Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Therapeutic Review

Clinical Review: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea

August 2010

Supporting Informed Decisions

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ABBREVIATIONS

A1C	glycosylated hemoglobin
BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CI	confidence interval
CrI	credible interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DPP-4	dipeptidyl peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FBG	fasting blood glucose
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
MTC	mixed treatment comparison
NPH	neutral protamine Hagedorn
RCT	randomized controlled trial
SE	standard error
TZD	thiazolidinediones
WDAE	withdrawals due to adverse events

EXECUTIVE SUMMARY

Background

Type 2 diabetes mellitus is a chronic, metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[1] 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. Following a detailed review of the clinical and cost-effectiveness of second-line agents for diabetes,[2] CADTH has recently issued a draft optimal therapy recommendation stating that sulfonylureas should be used as second-line therapy for most patients inadequately controlled on metformin alone.[3]

Eight classes of antidiabetes drugs are available as third-line therapy for patients with type 2 diabetes inadequately controlled on combination therapy with metformin and sulfonylureas: meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, basal insulins, bolus insulins, and biphasic insulins. A majority of guidelines[4-7] recommend that insulin should be started as a third-line agent for most patients; however, other guidelines recommend either insulin or an additional oral antidiabetes drug.[8,9] Given the increasing prevalence of type 2 diabetes, there is a need to evaluate the evidence related to the clinical and cost-effectiveness of third-line drugs in order to facilitate their optimal use.

Primary Research Question

What is the comparative efficacy and safety of third-line antidiabetes drugs in children and adults with type 2 diabetes mellitus treated with a combination of metformin and sulfonylureas who require additional or alternative glucose-lowering therapy due to inadequate glycemic control on existing therapy or intolerable adverse effects/contraindications to metformin and/or sulfonylureas?

Methods

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English language clinical articles published from 1980 to November 2009. Monthly Ovid AutoAlerts were reviewed from December to January 2009. Active and non-active randomized controlled trials (RCTs) published in English were included if they were at least four weeks in duration, and compared one or more relevant drugs in patients inadequately controlled or intolerant to the combination of metfromin and a sulfonylurea.

The relative effectiveness and safety of third-line agents was assessed according to the following outcomes: glycosylated hemoglobin (A1C), hypoglycemia (overall, severe, and nocturnal), body weight and body mass index (BMI), patient satisfaction, health-related quality of life (HRQoL), long-term diabetes-related complications (e.g., myocardial infarction), withdrawals due to adverse events, and serious or severe adverse events. We conducted mixed treatment comparisons (MTCs) and pairwise meta-analyses for A1C and body weight. The MTC primary analysis was restricted to RCTs using interventions added onto metformin and a sulfonylurea. A secondary MTC analysis was conducted using all treatment strategies from studies considered to be sufficiently homogenous to pool. Large variation in control group (i.e., metformin plus sulfonylurea) event rates and a lack of consistent definitions across RCTs prevented MTC analysis for overall hypoglycemia; therefore, only pairwise comparisons were performed for this outcome. Study level detail is presented for the remaining outcomes for one or more of the following reasons: limited number of available studies, small number of events, and/or clinical/methodological heterogeneity between studies. Due to the sparsity of evidence, conventional insulins were pooled with insulin analogues into groupings based on time-action profile (i.e., basal insulins, biphasic insulins, and bolus insulins).

Results

The systematic review of third-line antidiabetes drugs included 33 unique RCTs (reported in 36 full-text articles).[10-45] We identified evidence for the following eight drug classes: alpha-glucosidase inhibitors (four RCTs),[19,21,28,37] meglitinides (one RCT),[28] TZDs (nine RCTs),[10,17,20,22,27,29,30,38,46] DPP-4 inhibitors (one RCT),[41] GLP-1 analogues (six RCTs),[14,15,25,34,35,40] basal insulin (18 RCTs),[10-12,17,21,23,24,26,29,30,35,36,38-40,43,45,46] bolus insulin (one RCT),[43] and biphasic insulin (12 RCTs).[11,12,14,16,23-25,27,36,39,43,45] The evidence within these eight drug classes was further stratified based upon the following three scenarios:

- addition of a third-line agent while continuing metformin and sulfonylurea
- treatment with a third-line agent upon discontinuation of metformin or sulfonylurea (but not both)
- treatment with a third-line agent upon discontinuation of both metformin and sulfonylurea (e.g., insulin monotherapy).

The first scenario was the most common amongst the included RCTs, with 26 RCTs reporting comparisons of interventions added onto existing metformin and sulfonylurea therapy.[10,12,14,15,17,19-22,25-32,34-38,40,41,43,45]

Results for key outcomes are subsequently presented.

Long-term complications of diabetes:

- There were no adequately powered RCTs evaluating the comparative efficacy of any class of third-line antidiabetes drug for reducing clinically important long-term complications of diabetes. Longer-term studies with larger sample sizes are required to determine if any of the agents have an advantage over another in limiting diabetes-related complications.

Hemoglobin A1C:

- Compared with metformin and a sulfonylurea alone, basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, TZDs, or bolus insulin combined with metformin and a sulfonylurea produced statistically significant reductions in A1C (range: -0.9% to -1.2%), but meglitinides and alpha-glucosidase inhibitors did not. Biphasic insulin was also effective in reducing A1C (-1.9%) when given in combination with metformin alone (i.e., patients ceased taking sulfonylureas).
- There were no statistically significant differences in A1C reductions between basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, TZDs, and bolus insulin.
- The amount and quality of evidence was insufficient to draw conclusions regarding the relative efficacy of the add-on, partial-switch, and switch regimens in the initiation of insulin.

Body weight:

- When added to metformin and sulfonylurea therapy, treatment with basal insulin, biphasic insulin, bolus insulin, and TZDs was associated with statistically significantly greater increases in body weight than treatment with metformin and sulfonylurea alone. DPP-4 inhibitors, and alpha-glucosidase inhibitors were not associated with significant weight gain, and GLP-1 analogues were associated with statistically significant weight loss.

Hypoglycemia:

- TZDs, GLP-1 analogues, DPP-4 inhibitors, and basal insulin were associated with a significantly greater risk of overall hypoglycemia than placebo when given in combination with metformin and a sulfonylurea.
- The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators.
- Biphasic and bolus insulins were associated with a significantly greater risk of overall hypoglycemia than basal insulin.
- Events of severe and nocturnal hypoglycemia were relatively rare for all drug classes, limiting the ability to make meaningful comparisons between drug classes.

Withdrawals due to adverse events:

- GLP-1 analogues were associated with a higher incidence of withdrawals because of adverse events than placebo, basal insulin, and biphasic insulin. Nausea and vomiting were cited as the primary reasons for these withdrawals

Severe adverse events:

- Low event rates and a lack of consistent reporting prevented meaningful comparisons regarding the occurrence of serious or severe adverse events in the included RCTs.

Strengths of the Review

- Evidence has been presented in three different formats based on differing levels of aggregation:
  - MTC meta-analysis
  - direct pairwise meta-analysis
  - individual study-level results.
- Direct evidence was available for many comparisons including five of the eight possible comparisons against placebo. The good alignment between direct and indirect estimates in most comparisons supports the validity of the MTC meta-analysis results.
- Robustness of the results was demonstrated with extensive sensitivity analyses and meta-regression.
- Alternative modelling was used to ensure that pooling of trials reflected differences between trials in the concomitant use of metformin and sulfonylurea (i.e., primary analysis of add-on therapies only versus secondary analysis of all treatment strategies).

Limitations of the Review

- There were limited data for clinically relevant complications of diabetes.
- The primary methodological limitations of the included RCTs were failure to report adequate methods for allocation concealment, and the use of analyses other than intention-to-treat.
- Key limitations with respect to external validity of trials included the relatively short duration of trials, small sample sizes, failure to report definitions for hypoglycemia and adverse events, blood glucose targets that were different from those suggested in the Canadian Diabetes Association Clinical Practice Guidelines, and a level of contact between trial subjects and health care professionals that likely exceeds routine clinical practice.
- There was between-study heterogeneity with regard to baseline A1C, duration of diabetes, reporting of metformin and sulfonylurea dosing at baseline, glycemic targets specified in the included RCTs, inclusion, and characteristics of run-in periods. However, through sensitivity analyses and meta-regression, the impact of these factors on MTC meta-analysis results was found to be limited.

Conclusions

There was insufficient evidence to evaluate the comparative efficacy of third-line antidiabetes drugs in reducing clinically important long-term complications of diabetes. Compared with continued treatment with metformin and sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, TZDs, and bolus insulin produced statistically significant reductions in A1C in combination with metformin and sulfonylureas, whereas meglitinides and alpha-glucosidase inhibitors did not. Basal insulin, biphasic insulin, bolus insulin, and TZDs all resulted in an increase in body weight, while DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues were not associated with significant weight gain. The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators. Given the similar efficacy in terms of glycemic control, a cost-effectiveness analysis is warranted to help define the place in therapy for the various drug classes, particularly newer agents. Rigourously conducted, longer-term studies with larger sample sizes are required to determine if any of the available drug classes are superior in reducing diabetes-related complications.

1 INTRODUCTION

Type 2 diabetes mellitus is a chronic, metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[1] When inadequately managed, diabetes is likely to result in poor glycemic control.[47] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, lower limb amputation).[48,49] The global prevalence of diabetes is estimated to be 177 million and is projected to increase to 300 million by 2025.[50] It is estimated that 1.9 million Canadian men and women 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.[51]

Treatment of patients with type 2 diabetes mellitus usually begins with lifestyle modification and oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes mellitus when glycemic control cannot be achieved by lifestyle interventions alone.[8,52-55] Recent utilization data indicate that the majority of patients with type 2 diabetes mellitus initiating pharmacotherapy in Canada are started on metformin.[56] As type 2 diabetes mellitus 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 insulin, to achieve or maintain target blood glucose levels.[57,58] 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. Following a detailed review of the clinical and cost-effectiveness of second-line agents for diabetes,[2] the Canadian Agency for Drugs and Technologies in Health (CADTH) has recently issued an optimal therapy recommendation stating that sulfonylureas should be used as second-line therapy for most patients inadequately controlled on metformin alone.[3]

Eight classes of antidiabetes drugs are available as third-line therapy for patients with type 2 diabetes inadequately controlled on combination therapy with metformin and sulfonylureas: meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, basal insulins, bolus insulins, and biphasic insulins (Table 1). A majority of guidelines[4-7] recommend that insulin should be started as a third-line agent for most patients; however, other guidelines recommend either insulin or an additional oral antidiabetes drug.[8,9] Given the increasing prevalence of type 2 diabetes, there is a need to evaluate the evidence related to the clinical and cost-effectiveness of third-line drugs in order to facilitate their optimal use.

A glossary of terms used in this report can be found in Appendix 1.

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Health Canada 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.[59,60]
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.[61]
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.[62]
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.[63]
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.[64]
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.[65]
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.[66]
Meglitinides			
Nateglinide	Range: 180-360 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.[67]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Health Canada Indications**
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.[68]
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.[69]
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 as an adjunct to diet and exercise in adult patients with type 2 diabetes and for whom metformin is inappropriate due to contraindications or intolerance; in combination with metformin in adult patients with type 2 diabetes to improve glycemic control when diet and exercise, plus metformin, do not provide adequate glycemic control; and in combination with metformin and a sulfonylurea in adult patients with type 2 diabetes to improve glycemic control when diet and exercise, and dual therapy with these drugs, do not provide adequate glycemic control.[70]
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 used alone, with diet and exercise, does not provide adequate glycemic control.[71]
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	Indicated in adults with type 2 diabetes to improve glycemic control in combination with metformin or metformin with a sulfonylurea, when, with diet and exercise, metformin or metformin and a sulfonylurea alone do not provide adequate glycemic control.[72]
Bolus insulin			
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.[73]
Insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with DM who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of DM.[74]
Insulin glulisine	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes where treatment with insulin is required.[75]
Regular human insulin	Dosage is individualized	SC	For the treatment of insulin-requiring diabetic patients.
Basal insulin			
Insulin NPH	Dosage is individualized	SC	For the treatment of insulin-requiring diabetic patients.

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Admin.**	**Relevant Health Canada Indications**
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.[76]
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.[77]
Insulin NPL	Dosage is individualized	SC	Not approved in Canada.
Biphasic 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 DM who require insulin for the maintenance of normal glucose homeostasis.[78]
Biphasic insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with DM who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of DM.[74]

Admin. = administration; DDD = defined daily dose (World Health Organization); DM = diabetes mellitus; DPP-4 = dipeptidy peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagadorn; NPL= neutral protamine lispro; OADs = oral antidiabetes drugs; SC = subcutaneous;; TZD = thiazolidinediones.

1.1 Mechanisms of Action for Antidiabetes Pharmacotherapy

Metformin, a biguanide antidiabetic, is the preferred first-line therapy for most patients with type 2 diabetes.[79,80] While its exact mode of action remains unclear,[81,82] metformin likely lowers both fasting and post-prandial glucose concentrations by:

- decreasing hepatic glucose production[81,83]
- improving insulin sensitivity, thereby enhancing insulin-stimulated uptake and utilization of glucose in peripheral tissues[81,83]
- decreasing intestinal absorption of glucose.[83]

Insulin secretion remains unchanged.[81,84] Hypoglycemia is not an issue, except possibly in cases of extreme overdose.[84] 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.[84]

1.1.1 Sulfonylureas

Sulfonylureas (gliclazide, glimepiride, glyburide, chlorpropramide, glipizide, tolbutamide) increase the post-prandial secretion of insulin from functional islet beta cells of the pancreas.[82] Reduced hepatic glucose production and increased peripheral sensitivity to insulin also contribute to hypoglycemic action during prolonged administration of sulfonylureas.[82,85] Initial dosages vary depending on the specific agent, and are usually conservative because of the risk of hypoglycemia, but can be titrated until adequate glycemic control is achieved.[84-90]

Thiazolidinediones (pioglitazone, rosiglitazone), or TZDs, are peroxisome proliferator-activated receptor-gamma agonists. They increase transcription of insulin-responsive genes, increasing insulin sensitivity in muscle, fat, and liver cells.[91] Hepatic gluconeogenesis is also decreased.[92,93] TZDs depend on the availability of insulin to be effective, but do not increase insulin secretion, nor do they cause hypoglycemia.[92,93] The initial dose of rosiglitazone is usually 4 mg daily, and can be increased to 8 mg after two to three months if response is inadequate. Pioglitazone is usually initiated at 15 mg or 30 mg daily, and can be gradually increased to 45 mg if response is inadequate.[92]

Meglitinide analogues (nateglinide, repaglinide) induce rapid and short-term insulin secretion from functional pancreatic beta cells.[91,94,95] Like sulfonylureas, meglitinide analogues can induce hypoglycemia, but may do so less frequently.[91,94,95] Repaglinide is usually initiated at 0.5 m to1 mg two to four times daily before meals, with a maximum daily dose of 16 mg.[84,94] Approximately 90% of maximal glucose-lowering effect is seen at 1 mg three times daily.[94] Nateglinide is usually initiated at 120 mg three times daily before meals, although patients who are already near their glycosylated haemoglobin (A1C) targets may be started at 60 mg three times daily.[95]

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.[96] Alpha-glucosidase inhibitors do not themselves cause hypoglycemia, but may exacerbate it in patients taking insulin or sulfonylureas.[84] 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.[84] 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.[97]

GLP-1 receptor agonists (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.[91,98] GLP-1 receptor agonists suppress inappropriate glucagon secretion and slow gastric emptying. These agents may also lead to weight loss.[82,98] 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.[98] 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 (sitagliptin, vildagliptin, saxagliptin) decrease the ability of DPP-4 to degrade GLP-1, leading to lower fasting and post-prandial glucose concentrations.[84,91] The usual dosage of sitagliptin is 100 mg once daily[84,99] and the usual dosage of saxagliptin is 5 mg once daily.[71] 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.[100]

2 OBJECTIVE(S) AND METHODS

2.1 Primary Clinical Research Questions

2.1.1 Research question

What is the comparative efficacy and safety of third-line antidiabetes drugs in children and adults with type 2 diabetes mellitus treated with a combination of metformin and a sulfonylurea who:

- require additional or alternative glucose-lowering therapy because of inadequate glycemic control on existing therapy (i.e., A1C > 6.5% or fasting plasma glucose [FPG] > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)?
- require a switch to another glucose-lowering agent because of inadequate glycemic control on existing therapy (i.e., A1C > 6.5% or FPG > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)?
- require a switch to another glucose-lowering agent because of intolerable adverse effects or the development of contraindications to metformin and/or sulfonylureas?

2.2 Methods

See Appendix 2 for detailed study protocol.

2.2.1 Overview of methods

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, BIOSIS Previews, PubMed, and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English language clinical articles published from 1980 to November 2009. Monthly OVID AutoAlerts were reviewed from December to January 2009. See Appendix 3 for detailed literature search strategy.

The population of interest consisted of adults with type 2 diabetes requiring additional or alternative antihyperglycemic therapy due to inadequate control (A1C > 6.5%, FPG > 7 mmol/L, or 2-hour PPG > 10 mmol/L) on, or intolerance to, metformin and sulfonylurea combination therapy. We included agents from drug classes which had approval from Health Canada, the Food and Drug Administration, or the European Medicines Agency as of December 2009: meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, insulins/insulin analogues, and alpha-glucosidase inhibitors. Active and non-active randomized controlled trials (RCTs) published in English were included if they were at least four weeks in duration and compared one or more relevant drugs in any of the following scenarios:

- addition of a third agent while continuing metformin and sulfonylurea combination therapy (add-on therapy)
- initiation of third-line therapy upon discontinuation of metformin or sulfonylurea (partial switch)
- initiation of third-line therapy upon discontinuation of both metformin and sulfonylurea (full switch).

We included studies regardless of metformin and sulfonylurea dosage at baseline, or treatment history prior to metformin and sulfonylurea combination therapy. See Appendix 4 for QUORUM diagram, and Appendix 5 for a listing of included and excluded studies.

Outcomes of interest included A1C, hypoglycemia, body weight, quality of life, long-term complications of diabetes, withdrawals due to adverse events, and severe adverse events.
Bayesian mixed treatment comparison (MTC) meta-analysis and frequentist pairwise meta-analysis was performed where appropriate. This review used a random-effects model for the reference case of all pairwise and MTC meta-analyses, as there was a degree of heterogeneity across studies in trial duration, dosing of agents, baseline characteristics, and treatment history of the included patients. MTC and pairwise meta-analyses were conducted for A1C and body weight. The MTC primary analysis was restricted to RCTs in which third-line agents were added on to metformin and sulfonylureas. A secondary MTC analysis was conducted using all treatment strategies from studies considered to be sufficiently

homogenous to pool. Large variation in control group (i.e., metformin plus sulfonylurea) event rates and a lack of consistency in definitions across individual RCTs prevented MTC analysis for overall hypoglycemia; therefore, only pairwise comparisons were performed for this outcome. Only study level detail is presented for the remaining outcomes for one or more of the following reasons: limited number of available studies, small number of events, and/or clinical/methodological heterogeneity between studies. In the case of severe hypoglycemia and severe/serious adverse events, MTC meta-analyses could not be conducted due to the zero event rates observed in the majority of studies.

2.2.2 Handling of trial heterogeneity in MTC analysis

Both MTC and traditional meta-analysis require studies to be sufficiently similar in order to pool their results. A wide range of patient and trial characteristics were assessed to ensure similarity and/or investigate potential implications of heterogeneity across the 33 included RCTs. We identified a number of areas where there was clinical and methodological heterogeneity. The issues identified were similar to what has been reported in previous systematic reviews of antidiabetes drugs (e.g., differences in baseline hemoglobin A1C).[2,101,102] In most cases, we attempted to explore the possible effects of heterogeneity through the use of sensitivity analyses and meta-regression.

Table 2: Approach to Addressing Key Areas of Clinical and Methodological Heterogeneity

Issue	Description of Heterogeneity	Action
Duration of diabetes	Trials varied in duration of diabetes at baseline (range: 3.5 years to 12.7 years).	• Meta-regression
Baseline A1C	Trials varied in mean A1C at baseline (range: 8.1% to11.3%).	• Meta-regression • Sensitivity analysis with removal of studies specifying an A1C threshold < 7.0% for inclusion
Trial duration	Variability in trial duration (range: 3 months to 12 months; typical: 6 months).	• Meta-regression • Sensitivity analysis with removal of studies less than one year
Sulfonylurea dose at baseline	Trials varied in thresholds and reporting of sulfonylurea dosage at baseline.	• Sensitivity analysis with removal of studies failing report dosage at baseline
Concomitant use of metformin and sulfonylureas	Included RCTs used three distinct treatment scenarios in the included RCTs: • addition of a third-line agent while continuing metformin and sulfonylurea • initiation of a third-line agent upon discontinuation of metformin or sulfonylurea (but not both) • initiation of treatment with a third-line agent upon discontinuation of both metformin and sulfonylurea	• To maximize similarity across trials, only trials of add-on therapies were pooled in the primary MTC analysis • A secondary MTC analysis was conducted by pooling all treatment strategies (i.e., add-on, partial switch, and switch) deemed sufficiently similar
Previous treatment history	There was heterogeneity in reporting the previous treatment history of patients.	• Based on clinical opinion, the duration of diabetes was considered of greater importance in predicting treatment efficacy than prior pharmacotherapy, hence pooling was considered appropriate.
Crossover studies	Three crossover studies were included in the systematic review and meta-analyses	• Sensitivity analysis with removal of cross-over studies
Baseline body mass index	There was some heterogeneity in the baseline body mass index of patients	• Meta-regression for analysis of body weight

A1C = glycosylated hemoglobin; MTC = mixed treatment comparison; RCT = randomized controlled trial.

2.3 Supplemental research questions

Additional questions related to second- and third-line therapy for patients with type 2 diabetes were identified as being of interest by jurisdictions, expert committee members, and other experts:

1. What is the validity of A1C as a surrogate outcome for clinically important complications of diabetes (see Appendix 6)?
2. What do clinical practice guidelines recommend for second- and third-line therapy of type 2 diabetes (see Appendix 7)?
3. What constitutes an adequate trial of first- and second-line therapy (i.e., metformin and sulfonylureas) before the decision to increase doses, or to add or switch to other agents is made (see Appendix 8)?
4. What is the evidence regarding the safety and efficacy of high doses of metformin versus addition of second-line agents after inadequate control on low to moderate doses of metformin monotherapy (see Appendix 9)?
5. What is the evidence related to the safety and efficacy of increased doses of first- and second-line therapy (i.e., metformin and/or sulfonylureas) versus addition or switch to a third-line agent (see Appendix 10)?

2.3.1 Methods

The approach for all supplemental questions consisted of a specific literature search, a narrative summary of the data, and a critical appraisal of the available evidence.

3 RESULTS

3.1 Summary of Included Studies

Patient and study characteristics of the included trials are summarized in Table 3. For further details, see Appendices 11, 12, and 13.

Table 3: Characteristics of Included Studies

Author, Year	Interventions/Comparators	Randomized Sample Size	Avg. Age (years)	% Male	Avg. Duration of DM (years)	Avg. A1C (%)	Combination Therapy at Baseline		Duration of Stable Therapy (months)
							Metformin Dosage	Sulfonylurea Dosage	
Aljabri et al., 2004[10]	• Pioglitazone (30mg/day to 45 mg/day) + Met + SU • NPH insulin (titrated to FG < 6.0 mmol/L) + Met + SU	62	58.0	60.3	10.0	9.9	2050 mg/day ± 490 mg/day 2210 mg/day ± 504 mg/day	Glyburide (20 mg/day)	≥ 3
Al-Shaikh, 2006[12]	• Insulin glargine (h.s., started at 14 IU/d, titrated by 8 IU/d if FBG > 11 mmol/L and 4 IU/d if FBG > 7.8 but < 11 mmol/L) + Met + SU • Biphasic 30/70 human insulin, 2/3 dose in morning and 1/3 dose in evening (started at 1 IU/kg/day, morning dose titrated up 4 IU/week if FBG > 11 mmol/L, evening dose if FBG > 7.8 mmol/L)	221	56.3	56.1	*NR*	11.3	Max. tolerated dose	Max. tolerated dose	≥ 3
Bergenstal et al., 2009[14]	• BIAsp30 (QD, 12 IU q.d., titrated to BG 5.0-6.1 mmol/L) + Met + SU • BIAsp30 (b.i.d., 6 IU b.i.d., titrated to BG 5.0-6.1 mmol/L) + Met • Exenatide (10 μg b.i.d.) + Met + SU	372	52.6	48.4	9.0	10.2	> 1,500 mg/day	half max. dose	3

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
Berhanu et al., 2007[16]	• Insulin (Humulin N, Humalog, or Humulin 30/70 titrated to FPG < 7.8 mmol/L) + pioglitazone (45 mg/day) + Met • Insulin (Humulin N, Humalog, or Humulin 30/70 titrated to FPG < 7.8 mmol/L) + Placebo + Met	222	52.7	42.3	NR	8.5	≥ 2,000 mg/day	> 50% max. dose	≤3
Boye et al., 2006[18] Companion[40]	• Exenatide () + SU + Met • Insulin glargine (h.s.) + SU + Met	NR	58.5	55.2	9.5 ± 5.7	8.3 ± 1.0	NR	NR	NR
Charpentier and Halimi, 2009[20]	• Pioglitazone (30 mg/day to 45 mg/day) + Met + SU • Placebo + Met + SU	299	59.7	75.4	12.3	8.1	2,584 mg/day (mean)	Glyburide (15.1 mg, n = 105); glimepiride (5.2 mg, n = 97); gliclazide (146 mg, n = 91); glipizide (20 mg, n= 2); carbutamide (1,000 mg, n = 1)	≥ 3
Dailey et al., 2004[22]	• Rosiglitazone (4 mg to 8 mg) + Met + SU • Placebo + Met + SU	365	57.0	59.5	9.0	8.1	NR	NR	≥ 2
Davies et al., 2007[24]	• Biphasic 30/70 human insulin (b.i.d., average dose 0.63 ± 0.32 IU/kg) + Met • NPH Insulin (h.s., average dose 0.58 ± 0.21 IU/kg) + Met • NPH insulin (h.s., average dose 0.37 ± 0.22 IU/kg) + repaglinide (a.c., 1.5 mg to 12 mg) + Met	82	57.2	43.9	8.7	9.7	Max. tolerated dose	NR	NR

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
De Mattia et al., 2009[26]	• Insulin glargine (starting 10 IU/day, algorithmic titration to FBG < 5.5 mmol/L) + Met + SU • NPH Insulin (starting 10 IU/day, algorithmic titration to FBG < 5.5 mmol/L) + Met + SU	20	59.4	70.0	≥ 5	9.3 ± 1.4	800 mg/day to1,200 mg/day	Glyburide: 5 mg/day to 7.5 mg/day	3
Derosa et al., 2009[28]	• Acarbose (100 mg t.i.d.) + Met + SU • Rapaglinide (6 mg/day) + Met + SU	103	54.0	49.5	3.5	8.1	NR	NR	NR
Dorkhan et al., 2009[30]	• Pioglitazone (up to 45 mg/day) + Met + SU • Insulin glargine (titrated to FPG < 6 mmol/L) + Met + SU	30	61.2	66.7	10.3	8.2	NR	NR	NR
Esposito et al., 2008[32]	• NPL insulin (h.s., started at 10 IU/day and titrated to FPG < 5.6 mmol/L) + Met + SU • Insulin glargine (h.s., started at 10 IU/day and titrated to FPG < 5.6 mmol/L) + Met + SU	116	54.4	51.8	8.2	8.8	NR	NR	≥ 3
Gao et al., 2009[34]	• Exenatide (10 µg b.i.d.) + Met + SU • Placebo (b.i.d.) + Met + SU	472	54.5	44.4	8.0	8.3	1,000 mg to 3,000 mg	NR	≥ 3

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
Goudswaard et al., 2004[36]	• NPH insulin (h.s., starting dose 8 IU, titrated to FBG 4.0 mmol/L to7.0 mmol/L and postprandial BG 4.0 mmol/L to10.0 mmol/L) + Met + SU • Biphasic insulin (70/30) (b.i.d., starting dose 12 IU before breakfast and 6 IU before dinner, titrated to FBG 4.0 mmol/L to 7.0 mmol/L and postprandial BG 4.0 mmol/L to10.0 mmol/L)	69	58.5	48.4	7.4	8.5	*NR*	*NR*	*NR*
Hartemann-Heurtier et al., 2009[38]	• Pioglitazone (30 mg/day) + Met + SU • NPH insulin (0.2 IU/kg/d, q.d.)+ Met + SU	28	60.1	59.3	12.0	8.4	Max. tolerated dose	Max. tolerated dose	6
Heine et al., 2005[40]	• Exenatide (10 µg b.i.d.) + Met + SU • Insulin glargine (starting dose 10 IU/d, titrated in 2 IU increments every 3 days to FBG < 5.6 mmol/L) + Met + SU	551	58.9	61.1	9.6	8.2	NR	NR	≥ 3
Hermansen et al., 2007[41]	• Sitagliptin (100 mg/day) + Met + SU • Placebo + Met + SU	219	57.3	52.4	10.2	8.3	≥ 1,500 mg/day	Glimepiride ≥ 4 mg/d	2.5

Table 3: Characteristics of Included Studies								
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**	**Duration of Stable Therapy (months)**
							Metformin Dosage / **Sulfonylurea Dosage**	
Holman et al., 2007[43]	• Insulin aspart (t.i.d., median starting dose 18 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU • Insulin detemir (h.s. or b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU • Biphasic insulin aspart 30 (b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU	708	61.7	64.1	Median: 9.0	8.5 ± 0.8	Max. tolerated dose / Max. tolerated dose	≥ 4
Janka et al., 2005[11]	• Insulin glargine (titrated to 5.5 mmol/L) + Met + SU • 30/70 NPH (titrated to 5.5 mmol/L) + placebo	364	60.6	59.1	9.9	8.8	≥ 850 mg/day / Glimepiride: 3 mg/day to 4 mg/day	> 1
Janka et al., 2007[13] Subgroup[11]	• Insulin glargine (titrated to 5.5 mmol/L) + Met + SU • 30/70 NPH (titrated to 5.5 mmol/L) + placebo	130	69.4	56.1	11.6	8.9	≥ 850 mg/day / Glimepiride: 3-4 mg/day	≥ 1
Kendall et al., 2005[15]	• Exenatide (5 µg b.i.d.) + Met + SU • Exenatide (10 µg b.i.d.) + Met + SU • Placebo + Met + SU	734	55.3	58.1	8.9	8.5	NR / NR	≥ 3

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
Ko et al., 2006[17]	• Rosiglitazone (2 mg/day to 8 mg/day) + Met + SU • NPH Insulin (h.s., started at 6 IU, titrated to A1C < 7.5%) + Met + SU	112	58.2	50.0	12.7 ± 7.6	9.9 ± 1.0	2,400 ± 600 mg (significantly different between groups)	34% on glyburide (20 mg/day); 20% on glipizide (20 mg/day); 46% on gliclazide (320 mg/day)	≥ 6
Lam et al., 1998[19]	• Acarbose (150-300 mg/day) + Met + SU • Placebo + Met + SU	90	57.4	43.8	10.1	9.5	1,790 ± 750 (SD; acarbose) 1,790 ± 780 (SD; placebo)	Glyburide (10 mg b.i.d.) Gliclazide (160 mg b.i.d.)	≥ 6
Lopez-Alvarenga et al, 1999[21]	• Acarbose (100 mg TID) + Met + SU • Insulin NPH (starting dose 8 IU/day, titrated in 8 IU increments every 4 weeks to FPG < 7.7 mmol/L) + Met + SU • Placebo + Met + SU	37	52.6	27.6	10.1	11.3	1,200 mg/day	Chlorpropamide (500 mg/day)	≥ 3
Milicevic et al., 2009[23]	• Insulin NPH (h.s., average ending dose 21 ± 9.4 IU) + SU • Biphasic Insulin lispro 50/50 pre-breakfast, biphasic insulin lispro 25/75 pre-dinner (titrated, average ending dose 44.1 ± 19.9 IU)	135	57.4	31.9	9.1	9.7	NR	NR	≥ 1.5
Nauck et al., 2007[25]	• Exenatide (10 µg b.i.d.) + Met + SU • Biphasic insulin aspart 30/70 (titrated, average ending dose 24.4 ± 15.6 IU/day)	505	58.5	51.1	9.9	8.6	NR	NR	≥ 3

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
Ovalle et al., 2004[27]	• Rosiglitazone (8 mg/day) + Met + SU • Biphasic insulin 70/30 (starting dose 0.2 IU/kg, titrated to FBG < 6.7 mmol/L)	17	51.2	NR	7.6	8.8	NR	NR	NR
Reynolds et al., 2007[29]	• Rosiglitazone (4 mg/day to 8 mg/day) + Met + SU • Insulin glargine (h.s., started at 10 IU/d, increasing weekly in 2 IU to 4 IU increments to FBG < 6.7 mmol/L if no hypoglycemia) + Met + SU	40	NR	NR	NR	9.0	≥ half-max.	≥ half-max.	≥3
Rosenstock et al., 2006[31]	• Rosiglitazone (4 mg/day to 8 mg/day) + Met + SU • Insulin glargine (h.s., starting dose 10 IU, titrated to 5.5 mmol/L to 6.7 mmol/L if no severe hypoglycemia) + Met + SU	219	55.6	51.9	8.3	8.7	2,000 mg/day or max. tolerated dose	≥ 50% of the max. labelled dose	≥3
Ross et al., 2001[33]	• Insulin lispro + Insulin NPH • Human insulin + Insulin NPH	148	58.5	43.9	11.1	10.6	NR	NR	NR
Russell-Jones et al., 2009[35]	• Liraglutide (1.8 mg/day) + Met + SU • Insulin glargine (titrated, average dose 24 IU) + Met + SU • Placebo + Met + SU	581	57.5	56.6	9.4	8.3	2,000 mg/day	Glimepiride 4 mg/day	≥ 0.75
Standl et al., 2001[37]	• Miglitol (50 mg to 100 mg t.i.d.) + Met + glyburide • Placebo + Met + glyburide	154	61.5	52.6	Median: 8.0 and 9.0	8.8	NR	NR	≥ 6

Table 3: Characteristics of Included Studies									
Author, Year	**Interventions/Comparators**	**Randomized Sample Size**	**Avg. Age (years)**	**% Male**	**Avg. Duration of DM (years)**	**Avg. A1C (%)**	**Combination Therapy at Baseline**		**Duration of Stable Therapy (months)**
							Metformin Dosage	**Sulfonylurea Dosage**	
Stehouwer et al., 2003[39]	• NPH insulin (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5) + SU • NPH insulin (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4-10 mmol/L or A1C ≤ 6.5) • NPH insulin + 30/70 insulin NPH (titrated 2 IU/wk to 4 IU/wk until FPG 4-7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5)	261	57.9	50.2	7.9	9.4	1,000 mg/day	Glimepiride 6 mg/day	≥ 1
Strojek et al., 2009[45]	• Insulin glargine (titrated, average ending dose 0.29 IU/kg) + Met + SU • BIAsp30 (titrated, average ending dose 0.32 IU/kg) + Met + SU	480	56.0	43.9	9.3	8.5	2,550 mg/day	Glimepiride 4 mg/day to 8 mg/day	NR
Vinik and Zhang, 2007[42] Companion[31]	• Rosiglitazone (4 mg/day 8 mg/day) + Met + SU • Insulin glargine (h.s., starting dose 10 IU, titrated to 5.5 mmol/L to 6.7 mmol/L if no severe hypoglycemia) + Met + SU	219	55.6	51.9	8.3		2,000 mg/day or max. tolerated dose	≥ 50% of the max. labelled dose	≥ 3
Yki-Jarvinen et al., 2006[44]	• Insulin glargine + Met • NPH Insulin + Met	110	56.4	63.6	9	9.5	2.28 ± 0.06 2.19 ± 0.05	NR	0.75

A1C = glycosylated hemoglobin; a.c. = before meals; Avg = average; BG = blood glucose; BiAsp30 = biphasic insulin aspart (30/70); b.i.d.= twice daily; DM = diabetes mellitus; FG = fasting glucose; h.s.= at bedtime; max = maximum; Met = metformin; NPH = neutral protamine Hagedorn; NR = not reported; q.d.= once daily; SD = standard deviation; SU = sulfonylurea; t.i.d. = three times daily.

3.2 Trial Characteristics

The review included 33 unique RCTs (reported in 37 full-text articles) evaluating the effects of third-line agents in patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea[10-45,103] (see Table 4 and Appendix 12).

3.2.1 Treatments evaluated

Evidence was available for the following eight drug classes: alpha-glucosidase inhibitors (four RCTs),[19,21,28,37] meglitinides (one RCT),[28] TZDs (nine RCTs),[10,17,20,22,27,29,30,38,46] DPP-4 inhibitors (one RCT),[41] GLP-1 analogues (six RCTs),[14,15,25,34,35,40], basal insulin (18 RCTs[10-12,17,21,23,24,26,29,30,35,36,38-40,43,45,46]), bolus insulin (one RCT),[43] and biphasic insulin (12 RCTs).[11,12,14,16,23-25,27,36,39,43,45] (Sub-group data were extracted from two trials[34,41] that enrolled a mixture of patients requiring second- and third-line therapy.) A total of 17 distinct treatment strategies employing various combinations of third-line therapy with metformin and sulfonylurea were tested in the included studies. No studies compared third-line agents after discontinuation of metformin or sulfonylurea due to intolerance or contraindications.

3.2.2 Study design features

The vast majority of RCTs used a parallel design (n = 30)[10-20,22-25,27,29-44] and only three employed a crossover design.[21,26,28] RCTs conducted in a single country[10,12,14-17,19-22,24,26-33,36,38,42] were more common than multinational trials.[11,13,18,23,25,34,35,37,39-41,43,44] Randomized sample size ranged from 17[27] to 734.[15] Open-label trials (24/33) were more common than double-blind trials (9/33). 24 RCTs[10-12,14,16,17,23-33,36,38-40,43-45] compared two active treatments, seven RCTs[15,19,20,22,34,37,41] were placebo-controlled, and two RCTs[21,35] involved comparisons of active comparators as well as placebo.

3.2.3 Follow-up duration

The 33 included RCTs ranged from three to 12 months in duration, with six months being the most common length.

3.2.4 Funding

The majority of studies (81%) were sponsored by the pharmaceutical industry.

Table 4: Summary of Trial Characteristics

Trial Characteristics	Categories	Number (%) of Included Studies
Publication status	Full texts	36[10-45]
	Unique RCTs	33[10,12-17,19-41,43-45]
Country	Multinational	12[11,23,25,34,35,37,39-41,43-45]
	Single country	21[10,12,14-17,19-22,24,26-33,36,38]
Study design	Parallel RCTs	30[10-12,14-17,19,20,22-25,27,29-41,43-45]
	Crossover RCTs	3[21,26,28]
Sponsors	Industry	27[10,11,14,16,19-27,29-31,33-35,37-41,43-45]
	Public funding	3[17,28,32]
	Not reported	3[12,15,36]
Intervention comparison	Head to head	24[10-12,14,16,17,23-33,36,38-40,43-45]
	Placebo control	7[15,19,20,22,34,37,41]
	Both	2[21,35]
Publication year		Range: 1998[19] to 2009[14,20,23,26,28,30,33-35,38,45]
Randomized sample size		Range: 17[27] to 734[15]
Trial duration of study treatment (months)		Range 3[21,26] to 12[25,36,43]

RCTs = randomized controlled trials.

3.3 Populations

The 33 unique RCTs included in this review randomized a total of 8,148 adult patients; there were no studies involving children (< 18 years of age). Trial-level inclusion and exclusion criteria can be found in Appendix 13. The mean duration of diabetes at baseline ranged from 3.5 years[28] to 12.7 years.[17] The mean baseline A1C of trial subjects ranged from 8.1%[20,22,28] to 11.3%.[12,21] Regarding gender, the percentage of males ranged from 27.6%[21] to 75.4%.[20] The mean age of participants at baseline ranged from 51.2 years[27] to 69.4 years[13] (Table 5).

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%[28,39] or as high as 12%.[29] There was a lack of consistent reporting regarding the duration and dosage of stable metformin and sulfonylurea therapy prior to the study. Nearly half of all studies failed to report mean doses at enrollment or baseline. Only three RCTs[12,38,43] specifically stated that patients had to be receiving maximally tolerated doses of both sulfonylureas and metformin. RCTs typically specified a threshold in the inclusion criteria regarding the minimum duration of stable combination therapy. A minimum of three months was the most common criteria, and only six RCTs specified a lower threshold.[22,23,35,41,44,104]

There was insufficient evidence to conduct the subgroup analyses specified in the project protocol (e.g., First Nations people, other ethnic minorities). One included RCT[13] comparing insulin glargine with biphasic insulin reported the results of a subgroup analysis of patients ≥ 65 years old.

Table 5: Summary of Patient Characteristics

Patient Characteristics	Range Across All Included Studies
Mean age (years)	51.2[27] to 69.4[13]
Gender (% male)	27.6[21] to 75.4[20]
Mean duration of diabetes (years)	3.5[28] to 12.7[28]
Mean A1C at baseline (%)	8.1[20,22,28] to 11.3[12,21]

A1C = hemoglobin A1C.

3.4 Interventions

Table 6 summarizes the treatment comparisons reported in the 33 included studies. Eight RCTs[15,19,20,22,34,35,37,41] included a treatment arm where a placebo was added to ongoing metformin and sulfonylurea treatment. The remaining studies all compared active treatments. Titrated dosing of interventions (61/73) was more common than fixed dosing (12/73) among the active treatment arms.

The 17 treatment strategies tested in the included RCTs were stratified into the following three categories:

- addition of a third-line agent while continuing metformin and sulfonylurea
- initiation of a third-line agent upon discontinuation of metformin or sulfonylurea (but not both)
- initiation of treatment with a third-line agent upon discontinuation of both metformin and sulfonylurea (e.g., insulin monotherapy).

The first scenario was the most common, with 26 RCTs reporting comparisons of interventions added onto existing metformin and sulfonylurea therapy.[10,12,14,15,17,19-22,25-32,34-38,40,41,43,45] In three RCTs, patients discontinued sulfonylurea treatment and added one of several insulin regimens to ongoing metformin therapy.[16,24,44] One of these RCTs[16] had a unique design whereby all patients received basal insulin and were randomized to receive pioglitazone or placebo. One RCT (reported in two articles[11,13]) compared patients randomized to receive a basal insulin while continuing to receive metformin and sulfonylurea against patients who received a biphasic insulin regimen and discontinued both oral antidiabetes drugs. Three RCTs[23,33,39] compared patients switching to monotherapy with biphasic insulin, or basal insulin against patients commencing treatment with a basal insulin while continuing to receive sulfonylureas.

CADTH recently conducted a systematic review and meta-analysis comparing insulin analogues with conventional insulins. That review included 68 RCTs in the analysis of rapid-acting insulin analogues[105] and 49 RCTs for long-acting insulin analogues.[106] The conclusions of this review were that rapid- and long-acting insulin analogues were not substantially different from conventional insulins in terms of glycemic control or reduced hypoglycemia. For these reasons, and due to the sparsity of data, conventional insulins were pooled with insulin analogues according to their time-action profiles (i.e., basal insulins, biphasic insulins, or bolus insulins).

Table 6: Summary of Available RCT Comparisons														
	Add-On								**Partial Switch**			**Switch**		
	Placebo + Met + SU	**Basal + Met + SU**	**Biphasic + Met + SU**	**TZD + Met + SU**	**AGI + Met + SU**	**GLP-1 + Met + SU**	**Bolus + Met + SU**	**Repaglinide + Met + SU**	**Basal insulin + Met**	**NPH + Repaglinide + Met**	**Placebo + Insulin + Met**	**Basal insulin**	**Biphasic Insulin**	**Basal + Bolus insulin**
Basal + Met + SU	Russell-Jones et al.,[35] Lopez-Alvarenga et al.[21]	De Mattia et al.,[26] Esposito et al.[32]	Strojek et al.,[45] Holman et al.[43]	*	Lopez-Alvarenga et al.[21]	Boye et al.,[18] Heine et al.,[40] Russell-Jones et al.[35]	Holman et al.[43]						Janka et al.,[11,13] Al-Shaikh,[12] Goudswaard et al.[36]	
Biphasic + Met + SU		Strojek et al.,[45] Holman et al.[43]		Ovalle and Bell[27]		Bergenstal et al.,[14] Nauck et al.[25]	Holman et al.[43]							
TZD + Met + SU	Dailey et al.,[22] Charpentier and Halimi[20]	*	Ovalle and Bell[27]											
DPP-4 + Met + SU	Hermansen et al.[41]													
AGI + Met + SU	Lam et al.,[19] Standl et al.,[37] Lopez-Alvarenga et al.[21]	Lopez-Alvarenga et al.[21]						Derosa et al.[28]						
GLP-1 + Met + SU	Gao et al.,[34] Kendall et al.,[15] Russell-Jones et al.[35]	Boye et al.,[18] Heine et al.,[40] Russell-Jones et al.[35]	Bergenstal et al.,[14] Nauck et al.[25]											
Basal insulin + Met									Yki-Jarvinen et al.[44]	Davies et al.[24]				
Biphasic insulin + Met			Bergenstal et al.[14]			Bergenstal et al.[14]			Davies et al.[24]	Davies et al.[24]				
Basal insulin + SU												Stehouwer et al.[39]	Stehouwer et al.,[39] Milicevic et	

Table 6: Summary of Available RCT Comparisons														
	Add-On								**Partial Switch**			**Switch**		
	Placebo + Met + SU	**Basal + Met + SU**	**Biphasic + Met + SU**	**TZD + Met + SU**	**AGI + Met + SU**	**GLP-1 + Met + SU**	**Bolus + Met + SU**	**Repaglinide + Met + SU**	**Basal insulin + Met**	**NPH + Repaglinide + Met**	**Placebo + Insulin + Met**	**Basal insulin**	**Biphasic Insulin**	**Basal + Bolus insulin**
													al.[23]	
Insulin + TZD + Met											Berhanu et al.[16]			
Basal insulin													Stehouwer et al.[39]	
Biphasic Insulin		Janka et al.,[11,13] Al-Shaikh,[12] Goudswaard et al.[36]												
Basal + Bolus insulin														Ross et al.[33]

AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZD = thiazolidinediones.
*Six RCTs reported this comparison: Rosenstock et al.,[31,42] Reynolds et al.,[29] Dorkhan et al.,[30] Aljabri et al.,[10] Ko et al.,[17] Hartemann-Heurtier et al.[38]

3.5 Outcomes

The relative safety and efficacy of third-line antidiabetes drugs was assessed for the following outcomes: A1C; hypoglycemia (overall, severe, and nocturnal); body weight and body mass index (BMI); patient satisfaction; long-term, diabetes-related complications (e.g., myocardial infarction); mortality; quality of life; withdrawals due to adverse events (WDAE); and serious adverse events (SAE). Direct pairwise and MTC meta-analyses were conducted for hemoglobin A1C and body weight. Pairwise comparisons were performed for overall hypoglycemia, and study-level comparisons are presented for the remaining outcomes. There was no RCT evidence available for any of the following outcomes of interest: quality of life, retinopathy, nephropathy, hyperosmolar hyperglycemic nonketotic coma, and upper extremity fractures.

Due to the limited RCT data on adverse events, a supplemental review of safety was conducted based on systematic reviews, large RCTs, observational studies, and post-marketing information (see Appendix 14). Because renal impairment is commonly found among patients with diabetes, information concerning recommended dose adjustments in such cases is presented in Appendix 15.

An overview of the RCT evidence available for outcomes of interest is presented in Table 7.

Table 7: Overview of Evidence and Analyses Performed

Outcome	No. of Treatment Strategies (N)	No. of Studies	Type of Analysis Conducted
Hemoglobin A1C	15 (N = 7,238)	30 RCTs[10-12,14-17,19-31,33,35-41,43,45]	MTC & Pairwise
Body weight	15 (N= 6,717)	23 RCTs[10-12,14-16,19-25,28,31,35,36,38-41,43,45]	MTC & Pairwise
Overall hypoglycemia	13 (N = 7,238)	26 RCTs[10,11,14-17,20-26,29,31,33-41,43,45]	Pairwise
Severe hypoglycemia	16 (N = 6,368)	22 RCTs[10,14-16,19,22-26,29,31,34-41,43,45]	Pairwise
Nocturnal hypoglycemia	8 (N = 2,421)	7 RCTs[11,25,31,33,37,40,45]	Pairwise
Body mass index	6 (N = 245)	3 RCTs[17,28,30]	Pairwise
Withdrawals due to adverse events	16 (N = 5,635)	23 RCTs[10-12,14,16,17,19,20,22-24,28,29,31,32,34,35,37,38,40,41,43,44]	Pairwise
Severe adverse events	13 (N = 4,160)	12 RCTs[10,15,16,20,22,24,25,31,35,37,41,43]	Pairwise
Congestive heart failure	3 (N = 329)	2 RCTs[20,30]	Pairwise
Ischemic heart disease	2 (N = 222)	1 RCT[16]	Pairwise
Mortality	11 (N = 2,401)	6 RCTs[14,16,22,25,41,43]	Pairwise
Stroke/TIA	2 (N = 299)	1 RCT[20]	Pairwise
PaNcreatitis	3 (N = 576)	1 RCT[35]	Pairwise
Patient satisfaction	5 (N = 1,166)	4 RCTs[10,18,36,45]	Pairwise
Macular edema	———	———	———
Neuropathy	———	———	———
Retinopathy	———	———	———
Peripheral vascular disease	———	———	———
Upper extremity fractures	———	———	———
HHNC	———	———	———
Quality of life	———	———	———

DTSQ = Diabetes Treatment Satisfaction Questionnaire; HHNC = hyperosmolar hyperglycemic nonketotic coma; MTC = mixed treatment comparisons meta-analysis; N = total sample size; No. = number; RCT = randomized controlled trial; TIA = transient ischemic attack.

3.6 Patient Disposition

3.6.1 Early Withdrawals

Study-level detail regarding the proportion of patients who withdrew from each trial is presented in Table 8. Withdrawals were identified as a potential source of bias in nine RCTs due to either the overall proportion, distribution, or reasons for withdrawal (see Table 8).[11,14,15,21-23,36-38] However, the effect of these withdrawals on the overall results is uncertain. In the remaining 24 trials, withdrawals were not considered a potential source of bias because rates were low — i.e., <20% — and the proportions and reasons were similar between treatment groups.

WDAE were reported in 23 RCTs (see section 4.7 and Appendix 16). The proportion of patients withdrawing due to adverse events was generally low and ranged from 0%[10,12,24,32] to 9.8%.[34] The highest proportion of WDAE was consistently observed in patients treated with exenatide, with nausea and vomiting cited as the primary reasons.

In several placebo-controlled trials, patients were withdrawn due to hyperglycemia. One double-blind, placebo-controlled study withdrew patients from the study if they failed to achieve adequate glycemic control at maximum doses of study medications (rosiglitazone: 16/181 [8.8%]; placebo: 46/184 [25%]). A similar study[20] reported that eight patients withdrew due to inadequate glycemic control in the placebo arm (8/154) versus none in the pioglitazone arm (0/145).

Table 8: Trials Where Early Withdrawals Were Considered a Potential Source of Bias

Author, Year	Interventions/Comparators	Patients Withdrawn (%)	Primary Reason for Difference/Bias
Bergenstal et al., 2009[14]	• Exenatide + Met + SU	30%	WDAE — Nausea in exenatide group
	• BIAsp30 (q.d.) + Met + SU	16%	
	• BIAsp30 (b.i.d.) + Met + SU	19%	
Dailey et al., 2004[22]	• Rosiglitazone (4 mg to 8 mg) + Met + SU	20%	Inadequate glycemic control in placebo group
	• Placebo + Met + SU	38%	
Goudswaard et al., 2004[36]	• NPH insulin (q.d.) + Met + SU	24%	Inadequate glycemic control in add-on group
	• Biphasic insulin (70/30) (b.i.d.)	6.5%	
Hartemann-Heurtier et al., 2009[38]	• Pioglitazone + Met + SU	28%	Weight gain in the pioglitazone arm
	• NPH insulin + Met + SU	7%	
Janka et al., 2005[11]	• Insulin glargine + Met + SU	4%	Patients "unwilling to continue" and lack of efficacy in monotherapy arm
	• 30/70 NPH + placebo	15%	
Kendall et al., 2005[15]	• Exenatide (5 µg b.i.d.) + Met + SU	16%	Withdrawal of consent in the placebo; adverse event in the exenatide (10 µg b.i.d.) arm
	• Exenatide (10 µg b.i.d.) + Met + SU	22%	
	• Placebo + Met + SU	26%	
Lopez-Alvarenga et al., 1999[21†]	• Acarbose/placebo + Met + SU	23%	Primary concern is the pooling of withdrawals for the crossover periods
	• Insulin NPH + Met + SU	20%	
Milicevic et al., 2009[23]	• Insulin NPH (h.s.) + SU	18%	Higher number of adverse events in NPH + SU arm
	• Insulin lispro 50%/Insulin lispro 25%	6%	
Standl et al., 2001[37]	• Miglitol + Met + SU	NR	11% total withdrawals but not reported by treatment arm
	• Placebo + Met + SU	NR	
Stehouwer et al., 2003[39]	• NPH insulin + SU	NR	Proportion of withdrawals was not reported
	• NPH insulin + 30/70 insulin NPH	NR	
	• NPH insulin	NR	

b.i.d.= twice daily; BiAsp 30 = biphasic insulin aspart (30/70); h.s.= at bedtime; Met = metformin; NPH = neutral protamine Hagedorn; q.d.= once daily; SU = sulfonylurea; WDAE = withdrawals due to adverse events.

3.6.2 Handling of Missing Data

The majority of RCTs[10-13,17,24,26,28,29,33,37,38,40] failed to report methods for handling missing data. Among the RCTs[14-16,18,22,23,35,36,41] that provided methods, last observation carried forward techniques were the most commonly reported. One RCT[43] used a Bayesian Markov chain Monte Carlo multiple imputation technique to impute missing values.

3.7 Limitations of included studies

3.7.1 Methodological limitations

The primary methodological limitations of the included RCTs were failure to report adequate methods for allocation concealment and the use of analyses other than intention-to-treat (e.g., per-protocol analysis). See Appendices 17 and 18 for assessments of potential bias and internal validity of included studies.

Publication bias could not be formally assessed in this review due to a limited number of RCTs for each pairwise comparison.

The primary outcome in nearly all included RCTs was hemoglobin A1C. There was generally a lack of evidence for more clinically meaningful outcomes. In particular, studies were inadequately powered to detect differences between treatments in long-term complications because event rates were too low.

3.7.2 External validity

A number of limitations regarding the external validity of the included studies were also identified (see Appendix 19 for details):

- The population of interest in this review consisted of patients who were inadequately controlled with second-line combination therapy with metformin and sulfonylureas, and required a third-line agent. However, trials rarely reported the complete treatment history of their respective sample populations; therefore, it is possible that patients had been exposed to antidiabetes pharmacotherapy other than metformin and sulfonylureas (i.e., not a true third-line population) or had not been receiving maximally tolerated doses of metformin and sulfonylureas. Hence, it is possible that the applicability of evidence to the true population of interest may be somewhat limited.
- The duration of trials was relatively short (e.g., less than one year) and may not be indicative of long-term relative efficacy. In addition, statistical power was limited in many trials due to small sample sizes (e.g., nine RCTs[10,19,24,24,26,27,29,36,38] had fewer than 100 patients).
- The findings from RCTs conducted in Asia[12,17,19,34] and Mexico[21] may be less generalizable to the Canadian context.
- The included RCTs often failed to report definitions for outcomes such as hypoglycemia and adverse events (e.g., fifteen trials failed to provide definitions for hypoglycemia).[12,17,19-21,23,26-28,30,37-41]
- Blood glucose targets were often different from those suggested in the Canadian Diabetes Association Clinical Practice Guidelines, with 14 RCTs[10,11,14,20,23,24,26,30-32,35,38,43,44] having a lower target and four RCTs[12,16,17,21] having a higher target.
- The treatment protocol for seven RCTs[19,23,31,35,39,43,44] involved contact with health care professionals that would likely exceed that encountered in routine clinical practice (e.g., clinical visits every four weeks[23] or interim telephone contact with patients[35,43,44]), and one RCT employed forced titration of trial medications independent of glycemic control, which is not reflective of clinical practice.[28]

3.7.3 Clincial and methodological heterogeneity

Heterogeneity was observed across the studies included in this review. Methods for assessing the possible impact of heterogeneity on pooled results are discussed in section 2.2. The main sources of heterogeneity across trials are described below:

- There was heterogeneity in the study populations regarding baseline A1C and duration of diabetes. Larger reductions in A1C are likely to be observed in patients with higher baseline A1C. Furthermore, due to the progressive nature of type 2 diabetes, patients with a lower duration of diabetes may experience a greater response to a particular treatment in comparison with those who have had the condition for a longer period.
- There was significant variability in the reporting of metformin and sulfonylurea dosing at baseline, with most RCTs failing to report this information. The inclusion criteria of 12 RCTs[11,14,16,17,20,26,29,31,35,39,41,45] only required patients to be uncontrolled on half the maximum dosing of sulfonylureas to be eligible for enrollment in the study (see Table 9).

