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Third-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
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
NPH	neutral protamine Hagedorn
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
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 assessing the comparative efficacy and safety of all available antihyperglycemic drug classes for patients with type 2 diabetes with inadequate glycemic control on metformin and a sulfonylurea.[1] Insulins (basal, biphasic, bolus), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and thiazolidinediones (TZDs) all produced statistically significant reductions in glycated hemoglobin (A1C) in combination with metformin and a sulfonylurea (–0.89% to –1.17%); whereas, meglitinides and alpha-glucosidase inhibitors did not. Insulins and TZDs were associated with weight gain (1.85 kg to 5.00 kg), DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral, and GLP-1 analogues were associated with modest weight loss. Treatment regimens containing insulin were associated with increased hypoglycemia relative to comparators, but severe hypoglycemia was rare across all treatments. The results of the systematic review were used to assess the cost-effectiveness of the various options for third-line therapy after metformin and a sulfonylurea.[2] The findings suggested that the addition of insulin neutral protamine Hagedorn (NPH) to metformin and sulfonylurea combination therapy was the most cost-effective strategy. However, the addition of a DPP-4 inhibitor (sitagliptin) was potentially cost-effective under certain assumptions, such as if higher rates of hypoglycemia were assumed among patients using insulin than in the primary analysis. The Therapeutic Review Panel (TRP) deliberated on the clinical and cost-effectiveness evidence and recommended that for most patients, insulin NPH should be added to metformin and a sulfonylurea when these treatments alone are insufficient to adequately control hyperglycemia.[3]

Although the original systematic review included clinical evidence for GLP-1 analogues,[1] the cost-effectiveness analysis[2] and subsequent recommendations[3] 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 third-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, network meta-analysis, and cost-effectiveness analysis of third-line diabetes pharmacotherapy. The research questions that were addressed in the updated review were the same as in the original:

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

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 through Ovid; Embase through Ovid; The Cochrane Library through 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 the TRP in developing the original recommendations. These included mortality, diabetes-related complications, A1C, bodyweight, hypoglycemia, and serious adverse events (SAEs). Bayesian network meta-analyses and direct pairwise meta-analyses were conducted in a similar manner as in the original CADTH analysis.

The updated pharmacoeconomic study utilized similar methodology as the original analysis, except that GLP-1 analogues were modelled as a treatment option.[4] 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.[5]
- Treatment effect estimates were obtained from the updated systematic review and network meta-analysis.
- Costs for drugs, disease management, and long-term diabetes complications were updated to year 2012 costs and adjusted for inflation.

Key Findings of the Systematic Review

An additional 10 articles met the eligibility criteria for the updated review. These included 8 newly identified unique randomized controlled trials (RCTs) and 2 companion publications for RCTs that were included in the original analysis. Including the update, the systematic review of third-line pharmacotherapy included a total of 41 unique RCTs. Evidence was available for the following 8 drug classes: alpha-glucosidase inhibitors (5 RCTs), meglitinides (1 RCT), TZDs (10 RCTs), DPP-4 inhibitors (3 RCTs), GLP-1 analogues (7 RCTs), basal insulin (20 RCTs), bolus insulin (1 RCT), and biphasic insulin (12 RCTs).

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

- A total of 24 RCTs were included in the updated network meta-analysis for A1C (N = 8,517). With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in A1C (range –0.72% to –1.15%) relative to metformin and a sulfonylurea alone. The addition of a basal or biphasic insulin resulted in mean differences of –1.15% (95% credible interval [CrI], –1.49% to –0.83%) and –1.12% (95% CrI: –1.52% to –0.75%) respectively, and resulted in the most favourable rankings for reducing A1C.
- A total of 18 RCTs were included in the updated network meta-analysis for body weight (N = 7,907). When added to metformin and a sulfonylurea, basal insulin, biphasic insulin, a rapid-acting insulin analogue, or a thiazolidinedione was associated with a significantly greater increase in body weight than occurred with metformin and a sulfonylurea alone (range 1.9 kg to 5.0 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; whereas, GLP-1 analogues were associated with statistically significant weight loss (–1.6 kg, 95% CrI, –2.8 to –0.4). Meglitinides appeared to be trending toward an increase in body weight; however, the wide confidence intervals (CIs) indicate considerable uncertainty in the estimate of effect (2.6 kg [95% CrI, –0.7 to 6.0]).

