0.0%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Moderate/high dose	1 RCT[90]	263	-0.12 (-0.70, 0.95)	0.07 (-0.48, 0.62)			0.3%
Basal insulin	—	—	—	-0.11 (-0.72, 0.50)			2.9%
Biphasic insulin	—	—	—	-0.24 (-0.83, 0.35)			6.3%
Titrated meglitinides vs:							
Meglitinides	—	—	—		See above		
Low dose	—	—	—	0.43 (-0.14, 1.00)			0.0%
Moderate/high dose	—	—	—	0.28 (-0.29, 0.86)			0.1%
TZDs	—	—	—				
Titrated	—	—	—	-0.02 (-0.43, 0.40)			0.1%
Low dose	—	—	—	0.09 (-0.46, 0.64)			0.3%
Moderate/high dose	—	—	—	-0.14 (-0.62, 0.34)			1.2%
DPP-4 inhibitors	—	—	—				
Low dose	—	—	—	0.13 (-0.35, 0.62)			0.1%
Moderate/high dose	—	—	—	-0.03 (-0.44, 0.38)			0.1%
Alpha-glucosidase inhibitors	—	—	—				
Titrated	—	—	—	0.04 (-0.43, 0.51)			0.1%
GLP-1 analogues	—	—	—				
Titrated	—	—	—	-0.17 (-0.67, 0.35)			1.9%
Low dose	—	—	—	0.34 (-0.16, 0.85)			0.0%
Moderate/high dose	—	—	—	0.06 (-0.45, 0.56)			0.2%
Basal insulin	—	—	—	-0.13 (-0.67, 0.42)			1.9%
Biphasic insulin	—	—	—	-0.25 (-0.77, 0.27)			4.6%
Low-dose meglitinides vs:							
Meglitinides	—	—	—		See above		
Moderate/high dose	—	—	—	-0.15 (-0.61, 0.32)			1.0%
TZDs	—	—	—				
Titrated	—	—	—	-0.45 (-0.89, 0.00)			12.6%
Low dose	—	—	—	-0.34 (-0.89, 0.20)			9.4%
Moderate/high dose	—	—	—	-0.56 (-1.05, -0.08)			28.6%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
DPP-4 inhibitors	–––	–––	–––				
Low dose	–––	–––	–––	-0.29 (-0.78, 0.20)			4.8%
Moderate/high dose	–––	–––	–––	-0.45 (-0.88, -0.03)			11.9%
Alpha-glucosidase inhibitors	–––	–––	–––				
Titrated	–––	–––	–––	-0.38 (-0.85, 0.08)			8.7%
GLP-1 analogues	–––	–––	–––				
Titrated	–––	–––	–––	-0.59 (-1.12, -0.05)			34.1%
Low dose	–––	–––	–––	-0.09 (-0.60, 0.42)			0.9%
Moderate/high dose	–––	–––	–––	-0.37 (-0.87, 0.13)			9.5%
Basal insulin	–––	–––	–––	-0.56 (-1.12, 0.03)			30.7%
Biphasic insulin	–––	–––	–––	-0.68 (-1.24, -0.12)			46.9%
Moderate-/high-dose meglitinides vs:							
TZDs	–––	–––	–––		See above		
Titrated	–––	–––	–––	-0.30 (-0.75, 0.16)			4.0%
Low dose	–––	–––	–––	-0.19 (-0.74, 0.36)			3.5%
Moderate/high dose	–––	–––	–––	-0.41 (-0.92, 0.07)			12.3%
DPP-4 inhibitors	–––	–––	–––				
Low dose	–––	–––	–––	-0.14 (-0.63, 0.35)			1.3%
Moderate/high dose	–––	–––	–––	-0.30 (-0.74, 0.13)			3.8%
Alpha-glucosidase inhibitors	–––	–––	–––				
Titrated	–––	–––	–––	-0.24 (-0.71, 0.23)			2.7%
GLP-1 analogues	–––	–––	–––				
Titrated	–––	–––	–––	-0.44 (-0.99, 0.10)			16.8%
Low dose	–––	–––	–––	0.06 (-0.44, 0.57)			0.3%
Moderate/high dose	–––	–––	–––	-0.22 (-0.73, 0.28)			3.2%
Basal insulin	–––	–––	–––	-0.41 (-0.99, 0.17)			15.4%
Biphasic insulin	–––	–––	–––	-0.53 (-1.09, 0.03)			27.2%
Titrated TZDs vs:							
TZDs					See above		
Low dose	–––	–––	–––	0.11 (-0.32, 0.52)			0.0%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Moderate/high dose	—	—	—	-0.12 (-0.45, 0.21)			0.1%
DPP-4 inhibitors							
Low dose	—	—	—	0.15 (-0.18, 0.50)			0.0%
Moderate/high dose	—	—	—	-0.01 (-0.20, 0.19)			0.0%
Alpha-glucosidase inhibitors							
Titrated	—	—	—	0.06 (-0.26, 0.38)			0.0%
GLP-1 analogues							
Titrated	—	—	—	-0.14 (-0.51, 0.22)			0.2%
Low dose	—	—	—	0.36 (-0.01, 0.72)			0.0%
Moderate/high dose	—	—	—	0.08 (-0.29, 0.44)			0.0%
Basal insulin	—	—	—	-0.11 (-0.52, 0.31)			0.3%
Biphasic insulin	—	—	—	-0.23 (-0.63, 0.15)			1.1%
Low-dose TZDs vs:							
TZDs					See above		
Moderate/high dose	2 RCTs[69,72]	297	-0.35 (-0.17, 0.88)	-0.23 (-0.68, 0.23)			2.0%
DPP-4 inhibitors							
Low dose	—	—	—	0.04 (-0.41, 0.52)			0.1%
Moderate/high dose	—	—	—	-0.12 (-0.50, 0.29)			0.2%
Alpha-glucosidase inhibitors							
Titrated	—	—	—	-0.05 (-0.48, 0.40)			0.2%
GLP-1 analogues							
Titrated	—	—	—	-0.25 (-0.76, 0.26)			4.2%
Low dose	—	—	—	0.25 (-0.22, 0.73)			0.0%
Moderate/high dose	—	—	—	-0.03 (-0.5, 0.45)			0.3%
Basal insulin	—	—	—	-0.22 (-0.77, 0.35)			4.2%
Biphasic insulin	—	—	—	-0.34 (-0.87, 0.20)			9.2%
Moderate-/high-dose TZDs vs:							
DPP-4 inhibitors					See above		
Low dose	—	—	—	0.27 (-0.12, 0.67)			0.0%
Moderate/high dose	2 RCTs[57,101]	688	0.00 (-0.20, 0.20)	0.11 (-0.17, 0.39)			0.0%

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Alpha-glucosidase inhibitors							
Titrated	–––	–––	–––	0.18 (-0.19, 0.56)			0.0%
GLP-1 analogues							
Titrated	–––	–––	–––	-0.03 (-0.47, 0.42)			0.2%
Low dose	–––	–––	–––	0.48 (0.07, 0.89)			0.0%
Moderate/high dose	–––	–––	–––	0.19 (-0.22, 0.61)			0.0%
Basal insulin	–––	–––	–––	0.01 (-0.48, 0.50)			0.3%
Biphasic insulin	–––	–––	–––	-0.12 (-0.58, 0.36)			0.8%
Low-dose DPP-4 inhibitors vs:							
DPP-4 inhibitors					See above		
Moderate/high dose	1 RCT[58]	286	-0.40 (0.20, 0.60)	-0.16 (-0.47, 0.14)			0.1%
Alpha-glucosidase inhibitors							
Titrated	–––	–––	–––	-0.09 (-0.46, 0.27)			0.1%
GLP-1 analogues							
Titrated	–––	–––	–––	-0.30 (-0.75, 0.15)			4.1%
Low dose	–––	–––	–––	0.21 (-0.20, 0.61)			0.0%
Moderate/high dose	–––	–––	–––	-0.08 (-0.49, 0.34)			0.2%
Basal insulin	–––	–––	–––	-0.26 (-0.76, 0.24)			4.1%
Biphasic insulin	–––	–––	–––	-0.38 (-0.86, 0.09)			9.5%
Moderate-/high-dose DPP-4 inhibitors vs:							
Alpha-glucosidase inhibitors					See above		
Titrated	–––	–––	–––	0.07 (-0.21, 0.35)			0.0%
GLP-1 analogues							
Titrated	–––	–––	–––	-0.14 (-0.50, 0.23)			0.2%
Low dose	–––	–––	–––	0.37 (0.03, 0.70)			0.0%
Moderate/high dose	–––	–––	–––	0.08 (-0.25, 0.42)			0.0%
Basal insulin	–––	–––	–––	-0.10 (-0.51, 0.32)			0.3%
Biphasic insulin	–––	–––	–––	-0.23 (-0.61, 0.16)			1.0%
Titrated alpha-glucosidase inhibitors vs:							
GLP-1 analogues					See above		

Full MTC Results for A1C (Dose-Stratified Model)							
	No. of Trials	No. of Patients	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Probability of Largest A1C Reduction	Rank	Probability of A1C Reduction (> 0.7%)
Titrated	–––	–––	–––	-0.21 (-0.64, 0.22)			1.2%
Low dose	–––	–––	–––	0.30 (-0.09, 0.69)			0.0%
Moderate/high dose	–––	–––	–––	0.01 (-0.37, 0.40)			0.0%
Basal insulin	–––	–––	–––	-0.17 (-0.65, 0.31)			1.5%
Biphasic insulin	–––	–––	–––	-0.29 (-0.75, 0.16)			4.1%
Titrated GLP-1 analogues vs:							
GLP-1 analogues					See above		
Low dose	–––	–––	–––	0.51 (0.04, 0.97)			0.0%
Moderate/high dose	–––	–––	–––	0.22 (-0.24, 0.69)			0.0%
Basal insulin	2 RCTs[53,60]	207	0.01 (-0.28, 0.25)	0.03 (-0.28, 0.35)			0.0%
Biphasic insulin	–––	–––	–––	-0.09 (-0.47, 0.29)			0.1%
Low-dose GLP-1 analogues vs:							
GLP-1 analogues					See above		
Moderate/high dose	3 RCTs[64,90,93]	571	-0.29 (0.08, 0.49)	-0.28 (-0.65, 0.09)			1.3%
Basal insulin	–––	–––	–––	-0.47 (-0.97, 0.03)			18.5%
Biphasic insulin	–––	–––	–––	-0.59 (-1.09, -0.10)			33.3%
Moderate-/high-dose GLP-1 analogues vs:							
Basal insulin	–––	–––	–––	-0.19 (-0.70, 0.32)	See above		2.5%
Biphasic insulin	–––	–––	–––	-0.31 (-0.80, 0.19)			5.9%
Basal insulin v:							
Biphasic insulin	2 RCTs[80,94]	297	-0.16 (-0.56, 0.25)	-0.12 (-0.44, 0.19)	See above		0.0%

A1C = glycosylated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCT = randomized controlled trial; SC = study characteristics; TC = trial characteristics; TZDs = thiazolidinediones; vs = versus; WMD = weighted mean difference.

APPENDIX 16: FULL MTC RESULTS FOR BODY WEIGHT (DOSE-STRATIFIED MODEL)

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
Metformin monotherapy vs:						
Sulfonylureas						
Titrated	3 RCTs[63,83,89]	501	1.79 (1.29, 2.28)	2.10 (1.07, 3.15)	0.0%	12.8
Low dose	1 RCT[67]	122	2.10 (1.08, 3.12)	2.11 (-0.45, 4.68)	0.1%	12.7
Moderate/high dose	–––	–––	–––	2.80 (-0.67, 6.26)	0.2%	14.1
Meglitinides						
Titrated	1 RCT[87]	54	3.27 (1.88, 4.66)	2.37 (0.44, 4.32)	0.0%	13.7
Low dose	1 RCT[84]	307	0.30 (-0.20, 0.80)	0.30 (-2.09, 2.68)	1.7%	7.3
Moderate/high dose	1 RCT[84]	312	0.90 (0.20, 1.60)	0.89 (-1.54, 3.33)	0.7%	9.2
TZDs						
Titrated	1 RCT[78]	169	2.15 (1.56, 2.74)	2.64 (1.38, 3.90)	0.0%	14.8
Low dose	1 RCT[72]	69	1.12 (-0.41, 2.65)	0.92 (-1.76, 3.52)	1.0%	9.2
Moderate/high dose	3 RCTs[66,72,101]	583	2.39 (1.92, 2.86)	2.69 (1.39, 3.98)	0.0%	14.8
DPP-4 inhibitors						
Low dose	2 RCTs[52,58]	380	0.25 (-0.20, 0.71)	0.23 (-1.41, 1.90)	0.5%	7.0
Moderate/high dose	3 RCTs[58,73,101]	829	0.70 (0.21, 1.20)	0.62 (-0.41, 1.68)	0.0%	8.2
Alpha-glucosidase inhibitors						
Titrated	3[92,99,103]	404	-0.90 (-1.92, 0.13)	-0.91 (-2.37, 0.56)	5.5%	3.8
GLP-1 analogues						
Titrated	1 RCT[89]	72	-0.50 (-2.09, 1.09)	-1.22 (-3.45, 1.01)	16.0%	3.5
Low dose	1 RCT[64]	223	-1.30 (-2.28, -0.32)	-1.30 (-3.84, 1.24)	12.7%	3.6
Moderate/high dose	1 RCT[64]	226	-2.50 (-3.64, -1.36)	-2.51 (-5.14, 0.09)	61.7%	1.8
Basal insulin	–––	–––	–––	1.99 (-0.35, 4.36)	0.0%	12.3
Biphasic insulin	–––	–––	–––	3.28 (1.07, 5.54)	0.0%	16.1
Titrated sulfonylureas vs:						
Sulfonylureas						

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
Low dose	———	———	———	0.00 (-2.76, 2.78)		
Moderate/high dose	———	———	———	0.70 (-2.89, 4.28)		
Meglitinides						
Titrated	1 RCT[97]	213	-0.49 (-0.43, 1.41)	0.27 (-1.64, 2.17)		
Low dose	———	———	———	-1.81 (-4.41, 0.79)		
Moderate/high dose				-1.21 (-3.86, 1.44)		
TZDs						
Titrated	4 RCTs [62,71,77,102]	3373	0.92 (-1.53, -3.37)	0.54 (-0.52, 1.60)		
Low dose	———	———	———	-1.19 (-4.04, 1.61)		
Moderate/high dose	———	———	———	0.59 (-0.95, 2.12)		
DPP-4 inhibitors						
Low dose	———	———	———	-1.87 (-3.76, 0.01)		
Moderate/high dose	2 RCTs [68,88]	3961	-2.11 (-2.81,-1.42)	-1.48 (-2.61, -0.35)		
Alpha-glucosidase inhibitors						
Titrated	———	———	———	-3.02 (-4.79, -1.24)		
GLP-1 analogues						
Titrated	1 RCT[89]	72	-2.70 (-4.29,-1.11)	-3.33 (-5.53, -1.14)		
Low dose	———	———	———	-3.41 (-6.15, -0.67)		
Moderate/high dose	———	———	———	-4.61 (-7.46, -1.82)		
Basal insulin	———	———	———	-0.11 (-2.38, 2.17)		
Biphasic insulin	1 RCT[81]	222	0.66 (-0.14,1.46)	1.17 (-0.89, 3.27)		
Low-dose sulfonylureas vs:						
Sulfonylureas						
Moderate/high dose	———	———	———	0.69 (-3.62, 5.00)		
Meglitinides						
Titrated	———	———	———	0.26 (-2.95, 3.45)		
Low dose	———	———	———	-1.81 (-5.30, 1.68)		
Moderate/high dose	———	———	———	-1.21 (-4.78, 2.34)		
TZDs						

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
Titrated	–––	–––	–––	0.53 (-2.34, 3.40)		
Low dose	–––	–––	–––	-1.19 (-4.90, 2.44)		
Moderate/high dose	–––	–––	–––	0.58 (-2.31, 3.41)		
DPP-4 inhibitors						
Low dose	–––	–––	–––	-1.87 (-4.93, 1.19)		
Moderate/high dose	–––	–––	–––	-1.48 (-4.28, 1.26)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-3.02 (-5.97, -0.12)		
GLP-1 analogues						
Titrated	–––	–––	–––	-3.33 (-6.72, 0.08)		
Low dose	–––	–––	–––	-3.41 (-7.00, 0.18)		
Moderate/high dose	–––	–––	–––	-4.62 (-8.24, -0.99)		
Basal insulin	–––	–––	–––	-0.12 (-3.60, 3.36)		
Biphasic insulin	–––	–––	–––	1.17 (-2.22, 4.58)		
Moderate-/high-dose sulfonylureas vs:						
Meglitinides						
Titrated	–––	–––	–––	-0.43 (-4.39, 3.54)		
Low dose	–––	–––	–––	-2.50 (-6.66, 1.71)		
Moderate/high dose	–––	–––	–––	-1.91 (-6.12, 2.37)		
TZDs						
Titrated	–––	–––	–––	-0.16 (-3.81, 3.49)		
Low dose	–––	–––	–––	-1.89 (-6.15, 2.35)		
Moderate/high dose	1 RCT[91]	28	-0.10 (-2.37, 2.17)	-0.11 (-3.35, 3.15)		
DPP-4 inhibitors						
Low dose	–––	–––	–––	-2.57 (-6.41, 1.25)		
Moderate/high dose	–––	–––	–––	-2.18 (-5.70, 1.35)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-3.71 (-7.52, 0.06)		
GLP-1 analogues						
Titrated	–––	–––	–––	-4.02 (-8.11, 0.06)		

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
Low dose	---	---	---	-4.10 (-8.42, 0.21)		
Moderate/high dose	---	---	---	-5.31 (-9.66, -0.95)		
Basal insulin	---	---	---	-0.81 (-4.96, 3.36)		
Biphasic insulin	---	---	---	0.48 (-3.60, 4.56)		
Titrated meglitinides vs:						
Meglitinides						
Low dose	---	---	---	-2.07 (-5.19, 0.97)		
Moderate/high dose	---	---	---	-1.48 (-4.60, 1.64)		
TZDs						
Titrated	---	---	---	0.27 (-1.86, 2.38)		
Low dose	---	---	---	-1.46 (-4.71, 1.77)		
Moderate/high dose	---	---	---	0.32 (-1.96, 2.60)		
DPP-4 inhibitors						
Low dose	---	---	---	-2.14 (-4.67, 0.35)		
Moderate/high dose	---	---	---	-1.75 (-3.84, 0.34)		
Alpha-glucosidase inhibitors						
Titrated	---	---	---	-3.28 (-5.74, -0.88)		
GLP-1 analogues						
Titrated	---	---	---	-3.59 (-6.43, -0.76)		
Low dose	---	---	---	-3.67 (-6.86, -0.47)		
Moderate/high dose	---	---	---	-4.88 (-8.13, -1.67)		
Basal insulin	---	---	---	-0.38 (-3.30, 2.55)		
Biphasic insulin	---	---	---	0.91 (-1.87, 3.70)		
Low-dose meglitinides vs:						
Meglitinides						
Moderate/high dose	1 RCT[84]	315	0.60 (0.21, 0.99)	0.60 (-1.91, 3.07)		
TZDs						
Titrated	---	---	---	2.34 (-0.38, 5.05)		
Low dose	---	---	---	0.62 (-2.94, 4.18)		
Moderate/high dose	---	---	---	2.39 (-0.32, 5.09)		

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
DPP-4 inhibitors						
Low dose	—	—	—	-0.06 (-2.96, 2.84)		
Moderate/high dose	—	—	—	0.33 (-2.27, 2.95)		
Alpha-glucosidase inhibitors						
Titrated	—	—	—	-1.21 (-4.00, 1.60)		
GLP-1 analogues						
Titrated	—	—	—	-1.52 (-4.80, 1.75)		
Low dose	—	—	—	-1.60 (-5.08, 1.91)		
Moderate/high dose	—	—	—	-2.81 (-6.36, 0.70)		
Basal insulin	—	—	—	1.69 (-1.67, 5.09)		
Biphasic insulin	—	—	—	2.98 (-0.28, 6.27)		
Moderate-/high-dose meglitinides vs:						
TZDs						
Titrated	—	—	—	1.75 (-1.01, 4.50)		
Low dose	—	—	—	0.02 (-3.59, 3.62)		
Moderate/high dose	—	—	—	1.80 (-0.96, 4.54)		
DPP-4 inhibitors						
Low dose	—	—	—	-0.66 (-3.60, 2.31)		
Moderate/high dose	—	—	—	-0.27 (-2.92, 2.39)		
Alpha-glucosidase inhibitors						
Titrated	—	—	—	-1.81 (-4.66, 1.05)		
GLP-1 analogues						
Titrated	—	—	—	-2.12 (-5.42, 1.23)		
Low dose	—	—	—	-2.20 (-5.72, 1.36)		
Moderate/high dose	—	—	—	-3.40 (-6.96, 0.19)		
Basal insulin	—	—	—	1.10 (-2.29, 4.56)		
Biphasic insulin	—	—	—	2.38 (-0.90, 5.76)		
Titrated TZDs vs:						
TZDs						
Low dose	—	—	—	-1.73 (-4.67, 1.16)		
Moderate/high dose	—	—	—	0.05 (-1.65, 1.74)		

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
DPP-4 inhibitors						
Low dose	–––	–––	–––	-2.41 (-4.44, -0.38)		
Moderate/high dose	1 RCT[55]	2664	-0.91 (-1.46, -0.36)	-2.02 (-3.33, -0.69)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-3.55 (-5.50, -1.62)		
GLP-1 analogues						
Titrated	–––	–––	–––	-3.86 (-6.24, -1.48)		
Low dose	–––	–––	–––	-3.94 (-6.79, -1.12)		
Moderate/high dose	–––	–––	–––	-5.15 (-8.06, -2.27)		
Basal insulin	–––	–––	–––	-0.65 (-3.11, 1.83)		
Biphasic insulin	–––	–––	–––	0.63 (-1.65, 2.97)		
Low-dose TZDs vs:						
TZDs						
Moderate/high dose	1 RCT[72]	71	2.16 (3.73, 0.59)	1.77 (-0.95, 4.52)		
DPP-4 inhibitors						
Low dose	–––	–––	–––	-0.68 (-3.75, 2.42)		
Moderate/high dose	–––	–––	–––	-0.29 (-3.06, 2.51)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-1.83 (-4.85, 1.23)		
GLP-1 analogues						
Titrated	–––	–––	–––	-2.14 (-5.58, 1.32)		
Low dose	–––	–––	–––	-2.22 (-5.87, 1.46)		
Moderate/high dose	–––	–––	–––	-3.43 (-7.11, 0.28)		
Basal insulin	–––	–––	–––	1.08 (-2.40, 4.61)		
Biphasic insulin	–––	–––	–––	2.36 (-1.02, 5.83)		
Moderate-/high-dose TZDs vs:						
DPP-4 inhibitors						
Low dose	–––	–––	–––	-2.46 (-4.48, -0.41)		
Moderate/high dose	1 RCT[57]	576	-2.40 (-3.11, -1.69)	-2.07 (-3.43, -0.68)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-3.60 (-5.56, -1.63)		

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
GLP-1 analogues						
Titrated	–––	–––	–––	-3.91 (-6.44, -1.36)		
Low dose	–––	–––	–––	-3.99 (-6.85, -1.17)		
Moderate/high dose	–––	–––	–––	-5.20 (-8.10, -2.29)		
Basal insulin	–––	–––	–––	-0.70 (-3.32, 1.96)		
Biphasic insulin	–––	–––	–––	0.59 (-1.91, 3.13)		
Low-dose DPP-4 inhibitors vs:						
DPP-4 inhibitors						
Moderate/high dose	1 RCT[58]	286	0.60 (0.01, 1.19)	0.39 (-1.42, 2.20)		
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-1.15 (-3.33, 1.07)		
GLP-1 analogues						
Titrated	–––	–––	–––	-1.46 (-4.19, 1.31)		
Low dose	–––	–––	–––	-1.54 (-4.57, 1.46)		
Moderate/high dose	–––	–––	–––	-2.74 (-5.83, 0.33)		
Basal insulin	–––	–––	–––	1.76 (-1.06, 4.62)		
Biphasic insulin	–––	–––	–––	3.04 (0.33, 5.81)		
Moderate-/high-dose DPP-4 inhibitors vs:						
Alpha-glucosidase inhibitors						
Titrated	–––	–––	–––	-1.54 (-3.35, 0.26)		
GLP-1 analogues						
Titrated	–––	–––	–––	-1.85 (-4.19, 0.54)		
Low dose	–––	–––	–––	-1.93 (-4.67, 0.83)		
Moderate/high dose	–––	–––	–––	-3.13 (-5.97, -0.32)		
Basal insulin	–––	–––	–––	1.37 (-1.07, 3.83)		
Biphasic insulin	–––	–––	–––	2.65 (0.35, 5.00)		
Titrated alpha-glucosidase inhibitors vs:						
GLP-1 analogues						
Titrated	–––	–––	–––	-0.31 (-2.98, 2.35)		
Low dose	–––	–––	–––	-0.39 (-3.33, 2.58)		
Moderate/high dose	–––	–––	–––	-1.60 (-4.59, 1.38)		

Full MTC Results for Body Weight (Dose-Stratified Model)						
	No. of Trials	No. of Patients	Direct Estimates (95% CI)	MTC Estimates (95% CrI)	Probability of Largest Reduction in Weight	Rank
Basal insulin	———	———	———	2.90 (0.13, 5.69)		
Biphasic insulin	———	———	———	4.19 (1.55, 6.90)		
Titrated GLP-1 analogues vs:						
GLP-1 analogues						
Low dose	———	———	———	-0.08 (-3.47, 3.30)		
Moderate/high dose	———	———	———	-1.29 (-4.74, 2.12)		
Basal insulin	2 RCTs[53,60]	145	3.51 (1.79, 5.24)	3.21 (1.43, 5.02)		
Biphasic insulin	———	———	———	4.50 (2.35, 6.68)		
Low-dose GLP-1 analogues vs:						
GLP-1 analogues						
Moderate/high dose	1 RCT[64]	223	-1.20 (-2.18, -0.22)	-1.21 (-4.03, 1.54)		
Basal insulin	———	———	———	3.29 (-0.18, 6.80)		
Biphasic insulin	———	———	———	4.58 (1.20, 7.99)		
Moderate-/high-dose GLP-1 analogues vs:						
Basal insulin	———	———	———	4.50 (1.01, 8.06)		
Biphasic insulin	———	———	———	5.79 (2.36, 9.27)		
Basal insulin v:						
Biphasic insulin	2 RCTs[80,94]	297	1.57 (-0.23, 3.38)	1.28 (-0.39, 2.99)		

CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; RCTs = randomized controlled trials; SC = study characteristics; TC = trial characteristics; TZDs = thiazolidinediones; vs = versus.

APPENDIX 17: FULL MTC RESULTS FOR OVERALL HYPOGLYCEMIA (DOSE-STRATIFIED MODEL)

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Metformin monotherapy vs:								
Sulfonylureas								
Titrated	3 RCTs[63,83,89]	501	4.64 (1.27, 16.97)	10.60	9.38	4.47, 23.94	0.0%	13.80
Meglitinides								
Titrated	1 RCT[87]	54	28.24 (1.55, 515.5)	22.89	14.60	3.79, 89.73	0.0%	14.83
Low dose	1 RCT[84]	307	2.23 (0.82, 6.02)	3.37	2.30	0.44, 12.65	1.2%	9.10
Moderate/high dose	1 RCT[84]	312	4.51 (1.79, 11.32)	6.85	4.72	0.92, 25.40	0.1%	11.78
TZDs								
Titrated	2 RCTs[78,82]	405	1.91 (0.30, 12.29)	1.34	1.17	0.47, 3.18	1.0%	6.40
Low dose	2 RCTs[69,72]	304	1.47 (0.24, 8.99)	1.61	0.96	0.13, 6.83	10.5%	5.73
Moderate/high dose	4 RCTs[66,69,72,101]	805	1.42 (0.42, 4.85)	1.78	1.38	0.36, 5.49	1.6%	7.21
DPP-4 inhibitors								
Low dose	1 RCT[58]	358	1.02 (0.06, 16.48)	2.93	0.97	0.03, 17.89	19.3%	6.13
Moderate/high dose	7 RCTs[58,59,61,65,73,95,101]	2428	1.07 (0.59, 1.93)	1.29	1.16	0.57, 2.76	0.5%	6.35
Alpha-glucosidase inhibitors								
Titrated	2 RCTs[99,103]	321	0.49 (0.04, 5.55)	1.21	0.39	0.01, 6.91	42.7%	3.76
GLP-1 analogues								
Titrated	1 RCT[89]	72	3.08 (0.12, 78.27)	2.57	1.44	0.20, 11.36	5.5%	7.14
Low dose	1 RCT[64]	223	0.85 (0.25, 2.87)	1.30	0.84	0.13, 5.18	10.3%	5.19
Moderate/high dose	1 RCT[64]	226	1.00 (0.31, 3.20)	1.56	1.01	0.17, 5.92	6.6%	5.90
Basal insulin	———	———	———	11.16	6.47	1.28, 45.74	0.0%	12.54

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Biphasic insulin	———	———	———	19.97	13.27	3.18, 75.34	0.0%	14.75
Titrated sulfonylureas vs:								
Meglitinides							See above	
Titrated	1 RCT[97]	213	0.92 (0.45, 1.91)	2.13	1.56	0.44, 7.21		
Low dose	———	———	———	0.38	0.24	0.03, 1.47		
Moderate/high dose	———	———	———	0.76	0.50	0.07, 2.92		
TZDs								
Titrated	4 RCTs[62,71,77,102]	3373	0.16 (0.09, 0.28)	0.13	0.13	0.06, 0.23		
Low dose	———	———	———	0.18	0.10	0.01, 0.78		
Moderate/high dose	———	———	———	0.19	0.15	0.03, 0.65		
DPP-4 inhibitors								
Low dose	———	———	———	0.31	0.10	0.00, 1.86		
Moderate/high dose	2 RCTs[68,88]	3961	0.10 (0.07, 0.13)	0.13	0.12	0.06, 0.26		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	0.13	0.04	0.00, 0.78		
GLP-1 analogues								
Titrated	1 RCT[89]	72	0.31 (0.03, 3.17)	0.23	0.15	0.02, 0.93		
Low dose	———	———	———	0.15	0.09	0.01, 0.60		
Moderate/high dose	———	———	———	0.17	0.11	0.01, 0.71		
Basal insulin	———	———	———	0.99	0.69	0.15, 3.63		
Biphasic insulin	1 RCT[81]	222		1.82	1.42	0.39, 5.68		
Titrated meglitinides vs:								
Meglitinides								
Low dose	———	———	———	0.29	0.16	0.01, 1.28		
Moderate/high dose	———	———	———	0.57	0.32	0.03, 2.60		
TZDs								
Titrated	———	———	———	0.10	0.08	0.01, 0.31		
Low dose	———	———	———	0.13	0.06	0.00, 0.66		

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Moderate/high dose	———	———	———	0.15	0.09	0.01, 0.59		
DPP-4 inhibitors								
Low dose	———	———	———	0.23	0.06	0.00, 1.46		
Moderate/high dose	———	———	———	0.10	0.08	0.01, 0.32		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	0.10	0.02	0.00, 0.63		
GLP-1 analogues								
Titrated	———	———	———	0.18	0.10	0.01, 0.86		
Low dose	———	———	———	0.11	0.06	0.00, 0.52		
Moderate/high dose	———	———	———	0.13	0.07	0.01, 0.61		
Basal insulin	———	———	———	0.77	0.44	0.05, 3.39		
Biphasic insulin	———	———	———	1.42	0.91	0.12, 5.70		
Low-dose meglitinides vs:								
Meglitinides								
Moderate/high dose	1 RCT[84]	315	9.38 (2.77, 31.77)	2.81	2.06	0.45, 9.34		
TZDs								
Titrated	———	———	———	0.86	0.51	0.08, 3.64		
Low dose	———	———	———	1.10	0.41	0.03, 5.49		
Moderate/high dose	———	———	———	1.15	0.60	0.07, 5.22		
DPP-4 inhibitors								
Low dose	———	———	———	1.96	0.41	0.01, 12.36		
Moderate/high dose	———	———	———	0.83	0.50	0.08, 3.45		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	0.88	0.17	0.00, 4.78		
GLP-1 analogues								
Titrated	———	———	———	1.90	0.61	0.05, 9.27		
Low dose	———	———	———	0.86	0.36	0.03, 4.31		
Moderate/high dose	———	———	———	1.07	0.43	0.04, 5.03		

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Basal insulin	———	———	———	8.54	2.83	0.28, 38.97		
Biphasic insulin	———	———	———	14.76	5.78	0.64, 66.38		
Moderate-/high-dose meglitinides vs:								
TZDs								
Titrated	———	———	———	0.41	0.25	0.04, 1.71		
Low dose	———	———	———	0.51	0.20	0.01, 2.62		
Moderate/high dose	———	———	———	0.54	0.29	0.03, 2.48		
DPP-4 inhibitors								
Low dose	———	———	———	0.94	0.20	0.00, 5.87		
Moderate/high dose	———	———	———	0.40	0.24	0.04, 1.61		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	0.38	0.08	0.00, 2.29		
GLP-1 analogues								
Titrated	———	———	———	0.84	0.30	0.02, 4.39		
Low dose	———	———	———	0.41	0.18	0.01, 2.02		
Moderate/high dose	———	———	———	0.49	0.21	0.02, 2.38		
Basal insulin	———	———	———	3.76	1.36	0.14, 18.88		
Biphasic insulin	———	———	———	6.68	2.79	0.32, 31.88		
Titrated TZDs vs:								
TZDs								
Low dose	———	———	———	1.48	0.82	0.09, 6.79		
Moderate/high dose	———	———	———	1.64	1.18	0.23, 5.78		
DPP-4 inhibitors								
Low dose	———	———	———	2.59	0.82	0.02, 15.84		
Moderate/high dose	1 RCT[55]	2627	2.33 (0.67, 8.11)	1.11	0.98	0.42, 2.55		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	1.12	0.33	0.01, 6.76		
GLP-1 analogues								

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Titrated	———	———	———	2.08	1.21	0.17, 9.01		
Low dose	———	———	———	1.23	0.72	0.09, 5.34		
Moderate/high dose	———	———	———	1.46	0.86	0.11, 6.28		
Basal insulin	———	———	———	8.96	5.53	1.12, 36.06		
Biphasic insulin	———	———	———	16.11	11.26	2.80, 58.02		
Low-dose TZDs vs:								
TZDs								
Moderate/high dose	2 RCT[69,72]	303	1.79 (0.42, 7.67)	2.45	1.45	0.22, 10.72		
DPP-4 inhibitors								
Low dose	———	———	———	5.33	1.00	0.02, 33.18		
Moderate/high dose	———	———	———	2.30	1.21	0.16, 10.80		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	2.27	0.40	0.01, 14.01		
GLP-1 analogues								
Titrated	———	———	———	4.75	1.49	0.10, 27.10		
Low dose	———	———	———	2.48	0.87	0.06, 13.62		
Moderate/high dose	———	———	———	2.94	1.05	0.07, 15.79		
Basal insulin	———	———	———	21.23	6.81	0.56, 113.50		
Biphasic insulin	———	———	———	37.33	13.97	1.28, 198.50		
Moderate-/high-dose TZDs vs:								
DPP-4 inhibitors								
Low dose	———	———	———	2.59	0.69	0.02, 16.37		
Moderate/high dose	2 RCT[57,101]	756	0.94 (0.13, 6.70)	1.12	0.84	0.20, 3.70		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	1.13	0.28	0.01, 6.86		
GLP-1 analogues								
Titrated	———	———	———	2.33	1.03	0.10, 11.88		
Low dose	———	———	———	1.20	0.60	0.06, 5.78		

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Moderate/high dose	———	———	———	1.45	0.73	0.07, 6.75		
Basal insulin	———	———	———	10.02	4.69	0.59, 47.44		
Biphasic insulin	———	———	———	17.81	9.61	1.41, 80.47		
Low-dose DPP-4 inhibitors vs:								
DPP-4 inhibitors								
Moderate/high dose	1 RCT[58]	360	0.97 (0.06, 15.58)	8.00	1.21	0.07, 44.66		
Alpha-glucosidase inhibitors								
Titrated	———	———	———	8.00	0.40	0.00, 39.24		
GLP-1 analogues								
Titrated	———	———	———	15.40	1.51	0.05, 86.01		
Low dose	———	———	———	9.22	0.89	0.03, 47.70		
Moderate/high dose	———	———	———	10.80	1.06	0.03, 56.07		
Basal insulin	———	———	———	69.33	6.97	0.25, 374.30		
Biphasic insulin	———	———	———	123.20	14.23	0.58, 675.60		
Moderate-/high-dose DPP-4 inhibitors vs:								
Alpha-glucosidase inhibitors								
Titrated	———	———	———	1.08	0.33	0.01, 6.38		
GLP-1 analogues								
Titrated	———	———	———	2.06	1.23	0.17, 8.75		
Low dose	———	———	———	1.17	0.72	0.09, 4.82		
Moderate/high dose	———	———	———	1.38	0.86	0.11, 5.66		
Basal insulin	———	———	———	8.82	5.60	1.07, 34.91		
Biphasic insulin	———	———	———	16.03	11.44	2.68, 56.25		
Titrated alpha-glucosidase inhibitors vs:								
GLP-1 analogues	———	———	———					
Titrated	———	———	———	65.62	3.81	0.11, 244.5		
Low dose	———	———	———	28.85	2.19	0.07, 129.0		
Moderate/high dose	———	———	———	38.21	2.63	0.09, 155.6		

Full MTC Results for Overall Hypoglycemia (Dose-Stratified Model)								
	No. of Trials	No. of Patients	Direct Estimates OR (95% CI)	MTC Estimates OR (95% CrI)			Probability of Fewest Patients With Hypoglycemic Events	Rank
				Mean	Median	95% CrI		
Basal insulin	———	———	———	339.10	17.57	0.63, 1088.0		
Biphasic insulin	———	———	———	607.90	35.53	1.42, 2037.0		
Titrated GLP-1 analogues vs:								
GLP-1 analogues								
Low dose	———	———	———	1.52	0.59	0.04, 8.27		
Moderate/high dose	———	———	———	1.83	0.70	0.04, 9.81		
Basal insulin	2 RCTs[53,60]	145	4.58 (1.40, 15.03)	6.10	4.58	1.20, 20.19		
Biphasic insulin	———	———	———	13.57	9.41	1.93, 50.24		
Low-dose GLP-1 analogues vs:								
GLP-1 analogues								
Moderate/high dose	1 RCT[64]	223	1.18 (0.35, 3.98)	1.88	1.19	0.20, 7.59		
Basal insulin	———	———	———	23.35	7.75	0.71, 117.50		
Biphasic insulin	———	———	———	40.23	15.92	1.65, 207.90		
Moderate-/high-dose GLP-1 analogues vs:								
Basal insulin	———	———	———	19.23	6.48	0.59, 95.16		
Biphasic insulin	———	———	———	33.14	13.26	1.40, 165.70		
Basal insulin v:								
Biphasic insulin	2 RCTs[80,94]	297	2.23 (1.21, 4.09)	2.32	2.05	0.71, 5.52		

CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; OR = odds ratio; RCTs = randomized controlled trials; SC = study characteristics; TC = trial characteristics; TZDs = thiazolidinediones; vs = versus.