Table 9: Sulfonylurea Dosing at Baseline

Number of Articles	Details of Sulfonylurea Dosing at Baseline
6[12,19,21,37,38,43]	Maximal dosing of sulfonylureas
12[11,14,16,17,20,26,29,31,35,39,41,45]	At least half maximal dosing of sulfonylureas
12[10,15,21-25,27,28,30,32-34,36,38,40,44]	Dosing information for sulfonylureas not reported

- There was heterogeneity regarding the glycemic targets specified in the included RCTs (see Appendix 12). A majority of the included RCTs used fasting blood glucose (FBG) or FPG as glycemic targets. Targets based on FBG ranged from 4.0 mmol/L to 7.0 mmol/L and FPG targets from < 5.5 mmol/L to < 7.0 mmol/L. Five RCTs[17,20,22,30,39] specified a target A1C ranging from < 6.2%[30] to <7.5%.[17] Three RCTs also specified a target for two-hour post-prandial glucose ranging from < 8.0 mmoL[23] to <10.0 mmoL.[25] An attempt was made to perform a meta-regression by normalizing FPG targets to those stated in the 2008 Canadian Diabetes Association guidleines; however, the trials reporting the use of FPG targets did not form a closed network. Qualitiative analysis across trials within individual pairwise comparisons did not reveal consistent patterns regardingthe magnitude of effect sizes and treatment targets.
- Study design varied regarding the inclusion and characteristics of run-in periods (see Appendix 20). Twenty of the included RCTs included some form of run-in period[10,11,15-17,20-23,26,28,31,32,34,35,37,39,41,42,44,45] and 13 RCTs did not specify a run-in.[12,14,18,19,25,27,29,30,33,36,38,40,43] Of those that included a run-in period, four RCTs provided no information other than the duration.[10,20,28,37] Run-in durations ranged from one week[16,26] to 12 weeks,[17,22,39] with four weeks being the most common length.[15,24,28,32,37,44,45]
- The trial protocol for 20 RCTs specified that patients perform self-monitoring of blood glucose.[10,11,14,15,23-26,29,31-36,39,40,43-45] The details concerning the application of self-monitoring were typically limited, with many trials failing to provide either the timing or frequency of testing.[15,23,26,32,36,39,44] Six RCTs specified that patients used the results of self-monitoring to titrate insulin dosing.[11,14,25,35,40,43] One RCT[40] specified that patients in the insulin arm were to use results of self-monitoring of blood glucose to self-titrate dosing; whereas, those in the exenatide arm were not required to perform self-monitoring of blood glucose. The remaining 13 RCTs did not specify whether or not patients performed self-monitoring.[12,16,17,19-22,27,28,30,37,38,41] Overall, differences in the application and reporting of self-monitoring of blood glucose are unlikely to influence the results of the pooled analyses for patients with type 2 diabetes using oral antihyperglycemic agents.[107]

- There was some variability regarding the inclusion of dietary and lifestyle advice in the protocols of the included clinical trials. Ten RCTs specified some form of dietary education in the protocol.[17,19,21,23,26,28,29,32,36,39] Nine of these offered simple nutritional education and/or reinforcement of dietary advice from common diabetes guidelines (e.g., American Diabetes Association) and one specified a controlled-energy diet (~ 600 kcal daily deficit).[28] In all ten trials, each treatment arm received the same educational advice. No lifestyle interventions were specified for the remaining 23 RCTs.[10-12,14-16,20,22,24,25,27,30,31,33-35,37,38,40,41,43-45] Two of these trials specifically requested that patients not modify their dietary habits for the purpose of weight loss.[14,22] Since most patients with type 2 diabetes are provided with lifestyle and dietary advice in clinical practice, it is unlikely that heterogeneity across trials in this area was a significant source of bias in treatment differences between third-line strategies.

4 SUMMARY OF OUTCOMES

Individual study results for A1C, body weight, overall hypoglycemia, and patient withdrawals are summarized in Table 10. Results of the meta-analyses, as well as detailed results for each outcome, are presented below in sections 4.1 to 4.10.

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study

Study Reference	Study Details	Treatment 1	Treatment 2	A1C (%) MD (95% CI)	Weight (kg) MD (95% CI)	Overall Hypoglycemia	Withdrawals (n)
Aljabri et al., 2004[10]	Parallel, 4 months duration, 62 randomized patients, Canada	Pioglitazone (30 mg/day to 45 mg/day) + Met + SU	NPH insulin (titrated to FG < 6.0 mmol/L) + Met + SU	0.40 (-0.40, 1.20)	0.10 (-1.19,1.39)	TZD + Met + SU: 11/30 NPH + Met + SU: 19/29	Total: 4 WDAE: 0
Al-Shaikh, 2006[12]	Parallel, 6 months duration, 221 randomized patients, Saudi Arabia	Insulin glargine (h.s., started at 14 IU/d, titrated by 8 IU/d if FBG > 11 mmol/L and 4 IU/d if FBG >7.8 mmol/L but < 11 mmol/L) + Met + SU	Biphasic 30/70 human insulin, 2/3 dose in morning and 1/3 dose in evening (started at 1 IU/kg/day, morning dose titrated up 4 IU/week if FBG > 11mmol/L, evening dose if FBG > 7.8mmol/L)	-1.30 (-1.79, -0.81)	-3.90 (-6.61, -1.20)	NR	Total: 0 WDAE: 0
Bergenstal et al., 2009[14]	Parallel, 6 months duration, 372 randomized patients, USA	BIAsp30 (q.d., 12 IU q.d., titrated to BG 5.0-6.1 mmol/L) + Met + SU	Exenatide (10 μg b.i.d.) + Met + SU	0.59 (0.16, 1.02)	4.70 (5.62, 3.78)	Biphasic q.d. + Met + SU: 69/124 Biphasic b.i.d. + Met: 76/124 GLP-1+ Met + SU: 36/124	Total: 81 WDAE: 11
		BIAsp30 (b.i.d., 6 IU b.i.d., titrated to BG 5.0-6.1 mmol/L) + Met	Exenatide (10 μg b.i.d.) + Met + SU	1.01 (0.52, 1.50)	6.00 (7.16, 4.84)		
		BIAsp30 (q.d., 12 IU q.d., titrated to BG 5.0-6.1 mmol/L) + Met + SU	BIAsp30 (b.i.d., 6 IU b.i.d., titrated to BG 5.0 mmol/L to 6.1 mmol/L) + Met	-0.42 (-0.87, 0.03)	-1.30 (-0.16, -2.44)		

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Berhanu et al., 2007[16]	Parallel, 20 weeks duration, 222 randomized patients, USA	Insulin (Humulin N, Humalog, or Humulin 30/70 titrated to FPG < 7.8 mmol/L) + Pioglitazone (45 mg/day) + Met	Insulin (Humulin N, Humalog, or Humulin 30/70 titrated to FPG < 7.8 mmol/L) + Placebo + Met	-0.20 (-0.22, -0.18)	1.97 (1.15, 2.79)	Ins + Met: 35/112 Ins + TZD + Met: 51/110	Total: 24 WDAE: 5
Charpentier and Halimi et al., 2009[20]	Parallel, 7 months duration, 299 randomized patients, France	Pioglitazone (30 mg/day to 45 mg/day) + Met + SU	Placebo + Met + SU	-1.18 (-1.40, -0.96)	4.10 (3.28, 4.92)	TZD + Met + SU: 35/145 Met + SU: 11/154	Total: 32 WDAE: 5
Dailey et al., 2004[22]	Parallel, 4 months duration, 365 randomized pts, USA	Rosiglitazone (4 mg to 8 mg) + Met + SU	Placebo + Met + SU	-1.00 (-1.22, -0.78)	2.97 (2.15, 3.79)	TZD + Met + SU: 40/181 Met + SU: 6/184	Total: 104 WDAE: 15
Davies et al., 2007[24]	Parallel, 4 months duration, 82 randomized pts, UK	Biphasic 30/70 human insulin (b.i.d., average dose 0.63 ± 0.32 IU/kg) + Met	NPH Insulin (h.s., average dose 0.58 ± 0.21 IU/kg) + Met	-0.30 (-1.42, 0.82)	2.20 (-0.05, 4.45)	Biphasic + Met: 8/27 Basal + Meg + Met: 4/26 Basal + Met: 7/29	Total: 7 WDAE: 0
		NPH insulin (h.s., average dose 0.37 ± 0.22 IU/kg) + Repaglinide (a.c., 1.5 mg to 12 mg) + Met	NPH Insulin (h.s., average dose 0.58 ± 0.21 IU/kg) + Met	-1.10 (-2.39, 0.19)	1.50 (-0.03, 3.03)		
		Biphasic 30/70 human insulin (b.i.d., average dose 0.63 ± 0.32 IU/kg) + Met	NPH insulin (h.s., 0.37 ± 0.22 IU/kg) + repaglinide (a.c., 1.5 mg to 12 mg) + Met	0.80 (-0.26, 1.86)	0.70 (-0.01, 1.41)		
De Mattia et al., 2009[26]	Crossover, 3 months duration, 20 randomized patients, Italy	Insulin glargine (starting 10 IU/day, algorithmic titration to FBG < 5.5 mmol/L) + Met + SU	NPH Insulin (starting 10 IU/day, algorithmic titration to FBG < 5.5 mmol/L) + Met + SU	-0.10 (-1.10, 0.90)	NR	IGlar + Met + SU: 13/20 NPH + Met + SU: 15/20	Total: 1 WDAE: 0

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Derosa et al., 2009[28]	Crossover, 3.5 months duration, 103 randomized patients, Italy	Acarbose (100 mg t.i.d.) + Met + SU	Rapaglinide (6 mg/day) + Met + SU	-0.30 (-2.04, 1.44)	-3.10 (-5.25, -0.95)	NR	Total: 7 WDAE: 1
Dorkhan et al., 2009[30]	Parallel, 6.5 months duration, 30 randomized patients, Sweden	Pioglitazone (up to 45 mg/day) + Met + SU	Insulin glargine (titrated to FPG < 6 mmol/L) + Met + SU	0.90 (0.66, 1.14)	NR	NR	Total: 0 WDAE: 0
Gao et al., 2009[34]	Subgroup data used, parallel, 4 months duration, 472 randomized, China, India, Korea, Taiwan	Exenatide (10 µg b.i.d.) + Met + SU	Placebo (b.i.d.) + Met + SU	NR for Met + SU subgroup	NR for Met + SU subgroup	Exenatide: 4.7 (3.5, 6.5) evt/pt/year Placebo: 0.54 (0.34, 0.86) evt/pt/year	Total: 65 WDAE: 26
Goudswaard et al., 2004[36]	Parallel, 12 months duration, 69 randomized pts, Netherlands	NPH insulin (h.s., starting dose 8 IU, titrated to FBG 4.0 mmol/L to 7.0 mmol/L and postprandial BG 4.0 mmol/L to 10.0 mmol/L) + Met + SU	Biphasic insulin (70/30) (b.i.d., starting dose 12 IU before breakfast and 6 IU before dinner, titrated to FBG 4.0 mmol/L to 7.0 mmol/L and postprandial BG 4.0 mmol/L to10.0 mmol/L)	0.40 (-0.21, 1.01)	-3.00 (-5.29, -0.71)	NR	Total: 10 WDAE: NR
Hartemann-Heurtier et al., 2009[38]	Parallel, 6 months duration, 28 randomized pts, France	Pioglitazone (30 mg/day) + Met + SU	NPH insulin (0.2 IU/kg/d, q.d.) + Met + SU	0.40 (-0.05, 0.85)	1.30 (-0.76, 3.36)	TZD + Met + SU: 6/14 Basal + Met + SU: 10/13	Total: 1 WDAE: 1
Heine et al., 2005[40]	Parallel, 26 weeks, 551 randomized pts, multinational	Exenatide (10 µg b.i.d.) + Met + SU	Insulin glargine (starting dose 10 IU/d, titrated in 2 IU increments every 3 days to FBG < 5.6 mmol/L) + Met + SU	0.02 (-0.12, 0.16)	-4.10 (-4.65, -3.55)	Exenatide: 7.3 events/pt/year Insulin glargine: 6.5 events/pt/year	Total: 77 WDAE: 29

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Hermansen et al., 2007[41]	Parallel, 6 months duration, 441 randomized pts, USA and Denmark	Sitagliptin (100 mg/day) + Met + SU	Placebo + Met + SU	-0.89 (-1.11, -0.67)	1.10 (0.28, 1.92)	Met + SU: 1/113 DPP-4 + Met + SU: 19/116	Total: 35 WDAE: 4
Holman et al., 2007[43]	Parallel, 12 months duration, 708 randomized pts, Ireland and UK	Insulin aspart (t.i.d., median starting dose 18 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU	Insulin detemir (h.s. or b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0-7.0 mmol/L,) + Met + SU	-0.60 (-0.78, -0.42)	3.80 (2.00, 4.60)	Bolus + Met + SU: 229/238 Biphasic + Met + SU: 216/235 Basal + Met + SU: 173/234	Total: 40 WDAE: 6
		Insulin aspart (t.i.d., median starting dose 18IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU	Biphasic insulin aspart 30 (b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU	-0.10 (-0.30, 0.10)	1.00 (0.22, 1.78)		
		Insulin detemir (h.s. or b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to 7.0 mmol/L) + Met + SU	Biphasic insulin aspart 30 (b.i.d., median starting dose 16 IU/day, titrated to FBG 4.0 mmol/L to 5.5 mmol/L and 2-hr postprandial BG 5.0 mmol/L to7.0 mmol/L) + Met + SU	-0.50 (-0.70, -0.30)	-2.80 (-3.55, -2.06)		
Janka et al., 2005[11]	Parallel, 6 months duration, 364 randomized pts, multinational	Insulin glargine (titrated to 5.5 mmol/L) + Met + SU	30/70 NPH (titrated to 5.5 mmol/L) + placebo	-0.34 (-0.52, -0.16)	-0.70 (-1.48, 0.08)	Basal + Met + SU: 109/177 Biphasic: 127/187	Total: 35 WDAE: 7

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Kendall et al., 2005[15]	Parallel, 7.5 months duration, 734 randomized pts, USA	Exenatide (5 µg b.i.d.) + Met + SU	Placebo + Met + SU	-0.78 (-0.98, -0.58)	-0.70 (-1.25, -0.15)	GLP-1(5 µg) + Met + SU: 47/245 GLP-1(10 µg) + Met + SU: 67/241 Met+SU: 31/247	Total: 141 WDAE: NR
		Exenatide (10 µg b.i.d.) + Met + SU	Placebo + Met + SU	-1.00 (-1.22, -0.78)	-0.70 (-1.25, -0.15)		
Ko et al., 2006[17]	Parallel, 52 weeks duration, 112 randomized pts, Hong Kong	Rosiglitazone (2 mg/day to 8 mg/day) + Met + SU	NPH Insulin (h.s., started at 6 IU, titrated to A1C < 7.5%) + Met + SU	0.20 (-0.41, 0.81)	NR	TZD + Met + SU: 0/56 Basal + Met + SU: 5/56	Total : 8 WDAE: 4
Lam et al., 1998[19]	Parallel, 24 weeks, 90 randomized pts, Hong Kong	Acarbose (150 mg/day to 300 mg/day) + Met + SU	Placebo + Met + SU	-0.60 (-1.15, -0.05)	-0.96 (-1.80, -0.12)	NR	Total: 9 WDAE: 3
Lopez-Alvarenga et al., 1999[21]	Crossover, 3 months duration, 37 randomized pts, Mexico	Acarbose (100 mg t.i.d.) + Met + SU	Placebo + Met + SU	-0.60 (-3.27, 2.07)	-0.60 (-7.77, 6.57)	Met + SU: 0/19 AGI + Met + SU: 2/20 Basal + Met + SU: 2/15	Total: 8 WDAE: 0
		Insulin NPH (starting dose 8 IU/day, titrated in 8 IU increments every 4 weeks to FPG < 7.7 mmol/L) + Met + SU	Placebo + Met + SU	-2.10 (-4.92, 0.72)	-0.30 (-9.61, 9.01)		
		Acarbose (100 mg t.i.d.) + Met + SU	Insulin NPH (starting dose 8 IU/day, titrated in 8 IU increments every 4 weeks to FPG < 7.7 mmol/L) + Met + SU	1.50 (-1.50, 4.50)	-0.30 (-9.67, 9.07)		
Milicevic et al., 2009[23]	Parallel, 6 months duration, 135 randomized pts, multinational	Insulin NPH (HS, average ending dose 21 ± 9.4 IU) + SU	Biphasic Insulin lispro 50/50 pre-breakfast, biphasic insulin lispro 25/75 pre-dinner (titrated, average ending dose 44.1 ± 19.9 IU)	0.80 (0.19, 1.41)	-0.22 (-1.24, 0.80)	Insulin NPH: 0.09 ± 0.17 evt/pt/month (SD) Biphasic lispro: 0.37 ± 0.7 evt/pt/month (SD)	Total: 16 WDAE: 6

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Nauck et al., 2007[25]	Parallel, 12 months duration, 505 randomized pts, multinational	Exenatide (10 µg b.i.d.) + Met + SU	Biphasic insulin aspart 30/70 (titrated, average ending dose 24.4 ± 15.6 IU/day)	-0.15 (-0.31, 0.01)	-5.50 (-5.89, -5.11)	Exenatide: 4.7 ± 0.7 evt/pt/year (SE) Insulin: 5.6 ± 0.7 evt/pt/year (SE)	Total: 79 WDAE: 20
Ovalle and Bell, 2004[27]	Parallel, 6 months duration, 17 randomized pts, USA	Rosiglitazone (8 mg/day) + Met + SU	Biphasic insulin 70/30 (starting dose 0.2 IU/kg, titrated to FBG < 6.7 mmol/L)	0.30 (-1.07, 1.67)	NR	NR	Total: 0 WDAE: 0
Reynolds et al., 2007[29]	Parallel, 6 months duration, 40 randomized pts, USA	Rosiglitazone (4 mg/day to 8 mg/day) + Met + SU	Insulin glargine (h.s., started at 10 IU/d, increasing weekly in 2 IU to 4 IU increments to FBG < 6.7 mmol/L if no hypoglycemia) + Met + SU	-0.10 (-2.04, 1.84)	NR	Rosiglitazone: 3.3 ± 1 evt/pt (SD) Insulin glargine : 2.85 ± 0.7 evt/pt (SD)	Total : 5 WDAE: 3
Rosenstock et al., 2006[31]	Parallel, 6 months duration, 219 randomized pts, USA	Rosiglitazone (4 mg/day to 8 mg/day) + Met + SU	Insulin glargine (h.s., starting dose 10 IU, titrated to 5.5 mmol/L to 6.7 mmol/L if no severe hypoglycemia) + Met + SU	0.15 (-0.05, 0.35)	1.30 (0.18, 2.42)	TZD + Met + SU: 47/112 Basal + Met + SU: 57/104	Total : 29 WDAE: 11
Russell-Jones et al., 2009[35]	Parallel, 26 weeks duration, 581 randomized pts, multinational	Liraglutide (1.8 mg/day) + Met + SU	Placebo + Met + SU	-1.09 (-1.29, -0.89)	-1.39 (-2.10, -0.68)	Met + SU: 19/114 GLP-1 + Met + SU: 63/230 Basal + Met + SU: 67/232	Total: 54 WDAE: 17
		Insulin glargine (titrated, average dose 24 IU) + Met + SU	Placebo + Met + SU	-0.85 (-1.05, -0.65)	2.02 (1.02, 3.02)		
		Insulin glargine (titrated, average dose 24 IU) + Met + SU	Liraglutide (1.8 mg/day) + Met + SU	0.24 (0.08, 0.40)	3.40 (2.48, 4.32)		
Standl et al., 2001[37]	Parallel, 24 weeks duration, 154 randomized pts, multinational	Miglitol (50 mg to 100 mg TID) + Met + SU	Placebo + Met + SU	-0.35 (-0.70, 0.00)	NR	AGI + Met + SU: 0/65 Met + =SU: 0/68	Total: 21 WDAE: 6

Table 10: Summary of Key Trial Outcomes (A1C, Body Weight, and Overall Hypoglycemia) and Withdrawal Rates by Study							
Study Reference	**Study Details**	**Treatment 1**	**Treatment 2**	**A1C (%) MD (95% CI)**	**Weight (kg) MD (95% CI)**	**Overall Hypoglycemia**	**Withdrawals (n)**
Stehouwer et al., 2003[39]	Parallel, 9 months duration, 261 randomized pts, multinational	NPH insulin (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5) + SU	NPH insulin (titrated 2 IU/wk to IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to10 mmol/L or A1C ≤ 6.5)	-0.60 (-0.07, -1.13)	-1.60 (-7.21, 4.01)	Basal: 63/88 Basal + Biphasic: 63/87 Basal + SU: 53/86	Total: NR WDAE: NR
		NPH insulin (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5) + SU	NPH insulin + 30/70 insulin NPH (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5)	-0.60 (-0.07, -1.13)	-0.90 (-6.92, 5.12)		
		NPH insulin (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to 10 mmol/L or A1C ≤ 6.5)	NPH insulin + 30/70 insulin NPH (titrated 2 IU/wk to 4 IU/wk until FPG 4 mmol/L to 7 mmol/L or PPG 4 mmol/L to10 mmol/L or A1C ≤ 6.5)	0.00 (-0.51, 0.51)	0.70 (-4.91, 6.31)		
Strojek et al., 2009[45]	Parallel, 6.5 months duration, 480 randomized pts, multinational	Insulin glargine (titrated, average ending dose 0.29 IU/kg) + Met + SU	BIAsp30 (titrated, average ending dose 0.32 IU/kg) + Met + SU	0.16 (0.02, 0.3)	-0.07 (-0.81, 0.67)	NR	Total: 47 WDAE: 9

A1C = glycosylated hemoglobin; AGI = alpha glucosidase inhibitor; BG = blood glucose; BIAsp = biphasic insulin aspart; DPP-4 = dipeptidyl peptidase; evt = events, FBG = fasting blood glucose; FG = fasting glucose; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; h.s. = at bedtime; IGlar = insulin glargine; IU = international units; MD = mean difference; Met = metformin; NPH = neutral protamine Hagadorn; NR = not reported (outcome results were not present in article); PPG = post-prandial glucose; pt = patient; pts = patients; SD = standard deviation; SE = standard error; SU = sulfonylurea; TZD = thiazolidinedione; WDAE = withdrawals due to adverse events; wk = week.

4.1 Hemoglobin A1C

31 RCTs[10-12,14-17,19-31,33,35-41,43-45] (N = 7,238) reported the change from baseline in A1C (see Appendices 21 and 22). In the MTC analyses, basal insulin and biphasic insulin produced statistically significant reductions in hemoglobin A1C in combination with metformin and sulfonylureas as well as with metformin alone. DPP-4 inhibitors, GLP-1 analogues, TZDs, and rapid-acting insulin analogues also produced statistically significant reductions in A1C (i.e., 0.5 % to 1.0%) in combination with metformin and sulfonylureas, whereas meglitindes and alpha-glucosidase inhibitors did not. There were no statistically significant differences between basal insulin, biphasic insulin, DPP-4 inhibitors, TZDs, GLP-1 analogues, and bolus insulin. Estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from MTC meta-analyses in both direction and magnitude.

4.1.1 Primary MTC analysis: add-on therapies

The primary MTC analysis was restricted to studies in which a third-line agent was added to pre-existing therapy with metformin and sulfonylurea. This approach reflects common clinical practice, and also ensured a greater degree of homogeneity across trials. The MTC evidence network was composed of 21 RCTs[10,14,15,17,19-22,25,27-31,35,37,38,40,41,43,45] representing eight third-line drug classes in addition to placebo (N = 5928). Illustrations of the MTC evidence networks are presented in Appendix 23.

With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in hemoglobin A1C (range –0.89% to –1.17%) relative to metformin and sulfonylurea therapy alone. The addition of a basal or biphasic insulin produced the largest effects, with mean reductions of –1.17% (–1.57, –0.81) and –1.10% (–1.59, –0.67), respectively. Results for DPP-4 inhibitors, GLP-1 analogues, bolus insulin, and TZDs ranged from–0.89% to –1.06%, with no significant differences between these classes or the insulins. A summary of the results for the MTC and direct pairwise meta-analyses is shown in Table 11, and represented graphically in Figure 1. Complete results from the MTC meta-analysis for all possible comparisons are presented in Appendix 24, with pairwise meta-analysis forest plots available in Appendix 25.

The estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from the MTC analysis in both direction and magnitude. Furthermore, the posterior mean residual deviance (20.9) was less than the number of unconstrained data points (24), which is an indication of good model fit (see Appendix 31).

4.1.2 Sensitivity analyses

A number of sensitivity analyses, meta-regression analyses, and alternative modelling strategies were conducted on the primary MTC meta-analysis (Table 12). There were no significant differences in the MTC estimates of effect after removing studies meeting any of the following criteria: crossover design, failure to report sulfonylurea dosage at baseline, A1C threshold of < 7.0% in the inclusion criteria. An additional sensitivity analysis was performed where insulin neutral protamine Hagedorn (NPH) and the long-acting insulin analogues were separated in the MTC meta-analysis. Both classes resulted in a statistically significant reduction in hemoglobin A1C in comparison with placebo. The estimates of effect were –1.32% (–1.79, –0.85) and –1.05% (–1.39, –0.77) relative to placebo for insulin NPH and long acting insulin analogues, respectively, with no significant difference between them.

Meta-regression analyses, performed to account for heterogeneity across studies in baseline A1C and duration of diabetes, also yielded results that were consistent with the reference case analysis. Meta-regression coefficients are available in Appendix 32.

The reference case analysis was conducted using a random-effects model; these results were also compared against those obtained using a fixed-effects model, and found to be nearly identical.

4.1.3 Secondary analysis: all treatment strategies

A secondary MTC evidence network for A1C was constructed using all the available treatment strategies. This network was composed of 27 RCTs (N = 6,978).[10-12,14,15,17,19-25,27-31,35-41,43,45] Three trials[32,33,44] were intraclass comparisons of insulins, while the therapeutic strategy of a fourth trial could not be connected in the network due to the lack of a common comparator with other the other trials.[16] The evidence in the network represented 15 different therapeutic regimens and involved all eight drug classes. The most common comparison was TZDs versus basal insulin, both administered in combination with metformin and sulfonylureas (six RCTs).[10,17,29-31,38] A summary of the results is presented in the lower portion of Table 11 and represented graphically in Figure 2, with the complete results reported in Appendices 25 and 26.

The effect estimates for add-on therapy with TZDs, DPP-4 inhibitors, alpha-glucosidase inhibitors, GLP-1 analogues, bolus insulin aspart, and meglitinides were nearly identical in both the primary and secondary analyses. Similar to the primary analysis, the addition of a basal or biphasic insulin produced the largest effects, with mean reductions in A1C (95% credible interval [CrI]) of 1.20% (–1.66, –0.77) and –1.13% (–1.69, –0.60), respectively. An even larger result was observed for patients who received a biphasic insulin in combination with metformin alone, with a mean reduction of –1.90% (–2.80, –0.98). However, the effect size was lower when patients received a basal insulin (-0.69% [–1.87, 0.45]) or a biphasic insulin (–0.75% [–1.42, –0.12]) and discontinued both metformin and sulfonylurea. It should be noted that the only data available for patients switching to basal insulin alone were obtained from a single RCT[39] in which the authors reported relatively low A1C reductions for all treatment arms. Despite setting a low target A1C (6.5%) and treating patients for nine months, the authors found that only a minority of patients achieved good glycemic control. This is also reflected in the modest effect estimate for insulin NPH in combination with sulfonylurea (upon discontinuation of metformin), as this study was the only RCT to investigate that particular strategy. Overall, the amount and quality of evidence was insufficient to draw conclusions regarding the relative efficacy of the add-on, partial-switch, and switch regimens in the initiation of insulin.

The estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from the MTC in both direction and magnitude. Furthermore, the posterior mean residual deviance (30) was less than the number of unconstrained data points (31), which is an indication of good model fit.

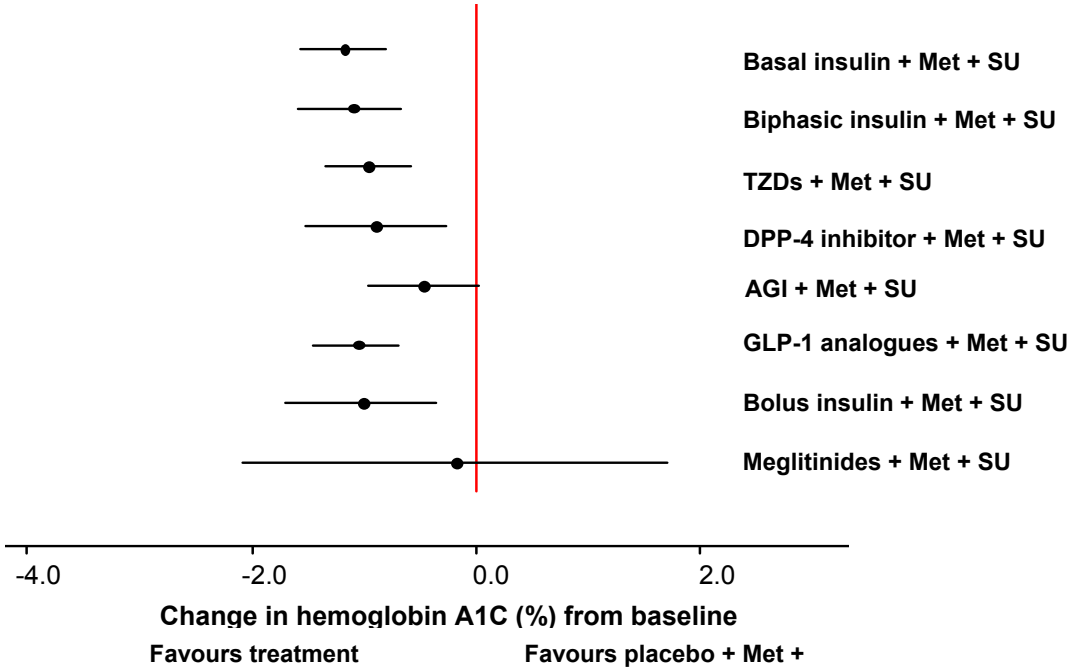
Table 11: Summary of MTC Results for Change In A1C From Baseline (Compared With Placebo)

Third-Line Treatment Strategy Versus Placebo + Met + SU	Direct Estimate WMD (%) (95% CI)	MTC Estimate (%) (95% CrI)	Probability of Largest A1C Reduction	Mean Rank
Add-on therapy (primary analysis)				
Basal Insulin + Met + SU	–1.22 (–2.33, –0.10)	–1.17 (–1.57, –0.81)	30.6%	2.3
Biphasic Insulin + Met + SU	———	–1.10 (–1.59, –0.67)	14.3%	3.2
TZD + Met + SU	–1.16 (–1.36, –0.96)	–0.96 (–1.35, –0.59)	2.7%	4.6
DPP-4 + Met + SU	–0.89 (–1.11, –0.66)	–0.89 (–1.51, –0.26)	12.5%	4.8
Alpha-glucosidase + Met + SU	–0.43 (–0.72, –0.14)	–0.46 (–0.96, 0.03)	0.2%	7.1
GLP-1 + Met + SU	–0.96 (–1.14, –0.77)	–1.06 (–1.45, –0.69)	8.7%	3.7
Bolus Insulin + Met + SU	———	–1.01 (–1.71, –0.35)	17.7%	4.0
Meglitinide + Met + SU	———	–0.18 (–2.08, 1.71)	13.3%	6.8
All treatment strategies (secondary analysis)				
Basal Insulin + Met + SU	–1.22 (–2.33, –0.10)	–1.20 (–1.66, –0.77)	1.8%	3.6
Biphasic Insulin + Met + SU	———	–1.13 (–1.69, –0.60)	1.0%	4.5
TZD + Met + SU	–1.16 (–1.36, –0.96)	–0.97 (–1.41, –0.53)	0.3%	6.1
DPP-4 + Met + SU	–0.89 (–1.11, –0.66)	–0.89 (–1.65, –0.15)	2.7%	6.5
alpha-glucosidase + Met + SU	–0.43 (–0.72, –0.14)	–0.46 (–1.03, 0.10)	0.1%	9.6
GLP-1 + Met + SU	–0.96 (–1.14, –0.77)	–1.07 (–1.53, –0.63)	0.3%	5.1
Bolus Insulin + Met + SU	———	–1.04 (–1.86, –0.24)	3.3%	5.5
Meglitinide + Met + SU	———	–0.14 (–2.17, 1.83)	5.2%	9.7
Biphasic Insulin + Met	———	–1.90 (–2.80, –0.98)	82.2%	1.4
Basal Insulin + SU	———	–0.05 (–1.00, 0.86)	0.0%	11.5
Basal Insulin	———	–0.69 (–1.87, 0.45)	3.1%	7.8
Biphasic Insulin	———	–0.75 (–1.42, –0.12)	0.1%	7.9

A1C = glycosylated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; MTC = mixed treatment comparison; SU = sulfonylurea; TZD = thiazolidinedione; WMD = weighted mean difference.

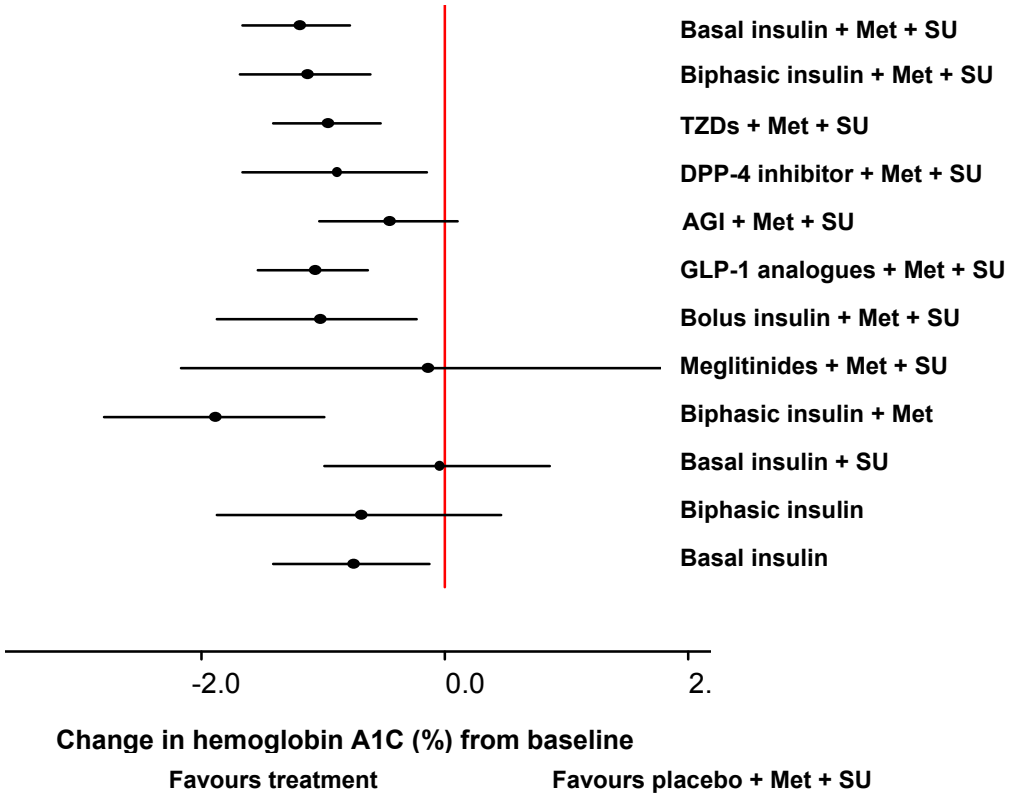
All values represent the difference in the change in A1C(%) from baseline between a particular third-line intervention strategy and the combination of metformin/sulfonylurea. The MTC results are presented as the mean pooled estimate of effect (95% CrI) and the direct comparisons as the mean difference for the change in A1C from baseline (95% CI). The table also presents the probability of achieving the largest reduction in A1C with each individual treatment, based on the results of 40,000 simulations. The "Rank" represents the average ranking for each treatment relative to the others over the 40,000 simulations; a lower number indicates that a particular treatment demonstrated the largest reduction in A1C relative to other treatments more often than treatments with a higher number.

Figure 1: Differences In Change From Baseline Hemoglobin A1C Between Active Third-Line Treatments and Placebo, Both In Combination With Metformin and a Sulfonlyurea: Results From the Primary MTC Analysis



AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZDs = thiazolidinediones.

Figure 2: Differences In Change From Baseline for Hemoglobin A1C Between Active Third-Line Treatments and Placebo: Results From Secondary MTC Analysis



AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZDs = thiazolidinediones.

Table 12: Sensitivity Analyses, Meta-regression Analyses, and Model Comparisons for the Primary MTC Analysis of Change From Baseline A1C

MTC estimate of effect (95% CrI) for change from baseline in A1C (%) (third-line treatment versus placebo)								
Analysis	**Basal Insulin**	**Biphasic Insulin**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-glucosidase Inhibitors**	**GLP-1 Analogues**	**Bolus Insulin**	**Meglitinides**
Random-effects model versus fixed-effects model								
Reference case – random-effects model	–1.17 (–1.57, –0.81)	-1.10 (–1.59, –0.67)	–0.96 (–1.35, –0.59)	–0.89 (–1.51, –0.26)	–0.46 (–0.96, 0.03)	–1.06 (–1.45, –0.69)	–1.01 (–1.71, –0.35)	–0.18 (–2.08, 1.71)
Reference case – fixed-effects model	–1.07 (–1.20, –0.95)	–0.94 (–1.09, –0.78)	–0.99 (–1.14, –0.85)	–0.89 (–1.09, –0.69)	–0.42 (–0.71, –0.14)	–1.01 (–1.14, –0.88)	–1.04 (–1.29, –0.79)	–0.12 (–1.87, 1.64)
Meta-regression adjusting for:								
Baseline A1C	–1.19 (–1.57, –0.84)	–1.09 (–1.55, –0.67)	–0.91 (–1.28, –0.53)	–0.89 (–1.49, –0.29)	–0.29 (–0.83, 0.25)	–1.06 (–1.44, –0.70)	–0.99 (–1.65, –0.35)	0.03 (–1.86, 1.90)
Baseline duration of diabetes	–1.18 (–1.59, –0.80)	–1.10 (–1.62, –0.65)	–0.96 (–1.39, –0.54)	–0.89 (–1.55, –0.23)	–0.46 (–0.98, 0.05)	–1.06 (–1.47, –0.67)	–1.02 (–1.74, –0.32)	–0.13 (–2.23, 1.96)
Sensitivity analyses with removal of:								
Crossover studies*	–1.13 (–1.51, –0.76)	–1.07 (–1.55, –0.61)	–0.94 (–1.33, –0.56)	–0.89 (–1.52, –0.26)	–0.45 (–0.97, 0.06)	–1.03 (–1.42, –0.64)	–0.98 (–1.66, –0.30)	————
A1C < 7.0% (inclusion criteria)†	–1.19 (–1.60, –0.83)	–0.98 (–1.54, –0.51)	–0.99 (–1.37, –0.61)	–0.89 (–1.52, –0.27)	–0.46 (–0.95, 0.04)	–1.02 (–1.43, –0.64)	–0.96 (–1.67, –0.29)	————
Failed to provide SU dosing at baseline‡	–1.31 (–2.03, –0.69)	–1.16 (–2.18, –0.26)	–1.09 (–1.83, –0.43)	–0.89 (–1.87, 0.11)	–0.58 (–1.51, 0.37)	–1.03 (–1.90, –0.20)	–1.10 (–2.26, –0.02)	————

A1C = glycosylated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SU = sulfonylurea; TZDs=thiazolidinediones.
*19 RCTs[10,14,15,17,19,20,22,25,27,29-31,35,37,38,40,41,43,108]
†18 RCTs[10,14,15,17,19-22,25,29-31,35,37,38,40,41,43]
‡12 RCTs[10,14,17,19-21,29,31,35,37,38,41,43]

4.1.4 Summary of RCTs that were not pooled

One three-arm RCT[24] compared insulin NPH and a meglitinide (i.e., repaglinide) in combination with metformin, biphasic insulin in combination with metformin, and insulin NPH with metformin. Change from baseline effect sizes were 1.9% (95% confidence interval [CI]: –1.03 to –2.77), –1.1% (95% CI: –0.51 to –1.69), and –0.8 (95% CI: 0.15 to –1.75), respectively. This particular study[24] was excluded from the MTC meta-analyses due to statistically significant differences in baseline A1C between treatment arms and the low clinical utility of the insulin NPH, repaglinide, and metformin treatment strategy. Another study[16] was excluded from the MTC analysis because it compared pioglitazone with placebo in patients taking insulin and metformin. TZDs are currently not approved for use in combination with insulin products; hence, this trial was not included in the reference case analyses. At the end of this particular 20-week trial, there was a non-statistically significant reduction in A1C with pioglitazone versus placebo (mean difference [95% CI] = –0.20 [–1.02, 0.62]).

There were three RCTs that reported intraclass comparisons of insulin analogues and conventional insulins. One RCT[44] compared combination therapy with insulin glargine, and metformin with NPH insulin combined with metformin, and reported no significant difference in A1C at end point (nine months). Another RCT[32] compared add-on therapy with neutral protamine lispro with insulin glargine. This trial reported no significant difference between the two groups. One RCT[33] compared insulin lispro with regular human insulin and reported no significant difference between the groups at end point (5.5 months).

4.2 4.2 Body Weight

There were 26 RCTs[10-12,14-16,19-26,28,31-33,35,36,38-41,43,45] (N = 7011) that reported change from baseline in body weight (see Appendices 27 and 28).

4.2.1 Primary MTC analysis: add-on therapies

As with hemoglobin A1C, the primary MTC analysis was restricted to studies that involved an add-on design regarding concomitant use of metformin and sulfonylurea. The evidence network was composed of 16 RCTs[10,14,15,19-22,25,28,31,35,38,40,41,43,45] representing eight third-line drug classes in addition to placebo (N = 5575). Illustrations of the MTC evidence networks are presented in Appendix 23.

The most common comparison was TZDs versus basal insulin, both in combination with metformin and sulfonylureas (three RCTs).[10,31,38] A summary of the results is presented in Table 13 and represented graphically in Figure 3. Complete results are presented in Appendix 29, with forest plots illustrating pairwise meta-analyses available in Appendix 25. When added to metformin and sulfonylurea therapy, treatment with basal insulin, biphasic insulin, rapid-acting insulin analogues, and TZDs were all associated with a significantly greater increase in body weight than treatment with metformin and sulfonylurea (range: 1.85 kg to 5.00 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral, whereas GLP-1 analogues were associated with statistically significant weight loss –1.59 kg (–3.01, –0.20). The large degree of uncertainty (i.e., very wide CI) for the effect of meglitinides makes it difficult to draw conclusions for this class (2.67 kg [–0.94, 6.32]).

The estimates of effect derived from the direct pairwise comparisons aligned well with those obtained from the MTC analysis in both direction and magnitude. Furthermore, the posterior mean residual deviance (19.2) was approximately equal to the number of unconstrained data points (19.0), an indication of good model fit (see Appendix 31).

4.2.2 Sensitivity analyses for body weight

Table 14 displays the results of sensitivity analyses, meta-regression analyses, and alternative modelling conducted to explore the results of the primary MTC meta-analysis for body weight (reference case). There were few significant differences in the MTC estimates of effect after removing studies with any of the following criteria: crossover design, failure to provide sulfonylurea dosage at baseline, and an A1C threshold of < 7.0% in the inclusion criteria. Removing studies that failed to report sufonylurea dosage at

baseline increased the uncertainty for several of the drug classes, resulting in loss of statistical significance for basal insulin (weight gain) and GLP-1 analogues (weight loss). An additional sensitivity analysis of add-on therapies was performed where insulin NPH and the long-acting insulin analogues were separated in the MTC meta-analysis. Relative to placebo, long-acting insulin analogues were associated with a statistically significant increase in body weight (2.4 kg [0.8, 3.9]) as was insulin NPH (1.3 kg [0.8, 3.9]). There was no significant difference between NPH and long-acting insulin analogues.

A meta-regression was performed to account for differences in baseline BMI and yielded results that were consistent with the reference case analysis. The meta-regression coefficients are available in Appendix 32. 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.

4.2.3 Secondary MTC analysis: all treatment strategies

The MTC analysis that included all treatment strategies was composed of 22 RCTs[10-12,14,15,19-25,28,31,35,36,38-41,43,45] representing 15 different therapeutic regimens that involved all eight drug classes (N = 6625). The most common comparison was TZDs versus basal insulin, both in combination with metformin and sulfonylureas (three RCTs)[10,31,38] and biphasic insulin as monotherapy compared with basal insulin in combination with metformin and sulfonylureas (3 RCTs each).[11,12,36] A summary of the MTC results and direct pairwise meta-analyses is shown in Table 13 and Figure 4, with detailed results presented in Appendix 25 and 30.

Results for the add-on therapies were similar between the primary and secondary models (i.e., significant weight gain with TZDs and the insulins; no significant weight gain with DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues). Increased weight gain was also observed for biphasic insulins when used as monotherapy, and basal insulin in combination with sulfonylurea or as monotherapy (see Table 13).

The posterior mean residual deviance (26) of the secondary MTC analysis was less than the number of unconstrained data points (28), an indication of good model fit.

Table 13: Summary of MTC Results for Change From Baseline In Body Weight (Kg) Compared With Placebo

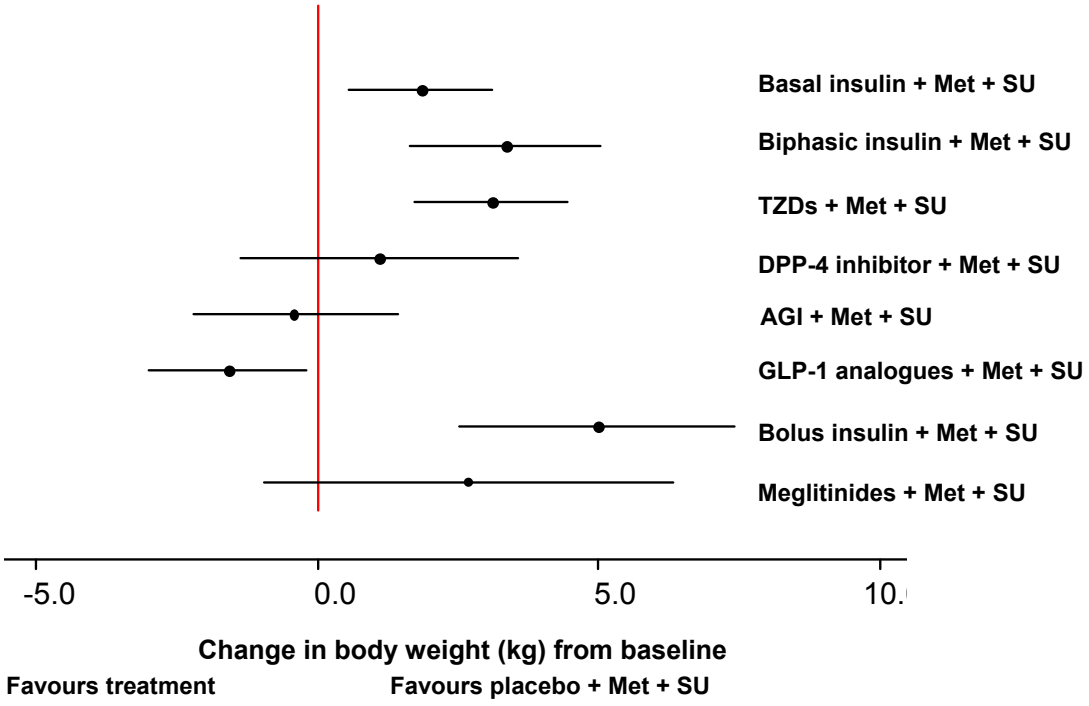
Third-Line Treatment Strategy Versus Placebo + Met + SU	Direct Estimate WMD (kg) (95% CI)	MTC Estimate (kg) (95% CrI)	Probability of Least Weight Gain	Mean Rank
Add-on therapy (primary analysis)				
Basal Insulin + Met + SU	0.88 (–1.39, 3.15)	1.85 (0.54, 3.09)	0.0%	5.07
Biphasic Insulin + Met + SU	———	3.35 (1.65, 5.03)	0.0%	7.24
TZD + Met + SU	3.54 (2.43, 4.64)	3.10 (1.73, 4.43)	0.0%	6.94
DPP-4 + Met + SU	1.10 (0.28, 1.29)	1.11 (–1.36, 3.57)	2.4%	4.32
Alpha-glucosidase + Met + SU	–0.88 (–1.63, –0.14)	–0.43 (–2.20, 1.44)	12.5%	2.37
GLP-1 + Met + SU	–0.88 (–1.29, –0.47)	–1.59 (–3.01, –0.20)	83.8%	1.19
Bolus Insulin + Met + SU	———	5.00 (2.52, 7.43)	0.0%	8.72
Meglitinide + Met + SU	———	2.67 (–0.94, 6.32)	0.8%	6.23
All treatment strategies (secondary analysis)				
Basal Insulin + Met + SU	1.99 (1.00,2.99)	1.85 (0.55, 3.06)	0.0%	5.2
Biphasic Insulin + Met + SU	———	3.36 (1.70, 5.00)	0.0%	8.5
TZD + Met + SU	3.54 (2.43, 4.64)	3.10 (1.72, 4.41)	0.0%	7.9
DPP-4 + Met + SU	1.10 (0.28, 1.29)	1.11 (–1.31, 3.51)	2.2%	4.5
alpha-glucosidase + Met + SU	–0.96 (–1.79, –0.12)	–0.43 (–2.17, 1.39)	12.5%	2.4
GLP-1 + Met + SU	–0.88 (–1.29, –0.47)	–1.59 (–2.97, –0.23)	84.1%	1.2
Bolus Insulin + Met + SU	1.99 (1.00,2.99)	5.01 (2.56, 7.42)	0.0%	11.6

Table 13: Summary of MTC Results for Change From Baseline In Body Weight (Kg) Compared With Placebo				
Third-Line Treatment Strategy Versus Placebo + Met + SU	**Direct Estimate WMD (kg) (95% CI)**	**MTC Estimate (kg) (95% CrI)**	**Probability of Least Weight Gain**	**Mean Rank**
Meglitinide + Met + SU	———	2.69 (–0.86, 6.35)	0.8%	7.3
Biphasic insulin + Met	———	4.52 (1.84, 7.22)	0.0%	10.7
Basal insulin + SU	———	3.27 (0.63, 6.09)	0.0%	8.1
Basal insulin	———	4.69 (1.68, 7.87)	0.0%	11.0
Biphasic Insulin	———	3.85 (1.83, 6.00)	0.0%	9.6

CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; MTC = mixed treatment comparison; SU = sulfonylurea; TZD = thiazolidinedione; WMD = weighted mean difference.

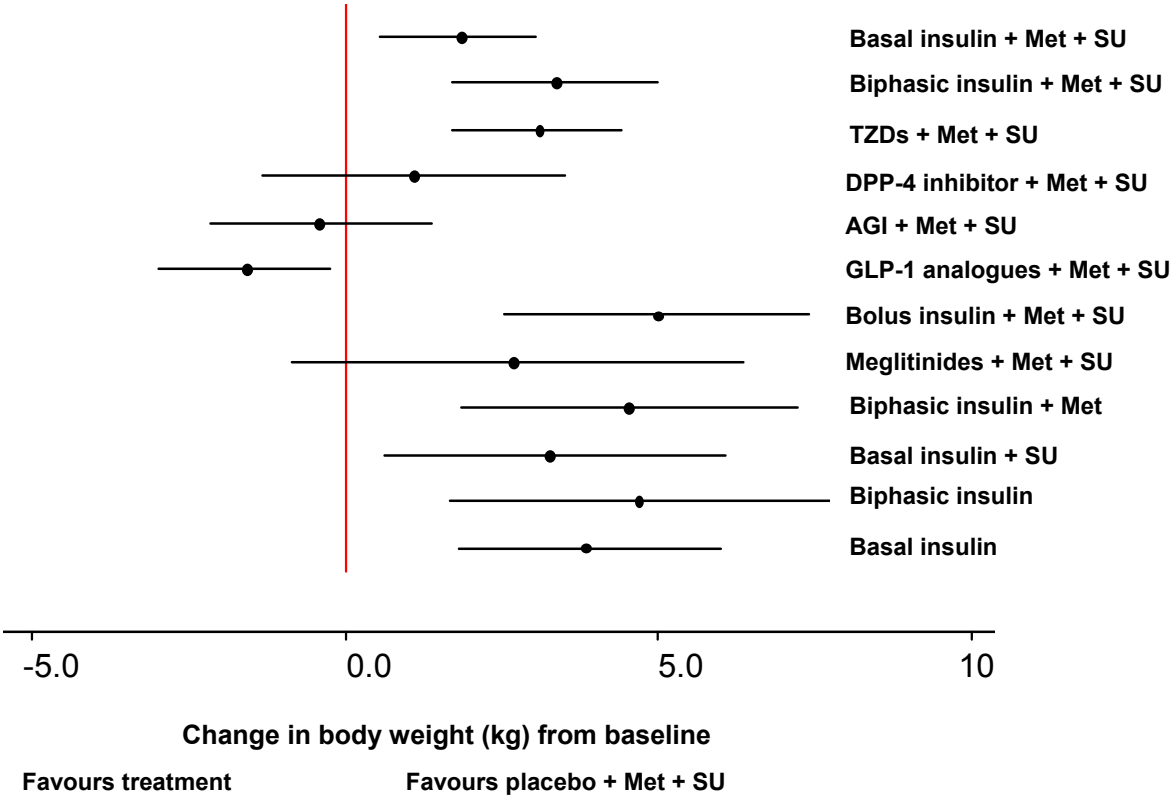
All values represent the difference in the change in body weight (kg) from baseline between a particular third-line intervention strategy and the combination of metformin/sulfonylurea. The MTC results are presented as the mean pooled estimate of effect (95% CrI) and the direct comparisons as the mean difference for the change in body weight from baseline (95% CI). The table also presents the probability of achieving the largest reduction (or least weight gain) in body weight with each individual treatment, based on the results of 40,000 simulations. The "Rank" represents the average ranking for each treatment relative to the others over the 40,000 simulations; a lower number indicates that a particular treatment demonstrated the largest reduction in body weight relative to other treatments more often than treatments with a higher number.

Figure 3: Differences In Change From Baseline for Body Weight Between Active Third-Line Treatments and Placebo, Both In Combination With Metformin and a Sulfonylurea: Results From the Primary MTC Analysis



AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZDs = thiazolidinediones.

Figure 4: Differences in change from baseline for body weight between active third-line treatments and placebo: results from secondary MTC analysis



AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZDs = thiazolidinediones.

Table 14: Sensitivity Analyses, Meta-regression Analyses, and Model Comparisons for the Primary MTC Analysis of Change From Baseline Body Weight

MTC Estimate of Effect (95% CrI) for Change From Baseline In Body Weight (Kg) (Third-Line Treatment Versus Placebo)								
Analysis	**Basal Insulin**	**Biphasic Insulin**	**TZDs**	**DPP-4 Inhibitors**	**Alpha-glucosidase inhibitors**	**GLP-1 Analogues**	**Bolus Insulin**	**Meglitinides**
Random-effects model versus fixed-effects model								
Reference case — random-effects model	1.85 (0.54, 3.09)	3.35 (1.65, 5.03)	3.10 (1.73, 4.43)	1.11 (–1.36, 3.57)	–0.43 (–2.20, 1.44)	–1.59 (–3.01, –0.20)	5.00 (2.52, 7.43)	2.67 (–0.94, 6.32)
Reference case — fixed-effects model	2.54 (2.12, 2.95)	3.67 (3.21, 4.12)	3.49 (3.00, 3.98)	1.10 (0.27, 1.93)	–0.88 (–1.63, –0.14)	–1.44 (–1.81, –1.07)	5.50 (4.81, 6.18)	2.22 (–0.02, 4.50)
Meta-regression adjusting for:								
Baseline BMI	1.86 (0.54, 3.08)	3.21 (1.48, 4.90)	3.27 (1.84, 4.62)	1.17 (–1.30, 3.60)	–0.43 (–2.17, 1.44)	–1.61 (–3.02, –0.23)	4.68 (2.10, 7.19)	1.96 (–1.81, 5.88)
Sensitivity analyses with removal of:								
Crossover studies*	2.63 (1.37, 3.81)	3.93 (2.45, 5.42)	3.51 (2.32, 4.69)	1.09 (–0.95, 3.16)	–0.97 (–3.01, 1.08)	–1.16 (–2.35, 0.04)	5.68 (3.51, 7.79)	————
A1C < 7.0% (inclusion criteria)†	1.85 (0.52, 3.10)	3.35 (1.63, 5.06)	3.10 (1.68, 4.45)	1.10 (–1.37, 3.54)	–0.44 (–2.21, 1.44)	–1.59 (–3.02, –0.19)	5.00 (2.49, 7.49)	2.64 (–0.97, 6.35)
Failed to provide SU dosing at baseline‡	1.39 (–0.45, 3.18)	3.77 (0.87, 6.62)	2.80 (0.66, 4.87)	1.10 (–2.01, 4.16)	–0.49 (–2.62, 1.79)	–1.33 (–3.92, 1.17)	4.98 (1.65, 8.27)	————

A1C = glycosylated hemoglobin; BMI = body mass index; CrI = credible interval, DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SU = sulfonylurea; TZDs = thiazolidinediones.

*14 RCTs [10,14,15,19-21,21,22,25,31,38,40,41,43]

†RCTs[10,14,15,19-22,25,31,35,38,40,41,43]

‡10 RCTs[10,14,19-21,31,35,38,41,43]

4.2.4 Summary of RCTs that were not pooled

As noted for A1C, one three-arm RCT[24] compared:

- a combination of insulin NPH, meglitinide (i.e., repaglinide), and metformin
- metformin with biphasic insulin
- metformin with insulin NPH.

This trial was not pooled with the others due to the low clinical utility of this treatment strategy, as well as other methodological limitations. There were no significant differences in change in body weight from baseline between any of the three regimens (P = 0.06).

One RCT[44] comparing insulin glargine combined with metformin to NPH insulin combined with metformin reported no significant difference in body weight [mean (standard error [SE]) = 2.6 ± 0.6 kg versus 3.5 ± 0.7 kg]. Another RCT[32] comparing add-on therapy with neutral protamine lispro to add-on therapy with insulin glargine also reported no significant difference between the two groups [mean (standard deviation) = 2.4 ± 3.1 kg vs. 2.8 ± 3.5]. A third RCT[33] compared insulin lispro with regular human insulin and reported no significant difference between treatments.

