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Second-Line Pharmacotherapy for Type 2 Diabetes — Update

Supporting Informed Decisions

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ABBREVIATIONS

A1C	glycated hemoglobin
BMI	body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CHF	congestive heart failure
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
EQ-5D	EuroQol 5-Dimension Questionnaire
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MC	multi-centre
MD	mean difference
Met	metformin
MTC	mixed-treatment comparison
N	total number of patients
N/A	not applicable
NICE	National Institute for Health and Clinical Excellence
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
OR	odds ratio
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SU	sulfonylurea
TZD	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
WMD	weighted mean difference

EXECUTIVE SUMMARY

Context and Policy Issues

In August 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a systematic review and network meta-analysis (NMA) assessing the comparative safety and efficacy of all available classes of antihyperglycemic therapies added to metformin in patients with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy.[1] The results of this review indicated that there were no apparent differences in efficacy across the available drug classes. Based on a cost-utility analysis performed using the results of the systematic review, sulfonylureas were found to be the most cost-effective treatment option.[1] Based on these analyses, the COMPUS Expert Review Committee (CERC) recommended that most patients requiring a second treatment after metformin should be prescribed a sulfonylurea.[2]

Although the original systematic review included clinical evidence for glucagon-like peptide-1 (GLP-1) analogues, the cost-effectiveness analysis[1] and subsequent recommendations[2] could not address this class, as there were no agents approved for use in Canada at the time. Two GLP-1 analogues, exenatide (Byetta) and liraglutide (Victoza), have since been approved. Therefore, there is interest in updated optimal therapy recommendations for second-line therapy in type 2 diabetes that incorporate the GLP-1 analogues.

Objectives and Research Questions

The objective of this study was to perform an update of CADTH's original systematic review, NMA, and cost-effectiveness analysis of second-line diabetes pharmacotherapy. The research questions that were addressed in the update were the same as in the original review:

1. What is the comparative efficacy and safety of second-line antidiabetes drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?
2. What is the cost-effectiveness of second-line antidiabetes drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?

Methods

The literature searches used in the original CADTH reviews were updated to identify English language documents published between January 1, 2009 (the end date of the search for the original review), and May 7, 2012. Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records & daily updates via Ovid; Embase via Ovid; The Cochrane Library via Ovid; and PubMed. Grey literature was identified by searching the Grey Matters checklist (www.cadth.ca/resources/grey-matters). These searches were supplemented by reviewing the bibliographies of key papers. Inclusion criteria for the updated review were similar to those in the previous analysis.

Compared with the original analysis, the updated review assessed a focused set of outcomes; i.e., those which were the primary considerations of CERC in developing the original recommendations. These include mortality, diabetes-related complications, glycated hemoglobin (A1C), body weight, hypoglycemia, and serious adverse events (SAEs). Bayesian network meta-analyses and direct pairwise meta-analyses were conducted in a similar manner to the original CADTH analysis.

The updated pharmacoeconomic study utilized similar methodology to the original analysis, except that GLP-1 analogues were modelled as a treatment option.[1] Other key revisions to the previous methods were:

- The latest United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (version 1.3) was used to forecast diabetes-related complications and cost consequences, and estimate incremental cost-utility ratios (ICURs) for each drug class added to metformin.[3]
- Treatment effect estimates were obtained from the updated systematic review and NMA.
- Costs for drugs, disease management, and long-term diabetes complications were updated to year 2012 costs and adjusted for inflation.

Key Findings of Systematic Review

An additional 27 articles met the eligibility criteria for the updated review. These included 20 newly-identified randomized controlled trials (RCTs) and seven companion publications for studies that had been included in the original review. Including the update, the systematic review of second-line pharmacotherapy included a total of 69 unique RCTs. Evidence was available for the following eight drug classes: sulfonylureas (28 RCTs), dipeptidyl peptidase-4 (DPP-4) inhibitors (24 RCTs), thiazolidinediones (TZDs) (20 RCTs), GLP-1 analogues (14 RCTs), basal insulin (6 RCTs), alpha-glucosidase inhibitors (5 RCTs), meglitinides (4 RCTs), and biphasic insulin (4 RCTs). Thirty-five RCTs included a placebo treatment group.

Network meta-analyses were conducted for change from baseline in A1C, change from baseline in body weight, and overall hypoglycemia.

- A total of 56 RCTs (N = 27,773) were included in the updated NMA for A1C. All classes of second-line agents added to metformin significantly reduced A1C relative to metformin alone. The effect estimates ranged from –0.64% (95% CrI: –0.91, –0.38) for meglitinides to –1.06 (95% CrI: –1.32, –0.80) for biphasic insulins.
- A total of 35 RCTs were included in the NMA for changes from baseline in body weight (N = 20,178). Treatment with sulfonylureas, meglitinides, TZDs, basal insulin, and biphasic insulin resulted in significantly greater increases in body weight than metformin monotherapy (range 1.7 to 3.1 kg), with no significant differences between these classes. DPP-4 inhibitors and alpha-glucosidase inhibitors did not significantly affect body weight. The only drug class associated with a significant reduction in body weight versus metformin monotherapy was GLP-1 analogues (–1.8 kg, 95% CrI: –2.9 to –0.8).
- A total of 48 RCTs were included in the updated NMA for overall hypoglycemia (N = 24,284). Relative to metformin monotherapy, the risk of hypoglycemia was significantly elevated with insulins, sulfonylureas, and meglitinides (odds ratios [ORs] were 4.1 to 7.0 for insulins, 7.5 for sulfonylureas, and 8.3 for meglitinides). There was no significant increase in hypoglycemia risk with TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors or GLP-1 analogues.

For all three NMAs, there was good agreement between indirect and direct estimates, and between the updated and original analyses. The results were found to be robust in sensitivity analyses.

There were no adequately powered RCTs evaluating the comparative efficacy of any class of second-line pharmacotherapy for reducing clinically important long-term complications of diabetes. Episodes of severe hypoglycemia were rare for all drug classes (including insulin and insulin secretagogues), affecting 0.1% to 1.6% of the total patient population. Overall, there were no events reported in 40 of the 48 treatment arms. Severe adverse events occurred in 0.7% to 9.1% of patients across all but two

studies, both of which were long-term extension trials in which as many as 21% of patients experienced a severe adverse event.

Key Findings of Economic Analysis

Despite the introduction of GLP-1 analogues as a treatment option in the economic model and reduction in the prices of some agents, the results of the updated economic evaluation remained similar to those of the original analysis. Sulfonylureas remained the most cost- effective second-line therapy in patients inadequately controlled on metformin, with an ICUR of $8,445 per quality-adjusted life-year gained. This was due primarily to the lower cost of agents in this drug class compared with insulin and newer agents, and similar efficacy regarding A1C lowering. Cost-effectiveness results were robust to variations in model inputs and assumptions. Threshold analyses indicated that the costs of DPP-4 inhibitors and GLP-1 analogues would have to be lower by 90% and 95%, respectively, in order to surpass sulfonylureas as the most cost-effective second-line treatment option.

Strengths and Limitations

The strengths of the systematic review were the rigorous and reproducible methods employed to identify relevant evidence and analyze the results. The NMAs were shown to be robust through various means: model diagnostic statistics were favourable, and there was good agreement between indirect and direct pairwise estimates. Although there was a degree of between-study heterogeneity in baseline A1C, duration of diabetes, reporting of metformin, and/or sulfonylurea doses at baseline, and glycemic targets, these factors did not appear to have a material impact given the consistency of results across the numerous sensitivity analyses and meta-regressions performed.

A key limitation of the available clinical evidence was the limited data on clinically relevant complications of diabetes, and the consequent need to rely on A1C as a surrogate outcome to assess comparative efficacy. Methodological limitations of the included RCTs were failure to report adequate methods for allocation concealment, the use of analyses other than intention-to-treat, and, in the case of trials of insulins, the frequent use of open-label designs. Rates of severe hypoglycemia were too low for meaningful comparisons between treatments of this important adverse event. Due to the relatively short duration of most included trials, it was impossible to accurately determine whether there were differences in the durability of antihyperglycemic effects across the various drug classes. Key limitations regarding the external validity of trials included the relatively short duration of trials, failure to report definitions for hypoglycemia and adverse events, and a level of contact between trial subjects and health care professionals that likely exceeds routine clinical practice. Furthermore, a number of trials were conducted in countries that may differ markedly from Canada in ethnic makeup, health system organization, or practice patterns.

Regarding limitations of the pharmacoeconomic analysis, it should be noted that the UKPDS model does not explicitly incorporate a number of diabetes-related morbidities (e.g., peripheral neuropathy and ulceration) or intermediate states (e.g., retinopathy and nephropathy) that may themselves be associated with reduced HRQoL. Hence, the UKPDS model may result in a slight overestimation of incremental cost-effectiveness ratios. However, the impact of this factor on cost-effectiveness estimates is likely small given the minimal differences in glycemic control across drug classes.

There was considerable uncertainty regarding the disutility associated with insulin use, weight gain, and hypoglycemia, as well as event rates for severe hypoglycemia. These are all important drivers of the cost-effectiveness of second-line options, particularly insulin secretagogues and insulins. In the absence

of sound data for these inputs, conservative estimates were used for the reference case analysis but were tested in sensitivity analyses.

In the reference case analysis, it was assumed that metformin plus the second-line treatment were continued at constant doses for the lifetime of the patient. Although this assumption allows for attribution of costs and consequences to the treatments in question, it does not represent the progressive nature of type 2 diabetes and the inevitable need for intensification of therapy over time. This limitation was addressed through a sensitivity analysis in which insulin neutral protamine Hagedorn (NPH) was added to all non-insulin second-line treatments once A1C reached 9%. Sulfonylureas remained the most cost-effective option in this analysis.

Conclusions and Implications for Decision- or Policy-Making

In this systematic review and NMA of RCT evidence related to the second-line use of antidiabetes therapies after inadequate control with metformin monotherapy, all drug classes added to metformin achieved statistically significant reductions in A1C. Events of severe hypoglycemia were rare for all agents; however, the insulins and insulin secretagogues were associated with a statistically significant increase in overall hypoglycemia relative to the other classes. Increased body weight was observed with the majority of second-line therapies, the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues.Further studies of adequate size and duration are required to assess comparative efficacy in durability of antihyperglycemic effect, long-term complications of diabetes, and quality of life.

The results of the updated cost-effectiveness analysis comparing second-line treatments for type 2 diabetes after inadequate control with metformin monotherapy were congruent with the results of the original analysis. Sulfonylureas added to metformin represented the most cost- effective second-line therapy, a finding that was robust in numerous sensitivity analyses. These results were primarily driven by the low cost of sulfonylureas relative to other drugs, marginal differences in glycemic control and long-term complications between sulfonylureas and other agents, and the expected low absolute risk of severe hypoglycemic episodes requiring health care resource use. GLP-1 analogues, which could not be considered in the original analysis, as no agents were approved in Canada at the time, were found to be associated with a high ICUR in the updated analysis. In order to surpass the sulfonylureas as the most cost-effective second-line therapy, reductions in cost of 90% or more would be required for this class and the DPP-4 inhibitors. Because of the lack of adequate clinical data, there was considerable uncertainty surrounding some of the key drivers in the economic analysis. These included the impact of insulin use and hypoglycemia on quality of life, and the incidence of severe hypoglycemia across various treatments.

1 CONTEXT AND POLICY ISSUES

1.1 Background

In August 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a systematic review and network meta-analysis (NMA) assessing the comparative safety and efficacy of all available classes of antihyperglycemic therapies added to metformin in patients with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy.[1,4] At the time, we identified 49 active and non-active randomized controlled trials (RCTs) that compared two or more of the following classes of antihyperglycemic agents (including weight-loss agents with glucose-lowering effects): sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, insulins, alpha-glucosidase inhibitors, sibutramine and orlistat. All classes of second-line antihyperglycemic therapies were found to achieve clinically meaningful reductions in glycated hemoglobin (A1C) (0.6% to 1.0%), and no significant differences were found between classes. Insulins and insulin secretagogues were associated with significantly more events of overall hypoglycemia than the other agents, but severe hypoglycemia was rarely observed. An increase in body weight was observed with the majority of second-line therapies (1.8 kg to 3.0 kg) — the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues (0.6 to –1.8 kg). There were insufficient data available for diabetes complications, mortality, or quality of life.

The results of the systematic review were used as inputs in a cost-effectiveness analysis of second-line treatments conducted using the UKPDS model. This analysis demonstrated that sulfonylureas, when added to metformin, were associated with the most favourable cost- effectiveness estimate, with an incremental cost of $12,757 per quality-adjusted life-year gained, relative to continued metformin monotherapy.[1,5]

CERC deliberated on the clinical and cost-effectiveness evidence and recommended that, for most patients, a sulfonylurea should be added to metformin when metformin alone is not enough to adequately control hyperglycemia.[2]

1.2 Rationale for Updating the Review of Second-Line Pharmacotherapy

Although the original clinical review of second-line pharmacotherapy for type 2 diabetes included GLP-1 analogues, the cost-effectiveness analysis[1] and subsequent recommendations[2] could not address this class, as there were no agents approved for use in Canada at the time of the reviews. Two GLP-1 analogues, exenatide (Byetta) and liraglutide (Victoza), have since been approved. Hence, there is interest in updated optimal therapy recommendations for second-line therapy for type 2 diabetes that incorporate the GLP-1 analogues.

1.3 Description of Second-Line Agents for Type 2 Diabetes

Except for the introduction of GLP-1 analogues, the drug classes currently available in Canada for use as second-line therapy in patients with type 2 diabetes inadequately managed on metformin remain the same as in 2010: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, basal insulins, bolus insulins, and biphasic insulins (Table 1).

Since the original CADTH review of second-line pharmacotherapy, severe restrictions have been placed on the use of rosiglitazone in Canada. Specifically, rosiglitazone is now indicated as an adjunct to diet

and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.[6] In addition, prior to prescribing rosiglitazone, physicians must:

- document the eligibility of patients to meet the above-mentioned criteria
- counsel each patient on the risks and benefits of rosiglitazone, including the cardiovascular risks
- obtain the patient's written informed consent.[6]

Table 1: Drug Classes Available in Canada as Second-Line Treatments for Type 2 Diabetes after Metformin

Drug Class	Generic Name	Dosage Information		RoA	Approved for Use with Metformin
		Range	DDD		
Sulfonylureas	Gliclazide	80 mg to 320 mg	160 mg	Oral	Not specified[7,8]
	Gliclazide MR	30 mg to 120 mg	60 mg	Oral	Not specified[7,8]
	Glimepiride	1 mg to 8 mg	2 mg	Oral	Yes[9]
	Glyburide	2.5 mg to 20 mg	10 mg	Oral	Not specified[10]
	Chlorpropamide	100 mg to 500 mg	375 mg	Oral	Not specified[11]
	Tolbutamide	500 mg to 3000 mg	1,500 mg	Oral	Not specified[12]
TZDs	Pioglitazone	15 mg to 45 mg	30 mg	Oral	Yes[13]
	Rosiglitazone	4 to 8 mg	6 mg	Oral	Yes[6]
Meglitinides	Nateglinide	180 mg to 360 mg	360 mg	Oral	Yes[14]
	Repaglinide	0.5 mg to 16 mg	4 mg	Oral	Yes[15]
AGIs	Acarbose	150 mg to 300 mg	300 mg	Oral	Yes[16]
DPP-4 inhibitors	Sitagliptin	100 mg	100 mg	Oral	Yes[17]
	Saxagliptin	5 mg	5 mg	Oral	Yes[18]
	Linagliptin	5 mg	NR	Oral	Yes[19]
GLP-1 analogues	Exenatide	10 mg to 20 mcg	15 mcg	SC	Yes[20]
	Liraglutide	1.2 mg to 1.8 mg	1.2 mg	SC	Yes[21]
Bolus insulin	Insulin aspart	Individualized	40 U	SC	Not specified[22]
	Insulin lispro	Individualized	40 U	SC	Not specified[23]
	Insulin glulisine	Individualized	40 U	SC	Yes[24]
	Human insulin	Individualized	40 U	SC	Not specified[25]
Basal insulin	Insulin NPH	Individualized	40 U	SC	Not specified[25]
	Insulin detemir	Individualized	40 U	SC	Yes[26]
	Insulin glargine	Individualized	40 U	SC	Not specified[27]
Biphasic insulins	Premixed regular NPH	Individualized	40 U	SC	Not specified[25]
	Biphasic insulin aspart	Individualized	40 U	SC	Not specified[28]
	Biphasic insulin lispro	Individualized	40 U	SC	Not specified[23]

AGIs = alpha-glucosidase inhibitors; DDD = World Health Organization Defined Daily Dose; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptid-1; NPH = neutral protamine Hagedorn; NR = not reported; MR = modified release; RoA = route of administration; SC = subcutaneous; TZD = thiazolidinedione; U = units.

2 SYSTEMATIC REVIEW

2.1 Objective

The objective of this review was to update the original CADTH systematic review and network meta-analyses of second-line therapies for type 2 diabetes.

2.2 Methods

2.2.1 Research Questions

1. What is the comparative efficacy and safety of second-line antidiabetes drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?
2. What is the cost-effectiveness of second-line antidiabetes drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?

2.2.2 Literature Search

The literature search for this update was performed by an information specialist using a peer-reviewed search strategy — the search methodology was similar to that of the original reviews. A combined search was performed for both the second- and third-line therapy updates. Published literature was identified by searching the following bibliographic databases: MEDLINE with In-process records & daily updates via Ovid; Embase via Ovid; The Cochrane Library via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were diabetes, and second- and third-line antidiabetes drugs.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 (the end date of the search for the original review) and May 7, 2012. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies. The initial search was completed on May 7, 2012. Regular alerts were established to update the search until the publication of the final report. Regular search updates were also performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers, and through contacts with appropriate experts and industry.

2.2.3 Eligibility Criteria

The eligibility criteria for the updated review of second-line diabetes pharmacotherapy were the same as for the original review. Key criteria are summarized in Table 2. Further details on inclusion and exclusion criteria can be found in the original report.[1]

Table 2: Key Eligibility Criteria for Updated Review of Second-Line Diabetes Pharmacotherapy	
Study Design	Randomized controlled trials
Population	Inadequately controlled* with metformin monotherapy
Interventions/ Comparators	Metformin plus any one of the following: placebo/no treatment, sulfonylurea, GLP-1 analogue, DPP-4 inhibitor, meglitinide, thiazolidinedione, alpha-glucosidase inhibitor, insulin (basal, bolus, biphasic). Agents within each drug class were included in the review only if they were approved for marketing in one or more of Canada, the United States, or the European Union.

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.
*Inadequate control was defined as A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.[29,30]

All of the agents listed in Table 1 were included in the updated review. In addition, certain agents not currently approved for sale in Canada were included in the review, as they belong to one of the drug classes listed in Table 1 and are approved in one or both of the United States or the European Union (Table 3).

Table 3: Agents Not Approved in Canada Included in the Updated Systematic Review

Drug Class	Generic Name	Dosage Information		RoA
		Range	DDD	
Sulfonylureas	Glipizide	5 mg to 40 mg	10 mg	Oral
AGIs	Miglitol	75 mg to 300 mg	300 mg	Oral
DPP-4 inhibitors	Vildagliptin	100 mg	100 mg	Oral
Basal insulin	Insulin NPL	Individualized	40 U	SC

AGIs = alpha-glucosidase inhibitors; DDD = World Health Organization Defined Daily Dose; DPP-4 = dipeptidyl peptidase-4; NPL = neutral protamine lispro; RoA = route of administration; SC = subcutaneous; U = units.

2.2.4 Outcomes of Interest

Compared with the original CADTH analysis, this update focused on outcomes that were primary considerations for CERC in developing the original recommendations. These include mortality, diabetes-related complications, A1C, body weight, hypoglycemia, and SAEs. Evidence for diabetes-related complications was only reviewed from RCTs that were designed and powered to compare the effect of two or more treatments on such end points.

2.2.5 Literature Selection, Data Extraction, and Critical Appraisal

The systematic review was conducted using similar methodology to the original CADTH review.[29,31] Literature selection was performed independently by two reviewers. Data extraction and risk of bias assessment were performed by one reviewer, and verified by a second reviewer. Disagreements at any of these stages were resolved through consensus, or by a third reviewer if consensus could not be reached. Risk of bias for the included RCTs was assessed using the Scottish Intercollegiate Guidelines Network questionnaire (SIGN-50).[32]

2.2.6 Statistical Analysis

The original NMAs for second-line therapy were updated with data from the newly-identified trials. The methodology employed was the same as that used in the original CADTH analysis.[29,31] WinBUGS[33] (MRC Biostatistics Unit, Cambridge, UK) was used for the network meta-analyses according to the routine developed at the Universities of Bristol and Leicester.[34] Metformin monotherapy (i.e., no second-line

therapy or addition of placebo to metformin) was the reference group for all network meta-analyses. Posterior densities for unknown parameters were estimated using Markov Chain Monte Carlo methods. Basic parameters were assigned non-informative or vague prior distributions. Point estimates and 95% credible intervals were used to summarize all findings. The probability of a drug class being optimal was estimated for each outcome based on the proportion of Markov Chain Monte Carlo simulations in which its relative measure of effect was best. We also calculated the mean rank for each drug class. Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic[35] were assessed to ensure model convergence. Two chains were fit into WinBUGS for each analysis, each employing ≥ 20,000 iterations, with a burn-in of ≥ 20,000 iterations.