APPENDIX 18: FULL MTC RESULTS FOR A1C FROM INDIVIDUAL AGENT-LEVEL META-ANALYSIS

MTC Sensitivity Analysis — A1C — Individual Agent-Level Meta-analysis					
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent-Level		
			MTC Effect Estimate (95% CI)	Probability Most Effective at Reducing A1C%	Probability of A1C Reduction (> 0.7%)
Metformin monotherapy vs:					
Glyburide	1[83]	207	-1.07 (-1.43, -0.70)	27.3%	97.6%
Gliclazide	——	——	-0.78 (-1.03, -0.53)	1.4%	75.1%
Glipizide	——	——	-0.75 (-1.08, -0.43)	2.5%	63.2%
Glimepiride	3[63,89,90]	663	-0.78 (-0.95, -0.60)	0.3%	83.3%
Nateglinide and repaglinide	2[84,87]	366	-0.63 (-0.92, -0.37)	0.2%	30.0%
Pioglitazone	2[66,78]	497	-0.82 (-1.02, -0.62)	1.5%	89.1%
Rosiglitazone	4[69,72,82,101]	308	-0.85 (-1.19, -0.53)	2.2%	80.9%
Vildagliptin and sitagliptin	5[58,61,65,73,95]	2190	-0.76 (-0.91, -0.62)	0.1%	79.7%
Acarbose and miglitol	5[74,92,98,99,103]	792	-0.74 (-0.97, -0.52)	0.9%	64.8%
Exenatide and liraglutide	3[64,89,93]	479	-0.85 (-1.07, -0.64)	1.4%	92.5%
Insulin NPH and glargine	——	——	-0.92 (-1.26, -0.57)	3.3%	90.5%
Biphasic insulin	——	——	-1.14 (-1.53, -0.75)	58.8%	98.6%
Glyburide vs:					
Gliclazide	——	——	0.29 (-0.15, 0.71)		0.0%
Glipizide	——	——	0.32 (-0.17, 0.79)		0.0%
Glimepiride	——	——	0.29 (-0.09, 0.67)		0.0%
Nateglinide and repaglinide	——	——	0.43 (-0.02, 0.88)		0.0%
Pioglitazone	——	——	0.25 (-0.16, 0.65)		0.0%
Rosiglitazone	1[71]	318	0.22 (-0.12, 0.52)		0.0%
Vildagliptin and sitagliptin	——	——	0.31 (-0.08, 0.69)		0.0%
Acarbose and miglitol	——	——	0.32 (-0.11, 0.74)		0.0%
Exenatide and liraglutide	——	——	0.21 (-0.17, 0.59)		0.0%
Insulin NPH and glargine	——	——	0.14 (-0.24, 0.53)		0.0%
Biphasic insulin	1[81]	130	-0.07 (-0.42, 0.28)		0.1%

MTC Sensitivity Analysis — A1C — Individual Agent-Level Meta-analysis					
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent-Level		
			MTC Effect Estimate (95% CI)	Probability Most Effective at Reducing A1C%	Probability of A1C Reduction (> 0.7%)
Gliclazide vs:					
Glipizide	——	——	0.03 (-0.37, 0.42)		0.1%
Glimepiride	1[100]	219	0.00 (-0.23, 0.24)		0.0%
Nateglinide and repaglinide	1[97]	262	0.15 (-0.15, 0.43)		0.0%
Pioglitazone	1[62]	630	-0.04 (-0.28, 0.20)		0.0%
Rosiglitazone	——	——	0.07 (-0.48, 0.31)		0.2%
Vildagliptin and sitagliptin	——	——	0.02 (-0.24, 0.27)		0.0%
Acarbose and miglitol	——	——	0.04 (-0.30, 0.37)		0.0%
Exenatide and liraglutide	——	——	-0.07 (-0.38, 0.24)		0.0%
Insulin NPH and glargine	——	——	-0.15 (-0.54, 0.28)		0.5%
Biphasic insulin	——	——	-0.36 (-0.80, 0.10)		6.1%
Glipizide vs:					
Glimepiride	——	——	-0.03 (-0.36, 0.33)		0.0%
Nateglinide and repaglinide	——	——	0.12 (-0.31, 0.53)		0.1%
Pioglitazone	——	——	-0.07 (-0.42, 0.30)		0.1%
Rosiglitazone	——	——	-0.10 (-0.56, 0.34)		0.8%
Vildagliptin and sitagliptin	1[88]	1172	-0.01 (-0.31, 0.29)		0.0%
Acarbose and miglitol	——	——	0.01 (-0.39, 0.41)		0.1%
Exenatide and liraglutide	——	——	-0.11 (-0.48, 0.29)		0.2%
Insulin NPH and glargine	——	——	-0.18 (-0.62, 0.31)		1.2%
Biphasic insulin	——	——	-0.39 (-0.88, 0.12)		9.9%
Glimepiride vs:					
Nateglinide and repaglinide	——	——	0.15 (-0.17, 0.43)		0.0%
Pioglitazone	2[91,102]	238	-0.04 (-0.24, 0.15)		0.0%
Rosiglitazone	1[104]	12	-0.07 (-0.43, 0.26)		0.1%
Vildagliptin and sitagliptin	1[68]	2789	0.02 (-0.18, 0.19)		0.0%
Acarbose and miglitol	——	——	0.04 (-0.26, 0.31)		0.0%
Exenatide and liraglutide	2[89,90]	1040	-0.08 (-0.32, 0.17)		0.0%
Insulin NPH and glargine	——	——	-0.15 (-0.51, 0.22)		0.2%

MTC Sensitivity Analysis — A1C — Individual Agent-Level Meta-analysis					
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent-Level		
			MTC Effect Estimate (95% CI)	Probability Most Effective at Reducing A1C%	Probability of A1C Reduction (> 0.7%)
Biphasic insulin	——	——	-0.36 (-0.77, 0.05)		5.0%
Nateglinide and repaglinide vs:					
Pioglitazone	——	——	-0.19 (-0.49, 0.13)		0.1%
Rosiglitazone	——	——	-0.22 (-0.64, 0.20)		1.3%
Vildagliptin and sitagliptin	——	——	-0.12 (-0.42, 0.17)		0.0%
Acarbose and miglitol	——	——	-0.11 (-0.46, 0.25)		0.1%
Exenatide and liraglutide	——	——	-0.22 (-0.56, 0.13)		0.3%
Insulin NPH and glargine	——	——	-0.29 (-0.71, 0.16)		2.9%
Biphasic insulin	——	——	-0.50 (-0.96, -0.03)		19.9%
Pioglitazone vs:					
Rosiglitazone	——	——	-0.03 (-0.41, 0.33)		0.0%
Vildagliptin and sitagliptin	1[57]	575	0.06 (-0.15, 0.25)		0.0%
Acarbose and miglitol	——	——	0.08 (-0.23, 0.37)		0.0%
Exenatide and liraglutide	——	——	-0.03 (-0.31, 0.25)		0.0%
Insulin NPH and glargine	——	——	-0.11 (-0.48, 0.28)		0.2%
Biphasic insulin	——	——	-0.32 (-0.74, 0.11)		3.8%
Rosiglitazone vs:					
Vildagliptin and sitagliptin	1[101]	181	0.09 (-0.25, 0.44)		0.0%
Acarbose and miglitol	——	——	0.11 (-0.29, 0.51)		0.0%
Exenatide and liraglutide	——	——	-0.01 (-0.36, 0.38)		0.0%
Insulin NPH and Glargine	——	——	-0.08 (-0.48, 0.36)		0.1%
Biphasic insulin	——	——	-0.29 (-0.69, 0.14)		2.3%
Vildagliptin and sitagliptin vs:					
Acarbose and miglitol	——	——	0.01 (-0.25, 0.28)		0.0%
Exenatide and liraglutide	——	——	-0.10 (-0.34, 0.16)		0.0%
Insulin NPH and glargine	——	——	-0.17 (-0.52, 0.21)		0.2%
Biphasic insulin	——	——	-0.38 (-0.78, 0.04)		5.7%
Acarbose and miglitol vs:					
Exenatide and liraglutide	——	——	-0.11 (-0.42, 0.21)		0.0%

MTC Sensitivity Analysis — A1C — Individual Agent-Level Meta-analysis					
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent-Level		
			MTC Effect Estimate (95% CI)	Probability Most Effective at Reducing A1C%	Probability of A1C Reduction (> 0.7%)
Insulin NPH and glargine	——	——	-0.18 (-0.58, 0.24)		0.7%
Biphasic insulin	——	——	-0.39 (-0.83, 0.06)		8.3%
Exenatide and liraglutide vs:					
Insulin NPH and glargine	2[53,60]	145	-0.07 (-0.37, 0.23)		0.0%
Biphasic insulin	——	——	-0.28 (-0.66, 0.09)		1.5%
Insulin NPH and glargine vs:					
Biphasic insulin	2[80,94]	297	-0.21 (-0.51, 0.08)		0.2%
	DIC = 41.458				

A1C = glycosylated hemoglobin; CI = confidence interval; DIC = deviance information criterion; MTC = mixed treatment comparison; NPH = neutral protamine Hagedorn; vs = versus.

APPENDIX 19: FULL MTC RESULTS FOR BODY WEIGHT FROM INDIVIDUAL AGENT-LEVEL META-ANALYSIS

MTC Sensitivity Analysis — Weight (Individual Agent-Level Meta-analysis)				
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent Level	
			MTC Effect Estimate (95% CrI)	Probability Most Effective at Reducing Weight
Metformin monotherapy vs:				
Glyburide	1[83]	207	2.74 (1.53, 4.02)	0.0%
Gliclazide	——	——	1.59 (0.18, 3.11)	0.0%
Glipizide	——	——	2.99 (1.18, 4.82)	0.0%
Glimepiride	2[63,89]	294	2.10 (1.15, 3.05)	0.0%
Nateglinide and repaglinide	2[84,87]	366	1.56 (0.43, 2.78)	0.0%
Pioglitazone	2[66,78]	497	2.47 (1.61, 3.35)	0.0%
Rosiglitazone	2[72,101]	258	2.12 (1.04, 3.26)	0.0%
Vildagliptin and sitagliptin	3[58,73,101]	923	0.49 (-0.31, 1.32)	0.1%
Acarbose and miglitol	3[92,99,103]	404	-0.89 (-1.97, 0.15)	17.9%
Exenatide and liraglutide	2[64,89]	408	-1.63 (-2.91, -0.35)	81.9%
Insulin NPH and glargine	——	——	1.86 (0.26, 3.48)	0.0%
Biphasic insulin	——	——	3.36 (1.75, 5.06)	0.0%
Glyburide vs:				
Gliclazide	——	——	-1.15 (-3.06, 0.77)	See above
Glipizide	——	——	0.25 (-1.93, 2.39)	
Glimepiride	——	——	-0.65 (-2.20, 0.87)	
Nateglinide and repaglinide	——	——	-1.18 (-2.86, 0.54)	
Pioglitazone	——	——	-0.28 (-1.79, 1.21)	
Rosiglitazone	1[71]	318	-0.62 (-1.93, 0.69)	
Vildagliptin and sitagliptin	——	——	-2.26 (-3.71, -0.84)	
Acarbose and miglitol	——	——	-3.64 (-5.30, -2.03)	
Exenatide and liraglutide	——	——	-4.38 (-5.98, -2.80)	
Insulin NPH and glargine	——	——	-0.89 (-2.52, 0.73)	
Biphasic insulin	1[81]	130	0.61 (-0.85, 2.10)	

MTC Sensitivity Analysis — Weight (Individual Agent-Level Meta-analysis)				
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent Level	
			MTC Effect Estimate (95% CrI)	Probability Most Effective at Reducing Weight
Gliclazide vs:				
Glipizide	——	——	1.39 (-0.91, 3.62)	See above
Glimepiride	——	——	0.50 (-1.17, 2.09)	
Nateglinide and repaglinide	1[97]	262	-0.03 (-1.45, 1.39)	
Pioglitazone	1[62]	630	0.87 (-0.55, 2.23)	
Rosiglitazone	——	——	0.53 (-1.29, 2.35)	
Vildagliptin and sitagliptin	——	——	-1.11 (-2.73, 0.43)	
Acarbose and miglitol	——	——	-2.49 (-4.34, -0.75)	
Exenatide and liraglutide	——	——	-3.23 (-5.18, -1.33)	
Insulin NPH and glargine	——	——	0.26 (-1.90, 2.41)	
Biphasic insulin	——	——	1.76 (-0.42, 3.98)	
Glipizide vs:				
Glimepiride	——	——	-0.89 (-2.81, 1.02)	See above
Nateglinide and repaglinide	——	——	-1.42 (-3.51, 0.76)	
Pioglitazone	——	——	-0.52 (-2.41, 1.37)	
Rosiglitazone	——	——	-0.86 (-2.88, 1.23)	
Vildagliptin and sitagliptin	1[88]	1172	-2.50 (-4.12, -0.87)	
Acarbose and miglitol	——	——	-3.88 (-5.98, -1.82)	
Exenatide and liraglutide	——	——	-4.62 (-6.81, -2.41)	
Insulin NPH and glargine	——	——	-1.13 (-3.52, 1.31)	
Biphasic insulin	——	——	0.37 (-2.01, 2.86)	
Glimepiride vs:				
Nateglinide and repaglinide	——	——	-0.53 (-1.95, 0.99)	See above
Pioglitazone	2[91,102]	238	0.37 (-0.65, 1.42)	
Rosiglitazone	——	——	0.03 (-1.38, 1.46)	
Vildagliptin and sitagliptin	1[68]	2789	-1.61 (-2.63, -0.58)	
Acarbose and miglitol	——	——	-2.99 (-4.41, -1.58)	
Exenatide and liraglutide	1[89]	72	-3.73 (-5.25, -2.19)	
Insulin NPH and glargine	——	——	-0.24 (-2.05, 1.60)	

MTC Sensitivity Analysis — Weight (Individual Agent-Level Meta-analysis)				
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent Level	
			MTC Effect Estimate (95% CrI)	Probability Most Effective at Reducing Weight
Biphasic insulin	——	——	1.26 (-0.56, 3.17)	
Nateglinide and repaglinide vs:				
Pioglitazone	——	——	0.90 (-0.49, 2.20)	See above
Rosiglitazone	——	——	0.56 (-1.07, 2.13)	
Vildagliptin and sitagliptin	——	——	-1.08 (-2.53, 0.27)	
Acarbose and miglitol	——	——	-2.46 (-4.08, -0.93)	
Exenatide and liraglutide	——	——	-3.20 (-4.94, -1.49)	
Insulin NPH and glargine	——	——	0.29 (-1.71, 2.25)	
Biphasic insulin	——	——	1.79 (-0.24, 3.80)	
Pioglitazone vs:				
Rosiglitazone	——	——	-0.34 (-1.70, 1.06)	See above
Vildagliptin and sitagliptin	1[57]	576	-1.98 (-2.97, -0.98)	
Acarbose and miglitol	——	——	-3.36 (-4.74, -2.02)	
Exenatide and liraglutide	——	——	-4.10 (-5.61, -2.57)	
Insulin NPH and glargine	——	——	-0.61 (-2.39, 1.23)	
Biphasic insulin	——	——	0.89 (-0.92, 2.78)	
Rosiglitazone vs:				
Vildagliptin and sitagliptin	1[101]	181	-1.64 (-2.91, -0.41)	See above
Acarbose and miglitol	——	——	-3.02 (-4.59, -1.52)	
Exenatide and liraglutide	——	——	-3.76 (-5.39, -2.17)	
Insulin NPH and glargine	——	——	-0.27 (-2.09, 1.54)	
Biphasic insulin	——	——	1.23 (-0.54, 3.05)	
Vildagliptin and sitagliptin vs:				
Acarbose and miglitol	——	——	-1.38 (-2.74, -0.06)	See above
Exenatide and liraglutide	——	——	-2.12 (-3.61, -0.64)	
Insulin NPH and glargine	——	——	1.37 (-0.38, 3.16)	
Biphasic insulin	——	——	2.87 (1.11, 4.73)	
Acarbose and miglitol vs:				
Exenatide and liraglutide	——	——	-0.74 (-2.38, 0.92)	See above

MTC Sensitivity Analysis — Weight (Individual Agent-Level Meta-analysis)				
Treatment vs Placebo	No. of Trials	No. of Patients	Individual Agent Level	
			MTC Effect Estimate (95% CrI)	Probability Most Effective at Reducing Weight
Insulin NPH and glargine	——	——	2.75 (0.86, 4.69)	
Biphasic insulin	——	——	4.25 (2.34, 6.28)	
Exenatide and liraglutide vs:				
Insulin NPH and glargine	2[53,60]	145	3.49 (2.18, 4.84)	See above
Biphasic insulin	——	——	4.99 (3.43, 6.64)	
Insulin NPH and glargine vs:				
Biphasic insulin	2[80,94]	297	1.50 (0.29, 2.75)	See above

CrI = credible interval; NPH = neutral protamine Hagedorn; MTC = mixed treatment comparison; vs = versus.

APPENDIX 20: MTC RESULTS FOR OVERALL HYPOGLYCEMIA FROM INDIVIDUAL AGENT-LEVEL META-ANALYSIS

MTC Sensitivity Analysis — Overall Hypoglycemia — Individual Agent-Level Meta-analysis						
Treatment vs Placebo	No. Trials	No. Patients	MTC Effect Estimate			
			Mean OR	Median OR	95% CrI	Probability Most Effective
Metformin monotherapy vs:						
Glyburide	1[83]	207	16.46	13.18	4.15, 48.00	0.0%
Gliclazide	——	——	4.52	3.61	1.30, 13.35	0.0%
Glipizide	——	——	12.64	8.95	2.29, 43.55	0.1%
Glimepiride	2[63,89]	294	10.89	9.54	4.34, 25.66	0.0%
Nateglinide and repaglinide	2[84,87]	366	7.08	5.55	2.21, 20.99	0.0%
Pioglitazone	2[66,78]	497	0.69	0.54	0.18, 2.07	34.8%
Rosiglitazone	4[69,72,82,101]	308	1.87	1.61	0.54, 4.73	1.8%
Vildagliptin and sitagliptin	7[58,59,61,65,73,95,101]	2428	1.09	0.98	0.49, 2.28	3.0%
Acarbose and miglitol	2[99,103]	321	1.15	0.41	0.01, 6.99	54.1%
Exenatide and liraglutide	2[53,64]	298	1.65	1.31	0.37, 4.93	4.5%
Insulin NPH and glargine	——	——	9.92	7.19	1.75, 34.19	0.0%
Biphasic insulin	——	——	22.02	16.19	3.99, 74.47	0.0%
Glyburide vs:						
Gliclazide	——	——	0.41	0.27	0.06, 1.48	See above
Glipizide	——	——	1.12	0.68	0.11, 4.49	
Glimepiride	——	——	0.97	0.72	0.18, 3.28	
Nateglinide and repaglinide	——	——	0.64	0.42	0.10, 2.38	
Pioglitazone	——	——	0.06	0.04	0.01, 0.24	
Rosiglitazone	1[71]	318	0.14	0.12	0.04, 0.34	
Vildagliptin and sitagliptin	——	——	0.10	0.07	0.02, 0.32	
Acarbose and miglitol	——	——	0.11	0.03	0.00, 0.71	
Exenatide and liraglutide	——	——	0.13	0.10	0.02, 0.42	
Insulin NPH and glargine	——	——	0.69	0.54	0.14, 2.12	
Biphasic insulin	1[81]	222	1.46	1.23	0.38, 3.93	

MTC Sensitivity Analysis — Overall Hypoglycemia — Individual Agent-Level Meta-analysis						
Treatment vs Placebo	No. Trials	No. Patients	MTC Effect Estimate			
			Mean OR	Median OR	95% CrI	Probability Most Effective
Gliclazide vs:						
Glipizide	——	——	3.69	2.51	0.41, 13.53	See above
Glimepiride	1[100]	484	3.01	2.63	0.89, 7.27	
Nateglinide and repaglinide	1[97]	213	1.85	1.54	0.55, 5.03	
Pioglitazone	1[62]	630	0.17	0.15	0.05, 0.45	
Rosiglitazone	——	——	0.58	0.44	0.08, 1.84	
Vildagliptin and sitagliptin	——	——	0.32	0.27	0.08, 0.87	
Acarbose and miglitol	——	——	0.35	0.11	0.00, 2.12	
Exenatide and liraglutide	——	——	0.50	0.36	0.06, 1.77	
Insulin NPH and glargine	——	——	3.00	1.98	0.31, 11.78	
Biphasic insulin	——	——	6.68	4.46	0.68, 25.81	
Glipizide vs:						
Glimepiride	——	——	1.46	1.06	0.23, 5.11	See above
Nateglinide and repaglinide	——	——	1.07	0.61	0.12, 4.13	
Pioglitazone	——	——	0.09	0.06	0.01, 0.37	
Rosiglitazone	——	——	0.26	0.18	0.03, 0.95	
Vildagliptin and sitagliptin	1[88]	1172	0.13	0.11	0.03, 0.38	
Acarbose and miglitol	——	——	0.16	0.04	0.00, 0.95	
Exenatide and liraglutide	——	——	0.23	0.15	0.02, 0.93	
Insulin NPH and glargine	——	——	1.42	0.80	0.10, 6.09	
Biphasic insulin	——	——	3.16	1.80	0.23, 13.21	
Glimepiride vs:						
Nateglinide and repaglinide	——	——	0.74	0.59	0.19, 2.14	See above
Pioglitazone	1[102]	203	0.07	0.06	0.02, 0.18	
Rosiglitazone	1[104]	12	0.21	0.17	0.04, 0.59	
Vildagliptin and sitagliptin	1[68]	2789	0.11	0.10	0.04, 0.25	
Acarbose and miglitol	——	——	0.13	0.04	0.00, 0.74	
Exenatide and liraglutide	1[89]	72	0.18	0.14	0.03, 0.55	
Insulin NPH and glargine	——	——	1.07	0.76	0.14, 3.84	

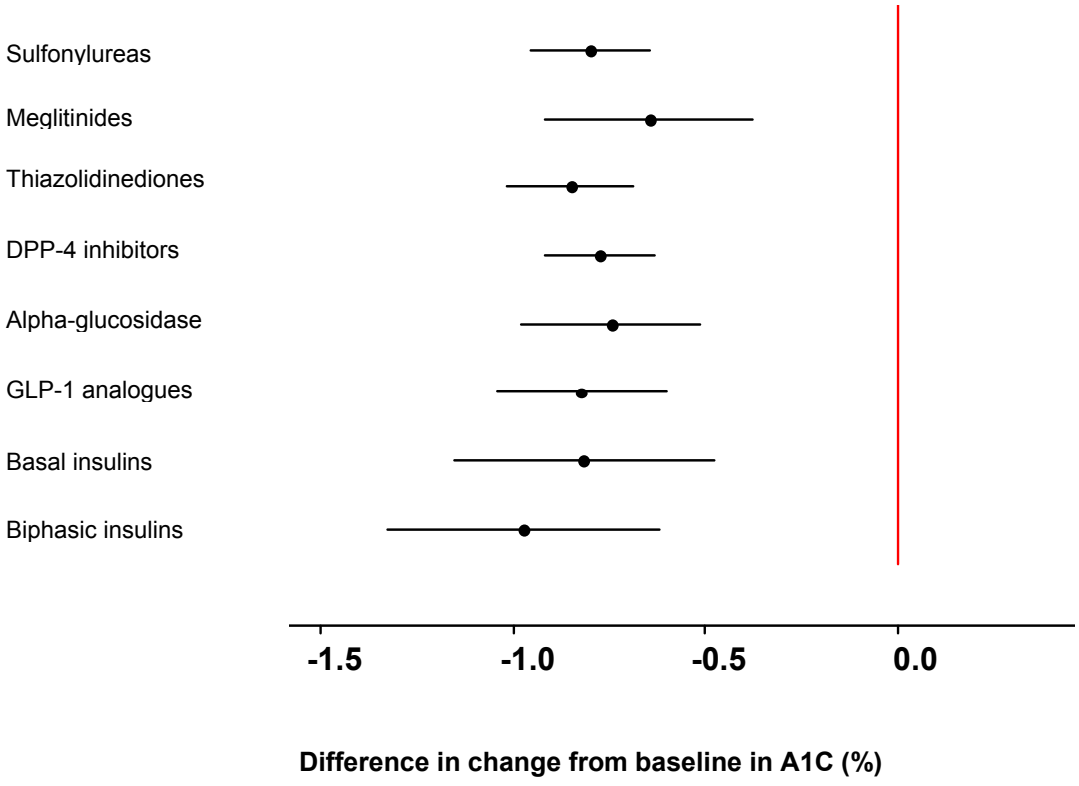
MTC Sensitivity Analysis — Overall Hypoglycemia — Individual Agent-Level Meta-analysis						
Treatment vs Placebo	No. Trials	No. Patients	MTC Effect Estimate			
			Mean OR	Median OR	95% CrI	Probability Most Effective
Biphasic insulin	——	——	2.39	1.70	0.31, 8.44	
Nateglinide and repaglinide vs:						
Pioglitazone	——	——	0.12	0.10	0.02, 0.36	See above
Rosiglitazone	——	——	0.36	0.28	0.05, 1.13	
Vildagliptin and sitagliptin	——	——	0.21	0.18	0.05, 0.55	
Acarbose and miglitol	——	——	0.22	0.07	0.00, 1.38	
Exenatide and liraglutide	——	——	0.31	0.23	0.04, 1.08	
Insulin NPH and glargine	——	——	1.89	1.28	0.19, 7.09	
Biphasic insulin	——	——	4.18	2.89	0.43, 15.52	
Pioglitazone vs:						
Rosiglitazone	——	——	3.99	2.95	0.53, 13.32	See above
Vildagliptin and sitagliptin	1[57]	575	2.20	1.82	0.50, 6.20	
Acarbose and miglitol	——	——	2.42	0.74	0.02, 14.64	
Exenatide and liraglutide	——	——	3.46	2.42	0.40, 13.03	
Insulin NPH and glargine	——	——	20.80	13.31	1.92, 84.61	
Biphasic insulin	——	——	46.61	29.89	4.33, 185.40	
Rosiglitazone vs:						
Vildagliptin and sitagliptin	1[101]	181	0.78	0.61	0.19, 2.42	See above
Acarbose and miglitol	——	——	0.91	0.26	0.01, 5.69	
Exenatide and liraglutide	——	——	1.13	0.82	0.19, 3.83	
Insulin NPH and glargine	——	——	6.40	4.43	1.03, 23.03	
Biphasic insulin	——	——	13.86	10.05	2.45, 46.53	
Vildagliptin and sitagliptin vs:						
Acarbose and miglitol	——	——	1.20	0.41	0.01, 6.87	See above
Exenatide and liraglutide	——	——	1.72	1.35	0.29, 5.44	
Insulin NPH and glargine	——	——	10.26	7.33	1.40, 36.65	
Biphasic insulin	——	——	22.90	16.55	3.07, 80.14	
Acarbose and miglitol vs:						
Exenatide and liraglutide	——	——	42.74	3.25	0.14, 154.90	See above

MTC Sensitivity Analysis — Overall Hypoglycemia — Individual Agent-Level Meta-analysis						
Treatment vs Placebo	No. Trials	No. Patients	MTC Effect Estimate			
			Mean OR	Median OR	95% CrI	Probability Most Effective
Insulin NPH and glargine	——	——	295.40	17.31	0.71, 871.80	
Biphasic insulin	——	——	649.60	39.02	1.63, 1953.00	
Exenatide and liraglutide vs:						
Insulin NPH and glargine	2[53,60]	145	6.86	5.45	1.65, 20.58	See above
Biphasic insulin	——	——	16.22	12.31	3.14, 51.82	
Insulin NPH and glargine vs:						
Biphasic insulin	2[80,94]	297	2.49	2.25	0.89, 5.48	See above
	DIC = 320.1					

CrI = credible interval; DIC = deviance information criterion; NPH = neutral protamine Hagedorn; MTC = mixed treatment comparison; OR = odds ratio; vs = versus.

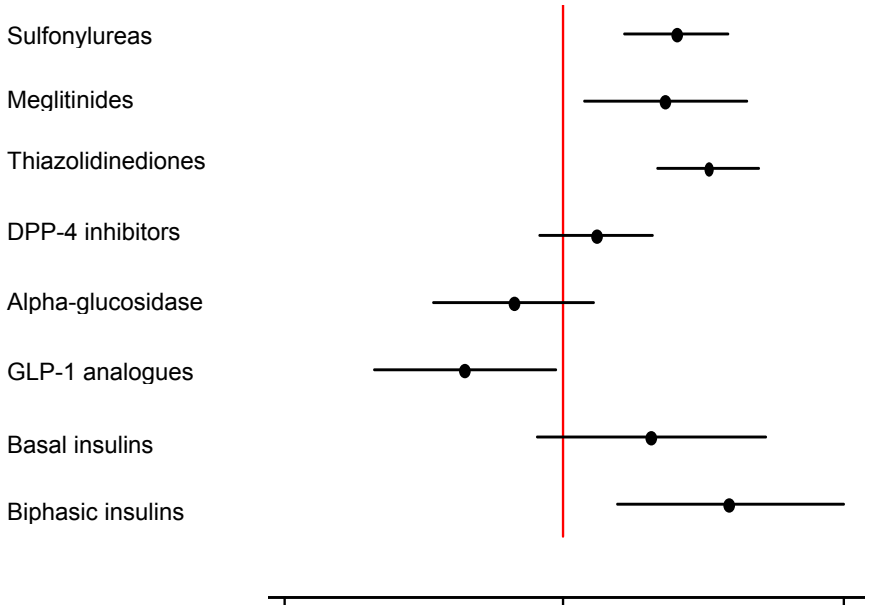
APPENDIX 21: FOREST PLOTS FOR REFERENCE CASE ANALYSIS

Forest Plot: Difference in change from baseline in A1C for second-line agents relative to placebo added to metformin



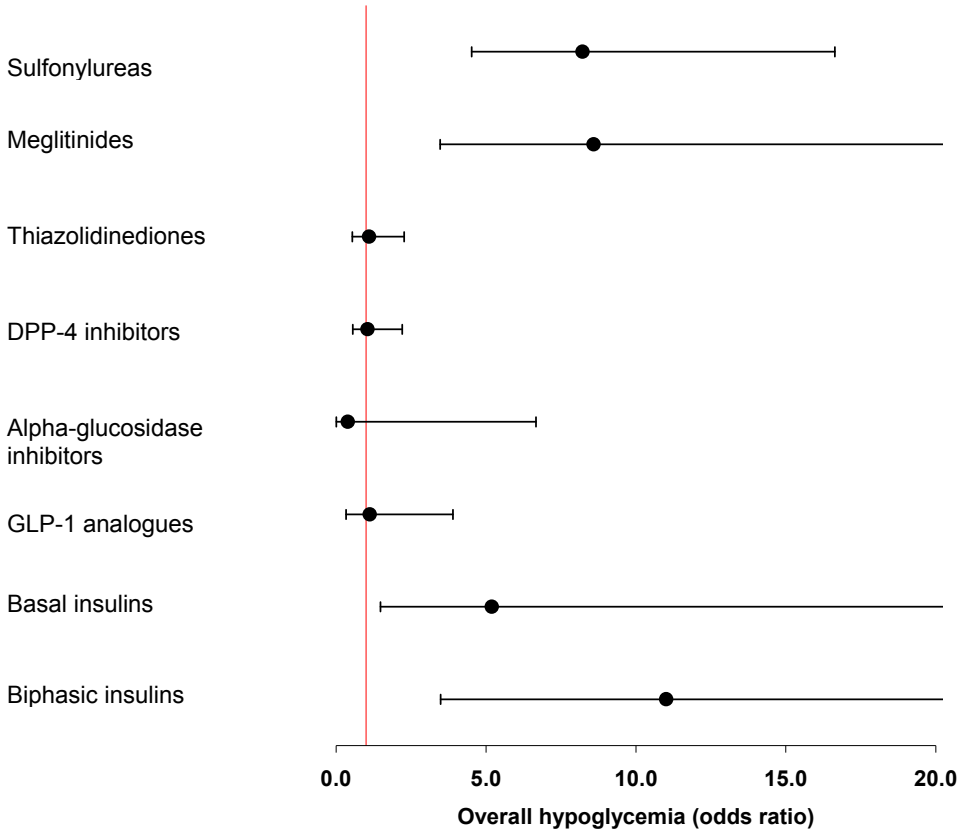
A1C = glycosylated hemoglobin; DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Forest Plot: Difference in change from baseline in body weight for second-line agents relative to placebo added to metformin



DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; kg = kilograms.