4.3 Body Mass Index

Three RCTs[17,28,30] (n = 245) reported change in body mass index (BMI) from baseline. Due to the limited evidence for this outcome, an MTC meta-analysis was not conducted. One small RCT[30] (n = 30) comparing pioglitazone with insulin glargine (both in combination with metformin and sulfonylureas) reported no significant difference in the change in BMI from baseline (P = 0.37). Another RCT[17] (n = 112) reported no significant difference in change from baseline between patients who received either rosiglitazone or insulin NPH added onto metformin and sulfonylurea therapy (0.9 ± 1.3 vs. 0.8 ± 0.9). One crossover RCT[28] (n = 103) reported a significant increase from baseline in the BMI of patients receiving repaglinide (P < 0.05) and a significant decrease in patients receiving acarbose (P < 0.05).

4.4 Hypoglycemia

4.4.1 Severe hypoglycemia

This review identified 22 RCTs[10,14-16,19,22-26,29,31,34-41,43,45] (n = 6368) that reported the number of patients experiencing severe hypoglycemia during the trial. Severe hypoglycemia was typically defined as an event requiring third-party assistance (see Appendix 33 for definitions from individual trials). Studylevel results for the individual RCTs are presented in Appendix 34. Events of severe hypoglycemia were relatively rare for all drug classes including the insulins. Overall, there were no events reported in 35 out of 52 treatment arms. Five RCTs[23,24,36,39,43] compared treatment strategies involving the use of biphasic or basal insulin. The largest was a three-arm trial that randomized patients to treatment with biphasic insulin (BiAsp30), basal insulin (determir), or bolus insulin (aspart), each in addition to continued metformin and sulfonylurea.[43] This RCT reported a statistically significant increase in severe hypoglycemia with bolus insulin versus basal insulins [odds ratio (95% CI): 4.14 (1.36, 12.59)] and a trend toward more events with biphasic versus basal insulin [odds ratio (95% CI): 2.82 (0.89, 9.00)].

4.4.2 Overall hypoglycemia

There were 26 RCTs[10,11,14-17,20-26,29,31,33-41,43,45] (N = 7,238) that reported overall hypoglycemia. Complete study-level data regarding the incidence of hypoglycemia in each of these trials is presented in Appendices 35 and 36. The most common comparison was TZDs versus basal insulin, both in combination with metformin and sulfonylureas (four RCTs).[10,17,38,46] Direct pairwise comparisons are shown in Table 15, with forest plots for comparisons with multiple included trials available in Appendix 25. Definitions of hypoglycemia used in the individual RCTs are provided in Appendix 33; 15 RCTs failed to provide definitions of overall hypoglycemia.[12,17,19-21,23,26-28,30,37-41] MTC analysis was not performed for this outcome due to the large variation in the control group (i.e., metformin plus sulfonylurea) event rates.

a) Placebo-controlled trials reporting overall hypoglycemia

Five placebo-controlled trials reported data for overall hypoglycemia.[15,20,22,35,41] Add-on therapy with basal insulin,[35] TZDs,[20,22] DPP-4 inhibitors,[41] and GLP-1 analogues[15,35] was associated with a significantly higher number of patients experiencing overall hypoglycemia than placebo. Amongst these trials, combination therapy with DPP-4 inhibitors, metformin, and a sulfonylurea was associated with the highest odds ratio (albeit, with the widest CIs). Data for DPP-4 inhibitors was limited to a single RCT[41] where 19 out of 116 patients receiving 100 mg/day sitagliptin experienced hypoglycemia compared with 1 out of 113 in the placebo arm (both in combination with metformin and sulfonylureas). It should be noted that the authors of this particular RCT failed to report their definition of overall hypoglycemia.

b) Active comparisons reporting overall hypoglycemia

There were a total of 15 pairwise comparisons involving active treatments with data for overall hypoglycemia. The majority of these consisted of different insulin regimens, with varying concomitant use of metformin and sulfonylurea.

- **Comparisons of insulins as add-on:** Add-on therapy with biphasic insulin[109] or bolus insulin[43] was associated with significantly more hypoglycemia than add-on basal insulin, although the difference between biphasic insulin and basal insulin was non-signficant in one RCT[45] (n = 469). There was also a trend towards more hypoglycemia with insulin aspart in comparison with biphasic insulin.[43]
- **Comparisons of insulins and GLP-1 analogues:** One RCT[14] reported that the addition of a GLP-1 analogue to sulfonylurea and metformin was associated with significantly fewer events of hypoglycemia than biphasic insulin in combination with both metformin and sulfonylurea, or with metformin alone. Another RCT[35] reported no significant difference in hypoglycemia between GLP-1 analogues and basal insulin.
- **Comparisons of insulins and TZDs:** Pooled data from four RCTs,[10,17,31,38] demonstrated that add-on basal insulin was associated with significantly more hypoglycemia than add-on TZDs.

Table 15: Pairwise Comparisons of Studies Reporting Overall Hypoglycemia

Intervention 1	Intervention 2	No. of RCTs	N	Direct Estimates OR (95% CI)	I^2 (%)
Placebo comparisons (intervention 1 versus intervention 2)					
Basal Insulin + Met + SU	Placebo + Met + SU	1[35]	346	2.03 (1.15, 3.58)	——
TZD + Met + SU	Placebo + Met + SU	2[20,22]	664	5.62 (2.81, 11.25)	33
DPP-4 Inhibitors + Met + SU	Placebo + Met + SU	1[41]	229	21.94 (2.88, 167)	——
GLP-1 + Met + SU	Placebo + Met + SU	2[15,35]	1324	2.07 (1.54, 2.77)	
Active comparisons (intervention 1 versus intervention 2)					
Biphasic Insulin + Met + SU	Basal Insulin + Met + SU	1[43]	469	4.01 (2.31, 6.96)	——
Biphasic Insulin + Met + SU	Basal Insulin + Met + SU	1[45]	469	1.29 (0.90, 1.86)	——
TZD + Met + SU	Basal Insulin + Met + SU	4[10,17,31,38]	413	0.40 (0.21, 0.75)	22
GLP-1 + Met + SU	Basal Insulin + Met + SU	1[35]	462	0.93 (0.62, 1.39)	——
Bolus insulin + Met + SU	Basal Insulin + Met + SU	1[43]	402	8.97 (4.34, 18.56)	——
Biphasic Insulin	Basal Insulin + Met + SU	1[11]	236	1.32 (0.86, 2.03)	——
GLP-1 + Met + SU	Biphasic Insulin + Met + SU	1[14]	105	0.33 (0.19, 0.55)	——
Bolus insulin + Met + SU	Biphasic Insulin + Met + SU	1[43]	445	2.24 (0.99, 5.05)	——
Biphasic insulin + Met	Biphasic Insulin + Met + SU	1[14]	248	1.26 (0.76, 2.09)	——
Biphasic insulin + Met	GLP-1 + Met + SU	1[14]	112	3.87 (2.28, 6.58)	——
Biphasic insulin + Met	Basal Insulin + Met	1[24]	56	1.32 (0.40, 4.33)	——
Basal insulin + Meg. + Met	Basal Insulin + Met	1[24]	55	0.57 (0.15, 2.23)	——
Basal insulin + Meg. + Met	Biphasic insulin + Met	1[24]	53	0.43 (0.11, 1.66)	——
Basal insulin	Basal Insulin + Met	1[39]	174	1.08 (0.01, 218.9)	——
Biphasic Insulin	Basal Insulin + Met	1[39]	173	1.12 (0.01, 115.9)	——
Biphasic Insulin	Basal insulin	1[39]	175	1.04 (0.09, 12.34)	——

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; IAsp = insulin aspart; Meg = meglitinide; Met = metformin; N = total sample size; No. = number; OR = odds ratio; RCTs = randomized controlled trials; SU = sulfonylurea; TZD = thiazolidinediones.

c) Intraclass comparisons

There were three RCTs that reported intraclass comparisons of insulin analogues and conventional insulins.

- One RCT[44] comparing combination therapy insulin glargine and NPH insulin, both combined with metformin, reported no significant difference in hypoglycemia at nine months.
- One RCT[32] comparing add-on therapy with neutral protamine lispro with insulin glargine reported no significant difference in hypoglycemia between the two groups.
- One RCT[33] reported no significant difference in hypoglycemia between insulin lispro (1.7 ± 0.3 [SE] episodes/30 days) and regular human insulin (1.8 ± 0.3 [SE] episodes/30 days) in patients who ceased taking both metformin and sulfonylurea.

4.4.3 Nocturnal hypoglycemia

This review identified seven RCTs (n = 2394)[11,25,31,33,37,40,45] that reported the number of patients with at least one episode of nocturnal hypoglycemia. Four of these RCTs[11,31,40,45] included a treatment arm where patients received insulin glargine in combination with metformin and sulfonylurea therapy.

- One RCT[11] (n = 364) compared the use of insulin glargine in combination with metformin and sulfonylurea against the use of biphasic insulin (30/70 NPH) with placebo and reported 0.5 events per patient per year and 1.04 events per patient per year, respectively (P = 0.0449). A sub-group analysis from this RCT focusing on patients ≥ 65 years of age reported no statistically significant difference between the two groups (p = 0.29).[13]
- Another study[45] compared add-on therapy with insulin glargine against add-on therapy with biphasic insulin aspart and reported 0.5 events per patient per year and 1.1 events per patient per year of nocturnal hypoglycemia, respectively [RR (95% CI) = 2.41 (1.34, 4.34); P = 0.003].
- One trial[31] comparing add-on therapy with insulin glargine against add-on therapy with rosiglitazone reported a significantly higher number of nocturnal hypoglycemic events in the insulin glargine group (P = 0.02).
- One RCT[40] (n = 549) reported a significant between-group difference of –1.6 events per patient per year (95% CI; –2.3 to –0.9) favouring the addition of exenatide (0.9 events per patient per year) over insulin glargine (2.4 events per patient per year) to ongoing treatment with metformin and sulfonylureas.
- Nauck et al.[25] (n = 501) reported no significant difference between patients receiving add-on therapy with exenatide and those receiving add-on therapy with biphasic insulin aspart when results were adjusted for baseline A1C and country; however, there was a significantly lower number of patients experiencing events in the exenatide arm in the unadjusted results (17% versus 25%; P < 0.038).
- One RCT[37] (n = 133) comparing the addition of miglitol or placebo to ongoing therapy with glyburide and metformin reported no events in either treatment arm.
- One comparison[33] (n = 148) of insulin lispro against regular human insulin (both in combination with insulin NPH) reported nocturnal hypoglycemia rates of 0.08 and 0.16 events per 30 days, respectively (p = 0.057).

4.5 Long-Term Diabetes-Related Complications

Results for long-term complications are shown in Table 16. The majority of RCTs included in this review did not report data for these outcomes, and those that did were inadequately powered to detect statistically significant differences between treatments. Congestive heart failure was reported in two RCTs,[20,30] both evaluated pioglitazone, and there were no events occurring in any of the treatment arms. Six RCTs[14,16,22,25,41,43] reported all-cause mortality and there were no statistically significant differences between any of the treatment arms. Only a single RCT[20] reported events of stroke or transient ischemic attacks, with only a single event occurring in the trial. Only one study[16] reported events of ischemic heart disease, with only a single event recorded during the trial. It should be noted that the experimental arm in this study involved a combination of insulin and pioglitazone, which is not an approved combination therapy in Canada. No studies reported data on neuropathy, retinopathy, peripheral vascular disease, or macular edema.

Table 16: Summary of Trials Reporting Data on Long Term Complications of Diabetes				
Author, Year	**Treatment 1**	**n/N (%)**	**Treatment 2**	**n/N (%)**
Ischemic heart disease				
Berhanu et al., 2007[16]	Insulin + Piog. + M	0/110 (0%)	Insulin + placebo + M	1/112 (0.9%)
Congestive heart failure				
Dorkhan et al., 2009[30]	Piog. + M + S	0/15 (0%)	Insulin glargine + M + S	0/15 (0%)
Charpentier and Halimi, 2009[20]	Piog. + M + S	0/145 (0%)	Placebo + M + S	0/154 (0%)
Mortality				
Berhanu et al., 2007[16]	Insulin + Piog. + M	0/110 (0%)	Insulin + Placebo + M	0/112 (0%)
Hermansen et al., 2007[41]	Sitagliptin + M + S	1/116 (0.9%)	Placebo + M + S	0/113 (0%)
Bergenstal et al., 2009[14]	Exenatide + M + S	0/124 (0%)	BIAsp30 (q.d.) + M + S	0/124 (0%)
	BIAsp30 (b.i.d.) + M	1/124 (0.8%)	———	———
Holman et al., 2007[43]	Insulin aspart + M + S	1/239 (0.4%)	BiAsp30 + M + S	3/235 (1.3%)
	Insulin detemir + M + S	0/234 (0%)	———	———
Nauck et al., 2007[25]	Exenatide + M + S	2/253 (0.8%)	BiAsp30	1/248 (0.4%)
Dailey et al., 2004[22]	Rosiglitazone + M + S	0/181 (0%)	Placebo + M + S	1/184 (0.5%)
Stroke/Transient Ischemic Attack				
Charpentier and Halimi, 2009[20]	Pioglitazone + M + S	1/145 (0.7%)	Placebo + M + S	0/154 (0%)

BiAsp = biphasic insulin aspart; b.i.d. = twice daily; M = metformin; N = total number of patients; n=number of patients with event; Piog. = pioglitazone; q.d. = once daily; S=sulfonylurea.

4.6 Patient Satisfaction With Diabetes Treatment

Four RCTs[10,18,36,45] used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) to assess within and between group differences in patients' overall satisfaction with the therapeutic regimen to which they were randomly allocated. One RCT[45] reported no significant difference in DTSQ scores between insulin glargine and biphasic insulin aspart, both given in combination with metformin and a sulfonylurea [-0.11 (-2.36, 2.14)]. A study[18] (n = 549) comparing exenatide with insulin glargine when added to metformin and sulfonylurea reported that both groups showed a statistically significant improvement from baseline to endpoint; however, there was no significant difference between groups. A small RCT[36] (n = 64) reported no statistically significant difference in DTSQ scores of patients treated with insulin NPH once daily in combination with metformin compared with those receiving biphasic insulin (70/30) twice daily. Another small RCT[10] (n = 62) compared pioglitazone and insulin NPH, both in combination with metformin and sulfonylureas, and found no statistically significant difference (P = 0.37).

4.7 Withdrawals Due to Adverse Events

WDAE were reported in 23 RCTs.[10-12,14,16,17,19,20,22-24,28,29,31,32,34,35,37,38,40,41,43,44] Study-level details for individual RCTs are presented in Table 17, Figures 5 and 6, and Appendix 16. Three RCTs[14,34,40] involving exenatide that reported WDAE all demonstrated a statistically significant increase in withdrawals relative to comparators (i.e., placebo, insulin glargine, or biphasic insulin aspart). All three of these studies cited nausea and vomiting as the primary reasons for withdrawal among exenatide-treated subjects. The other two RCTs[15,25] of exenatide failed to report WDAE. One three-arm trial[35] also showed an increase in WDAE for patients treated with the GLP-1 analogue, liraglutide (4.7%), in comparison with

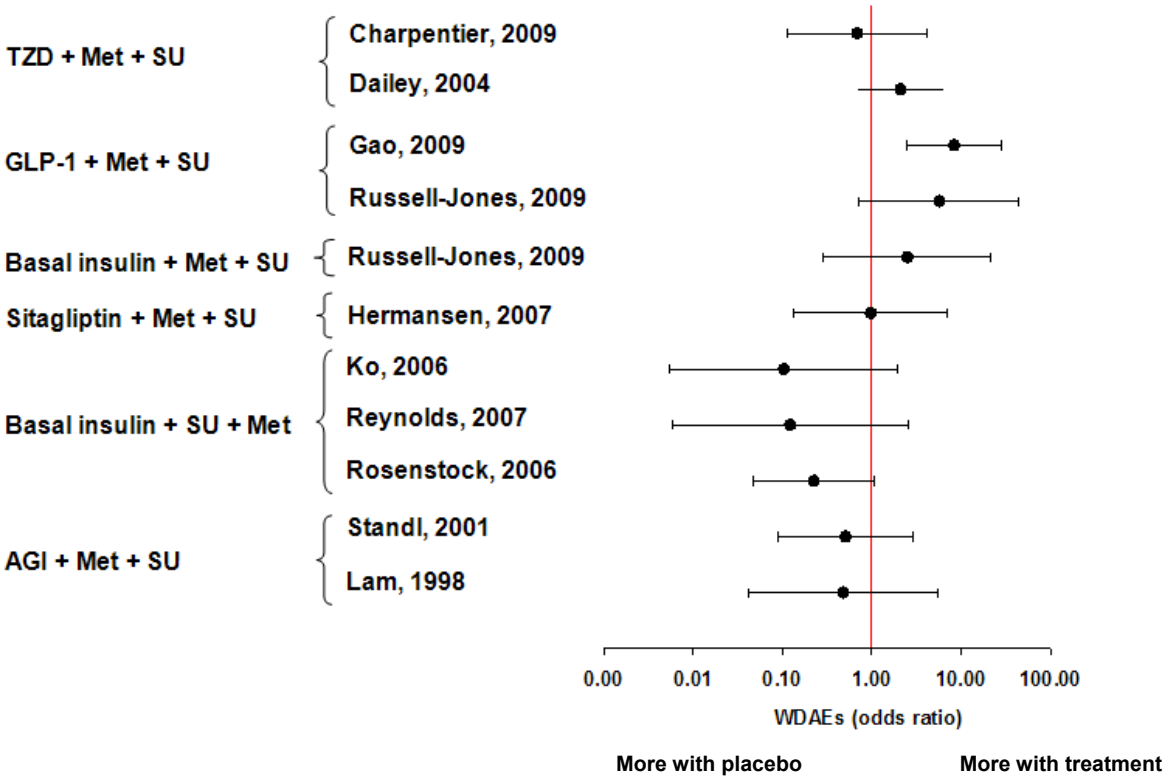
those receiving insulin glargine (2.1%) or placebo (0.9%). This study also cited nausea as the primary adverse event in the liraglutide treatment arm.

Table 17: Summary of Trials Reporting Withdrawals Due to Adverse Events

Comparisons	No. of Trials/Total N	OR (95% CI)
Placebo comparisons		
TZD + Met + SU vs. placebo + Met + SU	1[20] (N = 289)	0.69 (0.11, 4.17)
TZD + Met + SU vs. placebo + Met + SU	1[22] (N = 365)	2.09 (0.70, 6.25)
GLP-1 + Met + SU vs. placebo + Met + SU	1[34] (N = 466)	8.32 (2.46, 28.12)
GLP-1 + Met + SU vs. placebo + Met + SU	1[35] (N = 344)	5.68 (0.72, 44.5)
Basal insulin + Met +SU vs. placebo + Met + SU	1[35] (N = 346)	2.49 (0.29, 21.56)
Sitagliptin + Met + SU vs. placebo + Met + SU	1[41] (N = 229)	0.97 (0.13, 7.03)
AGI + Met + SU vs. placebo + Met + SU	1[37] (N = 133)	0.51 (0.09, 2.87)
AGI + Met + SU vs. placebo + Met + SU	1[19] (N = 89)	0.48 (0.04, 5.46)
Active comparisons		
Biphasic insulin vs. Insulin glargine + SU + Met	1[12] (N = 221)	*No events*
Biphasic insulin vs. Insulin glargine + SU + Met	1[11] (N = 364)	5.83 (0.70, 48.95)
Biphasic (q.d.) + Met + SU vs. GLP-1 + Met + SU	1[14] (N = 248)	0.05 (0.00, 0.85)
Biphasic (b.i.d.) + Met + SU vs. GLP-1 + Met + SU	1[14] (N = 248)	0.21 (0.04, 0.99)
Biphasic (b.i.d.) + M + SU vs. Biphasic (q.d.) + M + SU	1[14] (N = 248)	5.08 (0.24, 106.94)
GLP-1 + Met + SU vs. Basal insulin + Met +SU	1[35] (N = 462)	2.28 (0.78, 6.67)
GLP-1 + Met + SU vs. Basal insulin + Met +SU	1[40] (N = 549)	14.03 (3.30, 59.60)
Basal insulin + Met + SU vs. TZD + Met + SU	1[17] (N = 112)	0.10 (0.01, 1.96)
Basal insulin + Met + SU vs. TZD + Met + SU	1[29] (N = 40)	0.12 (0.01, 2.53)
Basal insulin + Met + SU vs. TZD + Met + SU	1[31] (N = 216)	0.22 (0.05, 1.06)
Basal insulin + Met + SU vs. TZD + Met + SU	1[10] (N = 58)	*No events*
Biphasic + Met + SU vs. Basal + Met + SU	1[43] (N = 469)	0.49 (0.09, 2.72)
Bolus + Met+ SU vs. Basal + Met + SU	1[43] (N = 473)	0.11 (0.01, 2.00)
Biphasic + Met+ SU vs. Bolus + Met + SU	1[43] (N = 474)	5.13 (0.24, 107.40)

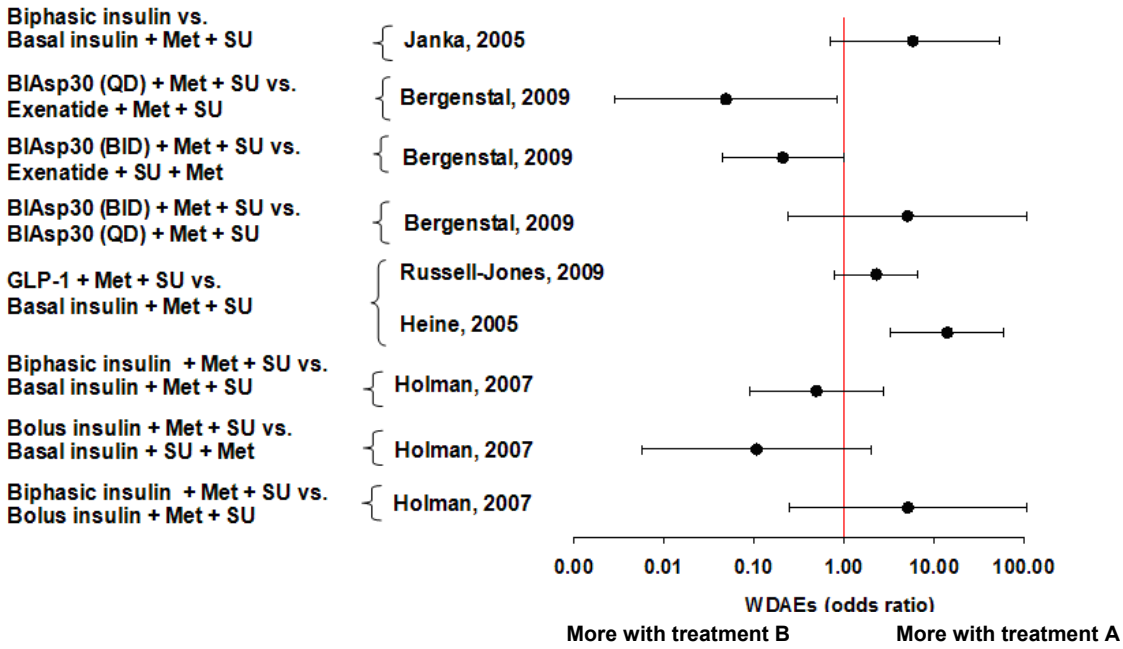
b.i.d. = twice daily; M = metformin; N = total number of patients; Piog. = pioglitazone; q.d. = once daily; S=sulfonylurea; vs. = versus.

Figure 5: Withdrawals Due to Adverse Events in Active Third-Line Treatments and Placebo, Both in Combination With Metformin and a Sulfonylurea



AGI = alpha glucosidase inhibitor; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZDs = thiazolidinediones.

Figure 6: Withdrawals Due to Adverse Events in Comparisons of Two Active Third-Line Treatments (A Vs. B)



AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; q.d. = once daily; SU = sulfonylurea; TZDs = thiazolidinediones; vs. = versus.

4.8 Serious and Severe Adverse Events

This review identified 13 RCTs[10,15,16,20,22,24,25,31,35,37,41,43,110] that reported total severe, serious, or major adverse events. It should be noted that only five studies[14,31,32,43,44] defined which adverse events were classified as "severe" or "serious". Study-level details for individual RCTs are presented in Appendix 16. The ability to compare adverse events acoss trials and drug classes was limited by the the small number of events that were reported, and the consequent limitations in statistical power.

Data for several treatments are highlighted below:

- **Trials involving exenatide:** One RCT[15] reported the number of severe adverse events in patients receiving 10 µg/day exenatide (29/245; 12%) and 20 µg/day exenatide (34/241; 14%) compared with placebo (20/247; 8%). However, there were no details regarding the nature of these events and no differences in the proportion of patients experiencing serious adverse events (also undefined). One RCT[25] reported the number of serious adverse events in patients receiving exenatide (19/253; 8%) in comparison with biphasic insulin aspart (11/248; 4%). No trials reported any events of pancreatitis.
- **Trial involving sitagliptin:** One RCT[41] reported the number of patients with serious adverse events with sitagliptin (7/116; 6%) compared with placebo (2/113; 2%); all were believed to be unrelated to the study medications and no definitions were provided.
- **Trials involving rosiglitazone:** One RCT[31] reported the number of patients with serious adverse effects with rosiglitazone (11/112; 10%) compared with insulin glargine (5/105; 5%); and one RCT[22] reported the number of events with rosiglitazone (3/181; 2%) compared with placebo (8/184; 4%).
- **Trial comparing biphasic, bolus, and basal insulin:** One RCT[43] comparing add-on therapy with three different insulin regimens reported serious adverse events in patients receiving biphasic insulin aspart (41/235; 17%) in comparison with insulin aspart (30/239; 13%) and insulin detemir (30/234; 13%). The events were described as any of the following: gastrointestinal and abdominal pain or infection, lower respiratory tract and lung infection, ischemic coronary-artery disorder, or other infection.

- **Trial involving liraglutide:** One RCT[35] reported the number of serious adverse events in patients treated with liraglutide (9/230; 4%), insulin glargine (16/232; 7%), and placebo (8/114; 7%), all in combination with metformin and a sulfonylurea.

4.9 Specific Adverse Effects

Only a single RCT[35] reported pancreatitis; no events were observed in any of the three treatment arms (liraglutide, insulin glargine, or placebo arms, all in combination with metformin and glimepiride). There was no evidence available from the included RCTs regarding the occurrence of upper extremity fractures, or hyperosmolar hyperglycemic, nonketotic coma.

4.10 Efficacy and Safety for Patients 65 Years and Older

Patients 65 years and older were identified as a population of special interest in this therapeutic review. The available evidence for this group is limited to a subgroup analysis from a single RCT. Janka et al.[11] reported a subgroup analysis of patients aged 65 or older (n = 67) in a companion publication[13] for their study comparing insulin glargine with biphasic insulin, both in combination with glimepiride and metformin. The subgroup analysis showed that patients in the insulin glargine arm had a greater reduction in hemoglobin A1C compared with the biphasic insulin arm [mean difference (95% CI) =– 0.46% (– 0.75, – 0.16); P = 0.003]. There was no significant difference in change in body weight from baseline (insulin glargine: 1.3 ± 3.0 kg, biphasic insulin: 2.2 ± 3.9 kg; P = 0.17). Patients receiving insulin glargine (n = 67) experienced significantly fewer events of overall hypoglycemia compared with patients treated with biphasic insulin (n = 63) (3.68 events per patient-year versus 9.09 events per patient-year; P = 0.008). There was no significant difference between treatments in the rates of severe hypoglycemia (0.00 versus 0.09 events per patient-year; P = 0.21) or confirmed nocturnal hypoglycemia (0.39 versus 0.71 events per patient-year; P = 0.26). These findings are consistent with those reported for the overall study population.[11] One patient in the insulin glargine group and two in the biphasic insulin group withdrew because of adverse events. The reasons for these withdrawals were not reported; however, it was indicated that hypoglycemia was not the cause. Five events of diabetic neuropathy were reported in three patients in the biphasic insulin arm and none were reported in the insulin glargine arm.

5 DISCUSSION

5.1 Summary of Available Evidence

In this systematic review, we identified 33 RCTs (N = 8,148) reporting the effects of eight classes of third-line therapies for patients with type 2 diabetes inadequately controlled on combination therapy with metformin and sulfonylureas. A total of 17 different treatment strategies were studied in these trials. The majority of studies randomized patients to the addition of a third-line agent while continuing metformin and sulfonylureas (28 articles).[10,12,14,15,17-22,25-32,34-38,40-43,45] Strategies that were less commonly tested included those where the patient commenced treatment with a third-line agent and discontinued metformin or sulfonylurea (but not both),[11,16,24,44] and those where the patients commenced treatment with a third-line agent and discontinued both metformin and sulfonylurea (three RCTs).[11,23,39] MTC meta-analyses were conducted whenever possible because of the large number of drug classes and treatment strategies, as a means to incorporate both direct and indirect evidence in a unified framework.

5.2 Interpretation of Results

Very few studies reported evidence regarding comparative safety and efficacy in terms of clinically important long-term complications of diabetes or mortality. All studies that did report diabetes-related complications had limited power and none reported significant differences between any of the drug classes compared. This finding is consistent with CADTH's systematic review of second-line diabetes pharmacotherapy[2] as well as those conducted by Bolen et al.[101] and Selvin et al.[102]

Regarding glycemic control, MTC meta-analyses demonstrated that, when added to ongoing therapy with metformin and a sulfonylurea, basal insulin, biphasic insulin, bolus insulin, DPP-4 inhibitors, TZDs, and GLP-1 analogues significantly reduced A1C relative to placebo; however, there were no significant differences between any of these classes. Meglitinides and alpha-glucosidase inhibitors were not shown to provide statistically significant reductions in A1C. Results were found to be robust in a wide range of sensitivity analyses, meta-regression, and alternative modelling strategies (i.e., random versus fixed effects). Statistically significant improvement in A1C was also observed for patients who received biphasic insulin as monotherapy or in combination with metformin. The evidence for basal insulin as monotherapy or in combination with metformin or sulfonylureas was limited to single RCTs with important methodological limitations. Overall, the amount and quality of evidence was inadequate to draw conclusions regarding the relative efficacy of add-on, partial-switch, or full-switch treatment strategies in the initiation of insulin.

When added to metformin and sulfonylurea therapy, treatment with basal insulin, biphasic insulin, rapid-acting insulin analogues, or TZDs resulted in statistically significantly greater increases in body weight than treatment with metformin and sulfonylurea alone. Increased weight gain was also observed with basal and biphasic insulins when used as monotherapy, or in combination with metformin or a sulfonylurea alone. MTC results demonstrated that DPP-4 inhibitors and α-glucosidase inhibitors were weight neutral and that GLP-1 analogues were associated with statistically signficant weight loss. There is no universally accepted minimal clinically important difference for body weight, although 5% is the smallest change cited as being of clinical importance in the literature.[8,111-113] Based on the overall weight of the patients included in the MTC analysis (weighted mean 87.0 kg), the only drug class that exceeded a change of 5% relative to placebo was bolus insulin (5.7%). However, two comparisons between GLP-1 analogues, which were associated with weight loss, and oral agents also exceeded the 5% threshold: TZDs (5.4%) and biphasic insulins (5.7%).

Given the large differences in baseline overall hypoglycemia event rates in the control (i.e., metformin plus sulfonylurea) arms across studies, MTC meta-analysis was not conducted for this outcome. Furthermore, definitions of hypoglycemia were variable and often not reported in the included clinical trials. These issues are commonly encountered in diabetes studies and make it difficult to accurately compare hypoglycemia data across trials.[114] The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators. Biphasic and bolus

insulins were associated with a significantly greater risk of hypoglycemia than basal insulin. When given in combination with metformin and sulfonylureas, TZDs, GLP-1 analogues, and DPP-4 inhibitors were associated with a significantly greater number of patients experiencing hypoglycemia than placebo. In contrast, CADTH's analysis of second-line therapy found no increased risk of hypoglycemia when these agents are administered in combination with metformin alone, suggesting that combined use with sulfonylureas may potentiate risk.[2]

Events of severe hypoglycemia were relatively rare for all drug classes including the insulins (no events reported in 35 out of 52 treatment arms), limiting the statistical power to make comparisons across drug classes. Bolus insulin was shown to be associated with more events of severe hypoglycemia than basal insulin. Nocturnal hypoglycemia was infrequently reported in the included trials. More patients reported nocturnal hypoglycemia with biphasic insulin in comparison with basal insulin, and with basal insulin in comparison with TZDs or GLP-1 analogues.

The GLP-1 analogues, exenatide and liraglutide, were associated with significantly more withdrawals due to adverse events relative to comparators (i.e., placebo, insulin glargine, or biphasic insulin aspart). Nausea and vomiting were cited as the primary reasons for withdrawal. There were no significant differences between treatment strategies in the occurrence of serious or severe adverse events in the included RCTs, although the power to detect differences was limited due to the small number of events. A supplementary section on the potential harms and safety issues related to the therapeutic agents included in this review can be found in Appendix 14. This section contains data from observational studies, FDA warnings, and large RCTs that did not meet the inclusion criteria for this review. Among the key findings from this literature review were that both randomized[115-117] and non-randomized[118,119] studies have found significantly more upper and distal lower limb fractures among women taking TZDs than those taking controls (generally placebo, metformin, and/or a sulfonylurea). Furthermore, RCTs, including the RECORD[116] and ADOPT[117] studies, reported significantly higher rates of congestive heart failure in patients taking rosiglitazone relative to comparatives and a meta-analysis[120] of pioglitazone. RCTs also reported an increased risk of congestive heart failure. Due to their recent introduction to the market, there is little information available on the long-term safety of DPP-4 inhibitors and GLP-1 analogues. Post-market studies are currently underway to obtain more information concerning the safety of these agents.[121]

5.3 Knowledge Gaps

There was insufficient evidence to draw conclusions regarding the relative safety and efficacy of discontinuing metformin and/or sulfonylureas when initiating insulin therapy, nor did any studies compare third-line agents after discontinuation of metformin or sulfonylureas due to intolerance.

Evidence for the DPP-4 inhibitor class was limited to a single RCT with sitagliptin; there were no trials involving saxagliptin, nor vildagliptin (which was not approved by Health Canada at the time of this therapeutic review).

There was no evidence regarding the comparative efficacy of third-line agents in children with type 2 diabetes or the following subgroups of interest: First Nations people, other ethnic minorities, or seniors ≥ 75 years of age. In addition, only a single RCT reported a subgroup analysis of patients ≥ 65 years of age. Studies in First Nations and the elderly are especially pertinent given the high prevalence of diabetes in these populations.

5.4 Strengths and Limitations of the Review

This is the first systematic review to simultaneously assess the relative safety and efficacy of available treatments for third-line antidiabetes therapy using both direct and indirect evidence, specifically in patients with type 2 diabetes who are inadequately controlled with metformin and sulfonylurea combination therapy. The review was conducted according to a protocol specified in advance, using standardized, reproducible methods for identification of evidence, data abstraction, quality assessment, and analysis. Unlike previous systematic reviews of therapies for type 2 diabetes,[101,102,122-124] this review

included every drug class available for the treatment of type 2 diabetes after inadequate control with metformin and sulfonylureas.

Despite the aforementioned strengths, a number of limitations related to the available evidence warrant discussion. There was relatively little evidence for the effect of third-line agents on long-term diabetes-related complications, quality of life, or mortality. Hemoglobin A1C, a surrogate outcome for long-term complications, was the primary outcome reported in the vast 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.[125,126] The evidence on hypoglycemia was primarily related to overall hypoglycemia, an outcome of uncertain clinical significance that was inconsistently defined across studies. Further study is required to determine whether differences exist between third-line agents regarding the risk for clinically meaningful hypoglycemia events.

A majority of RCTs were assessed as having significant methodological limitations (e.g., improper reporting of allocation concealment or failure to provide an intention to treat analysis) and were less than one year in duration. Longer, high-quality studies are required to evaluate the comparative efficacy of third-line agents over the long-term in terms of clinically relevant end points.

There was significant variability in the reporting of metformin and sulfonylurea dosing at baseline, with most RCTs failing to report this information. Furthermore, several studies only required half-maximum dosing of sulfonylureas before subjects were considered to have failed therapy. These limitations could affect the relative efficacy of third-line treatment strategies, and even compromise the generalizability of results. For example, patients who were inadequately controlled on maximally-tolerated doses of metformin and a sulfonylurea, may experience a lesser response to third-line therapy than a patient who was receving sub-maximal therapy, since the former patient is more likely to have more long-standing, treatment-resistant disease.

There were also several issues with the external validity of trials, such as relatively short durations, limited statistical power due to small sample sizes, failure to provide definitions for outcomes such as hypoglycemia and adverse events, contact with health care professionals that likely exceeded that encountered in routine clinical practice, and blood glucose targets different from those commonly employed in Canadian clinical practice. Furthermore, the population of interest for this review consisted of patients inadequately controlled with metformin and a sulfonylurea. However, the study populations in most identified trials included patients who may have received various antidiabetes drugs prior to the use of metformin and sulfonylurea combination therapy. The applicability of study results to the population of interest may therefore be somewhat limited. However, the robustness of the results in meta-regression analyses to adjust for differences in duration of diabetes or baseline A1C, both of which are likely important predictors of treatment efficacy, mitigate such concerns to some degree.

MTC meta-analysis involves pooling of trials within and between pairwise contrasts. To avoid the introduction of bias, it is imperative that clinical and methodological variation across studies is minimized. If variability does exist, assessment of its effects on MTC results is required. We observed variability in study and subject characteristics that may be important predictors of treatment effect including baseline A1C, baseline body weight, duration of diabetes, and study length. To address these, we performed alternative modelling, meta-regression analyses, and sensitivity analyses. Results from these analyses were consistent with each other and with the reference case, hence the observed variability across included studies did not appear to introduce an appreciable degree of bias. Furthermore, direct and indirect estimates were in close alignment.

Nevertheless, differences across trials in terms of other factors could have introduced bias in the MTC analysis. For example, the glycemic targets used in individual trial protocols varied somewhat between RCTs. It is possible that trials with more aggressive glycemic targets achieved larger effect sizes than those with more modest glycemic targets. An attempt to adjust for this source of heterogeneity through meta-regression was unsuccessful because of the lack of consistency in how targets were defined, although qualitative analysis did not reveal any consistent patterns regarding effect sizes and glycemic

targets. The possibility that differences in additional unmeasured or unreported factors contributed to bias in the MTC analysis cannot be entirely discounted.

6 CONCLUSIONS

There was insufficient evidence to evaluate the comparative efficacy of any class of third-line antidiabetes drugs in terms of reducing clinically important long-term complications of diabetes. Compared with continued treatment with metformin and sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, TZDs, and bolus insulin produced statistically significant reductions in A1C in combination with metformin and sulfonylureas; whereas, meglitinides and alpha-glucosidase inhibitors did not. Basal insulin, biphasic insulin, bolus insulin, and TZDs all resulted in an increase in body weight, but DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues were not associated with significant weight gain. The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators. Rigourously conducted, longer-term studies with larger sample sizes will be required to determine if any of the drug classes are superior with regards to reducing diabetes-related complications. Given the similar efficacy in terms of glycemic control, a cost-effectiveness analysis is also warranted to help define the place in therapy for the various drug classes.

APPENDIX 1: 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.

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.

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 indicate a better fitting model with a difference greater than two indicating a much 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 effect 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.

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).

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.

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.

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

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

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 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.

APPENDIX 2: PROTOCOL

1. METHODS

a. Reviewer Information

- Therapeutic Review of Clinical Trials and Review in Brief were prepared by two CADTH clinical reviewers in consultation with an external clinical expert specializing in endocrinology.
- Background Information on the Condition (Appendix 2) was prepared by an external clinical expert specializing in endocrinology.

b. Development of Research Questions

The research questions were developed jointly by jurisdictions, expert committee members, the external clinical expert and CADTH clinical reviewers in consultation with pharmacoeconomic reviewers.

c. Literature Search Methods

The literature search was performed by a CADTH information specialist using a peer-reviewed 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 vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit retrieval to randomized controlled trials (see web appendix for detailed search strategies). The search was restricted to English language clinical articles published from 1980 to May 2009. Monthly OVID AutoAlerts were established to update the search until therapeutic review recommendations are made. 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.

d. Study Selection

Each CADTH clinical reviewer independently selected studies for inclusion in the review according to the predetermined protocol. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion. A list of included and excluded studies (with reasons) is provided in Appendix 7.

Active and placebo-controlled RCTs were selected for inclusion if they were published in English, reported relevant outcomes, and involved patients inadequately controlled on combination therapy with metformin and a sulfonylurea. We included all study populations where patients received third-line agents as add-on to, or switch from, metformin and sulfonylurea therapy regardless of treatment history prior to combination therapy with metformin and sulfonylureas. Studies were excluded if: more than 15% of the patients used a therapeutic regimen other than combination therapy with metformin and sulfonylureas at baseline, and no results were reported for the subgroup of metformin users; or treatment duration was less than four weeks.

e. Quality Assessment

Quality assessment of RCTs was conducted independently by two reviewers, with a third reviewer used to resolve disputes. Assessment of study bias was performed using the SIGN-50 instrument for interval validity.[127] External validity was assessed using a predetermined checklist of criteria.

f. Data Analysis

Bayesian MTC meta-analysis and frequentist pairwise meta-analysis was performed where appropriate. A random-effects model was used for the reference case of all pairwise and MTC meta-analyses, since there was a certain degree of variability in trial duration, dosing of agents, baseline characteristics, and treatment history of the included patients. MTC meta-analyses and pairwise meta-analyses were conducted for hemoglobin A1C and body weight. Only study level detail is presented for the remaining outcomes due to the following: limited number of available studies; small number of events; and/or clinical/methodological heterogeneity between available studies. In the case of severe hypoglycemia and severe/serious adverse events, MTC analyses could not be conducted due to the zero event rates observed in many studies.

WinBUGS (MRC Biostatistics Unit, Cambridge, UK) was used for all MTC meta-analyses according to the routine developed by researchers from the universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/ mpes/). Metformin and sulfonylurea combination therapy (with placebo) was chosen as the reference group for all MTC analyses. Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo (MCMC) methods. Prior distributions were assigned non-informative or vague distributions. Point estimates and 95% credible intervals were used to summarize all findings. The probability of a drug class being the optimal treatment was estimated for each outcome based on the proportion of MCMC simulations in which its relative measure of effect was best. The mean rank of each drug class based on the proportion of MCMC simulations was also calculated. Inconsistency between direct and indirect estimates of effect was assessed using the statistical software package R, using a function (http://users.uoi.gr/hyepilab/assets/pdfs/help%20on%20MTcoherence.fun.pdf) assessing each closed loop of the network according to the method of Bucher. Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence. Two chains were fit in WinBUGS for each analysis. Each chain employed a total of 20,000 or more iterations, with a burn-in of 20,000 or more iterations.

g. Writing of the Review Report

- The review report was written by one CADTH clinical reviewer with input from the second CADTH clinical reviewer and the external clinical expert.
- A detailed internal review of the review report was undertaken.
- Comments were received from peer and external reviewers.

PROTOCOL FOR PRIMARY RESEARCH QUESTION

a. Systematic Review

Objective(s)
The objective of this review is to assess the comparative efficacy and safety of third-line antidiabetes drugs in children and adults with type 2 diabetes mellitus treated with a combination of metformin and sulfonylureas who:

- require additional or alternative glucose-lowering therapy because of inadequate glycemic control on existing therapy (i.e., glycosylated hemoglobin [A1C] > 6.5% or fasting plasma glucose [FPG] > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)
- require a switch to another glucose-lowering agent(s) because of inadequate glycemic control (i.e., A1C > 6.5% or FPG > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)
- require a switch to another glucose-lowering agent(s) because of intolerable adverse effects or the development of contraindications to metformin and/or sulfonylureas

Selection Criteria
A study was included if it met all of the inclusion criteria and none of the exclusion criteria summarized in table 20.

Table 18: Inclusion and Exclusion Criteria for Primary Studies

Inclusion criteria	
Population	Patients with type 2 diabetes mellitus inadequately controlled on combination therapy with metformin and sulfonylureas
Interventions	One or more of the agents listed table 1 was added to the combination therapy of metformin and sulfonylurea or the second line combination therapy was switched to one or more of the third line agents listed table 1.
Comparators	• metformin (any dose) + sulfonylurea (any dose) + placebo • metformin (any dose) + sulfonylurea (any dose) + intervention from table 1 • metformin (any dose) + intervention from table 1 • Intervention from table 1 • Increased dose of metformin + increased dose of sulfonylurea
Outcomes	• Glycemic control: hemoglobin A1C • Long-term clinical complications of diabetes: congestive heart failure; ischemic heart disease; stroke/transient ischemic attack; peripheral vascular disease; retinopathy; nephropathy; neuropathy; mortality • Short-term complications of diabetes or antidiabetes treatment: overall hypoglycemia; severe hypoglycemia; nocturnal hypoglycemia; hyperosmolar hyperglycemic non-ketotic coma • Quality-of-life: health-related quality-of-life (generic or diabetes specific) • Patient satisfaction: patient satisfaction with diabetes care; patient satisfaction with diabetes treatment • Other: weight, body mass index; serious/severe adverse events; pancreatitis; upper extremity fractures; macular edema
Study design	RCTs (including parallel, crossover, placebo-controlled, active comparator)
Exclusion criteria	
	• More than 15% of the sample used drugs other than metformin and sulfonylurea without a subgroup analysis for patients inadequately controlled on combination therapy with metformin and sulfonylureas* • Studies evaluating the switch from combination therapy to another antidiabetes drug(s) in which the comparator was placebo or no antidiabetes therapy (i.e., no active comparator) • Studies with a duration of less than four weeks • Non-English publications

*Given an absence of published information, this was based on clinical opinion

APPENDIX 3: LITERATURE SEARCH STRATEGY

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 [DATE].
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 #	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.
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 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 #	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.
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.
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 #	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.
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* 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 [DATE].
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 #	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 #	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 #	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.
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 anti diabetes agents, anti diabetic agents, type 2 diabetes. All keywords associated with each included drug
Limits:	Publication years 1980-present

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

Institute of Health Economics

http://www.ihe.ca/

Agence d'Evaluation 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/

The Therapeutics Initiative. Evidence-Based Drug Therapy. University of BritishColumbia.

http://www.ti.ubc.ca

Health Quality Council. Saskatchewan.

http://www.hqc.sk.ca/

International Network for 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/ (E)

NHS National Institute for Clinical Excellence (NICE)

http://www.nice.org.uk

Agency for Healthcare Research and Quality (AHRQ)

http://www.ahrq.gov/clinic/techix.htm

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

ECRI

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

http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/products.cfm

Veterans Affairs. Drug Class Reviews (U.S.)
http://www.pbm.va.gov/DrugClassReviews.aspx

Saskatoon Health Regions

http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx

Clinical Trials Database (U.S. National Institutes of Health)

http://clinicaltrials.gov/ct/gui

Current Controlled Trials

http://www.controlled-trials.com/

National Research Register. U.K. Dept. of Health.

http://www.update-software.com/national/

WHO - 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

http://www.euro-endo.org/

Society for Endocrinology

http://www.endocrinology.org/

European Society for Paediatric Endocrinology

http://www.eurospe.org/

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

European Association for the Study of Diabetes (EASD)

http://www.easd.org/

Association of British Clinical Diabetologists

www.diabetologists.org.uk

Primary Care Diabetes Europe (PCDE)

http://www.pcdeurope.org

International Diabetes Federation

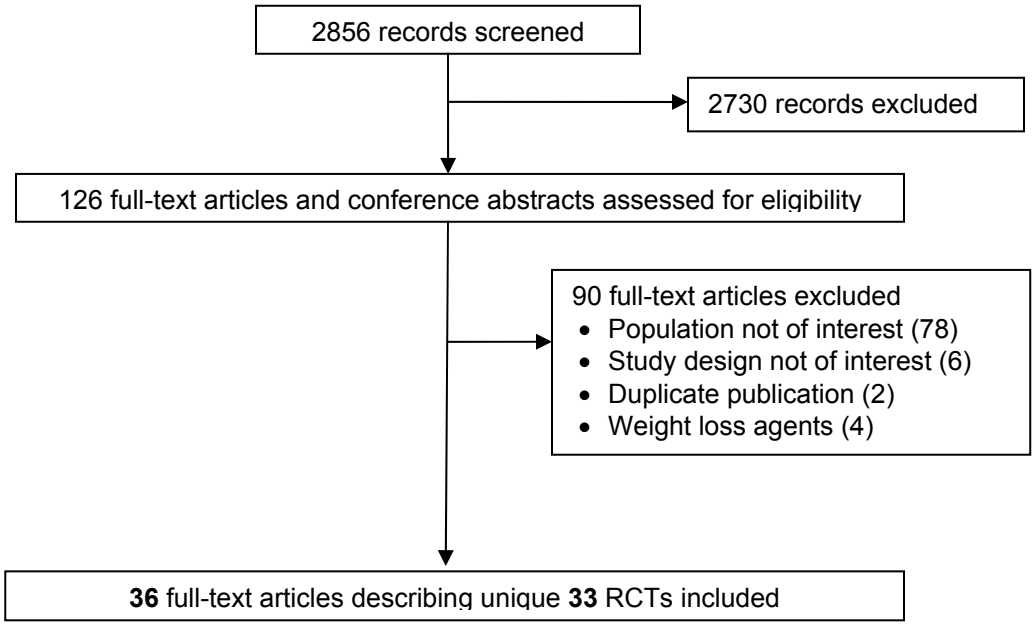
www.idf.org/home

Search Engines

Google

http://www.google.ca/

APPENDIX 4: QUORUM FLOW DIAGRAM



APPENDIX 5: INCLUDED AND EXCLUDED STUDIES

a. Included Studies

Aljabri et al, 2004[10]
Al-Shaikh, 2006[12]
Bergenstal et al, 2009[14]
Berhanu et al, 2007[16]
Boye et al, 2006[18]
Charpentier et al, 2009[20]
Dailey et al, 2004[22]
Davies et al, 2007[24]
De Mattia et al, 2009[26]
Derosa et al[28]
Dorkhan et al, 2009[30]
Esposito et al, 2008[32]
Gao et al, 2009[34]
Goudswaard et al, 2004[36]
Hartemann-Heurtier et al, 2009[38]
Heine et al, 2005[40]
Hermansen et al, 2007[41]
Holman et al, 2007[43]
Janka et al, 2005[11]
Janka et al, 2007[13]
Kendall et al, 2005[15]
Ko et al, 2006[17]
Lam et al, 1998[19]
Lopez-Alvarenga et al, 1999[21]
Milicevic et al, 2009[23]
Nauck et al, 2007[25]
Ovalle et al, 2004[27]
Reynolds et al, 2007[29]
Rosenstock et al, 2006[31]
Ross et al, 2001[33]
Russel-Jones et al, 2009[35]
Standl et al, 2001[37]
Stehouwer et al, 2003[39]
Strojek et al, 2009[45]
Vinik et al, 2007[42]
Yki-Jarvinen et al, 2006[44]

b. Excluded Studies

Rosskamp et al, 2003[128]	Population not of interest
Altuntas et al, 2003[129]	Population not of interest
Kilo et al, 2003[130]	Population not of interest
Kokic et al, 2003[131]	Population not of interest
Hermansen et al, 2006[132]	Population not of interest
Jacober et al, 2006[133]	Population not of interest
Kann et al, 2006[134]	Population not of interest
Malone et al, 2004[135]	Population not of interest
Brod et al, 2007[136]	Population not of interest
Jacob et al, 2007[137]	Population not of interest
Derosa et al, 2006[138]	Population not of interest
Fonseca et al, 2006[139]	Population not of interest
Isa et al, 2006[140]	Population not of interest
Goke et al, 2002[141]	Population not of interest
Bretzel et al, 2008[142]	Population not of interest
Rosenstock et al, 2008[143]	Population not of interest
Dorkhan et al, 2008[144]	Population not of interest
Raskin et al, 2005[145]	Population not of interest
Nauck et al, 2009[146]	Population not of interest
Papa et al, 2008[147]	Population not of interest
Klonoff et al, 2008[148]	Study design not of interest
Ushakova et al, 2007[149]	Population not of interest
Labrousse-Lhermine et al, 2007[150]	Population not of interest
Home et al, 2007[151]	Population not of interest
Kuo et al, 2006[152]	Weight loss agents

Blonde et al, 2006[153]	Study design not of interest
Wang et al, 2005[154]	Weight loss agents
Douek et al, 2005[155]	Population not of interest
Berne et al, 2005[156]	Weight loss agents
Reboussin et al, 2004[157]	Population not of interest
Derosa et al, 2004[158]	Population not of interest
Furlong et al, 2003[159]	Population not of interest
Fineman et al, 2003[160]	Population not of interest
Gokcel et al, 2001[161]	Weight loss agents
Sotaniemi et al, 1990[162]	Population not of interest
Malone, 2005[163]	Population not of interest
Aljabri et al, 2003[164]	Duplicate
Houlden et al, 2007[165]	Population not of interest
Raskin et al, 2007[166]	Population not of interest
Dormandy et al, 2005[167]	Population not of interest
Massi et al, 2003[168]	Population not of interest
Olsson et al, 2002[169]	Population not of interest
Zinman et al, 2009[170]	Population not of interest
Buse et al, 2009[171]	Population not of interest
Velojic-Golubovic et al, 2009[172]	Study design not of interest
Buse et al, 2009[173]	Population not of interest
Raskin et al, 2009[174]	Population not of interest
Raskin et al, 2009[175]	Duplicate
Raskin et al, 2009[176]	Population not of interest
Derosa et al, 2008[177]	Population not of interest
Civera et al, 2008[178]	Population not of interest
Robbins et al, 2007[179]	Population not of interest
Vahatalo et al, 2007[180]	Population not of interest
2006[181]	Population not of interest
Chow et al, 1995[182]	Population not of interest
Miyashita et al, 2008[183]	Population not of interest
Eermann et al, 2007[184]	Population not of interest
Martens et al, 2005[185]	Population not of interest
Soonthornpun et al, 1998[186]	Population not of interest
Rodier et al, 1995[187]	Population not of interest
Malloy et al, 2009[188]	Population not of interest
Zinman et al, 2009[189]	Population not of interest
Biswas et al, 2008[190]	Population not of interest
Meneghini et al, 2009[191]	Population not of interest
Hollander et al, 2009[192]	Study design not of interest
Shaqdan et al, 2009[193]	Population not of interest
Schmidt et al, 2009[194]	Population not of interest
Jogi et al, 2009[195]	Population not of interest
Vilsboll et al, 2009[196]	Population not of interest
Hsia et al, 2009[197]	Study design not of interest
Verges et al, 2009[198]	Study design not of interest
Swinnen et al, 2009[199]	Population not of interest
Franek et al, 2009[200]	Duplicate

APPENDIX 6: SUPPLEMENTAL RESEARCH QUESTION 1: VALIDITY OF HEMOGLOBIN A1C AS A SURROGATE OUTCOME

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

To review the evidence for the use of hemoglobin A1C in predicting diabetes related morbidity, including micro and macrovascular complications

2. Findings

Hemoglobin A1C is often used as a surrogate marker for diabetes complications and diabetes-related mortality in RCTs. Therefore it is important to clarify the relationship between glycemic control and patient-related diabetes outcomes in type 2 diabetes such as mortality, macrovascular events and microvascular events.

Type 2 diabetes mellitus and the UKPDS[201]

The UKPDS was a 14-year (1977-1991) prospective, randomized, multi-centre, controlled clinical trial in newly-diagnosed patients with type 2 diabetes (aged 25-65 years) that was designed to determine whether intensive glycemic management using a sulfonylurea or insulin vs. conventional management with diet lowered the risk of microvascular and macrovascular complications. The UKPDS enrolled 3,867 newly diagnosed patients with type 2 diabetes (median age: 54 [48 to 60] years old). These patients were randomly assigned to an intensive policy with a sulphonylurea (chlorpropamide or glyburide) or with insulin, or to conventional therapy with diet over 10 years. In the conventional arm, drugs were added if there were hyperglycemic symptoms or FPG > 15 mmol/L.

In the main analysis of the UKPDS, the median A1C was significantly lower in the intensive policy arm compared with the conventional after ten years (7% vs. 7.9%, $p < 0.0001$), which was associated with a 12% reduction in any diabetes-related endpoint. The number needed to treat (NNT) to prevent one patient developing any of the single endpoints over 10 years was 20 patients (95% CI: 10-500). Patients in the intensive treatment had a significant 25% risk reduction in the microvascular endpoints ($p = 0.0099$) compared with conventional treatment, most of which was due to fewer cases of retinal photocoagulation. The risk reduction was non-significant for myocardial infarction ($p = 0.052$), but significant for cataract extraction ($p = 0.046$). There was no significant difference among the three intensive treatments (chlorpropamide, glibenclamide or insulin) on microvascular endpoints or the risk reduction for retinal coagulation. There was no significant difference between intensive and conventional therapies in the following aggregate endpoints: any diabetes-related death (risk reduction: 10% [95% CI: -11 to 27], p=0.34) or for all-cause mortality (risk reduction: 6% [95% CI: -10 to 20], p=0.44). The only RCT data from the UKPDS to demonstrate a reduction in macrovascular events was an unplanned cohort analysis conducted in a subgroup of overweight patients, comparing intensive control with metformin vs. conventional control.[57]

Regression analyses of these data were conducted in UKPDS 35[202] and are quoted in clinical practice guidelines.[8] They demonstrated a significant reduction of 21% in the risk of death due related to diabetes per 1% absolute decrease in A1C. A 37% risk reduction in combined microvascular endpoints as well as a 43% reduction in amputation per 1% reduction in A1C was also reported. No thresholds were evident for any complications. Of note, the analysis was not adjusted for body mass index or waist circumference. Therefore, there is epidemiological data

from observational analyses to support an association between A1C and microvascular and macrovascular complications.

The design and analysis of the UKPDS have been criticized for the lack of pre-defined study duration, numerous interim analyses and multiple comparisons, rescue protocols that diluted differences between treatment arms and changes in the definitions of outcomes as the study progressed. As well, the main driver of the observed benefits of intensive glycemic control was reduced risk of photocoagulation. Because the UKPDS was not a blinded study, the possibility of bias in the perceived need for this procedure cannot be discounted.[203-205]

UKPDS Extension study (UKPDS-80)[206]

Of the 3,867 patients originally randomized, 2,998 patients enrolled in a post-trial monitoring programme that lasted an additional 10 years. The patients were not required to maintain their previously assigned therapies. Patients were followed in clinics for the first five years of this extension study, and for years six to 10, patient data was collected through questionnaires.