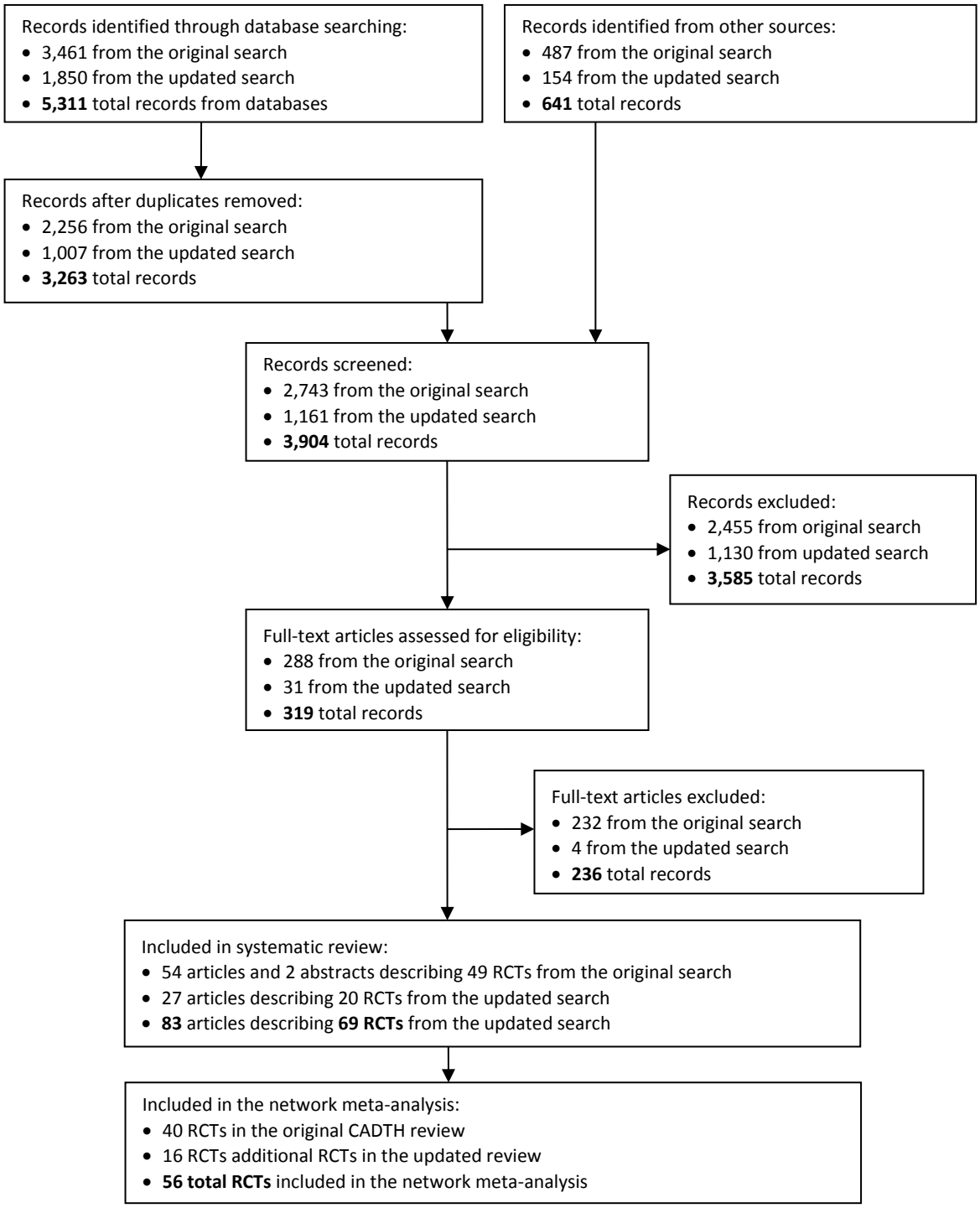
Frequentist pairwise meta-analysis was performed using R, a language and software environment for statistical computing. A random-effects model was used for the reference case in all pairwise meta-analyses and NMAs. The robustness of the reference case was assessed using alternative modelling, sensitivity analyses, and meta-regressions.

2.3 Results

2.3.1 Literature Selection

Compared with the original review, an additional 27 articles met eligibility criteria for inclusion in the update. These included 20 newly-identified RCTs and seven companion publications for studies that had been included in the 2010 review. Including the update, the systematic review of second-line pharmacotherapy included a total of 69 unique RCTs. A PRISMA diagram showing the results of the literature selection for the original and updated reviews is provided in Figure 1.

Figure 1: PRISMA Diagram for Literature Update



CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial.

2.3.2 Characteristics of Included Trials

In total (original review plus the update), evidence was available for the following eight drug classes added to metformin: sulfonylureas (28 RCTs), DPP-4 inhibitors (24 RCTs), TZDs (20 RCTs), GLP-1 analogues (14 RCTs), basal insulin (6 RCTs), alpha-glucosidase inhibitors (5 RCTs), meglitinides (4 RCTs), and biphasic insulin (four RCTs). Thirty-five RCTs included a metformin plus placebo group. There were no RCTs that investigated the use of bolus insulins. Detailed trial characteristics of the included studies are provided in Table 15. Sample sizes ranged from 13[36] to 2,789.[37] The threshold baseline A1C for inclusion in trials was typically in the range of 7.0% to 10%; however, a small number of studies employed a threshold as low as 6.5%[36-48] or as high as 11.5%.[49] The mean baseline A1C of trial subjects ranged from 6.6%[50] to 10%[51] (weighted mean [SD] = 8.0% [0.9]). The baseline duration of diabetes ranged from 1.8 to 10.3 years (weighted mean [SD] = 6.1 [5.1] years). There were some differences in the duration and dosage of metformin monotherapy prior to the addition of second-line drugs. The majority of studies were sponsored by the pharmaceutical industry.

Metformin monotherapy was not necessarily first-line therapy in most studies. The most common scenario in trials was that patients were treated with metformin monotherapy under routine clinical care and were required to have abstained from use of other antidiabetes drugs for a certain period (usually the past three months) before screening. However, treatment history prior to this period was unspecified. In the second scenario, patients using a variety of oral antidiabetes drugs underwent a run-in period with metformin monotherapy upon trial entry, and were randomized to add-on therapy if glycemic control was inadequate at the end of the run-in period. No studies assessed the effects of switching from metformin to another antidiabetes drug due to intolerable adverse effects, development of contraindications, or inadequate glycemic control.

2.3.3 Critical Appraisal

a) Internal Validity

The strengths and limitations of the newly-identified RCTs were generally consistent with the studies included in the original systematic review.[1] Common limitations included failure to adequately report methods for allocation concealment, open-label design, or failure to report a true intention-to-treat analysis (i.e., an analysis including all randomized patients). Study level results of internal validity assessment are reported in Appendix 9, Table 20.

b) External Validity

Limitations that may affect the external validity of the newly-identified RCTs were also similar to those reported in the original CADTH review.[1] Common limitations included a relatively short duration of follow-up (e.g., less than one year), limited sample sizes, the use of surrogate end points (e.g., A1C) versus more clinically meaningful end points (e.g., diabetes-related complications), and failure to report definitions for hypoglycemia. The population of interest for this review (as for the original review) was patients inadequately controlled with metformin monotherapy requiring a second-line agent to maintain glycemic control. However, there were several common limitations with the conduct and reporting of the included RCTs that may limit the generalizability of the study population to the population of interest. Studies often provided limited information regarding the dosage and duration of metformin monotherapy prior to randomization or included patients who had been using a stable metformin dosage for less than three months. Several RCTs also specified an A1C threshold of 6.5% for defining inadequate control, which is lower than the threshold commonly used in Canadian practice (7.0%). Hence, it is possible that study populations in the included RCTs may differ from patients in routine clinical practice who have failed to maintain glycemic control despite a maximum tolerated

dosage of metformin. In addition, many studies were conducted exclusively in countries where health care delivery and practice patterns may differ markedly from Canada.

Based on the inclusion criteria (Table 2), the review included RCTs that investigated four treatments that are not currently approved for use in Canada (once weekly exenatide, vildagliptin, miglitol, and glipizide). Sensitivity analyses were performed by removing these studies from the NMA. Study level details regarding the external validity assessment are reported in Appendix 9, Table 21.

2.3.4 Data Synthesis

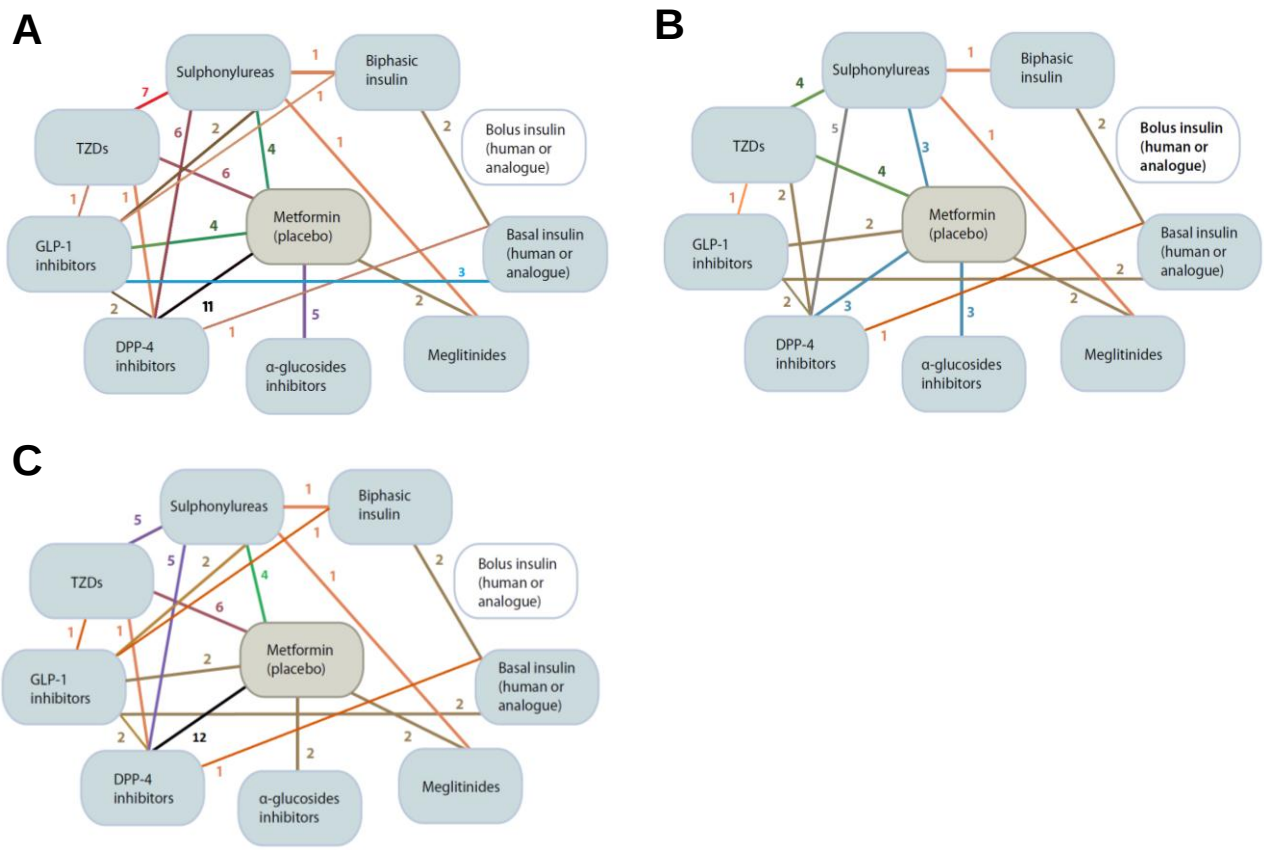
NMA and pairwise meta-analyses were conducted for A1C, body weight, and overall hypoglycemia. Evidence network diagrams for these outcomes are shown in Figure 2. In the case of severe hypoglycemia and SAEs, NMA could not be conducted because of the low event rates observed in many studies. Only pairwise direct comparisons were conducted for these outcomes. Data from several RCTs could not be included in any of the network or pairwise meta-analyses due to variation in the methods of reporting for key outcomes or because the study compared two treatments within the same drug class. The results of these studies are summarized in Appendix 8.

Table 4: Overview of Evidence and Analyses Performed

Outcome	Number of RCTs	Number of Patients	Type of Analyses Conducted
A1C	56	27,773	NMA and pairwise
Body weight	36	20,178	NMA and pairwise
Overall hypoglycemia	48	24,284	NMA and pairwise
Severe hypoglycemia	30	14,196	Pairwise
Serious adverse events	39	21,476	Pairwise

A1C = glycated hemoglobin; NMA = network meta-analysis; RCT = randomized controlled trial.

Figure 2: Evidence Networks for Meta-Analyses of A1C (A), Body Weight (B), Overall Hypoglycemia (C)



A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione.
Network diagrams showing the distribution of evidence for each NMA.
Note: Numbers denote number of randomized controlled trials (RCTs) reporting the comparison. (A) 56 RCTs reported change from baseline in A1C. (B) 35 RCTs reported change from baseline in body weight. (C) 46 RCTs reported the numbers of patients experiencing at least one event of overall hypoglycemia. All active treatments and placebo were provided in combination with metformin.

2.3.5 Efficacy Results

a) Diabetes-Related Complications

There were no adequately powered RCTs identified in the literature update that evaluated the comparative efficacy of any class of second-line pharmacotherapy for reducing clinically important long-term complications of diabetes, or mortality. Only a single trial in the original CADTH review (the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes [RECORD] trial) specified macrovascular complications as the primary outcome of interest.[52] This large RCT involved patients inadequately controlled on metformin (N = 2,228) or sulfonylurea (N = 2,230) monotherapy. However, data were not presented for the subgroup of subjects inadequately controlled on metformin monotherapy for most outcomes.

b) A1C

An additional 16 RCTs were included in the updated NMA for A1C, for a total of 56 RCTs (N = 27,773).[36-38,40-42,44,45,47,48,51-96] In general, results from the updated analysis were similar to those of the original; all classes of second-line agents added to metformin significantly reduced A1C relative to metformin alone

(Figure 3A). The effect estimates ranged from –0.64% (95% CrI: –0.92 to –0.38) for meglitinides to –1.04% (95% CrI: –1.30 to –0.78) for biphasic insulins. There was good agreement between direct pairwise estimates (where available) and NMA estimates Appendix 3. For GLP-1 analogues, the revised estimate of effect against metformin alone was –0.95%, slightly larger than the original estimate of –0.82%. For DPP-4 inhibitors, the revised estimate diminished somewhat from –0.80% in the original analysis to 0.69%.

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. The deviance information criterion for the fixed-effects model (44.5) was greater than that of the random-effects model (–26.3) suggesting that the random-effects model was a better-fitting model. Model parameters indicated good model fit for the reference case (e.g., the mean residual deviance was less than the number of unconstrained data points). Details regarding the model-fit parameters for all NMAs are provided in Appendix 7.

The robustness of the reference case was assessed using alternative modelling, sensitivity analyses, and meta-regressions (Table 5). Results of the NMA were similar when analyzed using random and fixed effects. Sensitivity analyses were conducted to assess the impact of removing studies with the following characteristics: investigated the use of rosiglitazone; involved an agent without Health Canada approval for marketing in Canada (i.e., agents listed previously in Table 3); RCTs that were less than one year in duration, or any studies where subgroup data were used. An additional sensitivity analysis was conducted using only studies that were six months in duration (i.e., 24 to 26 weeks). All of these sensitivity analyses demonstrated results that were similar to the reference case. Meta-regressions adjusting for baseline A1C and duration of diabetes at baseline also demonstrated results that were similar to the reference case.

An additional NMA was conducted where each of the drug classes were separated into their respective individual agents. All individual agents produced statistically significant reductions in A1C relative to placebo, with no apparent differences within classes (Appendix 4, Figure 5).

2.3.6 Safety Results

a) Body Weight

Compared with the original analysis, an additional six RCTs were included in the NMA for changes from baseline body weight, for a total of 36 RCTs (N = 20,178). [37,38,40,42,44,45,47,48,51-57,59,60,62,64,65,67,68,70-73,75,77,79,81-86,92] Results from the updated analysis were similar to those reported in the original review (Figure 3B). Treatment with metformin plus sulfonylureas, meglitinides, TZDs, and biphasic insulin resulted in significantly greater increases in body weight than metformin monotherapy (range 1.7 kg to 3.1 kg), with no significant differences between these classes. DPP-4 inhibitors and alpha-glucosidase inhibitors did not significantly affect body weight. The only drug class associated with a statistically significant reduction in body weight versus metformin monotherapy was GLP-1 analogues (–1.8 kg, 95% CrI: –2.9 to –0.8). There was good agreement between direct pairwise estimates (where available) and NMA estimates (Appendix 3). The mean residual deviance for the NMA was less than the number of unconstrained data points, indicating good model fit (Appendix 7).

b) Hypoglycemia

Overall Hypoglycemia

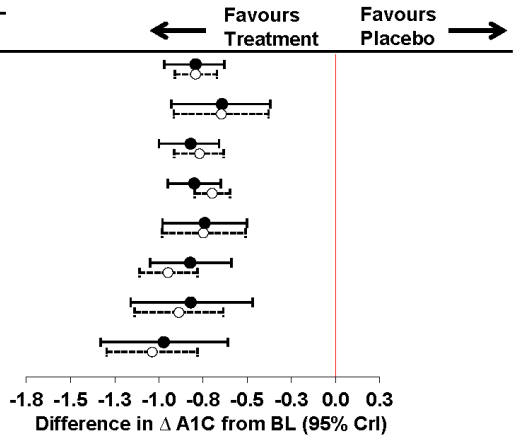
There was a degree of variability in the clinical definitions of this outcome across RCTs. The most common differences were the specific blood glucose threshold for hypoglycemia (range ≤ 2.8 to ≤ 3.9 mmol/L), and whether or not patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose.

An additional 13 RCTs were included in the NMA for overall hypoglycemia, for a total of 48 RCTs (N = 24,284).[36-42,44,45,47,51-65,67-73,77-79,81-86,89,90,92-96] Results from the updated meta-analysis were similar to those reported in the original review (Figure 3C). Relative to metformin monotherapy, risk was significantly elevated with insulins, sulfonylureas, and meglitinides (odds ratios [ORs] were 4.1 to 7.0 for insulins, 7.5 for sulfonylureas, and 8.3 for meglitinides). There were no significant differences between these classes. By contrast, there was no significant increase in hypoglycemia risk with TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors, or GLP-1 analogues. There was good agreement between direct pairwise estimates and NMA estimates (Appendix 3). The mean residual deviance for the NMA was less than the number of unconstrained data points, indicating good model fit (Appendix 7).

Figure 3: CADTH 2010 (●) and Updated Network Meta-Analyses (O) for A1C (%) (A), Weight (kg) (B), and Overall Hypoglycemia (C)

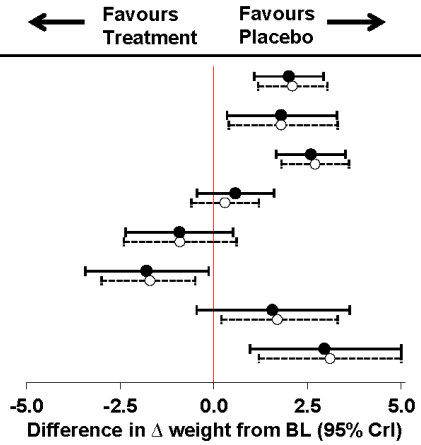
A

Treatment added-on to metformin	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Sulfonylureas	–0.79 (–0.95, –0.63)	–0.79 (–0.91, –0.67)
Meglitinides	–0.64 (–0.93, –0.37)	–0.64 (–0.91, –0.38)
Thiazolidinediones	–0.82 (–1.00, –0.66)	–0.77 (–0.92, –0.63)
DPP-4 inhibitors	–0.80 (–0.95, –0.65)	–0.69 (–0.79, –0.60)
AG inhibitors	–0.74 (–0.98, –0.50)	–0.74 (–0.98, –0.51)
GLP-1 analogues	–0.82 (–1.05, –0.59)	–0.96 (–1.13, –0.80)
Basal insulin	–0.82 (–1.16, –0.47)	–0.91 (–1.16, –0.67)
Biphasic insulin	–0.97 (–1.33, –0.61)	–1.06 (–1.32, –0.80)



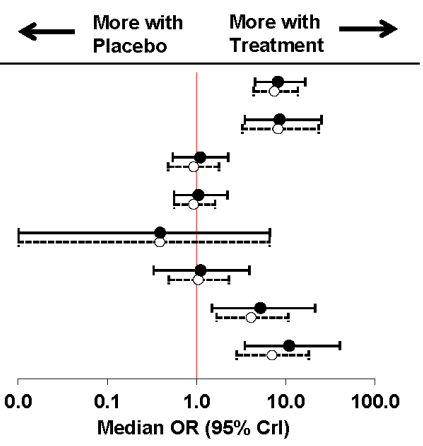
B

Treatment added-on to metformin	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Sulfonylureas	2.0 (1.1, 2.9)	2.1 (1.3, 2.9)
Meglitinides	1.8 (0.4, 3.3)	1.8 (0.5, 3.1)
Thiazolidinediones	2.6 (1.7, 3.5)	2.7 (1.9, 3.5)
DPP-4 inhibitors	0.6 (–0.5, 1.6)	0.3 (–0.4, 1.1)
AG inhibitors	–0.9 (–2.4, 0.5)	–0.9 (–2.2, 0.4)
GLP-1 analogues	–1.8 (–3.4, –0.1)	–1.8 (–2.9, –0.8)
Basal insulin	1.6 (–0.5, 3.6)	1.7 (0.3, 3.1)
Biphasic insulin	3.0 (1.0, 5.0)	3.1 (1.5, 4.7)



C

Treatment added-on to metformin	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Sulfonylureas	8.22 (4.50, 16.63)	7.51 (4.39, 13.66)
Meglitinides	8.59 (3.34, 25.20)	8.30 (3.25, 23.44)
Thiazolidinediones	1.10 (0.54, 2.27)	0.93 (0.48, 1.78)
DPP-4 inhibitors	1.05 (0.56, 2.21)	0.93 (0.56, 1.62)
AG inhibitors	0.39 (0.01, 6.67)	0.39 (0.01, 6.59)
GLP-1 analogues	1.12 (0.33, 3.90)	1.05 (0.49, 2.30)
Basal insulin	5.20 (1.48, 21.46)	4.11 (1.68, 10.73)
Biphasic insulin	11.02 (3.48, 40.43)	6.99 (2.83, 18.14)



Δ = change; A1C = glycated hemoglobin; AG = alpha-glucosidase; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; OR = odds ratio.
Note: Forest plots comparing the results of the original (●) and updated (O) CADTH network meta-analyses for change from baseline in A1C (A), change from baseline in body weight (B), and overall hypoglycemia (C).