For both network meta-analyses (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 RCTs designed to assess differences in long-term diabetes-related complications. Basal insulin, TZDs, DPP-4 inhibitors, and GLP-1 analogues were associated with a significantly greater risk of overall hypoglycemia than placebo when given in combination with metformin and a sulfonylurea. The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators. Biphasic and bolus insulins were associated with a significantly greater risk of overall hypoglycemia than basal insulin. Events of severe and nocturnal hypoglycemia were relatively rare for all drug classes, limiting the ability to make meaningful comparisons between drug classes.

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. Adding insulin NPH to metformin plus sulfonylurea remained the most cost-effective third-line therapy in patients inadequately controlled on metformin and sulfonylurea, with an ICUR of $68,442 per quality-adjusted life-year (QALY) gained. Insulin NPH remained the most cost-effective option in most sensitivity analyses, although the ICUR increased under some scenarios compared with the reference-case analysis. Threshold analyses indicated that the unit price of DPP-4 inhibitors and GLP-1 agonists would need to be lower by approximately 40% and 50% respectively to surpass insulin NPH as the most cost-effective third-line treatment option.

In a scenario where insulins were removed as treatment options (performed to assess cost-effectiveness in patients unable to use insulin), DPP-4 inhibitors were the most cost-effective treatment option with an ICUR of $113,254 per QALY gained.

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 with regard to 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 on 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 with respect to external validity of trials included the relatively short duration of trials, small sample sizes, failure to report definitions for hypoglycemia and adverse events, and a level of contact between trial patients 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.

With respect to 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 health-related quality of life (HRQoL). Hence, the UKPDS model may result in a slight overestimation of ICURs. 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 third-line options, particularly insulin therapy. 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, sulfonylurea and the third-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 NPH was added to all non-insulin third-line treatments once A1C reached 9%. Insulin NPH remained the most cost-effective option in this analysis.

Conclusions and Implications for Decision- or Policy-Making

Based on the updated systematic review, there was insufficient evidence to evaluate the comparative efficacy of third-line treatments added to metformin and a sulfonylurea in terms of clinically important long-term complications of diabetes. Compared with continued treatment with metformin and a sulfonylurea, addition of DPP-4 inhibitors, GLP-1 analogues, TZDs, and insulins produced statistically significant reductions in A1C; whereas, meglitinides and alpha-glucosidase inhibitors did not. Basal insulin, biphasic insulin, bolus insulin, and TZDs all resulted in an increase in body weight, DPP-4 inhibitors and alpha-glucosidase inhibitors were not associated with significant weight gain, and GLP-1 analogues were associated with weight loss. The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators, although the risk of severe hypoglycemia was low across all drug classes. Further studies of adequate size and duration are required to assess comparative efficacy in terms of durability of antihyperglycemic effect, long-term complications of diabetes, and quality of life.

The results of the updated cost-effectiveness analysis comparing third-line treatments were congruent with those of the original analysis. Addition of insulin NPH to metformin and sulfonylurea combination therapy represented the most cost-effective third-line therapy. GLP-1 analogues, which could not be considered in the original analysis since 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 insulin NPH as the most cost-effective third-line therapy, reductions in cost of 40% 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 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 pharmacoeconomic analysis assessing the comparative safety, efficacy, and cost-effectiveness of all available classes of antihyperglycemic therapies in patients with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy.[4,6] Based on these analyses, the COMPUS (Canadian Optimal Medication Prescribing and Utilization Service) Expert Review Committee recommended that for most patients, a sulfonylurea should be added to metformin when metformin alone is not enough to adequately control hyperglycemia.[7] The original analyses of second-line therapy have recently been updated by CADTH.[8]