The median follow-up time at the beginning of the extension study was 16.8 years sulfonylurea/insulin group and these patients were followed for an additional 8.5 years (median) in the extension study. At the beginning of the extension study, patients who were previously in the intensive therapy arm had lower A1C than those who were in the conventional therapy arm (median: 7.9% vs 8.5%). Differences in mean A1C between the intensive therapy and conventional therapy groups were lost within the first year of the extension study. Clinical outcomes were assessed by blinded committee. At the end of the extension study, statistically significant improvements were seen for the former intensive therapy arm compared to the conventional therapy arm for the following outcomes (RR, 95% CI): any diabetes-related endpoint (0.91, 0.83-0.99), diabetes related death (0.83, 0.73-0.96), death from any cause (0.87, 0.79-0.96), myocardial infarction (0.85, 0.74-0.97) and microvascular disease (0.76, 0.64-0.89). There was no difference between the intensive therapy arm and the conventional therapy arm for incidence of stroke or incidence of peripheral vascular disease.

In the original UKPDS study, overweight patients were separately randomized to intensive control with metformin (n = 342) and conventional treatment with diet (n = 411).[201] Of these, 279 and 309 patients, respectively, were enrolled in the extension study. At the beginning of the extension study, the A1C levels were similar between the metformin and conventional treatment arms (median: 8.9% vs 8.4%). The A1C levels remained similar over the course of the 10 year extension study. At the end of the extension study, statistically significant improvements were seen for the intensive metformin arm compared to the conventional treatment arm for the following outcomes (RR, 95% CI): any diabetes related endpoint (0.79, 0.66-0.95), diabetes related death (0.70, 0.53-0.92) and myocardial infarction (0.67, 0.51-0.89). There was no difference between the intensive therapy arm and the conventional therapy arm for incidence of stroke, incidence of peripheral vascular disease, or microvascular disease in the obese subgroup.

The uncontrolled design of the extension study does have some limitations. Treatment effects are potentially confounded by the numerous other therapies patients may have been exposed to over the follow up period. It is difficult to attribute the results to the originally randomized treatment strategies since 10 years had elapsed since those strategies were enforced. In addition, the less-than-strict blood pressure and lipid control used in the trial may not be reflective of current standards.[207] Nevertheless, the results of the UKPDS extension study have been accepted by many observers to suggest that a benefit extends beyond the period during which intensive glycemic control is achieved, in newly diagnosed type 2 diabetics. This so-called legacy effect occurred even though A1C levels between the intensive therapy and the conventional therapy did not persist beyond 1 year. It has been theorized that the delayed effect on macrovascular outcomes may be due to the cumulative effects of hyperglycemia, but the true mechanism remains unknown.

Veterans Affairs Diabetes Trial (VADT)[207]
In this trial, 1,791 military veterans who had a suboptimal response to therapy for type 2 diabetes were randomized to intensive or standard glucose control. Patients had had type 2 diabetes for a mean of 11.5 years, mean baseline A1C was 9.4 and 40% of patients had previously experienced a cardiovascular event. Obese patients were started on metformin and rosiglitazone and non-obese patients were started on glimepiride plus rosiglitazone. The goal for A1C was an absolute reduction of 1.5% in patients in the intensive therapy group, compared to those in the standard therapy group. Insulin could be added in the intensive therapy arm if needed and any other approved medication could be used at the investigator's discretion. All patients received aspirin and a statin for cholesterol control.

After a median follow-up of 5.6 years, there was no statistically significant difference in the primary outcome: time to the first occurrence of a cardiovascular event (hazard ratio: 0.88, 95% CI: 0.74-1.05). There was no statistically significant difference between the two groups in any component of the primary outcome, or in microvascular complications, or in the rate of death from any cause (hazard ratio for death from any cause: 1.07, 95% CI: 0.81-1.42). There was a statistically significant difference in progression to albuminuria, favouring the intensive group.

These results would appear, on the surface, to contradict the findings of the UKPDS. However, the population in the VADT had some unique characteristics: it was predominantly male, subjects were all treated for hypertension and hyperlipidemia and patients had longstanding type 2 diabetes. The authors of the VADT explain that the cardiovascular event rates were lower than anticipated. The characteristics of the study population may have required a longer follow up in order to demonstrate an improvement in macrovascular and microvascular outcomes.

type 2 diabetes and the ACCORD[208] and ADVANCE[209] trials
Recently, results were published from the ACCORD (n = 10,251) and the ADVANCE (n = 11,140) trials, which were designed to evaluate the effects of intensive versus standard glucose-lowering A1C targets in type 2 diabetes on macrovascular outcomes. The A1C target in the intensive glucose-lowering group was <6% in the ACCORD trial and ≤6.5% in the ADVANCE trial. The A1C target in the standard glucose-lowering group was 7 to 7.9% in the ACCORD trial, and according to local guidelines target in the ADVANCE trial. In ACCORD, therapeutic regimens were individualized at the discretion of the investigators and patients on the basis of study-group assignment and the response to therapy. In ADVANCE, the intensive glucose-lowering group received gliclazide whereas patients in the standard glucose-lowering group couldn't use gliclazide. Step-wise protocols were suggested for each group that could be used to individualize and add-on treatments.

In ACCORD, the trial was terminated early due to an excess risk of all-cause mortality in the intensive therapy group compared with the standardtherapy group (hazard ratio: 1.22; 95% CI: 1.01 to 1.46; P = 0.04). In addition, there was no significant difference between treatment groups with respect to the primary study outcome which included three components: nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (hazard ratio: 0.90; 95% CI: 0.78 to 1.04; P = 0.16). On the other hand, in ADVANCE, there were no significant effects of the type of glucose control on death from any cause (hazard ratio with intensive control, 0.93; 95% CI: 0.83 to 1.06; P = 0.28), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI: 0.74 to 1.04; P = 0.12) or major macrovascular events (hazard ratio with intensive control: 0.94; 95% CI: 0.84 to 1.06; P = 0.32). ADVANCE did demonstrate a significant reduction in major microvascular events with intensive control compared with standard control (9.4% vs. 10.9%; hazard ratio: 0.86; 95% CI: 0.77 to 0.97; P = 0.01). A significant driver of the microvascular results in ADVANCE was the reduction in risk of new or worsening nephropathy (hazard ratio: 0.79, 95% CI: 0.66-0.93).

Due to a number of differences between the two trials, it is difficult to pinpoint the cause of these contradictory results.[210] For example, patients in ACCORD had more non-glycemic risk factors, the rate of glucose lowering was faster in ACCORD, permitted treatments differed between the

two trials and frequency of rosiglitazone prescribing was higher in ACCORD, treatment targets were lower in ACCORD, duration of follow-up was shorter in ACCORD due to early termination and differences in primary endpoints.

Nonetheless, these trials are consistent in finding that maintaining near-normal glycemic control over a period of three to five years does not reduce cardiovascular events. Although this casts further doubt on role of A1C as a surrogate outcome for macrovascular disease, this should not necessarily be interpreted as due to the lack of importance of glycemic control in diabetes.

Meta-Analysis by Turnbull (2009)[211]

The results of the trials described above, UKPDS, ACCORD, ADVANCE and VADT were meta-analyzed to compare macrovascular event rates for more intensive versus less intensive glucose control regimens in patients with type 2 diabetes (N = 27,049). Statistically significant improvements were seen for the more intensive therapy group compared to the less intensive group for major cardiovascular events (HR: 0.91, 95% CI: 0.84-0.99) and this result was mainly because of reduced risk of myocardial infarction (HR: 0.85, 95% CI: 0.76 to 0.94). There were no reductions seen for overall mortality or cardiovascular death. Intensively treated subjects had more major hypoglycaemic events (HR: 2.48, 95% CI: 1.91 to 3.21). Exploratory subgroup analyses of macrovascular events suggested that patients with major cardiovascular disease did not show a benefit for the intensive therapy, but those without major cardiovascular disease did show a benefit (HR: 1.00, 95% CI: 0.89 to 1.13, vs HR: 0.84, 95% CI: 0.74 to 0.94). The effects of more versus less intensive glycemic control on major cardiovascular events are summarized in the Forest plot below:

The meta-analysis has some limitations because of the heterogeneity of the four included trials. These differences included duration of diabetes diagnosis, type of agents used to achieve glucose control, duration of follow-up, concomitant cardiovascular drugs, A1C levels at baseline and study completion, gender of subjects (VADT), and incidence of hypoglycaemia. Nevertheless, this meta-analysis provides the largest pool of data to generate estimates on the major cardiovascular effects of intensive glycemic control.

Meta-Analysis by Ray (2009)[212]

Ray *et al*. also conducted a meta-analysis of trials comparing intensive versus non-intensive glycemic control that reported cardiovascular outcomes. They included all trials included by Turnbull *et al*., as well as the PROactive study.[167] This trial compared pioglitazone with placebo in combination with existing treatments in 5238 patients with type 2 diabetes who had evidence of macrovascular disease over a mean follow up of 34 months. It is noteworthy that, unlike the other four studies included in the meta-analysis, PROactive was not a comparison of intensive glycemic control with standard control per se. Nevertheless, the mean reduction in A1C from baseline was higher in the pioglitazone arm (0.8%) than the placebo arm (0.3%), p<0.0001. The primary endpoint of the study was a composite of: all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention of the coronary or leg arteries, or amputation above the ankle. The main secondary outcome was the composite of non-fatal myocardial infarction, all-cause mortality, and stroke. The hazard ratio for the primary endpoint was not statistically significant (HR: 0.90, 95% CI: 0.80 to 1.02), although the result for the main secondary outcome was significant in favour of pioglitazone (HR: 0.84, 95% CI: 0.72 to 0.98).

Ray et al. reported that the pooled risk of non-fatal myocardial infarction was significantly lower in the intensively treated arm versus the standard treatment arm (RR: 0.83, 95% CI: 0.75 to 0.93), as was the risk of coronary heart disease (RR: 0.85, 95% CI: 0.77 to 0.93). There were no significant differences in the risk of stroke or all-cause mortality. Overall, the results reported by Ray *et al*. are similar to those of Turnbull *et al*. – intensive control appears to provide modest risk reduction (<20%) for myocardial infarction, but not stroke or all-cause mortality. The limitations of the two analyses are also similar, although inclusion of the PROactive study could be considered an additional limitation of the Ray analysis. Since

PROactive compared pioglitazone versus placebo rather than a strategy of intensive versus non-intensive glycemic control, it is uncertain whether any benefits in terms of macrovascular outcomes in the active treatment arm were due to improved glycemic control or a specific effect of pioglitazone.

Limitations of A1C as a Surrogate Outcome

In all of these trials, multiple anti-diabetic agents were used, each of which has unique pharmacological effects not restricted to glucose metabolism. The possibility that these effects have a clinically relevant impact on important outcomes such as cardiovascular disease cannot, therefore, be discounted. Drug class, patient factors, and other variables have important independent effects on clinically important outcomes. The rosiglitazone product monograph, for example, cites research that indicates a possible increase in risk of ischemic heart disease and congestive heart failure. Nevertheless, A1C has been used as a surrogate endpoint to measure the efficacy of agents with a variety of pharmacological effects, such as the incretins or thiazolidinediones. A1C may have greater validity when the intervention is similar to those used in studies such as the UKPDS and DCCT or in cases where the long-term benefits and harms of an intervention are well-characterized. It may be less valid for drugs with novel mechanisms because of possible effects on clinically important outcomes that are independent of reduced glycaemia. The use of A1C as a surrogate for cardiovascular disease in type 2 diabetes is problematic since cardiovascular risk in this population depends on a number of other factors such as blood pressure and lipid profile. Despite the limitations of A1C as a surrogate outcome in diabetes, its widespread implementation in clinical practice of A1C as a parameter to monitor treatment efficacy in both type 1 and type 2 diabetes patients has revolutionized diabetes care because it allows for the measurement of long-term glucose control. Furthermore, diabetes treatment guidelines define optimum glycemic control based on A1C targets.

3 Summary

Results from a number of large RCTs (UKPDS, ACCORD, ADVANCE, VADT) have not shown strong evidence linking glucose lowering with a reduction in macrovascular events in type 2 diabetes mellitus. However, long-term observational analyses of the UKPDS[213] and meta-analyses of large type 2 diabetes trials[202,206] are supportive of a relationship. The relationship between A1C and microvascular outcomes such as retinopathy and nephropathy have been demonstrated in RCT evidence from the UKPDS, the ADVANCE trial and the VADT (nephropathy, not retinopathy).

APPENDIX 7: SUPPLEMENTAL RESEARCH QUESTION 2: SUMMARY OF RECOMMENDATIONS FROM CLINICAL PRACTICE GUIDELINES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

To identify Canadian and international guidelines for management of type 2 diabetes and review the relevant recommendations for the second-line and third-line antidiabetes drugs.

2. Methods

An Internet search for major clinical guidelines on the management of type 2 diabetes (up to January, 2010) was conducted. Recommendations/suggestions for second line and third line pharmacotherapy in patients with type 2 diabetes inadequately controlled on metformin monotherapy and third line agent for patients inadequately controlled with combination therapy of metformin and sulfonylurea were summarized.

3. Findings

Guidelines from 9 organizations published between 2003 and 2010 were identified.[4-9,53,214-217] Two consensus reports[52,218] issued by the American Diabetes Association (ADA) and the European Association for Study of Diabetes (EASD) were also included.

All guidelines recommended that management of most patients with type 2 diabetes mellitus begins with lifestyle modification. Metformin was 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.[4-9,53,214,215,217] In the consensus report of ADA and EASD, it was suggested that metformin therapy should be initiated concurrently with the lifestyle intervention at the time of diagnosis.[52]

Recommendations on second line pharmacotherapy for most patients with type 2 diabetes inadequately controlled on metformin alone for ≥ 3 months: Guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK, the New Zealand Guidelines Group (NZGG), International Diabetes Federation (IDF), Diabetes Australia Guideline Development Consortium, and Scottish Intercollegiate Guideline Network (SIGN) recommend that a sulfonylurea be added to metformin as second-line therapy for most patients if glycemic target cannot be achieved with metformin monotherapy.[4,7,9,53,215,217] American Association of Clinical Endocrinologists /American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (AACE/ACE, 2009)[216] recommended that GLP-1 analogues or DPP-4 inhibitors be added to metformin for most of the patients. All other guidelines provided a list of two or more of the available options (i.e., sulfonylurea, DPP-4 inhibitors, GLP-1 analogues, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and insulin) without identifying a single preferred drug class. Almost no evidence was cited to support their recommendations regarding second-line therapy in type 2 diabetes.

Recommendations on third line pharmacotherapy for most patients inadequately controlled with the combination therapy of metformin and sulfonylurea: American Diabetes Association (ADA),[6] American Diabetes Association (ADA) and the European Association for the Study of Diabetes

(EASD),[52] NICE,[4] South Australia,[5] and NZGG recommend that insulin be started as a third line agent for most patients inadequately controlled with the combination therapy of metformin and sulfonylurea. The Canadian Diabetes Association (CDA) recommend an OAD from another class or insulin as a third line treatment. TZDs were recommended in International Diabetes Federation (IDF).[9]

Detailed recommendations/suggestions from each guideline are summarized in the table below. The strength and limitations assessed with AGREE of those included guideline documents was also provided.

Table 19: Summary of Existing Recommendations on First, Second, and Third line Therapy

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
Canadian Diabetes Association, 2008[8]	• A1C target: < 7%. • if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agents should be initiated *[Grade A, Level 1A (evidence cited: UK Prospective Diabetes Study (UKPDS) Group, 1990,[48]* • If A1C < 9%: initiate metformin • In the presence of marked hyperglycemia (A1C≥9.0%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents or initiating insulin treatment in symptomatic individuals *[Grade D, Consensus].* • for patients with symptomatic hyperglycemia with metabolic decompensation: Insulin ± metformin • Pharmacological treatment regimens should be individualized taking into consideration the degree of hyperglycemia and the properties of the antihyperglycemic agents including effectiveness in lowering BG, durability of glycemic control, side effects, contraindications, risk of hypoglycemia, presence of diabetes complications or comorbidities, and patient preferences *[Grade D,*	• If glycemic targets are not attained (A1C >7%) when a single antihyperglycemic agent is used initially, an antihyperglycemic agent or agents best suited to the patients based on the advantages/disadvantages from different classes below should be added ○ α-glucosidase inhibitors ○ DPP-4 inhibitor ○ Insulin/Insulin analogues ○ Sulfonylurea: Newer sulfonylureas (Gliclazide, blimeperide) are associated with less hypoglycaemia than glyburide ○ ○ Meglitinides ○ Thiazolidinediones ○ Weight loss agents (orlistat, sibutramine) • The lag period before adding other agent(s) should be kept to a minimum, taking into account the characteristics of the different agents. • Timely adjustments to and/or additions of antihyperglycemic	If target level was not achieved • Add another drug from a different class; or • Add bedtime basal insulin to other agent(s); or • Intensify insulin regimen • Evidence cited: None	**Primary sponsors:** GlaxoSmithKline Inc. Novo Nordisk Canada Inc, Sanofi-Aventis Canada Inc. Servier Canada Inc. **Secondary sponsors:** AstraZeneca Canada. Inc, Bayer Inc., Eli Lilly Canada Ltd., Pfizer Canada Inc., Hoffmann-La Roche Ltd **It was indicated that Sponsors were not involved in any aspect of guidelines development, literature interpretation, the decision to publish, or any other aspect of publication of the guidelines.*	**Strength:** Systematic methods was used to search the evidence; The health benefits, side effects and risks have been considered in formulating the recommendations; There is an explicit link between the recommendations and the supporting evidence The guideline has been externally reviewed by experts prior to its publication; A procedure for updating the guideline was provided. **Limitations:** The criteria for selecting the evidence are not clearly described; The methods used for formulating the recommendations were not clearly described.

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
	Consensus]. • Metformin should be the initial drug used in both overweight patients *[Grade A, Level 1A (evidence cited: UK Prospective Diabetes Study (UKPDS) Group, 1998,[57]* and nonoverweight • The following antihyperglycemic agents (listed in alphabetical order), should be considered to lower postprandial BG levels: ○ Alpha-glucosidase inhibitor *[Grade B, Level 2 evidence cited: Chiasson et al 1994,[219]]* ○ Premixed insulin analogues (i.e. biphasic insulin aspart and insulin lispro/protamine) instead of regular/NPH premixtures *[Grade B, Level 2 (evidence cited: Roach P et al[220] and Boehm BO et al.[221]* ○ DPP-4 inhibitor *[Grade A, Level 1 (evidence cited: Aschner P, [222] Charbonnel B, et al[223] and Ahren B, et al[224]* ○ Inhaled insulin *[Grade B, Level 2 (eviodence cited: Weiss SR, et al, [225]* ○ Meglitinides (repaglinide, nateglinide) instead of sulfonylureas *[Grade B, Level 2 (evidence cited: Derosa G, et al,[226] Ristic S, et al[227]* ○ Rapid-acting insulin analogues (aspart, glulisine, lispro) instead of short-acting insulin (i.e. regular insulin) *[Grade B, Level 2 (evidence cited: Dailey G, [228] Ross SA,[33] Rosenfalck AM,[229]* • Timely adjustments to and/or addition of antihyperglycemic agents should be made to attain target A1C within 6 to 12 months	agents should be made in order to attain target A1C within 6 to 12 months *[Grade D, Consensus].* • Evidence cited: None			

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
American Diabetes Association and the European Association for the Study of Diabetes, 2009 [6,52,214,218]	Information was extracted from the algorithm for the metabolic management of type 2 diabetes: <u>Step 1:</u> • Metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis.(consensus) • Metformin is recommended as the initial pharmacological therapy, in the absence of specific contraindications, for its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost. Metformin treatment should be titrated to its maximally effective dose over 1–2 months, as tolerated. Rapid addition of other glucose-	<u>Step 2:</u> Target A1C: < 7% • A second medication should be added if metformin failed to achieve or sustain glycemic goal within 2-3 months of maximal tolerated dose of metformin monotherapy or at any time when A1C target (<7%) is not achieved. <u>Tier 1: Well-validated, best established and preferred route</u>: Basal Insulin or Sulfonylurea other than glyburide or chlopropamide	<u>Step 3:</u> If A1C target not achieved or with symptoms of hyperglycemia after combination therapy of metformin and sulfonylurea or basal insulin, next step is: • Metformin + intensive insulin • Evidence cited: None ○ When insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be discontinued, or tapered and then discontinued, since they	Not reported. Some of the authors received research grants from various pharmaceutical companies such as, Sanofi-Aventis, GlaxoSmithKline, Pfizer, Hoffman-LaRoche, Eli Lilly, Novo Nordisk and Merck.	**Strength:** The health benefits, side effects and risks have been considered in formulating the recommendations; There is an explicit link between the recommendations and the supporting evidence A procedure for updating the guideline was provided. **Limitations:** Systematic methods was not used to search the evidence; but several technical reviews was conducted

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
	lowering medications should be considered in the setting of persistent symptomatic hyperglycemia.	(consensus) <u>Tier 2: Less well-validated therapies</u>: Pioglitazone or GLP-1 analogue • Another medication may also be necessary if metformin is contraindicated or not tolerated. • Evidence cited: None • If A1C >8.5% or with symptoms of hyperglycemia: Insulin can be initiated with a basal (intermediate- or long-acting) insulin. However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications, even if symptoms of hyperglycemia are present *(evidence cited: Peters AL, et al,[230])*	are not considered to be synergistic[52] • Although addition of a third oral agent can be considered, especially if the A1C level is close to target (A1C < 8.0%), this approach is usually not preferred, as it is no more effective in lowering glycemia, and is more costly, than initiating or intensifying insulin • Evidence cited : Schwartz et al, 2003[231]		The criteria for selecting the evidence are not clearly described; The methods used for formulating the recommendations are not clearly described. It was not identified that whether the guideline has been externally reviewed by experts prior to its publication;
American Association of Clinical Endocrinologists / American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm	A1C target: 6.5% or less, with recognition of the need for individualization to minimize the risks of hypoglycaemia. **For patients with A1C 6.5-7.5%** Start with monotherapy: Metformin is the cornerstone of monotherapy. DPP-4 inhibitors, GLP-1 analogues, TZD and □-glucosidase inhibitors (AGIs) are also recommended.	**<u>A1C 6.5-7.5%:</u>** • If failed from 2-3 months metformin monotherapy: adding another agent in the following order: GLP-1 analogue or DPP-4 inhibitor; TZD, a glinide or sulfonylurea; Colesevelam, AGIs; • If failed from TZD	**<u>A1C 6.5-7.5%:</u>** if failed from 2-3 months dual therapy, start triple therapy: Met + GLP1 analogues or DPP4 inhibitors +TZD or insulin secretagogue (glinide or SU). Star insulin if triple therapy failed.	Not reported: It was indicated that many authors received the consultant honoraria from various pharmaceutical companies	**Strength:** The health benefits, side effects and risks have been considered in formulating the recommendations The limitations: This algorithm represents a consensus of 14 highly experienced clinicians, clinical researchers, practitioners, and

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
for Glycemic Control (AACE/ACE, 2009)[216]		monotherapy: adding GLP1-analogue or DPP4 inhibitors **If A1C 7.6- 9.0%** Start with initial dual therapy as follow: Option 1 : Met+GLP1 analogue or DPP4 inhibitor or TZD Option 2: Met +SU or glinide	**If A1C 7.6- 9.0%** • If failed from 2-3 months initial dual theray: Start triple therapy: Option 1: Met+GLP1-analogue or DPP4 inhibitor +TZD; Option 2: Met+GLP1-analogue or DPP4 inhibitor +SU Option 3: Met+ TZD+SU Star insulin if triple therapy failed. **If A1C >9.0%** • For patients under treatment: start Insulin ± other agents; • For drug naïve patients with symptoms: initial treatment: Insulin ± other agents; • Drug naïve patients without symptom: • Option 1: Met + GLP-1 analogue or DPP-4 inhibitor ± SU • Option 2: Met + TZD ± SU • Option 3: Met + GLP-1		academicians and is based on the American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Guidelines and the recent medical literature. **(Endocr Pract. 2009;15:540-559).** Systematic methods was not used to search the evidence; The criteria for selecting the evidence are not clearly described; The methods used for formulating the recommendations (consensus) are not clearly described. It was not identified that whether the guideline has been externally reviewed by experts prior to its publication; No supporting evidence was directly cited for the algorithm No updating procedure for the algorithm was provided.

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
			analogue or DPP-4 inhibitor ± TZD		
National Institute for Health and Clinical Excellence (UK), 2008[4,53]	• Information extracted from the algorithm: Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes • A1C target: < 6.5% • Start metformin treatment in a person who is overweight or obese and whose blood glucose is inadequately controlled (≥ 6.5%) by lifestyle interventions (nutrition and exercise) alone. • Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. • **A sulfonylurea** may be considered as option for first line pharmacotherapy if: ○ the person is not overweight ○ the person does not tolerate metformin (or it is contraindicated) **or** ○ a rapid response to therapy is required because of hyperglycaemic symptoms • Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated.	• Sulfonylurea should be added to metformin as second line pharmacotherapy if A1C target (<6.5%) cannot be achieved. • Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (A1C ≥ 6.5%, or other higher level agreed with the individual) if: ○ the person is at significant risk of hypoglycemia or its consequences (e.g., older people, and people in certain jobs or those in particular social circumstances), or ○ The person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. • Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood	If A1C ≥ 7.5% with the treatment of metformin and sulfonylurea • Consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification not to (such as employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity).[4] ○ When starting basal insulin, continue metform and sulfonylurea ○ When starting premixed insulin: continue with metformin continue sulfonylurea initially discontinue if hypoglycaemia occurs. • Evidence cited: none • Consider adding sitagliptin as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes	National Institute for Health and Clinical Excellence	**Strength:** Systematic methods was used to search the evidence; The methods used for formulating the recommendations are clearly described. The health benefits, side effects and risks have been considered in formulating the recommendations; There is an explicit link between the recommendations and the supporting evidence The guideline has been externally reviewed by experts prior to its publication; A procedure for updating the guideline was provided. **Limitations:** The criteria for selecting the evidence were not clearly described;

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
	• When drug concordance is a problem, offer a once-daily, long-acting sulfonylurea. • Evidence cited: None	glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if the person does not tolerate metformin, or metformin is contraindicated. • Consider adding a TZD (pioglitazone, rosiglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. • Consider adding a TZD (pioglitazone, rosiglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose	inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate. • Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). • A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if: ○ further weight gain would cause or exacerbate significant problems associated with a high body weight, or ○ a TZD (pioglitazone, rosiglitazone) is contraindicated, or ○ The person has previously had a poor response to, or did not tolerate, a TZD (pioglitazone, rosiglitazone). • Consider adding a TZD (pioglitazone,		

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
		remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if the person does not tolerate metformin or metformin is contraindicated. Other options: • A rapid-acting insulin secretagogue may be considered for people with non-routine daily lifestyle patterns • Only consider a TZD if hypoglycemia on sulfonylurea is a potential problem • Evidence cited: None	rosiglitazone) or sitagliptin as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate. [4] • Only continue TZD therapy (pioglitazone, rosiglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). • Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has: ○ a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent (with		

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
			appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or ○ A BMI < 35.0 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months). • Evidence cited: none		
Scottish Intercollegiate Guideline Network (SIGN), 2010, (UK)[217]	A1C target: 7% is reasonable to reduce the risk of microvascular disease and macrovascular disease; 6.5% is appropriate at diagnosis; A1C target should be set for individual in order to balance benefit with harms, in particular hypoglycaemia and weight gain. Metformin should be considered as the first line oral treatment option for overweight patients with type 2	If not reaching A1C target with the 1st line therapy move to second line: Add one of following agents: 1. Usually, Sulfonylurea is the second line option [232] 2. TZD can be added to metformin and sulfonylurea or substitute for either in	If not reaching A1C target with the 2nd line therapy move to third line: Add on or substitute one of the following agents: •TZD if no heart failure •DPP4-inhibitors if weight a concern •Insulin (inject before	National Health Service, Scotland (NHS), UK	**Strengths:** Systematic methods were used to search for evidence The methods used for formulating the recommendations are clearly described.[233] The health benefits, side effects and risks have been considered in formulating the recommendations

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
	diabetes (Grade A. Evidence: SRs, RCTs etc. Sulfonylurea should be considered as first line oral agents in patients who are not overweight if intolerant of metformin or if weight loss/osmotic symptom (Grade A, Evidence: Kahn et al 2006[117]	cases of intolerance. ° TZD should not be used in patients with congestive heart failure. ° The risk of fracture should be considered in the long term care of female patients treated with TZD (GRADE A, Evidence: SRs RCTs etc.) ° Use TZD if hypoglycaemia is a concern (e.g. driving, occupational hazard, at risk of falls) °Patients prescribed TZD should be made aware of the increased risk of peripheral edema ° Rosiglitazone should not be used in patients with acute coronary syndrome or a history of myocardial infarction. 3.DPP-4 inhibitors may be used to improve blood glucose control in patients with type 2 diaetes: (GRADE A. Evidence: SRs RCTs etc.) °if hypoglycaemia is a concern (e.g. driving, occupational hazard, at risk of falls) ° if weight gain is a concern	bed) ° if osmotic symptoms/rising A1C NPH insulin initially; ° if hypoglycaemia is a concern, use basal insulin analogue as an alternative ° add prandial insulin with time if required. •GLP1-agonist may be used to improve glycemic control in obese adults(BMI≥30 kg/m2 with type 2 diabetes who are already prescribed metformin and/or sulfonylureas. A GLP1 agonist will usually be added as a third line agent in those who don reach target glycemia on dual therapy with metformin and sulfonylurea (as a alternative to adding insulin therapy) ° Liraglutide may be used as a third line agent to further improve glycemic control in obese adults with type 2 diabetes who are already prescribed metformin and a TZD and who do not reach target glycemia. (GRADE A . Evidence: SRs. RCTs, etc) °If a desire to lose		There is an explicit link between the recommendations and the supporting evidence The guideline has been externally reviewed by experts prior to its publication. A procedure for updating the guideline is provided. It will be updated in three years **Limitation**: The criteria for selecting the evidence are not clearly described in the guideline document.

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
			weight °Usually <10 years from diagnosis		
Diabetes Australia Guideline, 2009[215]	Recommendations and practice points: • A1C should be used to assess long term blood glucose control. • A1C targets: ≤7%. -A1C >7% may be appropriate in people with type 2 diabetes who have a history of severe hypoglycaemia, a limited life expectancy, co-morbidities or who are elderly. • It is recommended that interventions to achieve A1C target should begin with lifestyle modification followed by therapeutic options selected on the basis of individual clinical circumstances, side effects and contraindications. (Grade A) • Treatment should be intensified if diabetes control is not at target and is not improving or is worsening after 3-6 months of a specific treatment strategy. However, this time interval should be shortened in the presence of significant hyperglycaemia. • Information extracted from the management algorithm for blood glucose control in type 2 diabetes: - Start metformin if A1C target could not be achieved with lifestyle modification • People with newly diagnosed type	Second line pharmacotherapy was not specified in the recommendation. • Information extracted from the management algorithm for blood glucose control in type 2 diabetes: -Start sulfonylurea (add on to metformin) if A1C target not achieved after metformin treatment. - DPP-4 inhibitors: authorised only as dual therapy with metformin or sulfonylurea where combination metformin and sulfonylurea is contraindicated or not tolerated. - TZDs are approved only as dual therapy with metformin or sulfonylurea where combination metformin and sulfonylurea is contraindicated or not tolerated. • Evidence statement: the Exenatide is a new option for improving glycaemic control in people with type 2 diabetes as an add-on therapy. (*Level of Evidence I)* • Evidence cited: none	Third line agents was not specified: • Information extracted from the management algorithm for blood glucose control in type 2 diabetes: - Arcabose, DPP-4 inhibitors, Pioglitazone or insulin could be the options for (triple) therapy if the A1C target could not be achieved after the combination of metformin and Sulfonylurea. -Rosiglitazone is not authorised for triple therapy or for use with insulin • Evidence cited: none	Department of Health and Ageing (DoHA), Australia	**Strengths:** Systematic methods was used to search the evidence; The criteria for selecting the evidence are clearly described; The methods used for formulating the recommendations were described. The health benefits, side effects and risks have been considered in formulating the recommendations; There is an explicit link between the recommendations and the supporting evidence A procedure for updating the guideline was provided. **Limitations:** Whether the guideline has been externally reviewed by experts prior to its publication was not reported

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
	2 diabetes should routinely be offered a trial of lifestyle modification. However, pharmacotherapy may also be required in people presenting with significant hyperglycaemia. • It is preferable to add a second oral anti-diabetic medication rather than using a maximum dose of one medication alone. Metformin is contraindicated in people with an eGFR < 30 ml/min/1.73 m^2 and should be used with caution in people with an eGFR of 30-45 ml/min/1.73 m^2. Evidence cited: None				
Government of South Australia, Department of Health, 2008[5]	• *Information mainly extracted from treatment of hyperglycemia flowchart.* • Target glycemic levels: A1C < 7%; FPG 4.0-6.0 mmol/L; PPG 4.0-8.0 • If 3 months lifestyle modification do not achieve target glycemic level, add OAD as follow: • Metformin if BMI ≥ 25 kg/m^2 • Metformin or sulfonylurea if BMI < 25 kg/m^2 • If highly symptomatic, or BGL > 20.0 mmol/L, initial treatment with an OHA or insulin will be required to stabilise the blood glucose level. • Evidence cited: None	• Target glycemic control: ≤7% • If target levels (A1C < 7%; FPG 4.0-6.0 mmol/L; PPG 4.0-8.0 mmol/L) not achieved at maximum dosage of metformin, add an oral agent from a different class as combination therapy. • Evidence cited: None	If target blood glucose level is not achieved or combination therapy is contraindicated, add insulin either as an adjunct with OHA or as principal therapy • Evidence cited: None	Department of Human Services, Australia	**Limitations:** No methods was reported , it can not been fully assessed with AGREE The health benefits, side effects and risks have not been considered in formulating the recommendations; An explicit link between the recommendations and the supporting evidence was not provided

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
New Zealand Guidelines Group, 2003[7] (Note: DPP4-inhbitors and GLP-1 analogues was not included in the guideline because the new agents were not available when the guideline was developed)	*Information was extracted from a Stepwise approach to glycemic control:* • Metformin is first-line therapy if BMI ≥25 kg/m^2; • sulfonylurea may be used if BMI <25 kg/m^2, or metformin is not tolerated or contraindicated • Consider a glitazone if both metformin and a sulfonylurea are not tolerated or contraindicated • Consider acarbose if other oral agents are not tolerated or contraindicated • Titrate dose until maximum recommended or tolerated dose is reached – 'start low, go slow' • Evidence cited; None	• Sulfonylurea should be added on metformin as second line pharmacotherapy if A1C target (≤7%) cannot be achieved. • If already on sulfonylurea, add metformin • Consider a TZD in combination with either metformin or a sulfonylurea, if either is not tolerated or contraindicated. • Evidence cited: None	For those on maximum doses of oral therapy, • consider starting insulin therapy	The Ministry of Health, New Zealand	**Strength:** The health benefits, side effects and risks have been considered in formulating the recommendations; The methods used for formulating the recommendations were clearly described. **Limitations:** Systematic methods was not used to search the evidence; The criteria for selecting the evidence are not clearly described; There is an explicit link between the recommendations and the supporting evidence It was not identified that whether the guideline has been externally reviewed by experts prior to its publication; A procedure for updating the guideline was not provided.
International Diabetes Federation 2005[9] (Note: DPP4-inhbitors and	• Target A1C: <6.5% • Begin oral glucose-lowering drugs when lifestyle interventions alone are unable to maintain blood glucose control at target levels. • Begin with metformin unless	• Use sulfonylurea when A1C target (<6.5%) cannot be achieved within 2-6 months of metformin monotherapy. • When glucose concentrations are not	TZD when failed from the combination of metformin and a sulfonylurea	Various commercial partners providing unrestricted educational grants.	**Strength:** The health benefits, side effects and risks have been considered in formulating the recommendations; The methods used for

Guidelines (organization, country and year)	Recommended first line	Recommended second line therapy and evidence cited	Recommended third line therapy and evidence cited	Funding source	Strength/Limitations based on AGREE assessment (vigour of development)
GLP-1 analogues was not included in the guideline because the new agents were not available when the guideline was developed)	evidence or risk of renal impairment, titrating the dose over early weeks to minimize discontinuation due to gastro-intestinal intolerance. • Monitor renal function and risk of significant renal impairment (eGFR <60 ml/min/ 1.73 m^2) in people taking metformin. • Use sulfonylurea as a first-line option in the person who is not overweight. • Choose a drug of low cost, but exercise caution if hypoglycaemia may be a problem to the individual, including through renal impairment. • Once-daily sulfonylureas should be an available option where drug concordance is problematic. • Rapid-acting insulin secretagogues may be useful as an alternative to sulfonylureas in some insulin-sensitive people with flexible lifestyles.	controlled to target levels, adding TZD: ○ to metformin as an alternative to a sulfonylurea, or ○ to a sulfonylurea where metformin is not tolerated • Rapid-acting insulin secretagogues may be useful as an alternative to sulfonylureas in some insulin-sensitive people with flexible lifestyles. • Evidence cited: None			formulating the recommendations were clearly described; The guideline has been externally reviewed by experts prior to its publication; A procedure for updating the guideline was provided. Limitations: Systematic methods was not used to search the evidence; The criteria for selecting the evidence are not clearly described; An explicit link between the recommendations and the supporting evidence was not provided

* publication of these guidelines predated the emergence of DPP-4 inhibitors and GLP-1 analogues

APPENDIX 8: SUPPLEMENTAL RESEARCH QUESTION 3: ADEQUATE TRIAL OF DIABETES PHARMACOTHERAPY

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Research question: What constitutes an adequate trial of first and second-line therapy (i.e., metformin and sulfonylureas) before the decision to increase doses, or to add or switch to third-line agent(s) is made?

1. Objective

To determine the definition of an adequate trial of first and second-line therapies prior to decisions on dose increases, or adding or switching to a third-line agent.

2. Methods

The literature searches used to address the comparative efficacy of second-line agents added onto metformin monotherapy, and third-line agents added onto metformin and a sulfonylurea, were sufficiently broad in scope to allow their use for identification of studies addressing the supplemental questions. Randomized controlled trials identified in the searches were selected if they reported one or more of the following comparisons in patients inadequately controlled with existing therapy:

First-line failure:

- addition of second-line therapy at time x versus addition at time y
- increased dose of metformin at time x versus increase at time y
- continued first-line metformin at pre-trial doses versus increased dose of metformin
- continued first-line metformin at pre-trial doses versus addition of a second-line agent
- continued first-line metformin at pre-trial doses versus switch to a second-line agent

Second-line failure:

- addition of third-line therapy at time x versus addition at time y
- increased dose of metformin and/or sulfonylurea at time x versus increase at time y
- continued metformin and a sulfonylurea at pre-trial doses versus increased dose of metformin and/or sulfonylurea
- continued metformin and a sulfonylurea at pre-trial doses versus addition of a third-line agent
- continued metformin and a sulfonylurea at pre-trial doses versus switch to a third-line agent (i.e., discontinuation of metformin and/or sulfonylurea)

To provide additional context, guideline recommendations related to these research questions are summarized, and pertinent utilization data are reported.

3. Findings

Evidence from RCTs

There were no RCTs identified that addressed the research question.

Summary of Clinical Practice Guidelines

Recommended duration of metformin monotherapy across guidelines ranges from 2-3 months to as long as 6 months. The CDA guidelines[8] provide a more general recommendation that timely adjustment of medications is warranted if glycemic control is not achieved within 6 to 12 months.

Guidelines from NICE[4,53] and SIGN[217] do not specify either dose or duration of initial metformin monotherapy before second-line agents should be considered.

Table 20: Recommended duration of initial metformin monotherapy

Organization, year	Recommended duration of initial metformin monotherapy
CDA, 2008[8]	Timely adjustments to and/or addition of antihyperglycemic agents to attain target A1C recommended within 6 to 12 months
ADA/EASD, 2009 [6,52,214,218]	Duration: 2-3 months
AACE/ACE, 2009[216]	Duration: 2-3 months
NICE, 2008[4,53]	Dose and duration not specified
SIGN, 2010[217]	Dose and duration not specified
DAG, 2009[215]	Duration: 3-6 months. Treatment should be intensified if diabetes control is not at target and is not improving or is worsening after 3-6 months of a specific treatment strategy. However, this time interval should be shortened in the presence of significant hyperglycaemia.
South Africa*, 2008[5]	Duration: not specified
NZGG, 2003[7]	Duration: Not specified
IDF 2005[9]	Duration: 2-6 months of metformin

Abbreviations: **ADA/EASD=**American Diabetes Association and the European Association for the Study of Diabetes; **AACE/ACE=**American Association of Clinical Endocrinologists /American College of Endocrinology; **CDA=**Canadian Diabetes Association; **IDF=**International Diabetes Federation; **NICE=**National Institute for Health and Clinical Excellence; **DAG=**Diabetes Australia Guideline; **SIGN=**Scottish Intercollegiate Guideline Network; **NZGG=**New Zealand Guidelines Group
Footnote: * Government of South Australia, Department of Health

Evidence from Utilization Data

CADTH recently completed a utilization analysis of second-line therapies after metformin monotherapy among beneficiaries of the Ontario Public Drug Program (OPDP) and private drug plans across Canada.[234] Individuals were selected for the study if they initiated metformin between January 1, 2005 and December 31, 2005, and were followed until January 1, 2008. In the OPDP, 33% of subjects initiated second-line therapy after a mean (SD) of 372 (185) days from the start of metformin monotherapy (Table 25). The mean daily dose (SD) of metformin at initiation of second-line therapy was 1457 (418) mg. Similar results were found in the private drug plan analysis, although the mean duration of metformin monotherapy was somewhat lower.

Table 21: Duration and dose of metformin monotherapy prior to an initial claim for a second-line antidiabetes drug

	ONTARIO DRUG BENEFIT PROGRAM			PRIVATELY FUNDED DRUG PROGRAM		
	Metformin continued	Metformin discontinued	OVERALL	Metformin continued	Metformin discontinued	OVERALL
Average days to initiation of second-line therapy (± SD)	351.6 ± 171.4	393.0 ± 200.1	371.5 ± 185.2	324.3 ± 236.3	345.3 ± 230.0	338.5 ± 240.2
Average Metformin Daily Dose (mg) (± SD)	1510.4 ± 361.7	1400.4 ± 470.8	1457.4 ± 417.7	1609.7 ± 273.9	1388.8 ± 189.2	1495.3 ± 268.4

SD – standard deviation

Among individuals who initiated second-line therapy in the ODBP, 32% switched from metformin to a second-line agent (i.e., metformin was discontinued). The corresponding proportion in the private drug plans was 25%. Mean doses and duration of metformin monotherapy did not differ substantially between those who continued metformin upon addition of second-line therapy versus those who did not. This indicates that in most cases, metformin discontinuation was

unlikely to be a result of toxicities (such as gastrointestinal effects) experienced shortly after metformin initiation.

4. Summary

There is little evidence available on what constitutes an adequate trial of a first- or second-line anti-diabetes therapy before a decision to increase doses or to add or switch to a third-line agent should be made. The 2008 CDA guidelines[8] recommend the lag between agents be kept to a minimum and imply an adequate trial is less than six months. The available utilization data suggest that the majority of patients in Canada are treated with approximately 1500 mg per day or more of metformin as monotherapy before adding or switching to second-line therapy, and that most patients try metformin alone for at least one year before second-line therapy is initiated. Hence, there is no evidence that premature treatment progression among patients with type 2 diabetes is a significant issue in clinical practice. In light of the consensus across major guidelines that metformin be continued upon initiation of second-line therapy, the high rates of metformin discontinuation after a year or more of monotherapy may represent the greater concern.

APPENDIX 9: SUPPLEMENTAL RESEARCH QUESTION 4: SAFETY AND EFFICACY OF INCREASED DOSES OF METFORMIN VERSUS ADDITION OF SECOND-LINE AGENTS

1. Objective

To determine if evidence is available regarding the differences in safety and/or efficacy of increased doses of metformin monotherapy compared to adding second-line agents to submaximal metformin doses achieving inadequate control.

2. Methods

The literature searches used to address the comparative efficacy of second-line agents added onto metformin monotherapy, and third-line agents added onto metformin and a sulfonylurea, were sufficiently broad in scope to allow their use for identification of studies addressing the supplemental questions. Randomized controlled trials identified in the searches were selected if they reported one or more of the following comparisons in patients inadequately controlled with existing therapy:

- increased dose of metformin versus addition of a second-line agent
- increased dose of metformin versus switch to a second-line agent

To provide additional context, guideline recommendations related to these research questions are summarized,

3. Findings

The EMPIRE study[235] was a double-blind trial in which patients who'd been on diet therapy alone or taking metformin and/or a sulfonylurea were given a four to seven week run-in period where metformin was stabilized to 1,000 mg/day and any sulfonylureas were discontinued. 766 patients were then randomized to receive an additional 4 mg of rosiglitazone or 500 mg of metformin, which were uptitrated to either 8 mg of rosiglitazone or 1000 mg metformin in addition to the initial 1000mg metformin. After 24 weeks, patients in the rosiglitazone + metformin group showed greater, if modest, A1C improvements than those in the high-dose metformin group (between group difference -0.20%, 95% CI: -0.36% to -0.04%), with no statistically significant differences in hypoglycemia rates or overall adverse events.

A similar study[236] also randomized patients (n = 568) previously taking metformin to either an increased dose of metformin or the addition of rosiglitazone. After 24 weeks, the adjusted treatment difference (rosiglitazone + metformin – metformin) in A1C was -0.22% (p = 0.001). Although patients in the rosiglitazone + metformin group reported better outcomes in terms of treatment satisfaction and gastrointestinal function, patients in the metformin group had better outcomes in terms of cholesterol levels. Hypoglycemia rates were very low, non-severe, and not statistically different between groups.

Weissman *et al*, 2005[235]

Study design	• 24 week, multi-center, randomized, double-blind, parallel-group, n = 766
Population	• Patients on diet therapy alone or taking metformin and/or a sulfonylurea were given a four to seven week run-in period where metformin was stabilized to 1,000 mg/day and any sulfonylureas were discontinued • The inclusion criteria specified that patients on metformin monotherapy had to have an A1C of 7-10% at screening (6.5-8.5% for metformin and sulfonylurea combination therapy). Baseline measurements following the 4-7 week run-in

period were approximately 8.0% in each group; however, they did not report a threshold A1C to remove patients who responded to the metformin run-in.

Intervention
- Randomized to receive an additional 4 mg of rosiglitazone or 500 mg of metformin, which were uptitrated to either 8 mg of rosiglitazone or 1000 mg metformin in addition to the initial 1000 mg metformin

Results
- Patients in the rosiglitazone + metformin group showed greater A1C improvements than those in the high-dose metformin group (between group difference -0.20%, 95% CI: -0.36% to -0.04%).
- No statistically significant differences in hypoglycemia rates or overall adverse events.

Bailey *et al*, 2005[236]

Study design
- 24-week, multicenter, randomized, double-blind, parallel-group, n = 568

Population
- The inclusion criteria for this RCT specified that patients on metformin monotherapy (1-2 g/day) had to have a FPG of ≥ 7 mmol/l at screening.

Intervention
- Randomized patients to either an increased dose of metformin or the addition of rosiglitazone to metformin
  - **Dose level 1:** 4 mg rosiglitazone/2000 mg metformin (n = 37) vs. 2500 mg metformin (n = 48)
  - **Dose level 2:** 8 mg rosiglitazone/2000 mg metformin (n = 258) vs. 3000 mg metformin (n = 251)*

Results
- After 24 weeks, the adjusted treatment difference (rosiglitazone + metformin – metformin) in A1C was -0.22% (p = 0.001)
- Hypoglycemia rates were very low, non-severe, and not statistically different between groups

The 2008 CDA guidelines[8] emphasize that the early or even initial addition of a submaximal dose second-line agent is preferable to metformin monotherapy at maximal doses, providing the agent classes have different mechanisms of action. Recommendations from other internation guidelines are sumamrized in table 25.

Table 22: Recommended doses of initial metformin monotherapy

Organization, year	Recommended doses of initial metformin monotherapy
CDA, 2008[8]	• Dose and duration are not specified • Early or initial addition of submaximal doses of second-line agents are preferable to maximal metformin monotherapy
ADA/EASD, 2009 [6,52,214,218]	• Dose: Maximally effective and tolerated dose
AACE/ACE, 2009[216]	• Although the maximal recommended dose is 2,500 mg daily, little additional benefit is seen with dosages exceeding 2,000 mg daily.
NICE, 2008[4,53]	• Dose and duration not specified
SIGN, 2010[217]	• Dose and duration not specified
DAG, 2009 [215]	• Dose: not specified • Addition of a second oral anti-diabetic medication rather than using a maximum dose of one medication alone is preferred.
South Africa*, 2008[5]	• Dose: maximum dosage of metformin
NZGG, 2003[7]	• Dose: Maximal tolerable dose
IDF 2005[9]	• Dose: not specified

Abbreviations: **ADA/EASD=**American Diabetes Association and the European Association for the Study of Diabetes; **AACE/ACE=**American Association of Clinical Endocrinologists /American College of Endocrinology; **CDA=**Canadian Diabetes Association; **IDF=**International Diabetes Federation; **NICE=**National Institute for Health and Clinical Excellence; **DAG=**Diabetes Australia Guideline; **SIGN=**Scottish Intercollegiate Guideline Network; **NZGG=**New Zealand Guidelines Group
Footnote: * Government of South Australia, Department of Health

4. Summary

There is a paucity of data on the optimal dose and duration of metformin before initiation of third-line therapy. Given the lack of sufficient evidence, it is not surprising that major diabetes guidelines also vary in their recommendations, with some advising maximally tolerated metformin doses, and others add-on therapy to sub-maximal doses. According to the 2008 CDA guidelines,[8] the early or initial addition of submaximal doses of second-line antihyperglycemic agents are preferable to maximal metformin monotherapy dosing. Two RCTs[235,236] were found which support the addition of a TZD rather than increased metformin doses in patients on metformin monotherapy, albeit with minimal glycemic improvements. There was little evidence found to suggest that high doses of metformin or other initial therapies were any more or less safe than adding a second-line agent.

APPENDIX 10: SUPPLEMENTAL RESEARCH QUESTION 5: INCREASED DOSES OF FIRST- AND SECOND-LINE THERAPY VERSUS ADDITION OR SWITCH TO A THIRD-LINE AGENT

1. Objective

To determine if evidence is available regarding the differences in safety and/or efficacy of high doses of metformin and sulfonylurea combination therapy compared to adding a third-line agents to submaximal doses achieving inadequate control.

2. Methods

The literature searches used to address the comparative efficacy of second-line agents added onto metformin monotherapy, and third-line agents added onto metformin and a sulfonylurea, were sufficiently broad in scope to allow their use for identification of studies addressing the supplemental questions. Randomized controlled trials identified in the searches were selected if they reported one or more of the following comparisons in patients inadequately controlled with existing therapy:

- increased dose of metformin and/or sulfonylurea versus addition of a third-line agent
- increased dose of metformin and/or sulfonylurea versus switch to a third-line agent (i.e., discontinuation of metformin and/or sulfonylurea)

To provide additional context, guideline recommendations related to these research questions are summarized,

3. Findings

The 2008 CDA guidelines[8] make no specific mention of the addition of third-line agents to metformin and sulfonylurea, though the guidelines favour combining antihyperglycemic agents with different mechanisms of action where applicable.

An open label study[147] of 55 elderly patients with type 2 diabetes on oral antidiabetes drugs (approximately 75% of the population was using metformin and a sulfonylurea at baseline) randomized patients to receive either increased doses of their oral antidiabetes drugs or the addition of bedtime insulin glargine, with both arms titrated to reach glycemic targets. A1C levels in the glargine group were reduced by 1.5% by the end of 24 weeks, compared to 0.6% in the oral antidiabetes drugs group (p = 0.381). There were fewer hypoglycemic episodes (23 vs 79, p=0.03) and fewer patients experiencing hypoglycemia (9 vs 17, p=0.045) in the glargine group, though no patient in either group suffered severe hypoglycemia. However, the results of this study should be interpreted with caution due to the small sample size of the study, statistically significant differences in HbA_{1C} at baseline, and the wide range of pharmacotherapy at baseline.

Papa *et al*, 2008[147]	
Study design	• 24 week, open-label, randomized, parallel-group, n = 55
Population	• Patients aged 65 years or more with poor glycemic control • The inclusion criteria specified that patients had to have an A1C ≥ 7.5% despite treatment with OADs for at least one year. The patient population was treated with a wide range of oral antidiabetes drugs at baseline (primarily as combination therapy, but some monotherapy as well). The most common treatment strategies at baseline were: glyburide + metformin (75%); repaglinide + metformin (9%).
Intervention	• Randomized to adding insulin glargine to current therapy (n = 27) or increasing current OAD dosages (n = 28)
Results	• No significant difference in A1C levels at 24 weeks (p = 0.381)

- Fewer hypoglycemic episodes with glargine (23 vs 79, p=0.03)
- Fewer patients experiencing hypoglycemia with glargine (9 vs 17, p=0.045)
- No episodes of severe hypoglycemia.

4 Summary

A single RCT[147] reported that adding a basal insulin to submaximal doses of metformin and a sulfonylurea may be associated with fewer hypoglycemic episodes than higher doses of metformin and the sulfonylurea. There was no significant difference between the two treatments with regard to changes in hemoglobin A1C. In summary, the data to inform the optimal conditions under which additional therapy should be considered is very limited. The studies identified indicated little to no benefit of add-on therapy versus increased doses of existing therapy in terms of improved glycemic control.