Table 5: Sensitivity Analyses for Change from Baseline A1C (%) — NMA Estimates vs. Placebo[a]								
Analysis	**Sulfonylureas**	**Meglitinides**	**TZDs**	**DPP-4 Inhibitors**	**AGIs**	**GLP-1 Analogues**	**Basal Insulin**	**Biphasic Insulin**
Reference case	–0.79 (–0.91, –0.67)	–0.64 (–0.91, –0.38)	–0.77 (–0.92, –0.63)	–0.69 (–0.79, –0.60)	–0.74 (–0.98, –0.51)	–0.96 (–1.13, –0.80)	–0.91 (–1.16, –0.67)	–1.06 (–1.32, –0.80)
Modelling assumption								
Fixed effects (instead of random effects)	–0.74 (–0.80, –0.68)	–0.59 (–0.77, –0.41)	–0.65 (–0.72, –0.58)	–0.67 (–0.72, –0.61)	–0.73 (–0.92, –0.54)	–0.92 (–1.02, –0.82)	–0.83 (–0.98, –0.68)	–1.01 (–1.16, –0.86)
Meta-regressions adjusting for:								
Baseline hemoglobin A1C	–0.80 (–0.92, –0.69)	–0.63 (–0.90, –0.36)	–0.78 (–0.92, –0.64)	–0.71 (–0.81, –0.61)	–0.74 (–0.98, –0.51)	–0.98 (–1.14, –0.82)	–0.96 (–1.21, –0.71)	–1.05 (–1.31, –0.80)
Baseline duration of diabetes	–0.82 (–0.94, –0.70)	–0.65 (–0.91, –0.39)	–0.76 (–0.90, –0.63)	–0.72 (–0.82, –0.62)	–0.69 (–0.93, –0.46)	–1.00 (–1.16, –0.83)	–1.00 (–1.26, –0.75)	–1.02 (–1.27, –0.77)
Duration of RCT	–0.78 (–0.90, –0.67)	–0.63 (–0.89, –0.38)	–0.71 (–0.86, –0.58)	–0.68 (–0.77, –0.59)	–0.74 (–0.97, –0.51)	–0.95 (–1.10, –0.80)	–0.91 (–1.14, –0.68)	–1.05 (–1.29, –0.81)
Sensitivity analyses with removal of:								
RCTs of rosiglitazone	–0.78 (–0.89, –0.67)	–0.63 (–0.88, –0.39)	–0.72 (–0.87, –0.58)	–0.69 (–0.78, –0.60)	–0.74 (–0.96, –0.52)	–0.95 (–1.10, –0.80)	–0.90 (–1.13, –0.68)	–1.04 (–1.28, –0.81)
RCTs of agents without a NOC	–0.81 (–0.95, –0.68)	–0.65 (–0.92, –0.39)	–0.83 (–0.99, –0.67)	–0.65 (–0.76, –0.53)	–0.85 (–1.12, –0.58)	–0.97 (–1.13, –0.80)	–0.91 (–1.16, –0.67)	–1.06 (–1.33, –0.81)
RCTs < 1 year in duration	–0.87 (–1.18, –0.56)	–0.74 (–1.24, –0.23)	–1.00 (–1.35, –0.63)	–0.81 (–1.11, –0.50)	–0.80 (–1.43, –0.16)	————	————	————
RCTs from which subgroup data were used	–0.85 (–0.97, –0.73)	–0.66 (–0.92, –0.41)	–0.73 (–0.89, –0.59)	–0.70 (–0.80, –0.61)	–0.73 (–0.97, –0.49)	–1.04 (–1.21, –0.88)	–0.96 (–1.21, –0.71)	–1.12 (–1.37, –0.87)
RCTs of duration other than 6 months (i.e., 24 to 26 weeks)	–1.06 (–1.40, –0.72)	–0.70 (–1.07, –0.34)	–0.95 (–1.28, –0.64)	–0.69 (–0.84, –0.54)	–0.86 (–1.18, –0.53)	–1.29 (–1.63, –0.97)	–1.15 (–1.59, –0.72)	–1.44 (–1.96, –0.92)

A1C = glycated hemoglobin; AGIs = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; NOC = Notice of Compliance; RCTs = randomized controlled trials; TZDs = thiazolidinediones; vs. = versus.

[a]All active treatments and placebo were provided in combination with metformin.

Severe Hypoglycemia

Severe hypoglycemia was typically defined as an event requiring third-party assistance. A total of 30 RCTs (N = 14,196)[37,40,42-44,51,53,55,56,58-60,62-65,67,68,70-73,77,83-85,92,94,97,98] were identified that reported the number of patients with at least one episode of severe hypoglycemia (24 in the original review and six in the updated review). Events of severe hypoglycemia were rare for all drug classes including the insulins and insulin secretagogues (i.e., meglitinides and sulfonylureas). Results from NMA are not reported for this outcome, as the rarity of events prevented model convergence. Pairwise comparisons are summarized in Table 6; however, given the very low occurrence of severe hypoglycemia across all trials and the consequent limitations in study power, the interpretability of these results is limited. Detailed results for severe hypoglycemia are reported in Table 16, Appendix 5.

Table 6: Summary of Findings for Severe Hypoglycemia

Comparison[a]	No. of Trials/Total N	OR (95% CI)	I^2 (%)
Placebo Comparisons			
Sulfonylurea vs. placebo	4 RCTs[59,70,73,89] (N = 637)	2.24 (0.34,14.9)	0%
Meglitinide vs. placebo	2 RCTs[71,72] (N = 366)	*No events*	—
TZD vs. placebo	3 RCTs[51,62,63] (N = 627)	*No events*	—
DPP-4 inhibitor vs. placebo	7 RCTs[56,58,65,89,90,93,96] (N = 2960)	*No events*	—
AGI vs. placebo	1 RCT[84] (N = 153)	*No events*	—
GLP-1 vs. placebo	3 RCTs[73,84,97] (N = 389)	0.33 (0.01, 8.40)*	
Active Comparisons			
Sulfonylurea vs. TZD	4 RCTs[64,83,96,98] (N = 1439)	*No events*	—
Sulfonylurea vs. DPP-4 inhibitor	5 RCTs[37,42,44,89,94] (N = 5794)	12.22 (3.34, 44.7)	0%
Sulfonylurea vs. biphasic insulin	1 RCT[68] (N = 222)	*No events*	—
DPP-4 inhibitor vs. TZD	1 RCT[55] (N = 575)	*No events*	—
DPP-4 inhibitor vs. basal insulin	1 RCT[85] (N = 501)	*No events*	—
GLP-1 analogue vs. DPP-4 inhibitor	2 RCTs[86,92] (N = 766)	*No events*	—
GLP-1 analogue vs. TZD	1 RCT[86] (N = 325)	*No events*	—
GLP-1 analogue vs. basal insulin	2 RCTs[40,53] (N = 145)	0.32 (0.01, 8.22)[†]	
GLP-1 analogue vs. biphasic insulin	1 RCT[41] (N = 354)	*No events*	—
Biphasic insulin vs. basal insulin	2 RCTs[67,77] (N = 297)	*No events*	—

AGI = alpha-glucosidase inhibitor; CI=confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; OR = odds ratio; RCT = randomized controlled trial; TZD = thiazolidinediones, vs. = versus.

[a] All active treatments and placebo were provided in combination with metformin.

c) Serious Adverse Events

Thirty-nine RCTs (N = 21,476)[37,38,42-48,51,54-56,58,61,63,65,69,75,77-79,82-87,89-93,95,96,98-101] for second-line pharmacotherapy were identified that reported total SAEs. The number of patients who experienced at least one SAE in the 4- to 12-week studies was generally low, ranging from 0.7% to 9.1% of the patient population. Exceptions to this were reported in two longer-term extension studies,[42,43] where 13% to 21% of the patient population experienced an SAE. Events of severe pancreatitis were rare. No statistical tests were conducted due to limited statistical power. Detailed results for SAEs are reported in Table 17, Appendix 6.

3 PHARMACOECONOMIC ANALYSIS

3.1 Objective

To update the 2010 CADTH pharmacoeconomic analysis of second-line therapies for type 2 diabetes to incorporate all agents currently approved in Canada, based on the results of the updated systematic review and NMAs.

3.2 Methods

3.2.1 Type of Economic Evaluation

Cost-utility analyses comparing alternative second-line therapies in adults with type 2 diabetes experiencing inadequate glycemic control with metformin monotherapy.

3.2.2 Target Population

Adults with type 2 diabetes inadequately controlled with metformin monotherapy. When available, characteristics of simulated patients were derived from RCTs included in the systematic review and NMA.

3.2.3 Treatments

All classes of second-line antidiabetes drugs currently approved in Canada were assessed: sulfonylureas, meglitinides, TZDs, GLP-1 analogues, DPP-4 inhibitors, insulins (bolus, biphasic, basal), and alpha-glucosidase inhibitors.

3.2.4 Perspective

The analysis was conducted from the perspective of a provincial health Ministry.

3.2.5 Efficacy and Safety

Treatment effects (A1C, overall hypoglycemia, weight) for the analysis were derived from the updated systematic review investigating the use of second-line antidiabetic agents in patients inadequately controlled on metformin monotherapy. Where possible, estimates of efficacy for the economic analysis were obtained from the NMA of these RCTs.

Most RCTs included in the meta-analysis were unlikely to have had adequate sample size or been of sufficient duration to capture incidence rates of infrequent events that may be of economic importance. These include:

- severe hypoglycemia in patients using insulin secretagogues or insulin
- congestive heart failure (CHF) in patients using TZDs.

Rather than pool results from smaller RCTs, event rates and treatment effects for these events were derived from large observational studies and randomized controlled trials. The baseline rates of severe hypoglycemia among patients using metformin (60 per 100,000 patients years), as well as the increased risk among patients using metformin plus sulfonylureas (OR, 4.04 [95% CI, 3.27 to 4.98]) and metformin plus sulfonylureas plus insulin (OR, 8.86 [95% CI, 4.47 to 17.6]), were derived from a population-based study by Bodmer et al.[50] Sensitivity analyses for this parameter were conducted using the higher rates of severe hypoglycemia reported in a study by Leese et al.[102] The increased risk of severe hypoglycemia in patients using insulin was included in the reference case economic analysis.

An increased risk of CHF in patients using TZDs (HR, 2.10 [95% CI, 1.35 to 3.27])[52] was incorporated in a sensitivity analysis. As there is no direct means for doing so in the UKPDS Outcomes Model, CHF risk was increased by augmenting body weight by 30 kg in patients using TZDs. CHF is the only sub-model influenced by body mass index (BMI); therefore, the increase in BMI did not affect any other outcomes.[3] However, a sensitivity analysis incorporating a disutility associated with weight gain would have been impacted by the augmented body weight of TZD-treated patients.

Other class-specific adverse effects were modelled in sensitivity analyses in a similar manner as in the original analysis, including gastrointestinal effects of alpha-glucosidase inhibitors, and fracture risk with TZDs.

3.2.6 Time Horizon

A 40-year time horizon was used for the reference case analysis.

3.2.7 Modelling

The latest version of the UKPDS Outcomes Model (version 1.3) was used to forecast long-term diabetes-related complications and cost consequences for each treatment class. The UKPDS Outcomes Model is a computer simulation model developed by the University of Oxford Diabetes Trials Unit for estimating the long-term impact of health interventions for people with type 2 diabetes over an extrapolated lifetime. It is based on patient data from the UKPDS and uses a wide variety of input data, including knowledge of previous events for individuals, and has the ability to take into account changes in some risk factor levels (such as blood glucose level, blood pressure, lipid levels, and smoking status) over time. The UKPDS has been well-validated through comparison of its predictions, with results reported in published clinical and epidemiological studies.[103]

The UKPDS Outcomes Model (version 1.3) had been revised from the version of the UKPDS Outcomes Model used in the original CADTH reports on second- and third-line treatments.[1,30] Updates include changes in modelling of smoking status and new features such as output of event rate and long-term history rate instead of cumulative event rate, as well as separation of diabetes-related death from other death.

3.2.8 Costs

a) Cost of Treatments

Unit costs for drugs were obtained from the Ontario Public Drug Programs (November 2012), when available. Otherwise, prices were obtained from other public drug programs (Quebec and British Columbia) in Canada. For the reference case analysis, the price of the lowest cost alternative was applied for each drug class (i.e., price of generic glyburide for sulfonylureas, generic pioglitazone for TZDs, insulin NPH for basal insulin, biphasic human insulin for biphasic insulin, generic repaglinide for meglitinides, linagliptin for DPP-4 inhibitors, exenatide for GLP-1 analogues, generic acarbose for alpha-glucosidase inhibitors) plus a 10% markup and a $7.00 pharmacy fee per 90-day supply. With the exception of metformin for which we assumed the use of maximal doses (2,000 mg per day), it was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.[104] The doses for insulin products (0.53 U/kg, 0.75 U/kg, 1.2 U/kg, and 1.5 U/kg for long-acting insulin analogues, insulin NPH, biphasic insulin analogues, and biphasic human insulin, respectively) were obtained from a convenience sample of patients with type 2 diabetes in British Columbia (Dr. Marshall Dahl, unpublished data, 2008).

Patients using certain antidiabetes agents (i.e., insulin secretagogues, insulin) typically use more blood glucose test strips than those using other agents. For the reference case analysis, the average daily utilization of blood glucose test strips for each drug class was derived from a recent utilization study in Ontario (Table 7).[105] A cost of $0.729 per test strip (as listed in the Ontario Public Drug Programs) plus a pharmacy fee of $7.00 per 100 test strips was applied. No markup was applied, as test strips are not eligible for markup in the Ontario Public Drug Programs. A sensitivity analysis was conducted, where the additional cost of test strips was not considered.

Table 7: Mean Daily Utilization of Blood Glucose Test Strips in 2008 by Seniors in the Ontario Public Drug Programs, by Type of Pharmacotherapy[a]

Therapy	Daily Use	Standard Deviation
Insulin	2.08	1.71
Hypoglycemia-inducing oral glucose-lowering drugs	1.16	0.94
Non-hypoglycemia-inducing oral glucose-lowering drugs	0.94	1.19

[a] Gomes et al.[105]

A significant change from the previous analysis was the reduction in cost of generic pioglitazone by approximately 48% (down from $2.20 to $1.14 per 30 mg tablet). This resulted in the cost of generic pioglitazone being less than that of insulin NPH, in contrast to the original analysis. The older generation sulfonylurea, glyburide, remained the treatment with the lowest daily cost among active treatments, even after the additional cost of blood glucose test strips was applied (Table 8). Generic pioglitazone, DPP-4 inhibitors, and insulin NPH were less expensive than long-acting insulin analogues, biphasic human insulin, and GLP-1 analogues.

b) Costs Due to Long-Term Diabetes Complications

Resource utilization and costs associated with managing long-term diabetes-related complications were obtained from the Ontario Ministry of Health and Long-term Care (2006) (Table 9)[106] In-patient, outpatient, emergency room visits, prescription drug claims, long-term care, and home care costs for managing diabetes-related complications were included in the model. Costs were inflated to 2012 Canadian dollars using the Health Component of the Canadian Consumer Price Index. The average annual cost for patients without diabetes-related complications who were using metformin was $1,931, while those using second-line therapies had an annual cost of $1,931 plus the additional cost of second-line therapy and blood glucose test strips.

Table 8: Average Daily Cost of Treatments With and Without the Cost of Blood Glucose Test Strips			
Treatment	**Assumed Doses**	**Daily Treatment Cost Without Test Strips[a]**	**Daily Treatment Cost With Test Strips**
Alpha-glucosidase inhibitors	Acarbose 300 mg daily	$1.28	$2.04
DPP-4 inhibitors	Linagliptin 5 mg daily	$2.88	$3.63
GLP-1 analogues	Exenatide 20 mcg daily	$5.13	$5.88
Sulfonylureas	Glyburide 10 mg daily	$0.20	$1.13
TZDs[b]	Pioglitazone 30 mg daily	$1.33	$2.08
Meglitinides	Repaglinide 4 mg daily	$0.32	$1.25
Basal human insulin	Insulin NPH 0.75 U per kg per day[c]	$1.93	$3.60
Long-acting insulin analogues	Insulin glargine 0.53 U per kg per day[c]	$3.12	$4.78
Biphasic human insulin	Insulin NPH 30/70 1.50 U per kg per day[c]	$3.83	$5.48

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; TZD = thiazolidinediones; U = units.

[a] The cost of the lowest cost alternative was applied for each drug class, plus a 10% markup and $7.00 pharmacy fee per 90-day supply. It was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.[104]

[b] Based on the cost of 30 mg generic pioglitazone in Saskatchewan.[107]

[c] Insulin doses obtained from patient sample in British Columbia (Dr. Marshall Dahl, unpublished data, 2008). This dataset reported insulin doses of 0.53, 0.75, and 1.5 U/kg for long-acting insulin analogues, insulin NPH, and biphasic human insulin, respectively. Total daily costs for insulins are based on assumed body weight of 87 kg (derived from RCTs included in the systematic review).

Table 9: Management Costs of Long-Term Diabetes-Related Complications[a]			
Complications	**Fatal**	**Non-Fatal**	**In Subsequent Years**
Ischemic heart disease	$0	$5,950	$3,436
Myocardial infarction	$9,971	$19,012	$2,973
Heart failure	$0	$17,392	$4,876
Stroke	$9,382	$25,896	$3,593
Amputation	$0	$40,170	$5,502
Blindness	$0	$3,181	$2,267
Renal failure	$0	$25,774	$11,698

[a] Costs from the Ontario Diabetes Economic Model (ODEM)[106] inflated to 2012 Canadian dollars (C$) using the health component of the Consumer Price Index.

c) Costs Due to Hypoglycemic Episodes

For the reference case, it was assumed that episodes of mild to moderate hypoglycemia had no impact on health services resource use. Resource utilization associated with managing a severe hypoglycemic episode was based on studies by Leese et al.[102] and the National Institute for Health and Clinical Excellence (NICE).[108] Management costs were based on data from the Alberta case costing database (2006).[109] Because resource use was derived from the United Kingdom, the information for the previous analysis was presented to diabetes expert members of CERC for verification. In general, they felt the data were reasonable, although the percentage of patients receiving glucagon was thought to be higher than that in Canada. The average cost, therefore, of a severe hypoglycemic episode may be overestimated, potentially biasing results against therapies that are associated with an increased risk of hypoglycemia (e.g., insulin).

Table 10: Cost of Severe Hypoglycemic Events			
Resource Use	**Unit Cost**[a]	**% Receiving**[b]	**Weighted**
Glucagon	$77.72	90%	$69.94
Consultation with ambulance services only	$639	34%	$217.31
Consultation with primary/emergency care only	$218	7%	$15.24
Consultation with both primary/emergency care and ambulance service[c]	$857	52%	$445.58
Direct or indirect hospital admission[c]	$4,582	28%	$1,282.84
Total			**$2,030.92**

[a] Costs updated and inflated to 2012 Canadian dollars.
[b] Data from the United Kingdom.[108]
[c] Unit cost from Alberta.[109]

3.2.9 Valuing Outcomes

The primary outcomes measure in the analysis was the quality-adjusted life-year, which captures both quantity and quality of life. Patients with type 2 diabetes were assumed to have a EuroQol 5-dimension (EQ-5D) score of 0.753 based on a US catalogue of EQ-5D scores from Sullivan et al.[110,111] Quality weights for modelled long-term diabetes-related complications were obtained from Sullivan et al.[110,111] when available. Otherwise, utility scores were obtained from a study by Clarke et al.,[3] who also used the EQ-5D instrument. Estimates from Clarke et al.[3] are often used in cost- effectiveness studies related to diabetes interventions. However, unlike Sullivan et al.,[110,111] Clarke et al.[3] did not control for non–diabetes-related complications or other confounding variables such as income, education, ethnicity, and number of comorbidities — all of which may impact health-related quality of life (HRQoL). Multiple complications were assumed to have an additive effect on utility. For example, the utility of a patient who has a myocardial infarction and then an amputation would first be decremented 0.0409, and then by a further 0.28.

Table 11: Utility Decrements Associated With Modelled Diabetic Complication Health States		
Complication	**Utility Decrement (Year 1)**	**Utility Decrement in Subsequent Years (Year ≥ 2)**
Ischemic heart disease	–0.0412	–0.0240
Myocardial infarction	–0.0409	–0.0120
Heart failure	–0.0635	–0.0180
Stroke	–0.0524	–0.0400
Amputation[a]	–0.28	–0.28
Blindness	–0.0498	–0.0498
Renal failure [a]	–0.2630	–0.2630

[a] Utility decrements were not available from the US catalogue;[110,111] therefore, they were obtained from a study by Clarke et al.[3]

There is limited evidence that examines the impact of hypoglycemia and fear of hypoglycemia on HRQoL. Moreover, widely cited evidence in this area is of low quality. For the reference case analysis, patients experiencing mild to moderate hypoglycemia were assumed to have a transient reduction in HRQoL. Patients were assumed to move from having no problems to a health state characterized by moderate anxiety, with or without depression, and having some problems with performing usual activities, thus resulting in a disutility of 0.167 during the episode.[112] Each mild to moderate hypoglycemic episode was assumed to last for 15 minutes, which coincides with the 15/15 rule: 15 grams of carbohydrate followed

by 15 minutes of waiting.[113] Thus, each episode was associated with an annual decrement of 0.000004767 quality-adjusted life-years (QALYs). In contrast, those having a severe hypoglycemic episode were assumed to have a transient reduction in HRQoL followed by a chronic decrement in HRQoL due to fear of future hypoglycemic episodes. The same decrement applied in a published report by NICE[108] of an annual decrement of 0.01 was applied for each severe hypoglycemic event.

A utility decrement for weight gain in the primary economic analysis was not applied. Most widely cited studies derive such estimates from much larger weight differences (i.e., 13 kg to 30 kg) and it is unclear whether these can be applied to the smaller weight differences between agents observed in the NMA of second-line therapies. It is also uncertain whether these utility decrements are sustained over time. A sensitivity analysis was performed based on data presented in the NICE obesity guidelines,[114,115] which assumed a utility decrement of 0.001950135 per unit increase in BMI. This utility decrement was applied to each year of the simulation based on the estimated BMI for each treatment.

3.2.10 Handling of Uncertainty

a) Univariate Sensitivity Analyses

Univariate sensitivity analyses were conducted to explore the impact of variation in model inputs and assumptions. Parameters varied in sensitivity analyses were selected based on findings from the previous analysis, and in light of the magnitude of changes observed in the updated review of the clinical evidence. Therefore, not all parameters tested in the original analysis were reassessed.

b) Cost-Effectiveness Acceptability Curves

A non-parametric bootstrapping method (a technique used to approximate the accuracy — for example, the standard error and confidence interval — of a statistical estimate), consisting of 999 bootstrap iterations of 100 patients each, was used to estimate the mean quality-adjusted life expectancy and lifetime costs for each treatment arm. Costs and effectiveness for each treatment, as derived from the 999 bootstrap iterations, were plotted as cost-effectiveness acceptability curves to convey the inherent uncertainty in the reference case results. Net benefits cost- effectiveness acceptability curves were generated based on the proportion of bootstrap iterations with the highest net monetary benefit across a range of willingness-to-pay thresholds, according to the following formula:

Net monetary benefit = $\lambda * E - C$, where λ = decision-maker's willingness-to-pay per QALY gained; E = total QALYs for each treatment; C = total lifetime cost of each treatment.

c) Threshold Analysis

Threshold analyses were also conducted for treatments which were not cost-effective in the base case. They were done to determine the minimal price change necessary for each of those classes to become the second-line treatment strategy with the most favourable cost-effectiveness results in comparison with other second-line treatments strategies.

3.3 Results

3.3.1 Reference Case

From the updated analysis (Table 12), sulfonylureas were associated with the lowest total lifetime costs ($48,397), while use of biphasic insulin incurred the highest lifetime costs ($60,891). Cost-effectiveness estimates were largely driven by the difference in prices across treatments. Sulfonylureas were associated with the most favourable cost-effectiveness estimate, with an incremental cost of $8,445 per QALY gained relative to metformin monotherapy. Other active treatments were associated with unfavourable cost-effectiveness estimates (i.e., they were dominated or demonstrated very high ICURs) when compared with the next least costly treatment.