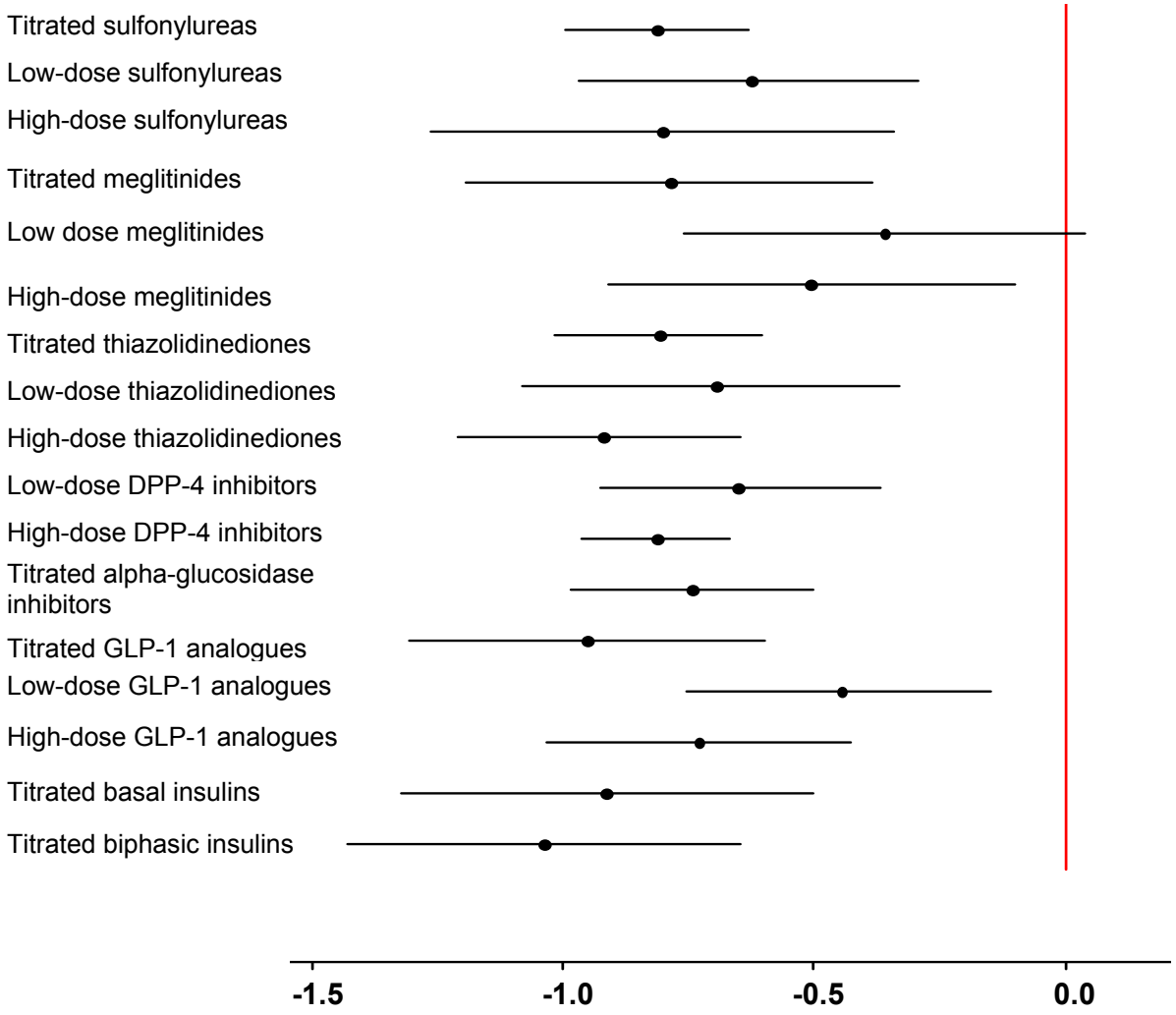
Forest Plot: Odds ratios for overall hypoglycemia for second-line agents relative to placebo added to metformin



DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

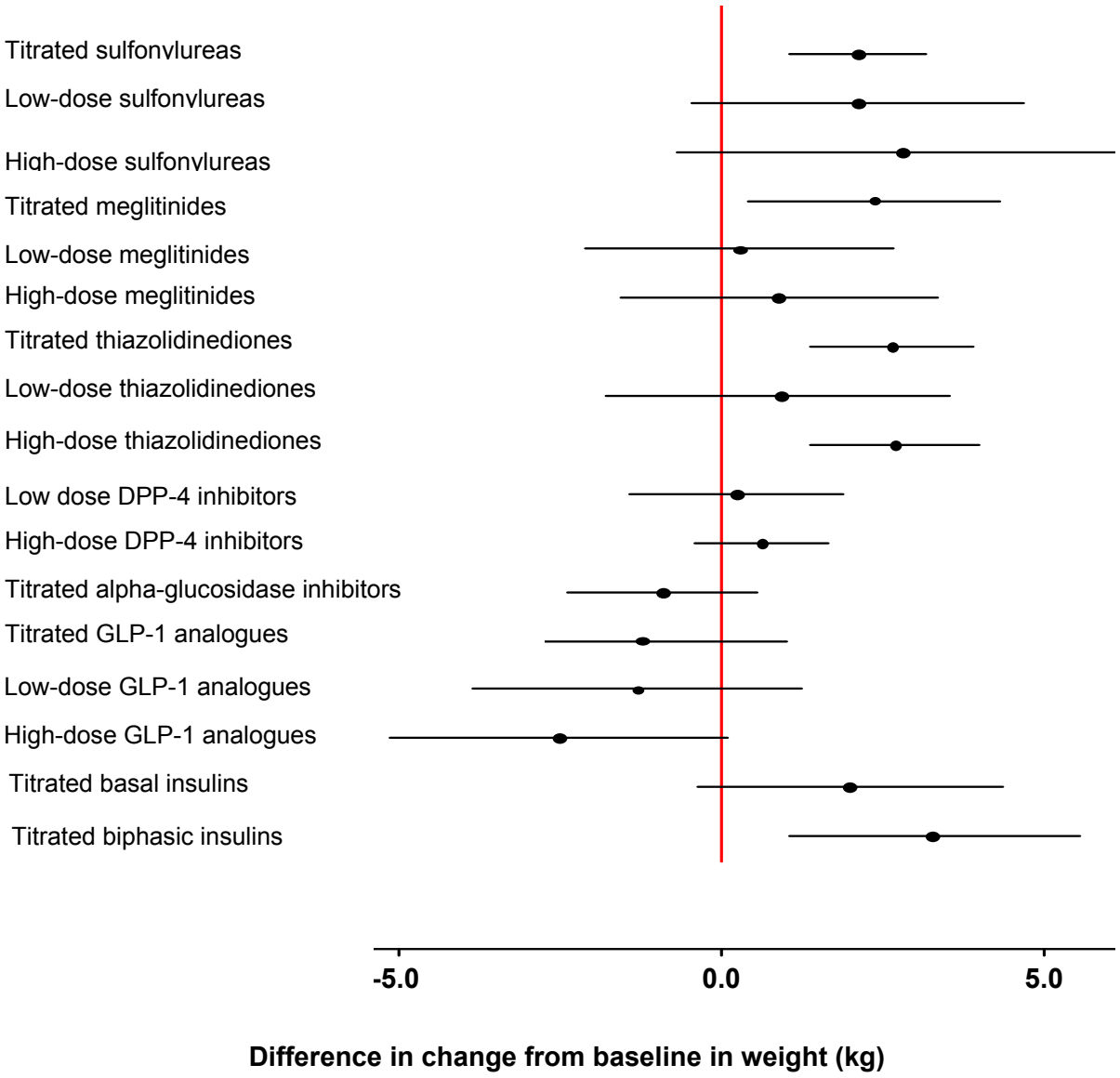
APPENDIX 22: FOREST PLOTS FOR DOSE-STRATIFIED ANALYSIS

Forest Plot: Difference in change from baseline in A1C for second-line agents relative to placebo added to metformin



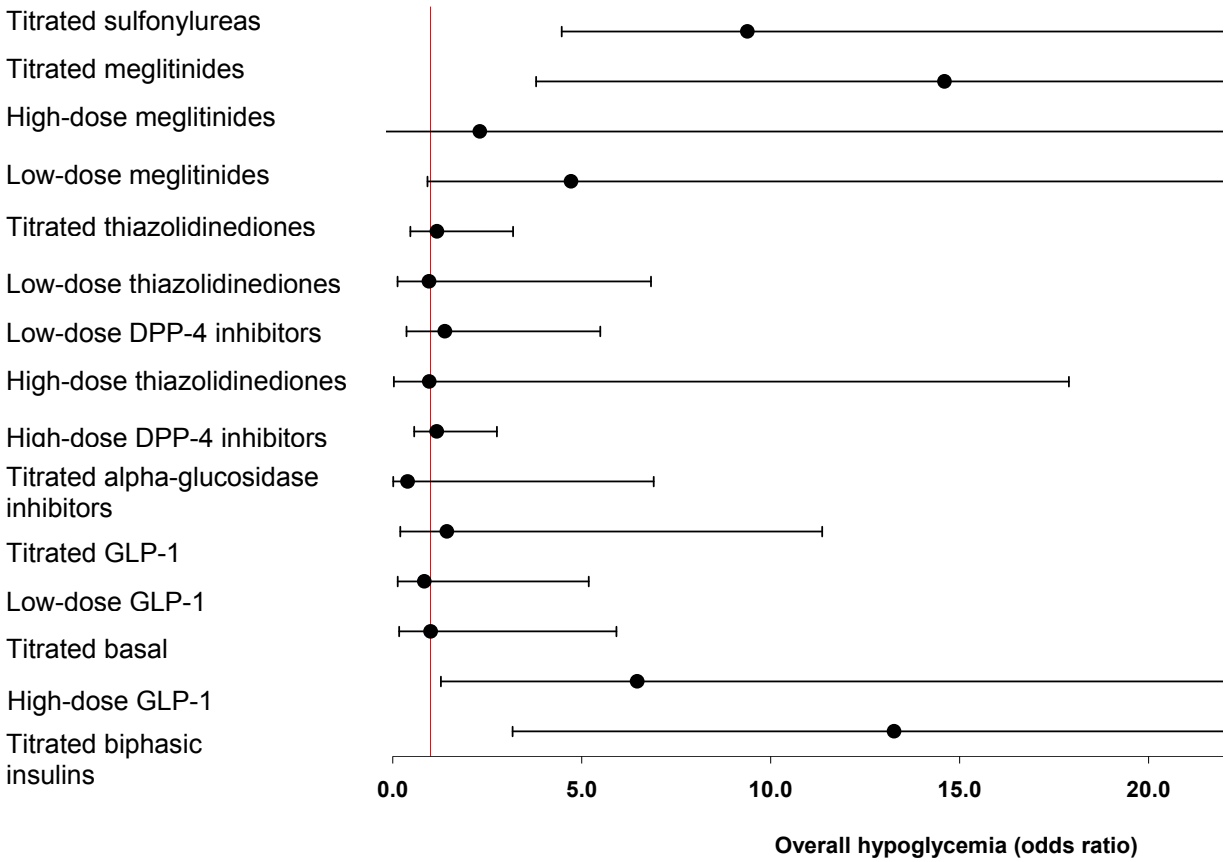
A1C = glycosylated hemoglobin; DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Forest Plot: Difference in change from baseline in body weight for second-line agents relative to placebo added to metformin



DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

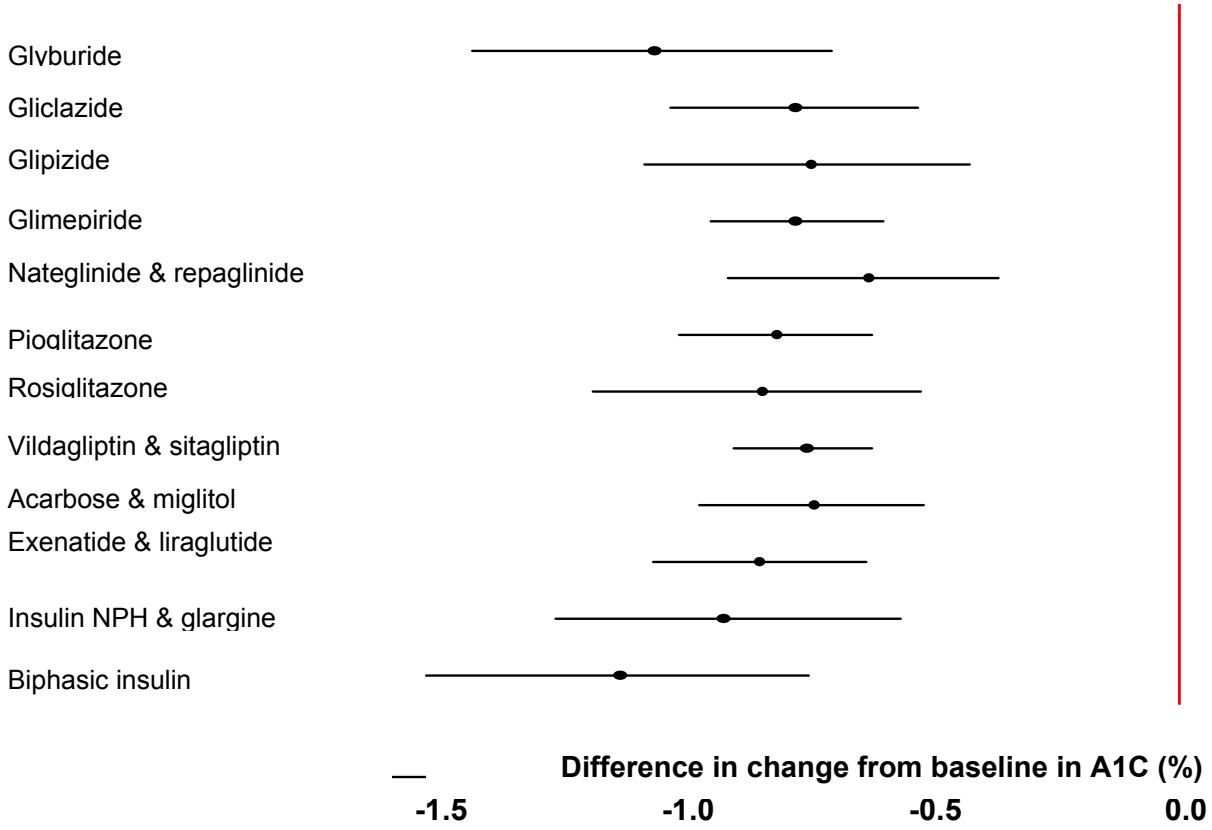
Forest Plot: Odds ratios for overall hypoglycemia for second-line agents relative to placebo added to metformin



DDP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

APPENDIX 23: FOREST PLOTS FOR INDIVIDUAL AGENT ANALYSIS

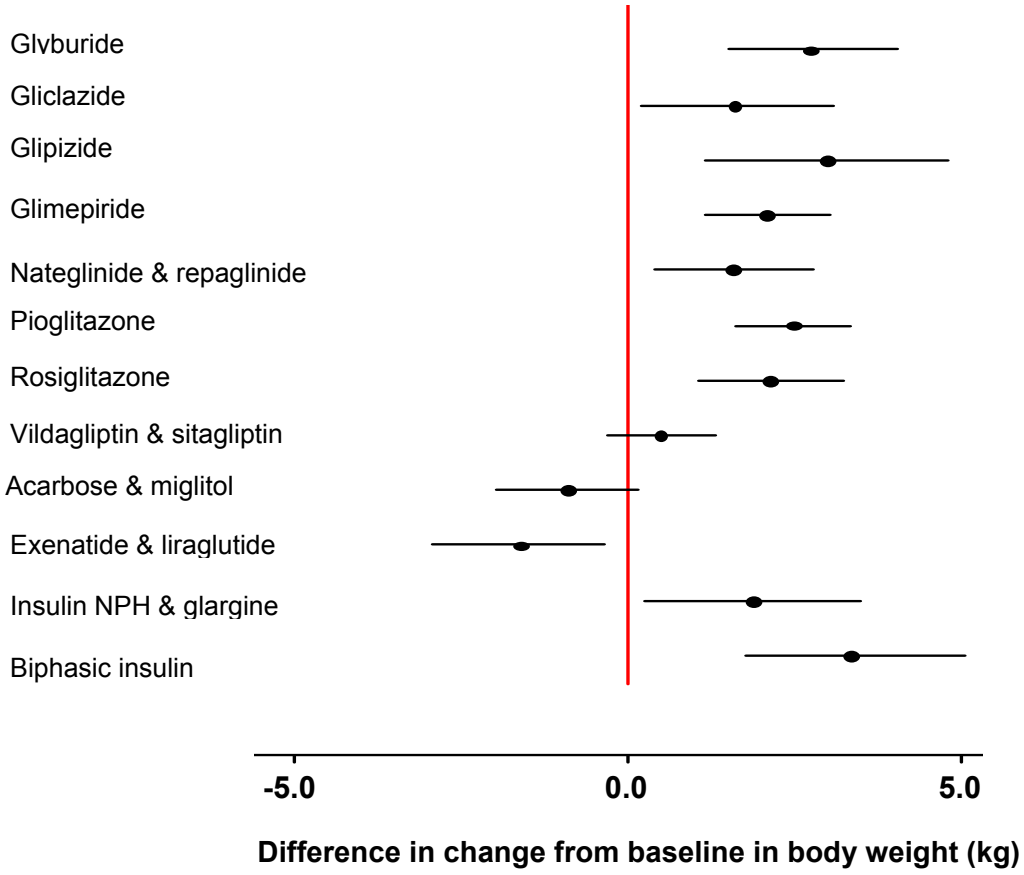
Forest Plot: Difference in change from baseline in hemoglobin A1C for second-line agents relative to placebo added to metformin



Difference in change from baseline in A1C (%)

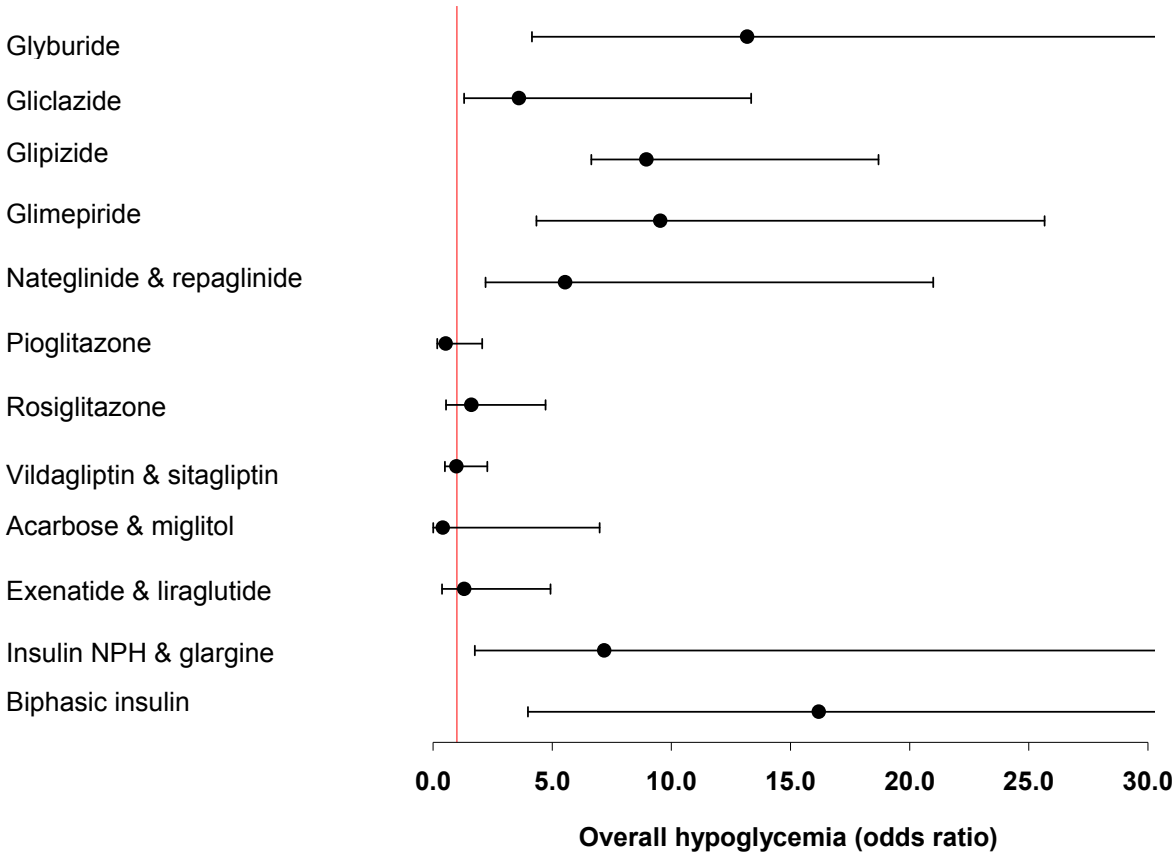
A1C = glycosylated hemoglobin; NPH = neutral protamine Hagedorn.

Forest Plot: Difference in change from baseline in body weight for second-line agents relative to placebo added to metformin



kg = kilogram; NPH = neutral protamine Hagedorn.

Forest Plot: Odds ratios for overall hypoglycemia for second-line agents relative to placebo added to metformin



NPH = neutral protamine Hagedorn.

APPENDIX 24: SENSITIVITY ANALYSES FOR HEMOGLOBIN A1C

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model;
- the results of the sensitivity analyses for A1C
- the results of meta-regressions adjusting for baseline A1C and duration of diabetes.

MTC results are presented as the mean estimate of effect for reducing A1C from baseline (95% credible interval), with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for A1C — MTC Estimate of Effect vs. Placebo								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random effects model vs fixed effects model:								
Reference case — random-effects model	-0.80 (-0.96, -0.65)	-0.64 (-0.92, -0.38)	-0.85 (-1.02, -0.69)	-0.77 (-0.92, -0.64)	-0.75 (-0.98, -0.51)	-0.82 (-1.05, -0.60)	-0.82 (-1.16, -0.48)	-0.97 (-1.33, -0.62)
Reference case — fixed-effects model	-0.79 (-0.87, -0.70)	-0.60 (-0.78, -0.43)	-0.85 (-0.94, -0.76)	-0.74 (-0.82, -0.66)	-0.73 (-0.92, -0.54)	-0.83 (-0.99, -0.68)	-0.84 (-1.09, -0.60)	-0.96 (-1.20, -0.72)
Meta-regressions adjusting for:								
Baseline A1C	-0.82 (-0.99, -0.65)	-0.64 (-0.93, -0.36)	-0.83 (-1.00, -0.66)	-0.80 (-0.95, -0.66)	-0.75 (-0.99, -0.51)	-0.84 (-1.07, -0.61)	-0.89 (-1.26, -0.52)	-1.00 (-1.36, -0.63)
Baseline duration of diabetes	-0.81 (-0.98, -0.64)	-0.65 (-0.95, -0.37)	-0.81 (-0.99, -0.64)	-0.80 (-0.95, -0.65)	-0.72 (-0.97, -0.47)	-0.86 (-1.11, -0.61)	-0.87 (-1.26, -0.49)	-0.97 (-1.34, -0.60)
Sensitivity analyses with removal of:								
Poor-quality studies	-0.87 (-1.35, -0.43)	-0.71 (-1.24, -0.24)	-0.83 (-1.46, -0.27)	-0.78 (-1.54, -0.02)	-0.73 (-1.23, -0.24)	-0.90 (-1.67, -0.14)	-0.95 (-2.05, 0.15)	-1.07 (-1.99, -0.20)
Crossover studies	-0.79 (-0.96, -0.63)	-0.65 (-0.94, -0.37)	-0.82 (-1.00, -0.65)	-0.80 (-0.95, -0.65)	-0.75 (-0.99, -0.51)	-0.83 (-1.07, -0.59)	-0.79 (-1.21, -0.36)	-0.95 (-1.35, -0.56)
Studies < 1 year in duration	-0.82 (-1.02, -0.61)	-0.64 (-1.02, -0.30)	-0.78 (-0.98, -0.60)	-0.80 (-0.97, -0.64)	-0.74 (-1.00, -0.48)	-0.82 (-1.06, -0.58)	-0.87 (-1.28, -0.46)	-1.02 (-1.42, -0.62)
Studies with < 1,500 mg/day of metformin at baseline	-0.83 (-1.04, -0.63)	-0.67 (-0.99, -0.36)	-0.86 (-1.13, -0.60)	-0.79 (-0.97, -0.62)	-0.74 (-1.02, -0.46)	-0.90 (-1.27, -0.52)	-0.88 (-1.31, -0.44)	-1.03 (-1.45, -0.61)
Studies < 3 months in duration	-0.83 (-1.00, -0.67)	-0.66 (-0.95, -0.38)	-0.85 (-1.03, -0.68)	-0.81 (-0.96, -0.67)	-0.74 (-0.99, -0.50)	-0.90 (-1.25, -0.56)	-0.89 (-1.28, -0.50)	-1.02 (-1.40, -0.65)
Studies with agents not sold in Canada	-0.82 (-1.04, -0.61)	-0.67 (-0.99, -0.37)	-0.88 (-1.11, -0.67)	-0.73 (-0.97, -0.51)	-0.85 (-1.14, -0.55)	———	-0.87 (-1.52, -0.23)	-1.02 (-1.55, -0.50)

A1C = glycosylated hamoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; N/A = not applicable; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for A1C
- the results of meta-regressions adjusting for baseline A1C and duration of diabetes.

MTC results are presented as the probability of having the largest reduction in A1C with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for A1C — Probability of Largest Reduction in A1C								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	1.8%	1.5%	12.8%	1.4%	6.0%	8.2%	7.9%	60.4%
Reference case — fixed-effects model	0.1%	0.1%	11.3%	0.0%	2.9%	7.9%	9.2%	68.5%
Meta-regressions adjusting for:								
Baseline A1c	2.6%	1.4%	6.3%	2.7%	5.2%	7.9%	16.9%	56.9%
Baseline duration of diabetes	2.6%	2.0%	5.8%	3.7%	4.7%	13.1%	17.6%	50.6%
Sensitivity analyses with removal of:								
Poor-quality studies	3.2%	2.3%	5.7%	10.2%	3.8%	10.6%	26.7%	37.6%
Crossover studies	2.1%	2.2%	8.9%	4.3%	7.3%	13.6%	8.5%	53.3%
Studies < 1 year in duration	4.3%	3.5%	2.4%	4.7%	4.8%	6.9%	12.1%	61.4%
Studies with < 1,500 mg/day of metformin at baseline	2.5%	1.8%	11.4%	1.8%	4.4%	16.4%	9.2%	52.4%
Studies < 3 months in duration	2.3%	1.2%	6.8%	2.4%	3.8%	17.6%	9.7%	56.2%
Studies with agents not sold in Canada	1.8%	2.0%	13.7%	1.8%	17.0%	———	15.5%	48.1%

A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for A1C
- the results of meta-regressions adjusting for baseline A1C and duration of diabetes.

MTC results are presented as the mean rank for each treatment, which represents the average ranking for that agent relative to the others over the 40,000 simulations. For example, a lower number indicates that a particular treatment had the largest reduction in A1C for the majority of simulations (relative to other treatments), while a higher number indicates that a treatment had the smallest reduction in A1C.

Sensitivity Analyses for A1C — Mean Rank								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	4.6	6.9	3.3	5.2	5.5	4.1	4.3	2.1
Reference case — fixed-effects model	4.6	7.6	2.9	6.2	5.7	3.6	3.7	1.7
Meta-regressions adjusting for:								
Baseline A1c	4.5	7.0	4.2	4.9	5.6	4.1	3.5	2.1
Baseline duration of diabetes	4.6	6.8	4.4	4.6	5.9	3.7	3.7	2.4
Sensitivity analyses with removal of:								
Poor-quality studies	4.2	5.7	4.7	5.0	5.5	4.1	3.9	3.0
Crossover studies	4.6	6.7	3.9	4.5	5.3	3.9	4.7	2.4
Studies < 1 year in duration	4.2	6.6	5.1	4.5	5.6	4.2	3.8	2.0
Studies with < 1,500 mg/day of metformin at baseline	4.5	6.6	4.0	5.2	5.8	3.7	4.1	2.2
Studies < 3 months in duration	4.6	7.0	4.1	4.9	5.9	3.6	4.0	2.1
Studies with agents not sold in Canada	4.1	5.8	3.1	5.3	3.7	———	3.8	2.2

A1C = glycosylated haemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1;MTC = mixed treatment comparison; N/A = not applicable; TZDs = thiazolidinediones; vs = versus.

The following presents the model fit parameters for each sensitivity analysis and meta regressionconducted for A1C.

Sensitivity Analyses for A1C — Model Fit Parameters			
Analysis	**Residual Deviance**	**Unconstrained Data Points**	**DIC**
Random-effects model vs fixed-effects model:			
Reference case — random-effects model	39.31	43	-5.704
Reference case — fixed-effects model	73.52	43	13.792
Meta-regressions adjusting for:			
Baseline A1C	37.14	43	-7.455
Baseline duration of diabetes	37.65	43	-6.635
Sensitivity analyses with removal of:			
Poor-quality studies	14.75	15	3.721
Crossover studies	37.19	41	-6.498
Studies > 1 year in duration	33.98	36	4.440
Studies with < 1,500 mg/day of metformin at baseline	28.8	31	-3.880
Studies < 3 months in duration	34.9	40	-7.156
Studies with agents not sold in Canada	25.22	29	1.573

A1C = glycosylated hemoglobin; DIC = deviance information criterion; vs = versus.

APPENDIX 25: SENSITIVITY ANALYSES FOR BODY WEIGHT

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference-case analysis) with a fixed- effects model
- the results of the sensitivity analyses for body weight
- the results of meta-regressions adjusting for baseline body mass index.

MTC results are presented as the mean estimate of effect for reducing body weight from baseline (95% credible interval) with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for Change In Body Weight from Baseline — MTC Estimate of Effect Vs. Placebo								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	2.01 (1.10, 2.93)	1.80 (0.36, 3.28)	2.59 (1.67, 3.51)	0.57 (-0.45, 1.61)	-0.92 (-2.35, 0.53)	-1.79 (-3.41, -0.15)	1.55 (-0.46, 3.61)	2.95 (0.95, 5.00)
Reference case — fixed-effects model	1.80 (1.51, 2.10)	1.36 (0.84, 1.89)	2.52 (2.24, 2.80)	0.32 (-0.02, 0.60)	-0.80 (-1.35, -0.24)	-1.86 (-2.65, -1.08)	1.34 (0.49, 2.17)	2.49 (1.79, 3.23)
Meta-regressions adjusting for:								
Baseline BMI (kg/m^2)	2.04 (1.09, 3.00)	1.79 (0.30, 3.30)	2.68 (1.63, 3.72)	0.63 (-0.45, 1.73)	-0.90 (-2.36, 0.55)	-1.86 (-3.55, -0.15)	1.49 (-0.60, 3.62)	2.93 (0.88, 5.03)
Sensitivity analyses with removal of:								
Crossover studies	2.04 (1.11, 2.98)	1.80 (0.33, 3.31)	2.59 (1.66, 3.51)	0.58 (-0.45, 1.62)	-0.91 (-2.36, 0.54)	-1.89 (-3.59, -0.18)	1.91 (-0.44, 4.31)	3.20 (1.01, 5.44)

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for removal of crossover studies
- the results of meta-regressions adjusting for baseline body mass index.

MTC results are presented as the probability of having the largest reduction in body weight with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for Change In Body Weight From Baseline — Probability of Largest Reduction In Body Weight								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random effects model	0.0%	0.0%	0.0%	0.2%	20.9%	78.7%	0.0%	0.0%
Reference case — fixed-effects model	0.0%	0.0%	0.0%	0.0%	1.4%	98.6%	0.0%	0.0%
Meta-regressions adjusting for:								
Baseline BMI (kg/m^2)	0.0%	0.0%	0.0%	0.2%	19.3%	80.4%	0.0%	0.0%
Sensitivity analyses with removal of:								
Crossover studies	0.0%	0.0%	0.0%	0.1%	18.7%	80.9%	0.1%	0.0%

BMI = body mass index, DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for body weight
- the results of meta-regressions adjusting for baseline body mass index.

MTC results are presented as the mean rank for each treatment, which represents the average ranking for that agent relative to the others over the 40,000 simulations. For example, a lower number indicates that a particular treatment had the largest reduction in body weight for the majority of simulations (relative to other treatments), while a higher number indicates that a treatment had the smallest reduction in body weight.