APPENDIX 11: CHARACTERISTICS OF INCLUDED STUDIES

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Aljabri et al, 2004[10]	Canada	Investigator-initiated grant from Eli Lilly	• Pioglitazone (30-45 mg/day) + Met + SU • NPH insulin (titrated to FG < 6.0 mg/dl) + Met + SU	FG < 6.0 mmol/L	4 months	A1C > 8.0%	62	Hypoglycemia
Al-Shaikh, 2006[12]	Saudi Arabia	Not reported	• Insulin glargine (HS) + Met + SU • Biphasic insulin (30% regular insulin + 70% NPH), 2/3 dose in morning and 1/3 dose in evening	FBG < 7.7 mmol/L	6 months	• A1c > 8.0% • FBG > 7.8mmol/L	221	A1C
Bergenstal et al, 2009[14]	United States	Novo Nordisk	• Exenatide + Met + SU • BIAsp30 (QD) + Met + SU • BIAsp30 (BID) + Met + SU	FBG 5.0-6.1 mmol/L	6 months	A1C ≥ 8.0%	372	A1C
Berhanu et al, 2007[16]	United States	Takeda Global Research and Development	• Insulin + Pioglitazone + Met • Insulin + Placebo + Met	FPG < 7.8 mmol/L	20 weeks	• A1C > 8.0% • FPG > 6.7mmol/L	222	Not reported
Boye et al, 2006[18]	Multinational	Takeda Global Research and Development Center	• Exenatide (BID) + SU + Met • Insulin glargine (HS) + SU + Met	FBG < 5.5 mmol/L	26 weeks	A1C 7.0-10.0%	Not reported	A1C
Charpentier et al, 2009[20]	France	Eli Lilly and Company	• Pioglitazone (30-45 mg/day) + Met + SU • Placebo + Met + SU	HbA1c < 6.5%	7 months	A1C 7.0–9.5%	299	A1C

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Dailey et al, 2004[22]	United States	Sponsored by Takeda France	• Rosiglitazone (4-8 mg) + Met + SU • Placebo + Met + SU	HbA1c <7.0% or mean BG < 7.0 mmol/L	4 months	A1C 7.0-10.0%	365	A1C
Davies et al, 2007[24]	United Kingdom	Grant from Bristol-Myers Squibb	• Biphasic 30/70 human insulin (BID) + Met • NPH insulin (HS) + Repaglinide (AC) + Met • NPH Insulin (HS) + Met	FBG < 6.0 mmol/L	4 months	A1C > 7.0%	82	A1C
De Mattia et al, 2009[26]	Italy	Sanofi-Aventis	• Insulin glargine + Met + SU • NPH Insulin + Met + SU	FBG < 5.5 mmol/L	3 months	A1C ≥ 8.0%	20	FBG
Derosa et al, 2009[28]	Italy	University of Pavia, Italy	• Acarbose + Met + SU • Rapaglinide + Met + SU	Forced titration independent of glycemic control	3.5 months	• A1C ≥ 6.5% • FPG ≥ 160mg/dl	103	FPG
Dorkhan et al, 2009[30]	Sweden	Grants from Sanofi-Aventis, Crafoord Foundation, Swedish Heart and Lung Association	• Pioglitazone + Met + SU • Insulin (glargine) + Met + SU	FBG < 6.0 mmol/L (glargine) or A1c < 6.2% (pioglitazone)	6.5 months	A1C > 6.2% measured with Mono-S method (= 7% NGSP)	30	Cardiac size and function, fluid retention, cardiac dysfunction.
Esposito et al, 2008[32]	Italy	Funded in part by the Second University of Naples	• NPL insulin (HS) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.6 mmol/L	9 months	• A1C 7.5%-10% • FPG ≥ 6.7 mmol/L	116	A1C
Gao et al, 2009[34‡]	China, India, Korea, Taiwan	Amylin Pharmaceuticals, Eli Lilly and Company	• Exenatide (10 µg BID) + Met + SU • Placebo (BID) + Met + SU	Fixed dose	4 months	A1C > 7.0%	472	A1C

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Goudswaard et al, 2004[36]	Netherlands	Not reported	• NPH insulin (QD) + Met + SU • Biphasic insulin (70/30) (BID)	FBG 4.0-7.0 mmol/L and PPG 7.0-10.0 mmol/L	12 months	A1C ≥ 7.0%	69	Not specified
Hartemann-Heurtier et al, 2009[38]	France	Public grant and Takeda Laboratory	• Pioglitazone + Met + SU • NPH insulin + Met + SU	FPG 6.1 mmol/L	6 months	A1C > 7.5%	28	Not reported
Heine et al, 2005[40]	Multinational	Amylin Pharmaceuticals, Eli Lilly and Company	• Exenatide (10 µg BID) + Met + SU • Insulin glargine + Met + SU	FBG < 5.5 mmol/L	26 weeks	A1C 7.0–10.0%	551	A1C
Hermansen et al, 2007[41‡]	USA and Denmark	Merck	• Sitagliptin (100 mg/day) + Met + SU • Placebo + Met + SU	Fixed dose; rescue therapy provided at decreasing FPG limits (15 mmol/L week 1, 11 mmol/L after week12)	6 months	A1C ≥ 7.5%	441	• A1C • Hypoglycemia
Holman et al, 2007[43]	Ireland, UK	Novo Nordisk and Diabetes UK	• Insulin aspart (TID) + Met + SU • Insulin detemir (HS or BID) + Met + SU • Biphasic insulin aspart 30 (BID) + Met + SU	FBG 4.0-5.5 mmol/L and 2-5.0-7.0 mmol/Lhr PPG	12 months	A1C 7.0-10.0%	708	A1C
Janka et al, 2005[11]	Germany, Finland etc	Aventis Pharma	• Insulin glargine + Met + SU • 30/70 NPH + placebo	FBG < 5.5 mmol/L	6 months	A1C > 7.5%	364	• A1C • Hypoglycemia
Janka et al, 2007[13]	10 European countries	Sanofi-aventis	• Insulin glargine (QD) + SU + Met • Biphasic insulin (30% regular, 70% NPH) (BID)	FBG < 5.5 mmol/L	6 months	• A1C 7.5-10.5% • FBG ≥ 6.7mmol/l	130	A1C

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Kendall et al, 2005[15]	United States	Not reported	• Exenatide (5 µg BID) + Met + SU • Exenatide (10 µg BID) + Met + SU • Placebo + Met + SU	Fixed dose dependant on GI effects	7.5 months	A1C 7.5-11.0%	734	A1C
Ko et al, 2006[17]	Hong Kong	Dept of Medicine, AH Nethersole Hospital	• Rosiglitazone + Met + SU • NPH Insulin (HS) + Met + SU	A1c < 7.5%	52 weeks	A1C ≥ 8.5%	112	Not reported
Lam et al, 1998[19]	Hong Kong	In part by Bayer China	• Acarbose (150-300 mg/day) + Met + glibenclamide (10 mg BID) or gliclazide (160 mg BID) • Placebo + Met + glibenclamide (10 mg BID) or gliclazide (160 mg BID)	Fixed dose	24 weeks	A1C 8.4-10.8% at least twice in previous 3 months	90	Not reported
Lopez-Alvarenga et al, 1999[21†]	Mexico	Grant from Bayer	• Acarbose (100 mg TID) + Met + SU • Insulin NPH + MET + SU • Placebo + Met + SU	FPG < 7.7 mmol/L	3 months	FBG > 8.8 mmol/l	37	Not specified
Milicevic et al, 2009[23]	Multinational	Sponsored by Eli Lilly	• Insulin NPH (HS) + Glyburide • 1) Insulin lispro 50%, Insulin lispro protamine suspension 50% (pre breakfast), 2) Insulin lispro 25%, Insulin lispro protamine suspension 75% (pre-dinner)	FBG < 6.7 mmol/L and 2-hr PPG < 8.0mmol.L	6 months	A1C > 20% the upper limit of normal	135	Post prandial glucose

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Nauck et al, 2007[25]	Multinational	Eli Lilly and Amylin	• Exenatide (10 µg BID) + Met + SU • Biphasic insulin aspart 30/70	FBG < 7.0 mmol/L and 2-hr PPG <10.0 mmol/L	12 months	A1C ≥ 7.0%	505	A1C
Ovalle et al, 2004[27]	United States	Grant from GlaxoSmith-Kline	• Rosiglitazone (8 mg/day) + Met + SU • Biphasic insulin 70/30	FBG < 6.7 mmol/L	6 months	Not reported	17	Beta cell function
Reynolds et al, 2007[29]	USA	Grant from GlaxoSimthKline	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FBG < 6.7 mmol/L	6 months	A1C 8-12%	40	PAI-1, hsCRP, and F2-isoprostanes
Rosenstock et al, 2006[31]	USA	Aventis Pharmaceuticals	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.5 mmol/L	6 months	A1C 7.5-11%	219	A1C
Ross et al, 2001[33]	Canada	Two authors from Eli Lilly	• Insulin lispro + Insulin NPH • Human insulin + Insulin NPH	2-hr PPG < 8.9 mmol/L	5.5 months	A1C < 130% above the upper limit of normal	148	Not reported
Russell-Jones et al, 2009[35]	Multinational	Novo Nordisk A/S	• Liraglutide (1.8 mg/day) + Met + glimepiride • Insulin glargine + Met + glimepiride • Placebo + Met + glimepiride	FPG < 5.5 mmol/L	26 weeks	FPG 7.5-12.8 mmol/L	581	A1C
Standl et al, 2001[37]	Multinational	Bayer and Sanofi-Synthelabo	• Miglitol (50-100 mg TID) + Met + glyburide • Placebo + Met + glyburide	Fixed dose	24 weeks	A1C 7.5-10.5%	154	Not reported
Stehouwer et al, 2003[39]	Multinational	Aventis	• NPH insulin + SU • NPH insulin + 30/70 insulin NPH • NPH insulin	FPG 4.0-7.0 mmol/L or PPG 4.0-10.0 mmol/L or A1C ≤6.5%	9 months	A1C > 6.5%	261	• A1C • Hypoglycemia

Author, year	Country	Sponsor	Interventions/ comparators	Glycemic target	Treatment duration	Criteria for defining combination therapy failure	Randomized Sample size	Primary outcome
Strojek et al, 2009[45]	Multinational	Novo Nordisk	• Insulin glargine + Met + SU • BIAsp30 + Met + SU	FPG 5-6.1 mmol/L	6.5 months	A1C 7.0-11%	480	A1C
Vinik et al, 2007[42]	United States	Sanofi-Aventis	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.5 mmol/L	6 months	A1C 7.5-11%	219	HRQoL
Yki-Jarvinen et al, 2006[44]	Finland and United Kingdom	Grants from Aventis and the Academy of Finland	• Insulin glargine + Met • NPH Insulin + Met	FPG 4.0-5.5 mmol/L	9 months	A1C ≥ 8.0%	110	A1C

A1C=glycosylated haemoglobin; **AC**=with meals; **BID**=twice daily; **FBG**=fasting blood glucose; **FPG**=fasting plasma glucose; **HRQoL**=health-related quality of life; **HS**=at bedtime; **Met**=metformin; **NGSP**=National Glycohemoglobin Standardisation Program; **NPH**=neutral protamine Hagadorn; **NPL**=neutral protamine lispro; **QD**=once daily; **SU**=sulfonylurea

† crossover study; ‡ sub-group data

APPENDIX 12: PATIENT CHARACTERISTICS IN INCLUDED STUDIES

Author, year	Avg. age (years)	% Male	Avg. duration of DM (years)	Avg. A1C (%)	Combination therapy at baseline		Duration of stable combination therapy (months)
					Metformin dosage	Sulfonylurea dosage	
Aljabri et al, 2004[10]	58.0	60.3	10.0	9.9	2050 ± 490 mg/day 2210 ± 504 mg/day	Glyburide (20 mg/day)	≥ 3
Al-Shaikh, 2006[12]	56.3	56.1	*NR*	11.3	Max. tolerated dose	Max. tolerated dose	≥ 3
Bergenstal et al, 2009[14]	52.6	48.4	9.0	10.2	> 1500 mg/day	half maximal dose	3
Berhanu et al, 2007[16]	52.7	42.3	*NR*	8.5	≥ 2000 mg/day	>50% maximal dose	≤3
Boye et al, 2006[18]	58.5 ± 9.2	55.2	9.5 ± 5.7	8.3 ± 1.0	*NR*	*NR*	*NR*
Charpentier et al, 2009[20]	59.7	75.4	12.3	8.1	2584 mg/day (mean)	Glyburide (15.1 mg, n = 105); Glimepiride (5.2 mg, n = 97); Gliclazide (146 mg, n = 91); Glipizide (20 mg, n= 2); Carbutamide (1000 mg, n = 1)	≥ 3
Dailey et al, 2004[22]	57.0	59.5	9.0	8.1	*NR*	*NR*	≥ 2
Davies et al, 2007[24]	57.2	43.9	8.7	9.7	Max. tolerated dose	*NR*	*NR*
De Mattia et al, 2009[26]	59.4 ± 8.2	70.0	≥ 5	9.3 ± 1.4	400 mg/day	Glyburide: 2.5 mg/d	3
Derosa et al[28]	54.0	49.5	3.5	8.1	*NR*	*NR*	*NR*
Dorkhan et al, 2009[30]	61.2	66.7	10.3	8.2	*NR*	*NR*	*NR*
Esposito et al, 2008[32]	54.4	51.8	8.2	8.8	*NR*	*NR*	≥ 3
Gao et al, 2009[34]	54.5	44.4	8.0	8.3	1000-3000 mg	*NR*	≥ 3
Goudswaard et al, 2004[36]	58.5	48.4	7.4	8.5	*NR*	*NR*	*NR*
Hartemann-Heurtier et al, 2009[38]	60.1	59.3	12.0	8.4	Max. tolerated dose	Max. tolerated dose	6
Heine et al, 2005[40]	58.9	61.1	9.6	8.2	*NR*	*NR*	≥ 3
Hermansen et al, 2007[41]	57.3	52.4	10.2	8.3	≥ 1500 mg/day	Glimepiride ≥ 4 mg/d	2.5
Holman et al, 2007[43]	61.7 ± 9.8	64.1	Median: 9.0	8.5 ± 0.8	Max. tolerated dose	Max. tolerated dose	≥ 4
Janka et al, 2005[11]	60.6	59.1	9.9	8.8	≥ 850 mg/day	Glimepiride: 3-4 mg/d	> 1
Janka et al, 2007[13]	69.4	56.1	11.6	8.9	≥ 850 mg/day	Glimepiride: 3-4 mg/d	≥ 1
Kendall et al, 2005[15]	55.3	58.1	8.9	8.5	*NR*	*NR*	≥ 3
Ko et al, 2006[17]	58.2 ± 11.0	50.0	12.7 ± 7.6	9.9 ± 1.0	2400 ± 600 mg (sig diff b/w groups)	34% on glyburide (20 mg/day); 20% on glipizide (20 mg/day); 46% on gliclazide (320 mg/day)	≥ 6
Lam et al, 1998[19]	57.4	43.8	10.1	9.5	1790 ± 750 (SD; acarbose) 1790 ± 780 (SD; placebo)	Glyburide (10 mg BID) Gliclazide (160 mg BID)	≥ 6

Author, year	Avg. age (years)	% Male	Avg. duration of DM (years)	Avg. A1C (%)	Combination therapy at baseline		Duration of stable combination therapy (months)
					Metformin dosage	Sulfonylurea dosage	
Lopez-Alvarenga et al, 1999[21†]	52.6	27.6	10.1	11.3	1200 mg/day	Chlorpropamide (500 mg/day)	≥ 3
Milicevic et al, 2009[23]	57.4	31.9	9.1	9.7	*NR*	*NR*	≥ 1.5
Nauck et al, 2007[25]	58.5	51.1	9.9	8.6	*NR*	*NR*	≥ 3
Ovalle et al, 2004[27]	51.2	*NR*	7.6	8.8	*NR*	*NR*	*NR*
Reynolds et al, 2007[29]	*NR*	*NR*	*NR*	9.0	≥ half-maximal	≥ half-maximal	≥3
Rosenstock et al, 2006[31]	55.6	51.9	8.3	8.7	2000 mg/day or max. tolerated dose	≥50% of the max. labelled dose	≥3
Ross et al, 2001[33]	58.5	43.9	11.1	10.6	*NR*	*NR*	*NR*
Russell-Jones et al, 2009[35]	57.5	56.6	9.4	8.3	2000 mg/day	Glimepiride 4 mg/day	≥ 0.75
Standl et al, 2001[37]	61.5	52.6	Median: 8.0 & 9.0	8.8	*NR*	*NR*	≥ 6
Stehouwer et al, 2003[39]	57.9	50.2	7.9	9.4	1000 mg/day	Glimepiride 6 mg/day	3
Strojek et al, 2009[45]	56.0	43.9	9.3	8.5	2550 mg/day	Glimepiride 4-8 mg/day	≥ 1
Vinik et al, 2007[42]	55.6	51.9	8.3		2000 mg/day or max. tolerated dose	≥50% of the max. labelled dose	≥ 3
Yki-Jarvinen et al, 2006[44]	56	63.6	9.0	9.5	2.28 ± 0.06 g/day 2.19 ± 0.05 g/day	*NR*	0.75

Avg=average; **DM**=diabetes mellitus; **NR**=not reported

APPENDIX 13: INCLUSION AND EXCLUSION CRITERIA FROM INCLUDED STUDIES

Author, year	Inclusion criteria	Exclusion criteria
Aljabri et al, 2004[10]	Patients were 30 to 85 years old, had type 2 diabetes for more than 1 year, and were taking maximally tolerated doses of an insulin secretagogue and metformin. All had received diabetes education, were on a diabetic diet, and were performing home blood glucose monitoring. Their most recent HbA1C measurement was >8.0% while undergoing stable diabetes treatment for >12 weeks.	Exclusion criteria were previous use of insulin or a thiazolidenedione, class III or IV New York Heart Association heart failure, myocardial infarction or stroke in the past 6 months, liver disease, serum creatinine level >2 mg/dL, proliferative retinopathy, current glucocorticoid use, excess alcohol use, and pregnancy or breastfeeding. Patients were allowed to use ACE inhibitors, angiotensin receptor blockers, or lipid-lowering drugs if they had been taking a stable dose for >6 weeks and there was no change in this therapy during the study. Patients could be withdrawn from the study if they had glucose levels that were considered to be acutely dangerous, had intolerable side effects from the therapy, or did not comply with the protocol.
Al-Shaikh, 2006[12]	Type 2 diabetes mellitus; treated on maximum dose of metformin and sulfonylureas for at least 3 months; A1c >8% and FBG>140 mg/dl	Patients with chronic renal failure and severe cardiac disease; elderly patients (age >70 years)
Bergenstal et al, 2009[14]	Male and female subjects with type 2 diabetes for >6 months (American Diabetes Association criteria), age ≥18 and ≤80 years, HbA1c ≥ 8%, were insulin naive (subjects not on insulin, who had received no insulin for more than 2 weeks of daily use within 6 months preceding this trial), and had received therapy with metformin (at least 1500 mg/day) and a sulfonylurea (at least half the maximal dose) for 3 months before screening. The entry criteria were chosen to reflect a level of HbA1c at which most guidelines would recommend starting on insulin therapy	Subjects were excluded if they had significant cardiac disease (New York Heart Association [NYHA] class III or IV congestive heart failure, unstable angina, and/or myocardial infarction) within 12 months prior to study, or had hepatic insufficiency (liver function tests ≥ 2.5 times the upper reference limit) or renal insufficiency (serum creatinine ≥1.3mg/dL for males; ≥1.2mg/dL for females). Subjects were excluded if they used thiazolidinediones, α-glucosidase inhibitors or meglitinides within the 6 months prior to the study, or had a history of an eating disorder or were receiving current treatment with a weight-reducing diet.
Berhanu et al, 2007[16]	Patients aged 18–80 years, with documented type 2 diabetes who could self-monitor blood glucose, were enrolled if previous combination therapy had failed (HbA1c > 8.0%) ≤3 months before screening. Previous combination therapy was defined as sulfonylurea with metformin, insulin plus metformin after failed sulfonylurea therapy or insulin alone after failed combination therapy with metformin and sulfonylurea. In these categories, >50% maximum sulfonylurea and ≥2000 mg/day metformin doses were required. In addition, C-peptide levels ≥0.7 ng/ml and fasting plasma glucose levels >120 mg/dl were required.	Exclusion criteria included TZD use <30 days or insulin treatment >3 months before screening; BMI <20 or >45 kg/m^2; history of myocardial infarction, acute cardiovascular event, or cerebrovascular accident <6 months before screening; cardiac rhythm disturbance; significant cardiovascular disease including New York Heart Association class III or IV; uncontrolled hypertension; low-density lipoprotein (LDL) ≥ 175 mg/dl, triglycerides > 500 mg/dl or alanine aminotransferase (ALT) > 1.5 X upper limit of normal; diabetic nephropathy or anemia. Before and during the study, excluded medications were hydrochlorothiazide (at doses >25 mg/day), glucocorticoids, steroid injections for joints and niacin. Concurrent use of weight-loss agents and antidiabetic medications not included in this study was not permitted.
Boye et al, 2006[18]	Type 2 diabetes mellitus; inadequately controlled with orally administered sulfonylurea and metformin (i.e. HbA1c between 7.0% and 10.0%)	Not reported

Author, year	Inclusion criteria	Exclusion criteria
Charpentier et al, 2009[20]	Male and female patients aged 30 years and older with type 2 diabetes diagnosed at least 2 years before inclusion were eligible for the study. Patients were also required to fulfill the following criteria: treatment for at least 3 months with a combination of metformin at a dose ≥ 1700 mg/day and a sulfonylurea or a glinide at the maximal tolerated dose, HbA1c of 7.0–9.5% (inclusive) within 3 months of the trial and a body mass index (BMI) of 24–35 kg/m^2 (inclusive).	Exclusion criteria included type 1 diabetes; history of ketoacidosis; treatment with oral glucose–lowering monotherapy, more than two oral glucose–lowering agents or insulin; history of insulin therapy lasting more than 1 week; myocardial infarction within 6 months of inclusion; class I–IV heart failure; hypersensitivity to pioglitazone; current renal dialysis; severe or malignant disease; pregnant or breastfeeding status and participation in another clinical trial < 1 month previously.
Dailey et al, 2004[22]	Patients with inadequately controlled type 2 diabetes (HbA1C >7.0% and ≤10.0%) were enrolled if they were between 20 and 78 years of age and had a body mass index between 23 and 40 kg/m^2 (inclusive). All patients were on a stable regimen with an oral antidiabetic agent for 8 weeks before screening. For the lead-in phase, the inclusion criterion for patients receiving maximum metformin (at least 2000 mg daily) and half-maximum sulfonylurea combination therapy was an HbA1C level >7.0% and ≤10.0%. For those receiving submaximal combination therapy or monotherapy, the inclusion criterion was an HbA1C level >7.5% and ≤11.0%. For the double-blind phase, the inclusion criterion was an HbA1C level >7.0% and ≤10.0% during the week before randomization with at least 7.5 mg of glyburide/1500 mg of metformin at the end of the lead-in phase.	Exclusion criteria included uncontrolled diabetes (HbA1C levels ≥10%); polyuria and polydipsia with >10% weight loss; use of hypoglycemic agents other than stable daily doses of metformin, sulfonylureas, or thiazolidinediones within 8 weeks before screening; renal dysfunction (serum creatinine level ≥1.5 mg/dL [men] or ≥1.4 mg/dL [women]); abnormal liver function (serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥twice the upper limit of normal); anemia; clinically substantial cardiac or psychiatric disease; and long-term insulin therapy. Patients were also excluded if they were unable or unwilling to perform self-monitoring of blood glucose levels.
Davies et al, 2007[24]	Insulin-naïve males and females with type 2 diabetes at least 12 months, aged 30-80 years with A1c >7.0%.	Myocardial infarction or cerebrovascular accident in preceding 6 months; severe concurrent disease; serum creatinine>150umol/L; BMI>43 kg/m^2; previous use of insulin for > 2 weeks; women of childbearing potential not on adequate contraceptives.
De Mattia et al, 2009[26]	The primary inclusion criteria included male or female patients ≥45 years old with a diagnosis of Type 2 diabetes mellitus (duration ≥5 years); treatment with OADs in fixed combination (glibenclamide [2.5 mg] + metformin [400 mg]; two or three tablets per day) at a stable dose in the last 3 months; HbA1c ≥8 and ≤11%; BMI 27-35 kg/m^2; and willingness and ability to inject insulin and perform SMBG.	The primary exclusion criteria included patients diagnosed with Type 1 insulin-dependent diabetes mellitus; patients with fasting C-peptide levels <1 ng/ml (to potentially exclude patients with latent autoimmune diabetes of adults); cardiac status New York Heart Association III–IV; impaired renal function as shown by (but not limited to) serum creatinine ≥1.5 mg/dl for males or ≥1.4 mg/dl for females; and planned pregnancy, pregnant or lactating females.
Derosa et al[28]	type 2 diabetes mellitus, according to the ADA criteria. All were required to have been diagnosed as being diabetic for at least 6 months, and did not have glycemic control with diet and oral hypoglycemic agents such as sulphonylureas and metformin [glycated hemoglobin (HbA1c) ≥6.5% and PPG ≥160mg/dl]	Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function (defined as plasma aminotransferase [aspartate aminotransferase (AST normal values: 11–39 mU/ml), and alanine aminotransferase (ALT normal values: 11–34 mU/ml)] and/or gamma-glutamyltransferase (γ-GT normal values: 11–53 mU/ml), impaired kidney function [defined as serum creatinine level (normal values: 0.6–1.3mg/dl)], or anaemia. Patients with unstable cardiovascular conditions (e.g., New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of study enrolment were also excluded. Women who were pregnant, lactating, or of child-bearing potential while not taking adequate contraceptive precautions were also excluded.
Dorkhan et al, 2009[30]	Patients with type 2 diabetes and inadequate glycemic control, defined as treatment with metformin and sulfonylurea/meglitinide in doses > 50% of maximum recommended doses and HbA1c > 6.2% measured with Mono-S method (= 7% National Glycohemoglobin Standardisation Program).	Patients with known heart failure or clinical signs of heart failure (New York Heart Association class II–IV) were excluded. Also excluded from the study were patients with significant valvular dysfunction (defined as more than mild regurgitation or presence of valvular stenosis), reduced ejection fraction (< 50%) or inappropriate acoustic window.

Author, year	Inclusion criteria	Exclusion criteria
Esposito et al, 2008[32]	Men and women age 30 to 70 years, with duration of known diabetes greater than 2 years who received treatment with stable doses of metformin and sulfonylurea for at least 90 days, were selected for the study. Other inclusion criteria were body mass index less than 40 kg/m2, HbA1c levels between 7.5% and 10%, and fasting plasma glucose (FPG) levels of 6.7 mmol/L or greater (≥120 mg/dL).	Exclusion criteria were pregnancy or breastfeeding, previous use of insulin, other antihyperglycemic drugs or triple oral antidiabetic treatment within the previous 6 months, any investigational drug within the previous 3 months, sight-threatening retinopathy, use of agents affecting glycemic control (systemic glucocorticoids and weight-loss drugs), unawareness of hypoglycemia or recurrent major hypoglycemia, anticipated changes in concomitant medication affecting glucose regulation, uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg), and any clinically relevant somatic or mental diseases that may result in poor adherence to insulin regimens. To minimize the likelihood of including participants with late-onset type 1 diabetes, we excluded candidates with a positive test result for antiglutamic acid decarboxylase antibody or with fasting plasma C-peptide levels less than 0.76 ng/L (<0.25 pmol/L). We also excluded patients with abnormal laboratory test results, including liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) greater than 3 times the upper limit of normal and serum creatinine levels greater than 123.8 µmol/L (>1.4 mg/dL), history of illicit drug use, and poor adherence to the 8-point daily glucose profile measurement during the screening phase.
Gao et al, 2009[34]	Male and female, 21 to 75 years, treated with a stable dose of one of the following for at least 3 months prior to screening: * >=1000 mg/day immediate-release metformin; or metformin ≥ 1000 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 analogs, or participated in 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 1 month of screening.
Goudswaard et al, 2004[36]	Younger than 76 years, had HbA1C ≥ 7.0% despite treatment with both sulfonylurea and metformin in maximally tolerated dosages, were willing to start insulin therapy, and were deemed by their family physician to be candidates for more tight glycemic control.	Exclusion criteria were severe comorbidity (i.e., an illness that surpasses the impact of diabetes or was associated with a short life expectancy) and insufficient understanding of spoken Dutch to follow instructions.
Hartemann-Heurtier et al, 2009[38]	The enrolled subjects were type 2 diabetic men or women (BMI ≥ 26 kg/m2) aged 18–80 years, with an HbA1c between 7.5% and 9.5%, and treated with maximal tolerated and stable doses of sulfonylurea and metformin for ≥6 months	Exclusion criteria included prior use of insulin or glitazone, use of other affecting glycemic control agents, ASAT or ALAT >2.5-fold above the upper limit of normal level, glomerular filtration rate <60 ml/min, heart failure ≥grade 2, hemoglobin <10 g/dl, and inability to provide informed consent.
Heine et al, 2005[40]	Patients were 30 to 75 years of age and were treated with stable and maximally effective doses of metformin and a sulfonylurea for at least 3 months before screening. General inclusion criteria included a hemoglobin A1c level ranging from 7.0% to 10.0% at the time of screening, body mass index ranging from 25 kg/m^2 to 45 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months before screening).	Patients were excluded if they 1) had participated in an interventional medical, surgical, or pharmaceutical study within 30 days before screening; 2) had more than 3 episodes of severe hypoglycemia within 6 months before screening; 3) were undergoing therapy for a malignant disease other than basal-cell or squamous-cell skin cancer; 4) had cardiac disease that was class III or IV according to the New York Heart Association criteria; 5) had a serum creatinine concentration of greater than 135 µmol/L (>1.5 mg/dL) for men or greater than 110 µmol/L (>1.2 mg/dL) for women or had obvious clinical signs or symptoms of liver disease; 6) were receiving long-term (lasting longer than 2 weeks) systemic glucocorticoid therapy or had received such therapy within 2 weeks immediately before screening; 7) had used any prescription drug to promote weight loss within 3 months before screening; or 8) had been treated (for more than 2 consecutive weeks) with insulin within 3 months before screening, with thiazolidinediones within 4 months before screening, with α-glucosidase inhibitors within 3 months before screening, or with meglitinides within 3 months before screening.

Author, year	Inclusion criteria	Exclusion criteria
Hermansen et al, 2007[41]	Men and women, ≥18 and ≤75 years of age, with type 2 diabetes were recruited for this study. Only the following patients were eligible to be screened: (i) already taking glimepiride alone (at any dose) or in combination with metformin (at any dose), (ii) taking another OAD in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any OADs over the prior 8 weeks.	History of type 1 diabetes; were treated with insulin within 8 weeks of the screening visit; had renal dysfunction (creatinine clearance <45 ml/min or <60 ml/min if on metformin); or had a history of hypersensitivity, intolerance or a contraindication to the use of glimepiride, sulphonylurea agents, metformin or pioglitazone (which was included in this study as rescue therapy).
Holman et al, 2007[43]	Type2 DM for at least 12 months; not been treated with insulin; ≥18 years; suboptimal glycemic control (A1c between 7.0% and 10.0%) after maximally tolerated doses of metformin and sulfonylurea for at least 4 months (or one agent if the other was not tolerated); BMI ≤40kg/m^2	History of thiazolidinedione therapy or triple oral antidiabetic treatment within the previous 6 months, sight-threatening retinopathy, a plasma creatinine level of 1.47 mg per deciliter (130 µmol/L) or more, cardiac disease (a history of unstable angina or myocardial infarction within the previous 6 months or NYHA class III or IV congestive heart failure), hepatic disease or an alanine aminotransferase level at least two times as high as the upper limit of the normal range, unawareness of hypoglycemia or recurrent major hypoglycemia, anticipated changes in concomitant medication affecting glucose regulation, uncontrolled hypertension (systolic pressure ≥180 mmHg or diastolic pressure ≥105 mmHg), and the likelihood of pregnancy
Janka et al, 2005[11]	Male or female patients aged 35–75 years with a type 2 diabetes duration of at least 1 year and treated with a stable dose of sulfonylurea and metformin for at least 1 month; BMI ≤ 35 kg/m^2, HbA1c 7.5-10.5%, and FBG levels ≥120 mg/dl (≥6.7 mmol/l).	Any additional use of other oral blood glucose lowering agents, prior use of insulin exceeding 3 days, and a history of ketoacidosis.
Janka et al, 2007[13]	Type 2 diabetes for at least 1 year, male or female, ≥65 years, treated with a stable dose of sulfonylurea and metformin for at least 1 month before enrollment, BMI ≤ 35 kg/m^2, A1c between 7.5% and 10.5% and FBG ≥120mg/dl (≥6.7mmol/l)	Any additional use of other oral blood glucose-lowering agents, prior use of insulin exceeding 3 days, and a history of ketoacidosis
Kendall et al, 2005[15]	Screening fasting plasma glucose concentration <13.3 mmol/l, BMI 27–45 kg/m2, inclusive, and an A1C value of 7.5–11.0%. The metformin dose was ≥1,500 mg/day, and the sulfonylurea dose was at least the maximally effective dose for 3 months before screening. In addition, subjects were weight stable (±10%) for 3 months before screening and had no clinically relevant (for a type 2 diabetes population) abnormal laboratory test values (>25% outside normal laboratory values). Female subjects were postmenopausal, surgically sterile, or using contraceptives for at least 3 months before screening and continuing throughout the study.	Subjects were excluded if they had evidence of other clinically significant medical conditions or had used thiazolidinediones, meglitinides, α-glucosidase inhibitors, exogenous insulin, or weight loss drugs within the prior 3 months. Further exclusion criteria included therapy with corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug.
Ko et al, 2006[17]	A1c ≥ 8.5% for 6 months or longer despite maximal doses of conventional OAD	Type 2 diabetes with secondary OAD failure
Lam et al, 1998[19]	Chinese men and women aged 35-70 with type 2 diabetes for over 6 months and stable weight (BMI < 30 kg/m^2), A1c 8-4-10.8% at least twice in past 3 months despite maximal doses of flibenclamide or gliclazide and metformin for over 6 months.	serum creatine > 200umol/l, serum transaminases two times the upper normal range; significant diseases or conditions, including emotional disorders and substance abuse; ketonuria or symptomatic hyperglycemia; gastrointestinal diseases likely to be associated with abnormal gut motility or absorption; known lactose intolerance; other investigational drugs or medications known to affect glucose homeostasis (such as glucocorticoids) taken in the past 3 months; pregnant and nursing patients.
Lopez-Alvarenga et al, 1999[21]	Type 2 diabetic patients aged 35–70 years with stable body weight (BMI 23-35 kg/m^2) and without severe chronic complications, but with fasting plasma glucose above 8.8 mmol/l despite maximal doses of chlorpropamide (≥ 500 mg/day) and metformin (≥1200 mg/day) for at least 2 months, were eligible for recruitment.	Exclusion criteria were as follows: serum creatinine > 200 mmol/l, fasting plasma glucose > 19.4 mmol/l, ketonuria, gastrointestinal diseases likely to be associated with malabsorption, women with child-bearing potential, and any other condition that the researchers considered as possible reasons for poor adherence to the treatments.

Author, year	Inclusion criteria	Exclusion criteria
Milicevic et al, 2009[23]	Patients with type 2 diabetes treated with OADs for at least 6 months before study entry and were on maximally tolerated doses of glibenclamide and metformin during at least the 6 week period preceding Visit 1, and had an A1C > 20% the upper limit of normal (in the local laboratory) on Visit 1 and at least on one occasion in the 6 month period before entry. Additional inclusion criteria included patients aged 40-80 years and a BMI between 25-32 kg/m^2.	Patients were excluded if type 1 diabetes could not be ruled out, if any other serious diseases were present (including ischemic heart disease, NYHA Class III or IV cardiac function status, liver disease, and end-stage kidney disease), or if they had advanced forms of diabetes complications. Patients were also considered ineligible if their treatment during the last month before the study included insulin or OADs other than glibenclamide and metformin or if their blood glucose values at randomization were in the optimal range (as judged by the investigator).
Nauck et al, 2007[25]	Eligible patients were between 30 and 75 years of age and had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for at least 3 months. Inclusion criteria included, at the time of screening, HbA1c levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months).	Patients were excluded if they: (1) had had more than three episodes of severe hypoglycemia within 6 months prior to screening; (2) had used any prescription drug to promote weight loss within 3 months; or (3) had been treated with insulin, thiazolidinediones, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months.
Ovalle et al, 2004[27]	Subjects with type 2 diabetes who were inadequately controlled on a regimen of a sulfonylurea and metformin	Not reported
Reynolds et al, 2007[29]	Type 2 diabetes; adults; recruited from the outpatient clinics of Lexington, Kentucky Veterans Administration Medical Center; receiving at least half-maximal stable doses of sulfonylurea and metformin for at least 3 months; with A1c ≥8% but <12%; expressing a willingness to take insulin; prescribed medications for concomitant conditions continued	Not reported
Rosenstock et al, 2006[31]	Type 2 diabetes; >18 years of age; A1c≥7.5 and ≤11%; BMI>25kg/m2; Continuously using stable daily doses of ≥50% of the maximally labeled dose of a sulfonylurea and at least 1000 mg metformin for ≥3 months before the screening visit	Stroke, myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the previous 12 months; history of congestive heart failure; treatment with nonselective β-blockers; hypoglycemia unawareness; impaired renal function; active liver disease; substance or alcohol abuse; and malignancy and planned radiological examinations requiring administration of contrasting agents
Ross et al, 2001[33]	Subjects were on maximum tolerated doses of metformin and sulfonylureas with achieving glycemic control, defined as A1C < 130% above the upper limit of normal despite full compliance with diet and medication, and were not on long-term insulin therapy.	Subjects with severe retinopathy or neuropathy and those who had had more than 2 severe hypoglycemic episodes in the past year.
Russel-Jones et al, 2009[35]	Type 2 diabetes aged 18-80 treated with OADs for at least 3 months before screening; A1c between 7-10%; BMI ≤45 kg/m^2.	Insulin use in previous 3 months unless for short-term intercurrent illness; impaired hepatic or renal function, clinically significant cardiovascular disease, proliferative retinopathy or maculopathy, hypertension ≥180/100 mmHg, cancer; pregnancy; recurrent hypoglycemia or unawareness of hypoglycemia; seropositive for Hepatitis B antigen or Hepatitis C antibody; used any drugs except OADs that could affect blood glucose levels.
Standl et al, 2001[37]	Male or female type 2 diabetes between ages 30-70 with diabetes for at least 3 years with diabetes uncontrolled by diet, glibenclamide and metformin at a stable dose for at least 3 mos. A1c ≥ 7.5% and ≤10.5%, BMI ≤ 35kg/m2 and stable body weight (±5%) over preceding 3 mos. Fertile females required to use reliable contraception.	Any medical condition that might affect the underlying diabetes or interpretation of study results; any medical condition or medication likely to affect gastrointestinal motility and/or absorption; the use of any oral glucose-lowing drugs other that metformin or glibenclamide in the preceding 6 months; diuretics and glucocorticoids unless at a constant dose for preceding 3 months; any other investigational drug in the 30 days preceding enrollment; weight-reducing diets ≤1000 kcal/day; patients who were pregnant or breastfeeding.
Stehouwer et al, 2003[39]	HbA1c >7.0% with diet and oral hypoglycemic drugs (at least 3 tablets of sulfonylurea and 1000 mg of metformin), age 40 to 70 years and BMI 25-40 kg/m^2.	Not reported

Author, year	Inclusion criteria	Exclusion criteria
Strojek et al, 2009[45]	Male and female insulin-naïve subjects with type 2 diabetes aged ≥ 18 years, A1C > 7.0% and ≤11.0%, with a BMI ≤ 40 kg/m^2, must have received OAD combination treatment with no more than three different OADs for at least 6 months prior to the trial. It was also a requirement that metformin and an insulin secretagogue had to be taken for at least 2 months prior to the trial (at doses of at least half their maximal dose). In order to be randomized, subjects must have received an unchanged daily dose of metformin and glimepiride during the preceding week. All self-measured plasma glucose values before breakfast measured on three consecutive days must have been ≥6.0mmol/L, and at least one postprandial plasma glucose value must have been ≥8mmol/L.	Subjects were excluded if they had known or suspected allergy to any of the trial products, were treated with thiazolidinediones during the preceding 5 months, had known hypoglycemia unawareness or recurrent major hypoglycemic episodes in the past 6 months, had serious heart disease, renal disease, or serious hematological or biochemical abnormalities or had any disease or used any drugs that might interfere with the trial. Females who were pregnant, breast-feeding or intending to become pregnant were excluded.
Vinik et al, 2007[42]	See Rosenstock et al, 2006[31]	See Rosenstock et al, 2006[31]
Yki-Jarvinen et al, 2006[44]	Male or female patients aged 35–75 years with type 2 diabetes who had been treated with a stable dose (any dose) of sulfonylurea and metformin (≥1.5 g) or with metformin alone for at least 3 months prior to the screening visit at −4 weeks were enrolled. Further inclusion criteria included a BMI of 20–40 kg/m2, HbA1c ≥8.0%, a mean FPG of ≥7 mmol/l during daily home glucose monitoring between the screening visit at −4 weeks and the phone call in week −2, and fasting serum C-peptide ≥0.33 nmol/l (reference range 0.33-0.69 nmol/l).	Exclusion criteria included use of other oral antihyperglycaemic agents, prior use of insulin, positive GAD antibodies or history of ketoacidosis, non-compliance with regard to daily measurement of FPG and one diurnal profile during the first 2 weeks of run-in (patients with <80% of all desired values were excluded), abnormal safety laboratory tests, including liver enzymes (serum alanine aminotransferase [S-ALT], serum aspartate aminotransferase [S-AST], serum alkaline phosphatase [SAFOS]) higher than three times the upper limit of normal and serum creatinine ≥120 μmol/l (≥1.4 mg/dl), current or past history of alcohol or drug abuse, night shift work, pregnancy, treatment with any investigational drug in the 2 months before study entry, use of drugs likely to interfere with glucose control, clinically relevant major systemic disease other than diabetes that would make implementation of study protocol or interpretation of the results difficult, and mental health condition rendering the subject unable to understand the nature, scope and possible consequences of the study. Patients with diabetic retinopathy requiring surgical (laser or other) treatment in the 3 months before or during the study were also excluded.

APPENDIX 14: SAFETY REVIEW OF SECOND- AND THIRD-LINE ANTIDIABETES DRUGS

The RCTs included in this therapeutic review of third-line antidiabetes drugs contained only limited data on the safety of these agents. To supplement this information, additional literature searches were performed in Medline and Embase from 2006 to 2009 to identify reviews and large observational studies related to the safety (adverse events/reactions, harms, toxins, etc.) of anti-diabetes agents in patients with type 2 diabetes. Furthermore, the FDA alerts database was searched from 2004 to 2009 for each agent of interest. Finally, safety information from several large RCTs which did not meet the inclusion criteria for the therapeutic review was assessed. These were identified from the systematic review search and from references in safety reviews. Safety information is presented in this review by drug class.

Sulfonylureas

As insulin secretegogues, sulfonylureas are associated with higher rates of hypoglycemia than non-secretagogue anti-diabetic agents.[84] In a cohort study, Leese et al[237] found that the incidence of severe hypoglycemia for patients with type 2 diabetes using a sulphonylurea was 0.9 (95% CI 0.6-1.3) events per 100 patient-years, compared with 0.05 (0.01-0.2) events per 100 patient-years for patients on diet alone or metformin.

A case-control study[238] found increased pancreatic cancer risk with insulin secretagogues (sulfonylureas and meglitinides) users compared to non-users (odds ratio (OR), 95% CI: 2.52, 1.32-4.84), though the risk was increased only in patients who had been using these agents for less than 2 years. The authors suggested the possibility of reverse causality, i.e., that pancreatic cancer may worsen diabetes before the cancer is diagnosed, thus leading to increased use of insulin secretagogues. A cohort study[239] found an increased risk of all solid tumours (HR:1.36, 1.19-1.54), colorectal (HR: 1.80, 1.29-2.53), and pancreatic (HR: 4.95, 2.74-8.96) cancer, but not breast or prostate cancer, in patients using a sulfonylurea compared to those taking metformin. Patients taking a combination of metformin and a sulfonylurea showed an increased risk of colon cancer (HR: 1.43, 1.05-1.94), but not breast, prostate, or total solid tumour cancer compared to those on metformin alone, with a nearly statistically significant *reduction* in risk of pancreatic cancer (HR: 0.38, 0.13-1.12) compared to metformin alone. The authors note that there is no evidence that sulfonylureas cause or promote cancer development, only that they are associated with a higher risk than metformin, which is increasingly being studied for its anti-cancer properties.[239]

Observational studies show that compared to metformin, sulfonylureas are associated with increased risk of mortality and cardiovascular events. A large American cohort study[240] found lower rates of congestive heart failure (CHF) (HR: 0.76, 0.64-0.91) and mortality (HR: 0.54, 0.46-0.64) with metformin compared to sulfonylureas. Similarly, a Scottish cohort study[241] associated sulfonylureas with higher risks of mortality (risk ratio (RR):1.43, 1.15-1.77) and cardiovascular mortality (RR: 1.70, 1.18-2.45) compared to metformin. However, as the authors point out, the risks associated with sulfonylureas are in line with those expected in a diabetic population; metformin may very well be cardioprotective rather than sulfonylureas cardiotoxic. Apart from adding information to safety labels about drug interactions which may potentiate hypoglycemia (e.g. clarithromycin), and that patients sensitive to sulfonamide derivatives may be sensitive to various sulfonylureas, there were no alerts of interest issued by the FDA regarding sulfonylureas.

Thiazolidindiones (TZDs)

Cardiovascular risk

A meta-analysis of RCTs by Nissen and Wolski[242] involving more than 25,000 patients raised concerns that rosiglitizone was associated with an increase in myocardial infarction (MI) (OR: 1.43, 95%CI 1.03-1.98)) and in deaths from cardiovascular causes (OR: 1.64, 0.98-2.74) over control groups, which were generally placebo, metformin, a sulfonylurea, or insulin, though death from cardiovascular causes did not achieve statistical significance. In contrast, the RECORD[116] trial, a large, long-term, open-label, industry-sponsored RCT, found no significant increases in mortality, cardiovascular mortality, MI, or stroke with

rosiglitazone and metformin or sulfonylurea use when compared to metformin and sulfonylurea, though there was a significant increase in the risk of CHF (Hazard Ratio (HR): 2.10, 1.35-3.27). The ADOPT[117] study, also a large, long-term, industry-sponsored RCT, found significantly higher rates of CHF in patients taking rosiglitazone compared to those taking glyburide (HR: 2.20, 1.01-4.79) but not those on metformin (HR: 1.22, 0.66-2.26). There were significantly more serious cardiovascular events in both the rosiglitazone and metformin groups when compared to the glyburide group ($p<0.05$), though the risk of any cardiovascular event or the risk of MI were not significantly different. Neither all-cause nor cardiovascular mortality were reported in ADOPT.

In comparison, a meta-analysis[120] of pioglitazone RCTs found no increase in the risk of myocardial infarction, death, or stroke compared to controls, but did find an increased risk of CHF (HR: 1.41, 1.14-1.76). The PROactive trial,[243] a large, long-term, industry-sponsored RCT, found no increased risk of mortality, cardiovascular mortality, MIs, or strokes with pioglitazone over controls. CHF was not reported in PROactive, though a smaller RCT[244] found no significant increase in CHF when pioglitazone was compared to gliclazide.

Many observational studies have assessed TZDs and cardiovascular risk, with variable results. A Taiwanese cohort study[245] involving almost the entire nation's type 2 diabetic population (>470,000 patients) found that patients receiving rosiglitazone monotherapy were at higher risk of cardiovascular events (a composite outcome of MI, CHF, stroke, angina pectoris and transient ischemic attack (TIA)) than those receiving metformin monotherapy (HR: 1.89, 1.29-1.85), though only MI, angina pectoris, and TIA were statistically significant individually. Similar results were observed when patients on sulfonylurea monotherapy were the reference group. No such increase in risk was observed with pioglitazone over metformin or sulfonylureas.

Two large cohort studies[246,247] found no significant differences in MI risk between TZD users and users of metformin and/or sulfonylureas. A large case-control study[248] found no additional risk of MI for individuals using TZDs for less than 12 months compared to non-TZD oral or insulin therapy users, but an increased risk when TZDs were used for longer than 12 months (pioglitazone OR: 1.13, 1.02-1.26; rosiglitazone OR: 1.15, 1.04-1.27). In contrast, another case-control study[249] found that rosiglitazone exposure only carried a higher risk of MI (OR: 1.69, 1.18-2.44) compared to non-exposure use was recent (prescription ending 1-60 days before index date), rather than current (prescription supply overlapped index date), or remote (prescription supply ended >60 days before index date).

A large cohort study[250] of seniors in an Ontario setting comparing pioglitazone to rosiglitazone, showed a decreased risk of CHF (HR: 0.77, 0.69-0.87) as well as all-cause mortality (HR: 0.86,0.75-0.98), but not MI (HR:0.95, 0.81-1.11) with pioglitazone use. Another large cohort study[251] found a significantly lower risk of hospitalizations due to MI for pioglitazone users compared to rosiglitazone users (HR: 0.78, 0.63-0.96).

Fracture risk

TZDs are associated with reduced bone mineral density in women.[252] Both randomized[115-117] and non-randomized[118,119] studies have found significantly more upper and distal lower limb fractures among women taking TZDs than those taking controls, which were generally placebo, metformin, and/or a sulfonylurea. A meta-analysis by Loke et al[252] of RCTs and observational studies found an overall higher risk of fracture in women (OR: 2.23, 1.65-3.01). The risk associated with TZDs appeared to increase with duration of therapy as well as age.[118] Loke et al[252] estimated that excess fractures with rosiglitazone ranged from 18 (95% CI: 10-29) per 1000 patient-years in a female cohort with a mean age of 56 years, to 48 (26-71) in a cohort of women with a mean age of 72 years. Studies comparing rosiglitazone to pioglitazone[119,252] found no significant intra-class differences in fracture risk.

Other safety events

A prospective cohort study[253] of over 140,000 patients found that TZD use (98% of which was pioglitazone) was associated with a higher risk of macular edema (OR: 1.6, 1.4-1.8). In terms of cancer risk, TZDs appear to pose no additional harm to patients over other antidiabetes drugs. In a large case-control study,[254] multiple analyses were performed to compare TZD use to other antidiabetes therapies in

terms of breast, colon, and prostate cancer; the authors concluded the TZDs had neither a beneficial or deleterious effect for those cancer types. A large cohort study[255] involving nearly 90,000 male patients found no significant differences in colorectal or prostate cancer risk, but a reduction in lung cancer risk for TZD users compared to non-TZD users (HR: 0.67, 0.51-0.87). TZDs have not been associated with increases in all-cause mortality over controls (mostly comprised of placebo, metformin, and/or sulfonylurea).[116,117,240,243] However, a large cohort study[250] found that pioglitazone was associated with a significantly lower risk of mortality compared to rosiglitazone (HR: 0.86, 0.75-0.98). In 2007, the FDA released notifications regarding increased risk of fracture in women, potential increased risk of myocardial ischemia, and strengthened a warning to watch for signs of congestive heart failure in patients taking pioglitazone or rosiglitazone, and of increased risk regarding macular edema with rosiglitazone.

Meglitinides

Like sulfonylureas, meglitinides are insulin secretegogues and can therefore increase the risk of hypoglycemia.[84,256] In a mid-sized RCT[256] comparing nateglinide with metformin to metformin with placebo, there were approximately twice as many hypoglycemic events in the 60 mg nateglinide arm and four times as many in the 120 mg nateglinide arm compared to the placebo arm (p=0.168 and 0.001, respectively). Little else is known concerning the risks of adverse events.[84,257,258] No alerts of interest were issued by the FDA regarding meglitinides. Please see the sulfonylurea section for information about a possible association between meglitinides and pancreatic cancer.

Alpha-glucosidase inhibitors

Little information is available on the safety of alpha-glucosidase inhibitors. Gastrointestinal side effects are very common (>10%) and usually consist of mild-to-moderate diarrhea, flatulence, or abdominal discomfort.[84,259,260] There have also been 62 reports worldwide of serum transaminase elevations in patients taking acarbose, half of which had developed jaundice.[97,259] Hepatic abnormalities resolved in the majority of these cases after acarbose was discontinued.

Incretin agents (DPP-4 inhibitors and GLP-1 analogues)

Due to their recent introduction to the market, there is little information available on the safety of incretin agents. As of 2008, the FDA had received 30 post-marketing reports of acute pancreatitis in patients taking the GLP-1 agonist Byetta (exenatide), six of which were hemorrhagic or necrotizing.[261] As of September 2009, the FDA had also received 88 reports of pancreatitis in patients taking the DPP-4 inhibitor Januvia (sitagliptin), two of which were hemorrhagic or necrotizing.[262] The manufacturer of exenatide has acknowledged that exenatide was associated with 1.7 cases of pancreatitis per thousand patient years during clinical development, compared to 3.0 and 2.0 cases per thousand patient-years for placebo and insulin respectively.[263] Furthermore, the manufacturer funded a large cohort study,[264] which found no difference in risk of pancreatitis among patients initiating exenatide [relative risk (RR):1.0, 0.6-1.7] or the DPP-4 inhibitor sitagliptin (RR: 1.0, 0.5-2.0), compared with those initiating metformin or glyburide.

In addition, as of October 2008, the FDA had received 62 cases of acute renal failure and 16 cases of renal insufficiency in patients receiving Byetta.[265] The prescribing information for Byetta has been altered to highlight that it should not be prescribed to patients with severe renal impairment or renal disease. Although upper respiratory infections are listed as a possible side effect on the product monograph of Januvia,[266] when it was compared by the manufacturer to placebo either alone or in combination with metformin or pioglitazone, no statistically significant differences were found.[266,267]

In December 2008, the FDA issued new guidance on assessing unacceptable cardiovascular risk for new type 2 diabetes treatments. The FDA independently analyzed cardiovascular data from the saxagliptin phase 2/3 clinical program (eight RCTs). The FDA concluded that saxagliptin was not associated with an increased risk for cardiovascular events in patients who were mainly at low risk for these events; however, they are requiring a post-market study that will specifically evaluate cardiovascular safety in a higher risk population.[121]

Insulins

The use of insulin carries a higher risk of hypoglycemia compared to other anti-diabetic medications. In a 2003 cohort study, Leese et al[237] found that the incidence of severe hypoglycemia for patients with type 2 diabetes using insulin was 11.8 (95% CI 9.5-14.1) events per 100 patient-years, compared with 0.05 (0.01-0.2) events per 100 patient-years for patients on diet alone or metformin. High circulating levels of insulin are thought to be linked to increased cancer risk.[239,268] Observational studies have reported increased risk of cancer with the use of exogenous human insulin and drugs that increase endogenous insulin levels (e.g., sulfonylureas).[239] While unconfirmed in humans, *in vitro* studies indicate that changes to the structure of conventional insulin (such as in insulin analogues) may increase its mitogenic effects, possibly further increasing the risk of cancer.[239]

Recently, four cohort studies[239,268-270] examined the risk of cancer in patients using insulin glargine compared to those using other types of insulins. One[270] of the four studies reported that women using insulin glargine alone had higher risk of breast cancer (RR: 1.97, 1.30-3.00) than women using an insulin other than glargine. Similarly, two[268,269] studies found a slightly higher overall risk (HRs ranged from 1.09, 1.00-1.19 to 1.31, 1.20-1.42 depending on dosing and study) of cancer when patients used insulin glargine alone compared to those using human insulin. One study[239] found no significant differences in cancer risk between insulin types. It is noteworthy that all four studies performed multiple statistical comparisons, only a few of which were significant.

Similar to insulin secretagogues, a case-control study[238] found increased pancreatic cancer risk with insulin users compared to non-users (OR: 4.99, 2.59-9.61). Again, this increased risk was seen only in patients who had been using insulin for less than 2 years, raising the possibility of reverse causality. A cohort study[239] found an increased risk of all cancers (HR:1.42, 1.27-1.60), colorectal (HR: 1.69, 1.23-2.33) and pancreatic (HR:4.63, 2.64-8.10), but not breast or prostate cancer, in patients using insulin compared to those taking metformin. Apart from a notice concerning the cohort studies linking glargine to cancer risk, no alerts of interest were issued by the FDA regarding insulins.

APPENDIX 15: DOSAGE ADJUSTMENTS IN PATIENTS WITH RENAL IMPAIRMENT

Table 23: Information regarding dosage adjustments in patients with renal impairment

Generic Name	Information for renal impairment
Sulfonylureas	
Gliclazide / Gliclazide MR	Gliclazide: Contraindicated in the presence of renal impairment Gliclazide MR: The efficacy and tolerance of Diamicron MR 30 mg, prescribed using the same therapeutic regimen in subjects with mild to moderate renal failure (creatinine clearance of between 15 and 80 mL/min), has been confirmed in clinical trials. The dosage will therefore be identical to that in subjects with normal renal function.
Glimepiride	Amaryl is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions
Glyburide	Avoid. Active metabolite but no dosage adjustment required
Chlorpropamide	Avoid. Active metabolite; assume ≥ 75% renal elimination for dosage adjustment
Glipizide	The metabolism and excretion of Glucotrol may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.
Tolbutamide	Patients with mild to moderate renal impairment should start with lower doses and have careful monitoring of the blood glucose levels. Tolbutamide should not be used in patients who have or have ever had serious impairment of renal function.
Thiazolidinediones	
Pioglitazone	No dose adjustment in patients with renal dysfunction is recommended.
Rosiglitazone	No dosage adjustments in patients with renal impairment.
Meglitinides	
Nateglinide	No dosage adjustment is necessary in patients with mild to severe renal insufficiency or in patients with mild hepatic insufficiency.
Repaglinide	Typically, GlucoNorm does not require initial dose adjustment in patients with reduced kidney function. However, subsequent increases in GlucoNorm should be made carefully in patients with type 2 diabetes who have renal function impairment or renal failure requiring hemodialysis
Alpha-glucosidase inhibitors	
Acarbose	Patients with severe renal impairment (creatinine clearance <25 mL/min/1.73 m2) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function.
Miglitol	Plasma concentrations of Glyset in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine > 2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with Glyset is not recommended.
DPP-4 inhibitors	
Sitagliptin	Use of sitagliptin in patients with moderate or severe renal insufficiency including those with end-stage renal disease is not recommended.
Vildagliptin	No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). The use of Galvus is not recommended in patients with moderate or severe renal impairment or in haemodialysis patients with end-stage renal disease.
Saxagliptin	Use of Onglyza in patients with moderate to severe renal impairment, including patients with end stage renal disease requiring hemodialysis is not recommended.

Table 19 (cont'd): Information regarding dosage adjustments in patients with renal impairment

Generic Name	Information for renal impairment
GLP-1 analogues	
Exenatide	CrCl 30-50: no adjustment, caution advised when initiating or escalating dose from 5 µg to 10 µg; CrCl <30, HD: not recommended
Liraglutide	No dose adjustment is required for patients with mild renal impairment (creatinine clearance ≤ 60-90 ml/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59 ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 ml/min). Victoza can currently not be recommended for use in patients with moderate and severe renal impairment including patients with end-stage renal disease.

AUC=area under curve; **CrCl**=Creatinine Clearance; **MR**=modified release

APPENDIX 16: DETAILED ADVERSE EVENT DATA FROM INDIVIDUAL TRIALS

The following table was compiled from original publications of the included RCTs, and provides a summary of the following: withdrawals due to adverse events, serious/severe adverse events, and deaths occurring during these trials. Following this information, a summary is provided of relevant information located from a supplemental safety data report.