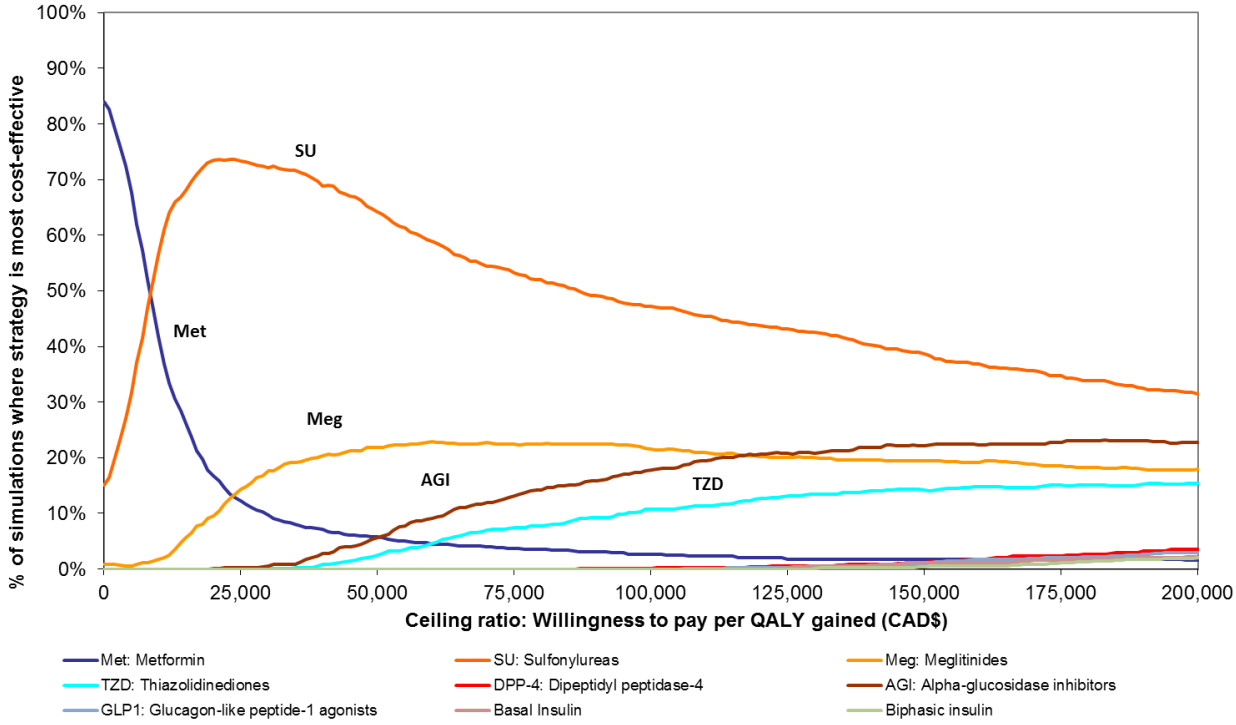
Table 12: Total Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Results from the Updated Reference Case Analysis

Treatment Added to Metformin	Cost	Effectiveness (QALY)	ICUR	
			Incremental vs. Metformin Monotherapy	Sequential
None/placebo	$47,949	8.6083		N/A
Sulfonylurea	$48,397	8.6613	$8,445	$8,445
Alpha-glucosidase inhibitor	$50,603	8.6662	$45,783	$452,630
GLP-1 analogue	$60,254	8.6824	$165,916	$595,653
Treatments Ruled Out by Dominance or Extended Dominance				
Meglitinide	$48,938	8.6520	$22,589	Dominated by sulfonylurea
TZD	$50,873	8.6600	$56,548	Dominated by sulfonylurea and alpha-glucosidase inhibitor
DPP-4 inhibitor	$54,744	8.6602	$130,710	Dominated by sulfonylurea and alpha-glucosidase inhibitor
Basal insulin	$56,077	8.6594	$158,934	Dominated by sulfonylureas; alpha-glucosidase inhibitor; TZD; and DPP-4 Inhibitor
Biphasic insulin	$60,891	8.6761	$190,713	Dominated by GLP-1 analogue

DPP-4 = dipeptidyl peptidase-4; in; GLP-1 = glucagon-like peptide-1; NA = not applicable; QALY = quality-adjusted life-year; TZD = thiazolidinedione.

Sulfonylureas demonstrated the highest net benefit among active treatments and the most favourable ranking across all willingness-to-pay thresholds considered. The cost-effectiveness acceptability curve (Figure 4) shows that the addition of a sulfonylurea to metformin had the highest probability of being the most cost-effective strategy for willingness-to-pay thresholds above approximately $22,000 per QALY gained.

Figure 4: Cost-Effectiveness Acceptability Curve for the Reference Case Analysis



3.3.2 Sensitivity Analyses

The results of the updated sensitivity analyses around the cost-effectiveness of second-line treatments indicated that sulfonylureas added to metformin remained the most cost-effective option. Full results from the sensitivity analyses are provided in Appendix 9. The following is a summary of some of the notable results from sensitivity analyses:

- When incorporating the effect estimates from direct pairwise comparisons, the ranking of generic pioglitazone (TZD) improved, largely due to the significant reduction in its unit cost, resulting in a lower incremental cost of treatment compared with metformin.
- Applying a higher disutility of 0.0052 to every mild or moderate hypoglycemic event (NICE)[116] deteriorated the cost-effectiveness of sulfonylureas compared with metformin monotherapy, but they remained the most cost-effective option. Other impacts of this change included alpha-glucosidase inhibitors being dominated by sulfonylureas, and the incremental cost-effectiveness of GLP-1 analogues deteriorated to $1,029,960 compared with metformin and sulfonylurea combination therapy.
- Assuming quality of life reduction resulting from weight gain (according to the NICE obesity guidelines,[114,115] a utility decrement of 0.001950135 per unit increase in BMI was applied) or higher rates of mild to moderate hypoglycemia[37] caused a deterioration in the cost- effectiveness results for DPP-4 inhibitors, so that they only remained favourable in relation to GLP-1 analogues, basal insulins, and biphasic insulin ( ).

Table 13: Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results From a Sensitivity Analysis Assuming a Utility Decrement of 0.001950135/U Increase in BMI				
Strategy	**Cost**	**Effectiveness**	**Incremental vs. Met**	**Sequential**
Met	$47,949	8.5945		
Met + SU	$48,511	8.6306	$15,540	$15,540
Met + AGI	$50,603	8.6600	$40,519	$71,291
Met + GLP-1	$60,254	8.6824	$139,931	$430,009
Dominance and Extended Dominance				
Met + Meg	$48,938	8.6241	$33,371	Dominated by: Met + SU
Met + TZD	$50,873	8.6246	$97,023	Dominated by: Met + SU; and Met + AGI
Met + DPP-4	$54,744	8.6439	$137,469	Dominated by: Met + AGI
Met + basal insulin	$56,077	8.6325	$213,843	Dominated by: Met + AGI; and Met + DPP-4
Met + biphasic insulin	$60,891	8.6370	$304,734	Dominated by: Met + AGI; Met + DPP-4; and Met + GLP-1

AGI = alpha-glucosidase inhibitor; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; in; GLP-1 = glucagon-like peptide-1 analogue; Meg = meglitinides; Met = metformin; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione; U = unit; vs. = versus.

- Upon initial reduction in A1C due to treatment, the UKPDS model assumes a gradual increase in A1C over time that occurs at the same slope in all treatment arms. To address the limitation of the reference case analysis in the absence of therapy progression over time, it was assumed in a sensitivity analysis that when A1C increased to 9%, insulin NPH (0.75 U/kg/day) would be added as a third-line treatment in all treatment arms (for the insulin NPH arm, this assumption represented an increase in dose by 0.75 U/kg/day). The results of this analysis showed that sulfonylureas remained the most favourable option, dominating all other treatment arms (including metformin), with the exception of GLP-1 analogues.

3.3.3 Threshold Analysis

The results of varying unit prices in the threshold analysis showed that, in order to become a more favourable second-line treatment strategy than sulfonylureas, the unit cost of the modelled DPP-4 inhibitor would have to be 90% lower (resulting in an ICUR of $7,539 per QALY gained relative to metformin monotherapy). When price reductions less than 90% were modelled, DPP-4 inhibitors remained either dominated or extendedly dominated. For GLP-1 analogues, a 95% reduction in unit price would be necessary for this class to be the most cost-effective treatment option (for an ICUR of $761 per QALY gained relative to metformin monotherapy). For price reductions between 75% and 90%, sulfonylureas were the most cost-effective option, and ICURs for the GLP-1 analogue relative to sulfonylureas ranged from approximately $104,000 to $12,000 per QALY gained. Price reductions below 75% resulted in a fifth or sixth place ranking for cost-effectiveness. The full results of the threshold analysis are presented in Table 14.

Table 14: Threshold Analysis for DPP-4 Inhibitors and GLP-1 Analogues as Second-line Treatments					
Class	**Price Reduction**	**New Unit Price**	**ICUR (vs. metformin monotherapy)**	**Sequential ICUR**	**Rank**
DPP-4 (linagliptin 5 mg)	Reference case	$2.55	$130,710 per QALY	Dominated by SU and AGI	5
	50%	$1.275	$62,282 per QALY	Dominated by SU and AGI	5
	60%	$1.02	$48,596 per QALY	Dominated by SU	4
	75%	$0.638	$28,067 per QALY	Dominated by SU	3
	80%	$0.510	$21,224 per QALY	Dominated by SU	2
	90%	$0.255	$7,539 per QALY	$7,539 per QALY (relative to metformin)	1
GLP-1 (exenatide 20 mcg)	Reference case	$2.295	$165,916 per QALY	$595,653 per QALY (relative to AGI)	8
	50%	$1.148	$78,992 per QALY	$197,787 per QALY (relative to AGI)	5
	60%	$0.918	$61,607 per QALY	$118,213 per QALY (relative to AGI)	6
	75%	$0.574	$36,530 per QALY	$103,759 per QALY (relative to SU)	3
	80%	$0.460	$26,838 per QALY	$73,168 per QALY (relative to SU)	3
	90%	$0.230	$9,453 per QALY	$11,990 per QALY (relative to SU)	2
	95%	$0.115	$761 per QALY	$761 per QALY (relative to metformin)	1

AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 analogue; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione; vs. = versus.

4 DISCUSSION

The objective of this review was to conduct an update of CADTH's 2010 systematic review and NMAs of diabetes pharmacotherapy for patients who were inadequately controlled with metformin monotherapy. The literature search identified 20 additional RCTs that were incorporated into the CADTH review, increasing the total number to 69 unique RCTs.

4.1 Interpretation of Systematic Review Results

The results of the updated NMAs for A1C, hypoglycemia, and body weight were consistent with the original CADTH analyses, as well as other systematic reviews and meta-analyses that have assessed the comparative efficacy of antidiabetes drugs in patients with inadequate glycemic control on metformin monotherapy.[117-119] Also consistent with other systematic reviews on oral antidiabetes drugs,[120,121] there remained a lack of conclusive evidence regarding the effects of various therapies on the long-term complications of diabetes.

Regarding glycemic control, the updated NMA demonstrated that each of the eight drug classes resulted in statistically significant reductions in A1C relative to placebo, with no statistically significant differences between any of the active treatments. For GLP-1 analogues, the revised estimate of effect against metformin alone was –0.95%, slightly larger than the original estimate of –0.82%. For DPP-4 inhibitors, the revised estimate diminished from –0.80% in the original analysis to –0.70%. Neither difference is within the range commonly cited as being of clinical importance (i.e., 0.5% to 1.0%).

Sulfonylureas, meglitinides, TZDs, and insulins were associated with statistically significant increases in body weight ranging from 1.8 kg to 3.1 kg relative to metformin alone. DPP-4 inhibitors and alpha-glucosidase inhibitors were found to not affect body weight, and GLP-1 analogues were associated with a statistically significant reduction in body weight of 1.7 kg. There are no well-accepted thresholds for the minimal weight change that is considered to be clinically significant, although weight reductions of 5% to 10% are cited as such in the literature.[114,122-126] In this context, the differences in body weight that we observed between classes are probably modest for most patients. The overall weighted mean body weight of patients represented in the NMA was 91 kg; therefore, the two situations where the estimated difference between two treatments approached the 5% threshold was the difference between GLP-1 analogues and biphasic insulin (4.9 kg), and GLP-analogues and TZDs (4.5 kg). The weight changes observed in the included trials represent treatment durations of up to one year, and often less. It remains uncertain whether weight gain with the insulin secretagogues and insulins continues over the long-term, or whether stabilization occurs at some point.

Both insulins and insulin secretagogues produced significantly increased hypoglycemia relative to placebo, whereas the TZDs, DPP-4 inhibitors, GLP-1 analogues, and alpha-glucosidase inhibitors did not. Severe hypoglycemia events were rarely observed across all drug classes, including the insulins and insulin secretagogues. In large observational studies and long-term RCTs, estimates of the risk of severe hypoglycemia vary considerably. Leese et al. reported 0.90 and 11.8 events requiring emergency medical care per 100 patient-years with insulin secretagogues and insulin, respectively,[102] while Bodmer et al. reported rates of 0.06 and 0.24 events resulting in hospitalization or death per 100 patient-years.[50] In comparison, the ADVANCE trial lists reported lower incidence rates than Leese et al. (0.7 per 100 patient-years in the intensive glycemic control arm versus 0.4 per 100 patient-years in the standard control arm), even though their definition of severe hypoglycemia was more liberal in that medical resource use was not

required.[127] In the RECORD study, only 0.3% of subjects in the control arm (all of whom used metformin and a sulfonylurea) experienced a severe hypoglycemic event over the 5.5-year mean follow-up of the study.[52] Overall, it appears that the risk of severe hypoglycemia with insulin secretagogues is generally low; therefore, any advantages of TZDs, GLP-1 analogues, and DPP-4 inhibitors are probably modest in absolute terms. More research is required to determine whether these agents provide greater benefits in patient groups recognized to be at higher risk of severe hypoglycemia or its consequences, such as the elderly.

Each class of antidiabetes therapy is associated with risks that partially offset its benefits. Among the older agents, the insulins and insulin secretagogues carry an increased risk of hypoglycemia and weight gain. TZDs have been shown to increase the risk of CHF, fractures, and weight gain.[52,128-133] Indeed, since publication of the original CADTH report on second-line therapy, severe restrictions have been placed on the use of rosiglitazone due to the risks of ischemic heart disease.[6] Furthermore, there is some evidence to show that pioglitazone may increase the risk of bladder cancer. [134,135] Although there is considerably more clinical experience with the DPP-4 inhibitors and GLP-1 analogues since the original CADTH report was published, the long-term safety profile of these newer agents compared with older classes is still evolving; results from ongoing long-term trials of these agents powered for cardiovascular outcomes will provide important insights in the coming years.[136-140] The product monographs for all of the incretins (i.e., DPP-4 inhibitors and GLP-1 analogues) currently marketed in Canada include a warning regarding the potential risk of acute pancreatitis with these agents. The association between pancreatitis and incretin agents has not been fully elucidated and is largely based on post-market reports.[17-21] A recent population-based, case-control study involving 1,269 hospitalized cases with acute pancreatitis and an equal number of controls reported a significantly increased risk of pancreatitis in users of exenatide or sitagliptin compared to non-users (odds ratio, 2.24 [95% CI, 1.36 to 3.68]).[141]

Several observational studies have suggested that sulfonylureas are associated with an increased risk of mortality and cardiovascular events and death compared to metformin.[142-144] Most recently, a large retrospective cohort study from the Agency for Healthcare Research and Quality reported that the use of sulfonylureas was associated with 2.2 (95% CI: 1.4 to 3.0) more cardiovascular disease events per 1,000 person-years than metformin.[144] All of the patients in the trials included in our systematic review were receiving metformin as background therapy; therefore, the results of these observational studies are not necessarily applicable to the population of interest for this review. In addition, it remains unclear if these results are attributable to cardioprotective effects of metformin, cardiotoxicity of sulfonylureas, or insufficient adjustment of known or unknown confounding factors.

4.2 Pharmacoeconomic Considerations

The reference case results of the 2010 CADTH report on the cost-effectiveness of second-line treatments indicated that sulfonylureas were associated with the most favourable cost- effectiveness estimate; with an incremental cost of $12,757 per QALY gained relative to metformin monotherapy (full results are provided in Appendix 10). The updated cost- effectiveness analysis, based on the results of the updated NMA, indicated that sulfonylureas remained the most cost-effective second-line therapy in patients inadequately controlled on metformin monotherapy, despite higher rates of hypoglycemia relative to newer oral antidiabetic drugs. Similar to the original analysis, the favourable cost-effectiveness results for sulfonylureas were attributable to the following:

- low price relative to other classes of drugs, especially newer agents and insulin
- minimal differences in glycemic control between active drug classes, resulting in small differences in complication rates and QALYs gained

- low absolute risk of severe hypoglycemia requiring health care resources use.

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

The GLP-1 analogue and DPP-4 inhibitors were among the classes with the least favourable cost-effectiveness results, largely driven by their high cost and similar gains in glycemic control as less costly drug classes. Threshold analyses revealed that significant unit price reductions would be necessary in order to displace sulfonylureas as the most cost-effective second-line therapy.

4.3 Strengths and Limitations

The updated systematic review was conducted according to a protocol specified in advance, using standard approaches for identification of evidence, data abstraction, quality assessment, and analysis.[29] By conducting an NMA, both direct and indirect estimates of effect were captured, and results are reported in a manner that is practical for health care professionals and decision-makers. Results from the NMA were highly consistent with those from direct pairwise comparisons across all outcomes, a finding that adds validity to the analysis. Sensitivity analyses and meta-regressions were conducted to explore methodological heterogeneity. The consistency of these results with the reference case analysis demonstrates the robustness of the findings. In addition, the findings reported by CADTH on the efficacy of second-line treatments added onto metformin have been independently confirmed in similar published NMAs.[117,118]

Despite the aforementioned strengths, limitations related to the available evidence warrant discussion. First, the population of interest for the systematic review consisted of patients inadequately controlled with first-line metformin monotherapy who required a second-line agent; but most identified trials included patients who might have received various antidiabetes agents prior to the use of metformin monotherapy. However, the relative treatment effects we report are likely transferable to patients treated with initial metformin monotherapy, as the reference case results were robust to adjustment (through meta-regression) for differences across studies in duration of diabetes and baseline A1C (likely more important predictors of efficacy than treatment history). Second, there was little evidence for the effect of second-line agents on long-term diabetes-related complications, hence comparative efficacy on such outcomes must be inferred from A1C, a surrogate with some important limitations, particularly with respect to the prediction of macrovascular outcomes.[145,146] As well, rates of severe hypoglycemia were too low for meaningful comparisons between treatments on this important adverse event. Finally, due to the relatively short duration of most included trials, it was impossible to accurately determine whether there were differences in the durability of antihyperglycemic effects across the various drug classes. However, it is noteworthy that one open-label study — EUREXA (which could not be included in the NMA) — suggested that patients treated with exenatide were able to maintain glycemic control longer than those treated with glimepiride.[43]

The reference case for the NMA was conducted by grouping agents into classes (e.g., sulfonylureas, DPP-4 inhibitors, and GLP-1 analogues) — an approach that requires the important assumption that agents within a particular drug class are similar enough to pool. The individual agent NMA was conducted to investigate the similarity of effect sizes within each drug class; the results suggested that the effects are similar within the classes, supporting the decision to conduct the class-level analysis. The decision to pool insulin NPH with long-acting insulin analogues (i.e., insulin glargine and insulin detemir) into a single “basal

insulin" drug class may be questioned by some, as these agents have different pharmacodynamics profiles. However, CADTH's prior assessment of long-acting insulin analogues found little to no difference between insulin NPH and insulin glargine for A1C (weighted mean difference [WMD] [95% CI] = –0.05% [–0.13% to 0.04%]) or insulin NPH and insulin detemir [WMD (95% CI) = 0.13% (0.03% to 0.22%)].[147,148] These findings suggest that it is appropriate to pool these agents into a single "basal insulin" class for the purposes of this NMA.

Regarding limitations of the pharmacoeconomic analysis, it should be noted that the UKPDS model does not explicitly incorporate a number of diabetes-related morbidities (e.g., peripheral neuropathy and ulceration). Furthermore, some complications are represented as a single end point (e.g., blindness and end-stage renal disease) in the model rather than intermediate states (e.g., retinopathy and nephropathy) that may themselves be associated with reduced HRQoL. Because a reduced incidence of these outcomes and the resulting benefits of HRQoL and reduced treatment costs are not captured, use of the UKPDS model may result in slight overestimation of incremental cost-effectiveness ratios. However, the impact of this factor on cost- effectiveness estimates is likely minimal given the minimal differences in glycemic control across drug classes.

Modelling changes in treatment sequences over time is challenging with any model, including the UKPDS Outcomes Model. There is uncertainty about which treatment patients will add on or switch to after inadequate control on second-line therapy. Furthermore, when patients use multiple treatments over time, it is difficult to assess whether benefits conferred are attributable to the treatment of interest or to subsequent treatments. Due to these considerations, it was assumed in the reference case that patients remained on their respective second-line therapy over their expected lifetime, without adding or switching to subsequent agents. This approach is admittedly not reflective of clinical practice given the progressive nature of diabetes. The effect of this assumption was tested through sensitivity analyses, whereby patients were assumed to add on NPH insulin as third-line therapy after predefined criteria were met (i.e., when a patient's A1C level reached or surpassed 9.0%). The addition of insulin to the treatment regimen of patients inadequately controlled with oral medications is recommended in clinical practice guidelines. However, to conduct these sensitivity analyses within the UKPDS model, the weight and hypoglycemia inputs had to be front-loaded (i.e., applied in Year One) because, unlike A1C, these parameters could not be modified over time. Some elements of the sensitivity analysis results could therefore not be discounted appropriately. In the future, if the UKPDS model is updated to enable a more seamless integration of changes in treatment sequences over time, re-analysis may be warranted.

Regarding the inputs used in the analysis, there was considerable uncertainty over the disutility associated with insulin use, weight gain, and hypoglycemia, as well as event rates for severe hypoglycemia. In the absence of sound data for these inputs, conservative estimates were used for the reference case analysis but were tested in the sensitivity analyses.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

In this systematic review and NMA of RCT evidence related to the second-line use of antidiabetes therapies after inadequate control with metformin monotherapy, all drug classes added to metformin achieved statistically significant reductions in A1C. Events of severe hypoglycemia were rare for all agents; however, the insulins and insulin secretagogues were associated with a statistically significant increase in overall hypoglycemia relative to the other classes. Increased body weight was observed with the majority of second-line therapies — the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues. Further studies of adequate size and duration are required to assess comparative efficacy in durability of antihyperglycemic effect, long-term complications of diabetes, and quality of life.