Sensitivity Analyses for Change In Body Weight From Baseline — Mean Rank								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed effects model:								
Reference case — random-effects model	6.5	6.2	7.9	4.1	2.0	1.2	5.7	8.3
Reference case — fixed-effects model	6.8	5.6	8.5	4.0	2.0	1.0	5.6	8.4
Meta-regressions adjusting for:								
Baseline BMI (kg/m^2)	6.6	6.2	8.0	4.2	2.0	1.2	5.5	8.2
Sensitivity analyses with removal of:								
Crossover studies	6.4	6.0	7.7	4.1	2.0	1.2	6.1	8.4

BMI = body mass index, DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

Sensitivity Analyses for Body Weight — Model Fit Parameters			
Analysis	**Residual Deviance**	**Unconstrained Data Points**	**DIC**
Random-effects model vs fixed-effects model:			
Reference case — random-effects model	30.98	32	69.219
Reference case — fixed-effects model	212.7	32	231.129
Meta-regressions adjusting for:			
Baseline body mass index	31.01	32	69.481
Sensitivity analyses with removal of:			
Crossover studies	30.12	31	66.997

DIC = deviance information criterion; vs = versus.

APPENDIX 26: SENSITIVITY ANALYSES FOR OVERALL HYPOGLYCEMIA

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for overall hypoglycemia
- the results of meta-regressions adjusting for baseline A1C.

MTC results are presented as the mean odds ratio (95% credible interval) for the number of patients experiencing hypoglycemia with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for Overall Hypoglycemia — MTC Estimate of Effect Vs. Placebo								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	8.2 (4.5, 16.6)	8.6 (3.5, 25.2)	1.1 (0.5, 2.3)	1.0 (0.6, 2.2)	0.4 (0.0, 6.7)	1.1 (0.3, 3.9)	5.2 (1.5, 21.5)	11.0 (3.5, 40.4)
Reference case — fixed-effects model	7.6 (5.0, 11.8)	7.6 (4.1, 14.8)	1.3 (0.8, 2.1)	0.9 (0.6, 1.4)	0.4 (0.0, 5.4)	1.0 (0.4, 2.5)	4.4 (2.0, 9.5)	9.7 (5.0, 19.3)
Meta-regressions adjusting for:								
Baseline A1C	8.6 (4.6, 18.1)	8.4 (3.3, 25.2)	1.1 (0.5, 2.2)	1.1 (0.6, 2.2)	0.4 (0.0, 6.6)	1.3 (0.4, 5.1)	7.1 (1.7, 36.7)	12.5 (3.8, 49.1)
Duration of trial	8.5 (4.8, 16.4)	8.3 (3.5, 22.8)	0.9 (0.5, 1.9)	1.0 (0.6, 2.1)	0.4 (0.0, 6.1)	1.1 (0.3, 3.8)	5.7 (1.7, 21.3)	11.7 (4.0, 39.2)
Sensitivity analyses with removal of:								
Crossover studies	8.0 (4.4, 16.3)	8.4 (3.4, 24.8)	1.1 (0.5, 2.2)	1.0 (0.6, 2.2)	0.4 (0.0, 6.8)	1.2 (0.4, 4.5)	4.6 (1.2, 19.8)	9.9 (3.1, 36.3)

A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for overall hypoglycemia
- the results of a meta-regression adjusting for baseline A1C.

MTC results are presented as the probability of having the fewest patients experiencing hypoglycemia with each individual treatment relative to metformin monotherapy.

Sensitivity Analyses for Overall Hypoglycemia — Probability of Having the Fewest Number of Patients With Hypoglycemic Episodes								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-Glucosidase Inhibitors**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	0.0%	0.0%	6.2%	7.7%	66.4%	12.9%	0.0%	0.0%
Reference case — fixed-effects model	0.0%	0.0%	0.1%	15.6%	67.5%	12.7%	0.0%	0.0%
Meta-regressions adjusting for:								
Baseline A1C	0.0%	0.0%	7.5%	7.5%	67.7%	10.1%	0.0%	0.0%
Duration of trial	0.0%	0.0%	11.5%	5.8%	66.2%	10.9%	0.0%	0.0%
Sensitivity analyses with removal of:								
Crossover studies	0.0%	0.0%	6.7%	8.3%	67.2%	10.8%	0.1%	0.0%

A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

The following information is presented in this table:

- a comparison of the MTC results generated using a random-effects model (i.e., the reference case analysis) with a fixed- effects model
- the results of the sensitivity analyses for overall hypoglycemia
- the results of a meta-regression adjusting for baseline A1C.

MTC results are presented as the mean rank for each treatment, which represents the average ranking for that agent relative to the others over the 80,000 simulations. For example, a lower number indicates that a particular treatment had the lowest odds ratio for the majority of simulations (relative to other treatments), while a higher number indicates that a treatment had higher odds ratios.

Sensitivity Analyses for Overall Hypoglycemia — Mean Rank

Analysis	Sulfonylureas	Meglitinides	TZDs	DPP-4 Inhibitors	Alpha-Glucosidase Inhibitors	GLP-1 Analogues	Basal Insulin	Biphasic Insulin
Random-effects model vs fixed-effects model:								
Reference case — random-effects model	7.5	7.6	3.4	3.2	2.1	3.4	6.4	8.3
Reference case — fixed-effects model	7.6	7.7	4.4	2.4	2.1	3.2	6.1	8.5
Meta-regressions adjusting for:								
Baseline A1C	7.3	7.3	3.2	3.2	2.1	3.7	6.9	8.3
Duration of trial	7.5	7.5	2.9	3.3	2.1	3.6	6.5	8.4
Sensitivity analyses with removal of:								
Crossover studies	7.6	7.7	3.4	3.1	2.1	3.6	6.3	8.2

A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; TZDs = thiazolidinediones; vs = versus.

Sensitivity Analyses for Overall Hypoglycemia — Model Fit Parameters			
Analysis	**Residual Deviance**	**Unconstrained Data Points**	**DIC**
Random effects model vs fixed effects model:			
Reference case —random effects model	64.63	72	325.26
Reference case — fixed effects model	84.08	72	343.42
Meta-regressions adjusting for:			
Baseline A1C	64.16	72	333.28
Duration of study	65.67	72	333.41
Sensitivity analyses with removal of:			
Crossover studies	62.54	67	325.26

A1C = glycosylated hemoglobin; DIC = deviance information criterion; vs = versus.

APPENDIX 27: PAIRWISE COMPARISONS

This summary of findings table presents the results of direct pairwise meta-analyses of studies that reported severe hypoglycemia (24 RCTs; N = 8,650) and nocturnal hypoglycemia (6 RCTs; N = 805). Pooled estimates of effect are presented as odds ratios (95% confidence interval). The overall quality of the evidence as assessed using GRADE is also presented. Definitions of severe hypoglycemia and nocturnal hypoglycemia are presented in separate tables.

Summary of Findings for Hypoglycemia (Direct Pairwise Comparisons)				
Outcome	**Comparison**	**No. of Trials/Total N**	**OR (95% CI)**	**Quality of Evidence**
Severe hypoglycemia	Sulfonylurea vs. placebo	3 RCTs[63,83,89] (N = 501)	2.24 (0.34, 14.87)	Low
	Meglitinide vs. placebo	2 RCTs[84,87] (N = 366)	*No events*	Low
	TZD vs. placebo	3 RCTs[66,69,72] (N = 627)	*No events*	Very low
	DPP-4 inhibitor vs. placebo	3 RCTs[58,61,73] (N = 1,435)	*No events*	Very low
	alpha-glucosidase inhibitor vs. placebo	1 RCT[103] (N = 153)	*No events*	Low
	GLP-1 vs. placebo	3 RCTs[70,89,103] (N = 389)	0.33 (0.01, 8.40)*	Very low
	Sulfonylurea vs. TZD	3 RCTs[71,85,102] (N = 1,151)	*No events*	Very low
	Sulfonylurea vs. DPP-4 inhibitor	1 RCT[68] (N = 2,789)	21.20 (1.24, 362.1)	Very low
	Sulfonylurea vs. biphasic insulin	1 RCT[81] (N = 222)	*No events*	Low
	GLP-1 analogue vs. basal insulin	2 RCTs[53,60] (N = 145)	0.32 (0.01, 8.22)†	Very low
	Biphasic insulin vs. basal insulin	2 RCTs[80,94] (N = 297)	*No events*	Very low
	TZD vs. DPP-4 inhibitor	1 RCT[57] (N = 575)	*No events*	Very low
Nocturnal hypoglycemia	Meglitinide vs. placebo	2 RCTs[84,87] (N = 366)	*No events*	Low
	TZD vs. placebo	1 RCT[72] (N = 70)	*No events*	Very low
	Alpha-glucosidase inhibitor vs. placebo	1 RCT[103] (N = 153)	*No events*	Low
	GLP-1 analogue vs. basal insulin	1 RCT[107] (N = 76)	0.18 (0.02, 1.61)	N/A: abstract only
	Biphasic insulin vs. basal insulin	1 RCT[80] (N = 140)	0.79 (0.34, 1.84)	Very low

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GRADE = Grading of Recommendations Assessment, Development and Evaluation; OR = odds ratio; RCT = randomized controlled trial; TZD = thiazolidinediones; vs. = versus.
*Only a single patient out of a total of 389 patients reported an episode of severe hypoglycemia.
†Only a single patient out of a total of 145 patients reported an episode of severe hypoglycemia.

This summary of findings table presents the results of direct pairwise meta-analyses of studies that reported body mass index (4 RCTs; N = 839). All values represent the change in body mass index (kg/m^2) from baseline between two treatment arms. Pooled estimates of effect are presented as mean differences (95% confidence interval). The overall quality of the evidence as assessed using GRADE is also presented.

Summary of Findings for Body Mass Index (kg/m^2)				
Other Outcomes				
Outcome	**Comparison**	**No. of Trials/Total N**	**WMD (95% CI)**	**Quality of Evidence**
Body mass index	Sulfonylurea vs. placebo	1 RCT[63] (N = 372)	0.46 (0.17, 0.75)	Moderate
	TZD vs. placebo	1 RCT[69] (N = 292)	3.1 (1.81, 4.39)	Moderate
	TZD vs. sulfonylurea	2 RCTs[91,102] (N = 238)	-0.11 (-0.47, 0.25)	Low

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; N = total number of patients; RCT = randomized controlled trials; TZD = thiazolidinediones; vs. = versus; WMD = weighted mean difference.

This summary of findings table presents the results of direct pairwise meta-analyses of studies that reported long-term complications of diabetes such as ischemic heart disease (6 RCTs; N = 2,896), congestive heart failure (4 RCTs; N = 4,147), macular edema (1 RCT; N = 2,222), all-cause mortality (11 RCTs; N = 9,108), neuropathy (1 RCT; N = 190), peripheral vascular disease (1 RCT; N = 2,789), stroke and transient ischemic attack (2 RCTs; N = 3,364). Pooled estimates of effect are presented as odds ratios (95% confidence interval). The overall quality of the evidence as assessed using GRADE is also presented.

Summary of Findings for Long-Term Complications (Direct Pairwise Comparisons)				
Outcome	**Comparison**	**No. of Trials/Total N**	**OR (95% CI)**	**Quality of Evidence**
Ischemic heart disease	TZDs vs. sulfonylureas	1 RCT[85] (N = 630)	2.97 (0.12, 73.22)	Very low
	Alpha-glucosidase inhibitors vs. placebo	1 RCT[103] (N = 153)	0.32 (0.01, 7.89)	Low
	Sulfonylureas vs. meglitinides	1 RCT[97] (N = 213)	0.18 (0.01, 3.73)	Low
	Sulfonylureas vs. DPP-4 inhibitors	1 RCT[88] (N = 1,135)	0.14 (0.01, 2.68)	Very low
	DPP-4 inhibitors vs. placebo	1 RCT[95] (N = 190)	3.10 (0.12, 76.97)	Very low
	DPP-4 inhibitors vs. TZDs	1 RCT[57] (N = 575)	1.05 (0.07, 16.93)	Very low
Congestive heart failure	TZDs vs. sulfonylureas	1 RCT[62] (N = 630)	2.49 (0.48, 12.94)	Low
	DPP-4 inhibitors vs. sulfonylureas	1 RCT[68] (N = 2,789)	1.00 (0.14, 7.09)	Very low
	DPP-4 inhibitors vs. TZDs	1 RCT[56] (N = 575)	*No events*	Very low
	Alpha-glucosidase inhibitors vs. placebo	1 RCT[103] (N = 153)	0.32 (0.01, 7.89)	Low
Macular edema	TZDs vs. sulfonylureas	1 RCT[77] (N = 2,222)	*No events*	Very low
All-Cause Mortality	TZD vs. sulfonylureas	1 RCT[85] (N = 630)	0.20 (0.01, 4.10)	Very low
	DPP-4 inhibitors vs. placebo	3 RCTs[65,73,95] (N = 1,117)	0.22 (0.02, 2.16)	Very low
	DPP-4 inhibitors vs. sulfonylureas	2 RCTs[68,88] (N = 3,924)	0.59 (0.14, 2.50)	Very low
	TZD vs. placebo	1 RCT[69] (N = 223)	*No events*	Low
	Alpha-glucosidase inhibitors vs. placebo	1 RCT[74] (N = 152)	*No events*	Very low
	Meglitinides vs. sulfonylureas	1 RCT[97] (N = 213)	*No events*	Low
	BiAsp 30 vs. sulfonylureas	1 RCT[81] (N = 222)	3.20 (0.13, 79.29)	Low
	TZD vs. DPP-4 inhibitors	1 RCT[55] (N = 2,627)	6.05 (0.25, 148.75)	Very low
Neuropathy	DPP-4 inhibitors vs. placebo	1 RCT[95] (N = 190)	2.00 (0.36, 11.19)	Very low
PVD	Sulfonylureas vs. DPP-4 inhibitors	1 RCT[68] (N = 2,789)	0.33 (0.01, 8.17)	Very low
Stroke/TIA	Sulfonylureas vs. DPP-4 inhibitors	1 RCT[68] (N = 2,789)	0.07 (0.00, 1.16)	Very low
	TZDs vs. DPP-4 inhibitors	1 RCT[57] (N = 575)	3.18 (0.33, 30.79)	Very low

BiAsp = biphasic insulin aspart; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GRADE = Grading of Recommendations Assessment, Development and Evaluation; N = total number of patients; OR = odds ratio; PVD = peripheral vascular disease; RCT = randomized controlled trial; TIA = transient ischemic attack; TZD = thiazolidinediones; vs. = versus.

This summary of findings table presents the results of direct pairwise meta-analyses of studies with a range of patient-reported outcomes, including the diabetes treatment satisfaction questionnaire (overall and subscales). Pooled estimates of effect are presented as mean differences (95% confidence interval). The overall quality of the evidence as assessed using GRADE is also presented.

Summary of Findings for Patient-Reported Outcomes (Direct Pairwise Comparisons)				
Outcome	**Comparison**	**No. of Trials/Total N**	**OR (95% CI)**	**Quality of Evidence**
DTSQ	TZD vs. placebo	1 RCT[82] (N = 187)	0.7 (-0.75, 2.15)	Very low
DTSQ (perceived hyperglycemia)	Sulfonylurea vs. placebo	1 RCT[106] (N = 272)	-0.3 (-1.03, 0.43)	N/A: abstract only
	GLP-1 analogue vs. placebo	1 RCT[106] (N = 276)	-1.1 (-1.83, -0.37)	N/A: abstract only
	GLP-1 analogue vs. sulfonylurea	1 RCT[106] (N = 366)	-0.8 (-1.33, -0.27)	N/A: abstract only
DTSQ (perceived hypoglycemia)	GLP-1 analogue vs. sulfonylurea	1 RCT[106] (N = 727)	0.65 (-0.27, 1.57)	N/A: abstract only
IWQoL lite	GLP-1 analogue vs. sulfonylurea	1 RCT[106] (N = 366)	0.9 (-0.18, 1.98)	N/A: abstract only
SF-36 physical component	TZD vs. placebo	1 RCT[82] (N = 185)	-0.16 (-2.65, 2.33)	Very low
SF-36 mental component	TZD vs. placebo	1 RCT[82] (N = 185)	-1.75 (-4.14, 0.64)	Very low

CI = confidence interval; DTSQ = diabetes treatment satisfaction questionnaire; GLP-1 = glucagon-like peptide-1; GRADE = Grading of Recommendations Assessment, Development and Evaluation; IWQoL = impact of weight on quality of life-lite; N = total number of patients; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SF-36 = short-form health survey;TZD = thiazolidinediones; vs. = versus.

This summary of findings table presents the results of direct pairwise meta-analyses of studies that reported severe adverse events. Pooled estimates of effect are presented as odds ratios (95% confidence interval). The overall quality of the evidence as assessed using GRADE is also presented.

Summary of Findings for Safety Outcomes (Direct Pairwise Comparisons)				
Outcome	**Comparison**	**No. of Trials/Total N**	**OR (95% CI)**	**Quality of Evidence**
Severe adverse events	Sulfonylureas vs. placebo	2 RCTs[63,83] (N = 429)	1.39 (0.35, 5.51)	Low
	TZDs vs. placebo	5 RCTs[69,72,78,82,101] (N = 882)	0.92 (0.43, 1.99)	Very low
	DPP-4 inhibitors vs. placebo	6 RCTs[58,61,65,73,95,101] (N = 2,372)	1.07 (0.65, 1.75)	Very low
	Alpha-glucosidase inhibitors vs. placebo	2 RCTs[92,103] (N = 236)	2.28 (0.83, 6.27)	Low
	DPP-4 inhibitors vs. sulfonylureas	2 RCTs[68,88] (N = 3,961)	0.83 (0.60, 1.16)	Very low
	Sulfonylureas vs. meglitinides	1 RCT[97] (N = 213)	4.10 (0.83, 20.19)	Low
	Sulfonylureas vs. TZDs	2 RCTs[91,102] (N = 231)	1.12 (0.38, 3.33)	Very low
	TZDs vs. DPP-4	3 RCTs[55,57,101] (N = 3,383)	1.71 (1.06, 2.77)	Very low
	GLP-1 analogues vs. basal insulin	1 RCT[60] (N = 69)	2.83 (0.11, 71.94)	Very low
	Biphasic insulin vs. basal insulin	1 RCT[94] (N = 157)	0.78 (0.20, 3.01)	Very low

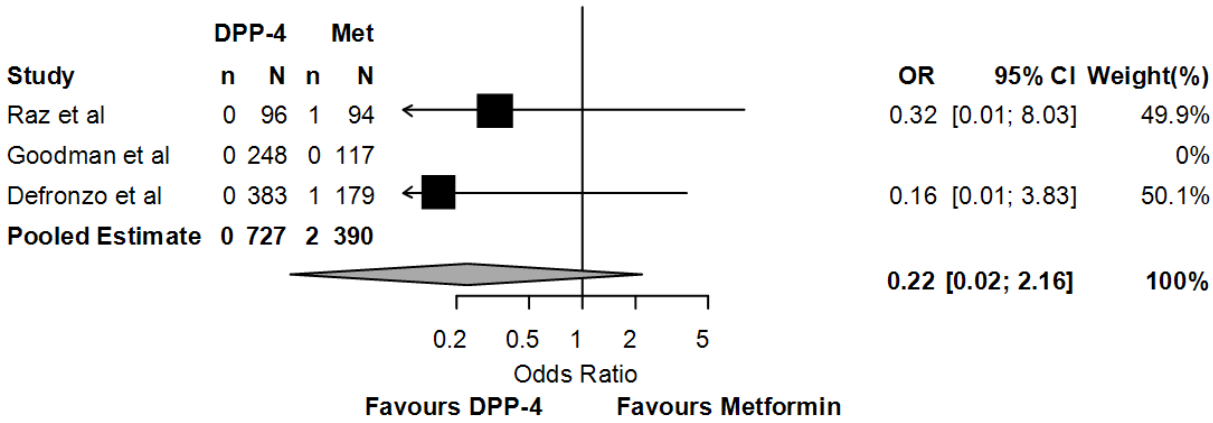
CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GRADE = Grading of Recommendations Assessment, Development and Evaluation; N = total number of patients; OR = odds ratio; RCT = randomized controlled trial;TZD = thiazolidinediones; vs. = versus.

APPENDIX 28: FOREST PLOTS FOR PAIRWISE COMPARISONS

Comparison of sulfonylureas vs. TZDs for change in BMI from baseline

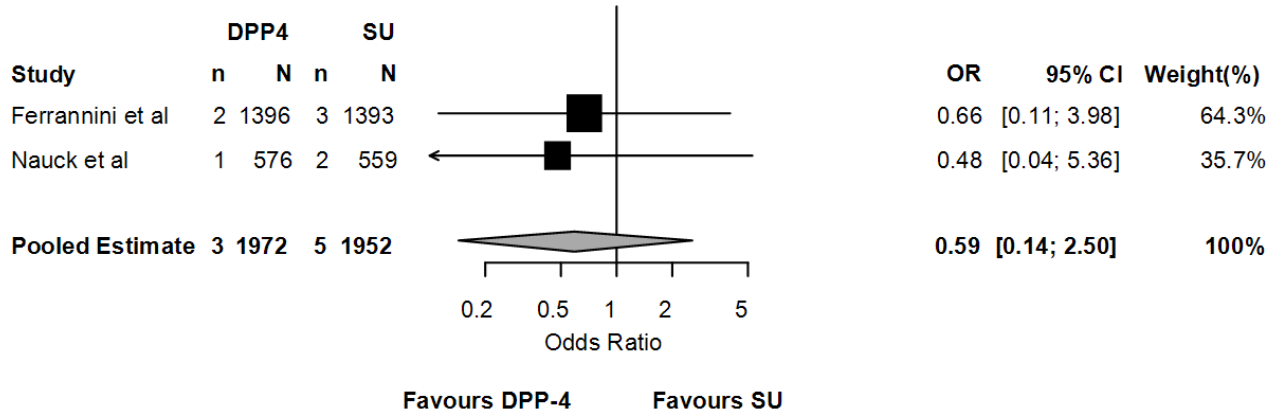
CI = confidence interval; BMI = body mass index; MD = mean difference; SU = sulfonylurea;TZDs = thiazolidinediones; vs. = versus.

Comparison of DPP-4 inhibitors vs. placebo for all-cause mortality



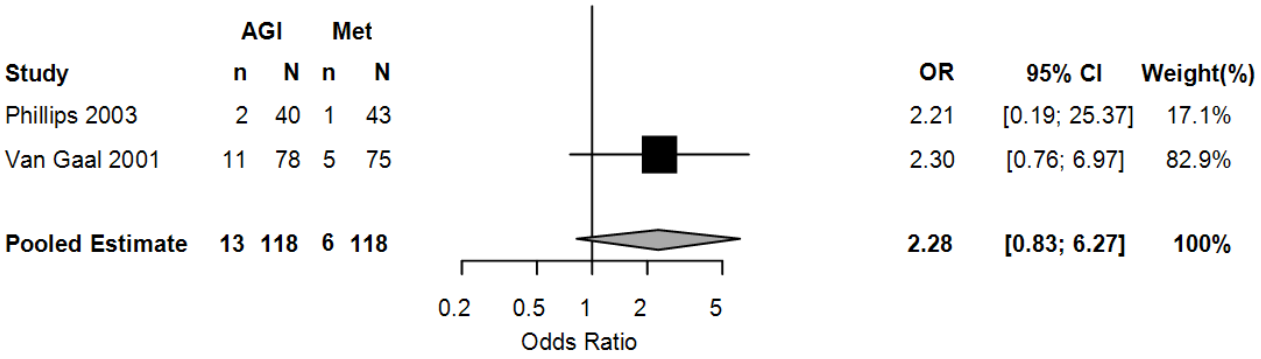
CI = confidence interval; DDP-4 = dipeptidyl peptidas-4; Met = metformin; OR = odds ratio; vs. = versus.

Comparison of sulfonylureas vs. DPP-4 inhibitors for all-cause mortality

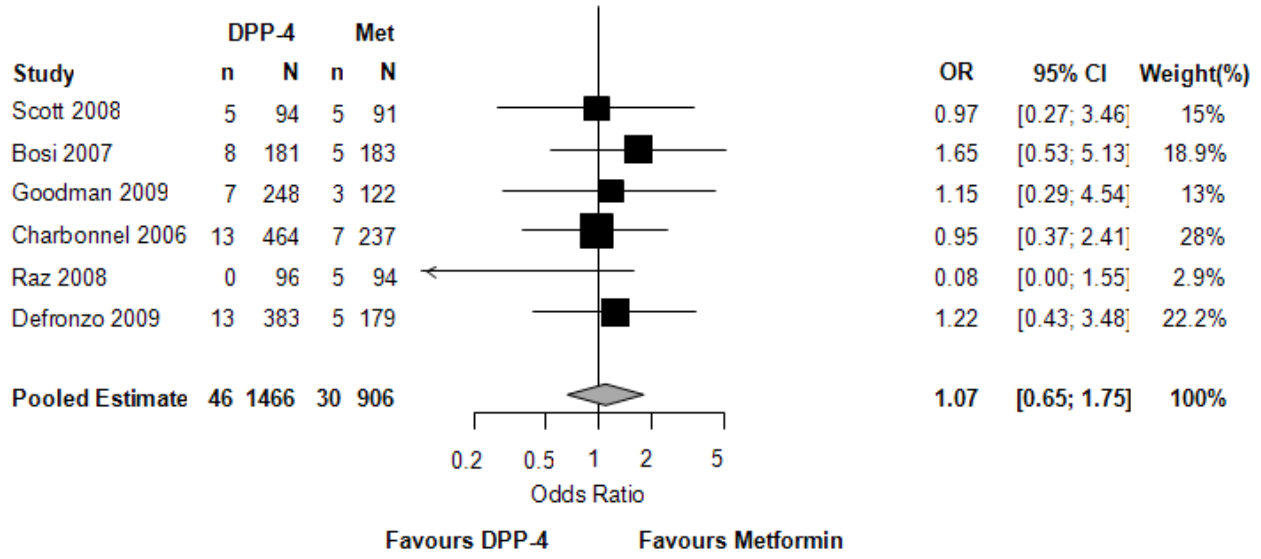


CI = confidence interval; DDP-4 = dipeptidyl peptidas-4; OR = odd ratio; SU = sulphonylurea; vs. = versus.

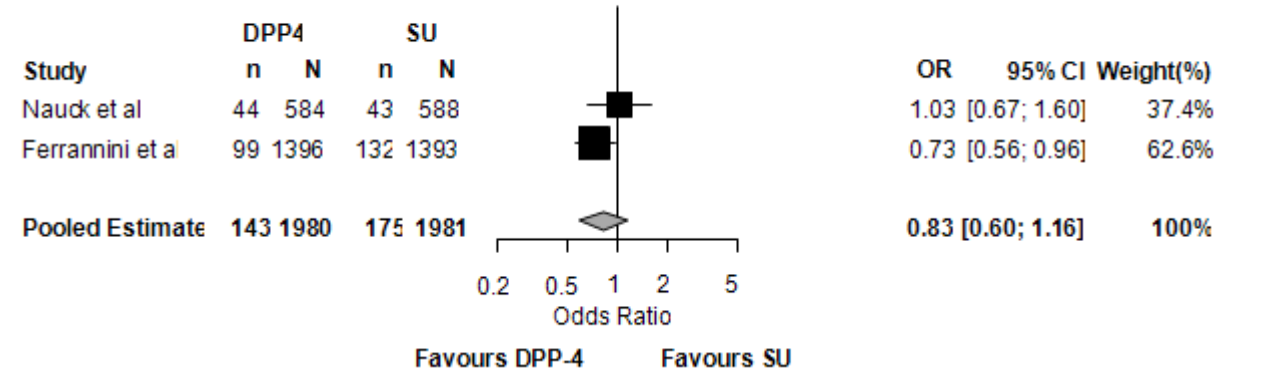
Comparison of alpha-glucosidase inhibitors vs. placebo for serious adverse events



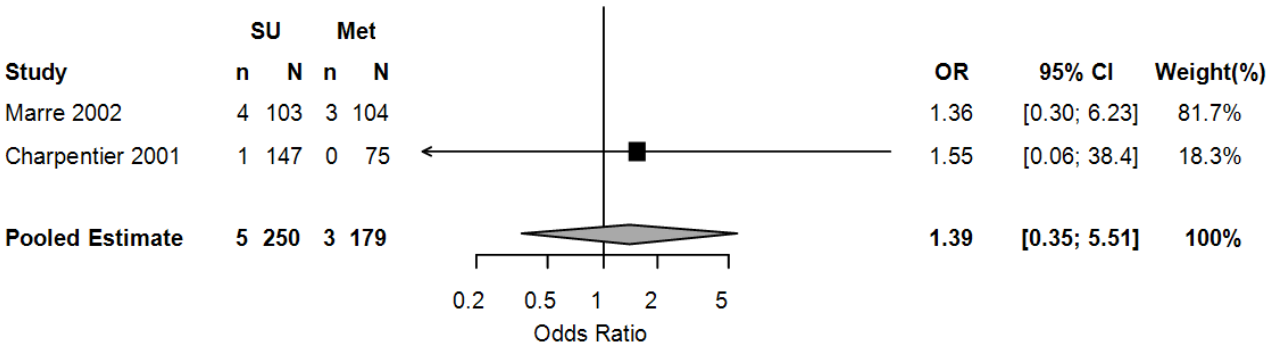
Comparison of DPP-4 inhibitors vs. placebo for serious adverse events



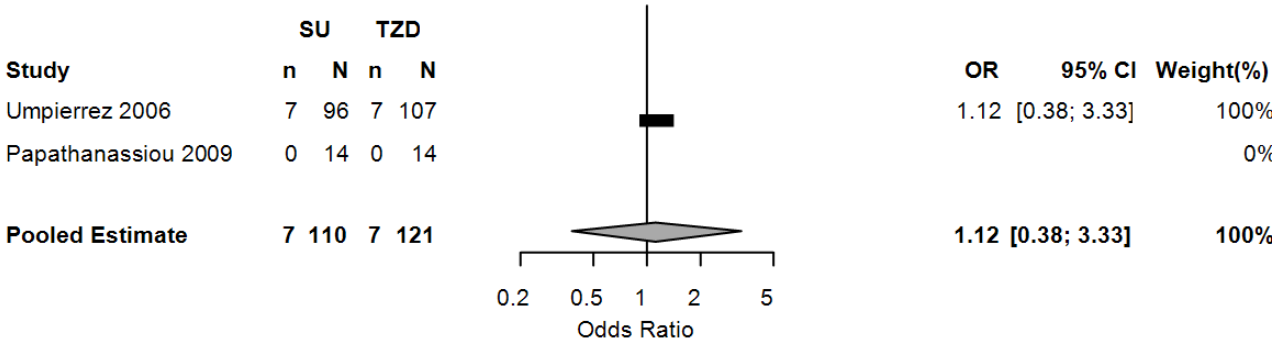
Comparison of sulfonylureas vs. DPP-4 inhibitors for serious adverse events



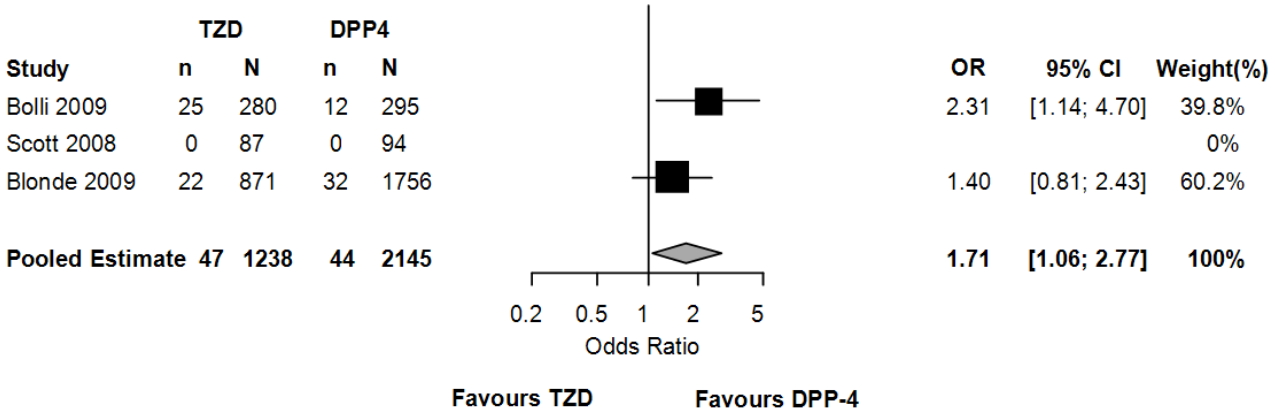
Comparison of sulfonylurea vs. placebo inhibitors for serious adverse events



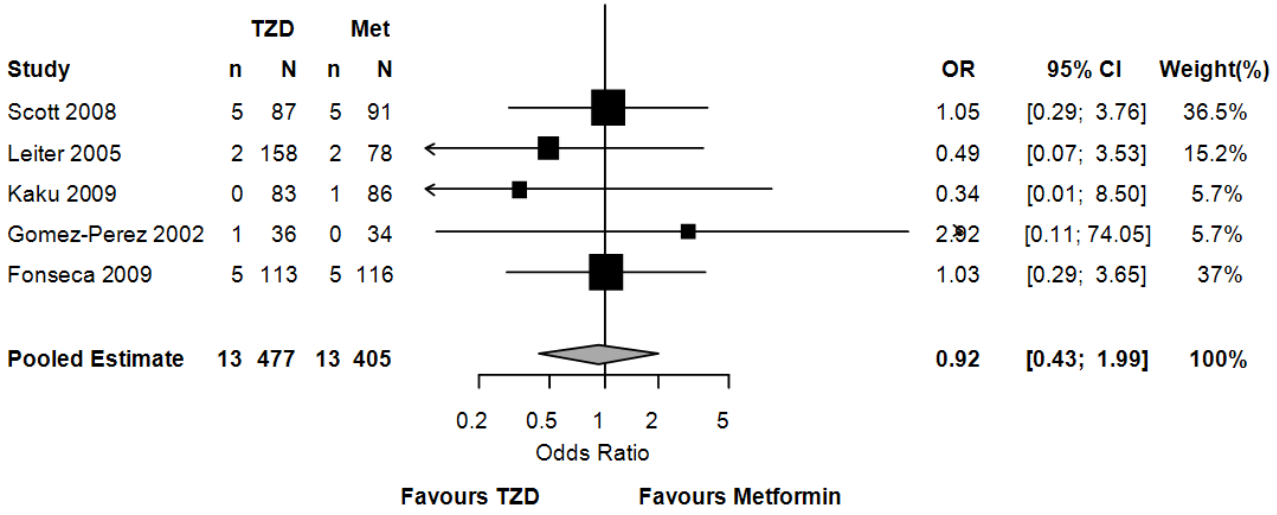
Comparison of sulfonylureas vs. TZDs inhibitors for serious adverse events



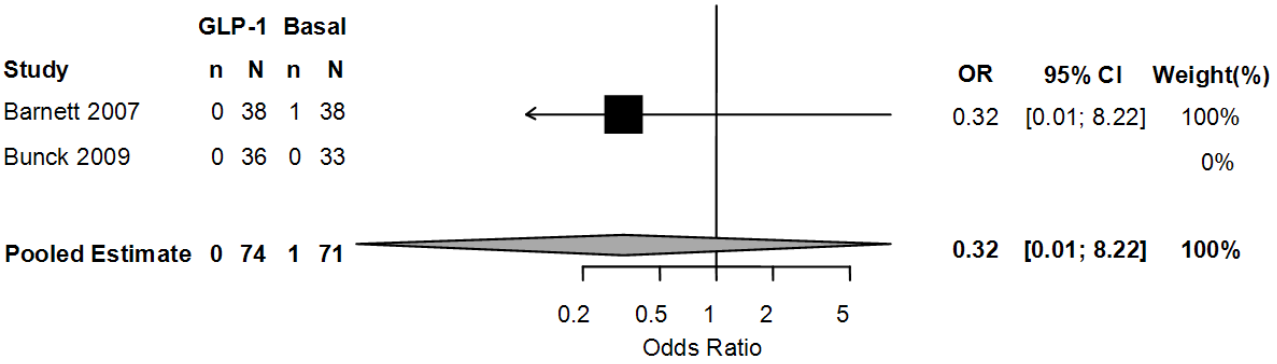
Comparison of TZDs vs. DPP-4 inhibitors for serious adverse events



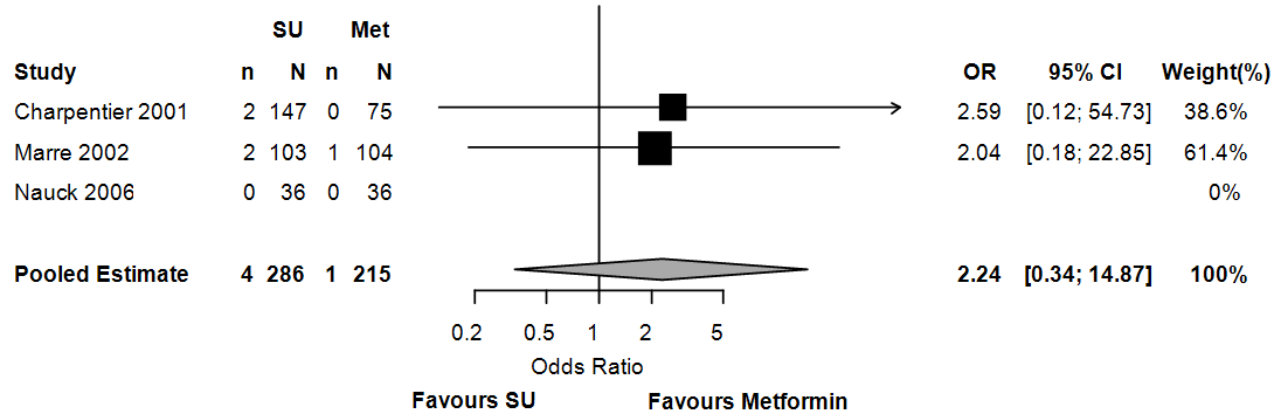
Comparison of TZDs vs. placebo for serious adverse events



Comparison of GLP-1 analogues vs. basal insulin for severe hypoglycemia



Comparison of sulfonylureas vs. placebo for severe hypoglycemia



APPENDIX 29: GRADE EVIDENCE PROFILES

GRADE Summary of Quality of Evidence for A1C (Change From Baseline)						
No. of Studies	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
40 RCTs[53,55,57,58,60-66,68,69,71-74,77,78,80-84,87-95,97-99,101-104]	Very serious limitations	Not assessed	No important imprecision	No important inconsistency	Very serious indirectness	**Very low**

A1C = glycolsylated hemoglobin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials.