Table 24: Summary of Trials Reporting Adverse Event Data

Study / Outcomes	Intervention 1	Intervention 2	Intervention 3
Aljabri et al, 2004[10]	**Pioglitazone + SU + Met**	**Insulin NPH + SU + Met**	———
Withdrawals due to AE	0/30	0/28	———
Patients with severe AE	0/30	0/28	———
Patients with serious AE	0/30	0/28	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Al-Shaikh, 2006[12]	**Insulin glargine + SU + Met**	**Biphasic insulin (30/70)**	———
Withdrawals due to AE	0/111	0/110	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Bergenstal et al, 2009[14]	**Exenatide + Met + SU**	**BIAsp30 (QD) + Met + SU**	**BIAsp30 (BID) + Met + SU**
Withdrawals due to AE	9/124	0/124	2/124
Patients with severe AE	*NR*	*NR*	*NR*
Patients with serious AE	*NR*	*NR*	3/124
Type of SAE	*NR*	*NR*	• hyperglycemia and hypokalemia: n = 2 (possibly drug related) • death from cardiac arrhythmia: n = 1 (not drug related)
Number of deaths	0/124	0/124	1/124
Berhanu et al, 2007[16]	**Insulin + Pioglitazone + Met**	**Insulin + Placebo + Met**	———
Withdrawals due to AE	1/110	4/112	
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	4/110	2/112	———
Type of SAE	*NR*	*NR*	———
Number of deaths	0/110	0/112	———
Boye et al, 2006[18]	**Exenatide + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	*NR*	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Charpentier et al, 2009[20]	**Pioglitazone + Met + SU**	**Placebo + Met + SU**	———
Withdrawals due to AE	2/142	3/147	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	7/145	5/154	———
Type of SAE	*NR*	*NR*	———
Number of deaths	1/145	0/154	———
Dailey et al, 2004[22]	**Rosiglitazone + Met + SU**	**Placebo + Met + SU**	———
Withdrawals due to AE	10/181	5/184	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	3/181	8/184	———

Study / Outcomes	Intervention 1	Intervention 2	Intervention 3
Type of SAE	*NR*	*NR*	———
Number of deaths	0/181	1/184	———
Davies et al, 2007[24]	**Biphasic 30/70 human insulin (BID) + Met**	**NPH insulin (HS) + Repaglinide (AC) + Met**	**NPH Insulin (HS) + Met**
Withdrawals due to AE	0/27	0/26	0/29
Patients with severe AE	*NR*	*NR*	*NR*
Patients with serious AE	*NR*	*NR*	*NR*
Patients with major AE	0/27	0/26	0/29
Type of SAE	*NR*	*NR*	*NR*
Number of deaths	*NR*	*NR*	*NR*
De Mattia et al, 2009[26]	**Insulin glargine + Met + SU**	**NPH Insulin + Met + SU**	———
Withdrawals due to AE	*NR*	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Derosa et al[28]	**Acarbose + Met + SU**	**Rapaglinide + Met + SU**	———
Withdrawals due to AE	1/52	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Dorkhan et al, 2009[30]	**Pioglitazone + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	*N/A*	*N/A*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Esposito et al, 2008[32]	**NPL insulin + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	0/58	0/58	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	1/58	1/58	———
Type of SAE	Gastroenteritis (not considered to be related to the study drug)	Atrial fibrilliation (not considered to be related to the study drug)	———
Number of deaths	0/58	0/58	———
Gao et al, 2009[34]	**Exenatide + Met + SU**	**Placebo + Met + SU**	———
Withdrawals due to AE	23/234	3/232	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Goudswaard et al, 2004[36]	**NPH insulin + Met + SU**	**Biphasic insulin (70/30)**	———
Withdrawals due to AE	*NR*	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Hartemann-Heurtier et al, 2009[38]	**Pioglitazone + Met + SU**	**NPH insulin + Met + SU**	———
Withdrawals due to AE	0/14	1/13	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Heine et al, 2005[40]	**Exenatide + Met + SU**	**Insulin glargine + Met + SU**	———

Study / Outcomes	Intervention 1	Intervention 2	Intervention 3
Withdrawals due to AE	27/282	2/267	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Hermansen et al, 2007[41]	**Sitagliptin + Met + SU**	**Placebo + Met + SU**	———
Withdrawals due to AE	2/116	2/113	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	7/116	2/113	———
Type of SAE	Not defined but all were not considered related to the study drug		———
Number of deaths	1/116	0/113	———
Holman et al, 2007[43]	**Insulin aspart + Met + SU**	**Insulin detemir + Met + SU**	**Biphasic insulin aspart 30 + Met + SU**
Withdrawals due to AE	0/239	4/234	2/235
Patients with severe AE	*NR*	*NR*	*NR*
Patients with serious AE	30/239	30/234	41/235
Type of SAE	Gastrointestinal and abdominal pain or infection, lower respiratory tract and lung infection, ischemic coronary-artery disorder, other infection		
Number of deaths	1/239	0/234	3/235
Janka et al, 2005[11]	**Insulin glargine + Met + SU**	**30/70 NPH + placebo**	———
Withdrawals due to AE	1/177	6/187	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Janka et al, 2007[13]	**Insulin glargine + Met + SU**	**30/70 NPH + placebo**	———
Withdrawals due to AE	1/67	2/63	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Kendall et al, 2005[15]	**Exenatide (5 µg BID) + Met + SU**	**Exenatide (10 µg BID) + Met + SU**	**Placebo + Met + SU**
Withdrawals due to AE	*NR*	*NR*	*NR*
Patients with severe AE	29/245	34/241	20/247
Patients with serious AE	15/245	12/241	15/247
Patients with nausea	12/245	7/241	2/247
Type of SAE	*NR*	*NR*	*NR*
Number of deaths	*NR*	*NR*	*NR*
Ko et al, 2006[17]	**Rosiglitazone + Met + SU**	**NPH Insulin + Met + SU**	———
Withdrawals due to AE	4/56	0/56	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Lam et al, 1998[19]	**Acarbose + Met + SU**	**Placebo + Met + SU**	———
Withdrawals due to AE	1/45	2/44	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Lopez-Alvarenga et al, 1999[21]	**Acarbose + Met + SU**	**Insulin NPH + MET + SU**	**Placebo + Met + SU**
Withdrawals due to AE	*N/A*	*N/A*	*N/A*
Patients with severe AE	*NR*	*NR*	*NR*
Patients with serious AE	*NR*	*NR*	*NR*
Type of SAE	*NR*	*NR*	*NR*

Study / Outcomes	Intervention 1	Intervention 2	Intervention 3
Number of deaths	*NR*	*NR*	*NR*
Milicevic et al, 2009[23]	**Insulin NPH + SU**	**LM50/50 and LM25/75**	———
Withdrawals due to AE	5/67	1/68	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Nauck et al, 2007[25]	**Exenatide + Met + SU**	**Biphasic insulin aspart**	———
Withdrawals due to AE	*NR*	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	19/253	11/248	———
Type of SAE	*NR*	*NR*	———
Number of deaths	2/253	1/248	———
Ovalle et al, 2004[27]	**Rosiglitazone + Met + SU**	**Biphasic insulin 70/30**	———
Withdrawals due to AE	*N/A*	*N/A*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Reynolds et al, 2007[29]	**Rosiglitazone + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	3/20	0/20	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Rosenstock et al, 2006[31]	**Rosiglitazone + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	9/112	2/104	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	11/112	5/105	———
Type of SAE	Hypoglycemia, overdose, fibroid tumors and iron deficiency		———
Number of deaths	*NR*	*NR*	———
Ross et al, 2001[33]	**Insulin lispro + Insulin NPH**	**Human insulin + Insulin NPH**	———
Withdrawals due to AE	*NR*	*NR*	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Russell-Jones et al, 2009[35]	**Liraglutide + Met + SU**	**Insulin glargine + Met + SU**	**Placebo + Met + SU**
Withdrawals due to AE	11/230	5/232	1/114
Patients with severe AE	*NR*	*NR*	*NR*
Patients with serious AE	9/230	16/232	8/114
Type of SAE	*NR*	*NR*	*NR*
Number of deaths	*NR*	*NR*	*NR*
Standl et al, 2001[37]	**Miglitol + Met + glyburide**	**Placebo + Met + glyburide**	———
Withdrawals due to AE	2/65	4/68	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	5/77	5/77	———
Type of SAE	*NR*	*NR*	———
Number of deaths	*NR*	*NR*	———
Stehouwer et al, 2003[39]	**NPH insulin + SU**	**NPH insulin + 30/70 insulin NPH**	**NPH insulin**
Withdrawals due to AE	*NR*	*NR*	*NR*
Patients with severe AE	*NR*	*NR*	*NR*

Study / Outcomes	Intervention 1	Intervention 2	Intervention 3
Patients with serious AE	*NR*	*NR*	*NR*
Type of SAE	*NR*	*NR*	*NR*
Number of deaths	*NR*	*NR*	*NR*
Strojek et al, 2009[45]	**Insulin glargine + Met + SU**	**BIAsp30 + Met + SU**	———
Withdrawals due to AE	4/241	5/239	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	*NR*	*NR*	———
Type of SAE	*NR*	*NR*	———
Number of deaths	1/241	0/239	———
Vinik et al, 2007[42]	**Rosiglitazone + Met + SU**	**Insulin glargine + Met + SU**	———
Withdrawals due to AE	9/112	2/104	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	11/112	5/105	———
Type of SAE	Hypoglycemia, overdose, fibroid tumors and iron deficiency		———
Number of deaths	*NR*	*NR*	———
Yki-Jarvinen et al, 2006[44]	**Insulin glargine + Met**	**NPH Insulin + Met**	———
Withdrawals due to AE	1/55 (pancreatic cancer)	1/55 (pulmonary cancer)	———
Patients with severe AE	*NR*	*NR*	———
Patients with serious AE	1/55	4/58	———
Type of SAE	Endometriosis (considered unrelated to the study medication)	Anaphylactic reaction, atrial fibrillation, gastoenteritis, pulmonary emphysema (considered unrelated to the study medication)	———
Number of deaths	0/55	0/55	———

APPENDIX 17: ASSESSMENT OF POTENTIAL SOURCES OF BIAS

Study	Double blind?	Adequate concealment	ITT analysis performed	A priori sample size calculation for primary outcome?	Notes regarding potential for bias
Aljabri et al, 2004[10]	No	Yes	No	Yes (hypoglycemia)	Open label design and the use of a per protocol analysis are the primary sources of bias for this trial.
Al-Shaikh, 2006[12]	No	Unclear	Yes	No	No methods provided for randomization, allocation concealment, and outcome assessment. The study used an open label design. Baseline characteristics were poorly reported.
Bergenstal et al, 2009[14]	No	Yes	No	Yes (A1C)	The potential sources of bias with this trial include: did not use an intention-to-treat analysis; the design was open-label; disproportionate number of withdrawals between treatment arms (BIAsp 30 QD: 16%, BIAsp 30 BID: 19%, exenatide: 30%).
Berhanu et al, 2007[16]	Yes	Yes	Yes	Yes (change in insulin dosage)	All components were well or adequately addressed.
Charpentier et al, 2009[20]	Yes	Unclear	No	Yes (A1C)	Poor description of methods for randomization, allocation concealment, and blinding. Did not use an ITT analysis.
Dailey et al, 2004[22]	Yes	Unclear	Yes	Yes (A1C)	Poor reporting of methods for randomization and allocation concealment. Methods of blinding and measuring of outcomes were not provided. Proportion of drop-out is high and disproportionate (rosiglitazone: 19.9% vs. placebo: 37%). This is primarily due to hyperglycemia, as the other reasons are relatively well-balanced.
Davies et al, 2007[24]	PA	Unclear	No	Yes (A1C)	No methods were provided for allocation concealment. Additional concerns include the failure to conduct an ITT analysis and the significant difference in baseline A1C between the groups.
De Mattia et al, 2009[26]	No	Unclear	Yes	No	No description of methods for randomization and allocation concealment. The trial used an open label design. Very little information provided concerning the baseline characteristics of each group.
Derosa et al[28]	Yes	Yes	Yes	Yes (PPG)	All major sources of bias were addressed.
Dorkhan et al, 2009[30]	No	Unclear	Yes	No	Open label design, no mention of allocation concealment, and uncertainty about sulfonylurea and metformin doses being similar between arms.
Esposito et al, 2008[32]	No	Yes	No	Yes (A1C)	Only concerns are the open-label design and the analysis was not ITT.

Study	Double blind?	Adequate concealment	ITT analysis performed	A priori sample size calculation for primary outcome?	Notes regarding potential for bias
Gao et al, 2009[34]	Yes	Unclear	Yes	Yes (A1C)	Failure to provide methods for allocation concealment and the disproportionate number of withdrawals (17.5% for add-on exenatide vs. 10.3% for add-on placebo) are the primary concerns with this trial.
Goudswaard et al, 2004[36]	No	Yes	Yes	Yes (A1C)	The open-label design and the statistically and clinically significant differences in body weight and BMI between groups are the primary concerns. The mean body weight differed by more than 15 kg between the groups. The overall proportion of withdrawals exceeded 20% and the number of treatment failures was substantially greater in the insulin combination treatment arm. The source of funding was not reported and the authors did not provide conflict of interest statements.
Hartemann-Heurtier et al, 2009[38]	PA	Yes	Yes	Yes (abdominal fat content)	The majority of components were adequately addressed. The exceptions were the failure to provide methods for the assessment of glycemic control and blinding.
Heine et al, 2005[40] Boye et al, 2006[18]	No	Unclear	Yes	Yes (A1C)	No methods were provided for randomization and allocation concealment. The trial used an open label design.
Hermansen et al, 2007[41]	Yes	Yes	No	No	A majority of the important sources of bias have been addressed. Only concerns are with the failure to conduct an ITT analysis and a slightly high dropout rate.
Holman et al, 2007[43]	No	Yes	Yes	Yes (A1C)	The only important source of bias is the open label design.
Janka et al, 2005[11] Janka et al, 2007[13]	No	Yes	Yes	Yes (A1C)	A majority of the important sources of bias have been addressed. Open-label design and higher proportion of drop-outs in one arm are the main concerns (4% for glargine + OADs vs. 15% for premixed insulin).
Kendall et al, 2005[15]	Yes	Unclear	Yes	Yes (A1C)	There were no methods reported for allocation concealment and the proportion of dropouts exceeded 20%.
Ko et al, 2006[17]	No	Unclear	No	Yes (A1C)	Primary concerns are the lack of methods for allocation concealment, differing baseline A1C and doses of metformin, a lack of clarity regarding ITT analysis, and the open label design.
Lam et al, 1998[19]	Yes	Unclear	No	No	No methods were provided for allocation concealment and the analysis was not ITT.
Lopez-Alvarenga et al, 1999[21]	No	Unclear	No	Yes (FPG)	Primary concerns are the use of a per-protocol analysis, high number of patient withdrawals, and use of an open-label design for the insulin treatment. Potential unit of analysis errors in reporting the results (i.e., does not properly reflect the crossover design).

Study	Double blind?	Adequate concealment	ITT analysis performed	A priori sample size calculation for primary outcome?	Notes regarding potential for bias
Milicevic et al, 2009[23]	No	Unclear	Yes	Yes (2 hour PPG)	Major sources of bias were the failure to properly report methods for allocation concealment, the open label trial design, and the disproportionate number of withdrawals in the Glib/NPH arm (17.9%) in comparison with the LM50/LM25 arm (5.9%).
Nauck et al, 2007[25]	No	Yes	Yes	Yes (A1C)	The trial used an open-label design. The proportion of withdrawals was twice as high in the exenatide arm (21%) than in the insulin arm (10%).
Ovalle et al, 2004[27]	No	Unclear	Yes	No	Primary concerns are the open label design and the failure to report methods for allocation concealment.
Reynolds et al, 2007[29]	No	Unclear	No	No	Blinding and allocation concealment were not addressed. The analysis was not ITT and the there was no comparison of drop-outs between the two groups.
Rosenstock et al, 2006[31] Vinik et al, 2007[42]	No	Unclear	Yes	No	There were no methods reported for randomization and allocation concealment. The trial used an open-label design. The proportion of withdrawals was twice as high in the rosiglitazone arm (10.7%; 12/112) than in the insulin glargine arm (5.8%; 6/104)
Ross et al, 2001[33]	No	Unclear	Yes	No	No description of methods for randomization and allocation concealment. The trial used an open label design. The proportion of withdrawals in each arm was not reported.
Russell-Jones et al, 2009[35]	Yes (2 of 3 arms)	Yes	Yes	Yes (A1C)	All major sources of bias were addressed; however, the insulin glargine arm was open-label.
Standl et al, 2001[37]	Yes	Unclear	No	Yes (A1C)	Primary concerns are the failure to specify methods of allocation concealment, and poor reporting of results from the ITT analysis. Some discrepancy with the number of withdrawals reported.
Stehouwer et al, 2003[39]	No	Unclear	Yes	No	No description of methods for allocation concealment and there was no mention of withdrawals. The trial used an open trial design.
Strojek et al, 2009[45]	No	Yes	No	Yes (A1C)	Primary concerns are the open-label design and the failure to conduct a proper ITT analysis (although 95% of patients were included in the analysis).
Yki-Jarvinen et al, 2006[44]	No	Unclear	Yes	Yes (A1C)	Major sources of bias are the open label design and failure to properly report methods for allocation concealment.

A1C=glycosylated haemoglobin; **BIAsp**=biphasic insulin aspart; **BID**=twice daily; **ITT**=intention to treat; **NPH**=neutral protamine Hagedorn; **OADs**=oral antidiabetes drugs; **PA**=Poorly Addressed; **PPG**=post-prandial glucose; **QD**=at bedtime

APPENDIX 18: SIGN-50 ASSESSMENT OF INTERNAL VALIDITY

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
Aljabri et al, 2004[10]	AA	WC	AA	NAd	AA	AA	AA	Yes	PA	N/A	Poor
Al-Shaikh, 2006[12]	WC	AA	NAd	NAd	PA	WC	PA	Yes	AA	N/A	Poor
Bergenstal et al, 2009[14]	WC	WC	WC	NAd	AA	AA	AA	No	PA	NAd	Poor
Berhanu et al, 2007[16]	AA	WC	WC	AA	AA	AA	AA	Yes	WC	NAd	Very good
Charpentier et al, 2009[20]	WC	NR	NAd	AA	WC	WC	WC	Yes	PA	NAd	Poor
Dailey et al, 2004[22]	AA	NR	PA	AA	AA	AA	PA	No	AA	NAd	Poor
Davies et al, 2007[24]	AA	WC	NAd	PA	PA	AA	AA	Yes	PA	N/A	Poor
De Mattia et al, 2009[26]	AA	AA	NAd	NAd	AA	AA	AA	Yes	AA	NAd	Poor
Derosa et al[28]	AA	WC	WC	AA	AA	AA	WC	Yes	AA	NAd	Good
Dorkhan et al, 2009[30]	AA	AA	NAd	NAd	PA	AA	AA	Yes	WC	N/A	Poor
Esposito et al, 2008[32]	WC	WC	WC	NAd	AA	AA	AA	Yes	PA	NAd	Good
Gao et al, 2009[34]	AA	AA	PA	AA	WC	AA	AA	Yes	AA	NAd	Poor
Goudswaard et al, 2004[36]	WC	WC	WC	NAd	PA	WC	WC	No	WC	N/A	Poor
Hartemann-Heurtier et al, 2009[38]	AA	WC	WC	PA	AA	AA	PA	No	AA	N/A	Good
Heine et al, 2005[40]	WC	AA	NAd	NAd	WC	WC	WC	Yes	AA	NAd	Poor
Hermansen et al, 2007[41]	WC	WC	WC	AA	AA	WC	WC	Yes	PA	NAd	Good
Holman et al, 2007[43]	AA	WC	WC	NAd	WC	AA	WC	Yes	WC	AA	Good
Janka et al, 2005[11]	AA	WC	AA	NAd	WC	WC	WC	No	AA	NAd	Good
Kendall et al, 2005[15]	AA	AA	PA	AA	AA	AA	AA	No	WC	PA	Poor
Ko et al, 2006[17]	AA	AA	NAd	NAd	PA	AA	AA	Yes	PA	N/A	Poor
Lam et al, 1998[19]	AA	AA	NAd	AA	AA	AA	AA	Yes	PA	NAd	Poor
Lopez-Alvarenga et al, 1999[21]	AA	AA	NR	NAd	AA	AA	PA	No	PA	N/A	Poor
Milicevic et al, 2009[23]	WC	AA	NAd	NAd	WC	WC	WC	No	AA	AA	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
Nauck et al, 2007[25]	AA	WC	WC	NAd	AA	AA	AA	Yes	WC	PA	Good
Ovalle et al, 2004[27]	AA	AA	NAd	NAd	PA	AA	AA	Yes	WC	N/A	Por
Reynolds et al, 2007[29]	WC	AA	NAd	NAd	AA	AA	WC	Yes	PA	N/A	Poor
Rosenstock et al, 2006[31]	WC	AA	NAd	NAd	WC	WC	PA	Yes	AA	NAd	Poor
Ross et al, 2001[33]	WC	AA	NAd	NAd	AA	AA	AA	NR	AA	NAd	Poor
Russel-Jones et al, 2009[35]	AA	WC	AA	AA	AA	AA	AA	Yes	AA	NAd	Good
Standl et al, 2001[37]	AA	AA	PA	AA	AA	AA	AA	No	PA	PA	Poor
Stehouwer et al, 2003[39]	WC	WC	NAd	NAd	AA	AA	AA	NR	AA	NAd	Poor
Yki-Jarvinen et al, 2006[44]	AA	WC	NR	NAd	WC	AA	WC	Yes	AA	AA	Poor

AA=adequately addressed, **ITT**=intention to treat, **NAd**=not addressed, **NAp**=not applicable, **NR**=not reported, **PA**=poorly addressed, **QA**=quality assessment, **WC**=well covered.

APPENDIX 19: ASSESSMENT OF EXTERNAL VALIDITY

Study	
Aljabri et al, 2004[10]	• Power likely limited (n = 58). Sample size calculated for hypoglycemia outcome. • Metformin and sulfonylurea doses at baseline were not reported. • Only 16 weeks in duration – may not be indicative of long-term efficacy. • Fasting glucose target (<6 mmol/L) was lower than recommended in Canada.
Al-Shaikh, 2006[12]	• Conducted in Saudi Arabia – population and care patterns may not be reflective of Canada. • 6 months duration – may not be indicative of long-term efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (<7.7 mmol/L) was higher than recommended in Canada.
Bergenstal et al, 2009[14]	• 24-week duration - may not be indicative of long-term relative efficacy. • Subjects were only required to take half-maximal doses of sulfonylureas before being classified as inadequately controlled – may not be reflective of clinical practice, where higher doses of sulfonylureas are likely to be tried before considering alternative therapy. • Disproportionate number of withdrawals between treatment arms (BIAsp 30 QD: 16%, BIAsp 30 BID:19%, exenatide: 30%). • Fasting glucose target (5.0-6.1 mmol/L) was lower than recommended in Canada.
Berhanu et al, 2007[16]	• Baseline demographic data not reported. • Sample size calculated for primary outcome of insulin dose change – not a relevant outcome for systematic review. • Subjects were only required to take half-maximal doses of sulfonylureas before being classified as inadequately controlled – may not be reflective of clinical practice, where higher doses of sulfonylureas are likely to be tried before considering alternative therapy. • Treatment sequence does not reflect usual clinical practice, i.e., sulfonylurea discontinued, insulin added, then TZD added. • Primary outcome of insulin dose change not as clinically relevant as standard measures of efficacy and safety. • Hypoglycemia definitions not reported. • Fasting glucose target (<7.8 mmol/L) was higher than recommended in Canada.
Charpentier et al, 2009[20]	• 7 months duration – may not be indicative of long-term efficacy. • Hypoglycemia definitions not reported. • A1C target <6.5% is lower than that recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.
Dailey et al, 2004[22]	• 24-week duration - may not be indicative of long-term relative efficacy. • Differential drop out between groups: 20% in active arm vs. 37% in placebo arm. • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved.
Davies et al, 2007[24]	• Power likely limited (<30 per treatment arm). No sample size calculation described. • 4 months duration – may not be indicative of long-term efficacy. • Sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported.' • Fasting glucose target (<6.0 mmol/L) was lower than recommended in Canada.

Study	
De Mattia et al, 2009[26]	• Very little information provided concerning the baseline characteristics of each group. • No sample size calculations. Power likely very low given sample size (n = 20). • Combined formulation of metformin and glyburide not available in Canada. • Metformin and sulfonylurea doses at baseline were only 400 mg/day and 2.5 mg/day, respectively. Higher doses are usually tried in clinical practice before adding third-line agents. • Study designed primarily to detect differences in glycemic variability; other clinical outcomes were secondary. • 12-week duration - may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.
Derosa et al[28]	• Diabetes duration substantially lower than most studies (mean = 3.3 to 3.7 years) – may limit generalizability of results since diabetes duration is related to pancreatic reserve. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • BMI lower than most studies (mean 27 kg/m^2). • No hypoglycemia data reported. • 12-week duration - may not be indicative of long-term relative efficacy. • Employed forced titration of trial medications independent of glycemic control, which is not reflective of clinical practice.
Dorkhan et al, 2009[30]	• No sample size calculations. Power likely limited due to very small sample (n = 30). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • Hypoglycemia data not reported. • Trial was designed to test differences b/w treatments in measures of fluid retention, an outcome that is of less clinical relevance as those of interest in the systematic review. • 26-week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<6.0 mmol/L) and A1C target (<6.2%) were lower than recommended in Canada.
Esposito et al, 2008[32]	• Powered to detect a difference in A1C of 0.25%. • NPL insulin not available in Canada. • Metformin and sulfonylurea doses at baseline were not reported. • Only statistical significance considered. • 36-week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.6 mmol/L) was lower than recommended in Canada.
Gao et al, 2009[34]	• Study conducted in Asian countries – may be less generalizable to Canada. e.g., baseline BMI was lower than in European or North American studies. • Care patterns in Asian countries may differ from Canada, but no obvious issues. • Sulfonylurea doses at baseline were not reported. • Disproportionate number of withdrawals (17.5% for add-on exenatide vs. 10.3% for add-on placebo). • Only 16 weeks in duration – may not be indicative of long-term efficacy.

Study	
Goudswaard et al, 2004[36]	• Power likely limited for most outcomes due to small sample (n = 64), although sample size was calculated for a minimal detectable difference of 0.8% in A1C. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • The overall proportion of withdrawals exceeded 20%. • Biweekly calls by nurse during insulin titration unrealistic in routine clinical care.
Hartemann-Heurtier et al, 2009[38]	• Power likely very limited due to small sample size (n = 28). • Study designed to measure surrogates such as abdominal fat distribution. The only reported outcome of interest to systematic review was A1C. • 24-week duration - may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (<6.1 mmol/L) was lower than recommended in Canada.
Heine et al, 2005;[40] Boye et al, 2006[18]	• Non-inferiority study – powered to detect difference of 0.4% in A1C. Likely adequately powered for other outcomes also given large sample size (n = 551). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • 26-week duration - may not be indicative of long-term relative efficacy. • Higher dropout in exenatide arm (19% vs. 9%), mostly due to adverse effects. • Hypoglycemia definitions not reported. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada.
Hermansen et al, 2007[41]	• 24-week duration - may not be indicative of long-term relative efficacy. • Minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • Hypoglycemia definitions not reported.
Holman et al, 2007[43]	• Powered to detect 0.4% difference in A1C. Large sample size (n = 708) therefore power likely adequate for most outcomes. • Interim telephone contacts with patients – unrealistic in clinical practice. • Fasting (<5.5 mmol/L) and postprandial (<7.0 mmol/L) glucose targets were lower than recommended in Canada.
Janka et al, 2005[11]	• Large study (n = 384), so power likely adequate for most outcomes. • Unequal dropout rate (4% for glargine + OADs vs. 15% for premixed insulin). • Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. Also, minimum metformin dose required at baseline was only 850 mg/day. • 24-week duration - may not be indicative of long-term relative efficacy. • Drop out rate higher in NPH 30/70 arm vs. glargine. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.

Study	
Janka et al, 2007[13]	• Patients 65 years and older only (mean age 67 and 63 in the 2 groups) – unlikely to affect results substantially. • Minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. Also, minimum metformin dose required at baseline was only 850 mg/day. • No sample size calculation. • 24-week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.
Kendall et al, 2005[15]	• Large sample size (n = 733), therefore likely adequate power for most outcomes. • Metformin and sulfonylurea doses at baseline were not reported. • 30-week duration - may not be indicative of long-term relative efficacy. • Proportion of dropouts exceeded 20%. • Effects observed in fixed low-dose arm of exenatide are of limited generalizability since doses are likely to be titrated based on level of glycemic control in clinical practice.
Ko et al, 2006[17]	• Study conducted in Hong Kong – population and treatment patterns may not be representative. • Mean BMI 25 kg/m^2 – lower than most other studies. • Likely limited power for rarer outcomes such as severe hypoglycemia due to small sample size (n = 112). • Target A1C was <7.5%, which is higher than recommended in Canada. • Hypoglycemia was not assessed.
Lam et al, 1998[19]	• Chinese patients – may be less generalizable to Canada. • Excluded subjects with BMI ≥ 30 (mean BMI was 24-25) – results may not be applicable to obese individuals. • Power likely limited due to small sample size (n = 89). No sample size calculation. • 6-week 'dietary reinforcement' likely not realistic. • 24-week duration - may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported.
Lopez-Alvarenga et al, 1999[21]	• Study conducted in Mexico – may limit generalizability to Canada. • BMI seems lower than most other studies (mean about 27), while A1C at baseline was much higher (>11%). • Sulfonylurea used was chlorpropamide, which is rarely used in Canada. • Insulin titration protocol appears to differ from other studies in that increments are not based on degree of hyperglycemia. • Hypoglycemia not defined. • 3 months duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<7.7 mmol/L) was higher than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.

Study	
Milicevic et al, 2009[23]	• Power likely limited for rarer outcomes such as severe hypoglycemia due to relatively small sample size (n = 135). • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • Clinic visits every 4 weeks likely exceeds visit frequency in routine care. • Disproportionate number of withdrawals in the Glib/NPH arm (17.9%) in comparison with the biphasic lispro arm (5.9%). • Frequent SMBG (9-point profiles) not reflective of usual care. • 24-week duration - may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Postprandial glucose target (<8.0 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 32 kg/m^2 – results may not be applicable to morbidly obese individuals.
Nauck et al, 2007[25]	• Somewhat lower insulin doses at endpoint than in past studies. • Metformin and sulfonylurea doses at baseline were not reported. • The proportion of withdrawals was twice as high in the exenatide arm (21%) than in the insulin arm (10%). • Clinical relevance of 0.4% A1C margin was considered, although clinical relevance of observed weight loss not considered.
Ovalle et al, 2004[27]	• Likely underpowered (n = 17). No sample size calculations presented. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • Study designed to detect differences in measures of pancreatic beta-cell function, not clinical outcomes. No data reported on hypoglycemia. • 6 month duration - may not be indicative of long-term relative efficacy.
Reynolds et al, 2007[29]	• Baseline demographic data not reported. • Limited power (n = 40), no sample size calculations. • Only half-maximal doses required for both metformin and sulfonylurea at baseline.
Rosenstock et al, 2006;[31] Vinik et al,2007[42]	• No sample size calculations. • Subjects were only required to take half-maximal doses of sulfonylureas before being classified as inadequately controlled – may not be reflective of clinical practice, where higher doses of sulfonylureas are likely to be tried before considering alternative therapy. • Central supervision of insulin titration – may not be realistic for usual care. • The proportion of withdrawals was twice as high in the rosiglitazone arm (10.7%) than in the insulin glargine arm 5.8%). • 24-week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada.
Ross et al, 2001[33]	• Baseline A1C quite high compared with other studies (10.6%). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • No sample size calculations presented.
Russel-Jones et al, 2009[35]	• Extensive patient contact (9 visits plus 2 phone calls) – likely not reflective of routine care. • 26 week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada.

Study	
Standl et al, 2001[37]	• BMI at baseline somewhat lower than in other studies (mean 28 kg/m^2). • Metformin and sulfonylurea doses at baseline were not reported. • Miglitol not available in Canada. • 24-week duration - may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Excluded patients with BMI > 35 kg/m^2 – results may not be applicable to morbidly obese individuals.
Stehouwer et al, 2003[39]	• No power calculations presented. Likely adequate power for most outcomes given sample size (n = 261). • Minimum dose of metformin at baseline was only 1000 mg/day – higher doses likely used in clinical practice. • Twice weekly adjustment by diabetes educator or diabetologist of insulin doses until targets reached is not realistic in clinical practice. • Hypoglycemia not defined. • 9 month duration - may not be indicative of long-term relative efficacy.
Strojek et al, 2009[45]	• Subjects were only required to take half-maximal doses of sulfonylureas before being classified as inadequately controlled – may not be reflective of clinical practice, where higher doses of sulfonylureas are likely to be tried before considering alternative therapy. • 26-week duration - may not be indicative of long-term relative efficacy.
Yki-Jarvinen et al, 2006[44]	• A1C mean 9.5% at baseline is higher than most other studies. • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • SMBG results sent to treatment centre by modem, and numerous phone calls by care providers -- not reflective of actual practice. • 36 week duration - may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada.

A1C=glycosylated haemoglobin; **BIAsp**=biphasic insulin aspart; **BID**=twice daily; **BMI**=body mass index; **NPH**=neutral protamine Hagedorn; **NPL**=neutral protamine lispro; **PPG**=post-prandial glucose; **OADs**=oral antidiabetes drugs; **QD**=at bedtime; **SMBG**=self-monitoring of blood glucose

APPENDIX 20: DESCRIPTION OF RUN-IN PERIODS

Author, year	Interventions/ comparators	Description of run-in period
Aljabri et al, 2004[10]	• Pioglitazone (30-45 mg/day) + Met + SU • NPH insulin (titrated to FG < 108 mg/dl) + Met + SU	• There was a 2-week run-in phase to determine if patients would likely comply with the study requirements (details were not specified)
Al-Shaikh, 2006[12]	• Insulin glargine (HS) + Met + SU • Biphasic insulin (30% regular insulin + 70% NPH), 2/3 dose in morning and 1/3 dose in evening	• None specified
Bergenstal et al, 2009[14]	• Exenatide + Met + SU • BIAsp30 (QD) + Met + SU • BIAsp30 (BID) + Met + SU	• None specified
Berhanu et al, 2007[16]	• Insulin + Pioglitazone + Met • Insulin + Placebo + Met	• After one week of screening, enrolled patients received instruction on insulin use and spent up to one week discontinuing sulfonylureas as applicable. Insulin was initiated and titrated to achieve FPG <140 and >70 mg/dl for four additional weeks; all patients received one or multiple daily injections of Humalog, Humulin 70/30 or Humulin N. • After the insulin titration period, the insulin type, dose and administration schedule were left to the discretion of the clinical investigator and adjusted to achieve FPG <140 mg/dl, while avoiding hypoglycaemia. • Throughout the insulin titration period, patients received instructions regarding diabetes, hypoglycaemia, nutrition and exercise. Patients attaining FPG <140 mg/dl during insulin titration were randomized.
Charpentier et al, 2009[20]	• Pioglitazone (30-45 mg/day) + Met + SU • Placebo + Met + SU	• 3 week run-in period (details were not specified)
Dailey et al, 2004[22]	• Rosiglitazone (4-8 mg) + Met + SU • Placebo + Met + SU	• Patients who had been receiving maximal combination therapy with metformin and a sulfonylurea (at least half-maximum dose) were enrolled in a 2-week, open-label, lead-in phase. • Patients in the 2-week phase received glyburide/metformin as two tablets each of 2.5/500 mg twice daily. No dose adjustment was necessary for this group. • Patients who had been receiving submaximal combination therapy with metformin (1000 to 1700 mg/d) or monotherapy (metformin up to 2000 mg/d) were enrolled in a 12-week, open-label, lead-in phase. • Patients in the 12-week phase were administered glyburide/metformin tablets at a dose of 2.5/500 mg once daily if they were already receiving monotherapy, or at a dose of 7.5/1500 mg once daily if they were already receiving submaximal combination therapy. • The dose was titrated to a maximum of 10/2000 mg daily, if needed. Dose titration was performed based on the mean daily glucose levels calculated from the average of self-measurements performed four times daily (morning fast, preprandial [twice], and bedtime) for 3 to 5 days before each study visit. The glyburide/metformin dose was titrated if the mean daily glucose level was ≥ 126 mg/dL, or if the A1C level was ≥ 7.0%. Downward dose titration of glyburide/ metformin was allowed during the open-label phase to alleviate symptoms of hypoglycemia.

Author, year	Interventions/ comparators	Description of run-in period
Davies et al, 2007[24]	• Biphasic 30/70 human insulin (BID) + Met • NPH insulin (HS) + Repaglinide (AC) + Met • NPH Insulin (HS) + Met	• Four week run-in period (details were not specified)
De Mattia et al, 2009[26]	• Insulin glargine + Met + SU • NPH Insulin + Met + SU	• One week run-in period where patients where given standardised diet instructions.
Derosa et al, 2009[28]	• Acarbose + Met + SU • Rapaglinide + Met + SU	• Four week run-in period (details were not specified)
Dorkhan et al, 2009[30]	• Pioglitazone + Met + SU • Insulin (glargine) + Met + SU	• None specified
Esposito et al, 2008[32]	• NPL insulin (HS) + Met + SU • Insulin glargine (HS) + Met + SU	• Four week screening phase where the investigators obtained informed consent, recorded medical histories, did physical examinations, and determined whether patients met inclusion and exclusion criteria. • Participants were trained to use the medical devices used in the study, either insulin pens or blood glucose meters, and were asked to discontinue the dinner sulfonylurea dose, if taken, and replace it with metformin, 850 mg.
Gao et al, 2009[34]	• Exenatide (10 µg BID) + Met + SU • Placebo (BID) + Met + SU	• Two-week, single blind, placebo lead-in period to acclimatize injection-naïve patients
Goudswaard et al, 2004[36]	• NPH insulin (QD) + Met + SU • Biphasic insulin (70/30) (BID)	• None specified
Hartemann-Heurtier et al, 2009[38]	• Pioglitazone + Met + SU • NPH insulin + Met + SU	• None specified
Heine et al, 2005[40] Companion[18]	• Exenatide (10 µg BID) + Met + SU • Insulin glargine + Met + SU	• None specified
Hermansen et al, 2007[41]	• Sitagliptin (100 mg/day) + Met + SU • Placebo + Met + SU	• Patients with A1C ≥7.5% and ≤10.5% who were already taking a stable dose of glimepiride (≥4 mg/day up to a maximum daily dose of 8 mg/day) alone or in combination with metformin (≥1500 mg/day up to a maximum daily dose of 3000 mg/day) for at least 10 weeks directly entered a 2-week, single-blind placebo run-in period. • Patients who were not on OADs with A1C ≤9%, who were taking other OADs in monotherapy with A1C ≥7.5%, or who were taking other OADs in dual or triple therapy with A1C ≥6.5% and ≤10.5%, discontinued their prior regimen and were switched to treatment with glimepiride alone or glimepiride in combination with metformin. Following the switch in treatments, these patients entered a dose titration period of up to four weeks and then a dose stabilization run-in period of up to 10 weeks. If A1C was ≥7.5% and ≤10.5% after this run-in period, patients entered a 2-week, single-blind placebo run-in period. • Patients with adequate compliance (≥75%) during this placebo run-in period underwent baseline evaluations and were randomized.
Holman et al, 2007[43]	• Insulin aspart (TID) + Met + SU • Insulin detemir (HS or BID) + Met + SU • Biphasic insulin aspart 30 (BID) + Met + SU	• None specified
Janka et al, 2005[11] Subgroup[11]	• Insulin glargine + Met + SU • 30/70 NPH + placebo	• 1- to 4-week screening phase where previous sulfonylurea therapies were replaced with 3 or 4 mg glimepiride.
Kendall et al, 2005[15]	• Exenatide (5 µg BID) + Met + SU • Exenatide (10 µg BID) + Met + SU • Placebo + Met + SU	• Four week single-blind lead-in period with injection of placebo twice daily

Author, year	Interventions/ comparators	Description of run-in period
Ko et al, 2006[17]	• Rosiglitazone + Met + SU • NPH Insulin (HS) + Met + SU	• Patients who fulfilled the inclusion criteria were referred to dieticians and diabetic nursing specialists for reinforcement of their dietary habits, drug compliance, and an understanding of OAD failure. • Those with A1C ≥ 8.5 three months after reinforcement were randomized.
Lam et al, 1998[19]	• Acarbose (150-300 mg/day) + Met + glibenclamide (10 mg BID) or gliclazide (160 mg BID) • Placebo + Met + glibenclamide (10 mg BID) or gliclazide (160 mg BID)	• None specified
Lopez-Alvarenga et al, 1999[21†]	• Acarbose (100 mg TID) + Met + SU • Insulin NPH + MET + SU • Placebo + Met + SU	• The study was begun with a run-in diet period of six weeks, in which an isocaloric diet was prescribed with a nutrient distribution in accordance with the ADA recommendations (50% carbohydrates, 20% protein, 30% lipids and 30 g fibre). • All patients received chlorpropamide (500 mg/day) plus metformin (1200 mg/day) during the full length of the trial. Only cases who remained hyperglycaemic (FPG > 8.8 mmol/l) were randomly assigned into three groups: acarbose (100 mg TID) followed by placebo (TID); placebo (TID) followed by acarbose (100 mg TID) and bedtime NPH insulin.
Milicevic et al, 2009[23]	• Insulin NPH (HS) + Glyburide • 1) Insulin lispro 50%, Insulin lispro protamine suspension 50% (pre breakfast); 2) Insulin lispro 25%, Insulin lispro protamine suspension 75% (pre-dinner)	• 2 week run in with maximum tltrated doses of glyburide and metformin
Nauck et al, 2007[25]	• Exenatide (10 µg BID) + Met + SU • Biphasic insulin aspart 30/70	• None specified
Ovalle et al, 2004[27]	• Rosiglitazone (8 mg/day) + Met + SU • Biphasic insulin 70/30	• None specified
Reynolds et al, 2007[29]	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	• None specified
Rosenstock et al, 2006[31] Companion[42]	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	• During the screening/titration phase, patients not on the maximum metformin dose were titrated to 2,000 mg/day. • Patients on 1,000 mg/day increased their dose to 1,500 mg/day immediately and to 2,000 mg/day 1 week later (or maximum tolerated dose), followed by a 2-week stabilization period. Patients on 1,500 mg/day increased their dose to 2,000 mg/day immediately followed by a 2-week stabilization period.
Ross et al, 2001[33]	• Insulin lispro + Insulin NPH • Human insulin + Insulin NPH	• None specified
Russell-Jones et al, 2009[35]	• Liraglutide (1.8 mg/day) + Met + glimepiride • Insulin glargine + Met + glimepiride • Placebo + Met + glimepiride	• 6 week run-in period during which participants were placed on a standard combination therapy with metformin and glimepiride: forced metformin and glimepiride dose escalation over 3 weeks followed by a 3 week maintenance period. • Participants already on 2 g metformin and sulfonylurea therapy could proceed directly to the maintenance regimen at the discretion of the investigator. • During the dose-escalation period, doses of metformin and glimepiride were increased by up to 2 g/day and 4 mg/day, respectively.
Standl et al, 2001[37]	• Miglitol (50-100 mg TID) + Met + glyburide • Placebo + Met + glyburide	• Single-blind, four week, placebo run-in period (details were not specified)

Author, year	Interventions/ comparators	Description of run-in period
Stehouwer et al, 2003[39]	• NPH insulin + SU • NPH insulin + 30/70 insulin NPH • NPH insulin	• During the 12-week run-in phase, patients received a combination of glimepiride and metformin (500 mg twice daily) and learned home blood glucose monitoring. The glimepiride dose was titrated up to 6 mg, targeting at a fasting blood-glucose level below 7.4 mmol/L. • Patients with A1C > 6.5% at the end of the run-in phase were randomized.
Strojek et al, 2009[45]	• Insulin glargine + Met + SU • BIAsp30 + Met + SU	• During the 4-week run-in period, metformin was titrated to a dose of 2550 mg. Subjects who had not been treated with glimepiride prior to the trial, were titrated to a dose of 4 mg glimepiride during the run-in period. Subjects who had previously been treated with glimepiride continued with their pre-trial dose (4, 6, or 8 mg)
Yki-Jarvinen et al, 2006[44]	• Insulin glargine + Met • NPH Insulin + Met	• Four week screening period where patients were taught home glucose monitoring and use of a modem to send glucose readings from home to the treatment centres. • No other education or lifestyle advice was recommended to be given at this or subsequent visits. • The patients were asked to measure FPG every morning, and to perform a diurnal profile once during weeks −4 and −3 with plasma glucose measurements before and 2 h after breakfast, lunch and dinner, and at 22.00 and 04.00 h. During weeks −2 and −1 the patients were also asked to perform a diurnal profile once a week and to measure FPG daily. • Patients received a phone call at −2 weeks to verify compliance with glucose measurements and to review the results of the laboratory tests performed at −4 weeks.

A1C=glycosyltaed haemoglobin; **AC**=with meals; **ADA**=American Diabetes Association; **BiAsp30**=biphasic insulin aspart (30/70); **BID**=twice daily; **FPG**=fasting plasma glucose; **FG**=fasting glucose; **Met**=metformin; **NPH**=neutral protamine Hagedorn; **OADs**=oral antidiabetes drugs; **QD**=at bedtime; **SD**=standard deviation; **SU**=sulfonylurea; **TID**=three times daily

APPENDIX 21: SUMMARY OF TRIALS REPORTING CHANGE IN A1C (%)

Study	Treatment 1	Treatment 2	Diff of (T1-T2) MD (95% CI)
Aljabri et al, 2004[10]	TZD + M + S	Basal + M + S	0.40 (-0.40, 1.20)
Al-Shaikh, 2006[12]	Basal + M + S	Biphasic Insulin	-1.30 (-1.79, -0.81)
Bergenstal et al, 2009[14]	Biphasic + M + S	GLP-1 + M + S	0.59 (0.16, 1.02)
Bergenstal et al, 2009[14]	Biphasic + M	GLP-1 + M + S	1.01 (0.52, 1.50)
Bergenstal et al, 2009[14]	Biphasic QD + M + S	Biphasic BID + M	-0.42 (-0.87, 0.03)
Berhanu et al, 2007[16]	Insulin + TZD + M	Insulin + Placebo + M	-0.20 (-0.22, -0.18)
Charpentier et al, 2009[20]	TZD + M + S	Placebo + M + S	-1.18 (-1.40, -0.96)
Dailey et al, 2004[22]	TZD + M + S	Placebo + M + S	-1.00 (-1.22, -0.78)
Davies et al, 2007[24]	Biphasic + M	Basal + M	-0.30 (-1.42, 0.82)
Davies et al, 2007[24]	NPH + Meg + M	Basal + M	-1.10 (-2.39, 0.19)
Davies et al, 2007[24]	Biphasic + M	NPH + Meg + M	0.80 (-0.26, 1.86)
De Mattia et al, 2009[26]	IGlar + M + S	NPH + M + S	-0.10 (-1.10, 0.90)
Derosa et al[28]	AGI + M + S	Meg + M + S	-0.30 (-0.34, -0.26)
Dorkhan et al, 2009[30]	TZD + M + S	Basal + M + S	0.90 (0.66, 1.14)
Goudswaard et al, 2004[36]	Basal + M + S	Biphasic Insulin	0.40 (-0.21, 1.01)
Hartemann-Heurtier et al, 2009[38]	TZD + M + S	Basal + M + S	0.40 (-0.05, 0.85)
Heine et al, 2005[40]	GLP-1 + M + S	Basal + M + S	0.02 (-0.12, 0.16)
Hermansen et al, 2007[41]	DPP-4 + M + S	Placebo + M + S	-0.89 (-1.11, -0.67)
Holman et al, 2007[43]	IAsp + M + S	Biphasic + M + S	-0.10 (-0.30, 0.10)
Holman et al, 2007[43]	Basal + M + S	Biphasic + M + S	-0.50 (-0.70, -0.30)
Holman et al, 2007[43]	IAsp + M + S	Basal + M + S	-0.60 (-0.78, -0.42)
Janka et al, 2005[11]	Basal + M + S	Biphasic Insulin	-0.34 (-0.52, -0.16)
Kendall et al, 2005[15]	GLP-1 + M + S	Placebo + M + S	-0.78 (-0.98, -0.58)
Kendall et al, 2005[15]	GLP-1 + M + S	Placebo + M + S	-1.00 (-1.22, -0.78)
Ko et al, 2006[17]	TZD + M + S	Basal + M + S	0.20 (-0.41, 0.81)
Lam et al, 1998[19]	AGI + M + S	Placebo + M + S	-0.60 (-1.15, -0.05)
Lopez-Alvarenga et al, 1999[21]	AGI + M + S	Placebo + M + S	-0.60 (-3.27, 2.07)
Lopez-Alvarenga et al, 1999[21]	Basal + M + S	Placebo + M + S	-2.10 (-4.92, 0.72)
Lopez-Alvarenga et al, 1999[21]	AGI + M + S	Basal + M + S	1.50 (-1.50, 4.50)
Milicevic et al, 2009[23]	Basal + S	Biphasic Insulin	0.80 (0.19, 1.41)
Nauck et al, 2007[25]	GLP-1 + M + S	Biphasic + M + S	-0.15 (-0.31, 0.01)
Ovalle et al, 2004[27]	TZD + M + S	Biphasic + M + S	0.30 (-1.07, 1.67)
Reynolds et al, 2007[29]	TZD + M + S	Basal + M + S	-0.10 (-2.04, 1.84)
Rosenstock et al, 2006[31]	TZD + M + S	Basal + M + S	0.15 (-0.05, 0.35)
Russell-Jones et al, 2009[35]	GLP-1 + M + S	Placebo + M + S	-1.09 (-1.29, -0.89)

Study	Treatment 1	Treatment 2	Diff of (T1-T2) MD (95% CI)
Russell-Jones et al, 2009[35]	Basal + M + S	Placebo + M + S	-0.85 (-1.05, -0.65)
Russell-Jones et al, 2009[35]	Basal + M + S	GLP-1 + M + S	0.24 (0.08, 0.40)
Standl et al, 2001[37]	AGI + M + S	Placebo + M + S	-0.35 (-0.70, 0.00)
Stehouwer et al, 2003[39]	Basal insulin	Basal + S	0.60 (0.07, 1.13)
Stehouwer et al, 2003[39]	Biphasic Insulin	Basal + S	0.60 (0.07, 1.13)
Stehouwer et al, 2003[39]	Basal insulin	Biphasic Insulin	0.00 (-0.51, 0.51)
Strojek et al, 2009[45]	Basal + M + S	Biphasic + M + S	0.16 (0.02; 0.3)

AGI=alpha glucosidase inhibitor; **CI**=confidence interval; **DPP**=dipeptidyl peptidase; **GLP**=glucagon-like peptide; **IAsp**=insulin aspart; **M**=metformin; **MD**=mean difference; **Meg**=meglitinide; **NPH**=neutral protamine Hagedorn; **S**=sulfonylurea, **T1**=treatment one; **T2**=treatment two; **TZD**=Thiazolidinedione

APPENDIX 22: FOREST PLOTS FOR A1C FROM INDIVIDUAL RCTS

Figure A: Difference in Change in A1C from Baseline from Placebo-controlled trials

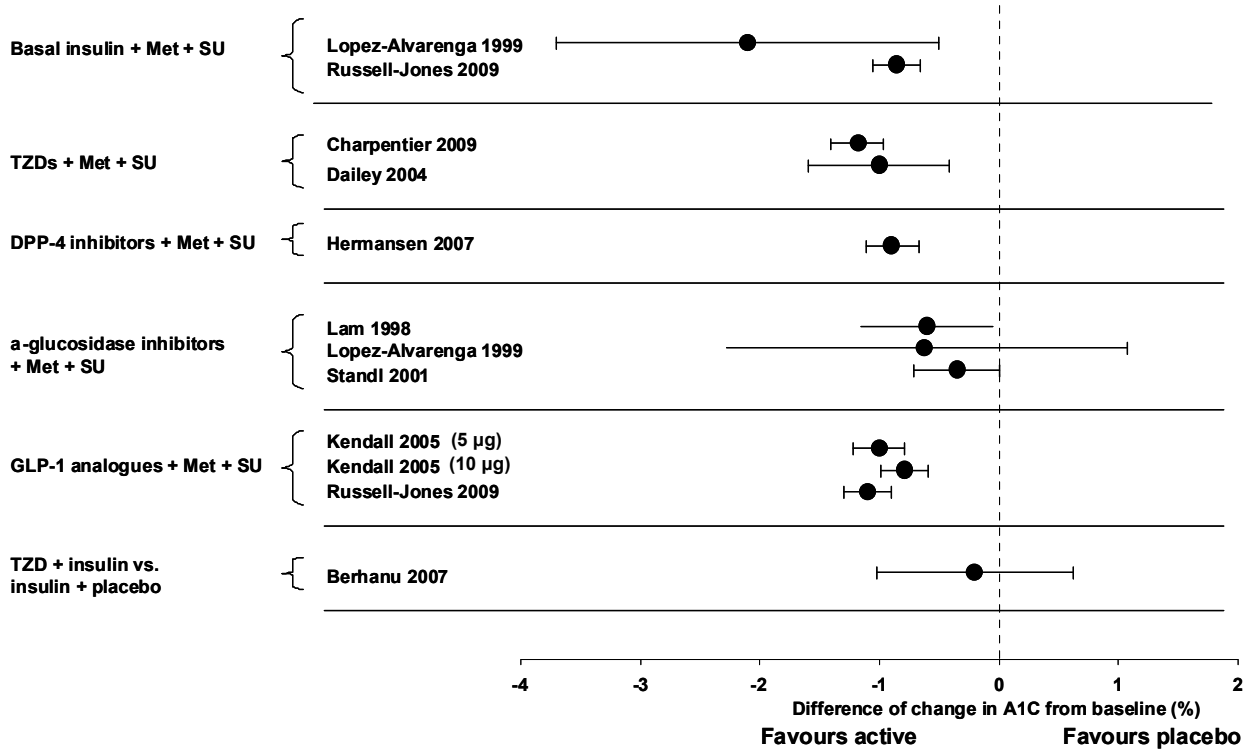
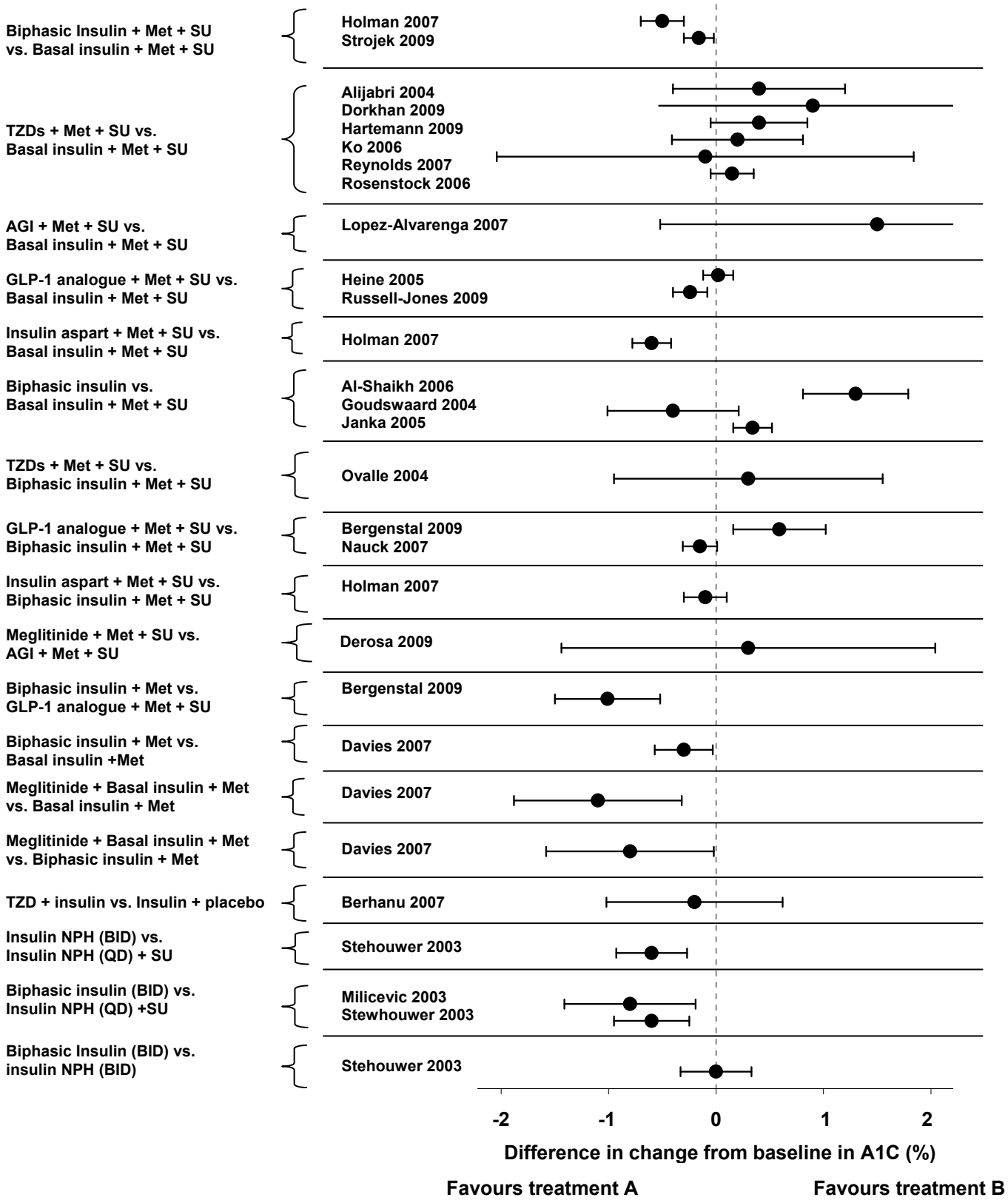
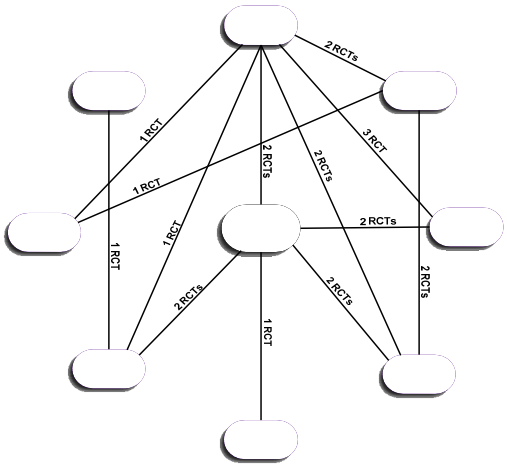


Figure B: Difference in Change in A1C from Baseline from Active Comparisons (A vs. B)



APPENDIX 23: MTC NETWORK DIAGRAMS

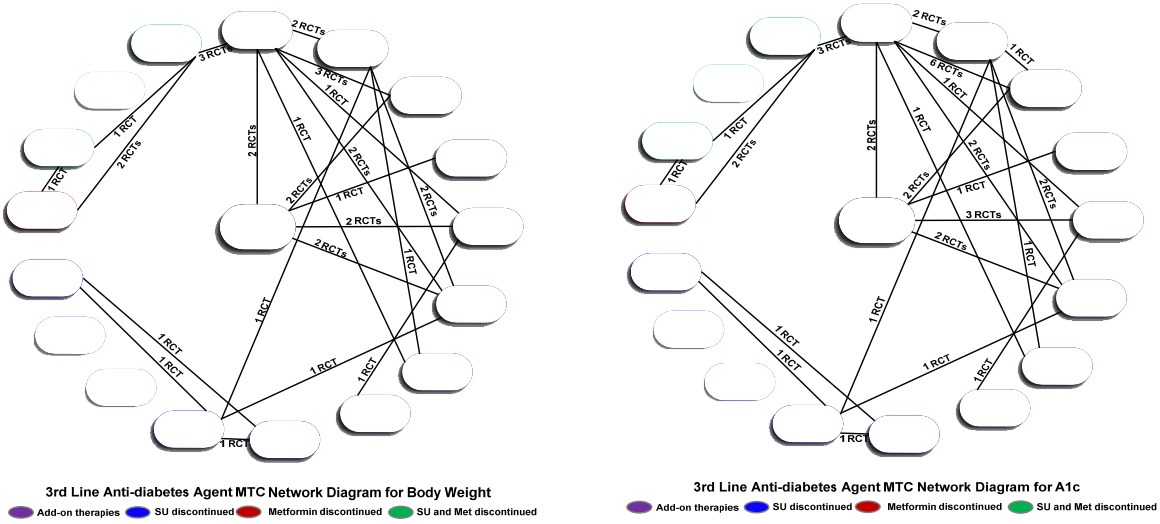
Figure A: Reference case MTC evidence networks for hemoglobin A1C and body weight