The results of the updated cost-effectiveness analysis comparing second-line treatments for type 2 diabetes after inadequate control with metformin monotherapy were congruent with the results of the original analysis. Sulfonylureas added to metformin represented the most cost-effective second-line therapy, a finding that was robust in numerous sensitivity analyses. These results were primarily driven by the low cost of sulfonylureas relative to other drugs, marginal differences in glycemic control and long-term complications between sulfonylureas and other agents, and the expected low absolute risk of severe hypoglycemic episodes requiring health care resource use. GLP-1 analogues, which could not be considered in the original analysis, as no agents were approved in Canada at the time, were found to be associated with a high ICUR in the updated analysis. In order to surpass the sulfonylureas as the most cost-effective second-line therapy, reductions in cost of 90% or more would be required for this class and the DPP-4 inhibitors. Because of the lack of adequate clinical data, there was considerable uncertainty surrounding some of the key drivers in the economic analysis. These included the impact of insulin use and hypoglycemia on quality of life, and the incidence of severe hypoglycemia across various treatments.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment EBM Reviews - NHS Economic Evaluation Database EMBASE Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 7, 2012
Alerts:	Monthly search updates ran until publication of the final report.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; and economic literature.
Limits:	Publication years January 1, 2009 onwards English language Humans

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
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	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

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
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 Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
8	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
10	275371-94-3.rn.
11	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
12	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
13	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.
14	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
15	(dpp adj IV adj inhibitor*).ti,ab.
16	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
17	DPP-4 inhibitors.ti,ab.
18	dipeptidyl peptidase-4 inhibitors.ti,ab.
19	exp Sulfonylurea Compounds/
20	(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.
21	(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.
22	alpha-Glucosidases/ai
23	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
24	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
25	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
26	Acarbose/
27	Lipase/ai
28	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
29	(96829-58-2 or 106650-56-0).rn.
30	(lipase adj inhibit*).ti,ab.
31	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
32	(135062-02-1 or 105816-04-4).rn.
33	Amyloid/
34	(Pramlintide or symlin).ti,ab.
35	(amylin adj analog*).ti,ab.
36	151126-32-8.rn.
37	exp insulin/
38	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
39	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
40	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
41	(nph insulin or humulin or novolin).ti,ab.
42	11061-68-0.rn.
43	(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.
44	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
45	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
46	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
47	or/1-46
48	exp Diabetes Mellitus, Type 2/
49	Diabetes mellitus/
50	((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.
51	(Mody or niddm or t2dm).ti,ab.
52	or/48-51
53	Metformin/
54	Metformin.ti,ab.
55	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
56	(657-24-9 or 1115-70-4).rn.
57	(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.
58	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
59	(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.
60	or/53-59
61	47 and 52 and 60
62	61 use pmez
63	Antidiabetic agent/
64	Oral Antidiabetic agent/
65	((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.
66	exp *glitazone derivative/
67	(glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab.
68	(122320-73-4 or 155141-29-0).rn.
69	exp *Dipeptidyl Peptidase IV Inhibitor/
70	(sitagliptin or Januvia or Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
71	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
72	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
73	275371-94-3.rn.
74	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
75	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
76	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab.
77	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
78	(dpp adj IV adj inhibitor*).ti,ab.
79	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
80	DPP-4 inhibitors.ti,ab.
81	dipeptidyl peptidase-4 inhibitors.ti,ab.
82	exp *sulfonylurea derivative/
83	(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.
84	(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.
85	exp *"Alpha Glucosidase Inhibitor"/
86	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
87	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
88	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
89	Lipase inhibitor/
90	*Tetrahydrolipstatin/
91	*Sibutramine/
92	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
93	(96829-58-2 or 106650-56-0).rn.
94	(lipase adj inhibit*).ti,ab.
95	*Meglitinide/
96	*Repaglinide/
97	*Nateglinide/
98	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
99	(135062-02-1 or 105816-04-4).rn.
100	*Pramlintide/
101	(Pramlintide or symlin).ti,ab.
102	(amylin adj analog*).ti,ab.
103	151126-32-8.rn.
104	*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/
105	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
106	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
107	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
108	(nph insulin or humulin or novolin).ti,ab.
109	11061-68-0.rn.
110	(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.
111	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
112	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
113	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
114	*exendin 4/
115	*albiglutide/ or *liraglutide/ or *lixisenatide/ or *taspoglutide/
116	or/63-115
117	*Diabetes Mellitus/
118	*Maturity Onset Diabetes Mellitus/
119	*Non Insulin Dependent Diabetes Mellitus/
120	*Lipoatrophic Diabetes Mellitus/
121	((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.
122	(Mody or niddm or t2dm).ti,ab.
123	or/117-122
124	Metformin/
125	Metformin.ti,ab.
126	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
127	(657-24-9 or 1115-70-4).rn.
128	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
129	(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.
130	(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 imethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
131	or/124-130
132	116 and 123 and 131
133	132 use emef
134	62 or 133
135	limit 134 to english
136	limit 135 to yr="2009 -Current"
137	exp animals/
138	exp animal experimentation/
139	exp models animal/
140	exp animal experiment/
141	nonhuman/
142	exp vertebrate/
143	animal.po.
144	or/137-143
145	exp humans/
146	exp human experiment/
147	human.po.
148	or/145-147
149	144 not 148
150	136 not 149
151	remove duplicates from 150

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
152	meta-analysis.pt.
153	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
154	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
155	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
156	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
157	(data synthes* or data extraction* or data abstraction*).ti,ab.
158	(handsearch* or hand search*).ti,ab.
159	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
160	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
161	(meta regression* or metaregression* or mega regression*).ti,ab.
162	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
163	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
164	(cochrane or (health adj2 technology assessment) or evidence report).jw.
165	(meta-analysis or systematic review).md.
166	or/152-165
167	Randomized Controlled Trial.pt.
168	Randomized Controlled Trials as Topic/
169	"Randomized Controlled Trial (topic)"/
170	Randomized Controlled Trial/
171	Randomization/
172	Random Allocation/
173	Double-Blind Method/
174	Double Blind Procedure/
175	Double-Blind Studies/
176	Single-Blind Method/
177	Single Blind Procedure/
178	Single-Blind Studies/
179	Placebos/
180	Placebo/
181	(random* or sham or placebo*).ti,ab,hw.
182	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
183	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
184	or/167-183
185	151 and 166
186	185 not conference abstract.pt.
187	151 and 184
188	187 not conference abstract.pt.
189	(economic adj2 model*).mp.
190	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
191	(cost effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
192	(life year or life years or qaly* or cost-benefit analys?s or cost effectiveness analys?s).ab.
193	(cost or costs or economic*).ti. and (costs or cost effectiveness or markov).ab.
194	or/189-193

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
195	151 and 194
196	195 not conference abstract.pt.
97	*Nateglinide/
98	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
99	(135062-02-1 or 105816-04-4).rn.
100	*Pramlintide/
101	(Pramlintide or symlin).ti,ab.
102	(amylin adj analog*).ti,ab.
103	151126-32-8.rn.
104	*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/
105	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
106	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
107	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
108	(nph insulin or humulin or novolin).ti,ab.
109	11061-68-0.rn.
110	(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.
111	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
112	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
113	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
114	*exendin 4/
115	*albiglutide/ or *liraglutide/ or *lixisenatide/ or *taspoglutide/
116	or/63-115
117	*Diabetes Mellitus/
118	*Maturity Onset Diabetes Mellitus/
119	*Non Insulin Dependent Diabetes Mellitus/
120	*Lipoatrophic Diabetes Mellitus/
121	((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.
122	(Mody or niddm or t2dm).ti,ab.
123	or/117-122
124	Metformin/
125	Metformin.ti,ab.
126	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
127	(657-24-9 or 1115-70-4).rn.
128	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
129	(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.
130	(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 imethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
131	or/124-130
132	116 and 123 and 131
133	132 use emef
134	62 or 133
135	limit 134 to english
136	limit 135 to yr="2009 -Current"
137	exp animals/
138	exp animal experimentation/
139	exp models animal/
140	exp animal experiment/
141	nonhuman/
142	exp vertebrate/
143	animal.po.
144	or/137-143
145	exp humans/
146	exp human experiment/
147	human.po.
148	or/145-147
149	144 not 148
150	136 not 149
151	remove duplicates from 150
152	meta-analysis.pt.
153	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
154	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
155	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
156	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
157	(data synthes* or data extraction* or data abstraction*).ti,ab.
158	(handsearch* or hand search*).ti,ab.
159	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
160	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
161	(meta regression* or metaregression* or mega regression*).ti,ab.
162	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
163	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
164	(cochrane or (health adj2 technology assessment) or evidence report).jw.
165	(meta-analysis or systematic review).md.
166	or/152-165
167	Randomized Controlled Trial.pt.
168	Randomized Controlled Trials as Topic/
169	"Randomized Controlled Trial (topic)"/
170	Randomized Controlled Trial/
171	Randomization/
172	Random Allocation/
173	Double-Blind Method/
174	Double Blind Procedure/

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
175	Double-Blind Studies/
176	Single-Blind Method/
177	Single Blind Procedure/
178	Single-Blind Studies/
179	Placebos/
180	Placebo/
181	(random* or sham or placebo*).ti,ab,hw.
182	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
183	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
184	or/167-183
185	151 and 166
186	185 not conference abstract.pt.
187	151 and 184
188	187 not conference abstract.pt.
189	(economic adj2 model*).mp.
190	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
191	(cost effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
192	(life year or life years or qaly* or cost-benefit analys?s or cost effectiveness analys?s).ab.
193	(cost or costs or economic*).ti. and (costs or cost effectiveness or markov).ab.
194	or/189-193
195	151 and 194
196	195 not conference abstract.pt.

Ovid Cochrane Strategy	
#	**Searches**
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 Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
8	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
10	275371-94-3.rn.
11	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
12	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
13	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.
14	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.

Ovid Cochrane Strategy	
#	**Searches**
15	(dpp adj IV adj inhibitor*).ti,ab.
16	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
17	DPP-4 inhibitors.ti,ab.
18	dipeptidyl peptidase-4 inhibitors.ti,ab.
19	exp Sulfonylurea Compounds/
20	(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.
21	(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.
22	alpha-Glucosidases/ai
23	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
24	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
25	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
26	Acarbose/
27	Lipase/ai
28	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
29	(96829-58-2 or 106650-56-0).rn.
30	(lipase adj inhibit*).ti,ab.
31	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
32	(135062-02-1 or 105816-04-4).rn.
33	Amyloid/
34	(Pramlintide or symlin).ti,ab.
35	(amylin adj analog*).ti,ab.
36	151126-32-8.rn.
37	exp insulin/
38	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
39	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
40	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
41	(nph insulin or humulin or novolin).ti,ab.
42	11061-68-0.rn.
43	(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.
44	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
45	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
46	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
47	or/1-46
48	exp Diabetes Mellitus, Type 2/
49	Diabetes mellitus/
50	((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.
51	(Mody or niddm or t2dm).ti,ab.

Ovid Cochrane Strategy	
#	**Searches**
52	or/48-51
53	Metformin/
54	Metformin.ti,ab.
55	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
56	(657-24-9 or 1115-70-4).rn.
57	(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.
58	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
59	(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.
60	or/53-59
61	47 and 52 and 60
62	remove duplicates from 61

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 7 to 15, 2012
Keywords:	Included terms for diabetes, and second- and third-line antidiabetes drugs
Limits:	Publication years 2009 to 2012

The following sections of the CADTH grey literature checklist *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* (www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 2: STUDY CHARACTERISTICS

Table 15: Detailed Study Characteristics of RCTs Included in the Systematic Review of Second-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Ahren et al. 2004[100]	Sweden	Novartis	• Vildagliptin (50 mg q.d.) • Placebo	12 weeks	≥ 1,500 mg/day	≥ 3 months	A1C 7.0 to 9.5%	107	DB
Arechavaleta et al. 2011[38]	NR	Merck	• Glimepiride (1 mg/day to 6 mg/day) • Sitagliptin (100 mg q.d.)	30 weeks	≥ 1,500 mg/day	≥ 12 weeks	A1C 6.5 to 9.0%	1,035	DB
Aschner et al. 2012[85]	17 countries	Sanofi	• Insulin glargine 0.2 U/kg (titrated up or down by two units depending on FPG) • Sitagliptin (100 mg q.d.)	24 weeks	NR	3 months	A1C 7.0 to 11.0%	515	OL
Barnett et al. 2007[53]	Multinational (Europe, Central America)	Eli Lilly	• Exenatide (10 mcg b.i.d.) • Insulin glargine q.d.	4 months	≥ 1,500	3 months	A1C ≥ 7.1%	76	OL
Bergenstal et al. 2010[86]	United States, India, Mexico	Eli Lilly, Amylin	• Exenatide (2 mg QW) • Sitagliptin (100 mg q.d.) • Pioglitazone (45 mg q.d.)	26 weeks	NR	≥ 2 months	A1C 7.1 to 11.0%	514	DB
Blonde et al. 2009[54]	United States	Novartis	• Vildagliptin (100 mg) • Pioglitazone or rosiglitazone	3 months	1,452 ± 500 (SD)	≥ 4 weeks	A1C 7 to 10%	2,664	OL
Bolli et al. 2009[55]	Multinational	Novartis	• Vildagliptin (100 mg/day) • Pioglitazone (30 mg/day)	12 months	2,020 ± 453 (SD)	43 ± 3 (SD) months	A1C 7.5 to 11%	576	DB
Bosi et al. 2007[56]	Multinational	Novartis	• Vildagliptin (50 mg/day) • Vildagliptin (100 mg/day)	6 months	2,101 ± 320 (SD)	18 ± 23 (SD) month	A1C > 7%	367	DB
Brazg et al. 2007[39]	United States	Merck	• Sitagliptin (50 mg b.i.d.) • Placebo	1 month	≥ 1,500	≥ 6 weeks	A1C ≥ 6.5%	28	DB
Bunck et al. 2009[40]	Sweden, Finland, Netherlands	Eli Lilly, Amylin	• Exenatide (5 mg/day to 20 mcg b.i.d.) • Glargine (titrated)	12 months	2,168 ± 773 (SD)	2 months	A1C ≥ 6.5%	69	OL
Charbonnel et al. 2006[58]	France, Israel, United States	Merck	• Sitagliptin (100 mg/day) • Placebo	6 months	≥ 1,500	≥ 19 weeks	A1C ≥ 7	701	DB

Table 15: Detailed Study Characteristics of RCTs Included in the Systematic Review of Second-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Charbonnel et al. 2005[57]	Multinational	Takeda, Eli Lilly	• Pioglitazone (15 mg/day to 45 mg/day) • Gliclazide (80 mg/day to 320 mg/day)	24 months	≥ 50% of maximum recommended or MTD	≥ 3 months	A1C - 7.5-11%	630	OL
Charpentier et al. 2001[59]	France	Hoechst Marion Roussel	• Glimepiride (1 mg/day to 6 mg/day) • Glimepiride + metformin • Metformin only	5 months	2,550	≥ 4 weeks	FBG 7.8 to 13.9 mmol/L	372	DB
Cho et al. 2010[99]	Korea	Choongwae Pharma	• Mitiglinide (10 mg b.i.d.) • Placebo	16 weeks	1,500 mg/day	4 weeks	A1C > 7.0%	145	DB
DeFronzo et al. 2005[60]	United States	Eli Lilly, Amylin	• Exenatide (5 mcg b.i.d.) • Exenatide (10 mcg b.i.d.) • Placebo	7.5 months	≥ 1,500	3 months	A1C 7.1 to 11%	226	DB
DeFronzo et al. 2009[61]	USA, Brazil	Bristol-Myers Squibb, AstraZeneca	• Saxagliptin (2.5 mg q.d.) • Saxagliptin (5 mg q.d.) • Saxagliptin (10 mg q.d.) • Placebo	6 months	1,500 to 2,550	≥ 8 weeks	A1C > 7.0%	562	DB
Derosa et al. 2012[149]	Italy	NR	• Exenatide (10 mcg b.i.d.) • Placebo	12 months	2,500 ± 500 mg/day	8 ± 2 months	A1C 8.0 to 11.0%	171	DB
Diamant et al. 2010[87]	Multinational (Europe, Asia, North America)	Eli Lilly, Amylin	• Exenatide 2 mg QW • Insulin glargine (target FBG range 4.0-5.5 mmol/L)	26 weeks	≥ 1,500 mg/day	≥3 months	A1C 7.1 to 11.0%,	321	OL
Einhorn et al. 2000[62]	United States	Takeda	• Pioglitazone (30 mg/day) • Placebo	4 months	Stable dose	≥ 30 days	A1C ≥ 8%	328	OL
Feinglos et al. 2005[150]	United States	Pfizer	• Glipizide (2.5 mg/day) • Placebo	4 months	151	≥ 3 months	A1C 7.0 to 8.5%	61	DB
Ferrannini et al. 2009[37]	Multinational	Novartis	• Vildagliptin (100 mg/day) • Glimepiride (mean 4.5 mg/day)	12 months	1,897 ± 410 (SD)	≥ 4 weeks	A1C 6.5 to 8.5%	2789	DB
Filozof and Gautier 2010[88]	NR	Novartis	• Vildagliptin 50 mg b.i.d. • Gliclazide 80 mg/day to 320 mg/day	52 weeks	≥ 1,500 mg/day	≥4 weeks	A1C 7.5 to 11.0%	1007	DB

Table 15: Detailed Study Characteristics of RCTs Included in the Systematic Review of Second-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)									
Author, Year	**Countries**	**Sponsor**	**Comparators (+ Metformin)**	**Treatment Duration**	**Prior Metformin Monotherapy**		**Criteria for Metformin Failure**	**Sample Size**	**Blinding**
					Dose (mg/day)	**Duration With Stable Dose**			
Fonseca et al. 2000[63]	United States	SmithKline Beecham	• Rosiglitazone (4 mg/day) • Rosiglitazone (8 mg/day) • Metformin (2,500 mg/day)	6.5 months	≤ 2,500	> 4 weeks	FPG > 7.7 mmol/L	348	DB
Forst et al. 2010[89]	Multinational (Europe)	Boehringer Ingelheim	• Linagliptin (1 mg q.d.) • Linagliptin (5 mg q.d.) • Linagliptin (10 mg q.d.) • Glimepiride (1 mg/day to 3 mg q.d.) t.i.d. • Placebo	12 weeks	NR	≥ 10 weeks	A1C 7.5-10%	333	DB
Frid et al. 2008[151]	Multinational (Europe, North America)	NR	• Glimepiride • Liraglutide (0.6 mg/day) • Liraglutide (1.2 mg/day) • Liraglutide (1.8 mg/day) • Placebo	6.5 months	NR	NR	NR	NR	DB
Gallwitz et al. 2011[41]	Germany	NR	• Exenatide (10 mcg b.i.d.) • Biphasic insulin aspart (b.i.d.)	26 weeks	NR	NR	A1C 6.5-10.0%	363	OL
Gallwitz et al. et al. 2012 [42]	Multinational (Europe, Asia, North America)	Boehringer Ingelheim	• Linagliptin (5 mg q.d.) • Glimepiride (1 mg/day to 4 mg/day)	104 weeks	≥ 1,500 mg/day	NR	A1C 6.5-10.0%	1551	DB
Gallwitz et al. 2012[43]	Multinational (Europe, Central America)	Eli Lilly, Amylin	• Exenatide (10 mcg b.i.d.) • Glimepiride (MTD)	4.5 years	MTD	NR	A1C 6.5-9.0%	1029	OL
Gao et al. 2009[97]	Multinational (Asia)	Eli Lilly, Amylin	• Exenatide (4 mg/day to10 mcg) • Placebo	4 months	1,000 to 3,000	≥ 3 months	A1C ≥ 7%	91	DB
Garber et al. 2006[64]	United States	Bristol-Myers Squibb	• Glyburide (5 mg to 10 mg) • Rosiglitazone (4 mg/day)	6 months	1,821	≥ 8 weeks	A1C > 7.0%	318	DB
Goke et al. 2010[44]	Multinational (Europe, Asia)	Bristol-Myers Squibb, AstraZeneca	• Saxagliptin 5 mg/day • Glipizide 5 to 20 mg/day	52 weeks	≥ 1,500 mg/day	≥8 weeks	A1C > 6.5-10.0%	858	DB
Gomez-Perez et al. 2002[51]	Mexico	GlaxoSmithKline	• Rosiglitazone (4 mg/day) • Rosiglitazone (8 mg/day) • Placebo	6 months	2,500 during 4-week titration phase	4-week titration phase	FPG ≥ 140 mg/dL	116	DB

Table 15: Detailed Study Characteristics of RCTs Included in the Systematic Review of Second-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Goodman et al. 2009[65]	Multinational	Novartis	• Vildagliptin (100 mg/day a.m.) • Vildagliptin (100 mg/day p.m.) • Placebo	6 months	1,896 ± 391 (SD)	≥ 3 months	A1C ≥ 7.5%	370	DB
Halimi et al. 2000[66]	France	Authors from Bayer	• Acarbose (1,700 mg/day to 2,550 mg/day) • Placebo	6 months	1,770 to 2,550	≥ 2 months	A1C > 7%	152	DB
Hamann et al. 2008[152]	Multinational	GlaxoSmithKline	• Sulfonylurea (glyburide or gliclazide 80 mg/day) • Rosiglitazone (4 mg/day)	12 months	1,500 to 2,000 (forced titration)	≥ 8 weeks prior to screening, then 4 weeks forced titration	A1C > 7%	596	DB
Home et al. 2009[52]	Multinational (Europe)	GlaxoSmithKline	• Sulfonylurea (titrated) • Rosiglitazone (titrated)	66 months	≥ 1,500	≥ 8 weeks	A1C > 7%	2,222	OL
Kaku et al. 2009[45]	Japan	Takeda	• Pioglitazone (15 mg/day to 30 mg/day) • Placebo	7 months	500 or 750	3 months	A1C ≥ 6.5%	169	DB
Khanolkar et al. 2008[46]	United Kingdom	NR	• Rosiglitazone (4 mg/day) • Gliclazide (80 mg/day)	6 months	≤ 2000	> 4 weeks	A1C > 6.5%	50	OL
Kilo et al. 2003[67]	United States	Novo Nordisk	• Biphasic insulin aspart • Biphasic human insulin • NPH insulin	3 months	500 to 2,500	4 weeks	FBG 90-126 mg/dL	140	OL
Kvapil et al. 2006[68]	Multinational	NR	• Biphasic insulin aspart (b.i.d.) • Biphasic insulin aspart (b.i.d.) + metformin • Glyburide (titrated)	4 months	1,660 (range 500 to 3,500)	≥ 1 month	A1C > 7%	230	OL
Leiter et al. 2005[69]	Canada	GlaxoSmithKline	• Rosiglitazone (4 mg/day to 8 mg/day) • Metformin	8 months	≤ 1,700	≥ 3 months	FPG > 7.0 mmol/L	236	OL
Marre et al. 2002[70]	Multinational	Merck Lipha	• Glyburide (5 mg) • Glyburide (2.5 mg) + metformin • Glyburide (5 mg) + metformin • Metformin	4 months	≥ 1,500	≥ 2 months	FPG ≥ 7 mmol/L	411	DB