Study limitations

- The majority of RCTs, including the largest trials, received a rating of "poor" using the Scottish Intercollegiate Guidelines Network SIGN 50 assessment of internal validity. In addition, the majority of trials failed to address two or more of the major sources of bias (i.e., proper allocation concealment, use of intention-to-treat analysis, and equal treatment between patients in each trial arm) (-2).

Publication bias

- Publication bias could not be formally assessed due to a limited number of randomized controlled trials (RCTs) for each pairwise comparison (no decrement).

Inconsistency

- I^2 values of greater than 50% were observed in some pairwise meta-analyses. However, the overall body of evidence was considered to be consistent, as a very small proportion of the RCTs included in the analysis contributed to the large I^2 values. The contribution of these studies to MTC results is likely to be negligible (no decrement).
- The deviance information criterion for the fixed-effects model (13.8) was greater than that of the random-effects model (-5.7) suggesting that the random-effects model is a better-fitting model.
- The residual deviance for both models is much less than the number of unconstrained data points indicating a good model fit (no decrement).
- The results of the primary analysis were highly consistent across a wide range of sensitivity analyses and meta-regression analyses (no decrement).

Imprecision

- Evidence was considered to be precise given that all agents achieved statistically significant reductions in A1C and that there were no significant differences between the active treatments with regard to A1C (no decrement).

Indirectness

- The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and required a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).
- A1C is a surrogate outcome for diabetes-related complications (-1).
- Direct and indirect estimates of effect are closely aligned (no decrement).

GRADE Summary of Quality of Evidence for Overall Hypoglycemia						
No. of Studies	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
34 RCTs[53,55,57-66,68,69,71-73,77,78,80-84,87-89,94,95,97,99,101-104]	Very serious limitations	Not assessed	No serious imprecision	No important inconsistency	Serious indirectness	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials.

Inconsistency

- Only 1/14 of the pairwise meta-analyses had an I^2 value of greater than 50%; therefore, the overall body of evidence was considered to be consistent (no decrement).
- The deviance information criterion for the fixed-effects model (343) was higher than the random-effects model (325), suggesting that the random-effects model is a better-fitting model
- The residual deviance for the random-effects model (64.3) is less than the number of unconstrained data points (72), indicating adequate model fit (no decrement).
- The results of the primary analysis were highly consistent across a wide range of sensitivity analyses and meta-regression analyses (no decrement).

Imprecision

- There is a distinct separation of agents regarding the occurrence of overall hypoglycemia (no decrement). For example, the probability of having the fewest patients with hypoglycemia was 0.0% for the insulins and insulin secretagogues. There were no statistically significant differences between the remaining agents, all of which were associated with a low rate of hypoglycemia.

Indirectness

- The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and required a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to the use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).
- Direct and indirect estimates of effect are closely aligned (no decrement).

Study limitations

- The majority of RCTs, including the largest trials, received a rating of "poor" using the SIGN 50 assessment of internal validity. In addition, the majority of trials failed to address two or more of the major sources of bias (i.e., proper allocation concealment, use of intention-to-treat analysis, and equal treatment between patients in each trial arm) (-2).

Publication bias

- Publication bias could not be formally assessed because of a limited number of RCTs for each pairwise comparison (no decrement).

GRADE Summary of Quality of Evidence for Body Weight (Change From Baseline)						
No. of Studies	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
30 RCTs[53,55,57,58,60,62-64,66,68,71-73,77,78,80,81,83,84,87-89,91,92,94,97,99,101-103]	Very serious limitations	Not assessed	No serious imprecision	No important inconsistency	Serious indirectness	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials.

Study limitations

- The majority of RCTs, including the largest trials, received a rating of "poor" using the SIGN 50 assessment of internal validity. In addition, the majority of trials failed to address two or more of the major sources of bias (i.e., proper allocation concealment, use of intention-to-treat analysis, and equal treatment between patients in each trial arm) (-2).

Publication bias

- Publication bias could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).

Inconsistency

- I^2 values of greater than 50% were observed in some pairwise meta-analyses. However, the overall body of evidence was considered to be consistent, as a very small proportion of the RCTs included in the analysis contributed to the large I^2 values. The contribution of these studies to MTC results is likely to be negligible (no decrement).
- The deviance information criterion for the fixed-effects model (231.1) was higher than the random-effects model (69.2), suggesting that the random-effects model is a better-fitting model
- The residual deviance for the random-effects model (31) is less than the number of unconstrained data points (32), indicating adequate model fit (no decrement).
- The results of the primary analysis were highly consistent across a wide range of sensitivity analyses and meta-regression analyses (no decrement).

Imprecision

- There is a distinct separation of agents that resulted in weight gain and those that resulted in weight loss; therefore, the evidence is considered to be precise (no decrement).

Indirectness

- The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and required a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).
- Direct and indirect estimates of effect are closely aligned (no decrement).

GRADE Summary of Quality of Evidence for Congestive Heart Failure							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZDs vs. sulfonylureas	1 RCT[62]	No serious limitations	Not assessed*	Sparse†	Not assessed*	Serious indirectness‡	**Low**
DPP-4 inhibitors vs. sulfonylureas	1 RCT[68]	Very serious limitations§	Not assessed*	Sparse†	Not assessed*	Serious indirectness‡	**Very low**
DPP-4 inhibitors vs. TZDs	1 RCT[56]	Very serious limitations¶	Not assessed*	Sparse†	Not assessed*	Serious indirectness‡	**Very low**
Alpha-glucosidase inhibitors vs. placebo	1 RCT[103]	No serious limitations	Not assessed*	Sparse†	Not assessed*	Serious indirectness‡	**Low**

A1C = glycolsylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials; TZDs = thiazolidinediones; vs. = versus.
* Publication bias could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).
† These RCTs were inadequately powered to detect long-term diabetes complications (-1).
‡ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).
§ This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address three major sources of bias (-2).
¶ This RCT received a rating of "poor" using the SIGN50 assessment of internal validity and failed to address two major sources of bias (-2).

GRADE Summary of Quality of Evidence for Diabetes Treatment Satisfaction Questionnaire							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZDs vs. placebo	1 RCT[82]	Very serious limitations*	Not assessed†	Sparse data‡	Not assessed†	Serious indirectness§	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials; TZDs = thiazolidinediones; vs. = versus.
* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).
† Publication bias could not be formally assessed because of a limited number of RCTs for each pairwise comparison (no decrement).
‡ Only a single comparison with a small sample size was available.
§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for Body Mass Index (Change From Baseline)							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylurea vs. placebo	1 RCT[63]	No serious limitations[*]	Not assessed[†]	Precise[‡]	Not assessed[†]	Serious indirectness[§]	**Moderate**
TZD vs. placebo	1 RCT[69]	No serious limitations[*]	Not assessed[†]	Precise[‡]	Not assessed[†]	Serious indirectness[§]	**Moderate**
TZD vs. sulfonylurea	2 RCTs[91,102]	Serious limitations[¶]	Not assessed[†]	Precise[‡]	Not assessed[†]	Serious indirectness[§]	**Low**
Sibutramine vs. placebo	1 RCT[86]	Very serious limitations[**]	Not assessed[†]	Precise[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials; TZDs = thiazolidinediones; vs. = versus.
[*] A rating of "good" using SIGN 50 assessment of internal validity was received.
[†] Publication bias and inconsistency could not be assessed due to the limited number of RCTs for these comparisons. No downgrade for not assessed.
[‡] Based on a relatively narrow 95% CI.
[§] The study populations included patients who had received diabetes pharmacotherapy other than metformin (-1).
[¶] These RCTs received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address one major source of bias (-1).
[**] This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).

GRADE Summary of Quality of Evidence for Severe Hypoglycemia							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylurea vs. placebo	3 RCTs[63,83,89]	Serious limitations[*]	Not assessed[†]	Sparse[‡]	No important inconsistency	Serious indirectness[§]	**Very low**
Meglitinide vs. placebo	2 RCTs[84,87]	No serious limitations	Not assessed[†]	Sparse[‡]	Not assessed[¶]	Serious indirectness[§]	**Low**
TZD vs. placebo	3 RCTs[66,69,72]	Serious limitations[**]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
DPP-4 inhibitor vs. placebo	3 RCTs[58,61,73]	Very serious limitations[††]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
Alpha-glucosidase inhibitor vs. placebo	1 RCT[103]	No serious limitations	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Low**
GLP-1 vs. placebo	3 RCTs[70,89,103]	Serious limitations[**]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

GRADE Summary of Quality of Evidence for Severe Hypoglycemia							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylurea vs. TZD	3 RCTs[71,85,102]	Serious limitations[**]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
Sulfonylurea vs. DPP-4 inhibitor	1 RCT[68]	Very serious limitations[‡‡]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
Sulfonylurea vs. biphasic insulin	1 RCT[81]	No serious limitations	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Low**
GLP-1 analogue vs. basal insulin	2 RCTs[53,60]	Serious limitations[§§]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
Biphasic insulin vs. basal insulin	2 RCTs[80,94]	Serious limitations[¶¶]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
TZD vs. DPP-4 inhibitor	1 RCT[57]	Serious limitations[***]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials; TZD = thiazolidinediones; vs. = versus.

* Two RCTs received a rating of "good" and one received a rating of "poor" using the SIGN 50 assessment of internal validity (-1).

† Publication bias could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).

‡ There were very few or zero events and low study power to detect severe hypoglycemia (-1).

§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to the use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

¶ Inconsistency could not be assessed due to zero events (no decrement).

** Two RCTs received a rating of "poor" and one received a rating of "good" using the SIGN 50 assessment of internal validity (-1).

†† All three RCTs received a rating of "poor" using the SIGN 50 assessment of internal validity and all failed to address at least two major sources of bias (-2).

‡‡ This RCT received a rating of '"poor" using SIGN 50 and failed to address two or more major sources of bias (-2).

§§ One RCT received a rating of "good" and one received a rating of "poor" using SIGN 50; a majority of the major sources of bias were addressed (-1).

¶¶ Two RCTs received a rating of "poor" using SIGN 50, but one addressed a majority of the major sources of bias (-1).

*** This RCT received a rating of "poor" using SIGN 50 and failed to address one major sources of bias (-1).

GRADE Summary of Quality of Evidence for Ischemic Heart Disease							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZDs vs. sulfonylureas	1 RCT[85]	Very serious limitations[*]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
Alpha-glucosidase inhibitors vs. placebo	1 RCT[103]	No serious limitations	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Low**
Sulfonylureas vs. meglitinides	1 RCT[97]	No serious limitations	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Low**
Sulfonylureas vs. DPP-4 inhibitors	1 RCT[88]	Very serious limitations[*]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
DPP-4 inhibitors vs. placebo	1 RCT[95]	Very serious limitations[*]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
DPP-4 inhibitors vs. TZDs	1 RCT[57]	Serious limitations[¶]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs = randomized controlled trials; TZD s= thiazolidinediones; vs. = versus.

* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two or more major sources of bias (-2).

† Publication bias could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).

‡ These RCTs were inadequately powered to detect long-term diabetes complications (-1).

§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

¶ This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address one major source of bias (-1).

GRADE Summary of Quality of Evidence for Macular Edema							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylurea vs. TZD	1 RCT[77]	Serious limitations[*]	Not assessed[†]	Sparse[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; TZD s= thiazolidinediones; vs. = versus.

[*] This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address one major source of bias (-1).

[†] Publication bias could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).

[‡] There were no events in either treatment arm (-1).

[§] The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for Mortality							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZD vs. sulfonylureas	1 RCT[85]	Very serious limitations*	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**
DPP-4 inhibitors vs. placebo	3 RCTs[65,73,95]	Very serious limitations¶	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**
DPP-4 inhibitors vs. sulfonylureas	2 RCTs[68,88]	Very serious limitations**	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**
TZD vs. placebo	1 RCT[69]	No serious limitations	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Low**
Alpha-glucosidase inhibitors vs. placebo	1 RCT[74]	Very serious limitations*	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**
Meglitinides vs. sulfonylureas	1 RCT[97]	No serious limitations	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Low**
BiAsp 30 vs. sulfonyureas	1 RCT[81]	No serious limitations	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Low**
TZD vs. DPP-4 inhibitors	1 RCT[55]	Very serious limitations*	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**

BiAsp = biphasic insulin aspart; DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; TZD = thiazolidinediones; vs. = versus.

* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two or more major sources of bias (-2).

† Publication bias and inconsistency could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).

‡ These RCTs were inadequately powered to detect long-term diabetes complications (-1).

§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

¶ For the three RCTs, two received a rating of "poor" and one received a rating of "good" using the SIGN 50 assessment of internal validity. The studies addressed more than 50% of the major sources of bias (-1).

**These RCTs received a rating of "poor" using the SIGN 50 assessment of internal validity and each failed to address a majority of the major sources of bias (-2).

GRADE Summary of Quality of Evidence for Neuropathy							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
DPP-4 inhibitors vs. placebo	1 RCT[95]	Very serious limitations*	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; vs. = versus.
* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).
† Publication bias and inconsistency could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).
‡ This RCT was inadequately powered to detect long-term diabetes complications (-1).
§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for Peripheral Vascular Disease							
Comparison	**No. of Btudies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylurea vs. DPP-4 inhibitors	1 RCT[68]	Very serious limitations*	Not assessed†	Sparse‡	Not assessed†	Serious indirectness§	**Very low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; vs. = versus.
* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address three major source of bias (-2).
† Publication bias and inconsistency could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).
‡ There was only one event in this RCT (-1).
§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes agents prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for Nocturnal Hypoglycemia							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Meglitinide vs. placebo	2 RCTs[84,87]	No serious limitations	Not assessed[*]	Sparse data[†]	Not assessed[*]	Serious indirectness[‡]	**Low**
TZD vs. placebo	1 RCT[72]	Very serious limitations[§]	Not assessed[*]	Sparse data[†]	Not assessed[*]	Serious indirectness[‡]	**Very low**
Alpha-Glucosidase inhibitor vs. placebo	1 RCT[103]	No serious limitations	Not assessed[*]	Sparse data[†]	Not assessed[*]	Serious indirectness[‡]	**Low**
GLP-1 analogue vs. basal insulin	1 RCT[107]	Not assessed[¶]	Not assessed[¶]	Not assessed[¶]	Not assessed[¶]	Not assessed[¶]	**N/A: abstract only**
Biphasic insulin vs. basal insulin	1 RCT[80]	Very serious limitations[§]	Not assessed[*]	Sparse data[†]	Not assessed[*]	Serious indirectness[‡]	**Very Low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; TZD = thiazolidinediones; vs. = versus.

* Publication bias and inconsistency could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).

† All comparisons reported very few events or no events and all had a relatively small sample size (-1).

‡ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

§ This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).

¶ Quality of evidence from abstracts was not assessed using GRADE

GRADE Summary of Quality of Evidence for Severe Adverse Events							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylureas vs. placebo	2 RCTs [63,83]	No serious limitations	Not assessed*	Sparse†,‡	No important inconsistency	Serious indirectness§	**Low**
TZDs vs. placebo	5 RCTs [69,72,78,82,101]	Very serious limitations¶	Not assessed*	Sparse†	No important inconsistency	Serious indirectness§	**Very low**
DPP-4 inhibitors vs. placebo	6 RCTs [58,61,65,73,95,101]	Very serious limitations**	Not assessed*	Sparse†	No important inconsistency	Serious indirectness§	**Very low**
Alpha-glucosidase inhibitors vs. placebo	2 RCTs [92,103]	No serious limitations	Not assessed*	Sparse†,‡	No important inconsistency	Serious indirectness§	**low**
DPP-4 inhibitors vs. sulfonylureas	2 RCTs [68,88]	Very serious limitations††	Not assessed*	Sparse†	No important inconsistency	Serious indirectness§	**Very low**
Sulfonylureas vs. meglitinides	1 RCT [97]	No serious limitations	Not assessed*	Sparse†,‡	Not assessed***	Serious indirectness§	**Low**
Sulfonylureas vs. TZDs	2 RCTs [91,102]	Serious limitations‡‡	Not assessed*	Sparse†	Not assessed***	Serious indirectness§	**Very low**
TZDs vs. DPP-4	3 RCTs [55,57,101]	Very serious limitations§§	Not assessed*	Spars†	No important inconsistency	Serious indirectness§	**Very low**
GLP-1 analogues vs. basal insulin	1 RCT [60]	Serious limitations¶¶	Not assessed*	Sparse†,‡	Not assessed***	Serious indirectness§	**Very low**
Biphasic insulin vs. basal insulin	1 RCT [94]	Serious limitations†††	Not assessed*	Sparse†	Not assessed***	Serious indirectness§	**Very low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; TZDs = thiazolidinediones; vs. = versus.

* Publication bias could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).

† This outcome was not clearly defined (-1).

‡ 95% confidence interval is too wide (-1).

§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

¶ Four out of five RCTs received a rating of "poor" with a failure to address a majority of the major sources of bias (-2).

** Five out of six RCTs received a rating of "poor" with a failure to address a majority of the major sources of bias (-2).

†† Two RCTs received a rating of "poor" using SIGN 50 and failed to address two or more major sources of bias (-2).

‡‡ Two RCTs received a rating of "poor" using SIGN50 but addressed a majority of the major sources of bias (-1).

§§ Three RCTs received a rating of "poor" with a failure to address a majority of the major sources of bias (-2).

¶¶ This RCT received a rating of "poor" using SIGN 50 and failed to address one major sources of bias (-1).

*** Inconsistency could not be assessed due to a limited number of events and/or RCTs for each pairwise comparison (no decrement).

††† This RCT received a rating of "poor" using SIGN 50 but addressed the major sources of bias (-1).

GRADE Summary of Quality of Evidence for SF-36 Mental Component (Change from Baseline)							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZDs vs. placebo	1 RCT[82]	Very serious limitations[*]	Not assessed[†]	Sparse data[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; SF-36 = short-form health survey;TZDs = thiazolidinediones; vs. = versus.
* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).
† Publication bias and inconsistency could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).
‡ 95% confidence interval is too wide (-1).
§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for SF-36 Physical Component (Change from Baseline)							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
TZDs vs. placebo	1 RCT[82]	Very serious limitations[*]	Not assessed[†]	Sparse data[‡]	Not assessed	Serious indirectness[§]	**Very low**

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial; SF-36 = short-form health survey;TZDs = thiazolidinediones; vs. = versus.
* This RCT received a ratin g of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).
† Publication bias and inconsistency could not be assessed due to the limited number of RCTs for each pairwise comparison (no decrement).
‡ 95% Confidence interval is too wide (-1).
§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

GRADE Summary of Quality of Evidence for Stroke and Transient Ischemic Attack							
Comparison	**No. of Studies**	**Limitations**	**Publication Bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Overall Quality of Evidence**
Sulfonylureas vs. DPP-4 inhibitors	1 RCT[68]	Very serious limitations[*]	Not assessed[†]	Sparse data[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**
TZDs vs. DPP-4 inhibitors	1 RCT[57]	Serious limitations[¶]	Not assessed[†]	Sparse data[‡]	Not assessed[†]	Serious indirectness[§]	**Very low**

DPP-4 = dipeptidyl peptidase-4; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial;TZDs = thiazolidinediones; vs. = versus.

* This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address two major sources of bias (-2).

† Publication bias could not be formally assessed due to a limited number of RCTs for each pairwise comparison (no decrement).

‡ This RCT was inadequately powered to detect long-term diabetes complications (-1).

§ The population of interest consists of patients who were inadequately controlled with first-line metformin monotherapy, and require a second-line agent. However, the study populations in most identified trials included patients who had received various antidiabetes drugs prior to use of metformin monotherapy. Hence, the applicability of study results to the population of interest may be limited (-1).

¶ This RCT received a rating of "poor" using the SIGN 50 assessment of internal validity and failed to address one major source of bias (-1).

APPENDIX 30: SEVERE HYPOGLYCEMIA DEFINITIONS

Severe Hypoglycemia Definitions	
Study	**Definition of Severe Hypoglycemia**
Barnett et al. 2007[53]	A symptomatic episode in which the patient required another person's assistance, and was associated with either a glucose level < 2.8 mmol/L or recovery after the administration of oral carbohydrate, glucagon, or intravenous glucose.
Bolli et al. 2009[57]	Any hypoglycemic episode requiring the assistance of a third party.
Bosi et al. 2007[58]	Any hypoglycemic episode requiring the assistance of a third party.
Bunck et al. 2009[60]	Not reported.
Charbonnel et al. 2006[61]	Not reported
Charpentier et al. 2001[63]	Any hypoglycemic episode requiring the assistance of a third party.
DeFronzo et al. 2005[64]	Subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.
Einhorn et al. 2000[66]	Not reported.
Ferrannini et al. 2009[68]	Any hypoglycemic episode requiring the assistance of a third party.
Fonseca et al. 2009[69]	Not reported.
Gao et al. 2009[70]	An episode with symptoms in which the patients required assistance of another person, and was associated with either a glucose level of < 2.8 mml/L or prompt recovery after oral carbohydrate, intravenous glucose, or intramuscular glucagon.
Garber et al. 2006[71]	Not reported.
Gomez-Perez et al. 2002[72]	Not reported.
Goodman et al. 2009[73]	Any hypoglycemic episode requiring the assistance of a third party or hospitalization.
Kilo et al. 2003[80]	Blood glucose < 50 mg/dL with severe central nervous system symptoms and patients unable to treat themselves.
Kvapil et al. 2006[81]	Requiring assistance; blood glucose <2.8 mmol/L and requiring food intake or IV glucose.
Marre et al. 2002[83]	Not reported.
Marre et al. 2002[84]	Grades 3 or 4 on a scale of 1 to 4 (1 = symptoms that did not sufficiently interfere with normal activities; 4 = symptoms that required hospitalization).
Matthews et al. 2005[85]	Not reported.
Moses et al. 1999[87]	Any hypoglycemic episode requiring the assistance of a third party.
Nauck et al. 2006[89]	Any hypoglycemic episode requiring the assistance of a third party.
Raskin et al. 2007[94]	Episode with neurological symptoms consistent with hypoglycemia that required assistance and had either a plasma glucose value < 56 mg/dL or reversal of symptoms after food intake, glucagon, or intravenous glucose.
Umpierrez et al. 2006[102]	Blood glucose < 36 mg/dL (2 mmol/L) and requiring the assistance of third party.
Van Gaal et al. 2001[103]	Not reported.

APPENDIX 31: NOCTURNAL HYPOGLYCEMIA DEFINITIONS

Nocturnal Hypoglycemia Definitions	
Study	**Definition of Nocturnal Hypoglycemia**
Marre et al. 2002[84]	Not reported.
Moses et al. 1999[87]	Not reported.
Gomez-Perez et al. 2002[72]	Not reported.
Van Gaal et al. 2001[103]	Not reported.
Trautmann et al. 2007[107]	Not reported.
Kilo et al. 2003[80]	Hypoglycemic episodes between midnight to 6:00 a.m.

APPENDIX 32: OVERALL HYPOGLYCEMIA DEFINITIONS

Overall Hypoglycemia Definitions	
Study	**Definition of Overall Hypoglycemia**
Barnett et al. 2007[53]	Any sign or symptom associated with hypoglycemia or a serum glucose concentration of < 3.3 mmol/L.
Blonde et al. 2009[55]	Not reported.
Bolli et al. 2009[57]	Symptoms suggestive of hypoglycemia and blood glucose < 3.1 mmol/L.
Bosi et al. 2007[58]	Symptoms suggestive of low blood glucose confirmed by self-monitoring of blood glucose measurement < 3.1 mmol/L plasma glucose equivalent.
Brazg et al. 2007[59]	Self-report signs and symptoms and glucose values during the 24-hour frequent blood sampling period at the end of each treatment period.
Bunck et al. 2009[60]	Blood glucose < 3.3 mmol/L.
Charbonnel et al. 2005[62]	Symptoms compatible with hypoglycemia.
Charbonnel et al. 2006[61]	Not reported.
Charpentier et al. 2001[63]	Patients reported clinical symptoms of hypoglycemia (such as hunger, profuse sweating, tachycardia, tremor, various sensory perceptions, headache, altered mood, deficit syndromes, disturbed vigilance) in a diary and rated the severity of each symptom using a 5-point scale (0 = no symptom, 1 = symptom allowing normal activity, 2 = symptom not allowing normal activity, 3 = symptom necessitating assistance from another person, 4 = loss of consciousness and/or medical intervention).
DeFronzo et al. 2005[64]	For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value < 3.3 mmol/L.
DeFronzo et al. 2009[65]	Finger-stick glucose value of < 50 mg/dL associated with symptoms.
Einhorn et al. 2000[66]	Not reported.
Ferrannini et al. 2009[68]	Defined as symptoms suggestive of hypoglycemia and confirmed by self-monitored plasma glucose < 3.1 mmol/L.
Fonseca et al. 2009[69]	Not reported.
Garber et al. 2006[71]	Hypoglycemic symptoms alone or accompanied by fingerstick blood glucose levels of ≤ 50 mg/dL.
Gomez-Perez et al. 2002[72]	Not reported.
Goodman et al. 2009[73]	Blood glucose < 3.1 mmol/L.
Home et al. 2009[77]	Not reported.
Kaku 2009[78]	Not reported.
Kilo et al. 2003[80]	Sign or symptoms of hypoglycemia with or without confirmed blood glucose measurements.
Kvapil et al. 2006[81]	Includes hypoglycemia symptoms with or without blood glucose < 2.8mmol/L; blood glucose < 2.8 mmol/L with or without symptoms.
Leiter et al. 2005[82]	Not reported.
Marre et al. 2002[83]	Defined either on the basis of reports of symptoms descriptive of hypoglycemia by the patient or from clinical laboratory measurements.
Marre et al. 2002[84]	Confirmed blood glucose ≤ 3.3 mmol/L.
Moses et al. 1999[87]	Hypoglycemia that could be self-treated was categorized as mild or moderate.

Overall Hypoglycemia Definitions	
Study	**Definition of Overall Hypoglycemia**
Nauck et al 2007[88]	Blood glucose ≤ 3.3 mmol/L.
Nauck et al. 2006[89]	Symptomatic (no plasma glucose or plasma glucose ≥ 3.1 mmol/L and minor (plasma glucose < 3.1 mmol/L) hypoglycemia.
Raskin et al. 2007[94]	Minor hypoglycemic episodes were defined as blood glucose values of < 56 mg/dL (3.1 mmol/L) with or without symptoms that were self-treated. Major hypoglycemia was an episode with neurological symptoms consistent with hypoglycemia that required assistance and had either a plasma glucose value < 56 mg/dL or reversal of symptoms after food intake, glucagon, or intravenous glucose.
Raz et al. 2008[95]	Not reported.
Ristic et al. 2007[97]	Not reported.
Rosenstock et al. 1998[99]	Not reported.
Scott et al. 2008[101]	Not reported.
Umpierrez et al. 2006[102]	Blood glucose ≤ 3.9 mmol/L.
Van Gaal et al. 2001[103]	Not reported.

APPENDIX 33: SUMMARY OF MODEL INPUTS AND ASSUMPTION(S) IN REFERENCE CASE COST-EFFECTIVENESS ANALYSIS

Model Parameter	Description of Model Input and Assumption(s)
Type of Analysis	Cost-utility analysis
Perspective	Canadian third-party payer perspective.[356] Only direct costs to the health care system are considered.
Time Horizon	Lifetime time horizon (i.e., 40 years).[356]
Discount Rate	5%.[356]
Model structure	UKPDS Outcomes Model[136] plus separate submodels for adverse events (see below).
Adverse events	Submodels for mild/moderate hypoglycemia and severe hypoglycemia added to UKPDS Outcomes Model. Other submodels (congestive heart failure and fractures in TZDs, gastrointestinal symptoms in alpha-glucosidase inhibitors, pancreatitis in DPP4-inhibitors) not included in reference case.
Clinical-effect estimates	A1C, weight, and hypoglycemia effect estimates derived from random-effects MTC meta-analysis of RCTs (class-level MTC).
Baseline event rate for mild/moderate hypoglycemia	Event rate derived from RECORD trial,[77] the longest and one of the largest (N=2,222) RCTs included in our MTC meta-analysis.
Event rates for severe hypoglycemia in patients using metformin, SU, and insulin	Event rates from population-based study (n=7,678), which use the DARTS (the diabetes audit and research in Tayside Scotland) study/MEMO (Medicines Monitoring Unit) database. Patients with type 2 diabetes using metformin, SU, and insulin had event rates of 0.05, 0.9, and 11.5 events per 100 patient-years, respectively.[129]
Patient characteristics	Patient characteristics (when available) reflective of those in RCTs were included in MTC meta-analysis. Otherwise, patient characteristics reflective of those in Canadian clinical setting were modelled.[357]
Sources for utilities for long-term diabetes-related complications	Community-based EQ-5D catalogue from the United States (when available).[126,358] Otherwise, EQ-5D scores were obtained from a study of patients with type 2 diabetes in the United Kingdom.[125]
Utility decrements for mild/moderate hypoglycemia	Transient reduction in HRQoL for mild/moderate hypoglycemia.[359] Patients move from having no health problems to a state characterized by moderate anxiety, with or without depression, and having some problems with performing usual activities, thus resulting in a disutility of 0.167 during the episode.[360] Each episode was assumed to last for 15 minutes.[361]
Utility decrement for severe hypoglycemia	Transient reduction in HRQoL followed by chronic reduction due to increased fear of future episodes.[15] Decrement of 0.01 obtained from National Institute for Health and Clinical Excellence.[15]
HRQoL improvement for weight loss	No HRQoL improvement associated with weight loss applied in reference case.
Source for price of drugs and test strips	Ontario Drug Benefit Program (when available). Otherwise, other public drug plans in Canada
Selection of agent within class	Low cost alternative within each drug class (e.g., apo-glyburide for SU, apo-pioglitazone for TZD, insulin NPH for basal insulin)
Dose of agent	Maximum dose (2 g/day) for metformin; average defined daily dose for other agents. Dose of insulin agents obtained from unpublished dataset

Model Parameter	Description of Model Input and Assumption(s)
	from British Columbia.
Test strip utilization	Unpublished dataset from Ontario Public Drug Programs. Patients using metformin, insulin secretagogues, and insulin used 2.08, 1.16, and 0.94 test strips per day, respectively.
Treatment trajectory	Patients initiate second-line therapy when they enter model and remain on therapy over their lifetime.
Sources for management cost of long-term diabetes-related complications	Ontario Ministry of Health and Long-Term Care.[362]
Management costs associated with hypoglycemia	No health resource use for mild/moderate hypoglycemia. Resource use for severe hypoglycemia obtained from study by Leese et al.[129] and costs based upon data from Alberta case-costing database. [363]

A1C = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; EQ-5D = EuroQoL self-report health questionnaire; HRQol = health-related quality of life; MTC = mixed treatment comparison; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; SU = sulphonylurea; TZDs = thiazolidinediones; UKPDS = United Kingdom Prospective Diabetes Study.

APPENDIX 34: RISK OF HYPOGLYCEMIA AND ITS IMPACT ON HEALTH-RELATED QUALITY OF LIFE AND RESOURCE USE

1 Objective

The following supplemental information quantifies the annual risk of overall and severe hypoglycemia among patients with type 2 diabetes. We also present inputs and assumption(s) pertaining to the impact that hypoglycemia has on health-related quality of life and health care resource use in our cost-effectiveness model.