3rd Line Anti-diabetes Agent MTC Network Diagram for Body Weight
Add-On Therapies

3rd Line Anti-diabetes Agent MTC Network Diagram for A1c
Add-On Therapies

Figure B: All treatment strategies MTC evidence networks for hemoglobin A1C and body weight



APPENDIX 24: FULL RESULTS FOR CHANGE FROM BASELINE IN A1C: PRIMARY MTC ANALYSIS

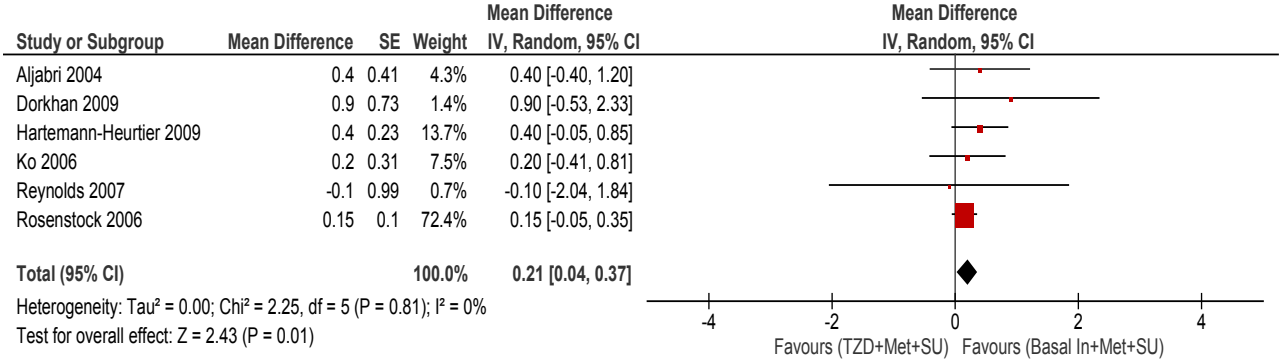
CHANGE IN A1C (%) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of largest A1C reduction**	**Mean Rank**
Vs. Placebo + Metformin + Sulfonylurea				
Basal Insulin + Met + SU	-1.22 (-2.33, -0.10)	-1.17 (-1.57, -0.81)	30.6%	2.30
Biphasic Insulin + Met + SU	———	-1.10 (-1.59, -0.67)	14.3%	3.23
TZD + Met + SU	-1.16 (-1.36, -0.96)	-0.96 (-1.35, -0.59)	2.7%	4.57
DPP-4 + Met + SU	-0.89 (-1.11, -0.66)	-0.89 (-1.51, -0.26)	12.5%	4.76
α-glucosidase + Met + SU	-0.43 (-0.72, -0.14)	-0.46 (-0.96, 0.03)	0.2%	7.08
GLP-1 + Met + SU	-0.96 (-1.14, -0.89)	-1.06 (-1.45, -0.69)	8.7%	3.66
IAsp + Met + SU	———	-1.01 (-1.71, -0.35)	17.7%	4.03
Meglitinide + Met + SU	———	-0.18 (-2.08, 1.71)	13.3%	6.84
Vs. Basal Insulin + Metformin + Sulfonylurea				
Biphasic Insulin + Met + SU	-0.32 (-0.66, 0.01)	0.07 (-0.28, 0.42)	See above	
TZD + Met + SU	0.21 (0.04, 0.37)	0.21 (-0.09, 0.54)		
DPP-4 Inhibitors + Met + SU	———	0.28 (-0.41, 1.04)		
α-glucosidase + Met + SU	1.50 (-1.52, 3.52)	0.71 (0.11, 1.34)		
GLP-1 + Met + SU	-0.11 (-0.36, 0.15)	0.12 (-0.21, 0.47)		
IAsp + Met + SU	-0.60 (-0.78, -0.42)	0.16 (-0.42, 0.76)		
Meglitinide +Met + SU	———	0.99 (-0.93, 2.92)		
Vs. Biphasic Insulin + Metformin + Sulfonylurea				
TZD + Met + SU	0.30 (-0.95, 1.55)	0.14 (-0.29, 0.60)	See above	
DPP-4 Inhibitors +Met + SU	———	0.21 (-0.53, 1.02)		
α-glucosidase + Met + SU	———	0.64 (-0.01, 1.33)		
GLP-1 + Met + SU	0.19 (-0.53, 0.91)	0.04 (-0.31, 0.43)		
IAsp + Met + SU	-0.10 (-0.30, 0.10)	0.09 (-0.48, 0.68)		
Meglitinide + Met + SU	———	0.92 (-1.02, 2.87)		
Vs. TZD + Metformin + Sulfonylurea				
DPP-4 Inhibitors + Met + SU	———	0.07 (-0.65, 0.81)	See above	
α-glucosidase + Met + SU	———	0.50 (-0.11, 1.12)		
GLP-1 + Met + SU	———	-0.09 (-0.52, 0.31)		
IAsp + Met + SU	———	-0.05 (-0.73, 0.59)		
Meglitinide + Met + SU	———	0.78 (-1.14, 2.71)		
Vs. DPP-4 Inhibitors + Metformin + Sulfonylurea				
α-glucosidase + Met + SU	———	0.43 (-0.37, 1.22)	See above	
GLP-1 + Met + SU	———	-0.16 (-0.91, 0.55)		
IAsp + Met + SU	———	-0.12 (-1.08, 0.79)		
Meglitinide + Met + SU	———	0.71 (-1.28, 2.71)		
Vs. Alpha-glucosidase inhibitors + Metformin + Sulfonylurea				
GLP-1 + Met + SU	———	-0.59 (-1.22, 0.02)	See above	
IAsp + Met + SU	———	-0.55 (-1.40, 0.27)		
Repaglinide + Met + SU	0.30 (-1.44, 2.04)	0.28 (-1.55, 2.09)		
Vs. GLP-1 + Metformin + Sulfonylurea				

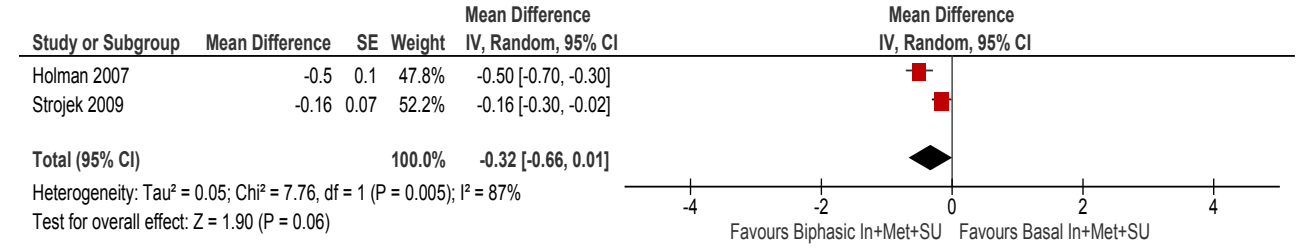
CHANGE IN A1C (%) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of largest A1C reduction**	**Mean Rank**
IAsp + Met + SU	———	0.04 (-0.60, 0.68)	See above	
Meglitinide + Met + SU	———	0.87 (-1.05, 2.81)		
Vs. IAsp + Metformin + Sulfonylurea				
Meglitinide + Met + SU	———	0.83 (-1.16, 2.84)	See above	

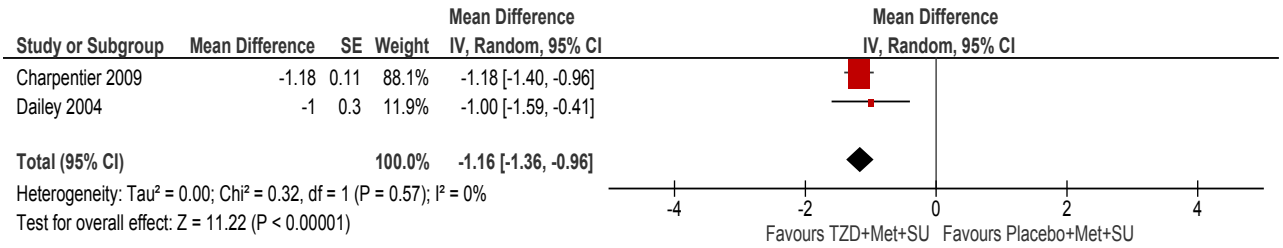
CI=confidence interval; **CrI**=credible interval; **DPP-4**=dipeptidyl peptidase-4; **GLP-1**=glucagon-like peptide-1; **IAsp**=insulin aspart; **Met**=metformin; **MTC**=mixed treatment comparison; **NPH**=neutral protamine Hagedorn; **SU**=sulfonylurea; **TZD**=thiazolidinediones; **WMD**=weighted mean difference

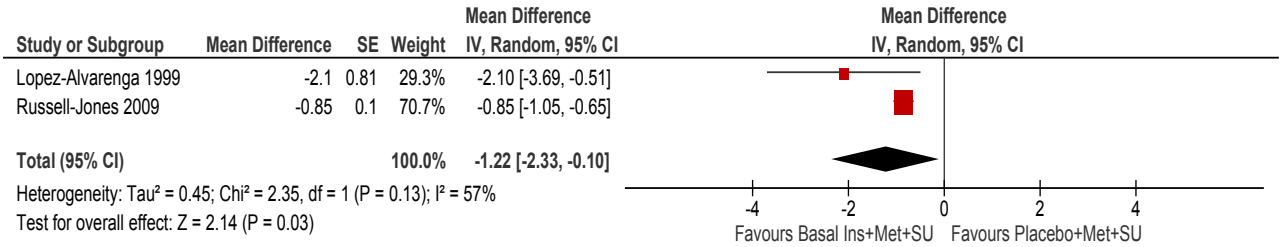
APPENDIX 25: FOREST PLOTS FOR PAIRWISE META-ANALYSES

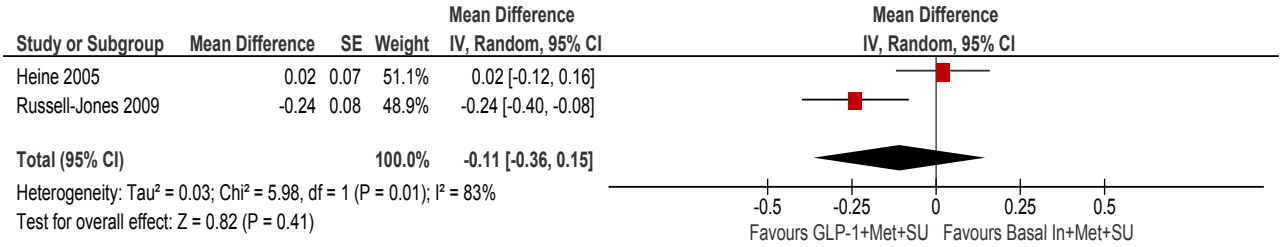
Difference in Change from Baseline for Hemoglobin A1C (%)

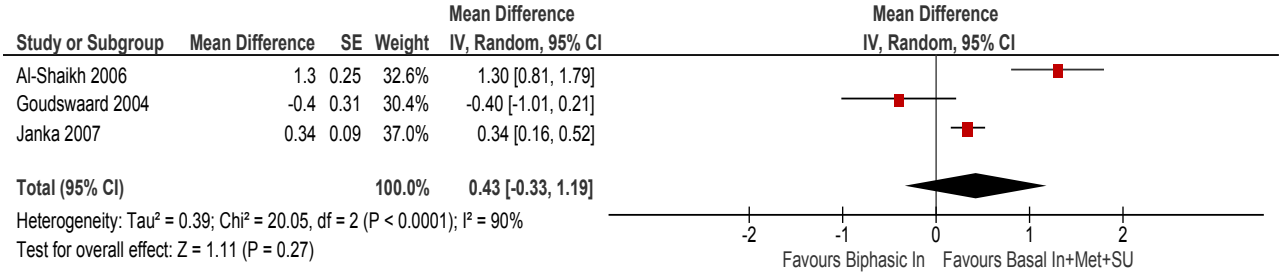


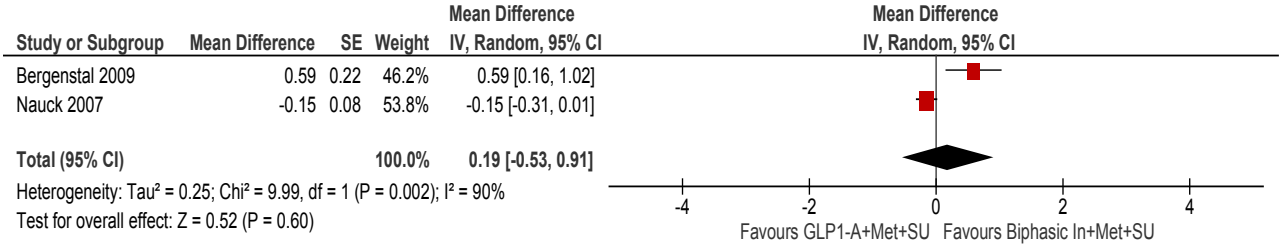


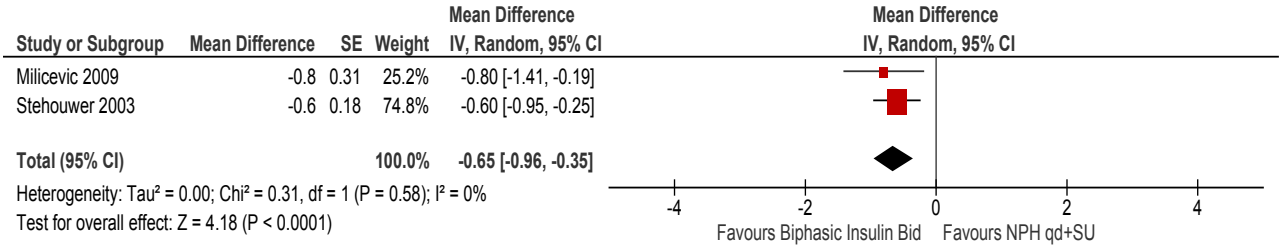




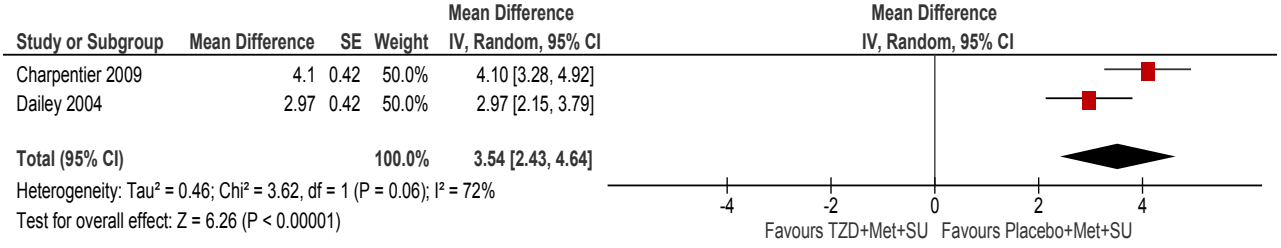


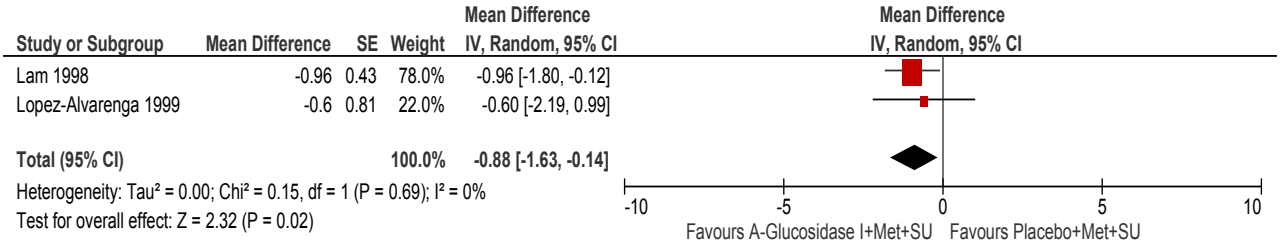


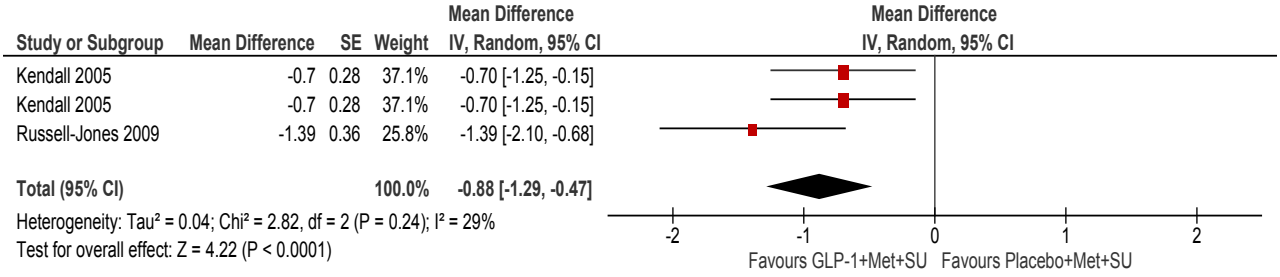


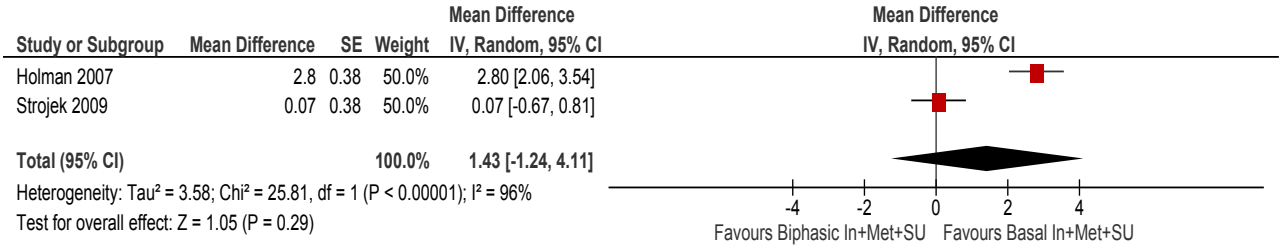


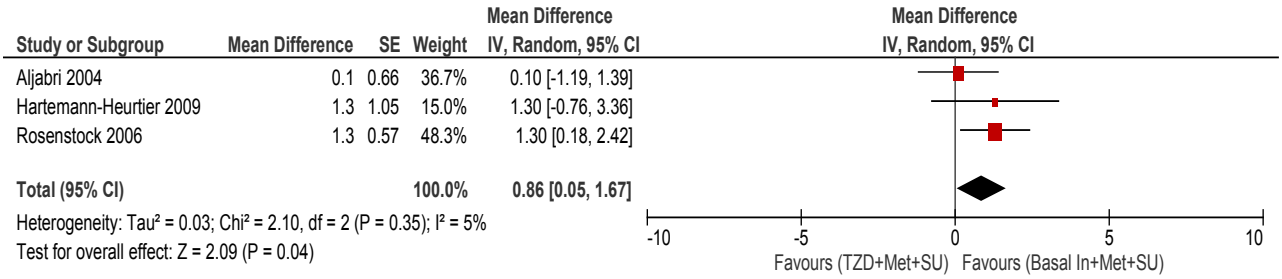
Difference in Change from Baseline in Body Weight (kg)



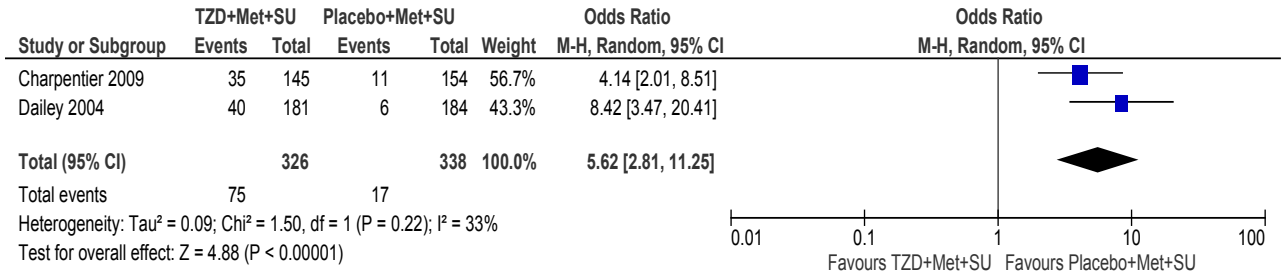

Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Random, 95% CI
Lam 1998 -0.96 0.43 78.0% -0.96 [-1.80, -0.12]
Lopez-Alvarenga 1999 -0.6 0.81 22.0% -0.60 [-2.19, 0.99]
Total (95% CI) 100.0% -0.88 [-1.63, -0.14]
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Mean Difference
IV, Random, 95% CI
-10 -5 0 5 10
Favours A-Glucosidase I+Met+SU
Favours Placebo+Met+SU

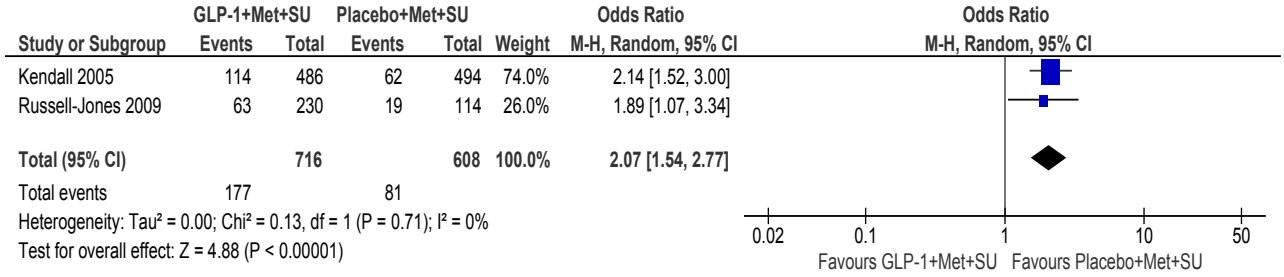

Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Random, 95% CI
Kendall 2005 -0.7 0.28 37.1% -0.70 [-1.25, -0.15]
Kendall 2005 -0.7 0.28 37.1% -0.70 [-1.25, -0.15]
Russell-Jones 2009 -1.39 0.36 25.8% -1.39 [-2.10, -0.68]
Total (95% CI) 100.0% -0.88 [-1.29, -0.47]
Heterogeneity: Tau² = 0.04; Chi² = 2.82, df = 2 (P = 0.24); I² = 29%
Test for overall effect: Z = 4.22 (P < 0.0001)
Mean Difference
IV, Random, 95% CI
-2 -1 0 1 2
Favours GLP-1+Met+SU
Favours Placebo+Met+SU

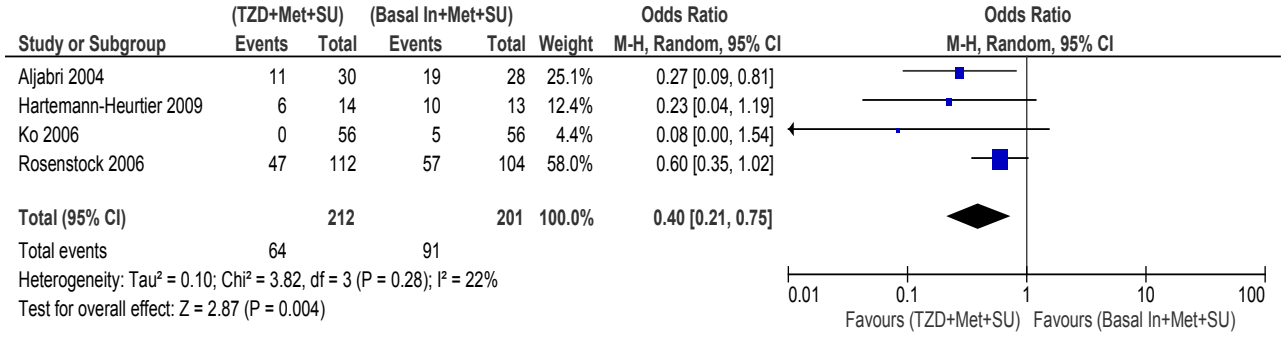

Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Random, 95% CI
Holman 2007 2.8 0.38 50.0% 2.80 [2.06, 3.54]
Strojek 2009 0.07 0.38 50.0% 0.07 [-0.67, 0.81]
Total (95% CI) 100.0% 1.43 [-1.24, 4.11]
Heterogeneity: Tau² = 3.58; Chi² = 25.81, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.05 (P = 0.29)
Mean Difference
IV, Random, 95% CI
-4 -2 0 2 4
Favours Biphasic In+Met+SU
Favours Basal In+Met+SU


Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Random, 95% CI
Aljabri 2004 0.1 0.66 36.7% 0.10 [-1.19, 1.39]
Hartemann-Heurtier 2009 1.3 1.05 15.0% 1.30 [-0.76, 3.36]
Rosenstock 2006 1.3 0.57 48.3% 1.30 [0.18, 2.42]
Total (95% CI) 100.0% 0.86 [0.05, 1.67]
Heterogeneity: Tau² = 0.03; Chi² = 2.10, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 2.09 (P = 0.04)
Mean Difference
IV, Random, 95% CI
-10 -5 0 5 10
Favours (TZD+Met+SU)
Favours (Basal In+Met+SU)

Overall Hypoglycemia (odds ratio)







APPENDIX 26: FULL RESULTS FOR CHANGE FROM BASELINE IN A1C: SECONDARY MTC ANALYSIS

DIFFERENCE IN CHANGE IN HEMOGLOBIN A1C (%) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of largest A1C reduction**	**Mean Rank**
Vs. Placebo + Metformin + Sulfonylurea				
Basal Insulin + Met + SU	-1.22 (-2.33, -0.10)	-1.20 (-1.66, -0.77)	1.8%	3.6
Biphasic Insulin + Met + SU	———	-1.13 (-1.69, -0.60)	1.0%	4.5
TZD + Met + SU	-1.16 (-1.36, -0.96)	-0.97 (-1.41, -0.53)	0.3%	6.1
DPP-4 + Met + SU	-0.89 (-1.11, -0.66)	-0.89 (-1.65, -0.15)	2.7%	6.5
α-glucosidase + Met + SU	-0.43 (-0.72, -0.14)	-0.46 (-1.03, 0.10)	0.1%	9.6
GLP-1 + Met + SU	-0.96 (-1.14, -0.89)	-1.07 (-1.53, -0.63)	0.3%	5.1
IAsp + Met + SU	———	-1.04 (-1.86, -0.24)	3.3%	5.5
Meglitinide + Met + SU	———	-0.14 (-2.17, 1.83)	5.2%	9.7
Biphasic Insulin + Met	———	-1.90 (-2.80, -0.98)	82.2%	1.4
Insulin NPH + SU	———	-0.05 (-1.00, 0.86)	0.0%	11.5
Insulin NPH	———	-0.69 (-1.87, 0.45)	3.1%	7.8
Biphasic Insulin	———	-0.75 (-1.42, -0.12)	0.1%	7.9
Vs. Basal Insulin + Metformin + Sulfonylurea				
Biphasic Insulin + Met + SU	-0.32 (-0.66, 0.01)	0.07 (-0.35, 0.49)	See above	
TZD + Met + SU	0.21 (0.04, 0.37)	0.23 (-0.12, 0.60)		
DPP-4 Inhibitors + Met + SU	———	0.31 (-0.56, 1.20)		
α-glucosidase + Met + SU	1.50 (-1.52, 3.52)	0.74 (0.05, 1.45)		
GLP-1 + Met + SU	-0.11 (-0.36, 0.15)	0.13 (-0.26, 0.55)		
IAsp + Met + SU	-0.60 (-0.78, -0.42)	0.16 (-0.54, 0.87)		
Meglitinide +Met + SU	———	1.06 (-1.02, 3.09)		
Biphasic Insulin + Met	———	-0.70 (-1.56, 0.19)		
Insulin NPH + SU	———	1.14 (0.32, 1.95)		
Insulin NPH	———	0.51 (-0.57, 1.57)		
Biphasic Insulin	0.43 (-0.33, 1.19)	0.45 (-0.04, 0.93)		
Vs. Biphasic Insulin + Metformin + Sulfonylurea				
TZD + Met + SU	0.30(-0.95, 1.55)	0.16 (-0.34, 0.69)	See above	
DPP-4 Inhibitors +Met + SU	———	0.24 (-0.68, 1.18)		
α-glucosidase + Met + SU	———	0.67 (-0.10, 1.45)		
GLP-1 + Met + SU	0.19 (-0.53, 0.91)	0.06 (-0.37, 0.51)		
IAsp + Met + SU	-0.10 (-0.30, 0.10)	0.09 (-0.60, 0.79)		
Meglitinide + Met + SU	———	0.99 (-1.12, 3.05)		
Biphasic Insulin + Met	-0.42 (-0.87, 0.03)	-0.77 (-1.60, 0.10)		
Insulin NPH + SU	———	1.08 (0.16, 1.99)		
Insulin NPH	———	0.44 (-0.72, 1.57)		
Biphasic Insulin	———	0.38 (-0.26, 1.02)		
Vs. TZD + Metformin + Sulfonylurea				
DPP-4 Inhibitors + Met + SU	———	0.08 (-0.79, 0.95)	See above	
α-glucosidase + Met + SU	———	0.51 (-0.21, 1.22)		
GLP-1 + Met + SU	———	-0.10 (-0.59, 0.38)		
IAsp + Met + SU	———	-0.07 (-0.85, 0.70)		

DIFFERENCE IN CHANGE IN HEMOGLOBIN A1C (%) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of largest A1C reduction**	**Mean Rank**
Meglitinide + Met + SU	———	0.83 (-1.25, 2.85)		
Biphasic Insulin + Met	———	-0.92 (-1.85, -0.01)		
Insulin NPH + SU	———	0.92 (0.01, 1.79)		
Insulin NPH	———	0.28 (-0.87, 1.39)		
Biphasic Insulin	———	0.22 (-0.40, 0.80)		
Vs. DPP-4 Inhibitors + Metformin + Sulfonylurea				
α-glucosidase + Met + SU	———	0.43 (-0.50, 1.38)	See above	
GLP-1 + Met + SU	———	-0.18 (-1.06, 0.70)		
IAsp + Met + SU	———	-0.14 (-1.26, 0.95)		
Meglitinide + Met + SU	———	0.75 (-1.40, 2.87)		
Biphasic Insulin + Met	———	-1.00 (-2.18, 0.18)		
Insulin NPH + SU	———	0.84 (-0.38, 2.01)		
Insulin NPH	———	0.21 (-1.20, 1.58)		
Biphasic Insulin	———	0.14 (-0.87, 1.13)		
Vs. Alpha-glucosidase inhibitors + Metformin + Sulfonylurea				
GLP-1 + Met + SU	———	-0.61 (-1.32, 0.10)	See above	
IAsp + Met + SU	———	-0.58 (-1.55, 0.39)		
Repaglinide + Met + SU	0.30 (-1.44, 2.04)	0.32 (-1.62, 2.22)		
Biphasic Insulin + Met	———	-1.44 (-2.50, -0.36)		
Insulin NPH + SU	———	0.40 (-0.69, 1.47)		
Insulin NPH	———	-0.23 (-1.54, 1.04)		
Biphasic Insulin	———	-0.29 (-1.16, 0.55)		
Vs. GLP-1 + Metformin + Sulfonylurea				
IAsp + Met + SU	———	0.03 (-0.74, 0.79)	See above	
Meglitinide + Met + SU	———	0.93 (-1.16, 2.96)		
Biphasic Insulin + Met	-1.01 (-1.50, -0.52)	-0.83 (-1.64, 0.00)		
Insulin NPH + SU	———	1.01 (0.08, 1.91)		
Insulin NPH	———	0.38 (-0.78, 1.51)		
Biphasic Insulin	———	0.32 (-0.32, 0.94)		
Vs. IAsp + Metformin + Sulfonylurea				
Meglitinide + Met + SU	———	0.90 (-1.30, 3.03)	See above	
Biphasic Insulin + Met	———	-0.86 (-1.91, 0.24)		
Insulin NPH + SU	———	0.98 (-0.10, 2.04)		
Insulin NPH	———	0.35 (-0.94, 1.61)		
Biphasic Insulin	———	0.29 (-0.58, 1.12)		
Vs. Meglitinide + Metformin + Sulfonylurea				
Biphasic Insulin + Met	———	-1.75 (-3.94, 0.48)	See above	
Insulin NPH + SU	———	0.09 (-2.10, 2.34)		
Insulin NPH	———	-0.55 (-2.84, 1.80)		
Biphasic Insulin	———	-0.61 (-2.70, 1.53)		
Vs. Biphasic Insulin + Metformin				
Insulin NPH + SU	———	1.84 (0.62, 3.03)	See above	
Insulin NPH	———	1.21 (-0.22, 2.58)		
Biphasic Insulin	———	1.15 (0.12, 2.14)		
Vs. Insulin NPH + Sulfonylurea				

DIFFERENCE IN CHANGE IN HEMOGLOBIN A1C (%) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of largest A1C reduction**	**Mean Rank**
Insulin NPH	-0.60 (-0.93, -0.27)	-0.63 (-1.51, 0.23)		
Biphasic Insulin	-0.65 (-96, -0.35)	-0.70 (-1.35, -0.02)		
Vs. Insulin NPH				
Biphasic Insulin	0 (-0.33, 0.33)	-0.06 (-1.01, 0.90)	See above	

CI=confidence interval; **CrI**=credible interval; **DPP-4**=dipeptidyl peptidase-4; **GLP-1**=glucagon-like peptide-1; **IAsp**=insulin aspart; **Met**=metformin; **MTC**=mixed treatment comparison; **NPH**=neutral protamine Hagedorn; **SU**=sulfonylurea; **TZD**=thiazolidinediones; **WMD**=weighted mean difference

APPENDIX 27: SUMMARY OF TRIALS REPORTING CHANGE IN BODY WEIGHT

Study	Treatment 1	Treatment 2	Diff of (T1-T2) MD kg (95% CI)
Aljabri, 2004[10]	Pioglitazone + M + S	Insulin NPH + M + S	0.10 (-1.19;1.39)
Al-Shaikh, 2006[12]	Insulin glargine + M + S	Mixed insulin (30% regular insulin + 70% NPH)	-3.90 (-6.61; -1.20)
Bergenstal, 2009[14]	Exenatide + M + S	BIAsp30 (QD) + M + S	-4.70 (-5.62; -3.78)
Bergenstal, 2009[14]	Exenatide + M + S	BIAsp30 (BID) + M + S	-6.00 (-7.16; -4.84)
Bergenstal, 2009[14]	BIAsp30 (BID) + M + S	BIAsp30 (QD) + M + S	1.30 (0.16; 2.44)
Davies, 2007[24]	Biphasic HI + M	Insulin NPH + M	2.20 (-0.05; 4.45)
Davies, 2007[24]	NPH + Repaglinide + M	Insulin NPH + M	1.50 (-0.03; 3.03)
Davies, 2007[24]	Biphasic HI + M	NPH + Repaglinide + M	0.70 (-0.01; 1.41)
Goudswaard, 2004[36]	Insulin NPH (QD) + M + S	Biphasic insulin (70/30; BID)	-3.00 (-5.29; -0.71)
Hartemann-Heurtier, 2009[38]	Pioglitazone + M + S	Insulin NPH + M + S	1.30 (-0.76; 3.36)
Heine, 2005[40]	Exenatide (10 µg BID) + M + S	Insulin glargine	-4.10 (-4.65; -3.55)
Hermansen, 2007[41]	Sitagliptin + M + S	Placebo + M + S	1.10 (0.28; 1.92)
Holman, 2007[43]	Insulin aspart + M + S	Insulin detemir + M + S	3.80 (2.00; 4.60)
Holman, 2007[43]	Insulin aspart + M + S	Biphasic insulin aspart 30 + M + S	1.00 (0.22; 1.78)
Holman, 2007[43]	Insulin detemir + M + S	Biphasic insulin aspart 30 + M + S	-2.80 (-3.55; -2.06)
Janka, 2005[11]	Insulin glargine + M + S	30/70 NPH + placebo	-0.70 (-1.48; 0.08)
Janka, 2007[13]	Insulin glargine + M + S	30/70 NPH + placebo	-0.90 (-2.10; 0.30)
Kendall, 2005[15]	Exenatide (5 µg BID) + M + S	Placebo + M + S	-0.70 (-1.25; -0.15)
Kendall, 2005[15]	Exenatide (10 µg BID) + M + S	Placebo + M + S	-0.70 (-1.25; -0.15)
Lam, 1998[19]	Acarbose (100 mg TID)	Placebo	-0.96 (-1.80; -0.12)
Lopez-Alvarenga, 1999[21]	Acarbose + M + S	Placebo + M + S	-0.60 (-7.77; 6.57)
Lopez-Alvarenga, 1999[21]	Insulin NPH + M + S	Placebo + M + S	-0.30 (-9.61; 9.01)
Lopez-Alvarenga, 1999[21]	Acarbose + M + S	Insulin NPH + M + S	-0.30 (-9.67; 9.07)

Study	Treatment 1	Treatment 2	Diff of (T1-T2) MD kg (95% CI)
Milicevic, 2009[23]	Glyburide (≥15 mg) + Insulin NPH (QD)	LM50 (before breakfast) + LM25 (before dinner)	-0.22 (-1.24; 0.80)
Nauck, 2007[25]	Exenatide (10 µg BID) + M + S	Biphasic insulin aspart + M + S	-5.50 (-5.89; -5.11)
Rosenstock et al, 2006[31]	Rosiglitazone + M + S	Insulin glargine + M + S	1.30 (0.18; 2.42)
Ross, 2009[33]	Insulin lispro + insulin NPH	Human Insulin + insulin NPH	1.00 (-6.84; 8.84)
Russell-Jones, 2009[35]	Liraglutide + M + S	Placebo + M + S	-1.39 (-2.10; -0.68)
Russell-Jones, 2009[35]	Insulin glargine + M + S	Placebo + M + S	2.02 (1.02; 3.02)
Russell-Jones, 2009[35]	Insulin glargine + M + S	Liraglutide + M + S	3.40 (2.48; 4.32)
Stehouwer, 2003[39]	Insulin NPH + S	Insulin NPH	-1.60 (-7.21; 4.01)
Stehouwer, 2003[39]	Insulin NPH + S	30/70 NPH	-0.90 (-6.92; 5.12)
Stehouwer, 2003[39]	Insulin NPH	30/70 NPH	0.70 (-4.91; 6.31)

HI=human insulin, **iGlar**=insulin glargine, **IAsp**=insulin aspart, **Meg**=meglitinide, **M**=metformin, **MD**=means difference, **NPH**=neutral protamine Hagedorn, **NR**=not reported, **QD**=at bedtime, **S**=sulfonylurea, **TID**=three times daily

APPENDIX 28: FOREST PLOTS FOR BODY WEIGHT FROM INDIVIDUAL RCTS

Figure A: Difference in Change from Baseline in Body Weight from Placebo-controlled Trials

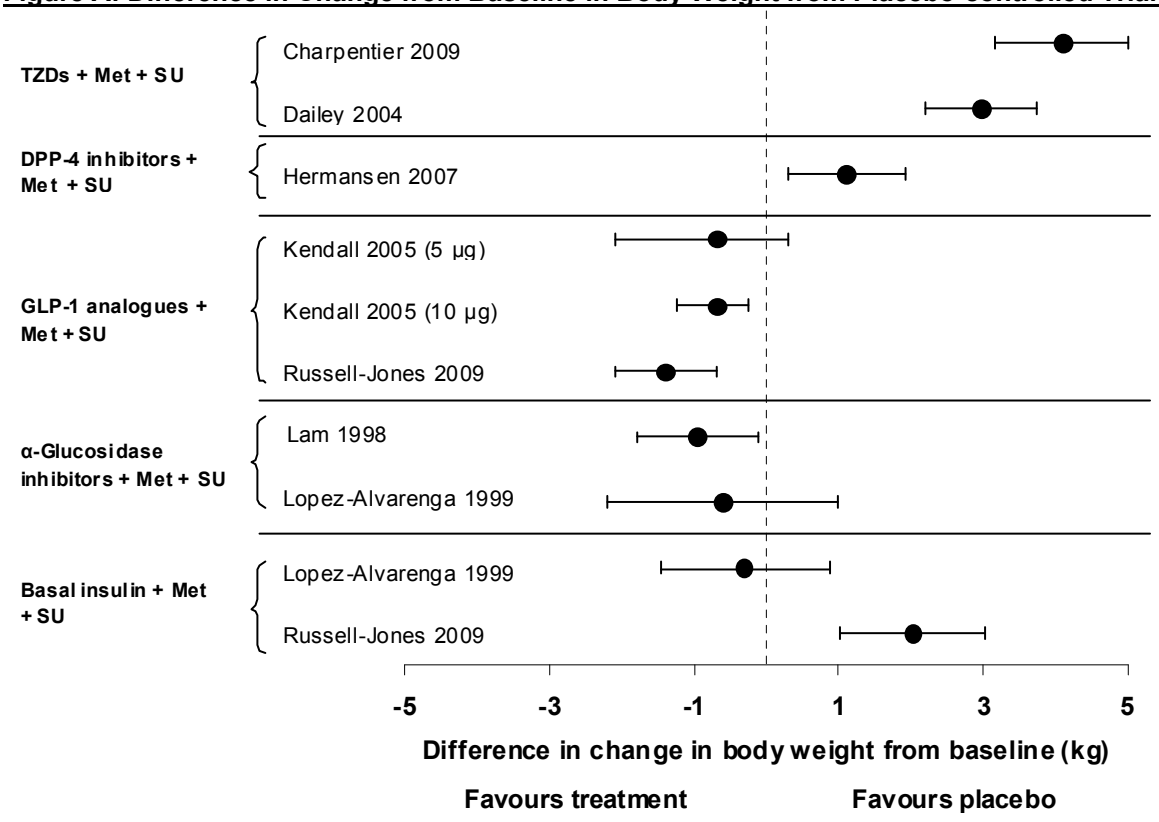
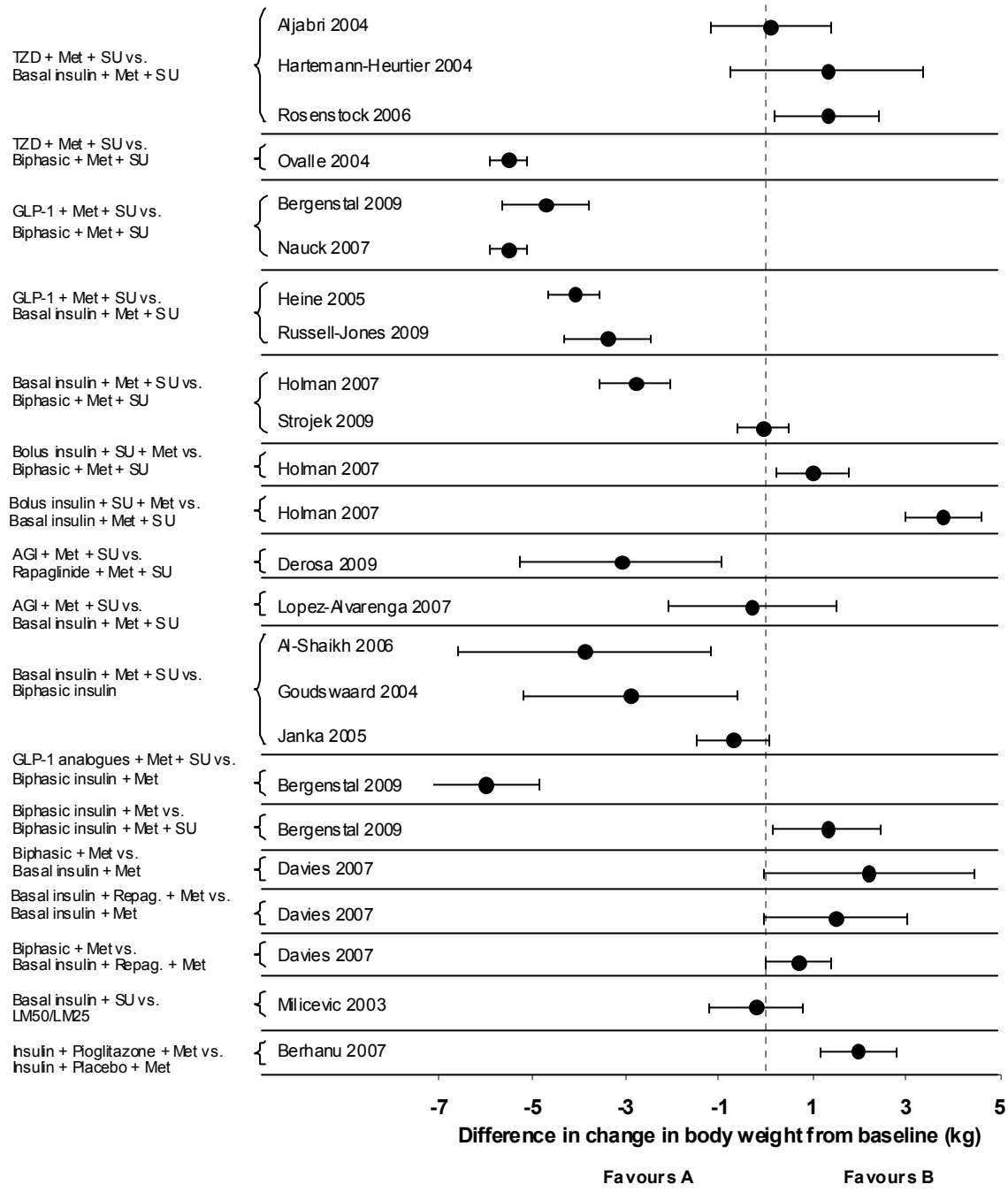


Figure B: Difference in Change from Baseline in Body Weight for Active Comparisons (A vs. B)



APPENDIX 29: FULL RESULTS FOR CHANGE FROM BASELINE IN BODY WEIGHT: PRIMARY MTC ANALYSIS

CHANGE IN BODY WEIGHT (KG) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of least weight gain**	**Mean Rank**
Vs. Placebo + Metformin + Sulfonylurea				
Basal Insulin + Met + SU	0.88 (-1.39, 3.15)	1.85 (0.54, 3.09)	0.0%	5.07
Biphasic Insulin + Met + SU	———	3.35 (1.65, 5.03)	0.0%	7.24
TZD + Met + SU	3.54 (2.43, 4.64)	3.10 (1.73, 4.43)	0.0%	6.94
DPP-4 + Met + SU	1.10 (0.28, 1.29)	1.11 (-1.36, 3.57)	2.4%	4.32
α-glucosidase + Met + SU	-0.88 (-1.63, -0.14)	-0.43 (-2.20, 1.44)	12.5%	2.37
GLP-1 + Met + SU	-0.88 (-1.29, -0.47)	-1.59 (-3.01, -0.20)	83.8%	1.19
IAsp + Met + SU	1.99 (1.00,2.99)	5.00 (2.52, 7.43)	0.0%	8.72
Meglitinide + Met + SU	———	2.67 (-0.94, 6.32)	0.8%	6.23
Vs. Basal Insulin + Metformin + Sulfonylurea				
Biphasic Insulin + Met + SU	1.43 (-1.25, 4.11)	1.50 (0.14, 2.93)	See above	
TZD + Met + SU	0.86 (0.05, 1.67)	1.25 (-0.04, 2.54)		
DPP-4 Inhibitors + Met + SU	———	-0.74 (-3.49, 2.04)		
α-glucosidase + Met + SU	-0.30 (-2.08, 1.48)	-2.28 (-4.29, -0.11)		
GLP-1 + Met + SU	-3.85 (-4.32, -2.48)	-3.44 (-4.69, -2.13)		
IAsp + Met + SU	3.80 (3.00, 4.60)	3.15 (0.98, 5.37)		
Meglitinide +Met + SU	———	0.81 (-2.89, 4.64)		
Vs. Biphasic Insulin + Metformin + Sulfonylurea				
TZD + Met + SU	———	-0.25 (-2.09, 1.55)	See above	
DPP-4 Inhibitors +Met + SU	———	-2.24 (-5.24, 0.76)		
α-glucosidase + Met + SU	———	-3.78 (-6.09, -1.32)		
GLP-1 + Met + SU	-5.21 (-5.97, -4.46)	-4.94 (-6.31, -3.56)		
IAsp + Met + SU	1.00 (0.22, 1.78)	1.65 (-0.56, 3.83)		
Meglitinide + Met + SU	———	-0.68 (-4.54, 3.28)		
Vs. TZD + Metformin + Sulfonylurea				
DPP-4 Inhibitors + Met + SU	———	-1.99 (-4.78, 0.84)	See above	
α-glucosidase + Met + SU	———	-3.53 (-5.63, -1.27)		
GLP-1 + Met + SU	———	-4.68 (-6.32, -3.01)		
IAsp + Met + SU	———	1.90 (-0.60, 4.43)		
Meglitinide + Met + SU	———	-0.43 (-4.23, 3.46)		
Vs. DPP-4 Inhibitors + Metformin + Sulfonylurea				
α-glucosidase + Met + SU	———	-1.54 (-4.53, 1.55)	See above	
GLP-1 + Met + SU	———	-2.70 (-5.56, 0.15)		
IAsp + Met + SU	———	3.89 (0.37, 7.35)		
Meglitinide + Met + SU	———	1.56 (-2.75, 6.01)		
Vs. Alpha-glucosidase inhibitors + Metformin + Sulfonylurea				
GLP-1 + Met + SU	———	-1.15 (-3.43, 0.99)	See above	
IAsp + Met + SU	———	5.43 (2.37, 8.30)		
Repaglinide + Met + SU	3.10 (0.95, 5.25)	3.10 (-0.03, 6.26)		

CHANGE IN BODY WEIGHT (KG) FROM BASELINE				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of least weight gain**	**Mean Rank**
Vs. GLP-1 + Metformin + Sulfonylurea				
IAsp + Met + SU	———	6.59 (4.21, 8.93)	See above	
Meglitinide + Met + SU	———	4.25 (0.48, 8.15)		
Vs. IAsp + Metformin + Sulfonylurea				
Meglitinide + Met + SU	———	-2.33 (-6.55, 2.03)	See above	

CI=confidence interval; **CrI**=credible interval; **DPP-4**=dipeptidyl peptidase-4; **GLP-1**=glucagon-like peptide-1; **IAsp**=insulin aspart; **Met**=metformin; **MTC**=mixed treatment comparison; **NPH**=neutral protamine Hagedorn; **SU**=sulfonylurea; **TZD**=thiazolidinediones; **WMD**=weighted mean difference

APPENDIX 30: FULL RESULTS FOR CHANGE FROM BASELINE IN BODY WEIGHT: SECONDARY MTC ANALYSIS

DIFFERENCE IN CHANGE FROM BASELINE IN BODY WEIGHT (KG)				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of least weight gain**	**Mean Rank**
Vs. Placebo + Metformin + Sulfonylurea				
Basal Insulin + Met + SU	0.88 (-1.39, 3.15)	2.57 (1.29, 3.78)	0.0%	6.6
Biphasic Insulin + Met + SU	———	3.89 (2.38, 5.41)	0.0%	9.9
TZD + Met + SU	3.54 (2.43, 4.64)	3.47 (2.24, 4.67)	0.0%	8.9
DPP-4 + Met + SU	1.10 (0.28, 1.29)	1.10 (-1.02, 3.19)	1.6%	4.6
α-glucosidase + Met + SU	-0.88 (-1.63, -0.14)	-0.93 (-2.96, 1.10)	39.4%	1.9
GLP-1 + Met + SU	-0.88 (-1.29, -0.47)	-1.18 (-2.42, 0.07)	55.2%	1.5
IAsp + Met + SU	———	5.63 (3.46, 7.78)	0.0%	13.5
Meglitinide + Met + SU	———	2.16 (-0.68, 5.01)	0.2%	6.5
Basal Insulin + Met	———	2.74 (-1.06, 6.55)	1.3%	7.3
Biphasic Insulin + Met	———	4.96 (2.58, 7.37)	0.0%	12.3
Insulin NPH + SU	———	4.17 (1.40, 7.13)	0.0%	10.4
NPH + Repaglinide + Met	———	4.25 (0.13, 8.33)	0.2%	10.6
Insulin NPH	———	5.29 (-1.02, 11.61)	1.7%	11.4
Biphasic Insulin	———	4.46 (2.56, 6.54)	0.0%	11.3
Vs. Basal Insulin + Metformin + Sulfonylurea				
Biphasic Insulin + Met + SU	1.43 (-1.25, 4.11)	1.33 (0.17, 2.57)	See above	
TZD + Met + SU	0.86 (0.05, 1.67)	0.90 (-0.26, 2.10)		
DPP-4 Inhibitors + Met + SU	———	-1.47 (-3.86, 1.01)		
α-glucosidase + Met + SU	-0.3 (-2.08, 1.48)	-3.50 (-5.82, -1.07)		
GLP-1 + Met + SU	-3.85 (-4.32, -2.48)	-3.75 (-4.83, -2.59)		
IAsp + Met + SU	3.8 (3.00, 4.60)	3.06 (1.22, 4.95)		
Meglitinide +Met + SU	———	-0.41 (-3.48, 2.73)		
Basal Insulin + Met	———	0.17 (-3.56, 3.94)		
Biphasic Insulin + Met	———	2.40 (0.14, 4.73)		
Insulin NPH + SU	———	1.61 (-0.87, 4.31)		
NPH + Repaglinide + Met	———	1.68 (-2.39, 5.72)		
Insulin NPH	———	2.72 (-3.53, 8.99)		
Biphasic Insulin	2.24 (0.1, 4.39)	1.89 (0.43, 3.57)		
Vs. Biphasic Insulin + Metformin + Sulfonylurea				
TZD + Met + SU	———	-0.42 (-2.01, 1.12)	See above	
DPP-4 Inhibitors +Met + SU	———	-2.80 (-5.42, -0.20)		
α-glucosidase + Met + SU	———	-4.83 (-7.32, -2.29)		
GLP-1 + Met + SU	-5.21 (-5.97, -4.46)	-5.08 (-6.26, -3.92)		
IAsp + Met + SU	1.00 (0.22, 1.78)	1.74 (-0.12, 3.57)		
Meglitinide + Met + SU	———	-1.74 (-4.94, 1.47)		
Basal Insulin + Met	———	-1.15 (-4.83, 2.50)		
Biphasic Insulin + Met	1.3 (0.16, 2.44)	1.07 (-1.10, 3.24)		

DIFFERENCE IN CHANGE FROM BASELINE IN BODY WEIGHT (KG)				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of least weight gain**	**Mean Rank**
Insulin NPH + SU	———	0.28 (-2.47, 3.19)		
NPH + Repaglinide + Met	———	0.35 (-3.66, 4.32)		
Insulin NPH	———	1.39 (-4.96, 7.75)		
Biphasic Insulin	———	0.56 (-1.30, 2.60)		
Vs. TZD + Metformin + Sulfonylurea				
DPP-4 Inhibitors + Met + SU	———	-2.38 (-4.81, 0.09)	See above	
α-glucosidase + Met + SU	———	-4.40 (-6.74, -2.00)		
GLP-1 + Met + SU	———	-4.66 (-6.08, -3.23)		
IAsp + Met + SU	———	2.16 (-0.01, 4.33)		
Meglitinide + Met + SU	———	-1.32 (-4.39, 1.81)		
Basal Insulin + Met	———	-0.73 (-4.59, 3.13)		
Biphasic Insulin + Met	———	1.49 (-0.98, 4.00)		
Insulin NPH + SU	———	0.70 (-2.06, 3.62)		
NPH + Repaglinide + Met	———	0.77 (-3.41, 4.91)		
Insulin NPH	———	1.81 (-4.55, 8.17)		
Biphasic Insulin	———	0.98 (-0.88, 3.03)		
Vs. DPP-4 Inhibitors + Metformin + Sulfonylurea				
α-glucosidase + Met + SU	———	-2.03 (-4.92, 0.90)	See above	
GLP-1 + Met + SU	———	-2.28 (-4.75, 0.18)		
IAsp + Met + SU	———	4.53 (1.53, 7.56)		
Meglitinide + Met + SU	———	1.06 (-2.47, 4.64)		
Basal Insulin + Met	———	1.65 (-2.68, 6.02)		
Biphasic Insulin + Met	———	3.87 (0.67, 7.08)		
Insulin NPH + SU	———	3.08 (-0.38, 6.73)		
NPH + Repaglinide + Met	———	3.15 (-1.48, 7.76)		
Insulin NPH	———	4.19 (-2.38, 10.87)		
Biphasic Insulin	———	3.36 (0.57, 6.33)		
Vs. Alpha-glucosidase inhibitors + Metformin + Sulfonylurea				
GLP-1 + Met + SU	———	-0.25 (-2.64, 2.08)	See above	
IAsp + Met + SU	———	6.56 (3.60, 9.49)		
Repaglinide + Met + SU	3.10 (0.95, 5.25)	3.09 (1.08, 5.09)		
Basal Insulin + Met	———	3.68 (-0.63, 7.96)		
Biphasic Insulin + Met	———	5.90 (2.77, 9.05)		
Insulin NPH + SU	———	5.11 (1.67, 8.67)		
NPH + Repaglinide + Met	———	5.18 (0.61, 9.75)		
Insulin NPH	———	6.22 (-0.43, 12.94)		
Biphasic Insulin	———	5.39 (2.62, 8.29)		
Vs. GLP-1 + Metformin + Sulfonylurea				
IAsp + Met + SU	———	6.82 (4.79, 8.84)	See above	
Meglitinide + Met + SU	———	3.34 (0.24, 6.48)		
Basal Insulin + Met	———	3.93 (0.29, 7.56)		
Biphasic Insulin + Met	6.00 (4.84, 7.16)	6.15 (4.04, 8.27)		
Insulin NPH + SU	———	5.36 (2.66, 8.27)		
NPH + Repaglinide + Met	———	5.43 (1.46, 9.34)		
Insulin NPH	———	6.47 (0.15, 12.83)		

DIFFERENCE IN CHANGE FROM BASELINE IN BODY WEIGHT (KG)				
Treatment	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Probability of least weight gain**	**Mean Rank**
Biphasic Insulin	———	5.64 (3.83, 7.62)		
Vs. IAsp + Metformin + Sulfonylurea				
Meglitinide + Met + SU	———	-3.48 (-7.04, 0.11)	See above	
Basal Insulin + Met	———	-2.89 (-6.93, 1.16)		
Biphasic Insulin + Met	———	-0.67 (-3.42, 2.14)		
Insulin NPH + SU	———	-1.46 (-4.52, 1.82)		
NPH + Repaglinide + Met	———	-1.39 (-5.71, 2.96)		
Insulin NPH	———	-0.35 (-6.81, 6.19)		
Biphasic Insulin	———	-1.18 (-3.48, 1.34)		
Vs. Meglitinide + Metformin + Sulfonylurea				
Basal Insulin + Met	———	0.59 (-4.20, 5.34)	See above	
Biphasic Insulin + Met	———	2.81 (-0.94, 6.50)		
Insulin NPH + SU	———	2.02 (-2.02, 6.16)		
NPH + Repaglinide + Met	———	2.09 (-2.91, 7.11)		
Insulin NPH	———	3.13 (-3.81, 10.16)		
Biphasic Insulin	———	2.30 (-1.11, 5.86)		
Vs. Basal Insulin + Metformin				
Biphasic Insulin + Met	2.20 (-0.05, 4.45)	2.22 (-0.76, 5.17)	See above	
Insulin NPH + SU	———	1.43 (-3.08, 6.07)		
NPH + Repaglinide + Met	1.50 (-0.03, 3.03)	1.50 (-0.94, 3.97)		
Insulin NPH	———	2.54 (-4.70, 9.84)		
Biphasic Insulin	———	1.71 (-2.27, 5.82)		
Vs. Biphasic Insulin + Metformin				
Insulin NPH + SU	———	-0.79 (-4.17, 2.73)	See above	
NPH + Repaglinide + Met	-0.7 (-1.41, 0.01)	-0.72 (-4.08, 2.60)		
Insulin NPH	———	0.32 (-6.30, 6.91)		
Biphasic Insulin	———	-0.51 (-3.18, 2.32)		
Vs. Insulin NPH + Sulfonylurea				
NPH + Repaglinide + Met	———	0.07 (-4.77, 4.81)	See above	
Insulin NPH	1.6 (-0.82, 2.38)	1.11 (-5.19, 7.51)		
Biphasic Insulin	0.90 (0.12, 1.68)	0.28 (-1.75, 2.34)		
Vs. NPH + Meglitinide + Metformin				
Insulin NPH	———	1.04 (-6.41, 8.46)	See above	
Biphasic Insulin	———	0.21 (-4.07, 4.61)		
Vs. Insulin NPH				
Biphasic Insulin	-0.7 (-1.48, 0.08)	-0.83 (-6.90, 5.24)	See above	

CI=confidence interval; **CrI**=credible interval; **DPP-4**=dipeptidyl peptidase-4; **GLP-1**=glucagon-like peptide-1; **IAsp**=insulin aspart; **Met**=metformin; **MTC**=mixed treatment comparison; **NPH**=neutral protamine Hagedorn; **SU**=sulfonylurea; **TZD**=thiazolidinediones; **WMD**=weighted mean difference

APPENDIX 31: MODEL FIT PARAMETERS FOR MTC META-ANALYSES

Analysis	Residual deviance	DIC	Unconstrained data points
Hemoglobin A1C			
Random effects model vs. fixed effects model			
Reference case – random effects model	20.9	10.9	31
Reference case – fixed effects model	56.4	37.7	31
Meta-regression adjusting for:			
Baseline hemoglobin A1C	20.0	10.2	31
Baseline duration of diabetes	21.2	11.7	31
Sensitivity analyses with removal of:			
Cross-over studies	18.6	2.8	28
A1C < 7.0% (inclusion criteria)	19.2	7.1	25
Failed to provide SU dosing at baseline	13.3	7.2	21
Body Weight			
Random effects model vs. fixed effects model			
Reference case – random effects model	19.2	41.9	26
Reference case – fixed effects model	85.8	72.3	26
Meta-regression adjusting for:			
Baseline body mass index	19.3	42.2	26
Sensitivity analyses with removal of:			
Cross-over studies	15.9	31.3	23
A1C < 7.0% (inclusion criteria)	19.2	41.9	21
Failed to provide SU dosing at baseline	13.2	32.1	18

APPENDIX 32: META-REGRESSION COEFFICIENTS FOR A1C AND BODY WEIGHT

Two meta-regression analyses were conducted for hemoglobin A1C to adjust for differences in baseline A1C and duration of diabetes. The estimated regression coefficient is β = -0.18 (95% CI: -0.41, 0.05) in the baseline A1C adjusted model. Although not statistically significant, this finding suggests that studies with a higher mean baseline A1C had larger effect sizes than those with a lower mean baseline A1C. The estimated regression coefficient for the mean duration of diabetes adjusted model [β = -0.01 (95% CI: -0.15, 0.14)] suggests that differences in this particular characteristic did not influence the effect sizes reported in the MTC meta-analysis. Similar to the model for duration of diabetes, adjustments for baseline body mass index did not significantly impact the results of the MTC meta-analysis for change from baseline in body weight [β = 0.16 (-0.14, 0.46)].