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Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Marre et al. 2002[71]	Multinational	Novartis	• Nateglinide (60 mg AC) • Nateglinide (120 mg AC) • Placebo (AC)	6 months	2,000	≥ 4 weeks	A1C ≥ 6.8%	467	DB
Matthews et al. 2005[98]	Multinational	Takeda Eli Lilly	• Pioglitazone (15 mg q.d.) • Gliclazide (80 mg q.d.)	12 months	50% of maximum recommended or MTD	≥ 3 months	A1C ≥ 7.5%	630	DB
Moses et al. 1999[72]	Australia	Novo Nordisk	• Repaglinide (0.5 mg/day to 4.0 mg) • Placebo	4.5 months	1,800 ± 700 (SD)	4 ± 3 (SD) years	A1C > 7.1%	54	DB
Nauck et al. 2006[73]	Germany, Poland, Demark	Novo Nordisk	• Liraglutide (0.5 mg/day to 2 mg q.d.) • Glimepiride (2 mg to 4 mg)	1 month	≤ 2,000	2 weeks to ≥ 3 months	FPG ≥ 9 mmol/L	36	DB
Nauck et al. 2007[47]	Germany, United States	Merck	• Sitagliptin (100 mg/day) • Glipizide (5 mg/day)	12 months	≥ 1,500	≥ 2 weeks	A1C 6.5-10%	1091	DB
Nauck et al. 2009[74]	Multinational	Novo Nordisk	• Glimepiride (4 mg/day) • Placebo • Liraglutide (0.6 mg/day to 1.8 mg/day)	6.5 months	1,500 to 2,000 (forced titration)	≥ 3 weeks (forced titration)	A1C > 7%	366	DB
Pan et al. 2012[90]	China	Novartis	• Vildagliptin (50 mg q.d.) • Vildagliptin (50 mg b.i.d.) • Placebo	24 weeks	≥1,500 mg/day	≥ 4 weeks	A1C 7.0-10.0%	438	DB
Papathanassiou et al. 2009[48]	Greece	University of Ioannina	• Glimepiride (4 mg q.d.) • Pioglitazone (30 mg q.d.)	6 months	NR	≥ 6 months of metformin	A1C > 6.5%	14	OL
Pfutzner et al. 2011[91]	Germany	NR	• Pioglitazone (15 mg b.i.d.) • Glimepiride (2 mg q.d.)	24 weeks	Maximum tolerated dose	NR	A1C ≥ 6.5%	305	DB
Phillips et al. 2003[75]	Australia, New Zealand	Bayer AG	• Acarbose (up to 100 mg b.i.d.) • Placebo	6 months	1,700	≥ 3 months	A1C > 7%	83	DB
Poon et al. 2005[76]	United States	Amylin	• Exenatide (2.5 mcg b.i.d.) • Exenatide (5 mcg b.i.d.) • Exenatide (7.5 mcg b.i.d.) • Exenatide (10 mcg b.i.d.) • Placebo	1 month	Unspecified	NR	A1C ≥ 6.8%	71	DB
Pratley et al. 2010[92]	Multinational (Europe, North America)	Novo Nordisk	• Liraglutide (1.2 mg q.d.) • Liraglutide (1.8 mg q.d.) • Sitagliptin (100 mg q.d.)	26 weeks	≥ 1,500 mg/day	≥ 3 months	A1C 7.5-10.0%	665	OL

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Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Raskin et al. 2007[77]	United States	Novo Nordisk	• Biphasic insulin aspart 30 (titrated) • Insulin glargine (titrated)	7 months	1,500 to 2,550 during 4-week run-in period	4 week run-in period	A1C > 8.0%	157	OL
Raz 2 et al. 008[78]	Israel, United States	Merck	• Sitagliptin (100 mg/day) • Placebo	7.5 months	1,500	1.5 months	A1C 8.0-11.0%	190	DB
Ristic et al. 2006[153]	Multinational	Novartis	• Gliclazide (80 mg/day to 240 mg/day) • Nateglinide (60 mg/day to 180 mg t.i.d.)	6 months	1,000	≥ 3 months	A1C 6.8-9.0%	262	DB
Ristic et al. 2007[79]	Switzerland	Novartis	• Gliclazide (80 mg/day to 240 mg/day) • Nateglinide (60 mg/day to 180 mg AC)	12 months	1,000	≥ 2 months	A1C > 6.8%	NR	DB
Rodger et al. 1995[80]	Canada	Bayer	• Acarbose (50 mg/day to 200 mg AC) • Placebo	12 months	NR	NR	A1C > 7%	83	DB
Rosenstock et al. 1998[81]	United States	Bayer	• Acarbose (25 mg/day 50 mg t.i.d.) • Placebo	6 months	2,000 to 2,500	≥ 56 days	A1C > 7%	84	DB
Schernthaner et al. 2004[49]	Multinational (Europe)	Servier	• Gliclazide MR (30 mg/day to 120 mg/day) • Glimepiride (1 mg/day to 6 mg/day)	7 months	NR	≥ 3 months	A1C 6.9-11.5%	219	DB
Scott et al. 2008[82]	Multinational	Merck & Co.	• Rosiglitazone (8 mg/day) • Sitagliptin (100 mg/day) • Placebo	4.5 months	≥1,500	≥ 10 weeks	A1C > 7%	273	DB
Taskinen et al. 2011[93]	Multinational (Europe, North America)	Boehringer Ingelheim	• Linagliptin (5 mg q.d.) • Placebo	24 weeks	≥ 1,500 mg/day	≥ 12 weeks	A1C 7.0–10.0%	701	DB
Trautmann et al. 2007[154]	United States, Australia, United Kingdom	NR	• Exenatide (5 mg/day to 10 mcg b.i.d.) • Insulin glargine	4 months	NR	NR	NR	NR	OL
Umpierrez et al. 2006[83]	United States	Sanofi-aventis	• Glimepiride (2 mg/day to 8 mg/day) • Pioglitazone (30 mg/day to 45 mg/day)	6 months	1,000 to 2,500 or 500 to 2,000 for extended release	2 months	A1C ≥ 7.5%	210	OL

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Author, Year	Countries	Sponsor	Comparators (+ Metformin)	Treatment Duration	Prior Metformin Monotherapy		Criteria for Metformin Failure	Sample Size	Blinding
					Dose (mg/day)	Duration With Stable Dose			
Van Gaal 2001[84] et al.	Belgium, Israel, Austria, Czech Republic	Bayer, Sanofi-Synthélabo	• Miglitol (25 mg/day to 100 mg t.i.d.) • Placebo	8 months	Unspecified stable dose	> 3 months	A1C ≥ 7.5	153	DB
Von Bibra et al. 2008[36]	Germany	NR	• Glimepiride (3 mg/day) • Rosiglitazone (8 mg/day)	4 months	1,600 ± 500 (SD)	NR	A1C 6.5-9.0%	13	OL
Wang et al. 2011[155]	Taiwan	NSC/VGH, Bayer Schering	• Acarbose 50 mg t.i.d. • Glyburide 2.5 mg t.i.d.	16 weeks	1,500 mg/day	8 weeks	A1C 7.0-11.0%	55	OL
Wolever et al. 1997[156]	Canada	Bayer Canada	• Acarbose (50 mg/day to 200 mg t.i.d.) • Placebo	12 months	NR	NR	A1C > 7%	83	DB
Yang et al. 2011[95]	China, Korea, India	Bristol-Myers Squibb, AstraZeneca	• Saxagliptin 5 mg q.d. • Placebo	24 weeks	≥ 1,500 mg/day	≥ 8 weeks	A1C 7.0-10.0%	570	DB
Yang et al. 2011[94]	China, Korea, India	Novo Nordisk	• Liraglutide (0.6 mg/day to 1.8 mg q.d.) • Glimepiride 4 mg q.d.	16 weeks	2,000 mg/day	≥ 3 months	A1C 7.0-11.0%	928	DB
Yang et al. 2012[96]	China	Merck Sharp	• Sitagliptin 100 mg q.d. • Placebo	24 weeks	1,000 or 1,700 mg/day	≥ 10 weeks	A1C 7.5-11.0%	395	DB

A1C = glycated hemoglobin; AC = before meals; b.i.d. = twice daily; DB = double-blind; FBG = fasting blood glucose; FPG = fasting plasma glucose concentration; MTD = maximum tolerated dose; NR = not reported; NSC/VGH = National Science Council and Veterans General Hospital; OL = open label; q.d. = once daily; QW = once weekly; RCTs = randomized controlled trials; SD = standard deviation; t.i.d. = three times daily; U = units.

APPENDIX 3: COMPARISON OF RESULTS FROM NMA (BLACK) AND DIRECT PAIRWISE (BLUE) META-ANALYSES FOR A1C (%) (A), WEIGHT (KG) (B), OVERALL HYPOGLYCEMIA (C)

A

Placebo ← Vs.								
–0.8 (–0.9, –0.7) *–0.9 (–1.0, –0.7)*	**Sulfonylureas**							
–0.6 (–0.9, –0.4) *–0.7 (–1.2, –0.2)*	0.2 (–0.13,0.4) *0.1 (–0.17,0.4)*	**Meglitinides**						
–0.8 (–0.9, –0.6) *–1.0 (–1.2, –0.8)*	0.0 (–0.1,0.1) *0.0 (–0.2,0.2)*	–0.1 (–0.4,0.2) *NA*	**TZDs**					
–0.7 (–0.8, –0.6) *–0.7 (–0.8, –0.6)*	0.10 (0.0,0.2) *0.08 (0.0,0.2)*	–0.1 (–0.3,0.2) *NA*	0.1 (–0.1,0.2) *–0.1 (–0.1,–0.0)*	**DPP-4 Inhibitors**				
–0.7 (–1.0, –0.5) *–0.7 (–0.9, –0.5)*	0.05 (–0.2,0.3) *NA*	–0.1 (–0.5,0.3) *NA*	0.0 (–0.2,0.3) *NA*	–0.1 (–0.3,0.2) *NA*	**AG Inhibitors**			
–1.0 (–1.1, –0.8) *–0.8 (–1.0, –0.5)*	–0.2 (–0.3, –0.0) *–0.1 (–0.2,0.1)*	–0.3 (–0.6,–0.0) *NA*	–0.2 (–0.4, –0.0) *–0.2 (–0.6, –0.1)*	–0.3 (–0.4,–0.1) *–0.6 (–0.6,–0.5)*	–0.2 (–0.5,0.1) *NA*	**GLP-1 Analogues**		
–0.9 (–1.2, –0.7) *NA*	–0.1 (–0.4,0.1) *NA*	–0.3 (–0.6,0.1) *NA*	–0.1 (–0.4,0.1) *NA*	–0.2 (–0.5,0.0) *–0.6 (–0.8,–0.4)*	–0.2 (–0.5,0.2) *NA*	0.1 (–0.2,0.3) *0.1 (0.0,0.3)*	**Basal Insulin**	
–1.1 (–1.3, –0.8) *NA*	–0.3 (–0.5, –0.0) *–0.2 (–0.5,0.1)*	–0.4 (–0.8,–0.1) *NA*	–0.3 (–0.6,–0.0) *NA*	–0.4 (–0.6,–0.1) *NA*	–0.3 (–0.7,0.0) *NA*	–0.1 (–0.3,0.1) *0.1 (0.0,0.3)*	–0.1 (–0.4,0.1) *–0.2 (–0.6,0.3)*	**Biphasic Insulin**

B

Placebo ← Vs.								
2.1 (1.3, 2.9) *1.8 (1.3,2.3)*	**Sulfonylureas**							
1.8 (0.5, 3.1) *2.0 (–0.3,4.3)*	–0.3 (–1.7, 1.1) *–0.5 (–1.4,0.4)*	**Meglitinides**						
2.7 (1.9, 3.5) *2.3 (1.9,2.7)*	0.6 (–0.1, 1.3) *0.8 (–1.5,3.0)*	0.9 (–0.6, 2.3) *NA*	**TZDs**					
0.3 (–0.4,1.1) *0.6 (0.3,0.9)*	–1.8 (–2.5, –1.1) *–2.2 (–2.5,–1.9)*	–1.5 (–2.9, 0.0) *NA*	–2.4 (–3.1, –1.6) *–1.7 (–2.6,0.8)*	**DPP-4 Inhibitors**				
–0.9 (–2.2,0.4) *–0.9 (–1.9,0.1)*	–3.0 (–4.5, –1.5) *NA*	–2.7 (–4.6,–0.9) *NA*	–3.6 (–5.1,–2.1) *NA*	–1.2 (–2.8, 0.3) *NA*	**AG Inhibitors**			
–1.8 (–2.9, –0.8) *–1.6 (–3.5,0.4)*	–3.9 (–5.0, –2.9) *–2.7 (4.3,–1.1)*	–3.6 (–5.2, –2.0) *NA*	–4.5 (–5.6, –3.4) *–5.1 (–5.9, –4.3)*	–2.2 (–3.1, –1.2) *–2.0 (–2.9, –1.1)*	–0.9 (–2.6,0.8) *NA*	**GLP-1 Analogues**		
1.7 (0.3, 3.1) *NA*	–0.4 (–1.7, 0.9) *NA*	–0.1 (–1.9, 1.7) *NA*	–1.0 (–2.4, 0.4) *NA*	1.3 (0.1, 2.6) *1.5 (0.9,2.1)*	2.6 (0.7, 4.5) *NA*	3.5 (2.2, 4.8) *3.5 (1.5,5.2)*	**Basal Insulin**	
3.1 (1.5, 4.7) *NA*	1.0 (–0.6, 2.5) *0.7 (–0.1,1.5)*	1.3 (–0.7, 3.3) *NA*	0.4 (–1.3, 2.0) *NA*	2.7 (1.2, 4.3) *NA*	4.0 (1.9, 6.1) *NA*	4.9 (3.2, 6.5) *NA*	1.4 (0.0, 2.8) *1.6 (–0.2,3.4)*	**Biphasic Insulin**

C

Placebo ← Vs.								
7.5 (4.4,13.7) *4.4 (1.6,12.2)*	**Sulfonylureas**							
8.3 (3.3,23.4) *6.6 (1.5,28.3)*	1.1 (0.4,3.0) *1.1 (0.5,2.3)*	**Meglitinides**						
0.9 (0.5,1.8) *1.6 (0.6,4.3)*	0.1 (0.1,0.2) *0.2 (0.1,0.3)*	0.1 (0.0,0.3) *NA*	**TZDs**					
0.9 (0.6,1.6) *0.8 (0.5,1.4)*	0.1 (0.1,0.2) *0.1 (0.1,0.2)*	0.1 (0.0,0.3) *NA*	1.0 (0.6,1.9) *1.7 (0.6,5.1)*	**DPP-4 Inhibitors**				
0.4 (0.0,6.6) *0.5 (0.0,5.6)*	0.1 (0.0,0.9) *NA*	0.1 (0.00,0.9) *NA*	0.4 (0.0,7.7) *NA*	0.4 (0.0 7.4) *NA*	**AG Inhibitors**			
1.1 (0.5,2.3) *1.0 (0.3,3.2)*	0.1 (0.1,0.3) *0.1 (0.0,0.4)*	0.1 (0.0,0.4) *NA*	1.1 (0.5,2.6) *0.5 (0.0,5.4)*	1.1 (0.6,2.2) *1.2 (0.5,2.7)*	2.7 (0.1,95.1) *NA*	**GLP-1 Analogues**		
4.1 (1.7,10.7) *NA*	0.6 (0.2,1.2) *NA*	0.5 (0.1,1.7) *NA*	4.5 (1.7,12.1) *NA*	4.4 (2.0,10.1) *5.5 (3.5,8.5)*	10.6 (0.5,395) *NA*	3.9 (1.8,9.4) *4.6 (1.4,15.0)*	**Basal Insulin**	
7.0 (2.8,18.1) *NA*	0.9 (0.4,2.1) *1.2 (0.7,2.2)*	0.8 (0.2,2.9) *NA*	7.6 (3.0,20.2) *NA*	7.5 (3.2,17.5) *NA*	17.9 (0.9,671) *NA*	6.7 (2.9,15.7) *2.9 (1.5,5.5)*	1.7 (0.8,3.7) *2.2 (1.2,4.1)*	**Biphasic Insulin**

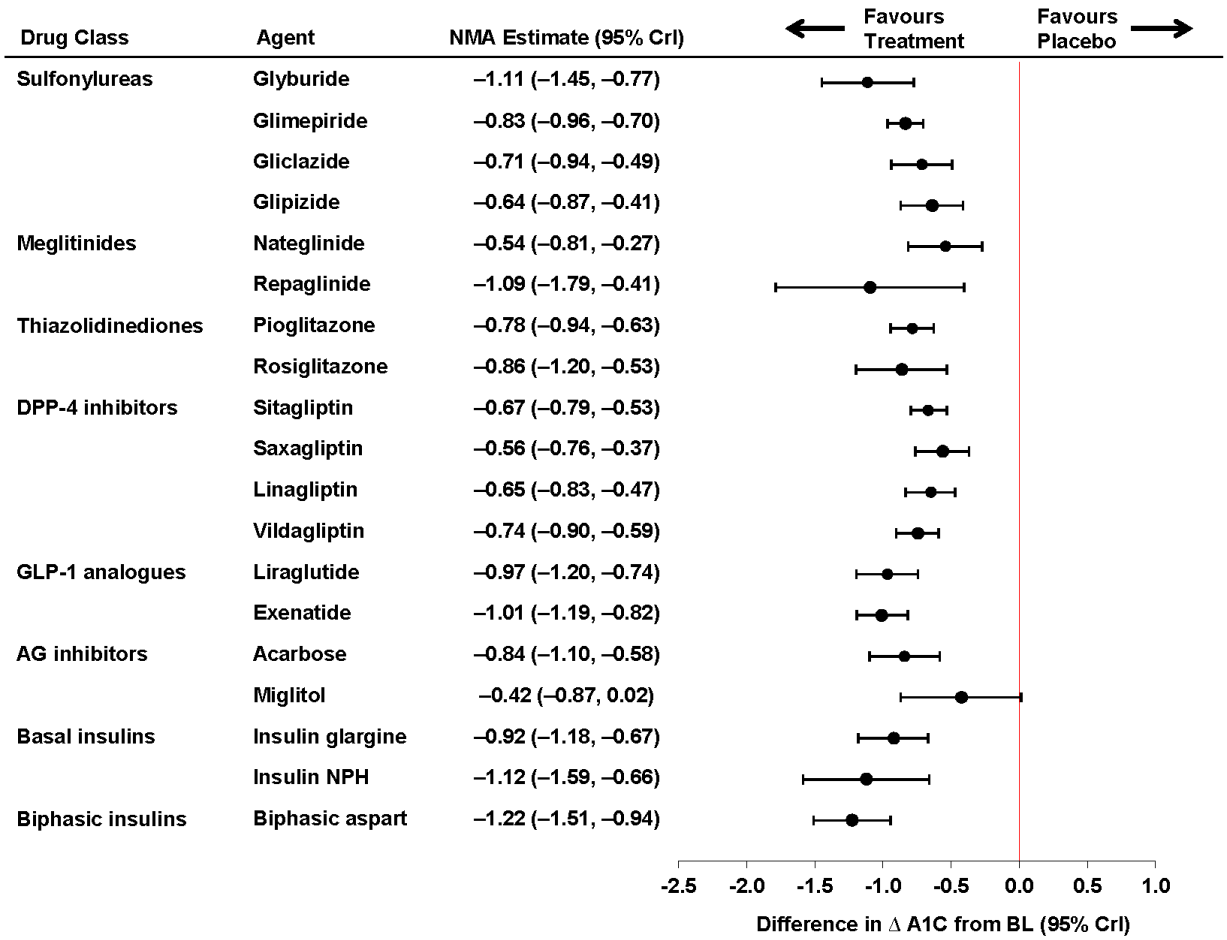
A1C = glycated hemoglobin; AG = alpha glucosidase; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not applicable; NMA = network meta-analysis; TZDs = thiazolidinediones; Vs. = versus.

Note: Tables showing the results of direct and mixed-treatment comparison network meta-analyses for A1C (A), body weight (B), and hypoglycemia (C). Results of the network meta-analysis are shown in black, non-italicized text, and the direct estimates are shown in blue, italicized text.

APPENDIX 4: NETWORK META-ANALYSIS OF INDIVIDUAL AGENTS

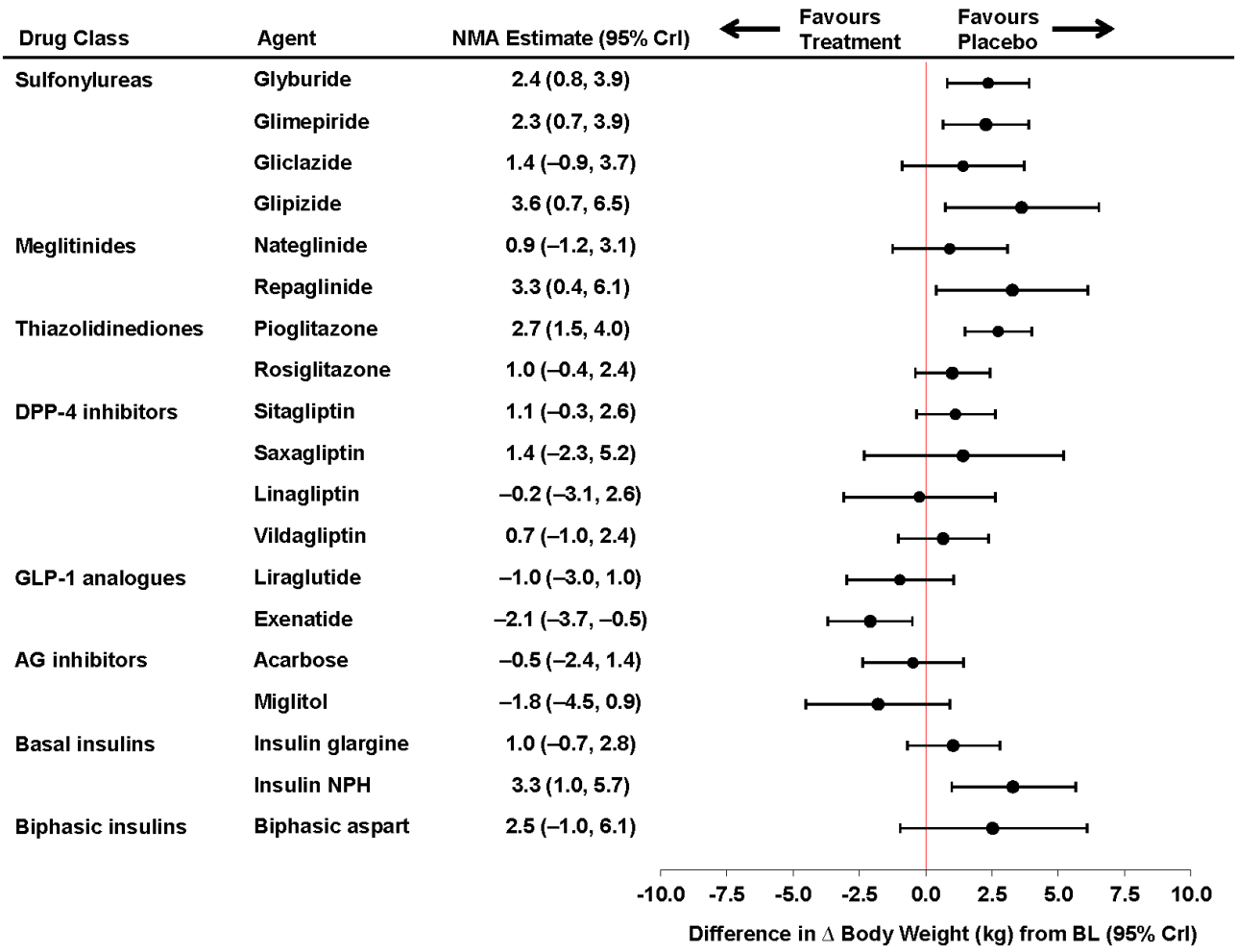
Figure 5 shows the results of a sensitivity analysis for A1C conducted at the level of individual agents versus the class-level analysis used in the reference case. The effect sizes observed with the individual agents are generally similar to the overall effect size reported for the drug classes. There is considerable uncertainty with the effect sizes of agents used in only a single RCT (e.g., repaglinide, miglitol); therefore, the results of this sensitivity analysis should be interpreted with caution. A similar sensitivity analysis for body weight is shown in Figure 6.