2 Annual Risk of Overall and Severe Hypoglycemia

2.1 Overall Hypoglycemia

In the RECORD trial,[77] 55 out of 1,117 patients (5.1%) who were not using sulfonylureas had a hypoglycemic episode (severe or non-severe) over a mean 5.5-year follow-up period. This translates into an annual risk of overall hypoglycemia of approximately 0.95% in patients who are using thiazolidinediones (TZDs) and metformin. Based upon data from our mixed-treatment comparison (MTC) meta-analysis, patients using metformin in combination with TZDs have slightly higher odds (odds ratio [OR], 1.13 [0.56, 2.21]) of overall hypoglycemia compared with those using metformin monotherapy. Therefore, we assumed that patients using metformin monotherapy had an annual risk of approximately 0.86%. Odds ratio derived from our MTC were converted to relative risks, and these values were multiplied by the baseline event rate in the metformin monotherapy arm to estimate the annual hypoglycemia risk for each drug class, and the corresponding number of patients that needed to treated with each treatment to incur an extra hypoglycemic episode, relative to metformin monotherapy (Table 1).

Table 1: Risk of Overall Hypoglycemia Across Treatment Strategies in Patients Who are Inadequately Controlled on Metformin Monotherapy

Treatment	Odds Ratio (95% CI) from MTC Analysis	Estimated Annual Risk (%)	NNH (NNT)
Metformin Monotherapy (reference category)	NA	0.86	NA
Metformin plus AGI	0.39 (0.01, 6.67)	0.31	(180)
Metformin plus DPP4-I	1.05 (0.56, 2.21)	0.92	1,923
Metformin plus TZD	1.10 (0.54, 2.27)	0.95	1,144
Metformin plus GLP-1	1.12 (0.33, 3.90)	0.97	961
Metformin plus basal insulin	5.20 (1.48, 21.46)	4.33	29
Metformin plus sulfonylureas	8.22 (4.52, 16.63)	6.57	18
Metformin plus meglitinides	8.59 (3.47, 25.20)	6.89	17
Metformin plus biphasic insulin	11.01 (3.48, 40.43)	8.55	13

AGI = alpha-glucosidase inhibitors; CI =confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP = glucagon-like peptide-1; MTC = mixed treatment comparison; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; TZDs = thiazolidinediones.

The baseline event rate of overall hypoglycemia reported in the RECORD trial[77] is lower than event rates reported in other large, long-term randomized controlled trials (RCTs) (≥ 1,000 patients and longer than 52 weeks)[68,88] included in the MTC network. In a study by Nauck et al.,[88] the authors reported an annual risk of 4.9% of patients using metformin and sitagliptin, while Ferrannini et al.[68] reported an annual risk of 1.7% among patients using vildagliptin and metformin. These events rates are much higher than annual risk values predicted for each treatment based on data from the RECORD trial (Table 1). To determine which baseline rate to use, we sought expert clinical opinion. It was suggested that we use the lower baseline rate (i.e., data from the RECORD trial[77]) because the probability of true hypoglycemia among patients using metformin monotherapy in the clinical setting is thought to be negligible based on the mechanism of the drug (Personal Communication, Marshall Dahl).

2.2 Severe Hypoglycemia

The majority of hypoglycemic episodes reported in the RCTs were not classified as severe episodes. Among the 21 RCTs[53,57,58,60,63,63,64,66,68,69,72,73,80,81,83,84,87,89,94,102,103] in the evidence network, which reported data for both overall and severe hypoglycemia, only 2.2% of overall hypoglycemic episodes were classified as severe episodes. These results should be interpreted with caution as trials may not have been long enough in duration, or of sufficient sample size, to capture rare events such as severe hypoglycemia. Moreover, there is a lack of consistency in how hypoglycemia is defined, and with respect to the duration of diabetes and the degree of insulin insufficiency among patients enrolled in the RCTs. We therefore obtained data on the frequency of hypoglycemia from a large observational study by Leese et al. (Table 2).[129] This retrospective observational study reported data from 7,687 patients with type 2 diabetes in Tayside, Scotland. This study[129] was used by the National Institute for Health and Clinical Excellence[15] in their evaluation of newer diabetes drugs. It was the only study we identified in a systematic search of the literature that provided event rates stratified by pharmacotherapy (i.e., metformin, sulfonylurea, insulin), as well as health care resource utilization data.

Table 2: Event Rates of Severe Hypoglycemia In Large Observational Study By Leese et al.[129]

Treatment	Reported Event Rate Per 100 Patient-Years (95% CI)	Annual Risk (%)	NNH
Patients using metformin (reference category)	0.05 (0.01-0.2)	0.05	NA
Patients using insulin secretagogues	0.9 (0.6-1.3)	0.90	118
Patients using insulin	11.8 (9.5 -14.1)	11.11	9

CI =confidence interval; NA = not applicable; NNH = number needed to harm.

The event rate for severe hypoglycemia among patients using metformin monotherapy in the study by Lesse et al.[129] is similar to that reported in another large case-control study by Bodmer et al.[108] (0.06 per 100 patient-years), which included 50,048 adults in the United Kingdom that were prescribed at least one diabetes drug. However, event rates for sulfonylureas and insulin in the study by Leese et al.[129] are much higher than those reported by Bodmer et al. (see Tables 2 and 3). Moreover, the annual risk of severe hypoglycemia in the insulin group exceeded that of overall hypoglycemia. Nevertheless, we used the larger event rates from the study by Leese et al.[129] as they represent a conservative estimate — any bias introduced in the economic analysis would be against sulphonylurea and insulin therapies, and in favour of newer classes of drugs.

Table 3: Event Rates of Severe Hypoglycemia In Large Observational Study By Bodmer et al.[108]			
Treatment	**Data Reported in Study[108]**	**Annual Risk (%)**	**NNH**
Patients using metformin	Event rate, 0.06 per 100 person-years	0.06	NA
Patients using insulin secretagogues	Odds ratio relative to metformin, 4.07 (3.33, 4.98)	0.24	550
Patients using insulin	Odds ratio relative to metformin, 8.73 (5.63,13.5)	0.52	217

NA = not applicable; NNH = number needed to harm.

3 Impact of Hypoglycemia on Health-Related Quality Of Life and Resource Use

3.1 Impact on Health-Related Quality of Life

There is limited evidence examining the impact of hypoglycemia and fear of hypoglycemia on health-related quality of life(HRQoL).[15] Moreover, widely-cited evidence[142] in this area is of low quality.[15] For the reference case cost-effectiveness analysis, patients experiencing mild to moderate hypoglycemia are assumed to have a transient reduction in HRQoL.[359] Patients were assumed to move from having no problems to a health state characterized by moderate anxiety, with or without depression, and problems with performing usual activities, thus resulting in a disutility of 0.167 during the episode.[360] Each mild to moderate hypoglycemic episode was assumed to last for 15 minutes, which coincides with the 15/15 rule: 15 grams of carbohydrate followed by 15 minutes of waiting.[361] Thus, each episode was associated with an annual decrement of 0.000004767 quality-adjusted life-years (QALYs).[360] This is the same approach taken in the insulin analogues and blood glucose test strip projects. For severe hypoglycemia, we assumed patients had a transient reduction in HRQoL, followed by a chronic decrement in HRQoL due to fear of future hypoglycemic episodes.[15] We applied the same decrement, which was applied in a recently published report[15] by the National Institute for Health and Clinical Excellence (NICE), where an annual decrement of 0.01 QALYs (equivalent to 3.65 days in a state equivalent to death) was applied for each severe hypoglycemic event. The estimated impact of severe hypoglycemia from NICE[15] is smaller than the decrements reported in an industry-sponsored study by Currie and colleagues, who estimated that each symptomatic hypoglycemic episode resulted in a disutility of 0.0142 (equivalent to 5.18 days in a state equivalent to death), while each severe episode resulted in a disutility of 0.047 (equivalent to 17.15 days in a state equivalent to death).[142] NICE considered these estimates at length; however, due to methodological limitations, they were felt to be overstated.[15] Nevertheless, we conducted sensitivity analyses where we explored the impact of using utility decrements by Currie and colleagues.[142] We also conducted a sensitivity analysis where we only assumed a transient reduction in HRQoL for severe hypoglycemic episodes (i.e., no chronic decrement in HRQoL for fear of future events). Cost-effectiveness results did not change significantly in either analysis compared with the reference case.

3.2 Impact on Health Care Resource Use

Resource utilization associated with managing a severe hypoglycemic episode is based upon a study by Leese et al.[129] (Table 4) and NICE.[15] Management costs are based upon costing data from the Alberta case-costing database.[363]

Table 4: Costs Associated With Managing A Severe Hypoglycemic Episode			
	Unit Cost	**% Receiving**	**Weighted**
Glucagon	$93.69	90%	$84.32
Consultation with ambulance services only	$600	34%	$204.07
Consultation with primary/emergency care only[363]	$208	7%	$14.59
Consultation with primary/emergency care and ambulance service	$809	52%	$420.49
Direct or indirect hospital admission	$4,302	28%	$1,204.67
Average cost per severe hypoglycemic episode			**$1,928.14**

Similar to NICE, we assumed in the reference case analysis that episodes of mild to moderate hypoglycemia have no impact on health service resource use.[15]

4 Summary

In patients with type 2 diabetes, overall hypoglycemia is more common among patients using insulin and insulin secretagogues. However, in this patient population, the majority of hypoglycemic episodes are mild to moderate in nature. As such, the absolute risk of severe hypoglycemia requiring health care resource use is low and the number of patients that need to be treated with newer, more expensive agents (as opposed to older oral antidiabetes drugs) to avoid a severe hypoglycemic episode is high. Therefore, this outcome had minimal impact on reference case cost-effectiveness results.

APPENDIX 35: RESULTS FROM SENSITIVITY ANALYSES — DISCOUNTED LIFETIME COSTS, DISCOUNTED LIFETIME EFFECTS (QALYS), AND INCREMENTAL COST-EFFECTIVENESS RATIO (ICUR) RELATIVE TO THE NEXT LEAST-COSTLY TREATMENT STRATEGY

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
Reference Case Analysis	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.778	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$12,757 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$939,479 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
a) Effect estimates								
Effect estimates from pairwise meta-analyses of RCTs	$39,924	$40,684	$42,237	$46,146	$47,209	$42,767	$47,348	$52,367
	8.719	8.777	8.770	8.789	8.780	8.780	8.769	8.776
	NA	$13,080 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$465,004 per QALY (relative to SU)	The strategy "DPP4-I" is dominated by "TZD"	The strategy "AGI" is dominated by a blend of "SU" and "TZD"	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Effect estimates from moderate to high-dose nodes in MTC meta-analysis of RCTs, which was stratified by dose	$39,924	$40,749	$42,255	$46,164	$47,185	$42,797	$47,348	$52,367
	8.72	8.78	8.76	8.79	8.78	8.78	8.77	8.78
	NA	$14,206 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$551,247 per QALY (relative to SU)	The strategy "DPP4-I" is dominated by "TZD"	The strategy "AGI" is dominated by a blend of "SU" and "TZD"	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Effect estimates from titrated	$39,924	$40,694	$42,218	$46,243	$47,191	$42,779	$47,386	$52,331
	8.719	8.776	8.775	8.777	8.779	8.779	8.767	8.792

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
nodes in MTC meta-analysis of RCTs, which was stratified by dose	NA	$13,518 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "AGI"	The strategy "DPP4-I" is dominated by a blend of "AGI" and "BipI"	$692,187 per QALY (relative to SU)	The strategy "BasI" is dominated by "DPP4-I"	$780,969 per QALY (relative to AGI)
Gliclazide price and gliclazide-effect estimates applied in SU arm	$39,924	$41,344	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.777	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$24,598 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative AGI)	The strategy "DPP4-I" is dominated by "TZD"	$501,649 per QALY (relative to Met)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Glimepiride price and glimepiride effect-estimates applied in SU arm	$39,924	$41,741	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.777	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$30,697 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$477,328 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Glyburide price and glyburide effect-estimates applied in SU arm	$39,924	$40,574	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.794	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$8,688 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "SU"	The strategy "DPP4-I" is dominated by "SU"	The strategy "AGI" is dominated by "SU"	The strategy "BasI" is dominated by "SU"	The strategy "BipI" is dominated by "SU"
b) Treatment trajectory								
All patients in model assumed to add insulin NPH when A1C ≥ 9%	$45,248	$44,373	$46,229	$50,097	$51,301	$46,998	$47,348	$52,367
	8.757	8.804	8.792	8.798	8.793	8.791	8.769	8.776
	The strategy "Met" is dominated by "SU"	NA	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "SU"	The strategy "DPP4-I" is dominated by "SU"	The strategy "AGI" is dominated by "SU"	The strategy "BasI" is dominated by "SU"	The strategy "BipI" is dominated by "SU"

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
c) Resource use and costing								
Price of most-expensive agent within class applied	$39,924	$41,716	$42,269	$52,946	$47,191	$42,797	$50,287	$53,804
	8.72	8.78	8.77	8.78	8.78	8.78	8.77	8.78
	NA	$30,697 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$13,715,159 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "AGI"	$476,276 per QALY (relative to SU)	The strategy "BasI" is dominated by "AGI"	The strategy "BipI" is dominated by "TZD"
Management cost for all long-term diabetes-related complications increased by 25%	$46,374	$46,951	$48,589	$52,484	$53,461	$49,058	$53,619	$58,632
	8.72	8.78	8.77	8.78	8.78	8.78	8.77	8.78
	NA	$9,894 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,649,762 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$930,154 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Gliclazide price and class-effect estimates applied in SU arm	$39,924	$41,368	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.778	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$24,736 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$630,844 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Glimepiride price and class-effect estimates applied in SU arm	$39,924	$41,716	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.777	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$30,697 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$476,276 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Model assumes a 50% reduction in the price of blood glucose test strips	$39,924	$40,456	$42,056	$46,202	$47,191	$42,797	$46,242	$51,259
	8.719	8.778	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$9,102 per QALY (relative to SU)	The strategy "Meg" is dominated	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated	$1,033,639 per QALY (relative to SU)	The strategy "BasI" is dominated	The strategy "BipI" is dominated

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
			by "SU"		by "TZD"		by "TZD"	by "TZD"
10% reduction in price/dose of insulin products	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$46,822	$51,339
	8.719	8.778	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$12,757 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$939,479 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
No test strip use among non–hypoglycemia-inducing OADs	$39,924	$42,669	$44,262	$46,202	$47,191	$42,797	$49,350	$54,371
	8.719	8.778	8.768	8.781	8.779	8.780	8.769	8.776
	NA	$47,023 per QALY (relative to Met)	The strategy "Meg" is dominated by "AGI"	$4,621,828 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$56,612 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
d) HRQoL								
Improvement in HRQoL resulting from weight loss	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.71	8.75	8.75	8.75	8.77	8.78	8.75	8.68
	NA	$17,839 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "AGI"	The strategy "DPP4" is dominated by "AGI"	$80,453 per QALY (relative to SU)	The strategy "BasI" is dominated by "AGI"	The strategy "BipI" is dominated by "AGI"
Disutilities for diabetes-related complications obtained from group of patients with type 2 diabetes	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.558	8.622	8.611	8.625	8.624	8.626	8.613	8.621
	NA	$11, 694 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "AGI"	The strategy "DPP4-I" is dominated by "AGI"	$575,841 per QALY (relative to SU)	The strategy "BasI" is dominated by "AGI"	The strategy "BipI" is dominated by "AGI"
Larger decrement in HRQoL associated with severe	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.764	8.753	8.780	8.779	8.780	8.713	8.712
	NA	$16,860 per QALY (relative	The strategy "Meg" is	$4,924,369 per QALY (relative	The strategy "DPP4-I" is	$130,967 per QALY (relative	The strategy "BasI" is	The strategy "BipI" is

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
hypoglycemia (Currie et al.)		to Met)	dominated by "SU"	to AGI)	dominated by "TZD"	to SU)	dominated by "TZD"	dominated by "TZD"
Larger decrement in HRQoL associated with mild to moderate hypoglycemia (Levy et al.)	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.775	8.766	8.781	8.779	8.780	8.769	8.776
	NA	$13,264 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$7,095,023 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$450,846 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
e) Hypoglycemia data								
Higher baseline rate of mild to moderate hypoglycemia	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.72	8.78	8.77	8.78	8.78	8.78	8.77	8.78
	NA	$12,757 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$4,619,894 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$938,719 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Event rates for severe hypoglycemia derived from another large observational study	$39,924	$40,574	$42,174	$46,202	$47,191	$42,797	$45,839	$50,855
	8.719	8.779	8.769	8.781	8.779	8.780	8.781	8.789
	NA	$10,989 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "BasI"	The strategy "DPP4-I" is dominated by "BasI"	The strategy "AGI" is dominated by a blend of "SU" and "BipI"	The strategy "BasI" is dominated by a blend of "SU" and "BipI"	$1,008,816 per QALY (relative to SU)
No HRQoL decrement for fear of severe hypoglycemia	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.779	8.769	8.781	8.779	8.780	8.780	8.787
	NA	$12,573 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by a blend of "SU" and "BipI"	The strategy "DPP4-I" is dominated by "TZD"	The strategy "AGI" is dominated by a blend of "SU" and "BipI"	The strategy "BasI" is dominated by "TZD"	$1,344,919 per QALY (relative to SU)

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
f) Other adverse events								
Model incorporates increased risk of CHF and upper extremity fractures in patients using TZDs (safety data)	$39,924	$40,669	$42,269	$48,064	$47,191	$42,797	$47,348	$52,367
	8.719	8.778	8.768	8.687	8.779	8.780	8.769	8.776
	NA	12,757 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "AGI"	The strategy "DPP4-I" is dominated by "AGI"	939,479 per QALY (relative to SU)	The strategy "BasI" is dominated by "AGI"	The strategy "BipI" is dominated by "AGI"
Model incorporates reduced HRQoL associated with increased gastrointestinal symptoms among patients using AGI	$39,924	$40,669	$42,269	$46,202	$47,191	$42,797	$47,348	$52,367
	8.719	8.778	8.768	8.781	8.779	8.707	8.769	8.776
	NA	$12,757 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$843,306 per QALY (relative to SU)	The strategy "DPP4-I" is dominated by "TZD"	The strategy "AGI" is dominated by "SU"	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
g) Discount rate, time horizon, and patient characteristics								
Discount rate of 0%	$69,809	$70,860	$73,355	$79,401	$80,909	$74,112	$81,150	$88,912
	14.12	14.24	14.22	14.24	14.24	14.24	14.23	14.24
	NA	$8,794 per QALY relative to Met	The strategy "Meg" is dominated by "SU"	The strategy "TZD" is dominated by "AGI"	The strategy "DPP4-I" is dominated by "AGI"	$642,200 per QALY (relative to SU)	The strategy "BasI" is dominated by "AGI"	The strategy "BipI" is dominated by "AGI"
Discount rate of 3%	$48,766	$49,612	$51,487	$56,075	$57,225	$52,088	$57,409	$63,276
	10.360	10.435	10.423	10.439	10.437	10.439	10.425	10.434
	NA	$11,138 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$8,508,580 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$803,495 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"

Sensitivity Analysis	Metformin	Sulfonylurea	Meglitinides	TZD	DPP-4 Inhibitor	Alpha-Glucosidase Inhibitor	Basal Insulin	Biphasic or Pre-Mixed Insulin
Time horizon of 10 years	$22,438	$22,995	$24,075	$26,778	$27,465	$24,472	$27,573	$30,984
	5.546	5.568	5.564	5.570	5.569	5.568	5.561	5.565
	NA	$25,245 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$1,588,639 per QALY(relative to SU)	The strategy "DPP4-I" is dominated by "TZD"	The strategy "AGI" is dominated by a blend of "SU" and "TZD"	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"
Time horizon of 25 years	$37,731	$38,478	$40,031	$43,871	$44,828	$40,546	$44,988	$49,873
	8.407	8.460	8.452	8.463	8.462	8.462	8.451	8.458
	NA	$14,127 per QALY (relative to Met)	The strategy "Meg" is dominated by "SU"	$2,725,057 per QALY (relative to AGI)	The strategy "DPP4-I" is dominated by "TZD"	$1,282,577 per QALY (relative to SU)	The strategy "BasI" is dominated by "TZD"	The strategy "BipI" is dominated by "TZD"

A1C = glycosylated hemoglobin; AGI = alpha-glucosidase inhibitors; BasI = basal insulin; BipI = biphasic or pre-mixed insulin; CHF = congestive heart failure; DPP4-I = dipeptidyl peptidase-4 inhibitor; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; Meg = meglitinides; Met = metformin; MTC = mixed treatment comparison; NA = not applicable; NPH = neutral protamine Hagedorn; OADs = oral antidiabetes drugs; QALY = quality-adjusted life-year; RCTs = randomized controlled trials; SU = sulfonylurea; TZDs = thiazolidinediones.

APPENDIX 36: MECHANISMS OF ACTION FOR ANTIDIABETES PHARMACOTHERAPY

Metformin, a biguanide antidiabetic, is the preferred first line therapy for most patients with type 2 diabetes.[364,365] While its exact mode of action remains unclear,[366,367] metformin likely lowers both fasting and post-prandial glucose concentrations by: 1) decreasing hepatic glucose production;[366,368] 2) improving insulin sensitivity, thereby enhancing insulin-stimulated uptake and utilization of glucose in peripheral tissues;[366,368] and 3) decreasing intestinal absorption of glucose.[368] Insulin secretion remains unchanged.[366,369] Hypoglycemia is not an issue, except possibly in cases of extreme overdose.[369] The usual initial dose of metformin is 500 mg two to three times daily with meals, and the maximum daily dose is 2.55 g.[369]

Sulfonylureas (gliclazide, glimepiride, glyburide, chlorpropramide, glipizide, tolbutamide) increase the post-prandial secretion of insulin from functional islet beta cells of the pancreas.[367] Reduced hepatic glucose production and increased peripheral sensitivity to insulin also contribute to hypoglycemic action during prolonged administration of sulfonylureas.[367,370] Initial dosages vary depending on the specific agent and are usually conservative due to the risk of hypoglycemia, but can be titrated until adequate glycemic control is achieved.[369-375]

Thiazolidinediones (pioglitazone, rosiglitazone), or TZDs, are peroxisome proliferator-activated receptor-gamma ($PPAR_{\gamma}$) agonists. They increase transcription of insulin-responsive genes, increasing insulin sensitivity in muscle, fat, and liver cells.[376] Hepatic gluconeogenesis is also decreased.[377,378] TZDs depend on the availability of insulin to be effective, but do not increase insulin secretion, nor do they cause hypoglycemia.[377,378] The initial dose of rosiglitazone is usually 4 mg daily, and can be increased to 8 mg after 2 to 3 months if response is inadequate. No further benefit is seen with a 12 mg dose.[378] Pioglitazone is usually initiated at 15 or 30 mg daily, and can be gradually increased to 45 mg if response is inadequate.[377]

Meglitinide analogues (nateglinide, repaglinide) induce rapid and short-term insulin secretion from functional pancreatic beta cells.[376,379,380] Like sulfonylureas, meglitinide analogues can induce hypoglycemia, but may do so less frequently.[376,379,380] Repaglinide is usually initiated at 0.5-1 mg two to four times daily before meals, with a maximum daily dose of 16 mg.[369,379] Approximately 90% of maximal glucose-lowering effect is seen at 1 mg three times daily.[379] Nateglinide is usually initiated at 120 mg three times daily before meals, though patients who are already near their A1c targets may be started at 60 mg three times daily.[380]

Alpha-glucosidase inhibitors (acarbose, miglitol) inhibit the alpha-glucosidase enzymes of the intestine, which break complex carbohydrates such as oligosaccharides down to glucose and other simple sugars. This delays glucose absorption in patients with type 2 diabetes and lowers post-prandial hyperglycemia.[381] Alpha-glucosidase inhibitors do not themselves cause hypoglycemia, but may exacerbate it in patients taking insulin or sulfonylureas.[369] The initial dose of acarbose is usually 50 mg once daily taken at the beginning of a meal containing complex carbohydrates. Dosage is generally increased gradually to 50 mg three times daily as the patient's tolerance increases, up to a maximum dose of 100 mg three times daily.[369] The initial dose of miglitol is usually 25 mg three times daily at the beginning of each main meal. Dosage may be gradually increased to a maximum of 100 mg three times daily.[382]

Incretin agents augment the effects of incretin hormones, including glucagon-like peptide-1 (GLP-1). These hormones regulate glucose homeostasis by increasing insulin secretion from pancreatic beta cells and decreasing glucagon secretion from alpha cells in response to a meal. The latter effect results in decreased glucose production from the liver, and a consequent reduction in blood glucose levels.[369,376,383] The dipeptidyl peptidase-4 (DPP-4) enzyme inactivates GLP-1.[376]

Incretin agents work in one of two ways:

- GLP-1 receptor agonists (i.e., exenatide, liraglutide) mimic the effects of GLP-1 while being resistant to inactivation by DPP-4. This results in lowering of fasting and post-prandial glucose concentrations.[376,384] Like GLP-1, GLP-1 receptor agonists also suppress inappropriate glucagon secretion and slow gastric emptying, possibly leading to weight loss.[367,384] Exenatide is injected subcutaneously at a usual initial dose of 5 µg twice daily and may be increased to 10 µg twice daily, if required.[384] Liraglutide is initiated with a dose of 0.6 mg once daily for one week (injected subcutaneously); the dose should be escalated to 1.2 mg once daily the second week and may be increased to 1.8 mg, if required.

- DPP-4 inhibitors (i.e., sitagliptin, vildagliptin, saxagliptin) decrease the ability of DPP-4 to degrade GLP-1, leading to lower fasting and post-prandial glucose concentrations.[369,376] The usual dosage of sitagliptin is 100 mg once a day.[369,383] and the usual dosage of saxagliptin is 5 mg once daily.[35] While not available in Canada or the US, vildagliptin is approved in the EU for combination therapy with metformin, TZDs, or sulfonylureas. The usual dose with metformin or TZDs is 50 mg twice daily. In combination with sulfonylureas, the usual dose is 50 mg once daily; higher doses in this population have not shown additional benefit.[385]

12 REFERENCES

1. Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes [Internet]. 2008 [cited 2010 Jan 27];32(suppl 1):i-S201. Available from: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
2. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009 Jan;32(1):193-203.
3. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: National clinical guideline for management in primary and secondary care (update) [Internet]. London (UK): Royal College of Physicians; 2008. [cited 2008 Dec 19]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG66diabetesfullguideline.pdf
4. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008 Feb;79(2):196-203.
5. Genuth S. The UKPDS and its global impact. Diabet Med. 2008 Aug;25 Suppl 2:57-62.
6. Utilization of oral antiglycemics in Canada. [unpublished dataset]. Ottawa (ON): Brogan, Inc.; 2008.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998 Sep 12;352(9131):854-65.
8. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999 Jun 2;281(21):2005-12.
9. Standards of medical care in diabetes--2009. Diabetes Care. 2009 Jan;32 Suppl 1:S13-S61.
10. Managing type 2 diabetes in south Australia [Internet]. Adelaide: Government of South Australia, Department of Health; 2008. [cited 2009 Jan 19]. Available from: http://www.publications.health.sa.gov.au/cgi/viewcontent.cgi?article=1001&context=dis
11. Management of type 2 diabetes [Internet]. Wellington: New Zealand Guidelines Group (NZGG); 2003. [cited 2009 Jan 19]. Available from: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineCatID=30&guidelineID=36
12. IDF clinical guidelines task force. Global guideline for type 2 diabetes [Internet]. Brussels: International Diabetes Federation; 2005. [cited 2009 Jan 19]. Available from: http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf
13. American Diabetes Association. Standards of medical care in diabetes - 2010. Diabetes Care [Internet]. 2010 Jan [cited 2010 Jan 21];33(Supp 1):S11-S61. Available from: http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html
14. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care [Internet]. 2008 Jan [cited 2010 Jan 27];31(1):173-5. Available from: http://care.diabetesjournals.org/content/31/1/173.full.pdf+html
15. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: the management of type 2 diabetes [Internet]. London: National Institute for Health and Clinical Excellence; 2009. (NICE clinical guideline 87). [cited 2010 Jan 21]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf
16. Morgan S, Raymond C, Mooney D, Martin D. The Canadian Rx atlas [Internet]. 2nd edition. Vancouver: UBC Centre for Health Services and Policy Research; 2008. [cited 2009 Apr 3]. Available from: http://www.chspr.ubc.ca/files/publications/2008/CanRxAtlas/Canadian_Rx_Atlas_2nd_Edition.pdf

17. McCann J, Dourdin N, Welner S, Minshall M, McKenzie E. Understanding the classes: drugs for diabetes mellitus. Provincial Reimbursement Advisor. 2008;11(3):52-65.

18. Diabetes in Canada: facts & figures [Internet]. Ottawa: Public Health Agency of Canada; 2008. [cited 2009 Mar 20]. Available from: http://www.phac-aspc.gc.ca/publicat/2008/ndfs-fnrd-08/ndfs_ff-fnrd_fc-eng.php

19. Diabetes in Canada [Internet]. 2nd edition. Ottawa: Health Canada; 2002. [cited 2007 Aug 1]. Available from: http://www.phac-aspc.gc.ca/publicat/dic-dac2/pdf/dic-dac2_en.pdf

20. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet. 1998;352(9131):837-53.

21. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

22. Report from the national diabetes surveillance system: diabetes in Canada, 2008 [Internet]. Ottawa: Public Health Agency of Canada; 2008. [cited 2009 Jan 23]. (Cat. HP32-2/2006). Available from: http://www.phac-aspc.gc.ca/publicat/2008/ndssdic-snsddac-08/index-eng.php

23. Product monograph: Diamicron MR (gliclazide modified release tablets) 30 mg. Laval (QC): Servier Canada Inc.; 2009 Jan 15.

24. Product monograph: Diamicron (gliclazide) 80 mg tablets. Laval (QC): Servier Canada Inc.; 2009 Jan 15.

25. Product monograph: Amaryl (glimepiride) tablets 1,2 and 4 mg. Laval (QC): Sanofi-Aventis Canada Inc.; 2009 Aug 7.

26. Product monograph: Diabßeta (glyburide) manufacturer's standard 2.5 and 5 mg tablets. Laval (QC): Sanofi-Aventis Canada Inc.; 2008 Jun 23.

27. Product monograph: Apo-Chlorpropamide (chlorpropamide tablets USP) 100 mg and 250 mg. Weston (ON): Apotex Inc.; 2009 Nov 20.

28. Product monograph: Tolbutamide - 500 (tolbutamide tablets USP) 500 mg. Laval (QC): Pro Doc Ltée; 2010 Feb 2.

29. Product monograph: Actos (pioglitazone hydrochloride) 15, 30, 45 mg tablets. Mississauga (ON): Takeda Canada, Inc.; 2009 Oct 22.

30. Product monograph: Avandia. Rosiglitazone (as rosiglitazone maleate) 1 mg, 2mg, 4mg and 8 mg tablets. Mississauga (ON): GlaxoSmithKline Inc.; 2009 Mar 12.

31. Product monograph: Starlix (nateglinide) 60 and 120 mg tablets. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2009 Nov 25.

32. Product monograph: GlucoNorm (repaglinide tablets) 0.5 mg, 1 mg and 2 mg. Mississauga (ON): Novo Nordisk Canada Inc.; 2009 Jul 8.

33. Product monograph: Glucobay (acarbose) 50 and 100 mg tablets. Toronto: Bayer Inc.; 2008 Jun 10.

34. Product monograph: Januvia. Sitagliptin tablets (as sitagliptin phosphate monohydrate) 100 mg. Kirkland (QC): Merck Frosst Canada Ltd.; 2009 Dec 14.

35. Product monograph: Onglyza (saxagliptin) tablets 5 mg. Montreal (QC): Bristol-Myers Squibb Canada; 2009 Sep 14.

36. Product monograph: NovoMix® 30. Mississauga (ON): Novo Nordisk Canada Inc; 2009 Dec 23.

37. Product monograph: Humalog, Humalog mix25, Humalog mix50 [Internet]. Scarborough (ON): Eli Lilly Canada Inc; 2009. [cited 2010 May 12]. Available from: http://www.lilly.ca/servlets/sfs?t=/documentManager/sfdoc.file.supply&e=UTF-8&i=1233164768976&l=0&fileID=1249679213779

38. Product monograph: Apidra [Internet]. Laval (QC): sanofi-aventis Canada Inc.; 2010 Apr 7. [cited 2010 May 12]. Available from: http://www.sanofi-aventis.ca/products/en/apidra.pdf

39. Product monograph: Levemir [Internet]. Mississauga (ON): Novo Nordisk Canada Inc; 2010 Oct 24. [cited 2010 May 12]. Available from: http://www.novonordisk.ca/PDF_Files/LevemirPM102408_En.pdf

40. Product monograph: Lantus [Internet]. Laval (QC): sanofi-aventis Canada Inc; 2010 Jul 4. [cited 2010 May 12]. Available from: http://www.sanofi-aventis.ca/products/en/lantus.pdf

41. Product monograph: Novorapid. Mississauga (ON): Novo Nordisk Canada Inc; 2010.

42. Product monograph: Xenical (orlistat) capsules 120 mg. Mississauga (ON): Hoffmann-La Roche Limited; 2009 Oct 6.

43. Product monograph: Meridia (sibutramine hydrochloride monohydrate) 10 mg and 15 mg capsules. St-Laurent (QC): Abbott Laboratories, Limited; 2009 Nov 26.

44. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with diabetes inadequately controlled on metformin — project protocol [Internet]. Ottawa: The Agency; 2009. (Optimal therapy report; vol. 4 no. 1). [cited 2009 Jul 31]. Available from: http://www.cadth.ca/media/pdf/compus_2nd_line_T2DM_Protocol_e.pdf

45. Canadian Agency for Drugs and Technologies in Health. Second-line Therapy for Patients with Diabetes Inadequately Controlled on Metformin: Addendum to Project Protocol - August 14, 2009 [Internet]. Ottawa: The Agency; 2009. [cited 2010 May 14]. Available from: http://www.cadth.ca/media/compus/pdf/C1110-Protocol-Addendum-as-posted.pdf

46. Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developers' handbook [Internet]. Edinburgh: The Network; 2008. Annex C. Methodology checklist 2: randomised controlled trials; p. 52. [cited 2008 Jun 6]. Available from: http://www.sign.ac.uk/pdf/sign50.pdf

47. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing. 2000;10:325-37.