The deviance information criterion (DIC) is a statistic that measures model fit and penalizes for complexity. Based on the DIC and residual deviance, the model adjusting for baseline A1C has a lower value than the unadjusted model (DIC, 10.2 vs. 21.6; Residual deviance, 20.0 vs. 31.7). This indicates that adjusting for the covariate - baseline hemoglobin A1C - improves model fit and explains some heterogeneity/inconsistency in the meta-analysis.

Table 25: Regression-coefficients

Outcome	Meta-regression parameter	Regression coefficient	DIC	RD
Hemoglobin A1C	Baseline hemoglobin A1C	β = -0.18 (-0.41, 0.05)	10.2	20.0
Hemoglobin A1C	Duration of diabetes	β = -0.01 (-0.15, 0.14)	11.7	21.2
Body weight	Baseline body mass index	β = 0.16 (-0.14, 0.46)	42.2	19.3
DIC=deviance information criterion, **RD**=residual deviance				

APPENDIX 33: DEFINITIONS OF OVERALL, SEVERE, AND NOCTURNAL HYPOGLYCEMIA FROM RCTS

Study	Overall Hypoglycemia	Severe Hypoglycemia	Nocturnal Hypoglycemia
Aljabri et al, 2004[10]	Hypoglycemia was defined as a glucose meter value of > 68 mg/dL	Severe hypoglycemia was defined as low glucose levels resulting in loss of consciousness or requiring assistance for treatment	Not Reported
Al-Shaikh, 2006[12]	Not Reported	Not Reported	Not Reported
Bergenstal et al, 2009[14]	minor hypo: BG < 3.1 mmo/l with or without hypoglycemia	BG < 3.1 mmol/l and requiring 3rd person assistance	Not Reported
Berhanu et al, 2007[16]	SMBG < 60 mg/dl or Laboratory value < 70 mg/dl, more than two simultaneous hypoglycemic symptoms relieved by oral glucose containing substance or resulting in needing assistance from simple tasks	Not Reported	Not Reported
Charpentier et al, 2009[20]	Not Reported	Not Reported	Not Reported
Dailey et al, 2004[22]	Documented blood glucose concentrations ≤ 50 mg/dL in association with symptoms of hypoglycemia	Required pharmacologic treatment or necessitated third-party assistance.	Not Reported
Davies et al, 2007[24]	symptomatic: if clinical symptoms were confirmed by a home BG reading of < 3.5 mmol/L asymptomatic: no symptoms but a reading of < 3.5 mmol/L	Symptoms consistent with hypoglycemia requiring 3rd party assistance with BG < 2.8 mmol/L or if prompt recovery after oral carbohydrate, IV glucose or glucagon administration	Hypoglycemia occurring while the patient was asleep between the evening injection and breakfast.
De Mattia et al, 2009[26]	Not Reported	Not Reported	Not Reported
Derosa et al[28]	Not Reported	Not Reported	Not Reported
Dorkhan et al, 2009[30]	Not Reported	Not Reported	Not Reported
Esposito et al, 2008[32]	Biochemical hypoglycemia (symptomatic or aymptomatic) as a documented glucose level less than 4.0 mmol/l (<72 mg/dL).	Symptoms consistent with hypoglycemia requiring the assistance of another person and that were associated with either a plasma glucose level ≤ 3.1 mmol/l (56 mg/dL) or with prompt recovery after oral carbohydrate, i.v. glucose or glucagon administration.	Hypoglycemia occurring after the bedtime injection and before the participant awakened in the morning.

Study	Overall Hypoglycemia	Severe Hypoglycemia	Nocturnal Hypoglycemia
Gao et al, 2009[34]	Any time a patient experienced a sign or symptom of hypoglycemia or documented blood glucose level < 3.3 mmol/L during self-monitoring, whether or not this level was associated with signs, symptoms, or treatment.	As an episode with symptoms in which the patients required assistance of another person and was associated with either a glucose level of < 2.8 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or intramuscular glucagon.	Not Reported
Goudswaard et al, 2004[36]	Symptoms with or without blood glucose reading < 4.0 mmol/L (results presented separately)	Unconsciousness and support needed from a third party	Not Reported
Hartemann-Heurtier et al, 2009[38]	Not Reported	Not Reported	Not Reported
Heine et al, 2005[40] Boye et al, 2006[18]	Not Reported	Not Reported	Not Reported
Hermansen et al, 2007[41]	Not Reported	Not Reported	Not Reported
Holman et al, 2007[43]	Grade 1: if a patient had symptoms with a self-measured capillary glucose level of 3.1 mmol/l or more; Grade 2 (minor): if the patient had symptoms with a self-measured capillary glucose level of less than 3.1 mmol/l	Grade 3 (major): if third party assistance was required	Not Reported
Janka et al, 2005[11] Janka et al, 2007[13]	Hypoglycemia was considered confirmed if documented by a BG level less than 60 mg/dL (< 3.3 mmol/l)	Symptoms consistent with hypoglycemia that required the assistance of another person and associated with a BG level <36 mg/dl (<2.0 mmol/l) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon	Not Reported
Kendall et al, 2005[15]	For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value (< 3.33 mmol/l).	For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.	Not Reported
Ko et al, 2006[17]	Not Reported	Not Reported	Not Reported
Lam et al, 1998[19]	Not Reported	Not Reported	Not Reported
Lopez-Alvarenga et al, 1999[21]	Not Reported	Not Reported	Not Reported
Milicevic et al, 2009[23]	Not Reported	Not Reported	Not Reported
Nauck et al, 2007[25]	Any time a patient experienced a sign or symptom of hypoglycemia or noted blood glucose level <3.4 mmol/l (60 mg/dl) during self monitoring, whether or not this level was associated with signs, symptoms or treatment. The severity (mild, moderate or severe) and timing (nocturnal or daytime) of each hypoglycemic event and whether it could be attributed to therapy (yes or no) were assessed by the investigator.		
Ovalle et al, 2004[27]	Not Reported	Not Reported	Not Reported

Study	Overall Hypoglycemia	Severe Hypoglycemia	Nocturnal Hypoglycemia
Reynolds et al, 2007[29]	A blood glucose value <70 mg/dl or events characterized by typical symptoms and relieved by feeding	Required third party assistance during a hypoglycemic episode	Not Reported
Rosenstock et al, 2006[31] Vinik et al, 2007[42]	Confirmed symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia (confirmed with a meter reading); Confirmed or documented hypoglycemia was defined as plasma glucose levels <70 mg/dl (<3.9 mmol/l), <50 mg/dl (<2.8 mmol/l), or <36 mg/dl (<2.0 mmol/l)	Requiring assistance with either a plasma glucose level <36 mg/dl (<2.0 mmol/l) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration	Symptomatic hypoglycemia occurring after the evening insulin injection and before getting up in the morning.
Ross et al, 2001[33]	Blood glucose < 3 mmol/L or development of typical hypoglycemic symptoms	Event requiring assistance by another person, coma, or seizure	Not Reported
Russell-Jones et al, 2009[35]	Symptoms and plasma glucose <3.1 mmol/L	3rd party medical assistance required	Not Reported
Standl et al, 2001[37]	Not Reported	Not Reported	Not Reported
Stehouwer et al, 2003[39]	Not Reported	Not Reported	Not Reported
Strojek et al, 2009[45]	Minor – self-measured plasma glucose < 3.1 mmol/L and symptoms only – symptoms that are considered to be related to hypoglycemia with or without confirmation by plasma glucose ≥ 3.1mmol/L.	An event requiring the assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions.	Hypoglycemic episode occurring from 00:00 to 06:00.
Yki-Jarvinen et al, 2006[44]	Biochemical hypoglycemia was defined as a plasma glucose level ≤ 4 mmol/l.	An event with symptoms consistent with hypoglycemia during which the subject required the assistance of another person and which was associated with either a plasma glucose level ≤ 3.1 mmol/l or with prompt recovery after oral carbohydrate, i.v. glucose or glucagon administration.	Not Reported
BG=blood glucose, **i.v.**=intravenous			

APPENDIX 34: SUMMARY OF TRIALS REPORTING SEVERE HYPOGLYCEMIA

Study	Severe Hypoglycemia				
	Treatment 1	n/N	Treatment 2	n/N	OR (95%CI)
Aljabri, 2004[10]	TZD + M + S	0/30	Basal + M + S	0/28	Not estimable
Al-Shaikh, 2006[12]	Biphasic Insulin	NR	Basal + M + S	NR	NR
Bergenstal, 2009[14]	GLP-1 + M + S	0/124	Biphasic QD + M + S	4/124	0.11 (0.01, 2.02)
Bergenstal, 2009[14]	Biphasic BID + M	6/124	GLP-1 + M + S	0/124	13.66 (0.76, 245.12)
Bergenstal, 2009[14]	Biphasic BID + M	6/124	Biphasic QD + M + S	4/124	1.53 (0.42, 5.54)
Berhanu, 2007[16]	Insulin + TZD + M	4/110	Insulin + Placebo + M	0/112	9.51 (0.51, 178.71)
Charpentier, 2009[20]	TZD + M + S	NR	Placebo + M + S	NR	NR
Dailey, 2004[22]	TZD + M + S	0/181	Placebo + M + S	0/184	Not estimable
Davies, 2007[24]	Biphasic + M	0/27	Basal + M	0/29	Not estimable
Davies, 2007[24]	NPH + Meg + M	1/26	Basal + M	0/29	3.47 (0.14, 88.99)
Davies, 2007[24]	NPH + Meg + M	1/26	Biphasic + M	0/27	3.24 (0.13, 83.08)
De Mattia, 2009[26]	IGlar + M + S	0/20	NPH + M + S	0/20	Not estimable
Derosa, 2009[28]	Meg + M + S	NR	AGI + M + S	NR	NR
Dorkhan, 2009[30]	Basal + M + S	NR	TZD + M + S	NR	NR
Gao, 2009[34]	GLP-1 + M + S	2/189	Placebo + M + S	0/186	4.97 (0.24, 104.29)
Goudswaard, 2004[36]	Biphasic Insulin	1/31	Basal + M + S	0/33	3.30 (0.13, 83.97)
Hartemann-Heurtier, 2009[38]	TZD + M + S	0/14	Basal + M + S	0/13	Not estimable
Heine, 2005[40]	GLP-1 + M + S	4/282	Basal + M + S	4/267	0.95 (0.23, 3.82)
Hermansen, 2007[41]	DPP-4 + M + S	0/116	Placebo + M + S	0/113	Not estimable
Holman, 2007[43]	IAsp + M + S	16/238	Basal + M + S	4/234	4.14 (1.36, 12.59)
Holman, 2007[43]	IAsp + M + S	16/238	Biphasic + M + S	11/235	1.47 (0.67, 3.23)
Holman, 2007[43]	Biphasic + M + S	11/235	Basal + M + S	4/234	2.82 (0.89, 9.00)
Janka, 2005[11]	Biphasic Insulin	NR	Basal + M + S	0/177	N/A
Janka, 2007[13]	Biphasic Insulin	NR	Basal + M + S	0/67	N/A
Kendall, 2005[15]	GLP-1 (5 µg BID and 10ug. Bid) + M + S	1/486	Placebo + M + S	0/247	1.53 (0.06, 37.68)
Ko, 2006[17]	TZD + M + S	NR	Basal + M + S	NR	N/A
Lam, 1998[19]	AGI + M + S	1/41	Placebo + M + S	0/40	3.00 (0.12, 75.85)
Lopez-Alvarenga, 1999[21]	AGI + M + S	NR	Placebo + M + S	NR	N/A
Lopez-Alvarenga, 1999[21]	Basal + M + S	NR	Placebo + M + S	NR	N/A
Lopez-Alvarenga, 1999[21]	AGI + M + S	NR	Basal + M + S	NR	N/A
Milicevic, 2009[23]	Biphasic Insulin	2/68	Basal + S	0/67	5.08 (0.24, 107.72)
Nauck, 2007[25]	GLP-1 + M + S	0/253	Biphasic + M + S	0/248	Not estimable

Study	Severe Hypoglycemia				
	Treatment 1	n/N	Treatment 2	n/N	OR (95%CI)
Ovalle, 2004[27]	Biphasic + M + S	NR	TZD + M + S	NR	NR
Reynolds, 2007[29]	Basal + M + S	0/18	TZD + M + S	0/17	Not estimable
Rosenstock, 2006[31]	TZD + M + S	6/112	Basal + M + S	3/104	1.91 (0.46, 7.82)
Ross, 2009[33]	Insulin lispro + NPH	NR	HI + NPH	NR	NR
Russell-Jones, 2009[35]	GLP-1 + M + S	5/230	Placebo + M + S	0/114	5.59 (0.31, 101.89)
Russell-Jones, 2009[35]	Basal + M + S	0/232	Placebo + M + S	0/114	Not estimable
Russell-Jones, 2009[35]	GLP-1 + M + S	5/230	Basal + M + S	0/232	11.34 (0.62, 206.30)
Standl, 2001[37]	AGI + M + S	0/65	Placebo + M + S	0/68	Not estimable
Stehouwer, 2003[39]	Basal insulin	0/88	Basal + S	0/86	Not estimable
Stehouwer, 2003[39]	Biphasic Insulin	0/87	Basal + S	0/88	Not estimable
Stehouwer, 2003[39]	Basal insulin	0/88	Biphasic Insulin	0/87	NR
Strojek, 2009[45]	Biphasic + M + S	3/231	Basal + M + S	2/238	NR

AGI=alpha glucosidase inhibitor, **Basal**=basal insulin, **BID**=twice daily, **biphasic**=biphasic insulin, **DPP**=dipeptidyl peptidase, **GLP**=glucagon-like peptide, **HI**=human insulin, **iGlar**=insulin glargine, **IAsp**=insulin aspart, **Meg**=meglitinide, **M**=metformin, **n**=number of patients with an event, **N**=total number of patients, **NPH**=neutral protamine Hagedorn, **NR**=not reported, **QD**=at bedtime, **RR**=relative risk , **S**=ulfonylurea, **TZD**=thiazolidinediones

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APPENDIX 35: SUMMARY OF TRIALS REPORTING OVERALL HYPOGLYCEMIA

Study	Overall Hypoglycemia				
	Treatment 1	n/N	Treatment 2	n/N	OR (95%CI)
Aljabri, 2004[10]	TZD + M + S	11/30	Basal + M + S	19/28	0.27 (0.09, 0.81)
Al-Shaikh, 2006[12]	Biphasic Insulin	NR	Basal + M + S	NR	NR
Bergenstal, 2009[14]	GLP-1 + M + S	36/124	Biphasic QD + M + S	69/124	0.33 (0.19, 0.55)
Bergenstal, 2009[14]	Biphasic BID + M	76/124	GLP-1 + M + S	36/124	3.87 (2.28, 6.58)
Bergenstal, 2009[14]	Biphasic BID + M	76/124	Biphasic QD + M + S	69/124	1.26 (0.76, 2.09)
Berhanu, 2007[16]	Insulin + TZD + M	51/110	Insulin + Placebo + M	35/112	1.90 (1.10, 3.29)
Charpentier, 2009[20]	TZD + M + S	35/145	Placebo + M + S	11/154	4.14 (2.01, 8.51)
Dailey, 2004[22]	TZD + M + S	40/181	Placebo + M + S	6/184	8.42 (3.47, 20.41)
Davies, 2007[24]	Biphasic + M	8/27	Basal + M	7/29	1.32 (0.40, 4.33)
Davies, 2007[24]	NPH + Meg + M	4/26	Basal + M	7/29	0.57 (0.15, 2.23)
Davies, 2007[24]	NPH + Meg + M	4/26	Biphasic + M	8/27	0.43 (0.11, 1.66)
De Mattia, 2009[26]	IGlar + M + S	15/20	NPH + M + S	13/20	0.62 (0.16, 2.43)
Derosa, 2009[28]	Meg + M + S	NR	AGI + M + S	NR	NR
Dorkhan, 2009[30]	Basal + M + S	NR	TZD + M + S	NR	NR
Gao, 2009[34]	GLP-1 + M + S	NR	Placebo + M + S	NR	NR
Goudswaard, 2004[36]	Biphasic Insulin	NR	Basal + M + S	NR	NR
Hartemann-Heurtier, 2009[38]	TZD + M + S	6/14	Basal + M + S	10/13	0.23 (0.04, 1.19)
Heine, 2005[40]	GLP-1 + M + S	NR	Basal + M + S	NR	NR
Hermansen, 2007[41]	DPP-4 + M + S	19/116	Placebo + M + S	1/113	21.94 (2.88, 166.90)
Holman, 2007[43]	IAsp + M + S	229/238	Basal + M + S	173/234	8.97 (4.34, 18.56)
Holman, 2007[43]	IAsp + M + S	229/238	Biphasic + M + S	216/235	2.24 (0.99, 5.05)
Holman, 2007[43]	Biphasic + M + S	216/235	Basal + M + S	173/234	4.01 (2.31, 6.96)
Janka, 2005[11]	Biphasic Insulin	127/187	Basal + M + S	109/177	1.32 (0.86, 2.03)
Janka, 2007[13]	Biphasic Insulin	NR	Basal + M + S	NR	NR
Kendall, 2005[15]	GLP-1 (5 µg BID and 10ug. Bid) + M + S	114/486	Placebo + M + S	31/247	2.14 (1.39, 3.29)
Ko, 2006[17]	TZD + M + S	0/56	Basal + M + S	5/56	0.08 (0.00, 1.54)
Lam, 1998[19]	AGI + M + S	NR	Placebo + M + S	NR	NR
Lopez-Alvarenga, 1999[21]	AGI + M + S	NR	Placebo + M + S	0/19	NR
Lopez-Alvarenga, 1999[21]	Basal + M + S	NR	Placebo + M + S	0/19	NR
Lopez-Alvarenga, 1999[21]	AGI + M + S	NR	Basal + M + S	NR	NR
Milicevic, 2009[23]	Biphasic Insulin	NR	Basal + S	NR	NR
Nauck, 2007[25]	GLP-1 + M + S	NR	Biphasic + M + S	NR	NR

Study	Overall Hypoglycemia				
	Treatment 1	n/N	Treatment 2	n/N	OR (95%CI)
Ovalle, 2004[27]	Biphasic + M + S	NR	TZD + M + S	NR	NR
Reynolds, 2007[29]	Basal + M + S	NR	TZD + M + S	NR	NR
Rosenstock, 2006[31]	TZD + M + S	47/112	Basal + M + S	57/104	0.60 (0.35, 1.02)
Ross, 2009[33]	Insulin lispro + NPH	NR	HI + NPH	NR	NR
Russell-Jones, 2009[35]	GLP-1 + M + S	63/230	Placebo + M + S	19/114	1.89 (1.07, 3.34)
Russell-Jones, 2009[35]	Basal + M + S	67/232	Placebo + M + S	19/114	2.03 (1.15, 3.58)
Russell-Jones, 2009[35]	GLP-1 + M + S	63/230	Basal + M + S	67/232	0.93 (0.62, 1.39)
Standl, 2001[37]	AGI + M + S	0/65	Placebo + M + S		Not estimable
Stehouwer, 2003[39]	Basal insulin	63/88	Basal + S	53/86	1.57 (0.83, 2.96)
Stehouwer, 2003[39]	Biphasic Insulin	63/87	Basal + S	53/86	1.63 (0.86, 3.10)
Stehouwer, 2003[39]	Basal insulin	63/88	Biphasic Insulin	63/87	1.04 (0.54, 2.02)
Strojek, 2009[45]	Biphasic + M + S	133/231	Basal + M + S	122/238	1.29 (0.90, 1.86)

AGI=alpha glucosidase inhibitor, **Basal**=basal insulin, **BID**=twice daily, **biphasic**=biphasic insulin, **DPP**=dipeptidyl peptidase, **GLP**=glucagon-like peptide, **HI**=human insulin, **iGlar**=insulin glargine, **IAsp**=insulin aspart, **Meg**=meglitinide, **M**=metformin, **n**=number of patients with an event, **N**=total number of patients, **NPH**=neutral protamine Hagedorn, **NR**=not reported, **QD**=at bedtime, **RR**=relative risk , **S**=ulfonylurea, **TZD**=thiazolidinediones

APPENDIX 36: FOREST PLOTS FOR HYPOGLYCEMIA FROM INDIVIDUAL RCTS

Figure A: Overall Hypoglycemia for Placebo-controlled Trials

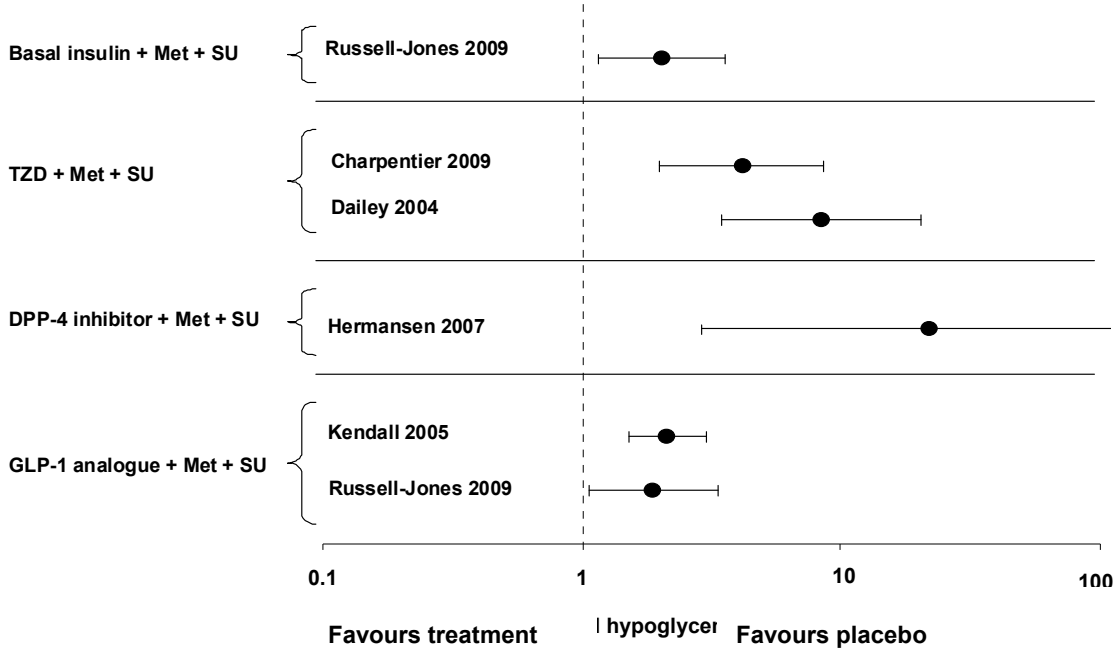
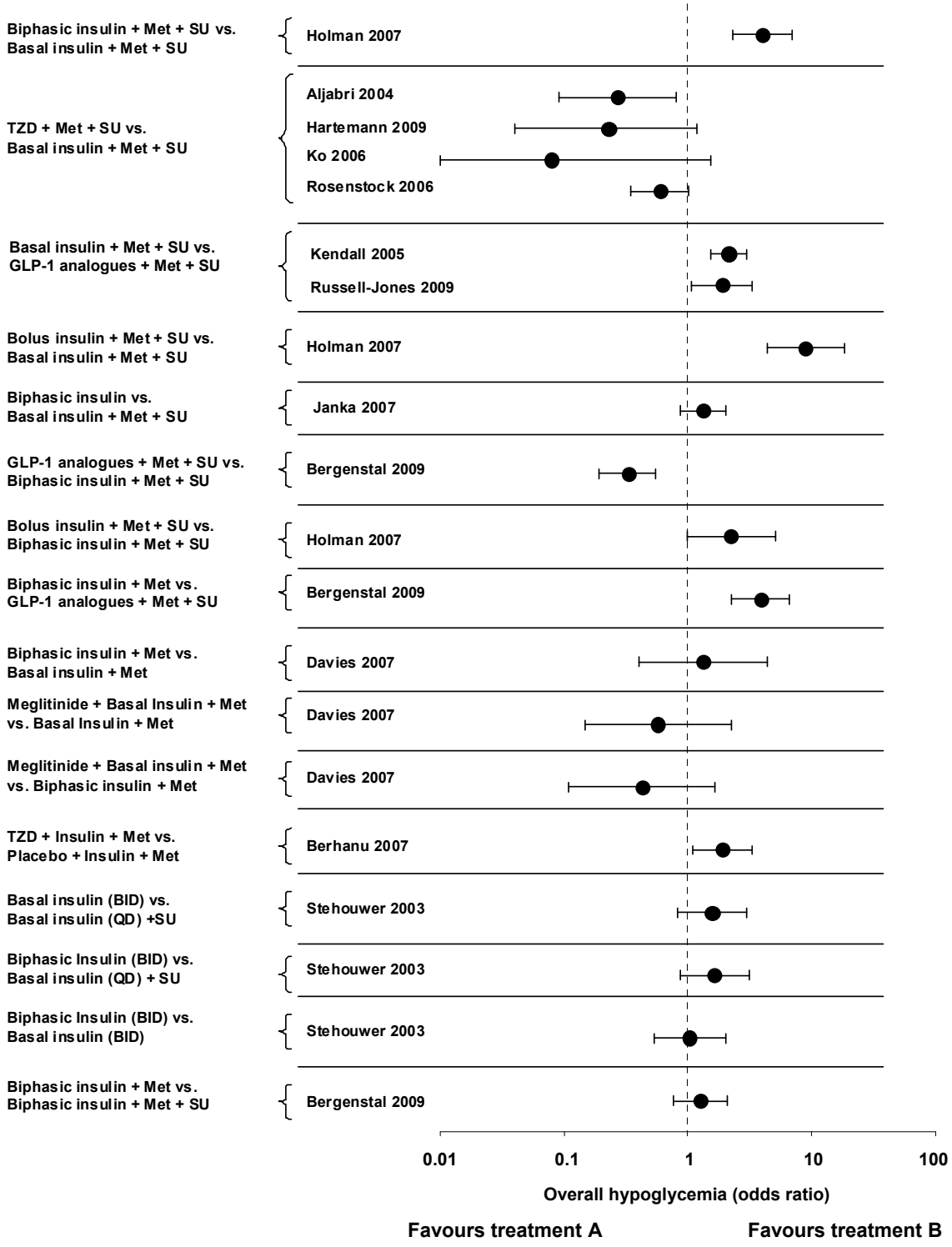


Figure B: Overall Hypoglycemia for Active Comparisons (A vs. B)



8 REFERENCES

1. 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
2. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with type 2 diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis [DRAFT]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 2).
3. Canadian Agency for Drugs and Technologies in Health. Optimal therapy recommendations for the prescribing and use of second-line therapy for patients with type 2 diabetes inadequately controlled on metformin [Internet]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 5). [cited 2010 Aug 6]. Available from: http://www.cadth.ca/media/pdf/C1110_OT_Reccommendations_final_e.pdf
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med. 2004;116(4):230-5.
11. 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. 2005 Feb;28(2):254-9.
12. Al-Shaikh AR. Comparison of basal insulin added to oral agents versus twice - daily premixed insulin as initial insulin therapy for type 2 diabetes. Pakistan Journal of Medical Sciences [Internet]. 2006 [cited 2009 Dec 9];22(1):14-7. Available from: http://pjms.com.pk/issues/janmar06/pdf/comparison.pdf
13. Janka HU, Plewe G, Busch K. Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. J Am Geriatr Soc. 2007 Feb;55(2):182-8.
14. Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V, et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Curr Med Res Opin. 2009 Jan;25(1):65-75.
15. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005 May;28(5):1083-91.

16. Berhanu P, Perez A, Yu S, Spanheimer R. Effect of pioglitazone in combination with insulin therapy on glycaemic control, insulin dose requirement and lipid profile in patients with type 2 diabetes previously poorly controlled with combination therapy. Diabetes Obes Metab. 2007;9(4):512-20.

17. Ko GTC, Tsang PCC, Wai HPS, Kan ECY, Chan HCK. Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: A 1-year randomized clinical trial. Adv Ther. 2006;23(5):799-808.

18. 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

19. 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

20. Charpentier G, Halimi S. Earlier triple therapy with pioglitazone in patients with type 2 diabetes. Diabetes Obes Metab. 2009 Jul 13;11(9):844-54.

21. Lopez-Alvarenga JC, Aguilar-Salinas CA, Velasco-Perez ML, rita-Melzer O, Guillen LE, Wong B, et al. Acarbose vs. bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. Diabetes Obes Metab. 1999 Jan;1(1):29-35.

22. Dailey GEI, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004 Feb 15;116(4):223-9.

23. Milicevic Z, Hancu N, Car N, Ivanyi T, Schwarzenhofer M, Jermendy G. Effect of Two Starting Insulin Regimens in Patients with Type II Diabetes not Controlled on a Combination of Oral Antihyperglycemic Medications. Exp Clin Endocrinol Diabetes. 2009 Mar 19;117(5):223-9.

24. 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.

25. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia. 2007 Feb;50(2):259-67.

26. 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.

27. Ovalle F, Bell DS. Effect of rosiglitazone versus insulin on the pancreatic beta-cell function of subjects with type 2 diabetes. Diabetes Care. 2004 Nov;27(11):2585-9.

28. Derosa G, Salvadeo SA, D'Angelo A, Ferrari I, Mereu R, Palumbo I, et al. Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double-blind, cross-over, clinical trial. Curr Med Res Opin. 2009 Mar;25(3):607-15.

29. 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.

30. 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. Cardiovasc diabetol [Internet]. 2009 [cited 2009 Dec 4];8(15). Available from: http://www.cardiab.com/content/pdf/1475-2840-8-15.pdf

31. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G, et al. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care [Internet]. 2006 [cited 2009 Dec 4];29(3):554-9. Available from: http://care.diabetesjournals.org/cgi/reprint/29/3/554

32. Esposito K, Ciotola M, Maiorino MI, Gualdiero R, Schisano B, Ceriello A, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med. 2008 Oct 21;149(8):531-9.

33. Ross SA, Zinman B, Campos RV, Strack T, Canadian Lispro Study Group. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Invest Med. 2001 Dec;24(6):292-8.

34. 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.

35. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009 Oct;52(10):2046-55.

36. 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

37. Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch L. Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. Diabetes Res Clin Pract. 2001 Mar;51(3):205-13.

38. Hartemann-Heurtier A, Halbron M, Golmard JL, Jacqueminet S, Bastard JP, Rouault C, et al. Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract. 2009 Oct;86(1):37-43.

39. Stehouwer MH, DeVries JH, Lumeij JA, Ader HJ, Engbers AM, van Iperen A, et al. Combined bedtime insulin--daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypoglycaemia rate--a randomised trial. Diabetes Metab Res Rev. 2003 Mar;19(2):148-52.

40. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med [Internet]. 2005 Oct 18 [cited 2009 Dec 3];143(8):559-69. Available from: http://www.annals.org/content/143/8/559.full.pdf+html

41. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007 Sep;9(5):733-45.

42. Vinik AI, Zhang Q. Adding insulin glargine versus rosiglitazone: health-related quality-of-life impact in type 2 diabetes. Diabetes Care. 2007;30(4):795-800.

43. 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

44. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, Vahatalo M, Virtamo H, Nikkila K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia. 2006 Mar;49(3):442-51.

45. Strojek K, Bebakar WM, Khutsoane DT, Pesic M, Smahelova A, Thomsen HF, et al. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. Curr Med Res Opin. 2009 Dec;25(12):2887-94.

46. Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A, Bartusch-Marrain P, Egger T, et al. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes Metab Res Rev. 2005;21(6):545-53.

47. 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

48. 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.

49. 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.

50. The prevalence and costs of diabetes [Internet]. Toronto: Canadian Diabetes Association; 2007. Pub no. 114007 06-295 06/06 Q-50M. [cited 2009 Aug 24]. Available from: http://www.diabetes.ca/Files/prevalence-and-costs.pdf

51. 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

52. 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.

53. 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

54. 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.

55. Genuth S. The UKPDS and its global impact. Diabet Med. 2008 Aug;25 Suppl 2:57-62.

56. Utilization of oral antiglycemics in Canada. [unpublished dataset]. Ottawa (ON): Brogan, Inc.; 2008.

57. 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.

58. 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

72. Product monograph: Victoza liraglutide 6 mg/ml solution for injection in a pre-filled pen. Mississauga (ON): Novo Nordisk Canada Inc.; 2010 May 21.

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

74. 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

75. 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

76. 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

77. 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

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

79. 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

80. 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.

81. Metformin. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

82. Antidiabetics. In: Sweetman SC, editor. Martindale: the complete drug reference. Chicago (IL): Pharmaceutical Press; 2007. p. 390-421.

83. Metformin: drug information [Internet]. 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.

84. 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.

85. Chlorpropramide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

86. Gliclazide: drug information [Internet]. Version 17.1. In: UpToDate. Waltham (MA): UpToDate, Inc; 2009 [cited 2009 Jun 23]. Available from: http://www.uptodate.com/home/index.html Subscription required.

87. Tolbutamide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

88. Glipizide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

89. Gylburide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

90. Glimeprimide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

91. Levetan C. Oral antidiabetic agents in type 2 diabetes. Curr Med Res Opin. 2007;23(4):945-52.

92. Pioglitazone [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

93. Rosiglitazone [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

94. Repaglinide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

95. Nateglinide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

96. Acarbose [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

97. 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.

98. Exenatide [Internet]. In: Dynamed. Ipswich (MA): EBSCO Industries, Inc.; 2009 [cited 2010 May 17]. Available from: http://www.ebscohost.com/dynamed/ Subscription required.

99. Sitagliptin: drug information [Internet]. 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.

100. 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/.

101. 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

102. 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.

103. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009 Oct 29;361(18):1736-47.

104. Mills E, Wu P, Seely D, Guyatt G. Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. Journal of Pineal Research. 2005;39(4):360-6.

105. Canadian Agency for Drugs and Technologies in Health. Rapid-acting insulin analogues for the treatment of diabetes mellitus: meta-analyses of clinical outcomes [Internet]. Ottawa: The Agency; 2008 Jan. (Optimal therapy report; vol. 2 no. 2). [cited 2008 Apr 9]. Available from: http://cadth.ca/media/compus/reports/compus_Rapid-Acting-Insulin-Analogues-Report_Clinical=Outcomes.pdf

106. Canadian Agency for Drugs and Technologies in Health. Long-acting insulin analogues for the treatment of diabetes mellitus: meta-analyses of clinical outcomes [Internet]. Ottawa: The Agency; 2008 Mar. (Optimal therapy report; vol. 2 no. 1). [cited 2008 Apr 9]. Available from: http://cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf

107. Canadian Agency for Drugs and Technologies in Health. Systematic review of use of blood glucose test strips for the management of diabetes mellitus [Internet]. Ottawa: The Agency; 2009. (Optimal therapy report; vol. 3 no. 2). [cited 2009 Oct 9]. Available from: http://www.cadth.ca/media/pdf/BGTS_SR_Report_of_Clinical_Outcomes.pdf

108. Strojek K, Bebakar WMW, Khutsoane DT, Pesic M, Smahelova A, Thomsen HF, et al. Once-Daily Initiation with NovoMix (R) 30 (BIAsp 30) vs Insulin Glargine in Patients with Type 2 Diabetes Inadequately Controlled with Oral Drugs: A Randomized Controlled Trial [abstract]. Diabetes. 2009;58(Suppl 1):A146, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

109. 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.

110. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care. 2000;23(11):1605-11.

111. WHO Consultation on Obesity (1999: Geneva, Switzerland). Obesity: preventng and managing the gloabal epidemic: report of a WHO consultation [Internet]. Geneva: World Health Organization (WHO); 2000. (WHO technical report series; 894). [cited 2009 Nov 29]. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_894.pdf

112. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med. 1987 Oct;147(10):1749-53.

113. Fujioka K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, et al. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2000 Jun;2(3):175-87.

114. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. Diabet Med [Internet]. 2008 Mar [cited 2010 Jan 22];25(3):245-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2327221

115. 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.

116. 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.

117. 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

118. 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.

119. 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

120. 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.

121. FDA news release: FDA approves new drug treatment for type 2 diabetes [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2009 Jul 31. [cited 2010 Mar 9]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm174780.htm

122. Edwards KL, Alvarez C, Irons BK, Fields J. Third-line agent selection for patients with type 2 diabetes mellitus uncontrolled with sulfonylureas and metformin. Pharmacotherapy. 2008 Apr;28(4):506-21.

123. 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.

124. 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.

125. 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.

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

127. 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

128. 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.

129. 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.

130. 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.

131. Kokic S, Bukovic D, Radman M, Capkun V, Gabric N, Lesko V, et al. Lispro insulin and metformin versus other combination in the diabetes mellitus type 2 management after secondary oral antidiabetic drug failure. Coll Antropol. 2003 Jun;27(1):181-7.

132. 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

133. 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.

134. Kann PH, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes. 2006;114(9):527-32.

135. 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.

136. Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. Health Qual Life Outcomes. 2007;5:8.

137. 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.

138. Derosa G, Cicero AF, D'Angelo A, Gaddi A, Ciccarelli L, Piccinni MN, et al. Effects of 1 year of treatment with pioglitazone or rosiglitazone added to glimepiride on lipoprotein (a) and homocysteine concentrations in patients with type 2 diabetes mellitus and metabolic syndrome: a multicenter, randomized, double-blind, controlled clinical trial. Clin Ther. 2006 May;28(5):679-88.

139. Fonseca VA, Theuma P, Mudaliar S, Leissinger CA, Clejan S, Henry RR. Diabetes treatments have differential effects on nontraditional cardiovascular risk factors. J Diabetes Complications. 2006 Jan;20(1):14-20.

140. Md Isa SH, Najihah I, Nazaimoon WM, Kamarudin NA, Umar NA, Mat NH, et al. Improvement in C-reactive protein and advanced glycosylation end-products in poorly controlled diabetics is independent of glucose control. Diabetes Res Clin Pract. 2006 Apr;72(1):48-52.

141. 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.

142. 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.

143. 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

144. 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.

145. 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

146. 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.

147. 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.

148. 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.

149. 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.

150. 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

151. 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

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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

161. 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

162. 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.

163. 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.

164. 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.

165. 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.

166. 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.

167. 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.

168. 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.

169. 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.

170. 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.

171. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009 Jul 4;374(9683):39-47.

172. Velojic-Golubovic M, Mikic D, Pesic M, Dimic D, Radenkovic S, Antic S. Biphasic insulin aspart 30: better glycemic control than with premixed human insulin 30 in obese patients with Type 2 diabetes. J Endocrinol Invest. 2009 Jan;32(1):23-7.

173. Buse JB, Wolffenbuttel BHR, Herman WH, Shemonsky NK, Jiang HH, Fahrbach JL, et al. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: Safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. Diabetes Care. 2009;32(6):1007-13.

174. Raskin P, Lewin A, Reinhardt R, Lyness W. Twice-daily dosing of a repaglinide/metformin fixed-dose combination tablet provides glycaemic control comparable to rosiglitazone/metformin tablet. Diabetes Obes Metab. 2009 May 19;947-52.

175. Raskin P, Lewin A, Reinhardt R, Lyness W. Twice-daily and three-times-daily dosing of a repaglinide/metformin fixed-dose combination tablet provide similar glycaemic control. Diabetes Obes Metab. 2009 Jun 16;11(10):947-52.

176. Raskin P, Matfin G, Schwartz SL, Chaykin L, Chu PL, Braceras R, et al. Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: The ACTION Study (Achieving Control Through Insulin plus Oral ageNts). Diabetes Obes Metab. 2009 Jan;11(1):27-32.

177. Derosa G, D'Angelo A, Salvadeo SA, Ferrari I, Gravina A, Fogari E, et al. Sibutramine effect on metabolic control of obese patients with type 2 diabetes mellitus treated with pioglitazone. Metabolism. 2008 Nov;57(11):1552-7.

178. Civera M, Merchante A, Salvador M, Sanz J, Martinez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. Diabetes Res Clin Pract. 2008 Jan;79(1):42-7.

179. Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther. 2007 Nov;29(11):2349-64.

180. Vahatalo M, Ronnemaa T, Viikari J. Recognition of fasting or overall hyperglycaemia when starting insulin treatment in patients with type 2 diabetes in general practice. Scand J Prim Health Care. 2007 Sep;25(3):147-53.

181. Relationship of body size and shape to the development of diabetes in the diabetes prevention program. Obesity (Silver Spring). 2006 Nov;14(11):2107-17.

182. Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care. 1995 Mar;18(3):307-14.

183. Miyashita Y, Nishimura R, Nemoto M, Matsudaira T, Kurata H, Yokota T, et al. Prospective randomized study for optimal insulin therapy in type 2 diabetic patients with secondary failure. Cardiovascular Diabetology. 2008;7(16).

184. 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;49(17):1772-80.

185. Martens FMAC, Visseren FLJ, De Koning EJP, Rabelink TJ. Short-term pioglitazone treatment improves vascular function irrespective of metabolic changes in patients with type 2 diabetes. J Cardiovasc Pharmacol. 2005;46(6):773-8.

186. Soonthornpun S, Thamprasit A, Rattarasarn C, Leetanaporn K. Effect of acarbose in treatment of type II diabetes mellitus: A double- blind, crossover, placebo-controlled trial. J Med Assoc Thai. 1998;81(3):195-200.

187. Rodier M, Colette C, Gouzes C, Michel F, Crastes de Paulet A, Monnier L. Effects of insulin therapy upon plasma lipid fatty acids and platelet aggregation in NIDDM with secondary failure to oral antidiabetic agents. Diabetes Res Clin Pract. 1995;28(1):19-28.

188. Malloy J, Capparelli E, Gottschalk M, Guan X, Kothare P, Fineman M. Pharmacology and tolerability of a single dose of exenatide in adolescent patients with type 2 diabetes mellitus being treated with metformin: a randomized, placebo-controlled, single-blind, dose-escalation, crossover study. Clin Ther. 2009 Apr;31(4):806-15.

189. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009;32(7):1224-30.

190. Biswas RK, Paul K, Mukherjee AK, Bhattacherjee I, Mondal S. A comparative assessment of efficacy and safety of oral antidiabetic drug combinations, metformin plus pioglitazone versus metformin plus glimepiride in type-2 diabetes mellitus [abstract]. Indian J Pharmacol. 2008;40(Suppl 2):51.

191. Meneghini LF, Rosenberg N, Hollander P, Rosenstock J, Riddle MC, Nesto RW, et al. Effects of Insulin Glargine vs Thiazolidinediones on Glycemic and Lipid Variables in Type 2 Diabetes Mellitus (T2DM): The Impact of Obesity [abstract]. Diabetes. 2009;58(Suppl 1):A523, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

192. Hollander P, Rosenberg N, Chaudhuri A, Nesto RW, Rosenstock J, Meneghini LF, et al. Effects of Insulin Glargine vs Thiazolidinediones (TZDs) on Glycemic and Lipid Variables in T2DM [abstract]. Diabetes. 2009;58(Suppl 1):A522, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

193. Shaqdan W, Abdulwahid NA. Addition of Pioglitazone to Type 2 Diabetic Patients with Uncontrolled Diabetes Regardless of Their Medication Status [abstract]. Diabetes. 2009;58(Suppl 1):A513, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

194. Schmidt WE, Christiansen JS, Hammer M, Zychma M, Buse J. Patient Reported Outcomes Are Superior in Patients with Type 2 Diabetes (T2D) Treated with Liraglutide as Compared to Exenatide, When Added to Metformin; Sulfonylurea or Both. Diabetes. 2009;58(Suppl 1):A483-A484, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

195. Jogi M, Sathyanarayana P, Samson S, Bajaj M. Effect of Combined Pioglitazone and Exenatide therapy on Plasma Adiponectin and Lipid Metabolism in Type 2 Diabetes [abstract]. Diabetes. 2009;58(Suppl 1):A166, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

196. Vilsboll T, Rosenstock JM, Yki-Jaervinen H, Cefalu WT, Chen Y, Ling Y, et al. Sitagliptin, a Selective DPP-4 Inhibitor, Improves Glycemic Control When-Added to Insulin, with or without Metformin, in Patients with Type 2 Diabetes [abstract]. Diabetes. 2009;58(Suppl 1):A158-A159, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

197. Hsia SH, Navar MD, Duran P, Davidson MB. Non-Inferiority of Sitagliptin Compared to Thiazolidinediones as a Third-Line Oral Anti-Hyperglycemic Agent in Ethnic Minority Type 2 Diabetic Patients: Interim Results [abstract]. Diabetes. 2009;58(Suppl 1):A146, JUN. (Presented at 69th Annual Meeting of the American-Diabetes-Association, New Orleans, LA, USA; June 05 -09, 2009).

198. Verges B, Brun JM, Tawil C, Alexandre B, Kerlan V. Long-acting insulin analogue therapy initiation and follow-up by healthcare practitioners in patients with type 2 diabetes mellitus uncontrolled with oral antidiabetic drugs: the LIGHT Study [poster]. Diabetologia. 2009;52(Suppl 1):S382.

199. Swinnen SGH, Dain MP, Aronson R, Roberts D, Davies M, Gerstein HC, et al. Once-daily insulin glargine requires a significantly lower dose than insulin detemir twice daily to achieve good glycaemic control in patients with type 2 diabetes failing oral therapy [poster]. Diabetologia. 2009;52(Suppl 1):S380.

200. Franek E, Kalra S, Pesic M, Smahelova A, Thomsen H, Strojek K. Once daily initiation with biphasic insulin aspart 30 (BIAsp 30) versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs - a randomized controlled trial [abstract]. Diabetologia. 2009;52(Suppl 1):S93.

201. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.

202. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

203. Ewart RM. The case against aggressive treatment of type 2 diabetes: critique of the UK prospective diabetes study. BMJ. 2001 Oct 13;323(7317):854-8.

204. McCormack J, Greenhalgh T. Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data. United Kingdom prospective diabetes study. BMJ. 2000 Jun 24;320(7251):1720-3.

205. Nathan DM. Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study. Lancet. 1998 Sep 12;352(9131):832-3.

206. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89.

207. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39.

208. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.

209. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.

210. Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials [editorial]. N Engl J Med. 2008 Jun 12;358(24):2630-3.

211. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009 Nov;52(11):2288-98.

212. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009 May 23;373(9677):1765-72.

213. Valle D, Santoro D, Bates P, Scarpa L. Italian multicentre study of intensive therapy with insulin lispro in 1184 patients with Type 1 diabetes. Diabetes Nutr Metab. 2001 Jun;14(3):126-32.

214. Standards of medical care in diabetes--2009. Diabetes Care. 2009 Jan;32 Suppl 1:S13-S61.

215. Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National evidence based guideline for blood glucose control in type 2 diabetes [Internet]. Canberra: Diabetes Australia and NHMRC; 2009. 290 p. [cited 2010 Feb 17]. Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di19-diabetes-blood-glucose-control.pdf

216. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract [Internet]. 2009 Sep [cited 2010 Mar 10];15(6):540-59. Available from: http://www.aace.com/pub/pdf/GlycemicControlAlgorithm.pdf

217. Management of diabetes [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010. [cited 2010 Mar 25]. (Guideline no 116). Available from: http://www.sign.ac.uk/pdf/sign116.pdf

218. 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

219. 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.

220. Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel protamine-based insulin lispro formulation. Humalog Mix25 Study Group. Diabetes Care [Internet]. 1999 Aug [cited 2006 Dec 18];22(8):1258-61. Available from: http://care.diabetesjournals.org/cgi/reprint/22/8/1258

221. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. Diabet Med. 2002 May;19(5):393-9.

222. 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

223. 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

224. 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

225. Weiss SR, Cheng SL, Kourides IA, Gelfand RA, Landschulz WH, Inhaled Insulin Phase II Study Group. Inhaled insulin provides improved glycemic control in patients with type 2 diabetes mellitus inadequately controlled with oral agents: a randomized controlled trial. Arch Intern Med. 2003 Oct 27;163(19):2277-82.

226. Derosa G, Mugellini A, Ciccarelli L, Crescenzi G, Fogari R. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. Clin Ther. 2003 Feb;25(2):472-84.

227. 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

228. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care [Internet]. 2004 Oct [cited 2008 Aug 11];27(10):2363-8. Available from: http://care.diabetesjournals.org/cgi/reprint/27/10/2363?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Dailey&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=27&firstpage=2363&resourcetype=HWCIT

229. Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, et al. Improved postprandial glycaemic control with insulin Aspart in type 2 diabetic patients treated with insulin. Acta Diabetol. 2000 Mar;37(1):41-6.

230. Peters AL, Davidson MB. Maximal dose glyburide therapy in markedly symptomatic patients with type 2 diabetes: a new use for an old friend. J Clin Endocrinol Metab. 1996 Jul;81(7):2423-7.

231. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P, Study Team. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. Diabetes Care [Internet]. 2003 [cited 2010 Feb 12];26(8):2238-43. Available from: http://care.diabetesjournals.org/cgi/reprint/26/8/2238

232. 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.

233. Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developers' handbook [Internet]. Revised edition. Edinburgh: The Network; 2008 Jan. [cited 2010 Mar 25]. Available from: http://www.sign.ac.uk/pdf/sign50.pdf

234. Canadian Agency for Drugs and Technologies in Health. Current utilization of second-line therapy by patients with type 2 diabetes inadequately controlled on metformin [DRAFT]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 3).

235. Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin. 2005;21(12):2029-35.

236. 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.

237. 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

238. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology [Internet]. 2009 Aug [cited 2009 Aug 25];137(2):482-8. Available from: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508509005551.pdf

239. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 Jul 2;52(9):1766-77.

240. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009 Jun;46(2):145-54.

241. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia. 2006 May;49(5):930-6.

242. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71.

243. Wilcox R, Kupfer S, Erdmann E, PROactive Si. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). Am Heart J. 2008 Apr;155(4):712-7.

244. 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.

245. Hsiao FY, Huang WF, Wen YW, Chen PF, Kuo KN, Tsai YW. Thiazolidinediones and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study of over 473 000 Patients Using the National Health Insurance Database in Taiwan. Drug Saf. 2009;32(8):675-90.

246. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf. 2007;16(7):711-25.

247. Johannes CB, Koro CE, Quinn SG, Cutone JA, Seeger JD. The risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy. Pharmacoepidemiol Drug Saf. 2007 May;16(5):504-12.

248. Koro CE, Fu Q, Stender M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol Drug Saf. 2008 Oct;17(10):989-96.

249. Stockl KM, Le L, Zhang S, Harada ASM. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol Drug Saf. 2009;18(2):166-74.

250. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ [Internet]. 2009 Aug 18 [cited 2009 Aug 20];339:b2942. Available from: http://www.bmj.com/cgi/reprint/339/aug18_2/b2942

251. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol Drug Saf. 2007 Aug 3;16(10):1065-71.

252. 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.

253. Fong DS, Contreras R. Glitazone use associated with diabetic macular edema. Am J Ophthalmol. 2009 Apr;147(4):583-6.

254. Koro C, Barrett S, Qizilbash N. Cancer risks in thiazolidinedione users compared to other anti-diabetic agents. Pharmacoepidemiol Drug Saf. 2007;16(5):485-92.

255. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol. 2007 Apr 20;25(12):1476-81.

256. 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.

257. Marshall V, Wilton L, Shakir S. Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. Acta Diabetol. 2006 May;43(1):6-13.

258. Twaites B, Wilton LV, Layton D, Shakir SA. Safety of nateglinide as used in general practice in England: results of a prescription-event monitoring study. Acta Diabetol. 2007 Dec;44(4):233-9.

259. Cobalt Laboratories. Acarbose. 2009 [cited 2009 Oct 8]. In: Drugs A to Z [Internet]. Auckland (NZ): Drugs.com; c2000 - c2009. Available from: http://www.drugs.com/pro/acarbose.html.

260. Pharmacia and Upjohn. Glyset. 2009 [cited 2009 Oct 8]. In: Drugs A to Z [Internet]. Auckland (NZ): Drugs.com; c2000 - c2009. Available from: http://www.drugs.com/pro/glyset.html.

261. 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

262. US Food and Drug Administration [Internet]. Silver Spring (MD): US Food and Drug Administration; c2009. Information for healthcare professionals - acute pancreatitis and sitagliptin (marketed as januvia and janumet); 2009 Sep 25 [cited 2009 Oct 23]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm

263. 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

264. 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.

265. Medwatch [Internet]. Silver Spring (MD): Food and Drug Administration. Byetta (exenatide) - Renal Failure; 2009 [cited 2009 Nov 16]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm

266. Product mongraph: Januvia. Kirkland (QC): Merck Frosst Canada Ltd; 2009.

267. Highlights of prescribing information Januvia™ (sitagliptin) tablets [Internet]. Whitehouse Station (NJ): Merck & Co., Inc; 2009. [cited 2009 Nov 9]. Available from: http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf

268. Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia [Internet]. 2009 Jun 30 [cited 2009 Aug 19];52(9):1732-44. Available from: http://www.springerlink.com/content/v3w757x262744345/fulltext.pdf

269. Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia. 2009 Jul 15;52(9):1755-65.

270. Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009 Jul 9;52(9):1745-54.