Figure 5: Sensitivity Analysis for A1C — Individual Agent-Level Network Meta-analysis



Δ = change; A1C = glycated hemoglobin; AG = alpha glucosidase; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not applicable; NMA = network meta-analysis; TZDs = thiazolidinediones.
Note: All active treatments and placebo were provided in combination with metformin.

Figure 6: Sensitivity Analysis for Body Weight — Individual Agent Level Network Meta-analysis



Δ = change; AG = alpha glucosidase; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not applicable; NMA = network meta-analysis; TZDs = thiazolidinediones.
Note: All active treatments and placebo were provided in combination with metformin.

APPENDIX 5: SEVERE HYPOGLYCEMIA RESULTS IN INCLUDED TRIALS (ORIGINAL REVIEW AND UPDATE)

Table 16: Summary of Severe Hypoglycemia in Second-Line RCTs

Study	Treatment 1	n/N	Treatment 2	n/N
Placebo Comparisons[a]				
Charpentier et. al. 2001[59]	Sulfonylurea	2/147	Placebo	0/75
Marre et. al. 2002[70]	Sulfonylurea	2/103	Placebo	1/104
Nauck et. al. 2006[73]	Sulfonylurea	0/36	Placebo	0/36
Forst et. al. 2010[89]	Sulfonylurea	0/65	Placebo	0/71
Marre et. al. 2002[71]	Meglitinide	0/160	Placebo	0/152
Moses et. al. 1999[72]	Meglitinide	0/27	Placebo	0/27
Einhorn et. al. 2000[62]	TZD	0/168	Placebo	0/160
Fonseca et. al. 2009[63]	TZD	0/113	Placebo	0/116
Gomez-Perez et. al. 2002[51]	TZD	0/36	Placebo	0/34
Goodman et. al. 2009[65]	DPP-4 inhibitor	0/248	Placebo	0/122
Charbonnel et. al. 2006[58]	DPP-4 inhibitor	0/464	Placebo	0/237
Bosi et. al. 2007[56]	DPP-4 inhibitor	0/183	Placebo	0/181
Forst et. al. 2010[89]	DPP-4 inhibitor	0/66	Placebo	0/71
Yang et. al. 2012[96]	DPP-4 inhibitor	0/197	Placebo	0/198
Taskinen et. al. 2011[93]	DPP-4 inhibitor	0/524	Placebo	0/177
Pan et. al. 2012[90]	DPP-4 inhibitor	0/148	Placebo	0/144
Van Gaal et. al. 2001[84]	AGI	0/78	Placebo	0/75
DeFronzo et. al. 2005[60]	GLP-1 analogue	0/113	Placebo	0/113
Gao et. al. 2009[97]	GLP-1 analogue	0/45	Placebo	1/46
Nauck et. al. 2006[73]	GLP-1 analogue	0/36	Placebo	0/36
Active Comparisons [a]				
Garber et. al. 2006[64]	Sulfonylurea	0/160	TZD	0/158
Matthews et. al. 2005[98]	Sulfonylurea	0/313	TZD	0/317
Umpierrez et. al. 2006[83]	Sulfonylurea	0/96	TZD	0/107
Pfutzner et. al. 2011[91]	Sulfonylurea	0/146	TZD	0/142
Ferrannini et. al. 2009[37]	Sulfonylurea	10/1393	DPP-4 inhibitor	0/1396
Forst et. al. 2010[89]	Sulfonylurea	0/65	DPP-4 inhibitor	0/66
Yang et. al. 2011[94]	Sulfonylurea	2/231	DPP-4 inhibitor	0/234
Gallwitz et. al. 2012[42]	Sulfonylurea	12/775	DPP-4 inhibitor	1/776
Goke et. al. 2010[44]	Sulfonylurea	7/430	DPP-4 inhibitor	0/428
Gallwitz et. al. 2012[43]	Sulfonylurea	0/508	GLP-1 analogue	1/511
Kvapil et. al. 2006[68]	Sulfonylurea	0/114	Biphasic insulin	0/108
Gallwitz et. al. 2011[41]	GLP-1 analogue	0/181	Biphasic insulin	0/173
Barnett et. al. 2007[53]	GLP-1 analogue	0/38	Basal insulin	1/38
Bunck et. al. 2009[40]	GLP-1 analogue	0/36	Basal insulin	0/33
Pratley et. al. 2010[92]	GLP-1 analogue	0/221	DPP-4 inhibitor	0/219
Bergenstal et. al. 2010[86]	GLP-1 analogue	0/160	DPP-4 inhibitor	0/166
Bergenstal et. al. 2010[86]	GLP-1 analogue	0/160	TZD	0/165
Bolli et. al. 2009[55]	DPP-4 inhibitor	0/295	TZD	0/280
Bergenstal et. al. 2010[86]	DPP-4 inhibitor	0/166	TZD	0/165
Aschner et. al. 2012[85]	DPP-4 inhibitor	1/264	Basal insulin	3/237
Kilo et. al. 2003[67]	Biphasic insulin	0/93	Basal insulin	0/47
Raskin et. al. 2007[77]	Biphasic insulin	0/79	Basal insulin	0/78

AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide; RCTs = randomized controlled trials; TZD = thiazolidinedione.

[a] All active treatments and placebo were provided in combination with metformin.

APPENDIX 6: SERIOUS ADVERSE EVENTS IN INCLUDED TRIALS (ORIGINAL REVIEW AND UPDATE)

Table 17: Summary of Serious Adverse Events in Second-Line RCTs

Study[a]	Treatment 1 + M	n (%)	Treatment 2 + Met	n (%)
Placebo Comparisons[b]				
Phillips et al. 2003[75]	AGI	2 (5)	Placebo	1 (2)
Van Gaal et al. 2001[84]	AGI	11 (14)	Placebo	5 (7)
Forst et al. 2010[89]	DPP-4 inhibitor	1 (2)	Placebo	1 (1)
Pan et al. 2012[90]	DPP-4 inhibitor	1 (0.7)	Placebo	1 (0.7)
Taskinen et al. 2011[93]	DPP-4 inhibitor	18 (3.4)	Placebo	4 (2.3)
Yang et al. 2011[95]	DPP-4 inhibitor	8 (2.8)	Placebo	3 (1)
Yang et al. 2012[96]	DPP-4 inhibitor	7 (3.6)	Placebo	5 (2.5)
Bosi et al. 2007[56]	DPP-4 inhibitor	5 (3)	Placebo	8 (4)
Ahren et al. 2004[100]	DPP-4 inhibitor	1 (2)	Placebo	4 (8)
Scott et al. 2008[82]	DPP-4 inhibitor	5 (5)	Placebo	5 (5)
Goodman et al. 2009[65]	DPP-4 inhibitor	7 (3)	Placebo	3 (2)
Raz et al. 2008[78]	DPP-4 inhibitor	0 (0)	Placebo	5 (5)
Charbonnel et al. 2006[58]	DPP-4 inhibitor	13 (3)	Placebo	7 (3)
DeFronzo et al. 2009[61]	DPP-4 inhibitor	8 (4)	Placebo	5 (3)
Cho et al. 2010[99]	Meglitinide	2 (2.8)	Placebo	0 (0)
Forst et al. 2010[89]	Sulfonylurea	1 (2)	Placebo	1 (1)
Scott et al. 2008[82]	TZD	5 (6)	Placebo	5 (5)
Kaku 2009[45]	TZD	0 (0)	Placebo	1 (1)
Fonseca et al. 2000[63]	TZD	5 (4)	Placebo	5 (4)
Gomez-Perez et al. 2002[51]	TZD	0 (0)	Placebo	0 (0)
Leiter et al. 2005[69]	TZD	2 (1)	Placebo	2 (3)
Active Comparisons[b]				
Nauck et al. 2007[47]	DPP-4 inhibitor	44 (8)	Sulfonylurea	43 (7)
Arechavaleta et al. 2011[38]	DPP-4 inhibitor	16 (3.1)	Sulfonylurea	11 (2.1)
Gallwitz et al. 2012[42]	DPP-4 inhibitor	135 (17)	Sulfonylurea	162 (21)
Goke et al. 2010[44]	DPP-4 inhibitor	39 (9.1)	Sulfonylurea	32 (7.4)
Ferrannini et al. 2009[37]	DPP-4 inhibitor	99 (7)	Sulfonylurea	132 (9)
Blonde et al. 2009[54]	DPP-4 inhibitor	32 (2)	TZD	22 (3)
Bolli et al. 2009[55]	DPP-4 inhibitor	12 (4)	TZD	25 (9)
Bolli et al. 2008[101]	DPP-4 inhibitor	6 (2)	TZD	13 (5)
Scott et al. 2008[82]	DPP-4 inhibitor	5 (5)	TZD	5 (6)
Aschner et al. 2012[85]	DPP-4 inhibitor	8 (3)	Basal insulin	15 (6)
Bergenstal et al. 2010[86]	GLP-1 analogue	4 (3)	TZD	10 (6)
Pratley et al. 2010[92]	GLP-1 analogue	7 (3)	DPP-4 inhibitor	8 (4)
Gallwitz et al. 2012[43]	GLP-1 analogue	73 (14)	Sulfonylurea	68 (13)
Diamant et al. 2010[87]	GLP-1 analogue	11 (5)	Basal insulin	10 (4)
Umpierrez et al. [83]	Sulfonylurea	7 (7)	TZD	7 (7)
Khanolkar et al. 2008[46]	Sulfonylurea	0 (0)	TZD	0 (0)
Papathanassiou et al. 2009[48]	Sulfonylurea	0 (0)	TZD	0 (0)
Matthews et al. 2005[98]	Sulfonylurea	20 (6)	TZD	15 (5)
Pfutzner et al. 2011[91]	Sulfonylurea	5 (3.5)	TZD	4 (2.7)
Ristic et al. 2007[79]	Sulfonylurea	7 (7)	Meglitinide	2 (2)
Raskin et al. 2007[77]	Biphasic insulin	4 (5)	Basal insulin	5 (6)

AGI = alpha glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; TZD = thiazolidinedione.

[a] SAEs were not reported in Charbonnel et al.,[57] Charpentier et al.,[59] Derosa 2012 et al.,[149] Derosa 2010 et al.,[157] Filozof and Gautier 2010,[88] Gallwitz et al.2011,[41] Gao et al.,[97] Hamann et al.,[152] Home et al.,[52] Kvapil et al.,[68] Moses et al.,[72] Poon et al.,[76] Ristic et al.,[153] Wang et al. 2011,[155] Yang 2011 et al..[94]

[b] All active treatments and placebo were provided in combination with metformin.

APPENDIX 7: SUMMARY OF MODEL-FIT PARAMETERS AND RANKING

Table 18: Model-fit Parameters for All Network Meta-Analyses

Outcome	Analysis	Mean Residual Deviance	Unconstrained Data Points	DIC
A1C	Random effects	57.7	61	–26.298
	Fixed effects	154.8	61	44.497
	Meta-regression for baseline A1C	55.87	61	–29.113
	Meta-regression for duration of diabetes	56.57	61	–28.996
	Meta-regression for duration of RCT	60.33	61	–25.677
	Removal of rosiglitazone studies	51.3	53	–33.357
	Removal of agents without an NOC	47.1	52	–15.478
	Removal of RCTs < 1 year in duration	12.09	13	–14.673
	Six-month RCTs only	25.14	27	–6.518
	Removal of subgroup data	51.13	51	–23.508
	Agent-level network meta-analysis	58.52	61	–17.162
Body weight	Random-effects	36.57	38	99.339
	Agent-level network meta-analysis	35.92	37	96.724
Hypoglycemia	Random-effects	91.67	100	484.632

A1C = glycated hemoglobin; DIC = deviance information criterion; NOC = Notice of Compliance; RCTs = randomized controlled trials.

Table 19: Probability Best and Ranking from Reference Case Analysis			
Analysis	**Treatment**	**Probability and Ranks — Mean (SD)**	
		Probability Best	**Ranking**
A1C	Placebo	0.00 (0.00)	9.0 (0.0)
	Sulfonylureas	0.00 (0.04)	4.7 (1.0)
	Meglitinides	0.00 (0.07)	6.9 (1.5)
	TZD	0.00 (0.05)	5.2 (1.2)
	DPP-4 inhibitor	0.00 (0.01)	6.8 (0.9)
	AGI	0.02 (0.14)	5.6 (1.9)
	GLP-1 analogue	0.16 (0.36)	2.2 (0.8)
	Basal insulin	0.08 (0.27)	3.1 (1.4)
	Biphasic insulin	0.74 (0.44)	1.4 (0.8)
Body weight	Placebo	0.00 (0.01)	3.1 (0.5)
	Sulfonylureas	0.00 (0.00)	6.6 (0.8)
	Meglitinides	0.00 (0.00)	6.1 (1.2)
	TZD	0.00 (0.00)	8.1 (0.7)
	DPP-4 inhibitor	0.00 (0.01)	3.8 (0.5)
	AGI	0.14 (0.34)	2.0 (0.6)
	GLP-1 analogue	0.86 (0.34)	1.1 (0.3)
	Basal insulin	0.00 (0.00)	5.8 (1.0)
	Biphasic insulin	0.00 (0.00)	8.4 (0.9)
Overall Hypoglycemia	Placebo	0.05 (0.21)	3.4 (1.2)
	Sulfonylureas	0.00 (0.00)	7.9 (0.8)
	Meglitinides	0.00 (0.00)	8.0 (1.1)
	TZD	0.12 (0.32)	3.0 (1.3)
	DPP-4 inhibitor	0.08 (0.28)	3.0 (1.1)
	AGI	0.68 (0.47)	2.2 (2.0)
	GLP-1 analogue	0.08 (0.27)	3.5 (1.3)
	Basal insulin	0.00 (0.00)	6.2 (0.7)
	Biphasic insulin	0.00 (0.00)	7.7 (0.9)

A1C = glycated hemoglobin; AG = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; TZD = thiazolidinedione.

APPENDIX 8: SUMMARY OF RCTS THAT WERE NOT INCLUDED IN THE NMA

Study ID	Comparators (Added-on to Metformin)	Description	Summary of Key Results		
			Glycemic Control	Body Weight	Hypoglycemia
EUREXA[43]	• Exenatide (10 mcg b.i.d.) • Glimepiride (1 mg – MTD)	• 48 months • Open-label • N = 1029	**Glycemic failure**[a] Fewer exenatide-treated patients had treatment failure (41% vs. 54%; *P* = 0.002), RD = 12.4 (6.2 to 18.6), HR = 0.748 (0.623 to 0.899) **A1C < 7% and < 6.5%** More exenatide-treated patients had A1C < 7% (44% vs. 31%; *P* < 0.0001)	Mean weight change favoured exenatide compared with glimepiride (–3.32 kg vs. 1.15 kg; *P* < 0.0001)	Significantly fewer patients in the exenatide group reported hypoglycemia (*P* < 0.0001)
Cho et al. 2010[99]	• Mitiglinide (10 mg t.i.d.) • Placebo	• 16 weeks • Double-blind • N = 145	Mean change in A1C was greater with mitiglinide compared with placebo (–0.7% vs. –0.4%; *P* = 0.002)	No difference between mitiglinide and placebo (–0.1 vs. –0.5 kg; *P* = 0.218)	One episode with mitiglinide and none with placebo
Derosa et al. 2012[149]	• Exenatide (10 mcg b.i.d.) • Placebo	• 12 months • Double-blind • N = 174	Mean decrease in A1C favoured exenatide over placebo (–1.2% vs. –0.4%; *P* < 0.05)	Mean weight change favoured exenatide over placebo (–6.4 kg vs. –2.3 kg; *P* < 0.01)	Not reported
Wang et al. 2011[155]	• Acarbose (100 mg t.i.d.) • Glyburide (5 mg t.i.d.)	• 24 weeks • Open-label • N = 55	A1C was significantly reduced with acarbose (–0.7%; *P* < 0.001) and glyburide (–1.2%; *P* < 0.001)	Mean weight decreased significantly with acarbose (–1.5 kg; *P* < 0.002). Not reported for glyburide	Hypoglycemia was more common with glyburide compared with acarbose (23.1% vs. 0%)
Ahren et al. 2004[100]	• Vildagliptin (50 mg q.d.) • Placebo	• 12 weeks • Double-blind • N = 107	A1C was significantly reduced with vildagliptin compared with placebo (MD = –0.7% [SE: 0.1]; *P* < 0.001)	No difference in change in body weight between vildagliptin and placebo groups (–0.2 kg in both)	2 patients in the vildagliptin group experience an episode of hypoglycemia
Schernthaner et al. 2004[49]	• Gliclazide MR (30-120 mg/day) • Glimepiride (1-6 mg/day)	• 7 months • Double-blind • N = 219	No significant difference between the groups	No significant difference between the groups	Hypoglycemia was less common with gliclazide compared with glimepiride (3.7% vs. 8.9%; *P* = 0.003)
Von Bibra et al. 2008[36]	• Glimepiride (3 mg/day) • Rosiglitazone (8 mg/day)	• 4 months • Open-label • N = 13	No significant difference between the groups	Not reported	One patient in the glimepiride group reported hypoglycemia
Khanolkar et al. 2008[46]	• Rosiglitazone (4 mg/day) • Gliclazide (80 mg/day)	• 6 months • Open-label • N = 50	No significant difference between the groups	Not reported	Not reported

b.i.d. = twice daily; HR = hazard ratio; MD = mean difference; MTD = maximum tolerated dose; NMA = network meta-analysis; RCT = randomized controlled trial; RD = risk difference; t.i.d. = three times daily; vs. = versus.

[a]The primary outcome of the EUREXA trial was time to inadequate glycemic control and need for alternative treatment (defined as an A1C of more than 9% after the first 3 months of treatment, or more than 7% at two consecutive visits after the first 6 months).

APPENDIX 9: CRITICAL APPRAISAL OF INCLUDED RCTS (ORIGINAL REVIEW AND UPDATE)

Table 20: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)

Study	Appropriate and Clearly Focused Question	Randomized Assignment	Adequate Concealment	Blinding of Subjects and Investigators	Groups are Similar at Baseline	Only diff. Between Groups is Treatment Under Investigation	Standard, Valid, and Reliable Measurement of Outcomes	Withdrawals are Acceptable (< 20%) and Comparable Between Groups	ITT Analysis Performed	Comparable Results for Multi-study Sites
Diamant et al. 2012[158]	AA	AA	AA	NAd	AA	PA	AA	Yes	AA	NAd
Wang et al. 2011[155]	AA	AA	NAd	NAd	AA	PA	AA	Yes	AA	NAd
Yang et al. 2011[95]	AA	AA	NAd	NAd	AA	AA	AA	Yes	AA	NAd
Gallwitz et al. 2011[41]	AA	NR	NAd	NAd	AA	PA	AA	No	NAd	NAd
Taskinen et al. 2011[93]	AA	NR	NAd	AA	AA	PA	AA	Yes	AA	NAd
Forst et al. 2010[89]	AA	NR	AA	AA	AA	AA	AA	Yes	AA	NAd
Bunck et al. 2010[159]	WC	AA	NAd	NAd	AA	AA	AA	Yes	WC	NAd
Bergenstal et al. 2010[86]	AA	AA	AA	WA	AA	AA	AA	Yes	AA	NAd
Forst et al. 2010[160]	AA	NR	NAd	NAd	AA	AA	AA	Yes	AA	NAd
Diamant et al. 2010[87]	AA	AA	AA	NAd	AA	PA	AA	Yes	AA	NAd
Seck et al. 2010[161]	WC	NR	NAd	AA	PA	WC	AA	No	PA	NAd
Derosa et al. 2012[149]	AA	AA	AA	AA	AA	PA	AA	Yes	AA	NAd
Pan et al. 2012[90]	AA	NR	NAd	AA	AA	AA	AA	Yes	AA	NAd
Pratley et al. 2010[92]	AA	NR	NAd	NAd	AA	PA	AA	No	AA	NAd

Table 20: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Subjects and Investigators**	**Groups are Similar at Baseline**	**Only diff. Between Groups is Treatment Under Investigation**	**Standard, Valid, and Reliable Measurement of Outcomes**	**Withdrawals are Acceptable (< 20%) and Comparable Between Groups**	**ITT Analysis Performed**	**Comparable Results for Multi-study Sites**
Aschner et al. 2012[85]	AA	AA	AA	NAd	AA	PA	AA	Yes	PA	NAd
Gallwitz et al. 2012[43]	AA	AA	AA	NAd	AA	PA	AA	Yes	PA	NAd
Cho et al. 2010[99]	AA	NR	NAd	NAd	AA	AA	AA	Yes	PA	NAd
Pratley et al. 2011[162]	AA	NR	NAd	NAd	AA	AA	AA	No	AA	NAd
Goke et al. 2010[44]	AA	AA	AA	AA	AA	PA	AA	No	NAd	NAd
Arechavaleta et al. 2011[38]	AA	AA	NAd	AA	AA	PA	AA	Yes	NAd	NAd
Yang et al. 2011[94]	AA	NR	NAd	AA	AA	PA	AA	No	NAd	NAd
Davies et al. 2011[163]	AA	AA	AA	AA	AA	PA	AA	Yes	AA	NAd
Pfutzner et al. 2011[91]	AA	NR	NAd	AA	AA	AA	AA	No	NAd	NAd
Gallwitz et al. 2012[42]	AA	NR	NAd	AA	AA	PA	AA	No	AA	NAd
Krobot et al. 2012[164]	AA	NR	NAd	AA	AA	PA	AA	NAd	NAd	NAd
Yang et al. 2012[96]	AA	AA	NAd	AA	AA	AA	AA	Yes	AA	NAd
Filozof and Gautier 2010[88]	AA	NR	NAd	AA	AA	AA	AA	No	PA	NAd
Ahren et al. [100]	AA	NR	NAd	NR	AA	AA	AA	No	WC	NAd
Barnett et al. [53]	AA	AA	AA	NAd	AA	AA	AA	Yes	AA	NAd
Berne et al. [165]	AA	AA	NAd	AA	PA	AA	WC	Yes	AA	NAd
Blonde et al. [54]	WC	WC	AA	NAd	WC	PA	AA	Yes	PA	NAd
Bolli et al. [101]	AA	NR	NAd	NR	AA	AA	AA	Yes	NAd	NAd
Bolli et al. [55]	WC	WC	WC	AA	WC	WC	WC	No	PA	NAd