48. Mixed treatment comparisons [Internet]. Bristol (UK): University of Bristol; 2010. [cited 2010 May 17]. Available from: http://www.bris.ac.uk/cobm/research/mpes/mtc.html

49. Salanti G. Graphical exploration of incoherence in a network of randomized trials in R [Internet]. version 2.2. Ioannina (GR): University of Ioannina; 2009. [cited 2010 Jul 9]. Available from: http://users.uoi.gr/hyepilab/assets/pdfs/help%20on%20MTcoherence.fun.pdf

50. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J Clin Epidemiol. 2009 Aug;62(8):857-64.

51. Ntzoufras I. Bayesian Modeling Using WinBUGS. Hoboken (NJ): Wiley; 2009.

52. Ahren B, Gomis R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care [Internet]. 2004 Dec [cited 2009 Feb 26];27(12):2874-80. Available from: http://care.diabetesjournals.org/cgi/reprint/27/12/2874

53. Barnett AH, Burger J, Johns D, Brodows R, Kendall DM, Roberts A, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther. 2007 Nov;29(11):2333-48.

54. Berne C, the Orlistat Swedish Type 2 diabetes Study Group. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. Diabet Med. 2005 May;22(5):612-8.

55. Blonde L, Dagogo-Jack S, Banerji MA, Pratley RE, Marcellari A, Braceras R, et al. Comparison of vildagliptin and thiazolidinedione as add-on therapy in patients inadequately controlled with metformin: results of the GALIANT trial - a primary care, type 2 diabetes study. Diabetes Obes Metab. 2009 Oct;11(10):978-86.

56. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab. 2008 Jan;10(1):82-90.

57. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab. 2009 Jun;11(6):589-95.

58. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care [Internet]. 2007 Apr [cited 2009 Feb 26];30(4):890-5. Available from: http://care.diabetesjournals.org/cgi/reprint/30/4/890

59. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. Diabetes Obes Metab. 2007 Mar;9(2):186-93.

60. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009 May;32(5):762-8.

61. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care [Internet]. 2006 Dec [cited 2009 Feb 26];29(12):2638-43. Available from: http://care.diabetesjournals.org/cgi/reprint/29/12/2638

62. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia. 2005 Jun;48(6):1093-104.

63. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001 Oct;18(10):828-34.

64. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care [Internet]. 2005 May [cited 2009 Feb 26];28(5):1092-100. Available from: http://care.diabetesjournals.org/cgi/reprint/28/5/1092

65. DeFronzo RA, Hissa MN, Garber AJ, Gross JL, Duan RY, Ravichandran S, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes on metformin alone. Diabetes Care. 2009 Sep;32(9):1649-55.

66. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. Clin Ther. 2000;22(12):1395-409.

67. Feinglos M, Dailey G, Cefalu W, Osei K, Tayek J, Canovatchel W, et al. Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. Diabetes Res Clin Pract. 2005 May;68(2):167-75.

68. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahren B, Byiers S, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2009 Feb;11(2):157-66.

69. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000;283(13):1695-702.

70. Gao Y, Yoon KH, Chuang LM, Mohan V, Ning G, Shah S, et al. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. Diabetes Res Clin Pract. 2009 Jan;83(1):69-76.

71. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006;8(2):156-63.

72. Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, Montes-Villarreal J, Berry RA, Warsi G, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev. 2002;18(2):127-34.

73. Goodman M, Thurston H, Penman J. Efficacy and Tolerability of Vildagliptin in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy. Horm Metab Res. 2009 May;41(5):368-73.

74. Halimi S, Le Berre MA, Grange V. Efficacy and safety of acarbose add-on therapy in the treatment of overweight patients with Type 2 diabetes inadequately controlled with metformin: a double-blind, placebo-controlled study. Diabetes Res Clin Pract. 2000 Sep;50(1):49-56.

75. Hamann A, Garcia-Puig J, Paul G, Donaldson J, Stewart M. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes. 2008 Jan;116(1):6-13.

76. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007;24(6):626-34.

77. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 5;373:2125-35.

78. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin. 2009 May;25(5):1111-9.

79. Khanolkar MP, Morris RH, Thomas AW, Bolusani H, Roberts AW, Geen J, et al. Rosiglitazone produces a greater reduction in circulating platelet activity compared with gliclazide in patients with type 2 diabetes mellitus--an effect probably mediated by direct platelet PPARgamma activation. Atherosclerosis. 2008 Apr;197(2):718-24.

80. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. J Diabetes Complicat. 2003;17(6):307-13.

81. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab. 2006 Jan;8(1):39-48.

82. Leiter LA, Harris SB, Chiasson JL, Edwards L, O'neill MC, Van DM. Efficacy and safety of rosiglitazone as monotherapy or in combination with metformin in primary care settings. Can J Diabetes. 2005;29(4):384-92.

83. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance®) in Type 2 diabetic patients inadequately controlled on metformin. Diabet Med. 2002 Aug;19(8):673-80.

84. Marre M, Van Gaal L, Usadel KH, Ball M, Whatmough I, Guitard C. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes Obes Metab. 2002 May;4(3):177-86.

85. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. Diabetes Metab Res Rev. 2005;21(2):167-74.

86. McNulty SJ, Ur E, Williams G, Multicenter Sibutramine Study Group. A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin. Diabetes Care [Internet]. 2003 Jan [cited 2009 May 15];26(1):125-31. Available from: http://care.diabetesjournals.org/cgi/reprint/26/1/125

87. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care [Internet]. 1999 Jan [cited 2009 May 14];22(1):119-24. Available from: http://care.diabetesjournals.org/cgi/reprint/22/1/119

88. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007 Mar;9(2):194-205.

89. Nauck MA, Hompesch M, Filipczak R, Le TD, Zdravkovic M, Gumprecht J. Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. Exp Clin Endocrinol Diabetes. 2006 Sep;114(8):417-23.

90. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. Diabetes Care. 2009;32(1):84-90.

91. Papathanassiou K, Naka KK, Kazakos N, Kanioglou C, Makriyiannis D, Pappas K, et al. Pioglitazone vs glimepiride: Differential effects on vascular endothelial function in patients with type 2 diabetes. Atherosclerosis. 2009;205(1):221-6.

92. Phillips P, Karrasch J, Scott R, Wilson D, Moses R. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. Diabetes Care [Internet]. 2003 Feb [cited 2009 Feb 26];26(2):269-73. Available from: http://care.diabetesjournals.org/cgi/reprint/26/2/269

93. Poon T, Nelson P, Shen L, Mihm M, Taylor K, Fineman M, et al. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. Diabetes Technol Ther. 2005 Jun;7(3):467-77.

94. Raskin PR, Hollander PA, Lewin A, Gabbay RA, Bode B, Garber AJ. Basal insulin or premix analogue therapy in type 2 diabetes patients. Eur J Intern Med. 2007;18(1):56-62.

95. Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin. 2008 Feb;24(2):537-50.

96. Ristic S, Collober-Maugeais C, Pecher E, Cressier F. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. Diabet Med [Internet]. 2006 Jul [cited 2009 Feb 26];23(7):757-62. Available from: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1569640&blobtype=pdf

97. Ristic S, Collober-Maugeais C, Cressier F, Tang P, Pecher E. Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results. Diabetes Obes Metab. 2007 Jul;9(4):506-11.

98. Rodger NW, Chiasson JL, Josse RG, Hunt JA, Palmason C, Ross SA, et al. Clinical experience with acarbose: results of a Canadian multicentre study. Clin Invest Med. 1995 Aug;18(4):318-24.

99. Rosenstock J, Brown A, Fischer J, Jain A, Littlejohn T, Nadeau D, et al. Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care [Internet]. 1998 Dec [cited 2009 Feb 26];21(12):2050-5. Available from: http://care.diabetesjournals.org/cgi/reprint/21/12/2050

100. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest. 2004 Aug;34(8):535-42.

101. Scott R, Loeys T, Davies MJ, Engel SS, Sitagliptin Study 801 Group. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008 Sep;10(10):959-69.

102. Umpierrez G, Issa M, Vlajnic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Curr Med Res Opin. 2006 Apr;22(4):751-9.

103. Van Gaal L, Maislos M, Schernthaner G, Rybka J, Segal P. Miglitol combined with metformin improves glycaemic control in type 2 diabetes. Diabetes Obes Metab. 2001 Oct;3(5):326-31.

104. Von Bibra H, Diamant M, Scheffer PG, Siegmund T, Schumm-Draeger PM. Rosiglitazone, but not glimepiride, improves myocardial diastolic function in association with reduction in oxidative stress in type 2 diabetic patients without overt heart disease. Diab Vasc Dis Res. 2008 Nov;5(4):310-8.

105. Wolever TM, Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, et al. Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes. Int J Obes Relat Metab Disord. 1997 Sep;21(9):756-63.

106. Frid A, Nauck MA, Hermansen K, Kolotkin RL, Hammer M, Zdrav-Kovic M, et al. Evaluation of patient reported outcomes in subjects with type 2 diabetes treated with the once-daily human GLP-1 analog liraglutide or glimepiride both as add-on to metformin. Diabetes. 2008;57(Suppl 1):A574-A575, JUN.

107. Trautmann M, Burger J, Johns D, Brodows R, Okerson T, Roberts A, et al. Less hypoglycemia with exenatide versus insulin glargine, despite similar Hba_{1c} improvement, in patients with T2dm adjunctively treated with metformin. Diabetes. 2007;56(Suppl 1):A45, JUN.

108. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care. 2008 Nov;31(11):2086-91.

109. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care [Internet]. 2005 Feb [cited 2009 May 14];28(2):260-5. Available from: http://care.diabetesjournals.org/cgi/reprint/28/2/260

110. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary / comparative drug index [database on the Internet]. Toronto: The Ministry; 2009 [cited 2009 Oct 10]. Available from: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html

111. Alberta Health & Wellness. Interactive Drug Benefit List [database on the Internet]. Edmonton: Government of Alberta; 2009 [cited 2009 Oct 19]. Available from: http://idbl.ab.bluecross.ca/idblprod/load.do

112. Manitoba Health. Manitoba drug interchangeability formulary: schedule [Internet]. 61st ed. Winnipeg: Manitoba Health; 2009 Aug 17. [cited 2007 Feb 13]. Available from: http://www.gov.mb.ca/health/mdbif/schedule.pdf

113. Régie de l'assurance maladie du Québec. List of medications [Internet]. Amended edition. Québec (QC): Gouvernement du Québec; 2009 Aug 19. [cited 2009 Oct 19]. Available from: https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_mod2_2009_08_19_en.pdf Including amendment no.2, correction no.3.

114. Saskatchewan Health. Online formulary [database on the Internet]. Regina: Government of Saskatchewan; 2000 -; 2009 [cited 2009 Oct 19]. Available from: http://formulary.drugplan.health.gov.sk.ca/

115. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med [Internet]. 2007 Oct 25 [cited 2009 Dec 3];357(17):1716-30. Available from: http://content.nejm.org/cgi/reprint/357/17/1716.pdf

116. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care [Internet]. 2005 Feb [cited 2009 Dec 4];28(2):254-9. Available from: http://care.diabetesjournals.org/content/28/2/254.full.pdf+html

117. Goudswaard AN, Stolk RP, Zuithoff P, de Valk HW, Rutten GE. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. J Fam Pract [Internet]. 2004 May [cited 2009 Dec 4];53(5):393-9. Available from: http://www.jfponline.com/Pages.asp?AID=1703

118. De Mattia G, Laurenti O, Moretti A. Comparison of glycaemic control in patients with Type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment: results of a pilot study. Acta Diabetol. 2009 Mar;46(1):67-73.

119. Gomes T, Juurlink DN, Shah BR, Paterson JM, Mamdani M. Blood glucose test strip use: patterns, costs, and potential savings associated with reduced testing. ICES Investigative Report [Internet]. Toronto: Institute for Clinical Evaluative Sciences; 2009. [cited 2010 May 14]. Available from: http://www.ices.on.ca/file/Blood%20Glucose%20Test%20Strip_Dec2009.pdf

120. ATC/DDD Index 2010 [Internet]. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health; 2009. [cited 2010 May 17]. Available from: http://www.whocc.no/atc_ddd_index/

121. Non-insured health benefits: First Nations and Inuit health branch, drug benefit list [Internet]. Ottawa: Health Canada; 2009. [cited 2010 May 17]. Available from: http://www.hc-sc.gc.ca/fniah-spnia/alt_formats/fnihb-dgspni/pdf/nihb-ssna/list_drug_med-eng.pdf

122. Canadian Agency for Drugs and Technologies in Health. Therapeutic review report: Clinical review. Third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylureas [DRAFT]. Ottawa: The Agency; 2010 Mar 31.

123. National Collaborating Centre for Primary Care. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children [Internet]. London: National Institute for Health and Clinical Excellence (NICE); 2006. (NICE clinical guideline 43). [cited 2009 Dec 1]. Available from: http://guidance.nice.org.uk/CG43

124. Macran S. The relationship between body mass index and health-related quality of life [Internet]. York (UK): Outcomes Research Group, Centre for Health Economics; 2004. (Discussion paper 190). [cited 2010 Jan 22]. Available from: http://www.york.ac.uk/inst/che/pdf/DP190.pdf

125. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making. 2002;22(4):340-9.

126. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006 Jul;26(4):410-20.

127. Pickup JC, Hussain F, Evans ND, Sachedina N. In vivo glucose monitoring: the clinical reality and the promise. Biosens Bioelectron. 2005 Apr 15;20(10):1897-902.

128. Levy AR, Christensen TL, Johnson JA. Utility values for symptomatic non-severe hypoglycaemia elicited from persons with and without diabetes in Canada and the United Kingdom. Health Qual Life Outcomes [Internet]. 2008 [cited 2010 Mar 17];6:73. Available from: http://www.hqlo.com/content/pdf/1477-7525-6-73.pdf

129. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care [Internet]. 2003 Apr [cited 2009 Feb 26];26(4):1176-80. Available from: http://care.diabetesjournals.org/cgi/reprint/26/4/1176

130. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ. 2009 Feb 17;180(4):400-7.

131. Rose K. Project quality management: why, what and how. Fort Lauderdale (FL): J. Ross Publishing; 2005.

132. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

133. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med [Internet]. 2007 Jul 16 [cited 2010 May 14];147(6):386-99. Available from: http://www.annals.org/cgi/reprint/147/6/386.pdf

134. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007 Jul 11;298(2):194-206.

135. Price N, Bartlett C, Gillmer M. ; received 12 Feb 2008, cost $ 11.25Use of insulin glargine during pregnancy: a case-control pilot study. BJOG. 2007 Apr;114(4):453-7.

136. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004 Oct;47(10):1747-59.

137. Lassere MN, Johnson KR, Boers M, Tugwell P, Brooks P, Simon L, et al. Definitions and validation criteria for biomarkers and surrogate endpoints: development and testing of a quantitative hierarchical levels of evidence schema. J Rheumatol. 2007 Mar;34(3):607-15.

138. Rosen CJ. The rosiglitazone story--lessons from an FDA Advisory Committee meeting. N Engl J Med. 2007 Aug 30;357(9):844-6.

139. Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. Qual Life Res. 2007 Sep;16(7):1251-65.

140. Maddigan SL, Feeny DH, Majumdar SR, Farris KB, Johnson JA. Health Utilities Index mark 3 demonstrated construct validity in a population-based sample with type 2 diabetes. J Clin Epidemiol. 2006 May;59(5):472-7.

141. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections: preferences of Canadians with type 2 diabetes. Diabetes Care. 2005 Sep;28(9):2243-5.

142. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006 Aug;22(8):1523-34.

143. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008;(2):CD006739.

144. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;(2):CD004654.

145. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med. 2008 Oct 27;168(19):2070-80.

146. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes. 1995 Nov;44(11):1249-58.

147. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med [Internet]. 2006 Dec 7 [cited 2010 Jan 27];355(23):2427-43. Available from: http://content.nejm.org/cgi/reprint/355/23/2427.pdf

148. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009;180(1):32-9.

149. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 May;31(5):845-51.

150. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008 Apr 28;168(8):820-5.

151. Jones SG, Momin SR, Good MW, Shea TK, Patric K. Distal upper and lower limb fractures associated with thiazolidinedione use. Am J Manag Care [Internet]. 2009 Aug [cited 2010 May 17];15(8):491-6. Available from: http://www.ajmc.com/media/pdf/AJMC_09augJones_491to496.pdf

152. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298(10):1180-8.

153. MedWatch the FDA safety information and adverse event reporting program: safety information [Internet]. Silver Spring (MD): US Food and Drug Administration. Byetta (exenatide); 2007 [cited 2009 Oct 8; updated 2008 Aug 19]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150839.htm

154. Maggs D, Garnett T. Important prescribing information: byetta [Internet]. Silver Spring (MD): US Food and Drug Administration; 2007. [cited 2009 Oct 8]. Available from: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMeicalProducts/ucm126437.pdf

155. Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin. 2009;25(4):1019-27.

156. Alba M, Swern AS, Langdon RB, Willianis-Herinan D. In patients with type 2 diabetes, sitagliptin added to metformin effectively lowers HbA(1c) regardless of patient age, gender, body mass index, or baseline measures of beta cell function. Diabetologia. 2008;51(Suppl 1):S364-S365.

157. Balu S, Arondekar B, Lee WC, Horblyuk R, Pashos CL. Economic analysis of add-on therapy with thiazolidinedione (TZD) versus insulin (INS) to metformin (MET) monotherapy. Diabetes. 2007;56(Suppl 1):A653.

158. Ushakova O, Sokolovskaya V, Morozova A, Valeeva F, Zanozina O, Sazonova O, et al. Comparison of biphasic insulin aspart 30 given three times daily or twice daily in combination with metformin versus oral antidiabetic drugs alone in patients with poorly controlled type 2 diabetes: a 16-week, randomized, open-label, parallel-group trial conducted in russia. Clin Ther. 2007 Nov;29(11):2374-84.

159. Sharma AD, Bagchi A, Mishra A, Kinagi S, Sharma YK, Bolmall C, et al. Comparative evaluation of a fixed-dose combination of Miglitol(50 mg)+Metformin SR(500 mg) vs. Metformin SR(500 mg) in patients with uncomplicated type 2 diabetes. Diabetes. 2008;57(Suppl 1):A568.

160. Olsson PO, Lindstrom T. Combination-therapy with bedtime NPH insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. Diabetes Metab. 2002;28(4 I):272-7.

161. Bao Y, Wang Q, Arondekar B, Dutcher S, Menditto L, Lee W, et al. Adherence and resource utilization of rosiglitazone (RSG) versus sulfonylurea (SU) as an add-on to metformin (MET) monotherapy among patients with type 2 diabetes. Diabetes. 2008;57(Suppl 1):A131-A132.

162. Bosil E, Collober C, Rochotte E, Camisasca RP, Garber AJ. Vildagliptin added to metformin improves glycacmic control by decreasing fasting and postprandial glucose in patients with type 2 diabetes. Diabetologia. 2006;49(Suppl 1):480-1.

163. Bosi E, Shao Q, Cohen SE. Improved blood pressure (BP) lowering in hypertensive patients (pts) with type 2 diabetes (T2DM) with vildagliptin combined with metformin compared with metformin alone. Diabetes. 2007;56(Suppl 1):A549.

164. Brandle M, Chen J, Alemao E, Yin D, Cook J, Szucs T. Cost-effectiveness of adding sitagliptin vs. an sulfonylurea in Swiss patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetologia. 2008;51(Suppl 1):S446.

165. Brodows R, Mohan V, Chuang LM, Yoon KH, Gao Y. Safety and efficacy of exenatide in patients of Asian descent with type 2 diabetes taking metformin or metformin with a sulfonylurea. Diabetes. 2008;57(Suppl 1):A158.

166. Brook R, Kleinman NL, Wingenbach D, Bron MS, Pandya B, Baran RW. Medication possession ratio and health benefit cost comparisons in type 2 diabetes patients using fixed- and loose-dose thiazolidinedione combination products. Diabetes. 2008;57(Suppl 1):A346.

167. Moses R. Repaglinide in combination therapy with metformin in Type 2 diabetes. Exp Clin Endocrinol Diabetes. 1999;107 Suppl 4:S136-S139.

168. Josse RG. Acarbose for the treatment of type II diabetes: the results of a Canadian multi-centre trial. Diabetes Res Clin Pract. 1995 Aug;28 Suppl:S167-S172.

169. Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med. 1994 Dec 15;121(12):928-35.

170. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, et al. Beta-cell function and glycemic control following one year exenatide therapy, and after 12 week wash out, in patients with type 2 diabetes. Diabetes. 2008;57(Suppl 1):A32.

171. Bunck MC, Corner A, Diamant M, Eliasson B, Malloy JL, Shaginian RM, et al. Exenatide improves postprandial hyperglycaemia and dyslipidaemia in metformin treated patients with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S351.

172. Bunck MC, Corner A, Diamant M, Eliasson B, Malloy JL, Shaginian RM, et al. Exenatide improves postprandial hyperglycemia and dyslipidemia in metformin treated patients with type 2 diabetes. Diabetes. 2008;57(Suppl 1):A33, JUN.

173. Chan J, Frier B, Leyk M, Jones CA, Demeter RJ, Tan MH. Relationship between A1C and hypoglycemia in type 2 diabetes (T2D) patients treated with basal plus prandial insulin mixture or basal insulin regimens. Diabetes. 2007;56(Suppl 1):A539-A540.

174. Chapman R, Ferrufino C, MaClean JR, Krishnarajah G. Treatment failures in type 2 diabetes patients taking oral anti-diabetes drugs. Diabetes. 2008;57(Suppl 1):A348-A349.

175. Choe C, Christiansen L, Edelman S, Mudaliar S, Henry RR. Effects of initial use of half-maximal dose rosiglitazone-metformin combination therapy, compared with maximum dose rosiglitazone or metformin, on glucose metabolism in type 2 diabetes mellitus. Diabetes. 2006;55(Suppl 1):A107.

176. Corner A, Bunck MC, Diamant M, Eliasson B, Malloy JL, Shaginian RM, et al. Beta cell function and glycaemic control following one year exenatide therapy, and after 12 week wash-out, in patients with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S351.

177. De Mattia G, Laurenti O, Moretti A, Mollica MR, Italian SG. Glycemic variability in patients with type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment - Results of a pilot study. Diabetes. 2007;56(Suppl 1):A148.

178. Defronzo R, Hissa M, Blauwet MB, Chen RS. Saxagliptin Added to Metformin Improves Glycemic Control in Patients with Type 2 Diabetes [Internet]. Poster presented at: American Diabetes Association, 67th Scientific Sessions, June 22 - 26, 2007, Chicago, Illinois. 2007. [cited 2009 Jun 3]. Available from: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=55427

179. Betteridge DJ, Verges B. Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. Diabetologia. 2005;48(12):2477-81.

180. Ahren B, Pacini G, Foley JE, Schweizer A. Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes Care [Internet]. 2005 Aug [cited 2009 May 13];28(8):1936-40. Available from: http://care.diabetesjournals.org/cgi/reprint/28/8/1936

181. Garcia-Soria G, Gonzalez-Galvez G, Argoud GM, Gerstman M, Littlejohn TW, III, Schwartz SL, et al. The dipeptidyl peptidase-4 inhibitor PHX1149 improves blood glucose control in patients with type 2 diabetes mellitus. Diabetes Obes Metab [Internet]. 2008 Apr;10(4):293-300.

182. Goke B, Gause-Nilsson I, Persson A, Study Group. The effects of tesaglitazar as add-on treatment to metformin in patients with poorly controlled type 2 diabetes. Diab Vasc Dis Res. 2007 Sep;4(3):204-13.

183. Roger P, Auclair J, Drain P. Addition of benfluorex to biguanide improves glycemic control in obese non-insulin-dependent diabetes: a double-blind study versus placebo. J Diabetes Complications. 1999 Mar;13(2):62-7.

184. O'Brien R, Scott RS, Whisnant JK. Synergistic efficacy by addition of mitiglinide, a new rapid onset and short duration insulin secretagogue, to standard metformin for type 2 diabetes mellitus (T2DM) in a large randomized, double-blind trial. Diabetes. 2007;56(Suppl 1):A553.

185. Testa MA, Hayes JF, Turner RR, Simonson DC. Quality of life improvements in type 2 diabetes when Exubera((R)) is added after failure on metformin monotherapy: An international randomized phase 3 trial. Diabetes. 2004;53(Suppl 2):A437.

186. Nauck MA, Ratner RE, Kapitza C, Berria R, Boldrin M, Balena R. Treatment with the human once-weekly GLP-1 analogue taspoglutide in combination with metformin improves glycemic control and lowers body weight in patients with type 2 diabetes mellitus inadequately controlled with metformin alone: a double-blind placebo-controlled study. Diabetes Care. 2009 Apr 14;32(7):1237-43.

187. Dejager S, Lebeaut A, Couturier A, Schweizer A. Sustained reduction in HbA(1c) during one-year treatment with vildagliptin in patients with type 2 diabetes (T2DM). Diabetes. 2006;55(Suppl 1):A29.

188. Dornhorst A, Merilaeinen M, Ratzmann KP. Initiating insulin detemir improves glycemic control without weight gain in OAD-treated insulin naive patients with type 2 diabetes: Results from a German subgroup of the PREDICTIVE study. Diabetes. 2006;55(Suppl 1):A110.

189. Evangelista V, Ceriello A, De Berardis G, Pellegrini F, Totani L, Di Pietro C, et al. Effect of pioglitazone vs metformin on cardiovascular risk markers in type 2 diabetes: Results of a double blind, randomized study. Diabetes. 2007;56(Suppl 1):A580.

190. Foos V, Munro V, nn-Sofie B, Ray JA, Valentine WJ, Roze S, et al. Long-term cost-effectiveness of treatment with metformin in combination with either repaglinide or nateglinide in type 2 diabetes patients with inadequate glycemic control: A Swedish analysis. Diabetes. 2006;55(Suppl 1):A552.

191. Reboussin DM, Goff DC, Jr., Lipkin EW, Herrington DM, Summerson J, Steffes M, et al. The combination oral and nutritional treatment of late-onset diabetes mellitus (CONTROL DM) trial results. Diabet Med. 2004 Oct;21(10):1082-9.

192. Dhindsa P, Holt M, Davis K, Donnelly R. Effects of additional Glimepiride and Gliclazide on metabolic and haemodynamic function in metformin-treated patients with type 2 diabetes: A double-blind, crossover study. Diabetes. 2001;50(Suppl 2):A433.

193. Fordan S, Hang Y, Lyness W, Raskin P. Twice-daily vs thrice-daily dosing of a repaglinide/metformin fixed-dose combination tablet in T2DM subjects previously treated with monotherapy vs dual therapy. Diabetes. 2008;57(Suppl 1):A596-A597.

194. Gallwitz B. What to do next when metformin does not work in diabetes Type 2? Add incretin [Internet]. Abstract presented at: European Congress of Endocrinology. 2009 Apr 25-29; Istanbul. [cited 2009 May 29]. Available from: http://www.endocrine-abstracts.org/ea/0020/ea0020d1.3.htm

195. Dorkhan M, Dencker M, Stagmo M, Groop L. Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes. Cardiovascular Diabetology [Internet]. 2009 [cited 2009 May 13];8(15). Available from: http://www.cardiab.com/content/pdf/1475-2840-8-15.pdf

196. D'Alessio DA, Denney AM, Hermiller LM, Prigeon RL, Martin JM, Tharp WG, et al. Treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin improves fasting islet-cell function in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2009 Jan;94(1):81-8.

197. Derosa G, D'Angelo A, Fogari E, Salvadeo S, Gravina A, Ferrari I, et al. Nateglinide and glibenclamide metabolic effects in naive type 2 diabetic patients treated with metformin. J Clin Pharm Ther. 2009 Feb;34(1):13-23.

198. Dorkhan M, Frid A, Groop L. Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes: what to add--insulin glargine or pioglitazone? Diabetes Res Clin Pract. 2008 Dec;82(3):340-5.

199. Comaschi M, Corsi A, Di Pietro C, Bellatreccia A, Mariz S, COM06 Study Investigators. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. Nutr Metab Cardiovasc Dis. 2008 Jun;18(5):373-9.

200. Papa G, Fedele V, Chiavetta A, Lorenti I, Leotta C, Luca S, et al. Therapeutic options for elderly diabetic subjects: open label, randomized clinical trial of insulin glargine added to oral antidiabetic drugs versus increased dosage of oral antidiabetic drugs. Acta Diabetol. 2008 Mar;45(1):53-9.

201. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin. 2008 Jan;24(1):275-86.

202. Chien HH, Chang CT, Chu NF, Hsieh SH, Huang YY, Lee IT, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. J Chin Med Assoc. 2007 Nov;70(11):473-80.

203. Kelly AS, Thelen AM, Kaiser DR, Gonzalez-Campoy JM, Bank AJ. Rosiglitazone improves endothelial function and inflammation but not asymmetric dimethylarginine or oxidative stress in patients with type 2 diabetes mellitus. Vasc Med [Internet]. 2007 Nov [cited 2009 May 13];12(4):311-8. Available from: http://vmj.sagepub.com/cgi/reprint/12/4/311

204. Derosa G, D'Angelo A, Fogari E, Salvadeo S, Gravina A, Ferrari I, et al. Effects of nateglinide and glibenclamide on prothrombotic factors in naive type 2 diabetic patients treated with metformin: a 1-year, double-blind, randomized clinical trial. Intern Med [Internet]. 2007 [cited 2009 May 13];46(22):1837-46. Available from: http://www.jstage.jst.go.jp/article/internalmedicine/46/22/1837/_pdf

205. Labrousse-Lhermine F, Cazals L, Ruidavets JB, GEDEC Study Group, Hanaire H. Long-term treatment combining continuous subcutaneous insulin infusion with oral hypoglycaemic agents is effective in type 2 diabetes. Diabetes Metab [Internet]. 2007 Sep [cited 2009 Dec 4];33(4):253-60. Available from: http://www.em-consulte.com/showarticlefile/137459/main.pdf

206. Pala L, Mannucci E, Dicembrini I, Rotella CM. A comparison of mealtime insulin aspart and human insulin in combination with metformin in type 2 diabetes patients. Diabetes Res Clin Pract. 2007;78(1):132-5.

207. Comaschi M, Demicheli A, Di PC, Bellatreccia A, Mariz S, Alessi R, et al. Effects of pioglitazone in combination with metformin or a sulfonylurea compared to a fixed-dose combination of metformin and glibenclamide in patients with type 2 diabetes. Diabetes Technol Ther. 2007;9(4):387-98.

208. Nelson P, Poon T, Guan X, Schnabel C, Wintle M, Fineman M. The incretin mimetic exenatide as a monotherapy in patients with type 2 diabetes. Diabetes Technol Ther. 2007 Aug;9(4):317-26.

209. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, et al. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. N Engl J Med [Internet]. 2007 Jul 5 [cited 2010 May 17];357(1):28-38. Available from: http://content.nejm.org/cgi/reprint/357/1/28.pdf

210. Davies MJ, Thaware PK, Tringham JR, Howe J, Jarvis J, Johnston V, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med. 2007 Jul;24(7):714-9.

211. Derosa G, Fogari E, Cicero AF, D'Angelo A, Ciccarelli L, Piccinni MN, et al. Blood pressure control and inflammatory markers in type 2 diabetic patients treated with pioglitazone or rosiglitazone and metformin. Hypertens Res. 2007 May;30(5):387-94.

212. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care [Internet]. 2007 Jun [cited 2009 May 13];30(6):1487-93. Available from: http://care.diabetesjournals.org/cgi/reprint/30/6/1487

213. Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR. Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract. 2007 Aug;77(2):180-7.

214. Jacob AN, Salinas K, ms-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. Diabetes Obes Metab. 2007 May;9(3):386-93.

215. Derosa G, D'Angelo A, Ragonesi PD, Ciccarelli L, Piccinni MN, Pricolo F, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with metformin. Intern Med J. 2007 Feb;37(2):79-86.

216. Derosa G, Gaddi AV, Ciccarelli L, Fogari E, Ghelfi M, Ferrari I, et al. Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial. J Int Med Res [Internet]. 2005 May [cited 2009 May 14];33(3):284-94. Available from: http://www.jimronline.net/content/full/2005/60/0584.pdf

217. Bakris GL, Ruilope LM, McMorn SO, Weston WM, Heise MA, Freed MI, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006 Oct;24(10):2047-55.

218. Kuo CS, Pei D, Yao CY, Hsieh MC, Kuo SW. Effect of orlistat in overweight poorly controlled Chinese female type 2 diabetic patients: a randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2006 Aug;60(8):906-10.

219. Derosa G, D'Angelo A, Ragonesi PD, Ciccarelli L, Piccinni MN, Pricolo F, et al. Metformin-pioglitazone and metformin-rosiglitazone effects on non-conventional cardiovascular risk factors plasma level in type 2 diabetic patients with metabolic syndrome. J Clin Pharm Ther. 2006 Aug;31(4):375-83.

220. Derosa G, Gaddi AV, Piccinni MN, Salvadeo S, Ciccarelli L, Fogari E, et al. Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. Diabetes Obes Metab. 2006;8(2):197-205.

221. Bailey CJ, Bagdonas A, Rubes J, McMorn SO, Donaldson J, Biswas N, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005;27(10):1548-61.

222. Derosa G, Cicero AF, Gaddi AV, Ciccarelli L, Piccinni MN, Salvadeo S, et al. Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. Clin Ther. 2005;27(9):1383-91.

223. Feinglos MN, Saad MF, Pi-Sunyer FX, An B, Santiago O, Liraglutide Dose-Response Study Group. Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes. Diabet Med. 2005 Aug;22(8):1016-23.

224. Wang TF, Pei D, Li JC, Tsai WC, Tsai CC, Yao CY, et al. Effects of sibutramine in overweight, poorly controlled Chinese female type 2 diabetic patients: a randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2005 Jul;59(7):746-50.

225. Derosa G, Gaddi AV, Piccinni MN, Ciccarelli L, Salvadeo S, Peros E, et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy. 2005 May;25(5):637-45.

226. Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ. Continuing metformin when starting insulin in patients with Type 2 diabetes: a double-blind randomized placebo-controlled trial. Diabet Med. 2005 May;22(5):634-40.

227. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med. 2005 Apr;22(4):374-81.

228. Brunetti P, Pagano G, Turco C, Gori M, Perriello G, Study Group. Effects of two different glibenclamide dose-strengths in the fixed combination with metformin in patients with poorly controlled T2DM: a double blind, prospective, randomised, cross-over clinical trial. Diabetes Nutr Metab. 2004 Dec;17(6):350-7.

229. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004;26(12):2034-44.

230. Derosa G, Cicero AF, Gaddi A, Ragonesi PD, Fogari E, Bertone G, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. Clin Ther. 2004 May;26(5):744-54.

231. Raskin P, McGill J, Saad MF, Cappleman JM, Kaye W, Khutoryansky N, et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. Diabet Med. 2004;21(4):329-35.

232. Jovanovic L, Hassman DR, Gooch B, Jain R, Greco S, Khutoryansky N, et al. Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. Diabetes Res Clin Pract. 2004;63(2):127-34.