Table 20: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Subjects and Investigators**	**Groups are Similar at Baseline**	**Only diff. Between Groups is Treatment Under Investigation**	**Standard, Valid, and Reliable Measurement of Outcomes**	**Withdrawals are Acceptable (< 20%) and Comparable Between Groups**	**ITT Analysis Performed**	**Comparable Results for Multi-study Sites**
Bosi et al. [56]	AA	NR	NAd	NR	AA	AA	AA	No	PA	NAd
Brazg et al. [39]	AA	NR	NAd	AA	PA	AA	PA	Yes	NAd	NAd
Bunck et al. [40]	WC	AA	NAd	NAd	AA	AA	AA	Yes	WC	NAd
Charbonnel et al. [58]	AA	NR	NAd	AA	AA	PA	AA	No	PA	NAd
Charbonnel et al. [57]	AA	NR	NAd	AA	AA	AA	AA	No	AA	NAd
Charpentier et al. [59]	AA	AA	AA	AA	AA	AA	AA	Yes	AA	NAd
DeFronzo et al. [61]	WC	WC	WC	AA	AA	AA	PA	No	AA	NAd
DeFronzo et al. [60]	AA	NR	NAd	AA	AA	AA	AA	Yes	WC	NAd
Einhorn et al. [62]	WC	NR	NAd	NR	AA	WC	WC	No	AA	NAd
Feinglos et al. [150]	AA	NR	NAd	NR	AA	WC	WC	Yes	WC	NAd
Ferrannini et al. [37]	WC	NR	NAd	AA	WC	PA	WC	Yes	PA	NAd
Fonseca et al. [63]	WC	WC	AA	AA	AA	WC	WC	Yes	AA	NAd
Gao et al. [97]	AA	AA	NAd	AA	AA	AA	PA	No	PA	NR
Garber et al. [64]	AA	NR	NAd	WC	WC	WC	AA	Yes	PA	NAd
Gomez-Perez et al. [51]	AA	NR	NAd	AA	AA	WC	WC	No	PA	NAd
Goodman et al. [65]	AA	NR	NAd	NR	AA	AA	AA	No	PA	NAd
Halimi et al. [66]	AA	NR	NAd	AA	AA	WC	WC	No	PA	NAd
Hamann et al. [152]	AA	AA	AA	NR	AA	AA	AA	No	AA	NAd
Home et al. [52]	AA	WC	AA	NAd	AA	PA	AA	NR	AA	NAd
Home et al. [166]	AA	WC	AA	NAd	AA	PA	AA	No	AA	NAd
Kaku[45]	AA	NR	NAd	AA	AA	WC	AA	Yes	AA	NAd
Khanolkar et al. [46]	AA	NR	NAd	AA	AA	AA	PA	Yes	AA	NAd

Table 20: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Subjects and Investigators**	**Groups are Similar at Baseline**	**Only diff. Between Groups is Treatment Under Investigation**	**Standard, Valid, and Reliable Measurement of Outcomes**	**Withdrawals are Acceptable (< 20%) and Comparable Between Groups**	**ITT Analysis Performed**	**Comparable Results for Multi-study Sites**
Kilo et al. [67]	AA	NR	NAd	NAd	AA	AA	AA	Yes	PA	NAd
Kvapil et al. [68]	AA	AA	AA	NAd	AA	AA	AA	Yes	PA	NAd
Leiter et al. [69]	AA	NR	NAd	NAd	AA	AA	PA	Yes	PA	NAd
Marre et al. [70]	AA	NR	NAd	AA	AA	AA	AA	Yes	WC	NAd
Marre et al. [71]	AA	WC	AA	WC	WC	WC	WC	Yes	WC	NAd
Matthews et al. [98]	AA	NR	NAd	AA	AA	PA	NR	Yes	PA	NAd
McNulty et al. [167]	AA	NR	NAd	AA	AA	PA	PA	No	AA	NAd
Moses et al. [72]	AA	NR	NAd	AA	AA	AA	AA	No	AA	NAd
Nauck et al. [47]	WC	NR	NAd	AA	WC	WC	AA	No	PA	NAd
Nauck et al. [73]	AA	NR	NAd	NAd	AA	AA	AA	No	AA	NAd
Nauck et al. [74]	AA	AA	AA	AA	PA	PA	AA	No	PA	NAd
Papathanassiou et al. [48]	AA	PA	NAd	NAd	WC	AA	AA	Yes	WC	N/A
Phillips et al. [75]	AA	NR	NAd	WC	WC	WC	WC	Yes	AA	NAd
Poon et al. [76]	WC	NR	NAd	WC	AA	WC	PA	Yes	AA	NAd
Raskin et al. [168]	WC	NR	AA	NAd	WC	WC	AA	No	WC	NAd
Raskin et al. [77]	WC	NR	AA	NAd	AA	WC	AA	No	WC	NAd
Raz et al. [78]	WC	WC	NAd	NR	AA	PA	AA	Yes	AA	NAd
Ristic et al. [153]	WC	WC	AA	WC	WC	AA	AA	Yes	AA	NAd
Ristic et al. [79]	WC	WC	WC	WC	AA	WC	WC	No	AA	NAd
Rodger et al. [80]	AA	NR	NAd	AA	PA	AA	PA	NR	PA	NAd
Rosenstock et al. [81]	AA	NR	NAd	AA	WC	WC	WC	Yes	PA	NAd
Schernthaner et al. [49]	AA	AA	NAd	WC	NAd	WC	WC	Yes	PA	NAd
Scott et al. [82]	AA	NR	NAd	AA	AA	AA	AA	Yes	PA	NAd

Table 20: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Subjects and Investigators**	**Groups are Similar at Baseline**	**Only diff. Between Groups is Treatment Under Investigation**	**Standard, Valid, and Reliable Measurement of Outcomes**	**Withdrawals are Acceptable (< 20%) and Comparable Between Groups**	**ITT Analysis Performed**	**Comparable Results for Multi-study Sites**
Umpierrez et al. [83]	WC	NR	NAd	NAd	AA	AA	AA	Yes	AA	NAd
Van Gaal et al. [84]	WC	AA	NAd	AA	WC	AA	AA	No	AA	NAd
Von Bibra et al. [36]	WC	NR	NAd	AA	PA	AA	WC	Yes	PA	NAp
Wolever et al. [156]	AA	NR	NAd	AA	PA	AA	AA	NR	PA	NAd

AA = adequately addressed; NAd = not addressed; Nap = not applicable; NR = not reported; PA = poorly addressed; QA = quality assessment; RCTs = randomized controlled trials SIGN-50 = Scottish Intercollegiate Guidelines Network; WC = well-covered.

Table 21: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with External Validity**
Arechavaleta et al. 2011[38]	• 30 weeks in duration — may not be indicative of long-term efficacy. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • A1C target (lower end) (< 6.5%) was lower than recommended in Canada.
Aschner et al. 2012[85]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Metformin doses at baseline were not reported. • Hypoglycemia definitions were not reported.
Bergenstal et al. 2010 [86]	• 26 weeks in duration — may not be indicative of long-term efficacy. • Metformin doses at baseline were not reported. • A1C target (lower end) (< 6.5%) was lower than recommended in Canada. • Hypoglycemia definitions were not reported. • Exenatide QW was not available in Canada.
Cho et al. 2010[99]	• Conducted in Korea — population and care patterns may not be reflective of Canada. • 16 weeks in duration — may not be indicative of long-term efficacy. • Required < 3 months of stable metformin dose before determining metformin failure.
Derosa et al. 2012[149]	• Study designed primarily to detect differences in beta-cell function; other outcomes were secondary. • Employed forced titration of trial medications independent of glycemic control, which is not reflective of clinical practice. • Limited patients with BMI < 30 kg/m^2 — results may not be applicable to morbidly obese individuals.
Diamant et al. 2010[87] 2012[158]	• A1C target (lower end) (< 6.5%) was lower than recommended in Canada. • Exenatide QW was not available in Canada.
Filizof and Gauthier 2010[88]	• Required < 3 months of stable metformin dose before determining metformin failure. • Hypoglycemia definitions were not reported.
Forst et al. 2010[89]	• 12 weeks in duration — may not be indicative of long-term efficacy. • Metformin doses at baseline were not reported. • Hypoglycemia definitions were not reported.
Forst et al. 2010[160]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • Study designed primarily to detect erythrocyte deformability; other clinical outcomes were secondary.
Gallwitz et al. 2011[41]	• 26 weeks in duration — may not be indicative of long-term efficacy. • Metformin doses at baseline were not reported. • Stable metformin dose duration for determining metformin failure was not reported. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • Hypoglycemia definitions were not reported. • Exenatide QW was not available in Canada.
Gallwitz et al. 2012[43]	• Stable metformin dose duration for determining metformin failure was not reported. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • Hypoglycemia definitions were not reported. • Exenatide QW was not available in Canada.
Gallwitz et al. 2012[42]	• Stable metformin dose duration for determining metformin failure was not reported. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%)
Goke et al. 2010[44]	• Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • Required < 3 months of stable metformin dose before determining metformin failure. • Severe hypoglycemia definitions were not reported
Pan et al. 2012[90]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Conducted in China — population and care patterns may not be reflective of Canada. • Required < 3 months of stable metformin dose before determining metformin failure. • Vildagliptin was not approved for use in Canada. • Hypoglycemia definitions were not reported.

Table 21: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with External Validity**
Pfutzner et al. 2011[91]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%). • Study was designed primarily to detect diabetic dyslipidemia; other clinical outcomes were secondary. • Pioglitazone/metformin fixed combination is not available in Canada.
Pratley 2010[92]	• 26 weeks in duration — may not be indicative of long-term efficacy.
Pratley et al. 2011[162]	• 26 weeks in duration (randomization phase) – may not be indicative of long-term efficacy
Seck et al. 2010[161]	• Lower A1C threshold for determining metformin failure (6.5%) than recommended in Canada (7%).
Taskinen et al. 2011[93]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Hypoglycemia definitions were not reported.
Wang et al. 2011[155]	• Conducted in Taiwan — population and care patterns may not be reflective of Canada. • Required < 3 months of stable metformin dose before determining metformin failure. • Study designed primarily to detect differences in glycemic excursion and oxidative stress; other clinical outcomes were secondary.
Yang et al. 2011[95]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Conducted in Asian countries — population and care patterns may not be reflective of Canada. • Required < 3 months of stable metformin dose before determining metformin failure.
Yang et al. 2011[94]	• 16 weeks in duration — may not be indicative of long-term efficacy. • Conducted in Asia — population and care patterns may not be reflective of Canada.
Yang et al. 2012[96]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Conducted in China — population and care patterns may not be reflective of Canada. • Metformin doses at baseline were 1,000 mg or 1,700 mg (did not specify maximal tolerated dose). • Required < 3 months of stable metformin dose before determining metformin failure • A1C target (< 6.5%) was lower than recommended in Canada.

A1C = glycated hemoglobin; BMI = body mass index; QW = once weekly; RCTs = randomized controlled trials.

APPENDIX 10: RESULTS OF PHARMACOECONOMIC SENSITIVITY ANALYSES

Scenario	Result ($/QALY)
Reference Case Analysis	Met+SU vs. Met: $8,445 Met+AGI vs. Met+SU: $452,630 Met+GLP-1 vs. Met+AGI: $595,653 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1
All patients in the model assumed to add insulin NPH when A1C ≥ 9%	Met+AGI vs. Met+SU: $515,034 Met+GLP1 vs. Met+SU: $1,284,667 Met, Met+TZD, Met+AGI, Met+Meg, and Met+DPP-4 are dominated by Met+SU Met+basal insulin is dominated by Met+SU, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1
Insulins are removed as treatment options	Met+SU vs. Met: $8,445 Met+AGI vs. Met+SU: $452,630 Met+GLP1 vs. Met+AGI: $595,653 Met+Meg is dominated by Met+SU Met+TZD is dominated by Met+SU and Met+AGI Met+DPP-4 is dominated by Met+SU and Met+AGI
Effect estimates from pairwise meta-analyses of RCTs	Met+SU vs. Met: $11,717 Met+TZD vs. Met+SU: $164,004 Met+AGI vs. Met+TZD: $13,585 Met+Meg is dominated by Met+SU Met+DPP-4 and Met+GLP-1 are dominated by Met+TZD Met+basal insulin is dominated by Met+SU, Met+Meg, Met+TZD, Met+AGI, and Met+DPP-4 Met+biphasic insulin is dominated by Met+TZD and Met+GLP-1
Use of gliclazide instead of glyburide as SU	Met+SU vs. Met: $14,335 Met+AGI vs. Met+SU: $388,457 Met+GLP1 vs. Met+AGI: $181,421 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP1
Model assumes a 50% reduction in the price of blood glucose test strips	Met+SU vs. Met: $22,916 Met+AGI vs. Met+SU: $494,680 Met+GLP-1 vs. Met+AGI: $595,959 Met+biphasic insulin vs. Met+GLP-1: $67,246 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4
No test strip use among non– hypoglycemia-inducing OADs	Met+SU vs. Met: $18,221 Met+AGI vs. Met+SU: $521,171 Met+GLP-1 vs. Met+AGI: $805,204 Met+biphasic insulin vs. met+GLP-1: $267,289 Met+Meg is dominated by Met+SU

Scenario	Result ($/QALY)
	Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, and Met+TZD
Reduction in HRQoL resulting from weight gain (NICE)[114,115]	Met+SU vs. Met: $15,540 Met+AGI vs. Met+SU: $71,291 Met+GLP-1 vs. Met+AGI: $430,009 Met+Meg is dominated by Met+SU Met+TZD is dominated by Met+AGI and Met+DPP-4 Met+DPP-4 is dominated by Met+AGI Met+basal insulin is dominated by Met+AGI and Met+DPP-4 Met+biphasic insulin is dominated by Met+AGI, Met+DPP-4, and Met+GLP-1
Disutilities for diabetes-related complications obtained from group of patients with type 2 diabetes	Met+SU vs. Met: $9,574 Met+AGI vs. Met+SU: $323,333 Met+GLP-1 vs. Met+AGI: $523,205 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, and Met+TZD Met+biphasic insulin is dominated by Met+GLP-1
No HRQoL decrement for fear of severe hypoglycemia	Met+SU vs. Met: $10,416 Met+AGI vs. Met+SU: $519,194 Met+basal insulin vs. Met+AGI: $1,300,360 Met+GLP-1 vs. Met+Basal lnsulin: $348,297 Met+Meg is dominated by Met+SU Met+DPP-4 and Met+TZD are dominated by Met+SU and Met+AGI Met+biphasic insulin is dominated by Met+GLP-1
Model incorporates increased risk of CHF and upper extremity fractures in patients using TZDs (safety data)	Met+SU vs. Met: $8,445 Met+AGI vs. Met+SU: $452,630 Met+GLP-1 vs. Met+AGI: $595,653 Met+Meg is dominated by Met+SU Met+DPP-4 is dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1 Met+TZD is dominated by Met+SU, Met+Meg, and Met+AGI
Model incorporates reduced HRQoL associated with increased gastrointestinal symptoms among patients using AGI	Met+SU vs. Met: $8,445 Met+GLP-1 vs. Met+SU: $562,589 Met+Meg, Met+TZD and Met+DPP-4 are dominated by Met+SU Met+AGI is dominated by Met+SU and Met+Meg Met+basal insulin is dominated by Met+SU, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1
Long-acting insulin analogue cost instead of insulin NPH	Met+SU vs. Met: $8,445 Met+AGI vs. Met+SU: $452,630 Met+GLP-1 vs. Met+AGI: $595,653 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+biphasic insulin is dominated by Met+GLP-1 Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and DPP-4
Higher baseline rate of mild to moderate hypoglycemia	Met+SU vs. Met: $10,581 Met+AGI vs. Met+SU: $429,361 Met+GLP-1 vs. Met+AGI: $595;653 Met+Meg is dominated by Met+SU

Scenario	Result ($/QALY)
	Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1
Larger disutility for mild to moderate hypoglycemia	Met+SU vs. Met: $11,039 Met+AGI vs. Met+SU: $286,884 Met+GLP-1 vs. Met+AGI: $604,415 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and DPP-4 Met+biphasic insulin is dominated by Met+AGI and Met+GLP-1
Disutility of mild or moderate hypoglycemia set at 0.0052, as per NICE study[116]	Met+SU vs. Met: $15,056 Met+GLP1 vs. Met+SU: $1,029,960 Met+Meg is dominated by Met+SU Met+AGI is dominated by Met+SU Met+TZD is dominated by Met+SU and Met+AGI Met+DPP-4 is dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, Met+Meg, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP1
Cost of mild to moderate hypoglycemia event set at $93 (Canadian), as per Brod et al.[169]	Met+SU vs. Met: $12,502 Met+AGI vs. Met+SU: $429,404 Met+GLP1 vs. Met+AGI : $595,681 Met+Meg is dominated by Met+SU Met+TZD is dominated by Met+SU and Met+AGI Met+DPP-4 is dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP1
Cost of DPP-4 inhibitors is $2.25 instead of $2.55	Met+SU vs. Met : $8,445 Met+AGI vs. Met+SU: $452,630 Met+GLP-1 vs. Met+AGI: $595,653 Met+Meg is dominated by Met+SU Met+TZD and Met+DPP-4 are dominated by Met+SU and Met+AGI Met+basal insulin is dominated by Met+SU, Met+AGI, Met+TZD, and Met+DPP-4 Met+biphasic insulin is dominated by Met+GLP-1

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HRQoL = health-related quality of life; Meg = meglitinide; Met = metformin; NICE = National Institute for Health and Clinical Excellence; NPH = neutral protamine Hagedorn; OADs = oral antidiabetes drugs; RCT = randomized controlled trial; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione; vs. = versus.

APPENDIX 11: BASE-CASE RESULTS FROM THE 2010 CADTH PHARMACOECONOMIC REPORT

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

CADTH = Canadian Agency for Drugs and Technologies in Health; DPP-4 = dipeptidyl peptidase-4; in; N/A = not applicable; QALY = quality-adjusted life-year; TZD = thiazolidinedione.

APPENDIX 12: SENSITIVITY ANALYSES FROM 2010 CADTH PHARMACOECONOMIC REPORT

Scenario	Result ($/QALY)
Reference case analysis	Met+SU vs. Met: $12,757 Met+AGI vs. Met+SU: $939,479 Met+TZD vs. Met+AGI:$4,621,828 Met+Meg is dominated by Met+SU Met+DPP-4, Met+basal insulin, and Met+biphasic insulin are dominated by Met+TZD
All patients not on an insulin assumed to add insulin NPH (0.75 U/kg/day) when A1C ≥ 9%	Met+SU vs. Met: $44,373 Met+AGI, Met+Meg, Met+TZD, Met+DPP-4, Met+basal insulin, and Met+biphasic insulin are dominated by Met+SU
Effect estimates from pairwise meta-analyses of RCTs	Met+SU vs. Met: $13,080 Met+TZD vs. Met+SU: $465,004 Met+AGI is dominated by a blend of Met+SU and Met+TZD Met+Meg is dominated by Met+SU Met+DPP-4, Met+basal insulin and Met+biphasic insulin are dominated by Met+TZD
Model assumes a 50% reduction in the price of blood glucose test strips	Met+SU vs. Met: $9,102 Met+AGI vs. Met+SU: $1,033,639 Met+TZD vs. Met+AGI: $4,621,828 Met+Meg is dominated by Met+SU Met+DPP-4, Met+basal insulin, and Met+biphasic insulin are dominated by Met+TZD
No test strip use among non–hypoglycemia- inducing OADs	Met+SU vs. Met: $47,023 Met+AGI vs. Met+SU: $56,612 Met+TZD vs. Met+AGI: $4,621,828 Met+Meg is dominated by Met+SU Met+DPP-4, Met+baal insulin, and Met+biphasic insulin are dominated by Met+TZD
Reduction in HRQoL resulting from weight gain	Met+SU vs. Met: $17,839 Met+AGI vs. Met+SU: $80,453 Met+Meg is dominated by Met+SU Met+TZD, Met+DPP-4, Met+basal insulin, and Met+biphasic are dominated by Met+AGI
Disutilities for diabetes-related complications obtained from group of patients with type 2 diabetes	Met+SU vs. Met: $11,694 Met+AGI vs. Met+SU: $575,841 Met+Meg is dominated by Met+SU Met+TZD, Met+DPP-4, Met+basal insulin, and Met+biphasic are dominated by Met+AGI
Higher baseline rate of mild to moderate hypoglycemia	Met+SU vs. Met: $12,757 Met+AGI vs. Met+SU: $938,719 Met+TZD vs. Met+AGI: $4,619,894 Met+Meg is dominated by Met+SU Met+DPP-4, Met+basal insulin, and Met+biphasic are dominated by Met+TZD

Scenario	Result ($/QALY)
No HRQoL decrement for fear of severe hypoglycemia	Met+SU vs. Met: $16,860 Met+AGI vs. Met+SU: $130,967 Met+TZD vs. Met+AGI: $4,924,369 Met+Meg is dominated by Met+SU Met+DPP-4, Met+basal insulin, and Met+biphasic insulin are dominated by Met+TZD
Model incorporates increased risk of CHF and upper extremity fractures in patients using TZDs (safety data)	Met+SU vs. Met: $12,757 Met+AGI vs. Met+SU: $939,479 Met+Meg is dominated by Met+SU Met+TZD, Met+DPP-4, Met+basal insulin, and Met+biphasic are dominated by Met+AGI
Model incorporates reduced HRQoL associated with increased gastrointestinal symptoms among patients using AGI	Met+SU vs. Met: $12,757 Met+TZD vs. Met+SU: $843,306 Met+Meg and Met+AGI are dominated by Met+SU Met+DPP-4, Met+basal insulin, and Met+biphasic insulin are dominated by Met+TZD

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; HRQoL = health-related quality of life; Meg = meglitinide; Met = metformin; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione; U = units; vs. = versus.