233. Furlong NJ, Hulme SA, O'Brien SV, Hardy KJ. Comparison of repaglinide vs. gliclazide in combination with bedtime NPH insulin in patients with Type 2 diabetes inadequately controlled with oral hypoglycaemic agents. Diabet Med. 2003 Nov;20(11):935-41.

234. Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract. 2003 Dec;62(3):187-95.

235. Altuntas Y, Ozen B, Ozturk B, Sengul A, Ucak S, Ersoy O, et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. Diabetes Obes Metab. 2003 Nov;5(6):371-8.

236. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, et al. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. Diabetes Care [Internet]. 2003 Aug [cited 2009 Dec 3];26(8):2370-7. Available from: http://care.diabetesjournals.org/cgi/reprint/26/8/2370

237. Raskin P, Klaff L, McGill J, South SA, Hollander P, Khutoryansky N, et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care [Internet]. 2003 Jul [cited 2009 May 14];26(7):2063-8. Available from: http://care.diabetesjournals.org/cgi/reprint/26/7/2063

238. Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. Diabetes Care [Internet]. 2002 Jul [cited 2009 May 14];25(7):1123-8. Available from: http://care.diabetesjournals.org/cgi/reprint/25/7/1123

239. Gokcel A, Karakose H, Ertorer EM, Tanaci N, Tutuncu NB, Guvener N. Effects of sibutramine in obese female subjects with type 2 diabetes and poor blood glucose control. Diabetes Care [Internet]. 2001 Nov [cited 2009 May 14];24(11):1957-60. Available from: http://care.diabetesjournals.org/cgi/reprint/24/11/1957

240. Raskin P, Jovanovic L, Berger S, Schwartz S, Woo V, Ratner R. Repaglinide/troglitazone combination therapy: improved glycemic control in type 2 diabetes. Diabetes Care [Internet]. 2000 Jul [cited 2009 May 14];23(7):979-83. Available from: http://care.diabetesjournals.org/cgi/reprint/23/7/979

241. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44) [erratum appears in Diabetes Care 1999 Nov;22(11):1922. Diabetes Care. 1999 Jun;22(6):960-4.

242. Lam KS, Tiu SC, Tsang MW, Ip TP, Tam SC. Acarbose in NIDDM patients with poor control on conventional oral agents. A 24-week placebo-controlled study. Diabetes Care [Internet]. 1998 Jul [cited 2009 Dec 8];21(7):1154-8. Available from: http://care.diabetesjournals.org/cgi/reprint/21/7/1154

243. Sotaniemi EA, Vierimaa E, Huupponen R, Karvonen I, Vuoti MJ, Rytomaa K. Insulin and sulphonylurea in the therapy of type 2 diabetes. Diabetes Res Clin Pract. 1990 Mar;8(3):243-51.

244. Perez A, Spanheimer R, Khan M. Glycaemic control in patients with type 2 diabetes: the effects of pioglitazone vs glyburide in a 3-year randomized double-blind trial [abstract]. Diabetologia. 2006;49(Suppl 1):490.

245. Gottschalk M, Danne T, Cara J, Vlajinic A, Issa M. Glimepiride (GLIM) versus metformin (MET) as monotherapy in pediatric subjects with T2DM: A single blind comparison study. Diabetes. 2005;54(Suppl 1):A65.

246. Belcher G, Lambert C, Edwards GC, Tan MH, Herz M. Results of liver safety testing in 3713 type 2 diabetic patients treated for one year in double blind controlled trials with pioglitazone, metformin or gliclazide. Diabetologia. 2003;46(Suppl 2):A291.

247. Maher LJ, Edwards GC, Lee CEF, Urquhart R, Herz M, Tan MH. Long-term combination therapy with pioglitazone plus metformin for type 2 diabetes: A randomised, comparative study with gliclazide plus metformin. Diabetologia. 2003;46(Supplement 2):A 288.

248. Aljabri K, Kozak S, Thompson D. A comparison of adding pioglitazone or insulin to patients with type 2 diabetes in poor control on maximal doses of sulphonylurea and metformin: A prospective, randomized Trial [abstract]. Diabetes. 2003;52(Suppl 1):A109.

249. Davis K, Dhindsa P, Holt M, Donnelly R. Comparison of glimepiride and gliclazide in metformin-treated patients with type 2 diabetes: A double-blind, crossover study of vascular function. Diabetologia. 2001;44(Supplement 1):A234.

250. Holman RR, Cull CA, Turner RC. Glycaemic improvement over one year in a double-blind trial of acarbose in 1,946 NIDDM patients. Diabetologia. 1996;39(Suppl 1):A44.

251. Li H, Li W, Gu Y, Han Y, Wang J, Xu B, et al. Comparison of continual insulin or secretagogue treatment in type 2 diabetic patients with alternate insulin-secretagogue administration. Diabetes Res Clin Pract. 2009;84(2):158-62.

252. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. The Lancet. 2009;373(9662):473-81.

253. King AB. Once-daily insulin detemir is comparable to once-daily insulin glargine in providing glycaemic control over 24 h in patients with type 2 diabetes: A double-blind, randomized, crossover study. Diabetes Obes Metab. 2009;11(1):69-71.

254. Bretzel RG, Nurber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet. 2008;371:1073-84.

255. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia [Internet]. 2008 Mar [cited 2009 Dec 4];51(3):408-16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2235909/pdf/125_2007_Article_911.pdf

256. Houlden R, Ross S, Harris S, Yale JF, Sauriol L, Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral therapy in the management of Type 2 diabetes: The Canadian INSIGHT Study. Diabetes Res Clin Pract. 2007;78(2):254-8.

257. Tan KC, Chow WS, Tso AW, Xu A, Tse HF, Hoo RL, et al. Thiazolidinedione increases serum soluble receptor for advanced glycation end-products in type 2 diabetes. Diabetologia. 2007 Jul 18;50(9):1819-25.

258. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol. 2007 May 1;49(17):1772-80.

259. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care [Internet]. 2006 [cited 2009 May 13];29(12):2632-7. Available from: http://care.diabetesjournals.org/cgi/reprint/29/12/2632

260. Boye KS, Matza LS, Oglesby A, Malley K, Kim S, Hayes RP, et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. Health Qual Life Outcomes [Internet]. 2006 [cited 2009 May 15];4(80). Available from: http://www.hqlo.com/content/pdf/1477-7525-4-80.pdf

261. Jacober SJ, Scism-Bacon JL, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naive patients with type 2 diabetes receiving oral antidiabetes agents. Diabetes Obes Metab. 2006;8(4):448-55.

262. Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-Week, Randomized, Parallel, Treat-to-Target Trial Comparing Insulin Detemir With NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin-Naive People With Type 2 Diabetes. Diabetes Care [Internet]. 2006 [cited 2009 Dec 3];29(6):1269-74. Available from: http://care.diabetesjournals.org/cgi/reprint/29/6/1269

263. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-89.

264. Derosa G, Cicero AFG, Murdolo G, Ciccarelli L, Fogari R. Comparison of metabolic effects of orlistat and sibutramine treatment in Type 2 diabetic obese patients. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 2004;17(4):222-9.

265. Drouin P, Standl E, Sechser T, Thalassinos N, Halmos T, Nosadini R, et al. Gliclazide modified release: Results of a 2-year study in patients with type 2 diabetes. Diabetes Obes Metab. 2004;6(6):414-21.

266. Tan MH, Johns D, Strand J, Halse J, Madsbad S, Eriksson JW, et al. Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with Type 2 diabetes. Diabet Med. 2004;21(8):859-66.

267. Meneilly GS, Greig N, Tildesley H, Habener JF, Egan JM, Elahi D. Effects of 3 months of continuous subcutaneous administration of glucagon-like peptide 1 in elderly patients with type 2 diabetes. Diabetes Care. 2003;26(10):2835-41.

268. Rosskamp R, HOE 901/2004 Study Investigators Group. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients. Diabet Med. 2003 Jul;20(7):545-51.

269. Massi BM, Humburg E, Dressler A, Ziemen M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with Type 2 diabetes. Horm Metab Res. 2003;35(3):189-96.

270. Goke B, German Pioglitazone Study Group. Improved glycemic control and lipid profile in a randomized study of pioglitazone compared with acarbose in patients with type 2 diabetes mellitus. Treat Endocrinol. 2002;1(5):329-36.

271. Finer N, Bloom SR, Frost GS, Banks LM, Griffiths J. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: A randomised, double-blind, placebo-controlled study. Diabetes Obes Metab. 2000;2(2):105-12.

272. Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, et al. Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism. 2009 Apr 22;58(8):1059-66.

273. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met+TZD). Diabetes Care. 2009 Mar 16;32(7):1224-30.

274. Garber A, Camisasca RP, Ehrsam E, Collober-Maugeais C, Rochotte E, Lebeaut A. Vildagliptin added to metformin improves glycemic control and may mitigate metformin-induced GI side effects in patients with type 2 diabetes (T2DM). Diabetes. 2006;55(Suppl 1):A29.

275. Garber AJ, Goldfine AB, Truitt K, Dmuchowski C, Jones M. Colesevelam HCl improves glycemic control, independent of glomerular filtration rate, in patients with type 2 diabetes inadequately controlled on metformin, sulfonylurea, or insulin-based therapy. Diabetes. 2007;56(Suppl 1):A577.

276. Garber AJ, Goldfine AB, Truitt K, Dmuchowski C, Jones M. Colesevelam HC1 improves glycemic control in patients on statin therapy with type 2 diabetes inadequately controlled by metformin, sulfonylurea, or insulin-based therapy. Diabetes. 2007;56(Suppl 1):A536-A537.

277. Garber AJ, Rood JA, Waterhouse BR, Wolstenholme AR, Cobitz AR, Rosenstock J. Benefits of rosiglitazone (RSG) plus metformin (MET) vs MET uptitration in older patients (Pts) with type 2 diabetes (T2D). Diabetes. 2006;55(Suppl 1):A476-A477.

278. Goldberg M, Dinh S, Castelli C, Majuru S, Arbit E. Improved glycemic control with oral recombinant human insulin in patients with type 2 diabetes (T2DM) inadequately controlled on metformin. Diabetes. 2007;56(Suppl 1):A121-A122.

279. Golubovic MV, Mikic D, Pesic M, Dimic D, Radenkovic S, Kocic R. Effect of repaglinide vs glimepirid on glycaemic control in overweight and obese patients with type 2 diabetes mellitus uncontrolled by metformin [Internet]. Abstract presented at: European Congress of Endocrinology. 2006 Apr 1-5; Glasgow (UK). [cited 2009 May 29]. Available from: http://www.endocrine-abstracts.org/ea/0011/ea0011p351.htm

280. Goodman M, Thurston H, Minic B, Thuren T. Improved glycaemic control with vildagliptin 100 mg administered either as a morning or evening dose as add-on therapy to metformin in type 2 diabetes mellitus. Diabetologia. 2008;51(Suppl 1):S366.

281. Halimi S, Charpentier G, F-PIO-10 Investigators. Effects of the addition of pioglitazone on insulin resistance, beta cell function and proinsulin/insulin ratio in patients with type 2 diabetes inadequately controlled on metformin and a sulphonylurea. Diabetologia. 2006;49(Suppl 1):491-2.

282. Heddaeus H, Karagiannis E, Luebben G. Glycaemic response of pioglitazone in dual combination and triple therapy in patients with type 2 diabetes mellitus. Diabetologia. 2006;49(Suppl 1):493.

283. Henriksen JE, Gram J, Beck-Niel-Sen H, Sdds SG. Combining rosiglitazone with insulin and metformin in patients with type 2 diabetes. Effect on body weight. The SDDS study. Diabetes. 2008;57(Suppl 1):A136.

284. Henry R, Ratner R, Stonehouse A, Guan X, Poon T, Malone J, et al. Exenatide maintained glyeaemic control with associated weight reduction over two years in patients with type 2 diabetes. Diabetologia. 2006;49(Suppl 1):473-4.

285. Herman WH, Hafner SM, Kahn SE, Zinman B, Holman BR, Viberti GF, et al. The effectiveness of metformin versus glyburide in type 2 diabetes: Results from ADOPT (A diabetes outcomes progression trial). Diabetes. 2007;56(Suppl 1):A146.

286. Hermansen K, Nauck MA, Frid A, Shah NS, Tankova T, Mitha IH, et al. Liraglutide, a once-daily human GLP-1 analogue, in type 2 diabetes provides similar glycaemic control with reduced body weight compared with glimepiride when added to metformin. Diabetologia. 2008;51(Suppl 1):S358.

287. Hsia SH. Single-dose regimens of insulin glargine compared to NPH in ethnic minority type 2 diabetic patients uncontrolled on oral agents: Interim results. Diabetes. 2008;57(Suppl 1):A60.

288. Israel MK, Dabrowski I, Purkayastha D. Effects of nateglinide in combination with basal insulin glargine with metformin and/or thiazolidinedione in type 2 diabetes patients. Diabetes. 2008;57(Suppl 1):A572.

289. Ivanyi T, Guan X, Mac S, Holcombe J, Blonde L. Reductions in HbA1c and body weight with 2 years of exenatide treatment in overweight patients with type 2 diabetes. International Journal of Obesity. 2007;31(Suppl 1):S27.

290. Jendle J, Nauck MA, Matthews D, Frid A, Hermansen K, Duering M, et al. Liraglutide, a once-daily human GLP-1 analog, reduces fat percentage, visceral and subcutaneous adipose tissue and hepatic steatosis compared with glimepiride when added to metformin in subjects with type 2 diabetes. Diabetes. 2008;57(Suppl 1):A32-A33.

291. Jendle J, Nauck MA, Matthews D, Frid A, Hermansen K, During M, et al. The reduction of body weight with liraglutide, a once-daily human GLP-I analogue for type 2 diabetes, primarily comes from fat tissue and the fat tissue lost is predominantly visceral fat. Diabetologia. 2008;51(Suppl 1):S318.

292. Kadowaki T, Tajima N, Odawara M, Nishii M, Nonaka K, Stein PP. Sitagliptin added to ongoing treatment with metformin improved glycemic control and was well tolerated in Japanese patients with type 2 diabetes (T2DM). Diabetes. 2008;57(Suppl 1):A589-A590.

293. Karasik A, Charbonnel B, Liu J, Wu M, Meehan A, Meininger G. Sitagliptin added to ongoing metformin therapy enhanced glycemic control and beta-cell function in patients with type 2 diabetes. Diabetes. 2006;55(Suppl 1):A119-A120.

294. Kawai T, Funae O, Shimada A, Hirata T, Tabata M, Atsumi Y, et al. Efficacy of additional pioglitazone administration on to metformin in inadequately controlled patients with type 2 diabetes. Diabetes. 2007;56(Suppl 1):A545.

295. Kendall D, Nielsen L, Han J, Brodows R, Bhole D. Metabolic improvement associated with temporal pattern of weight loss in exenatide-treated patients with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S353-S354.

296. Kim D, MaCconell L, Zhuang D, Schnabel C, Taylor K, Li WI, et al. Safety and effects of a once-weekly, long-acting release formulation of exenatide over 15 weeks in patients with type 2 diabetes. Diabetes. 2006;55(Suppl 1):A116.

297. Kurashvili R, Asatiani N, Nishnianidze M, Dundua M, Shelestova E. Rapid effect of repaglinide in combination with metformin in poorly controlled obese patients with type 2 diabetes mellitus. International Journal of Obesity. 2008;32(Suppl 1):S163.

298. Kurashvili RB, Asatiani NG, Nishnianidze MG, Shelestova EL. Rapid effect of repaglinide in combination with metformin in poorly controlled obese patients with type 2 diabetes mellitus [Internet]. Abstract presented at: European Congress of Endocrinology. 2006 Apr 1-5; Glasgow (UK). [cited 2009 May 29]. Available from: http://www.endocrine-abstracts.org/ea/0011/ea0011p418.htm

299. Lund SS, Tarnow L, Nielsen BB, Hansen BV, Pedersen O, Parving HH, et al. Effect of BIAsp 30 (biphasic insulin aspart 30) in combination with oral hypoglycaemic agents on glycaemic regulation in non-obese patients with type 2 diabetes. Diabetologia. 2006;49(Suppl 1):600.

300. Maggs D, MacConell L, Zhuang D, Schnabel C, Taylor K, Trautmann M, et al. Safety and effects of a once-weekly, long-acting release formulation of exenatide over 15 weeks in patients with type 2 diabetes. Diabetologia. 2006;49(Suppl 1):3-4.

301. Markolf H, Luebben G, Pfuetzner A, Forst T. Pioglitazone vs. glibenclamide: Significant differences in glycaemic control and treatment failure rates in patients with type-2-diabetes mellitus. Diabetes. 2006;55(Suppl 1):A144.

302. Matthews D, Marre M, Le-Thl TUD, Zdravkovic M, Simo R. Liraglutide, a once-daily human GLP-1 analog, significantly improves beta-cell function in subjects with type 2 diabetes. Diabetes. 2008;57(Suppl 1):A150-A151.

303. Matthews DR, Marre M, Le-Thi TD, Zdravkovic M, Simo R, Garber A, et al. Liraglutide, a human GLP-1 analogue, significantly improves beta cell function in subjects with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S356.

304. Meininger G, Charbonnel B, Karasik A, Liu J, Wu M, Meehan A. Efficacy and safety of sitagliptin added to ongoing metformin therapy in type 2 diabetes patients who were inadequately controlled on metformin alone. Diabetologia. 2006;49(Suppl 1):5-6.

305. Meneghini L, Schwartz S, Strange P, Oster G. Health-related quality of life and costs of receiving add-on therapy with insulin glargine or pioglitazone in patients with type 2 diabetes. Diabetologia. 2006;49(Suppl 1):543.

306. Naiker P, Makan HA, Omar MAK, Kedijang T, Kong LLL, study g. Effect of biphasic insulin aspart 30/70 (BIAsp30) in combination with metformin on glycaemic control in subjects with type 2 diabetes not optimally controlled on oral antidiabetic agents. Diabetologia. 2006;49(Suppl 1):599-600.

307. Nathwani A, Lebeaut A, Byiers S, Gimpelewicz C, Chang I. Reduction in blood pressure in patients treated with vildagliptin as monotherapy or in combination with metformin for type 2 diabetes. Diabetes. 2006;55(Suppl 1):A113.

308. Nauck MA, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Liraglutide, a once-daily human GLP-1 analog, in type 2 diabetes provides similar glycemic control with reduced body weight compared with glimepiride when added to metformin. Diabetes. 2008;57(Suppl 1):A150.

309. Nauck MA, Duran S, Kim D, Johns D, Festa A, Trautmann M. Effects of exenatide compared with twice-daily biphasic insulin aspart in patients with type 2 diabetes using metformin and a sulphonylurea. Diabetologia. 2006;49(Suppl 1):3.

310. Oster G, Meneghini LF, Schwartz S, Zhang Q. Health-related quality of life (HRQL) in patients with type 2 diabetes (T2DM) receiving add-on therapy with insulin glargine (GLAR) or pioglitazone (PIO). Diabetes. 2006 Jun 9;55(Suppl 1):A477.

311. Ovalle F, Philis-Tsimikas A, Truitt K, Dmuchowski C, Jones M. Colesevelam HC1 improves glycemic control, independent of age, in patients with type 2 diabetes uncontrolled on metformin, sulfonylurea, or insulin-based therapy. Diabetes. 2007;56(Suppl 1):A536.

312. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. Curr Med Res Opin. 2008 Oct;24(10):2943-52.

313. Schwartz SL, Ratner RE, Kim DD, Qu Y, Fechner LL, Lenox SM, et al. Effect of exenatide on 24-hour blood glucose profile compared with placebo in patients with type 2 diabetes: a randomized, double-blind, two-arm, parallel-group, placebo-controlled, 2-week study. Clin Ther. 2008 May;30(5):858-67.

314. Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006 Jul;8(4):436-47.

315. Ratner RE, Maggs D, Nielsen LL, Stonehouse AH, Poon T, Zhang B, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2006 Jul;8(4):419-28.

316. Rajagopalan R, Iyer S, Khan M. Effect of pioglitazone on metabolic syndrome risk factors: results of double-blind, multicenter, randomized clinical trials. Curr Med Res Opin. 2005 Jan;21(1):163-72.

317. Malone JK. Combined therapy with insulin lispro mix 75/25 plus metformin or insulin glargine plus metformin: A 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy (vol 26, pg 2034, 2004) [Correction]. Clin Ther. 2005;27(7):1112.

318. Sitagliptin and metformin combination therapy improves glycemic control. Nature Clinical Practice Endocrinology and Metabolism. 2007;3(9):621.

319. Lofthouse M. Exenatide and insulin glargine are equally effective in patients with suboptimally controlled type 2 diabetes. Nature Clinical Practice Endocrinology & Metabolism. 2006;2(1):7.

320. Paisey RB, Hodge D, Bower L. Weight and glycaemic responses to 6 months Exenatide treatment in 9 Alstrom syndrome subjects with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S124.

321. Pfützner A, Gurieva I, Antsiferov M, Allen E, Ravichandran S, Chen R. Saxagliptin either as add-on therapy to metformin or as initial combination therapy with metformin improves glycaemic control in patients with type 2 diabetes [Internet]. Abstract presented at: European Congress of Endocrinology. 2009 Apr 25-29; Istanbul. [cited 2009 May 29]. Available from: http://www.endocrine-abstracts.org/ea/0020/ea0020p359.htm

322. Pirags V. What to do next when metformin does not work in diabetes Type2? Add SU [Internet]. Abstract presented at: European Congress of Endocrinology. 2009 Apr 25-29; Istanbul. [cited 2009 May 29]. Available from: http://www.endocrine-abstracts.org/ea/0020/ea0020d1.1.htm

323. Qi DS, Teng R, Jiang M, Davies MJ, Kaufman KD, Amatruda JM, et al. Two-year treatment with sitagliptin and initial combination therapy of sitagliptin and metformin provides substantial and durable glycaemic control in patients with type 2 diabetes. Diabetologia. 2008;51(Suppl 1):S36.

324. Raskin P, Braceras R, Schwartz S, Chaykin L, Chu PL, Wynne A. Over 75% of patients with type 2 diabetes reached HbA(1c) < 7% by adding biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment. Diabetologia. 2006;49(Suppl 1):487.

325. Raskin P, Braceras R, Schwartz S, Chaykin L, Chu PL, Wynne A. Over 75% of patients with type 2 diabetes reached target A1C by adding biphasic insulin aspart 70/30 to optimized metformin and pioglitazone treatment. Diabetes. 2006;55(Suppl 1):A131.

326. Rhee C, Hang Y, Lyness W, Raskin P. Repaglinide/metformin fixed-dose combination tablet vs. rosiglitazone/metformin fixed-dose combination tablet in T2DM subjects evaluated by prior OAD treatment regimen. Diabetes. 2008;57(Suppl 1):A586-A587.

327. Rijzewijk LJ, van der Meer RW, lamb HJ, Jong HWA, Lubberink M, Romijn JA, et al. Effect of pioglitazone versus metformin on myocardial function, metabolism and triglyceride content in men with well-controlled type 2 diabetes and verified absence of cardiac ischaemia. Diabetologia. 2008;51(Suppl 1):S53.

328. Rijzewijk LJ, Van Der Meer RW, Lamb HJ, De Jong HW, Lubberink M, Romijn JA, et al. Effect of pioglitazone versus metformin on myocardial function, metabolism and triglyceride content in men with well-controlled type 2 diabetes mellitus and verified absence of cardiac ischemia in the PIRAMID study (Pioglitazone influence on tRiglyceride accumulation in the myocardium in diabetes): A randomized controlled trial. Diabetes. 2008;57(Suppl 1):A113.

329. Robbins DC, Beisswenger PJ, Moses RG, Ceriello A, Milicevic Z, Sarwat S, et al. Comparison of insulin lispro mid mixture (MM) plus metformin (Met) with glargine (G) plus met on HbA(1c) (A1C) and blood glucose (BG) profiles in patients with type 2 diabetes (T2D). Diabetologia. 2006;49(Suppl 1):603-4.

330. Robbins DC, Beisswenger PJ, Ceriello A, Sarwat S, Jones CA, Tan MH. Thrice-daily lispro mid mixture (MM) plus metformin (Met) improved glycemic control better than glargine (G) plus Met in patients with type 2 diabetes (T2D). Diabetes. 2006;55(Suppl 1):A132.

331. Russell-Jones D, Shaw JE, Brandle M, Matthews D, Frid A, Zdravkovic M, et al. The once-daily human GLP-1 analog liraglutide reduces body weight in subjects with type 2 diabetes, irrespective of body mass index at baseline. Diabetes. 2008;57(Suppl 1):A593-A594.

332. Scheen A, Finer N, Jensen M, Hollander P, Van Gaal L. Rimonabant improves cardiometabolic risk factors in overweight/obese patients with poorly controlled type 2 diabetes (HbA(1c)>= 8%) on monotherapy with metformin or sulfonylureas. Diabetologia. 2006;49(Suppl 1):483-4.

333. Schmitz O, Russell-Jones D, Shaw J, Brandle M, Matthews D, Frid A, et al. Liraglutide, a human GLP-1 analogue, reduces bodyweight in subjects with type 2 diabetes, irrespective of body mass index at baseline. Diabetologia. 2008;51(Suppl 1):S354-S355.

334. Schoendorf T, Grabellus M, Jenke B, Roth W, Forst T, Pfuetzner A, et al. ActoplusMet, a fixed combination of pioglitazone and metformin, improves metabolic markers under daily routine conditions in type 2 diabetes patients with insufficient glycemic control by treatment with metformin alone. Diabetes. 2008;57(Suppl 1):A567.

335. Schondorf T, Grabellus M, Jenke B, Roth W, Forst T, Pfutzner A, et al. ActoplusMet, a Fixed cCmbination of Pioglitazone and Metformin, Improves Metabolic Markers under Daily Routine Conditions in Type 2 Diabetes Patients with Insufficient Glycemic Control by Treatment with Metformin Alone [Internet]. Abstract presented at: American Diabetes Association. 68th Scientific Sessions; 2008 Jun 6-10; San Francisco. [cited 2009 Jun 3]. Available from: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=70807

336. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P, Quartet [corrected] Study Group. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. Journal of Clinical Endocrinology & Metabolism. 2004;89(12):6068-76.

337. Tan MH, Le NA, Goldberg RB, Brown WV, Ceriello A, Beisswenger PJ, et al. Postprandial increase in hs-CRP in patients with type 2 diabetes (T2D): comparison of lispro mid mixture (MM) plus metformin (Met) with glargine (G) plus met. Diabetologia. 2006;49(Suppl 1):604-5.

338. Tan MH, Brown WV, Goldberg RB, Le NA, Ceriello A, Beisswenger PJ, et al. Lispro mid mixture (MM) plus metformin (Met) reduced post-prandial hs-CRP more than glargine (G) plus met in type 2 diabetes (T2D) patients. Diabetes. 2006;55(Suppl 1):A496.

339. Taylor M, Shearer A, Bagust A, Vaz JP, Pereira J. Lifetime cost-effectiveness of rosiglitazone/metformin fixed dose combination for the treatment of type 2 diabetes in Portugal. Diabetes. 2006;55(Suppl 1):A548.

340. Vaag A, Nauck MA, Brandle M, Colagiuri S, Schmitz O, Zdravkovic M, et al. Liraglutide, a human GLP-1 analogue, substantially reduces HbA(1c) in subjects with type 2 diabetes, irrespective of HbA(1c) at baseline. Diabetologia. 2008;51(Suppl 1):S68-S69.

341. Von Bibra H, Schumm-Draeger PM, Siegmund T. Rosiglitazone improves diastolic myocardial dysfunction compared to glimipiride in patients with type 2 diabetes mellitus. Diabetes. 2007;56(Suppl 1):A587.

342. Wajcberg E, Triplitt C, Sriwijitkamol A, Defronzo RA, Cersosimo E. Contribution of glucagon suppression to improved postprandial hyperglycemia induced by exenatide in patients with T2DM. Diabetes. 2006;55(Suppl 1):A28.

343. Wang CP. Comparison of glycemic control in type 2 diabetics due to subsequent use of insulin sensitizers and/or sulfonylureals after mono oral therapy in south Texas VA. Diabetes. 2007;56(Suppl 1):A635.

344. Williams-Herman D, Xu L, Davies MJ, Stein PP, Amatruda JM. Substantial improvement in beta-cell function with initial combination therapy of sitagliptin and metformin in patients with type 2 diabetes after 1 year of treatment. Diabetes. 2008;57(Suppl 1):A161.

345. Williams-Herman D, Xu L. Initial combination therapy with sitagliptin, a selective DPP-4 inhibitor, and metformin leads to marked improvement in beta-cell function in patients with type 2 diabetes. Diabetes. 2007;56(Suppl 1):A142.

346. Wintle ME, Nielsen L, Guan X, Holcombe JH, Maggs DG. Exenatide reduced weight and decreased elevated hepatic alanine transaminase (ALT) in patients with Type 2 diabetes: 82-week interim analysis. Gastroenterology. 2006;130(4 Suppl 2):A822.

347. Wolffenbuttel BHR, Buse J, Herman WH, Jiang H, Fahrbach J, Palaisa M, et al. The DURABLE trial 24-week results: Safety and efficacy of insulin lispro mix 25 vs. insulin glargine added to oral antihyperglycaemic agents (OHAs) in patients with type 2 diabetes (T2D). Diabetologia. 2008;51(Suppl 1):S386.

348. Wu E, Pandya BJ, Yu A, Chen K, Seale J, Kaltenboeck A, et al. Comparative glycemic goal achievement among type 2 diabetes mellitus patients treated with oral antidiabetic monotherapies. Diabetes. 2008;57(Suppl 1):A136.

349. Zinman B, Hoogwerf B, Garcia SD, Milton D, Giaconia J, Kim D, et al. Safety and efficacy of exenatide over 16 weeks in patients with type 2 diabetes mellitus using a thiazolidinedione with or without metformin. Diabetologia. 2006;49(Suppl 1):475-6.

350. Zinman B, Hoogwerf B, Garcia SD, Milton D, Giaconia J, Kim D, et al. Safety and efficacy of exenatide in patients with type 2 diabetes mellitus using thiazolidenediones with or without metformin. Diabetes. 2006;55(Suppl 1):A28.

351. Tankova T, Koev D, Dakovska L, Kirilov G. The effect of repaglinide on insulin secretion and oxidative stress in type 2 diabetic patients. Diabetes Res Clin Pract. 2003 Jan;59(1):43-9.

352. Ligthelm RJ. Self-titration of biphasic insulin aspart 30/70 improves glycaemic control and allows easy intensification in a Dutch clinical practice. Prim Care Diabetes. 2009 Mar 12;3(2):97-102.

353. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2007 Nov 22];7:10. Available from: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1810543&blobtype=pdf

354. Belsey J, Krishnarajah G. Glycaemic control and adverse events in patients with type 2 diabetes treated with metformin + sulphonylurea: a meta-analysis. Diabetes, Obesity & Metabolism. 2008 Jun;10(Suppl 1):1-7.

355. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2004;(4):CD003418.

356. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd. ed. Ottawa: The Agency; 2006. [cited 2007 Feb 9]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

357. Harris SB, Ekoe JM, Zdanowicz Y, Webster-Bogaert S. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes Res Clin Pract. 2005 Oct;70(1):90-7.

358. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care. 2005 Jul;43(7):736-49.

359. Canadian Agency for Drugs and Technologies in Health. An economic evaluation of insulin analogues for the treatment of patients with type 1 and type 2 diabetes mellitus in Canada [Internet]. Ottawa: The Agency; 2008. (Optimal therapy report; vol. 2 no. 4). [cited 2008 Apr 11]. Available from: http://cadth.ca/media/compus/reports/compus_Economic_IA_Report.pdf

360. Agency for Healthcare Research and Quality [Internet]. Rockville (MD): Agency for Healthcare Research and Quality. Calculating the U.S. population-based EQ-5D index score; 2005 [cited 2007 Oct 10]. Available from: http://www.ahrq.gov/rice/EQ5Dscore.htm

361. Ahern J, Tamborlane WV. Steps to reduce the risks of severe hypoglycemia. Diabetes Spectr [Internet]. 1997 [cited 2008 Jan 18];10(1):39-41. Available from: http://journal.diabetes.org/diabetesspectrum/97v10n01/pg39.htm

362. O'Reilly D, Hopkins R, Blackhouse G, Clarke P, Hux J, Guan J, et al. Development of an Ontario Diabetes Economic Model (ODEM) and application to a multidisciplinary primary care diabetes management program [Internet]. Hamilton (ON): Program for Assessment of Technology in Health (PATH); 2006. 120 p. [cited 2007 Jul 12]. Available from: http://www.path-hta.ca/diabetes.pdf

363. Health costing in Alberta: 2006 annual report [Internet]. Edmonton: Alberta Health and Wellness; 2006 Jul. 323 p. [cited 2007 Feb 14]. Available from: http://www.health.alberta.ca/documents/Case-Cost-Hospital-04-05.pdf

364. Nathan DMB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia [Internet]. 2006 [cited 2010 May 17];49(8):1711-21. Available from: http://www.springerlink.com/content/24j1675h2p72636v/fulltext.pdf

365. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2003;27(Suppl 2):i-S140.

366. Metformin [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

367. Antidiabetics. In: Sweetman SC, editor. Martindale: the complete drug reference. Chicago (IL): Pharmaceutical Press; 2007. p. 390-421.

368. Metformin: drug information. Version 17.1. In: UpToDate [Internet]. Waltham (MA): UpToDate, Inc; 2009 [cited 2010 May 17]. Available from: https://www.uptodate.com/home/store.do.

369. Canadian Pharmacists Association. e-CPS: Compendium of pharmaceuticals and specialties [database on the Internet]. Ottawa: The Association; c2007 - [cited 2010 Mar 22]. Available from: www.e-therapeutics.ca/ Subscription required.

370. Chlorpropramide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

371. Gliclazide: drug information. Version 17.1. In: UpToDate [Internet]. Waltham (MA): UpToDate, Inc; 2009.

372. Tolbutamide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

373. Glipizide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

374. Gylburide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

375. Glimeprimide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

376. Levetan C. Oral antidiabetic agents in type 2 diabetes. Curr Med Res Opin. 2007;23(4):945-52.

377. Pioglitazone [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

378. Rosiglitazone [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

379. Repaglinide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

380. Nateglinide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

381. Acarbose [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

382. Alpha-glucosidase inhibitors [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

383. Sitagliptin: drug information. Version 17.1. In: UpToDate [Internet]. Waltham (MA): UpToDate, Inc; 2009 [cited 2010 May 17]. Available from: https://www.uptodate.com/home/store.do Subscription required.

384. Exenatide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

385. Galvus 50 mg tablets [Internet]. In: The electronic Medicines Compendium (eMC). Frimley (UK): Novatris Pharmaceuticals; 2009 [cited 2009 Jun 30]. Available from: http://emc.medicines.org.uk/medicine/20734/SPC/Galvus+50+mg+Tablets/.