CADTH subsequently conducted a systematic review and network meta-analysis (NMA) to determine the comparative efficacy and safety of all available antihyperglycemic drug classes for patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea.[1] At the time, we identified 33 randomized controlled trials (RCTs) meeting the inclusion criteria. Insulins (basal, biphasic, bolus), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and thiazolidinediones (TZDs) all produced statistically significant reductions in A1C in combination with metformin and a sulfonylurea (–0.89% to –1.17%); whereas, meglitinides and alpha-glucosidase inhibitors did not. Biphasic insulin, bolus insulin, and TZDs were associated with weight gain (1.85 kg to 5.00 kg); whereas, DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral, and GLP-1 analogues were associated with modest weight loss. Treatment regimens containing insulin were associated with increased hypoglycemia relative to comparators, but severe hypoglycemia was rare across all treatments.

The results of the systematic review were used to assess the cost-effectiveness of the various options for third-line therapy after metformin and a sulfonylurea.[2] The findings suggested that the addition of insulin neutral protamine Hagedorn (NPH) to metformin and sulfonylurea combination therapy was the most cost-effective strategy. However, under certain assumptions, the addition of a DPP-4 inhibitor (sitagliptin) may also be cost-effective. The Therapeutic Review Panel (TRP) deliberated on the clinical and cost-effectiveness evidence and recommended that for most patients, insulin NPH should be added to metformin and a sulfonylurea when these treatments alone are insufficient to adequately control hyperglycemia.[3]

1.2 Rationale for Updating the Review of Third-line Pharmacotherapy

Although the original clinical review of third-line pharmacotherapy for type 2 diabetes included GLP-1 analogues,[1] the cost-effectiveness analysis[2] and subsequent recommendations[3] 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 third-line therapy for type 2 diabetes that incorporate the GLP-1 analogues.

1.3 Description of Third-line Pharmacotherapy

Except for the introduction of GLP-1 analogues, the drug classes currently available in Canada for use as third-line therapy in patients with type 2 diabetes inadequately managed on metformin and a sulfonylurea remain the same as in 2010: meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, basal insulins, bolus insulins, and biphasic insulins (Table 1). It should be noted that not all agents in each class are approved by Health Canada for combination therapy with metformin and a sulfonylurea.

Since the original CADTH review of third-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 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.[9] In addition, before prescribing rosiglitazone, physicians must document the eligibility of patients to meet the above criteria; counsel each patient on the risks and benefits of rosiglitazone, including the cardiovascular risks; and obtain the patient's written informed consent.[9]

Table 1: Drug Classes Available in Canada as Third-Line Treatments for Type 2 Diabetes After Metformin and a Sulfonylurea

Drug Class	Generic Name	Dosage Information		RoA	Approved for Use With MET + SU
		Range	DDD		
TZDs	Pioglitazone	15 mg to 45 mg	30 mg	Oral	No[10]
	Rosiglitazone	4 mg to 8 mg	6 mg	Oral	No[9]
Meglitinides	Nateglinide	180 mg to 360 mg	360 mg	Oral	No[11]
	Repaglinide	0.5 mg to 16 mg	4 mg	Oral	No[12]
AGIs	Acarbose	150 mg to 300 mg	300 mg	Oral	Not specified[13]
DPP-4 inhibitors	Sitagliptin	100 mg	100 mg	Oral	Yes[14]
	Saxagliptin	5 mg	5 mg	Oral	Yes[15]
	Linagliptin	5 mg	NA	Oral	Yes[16]
GLP-1 analogues	Exenatide	10 mg to 20 mcg	15 mcg	SC	Yes[17]
	Liraglutide	1.2 mg to 1.8 mg	1.2 mg	SC	Yes[18]
Bolus insulin	Insulin aspart	Individualized	40 U	SC	Not specified[19]
	Insulin lispro	Individualized	40 U	SC	Not specified[20]
	Insulin glulisine	Individualized	40 U	SC	Yes[21]
	Human insulin	Individualized	40 U	SC	Not specified[22]
Basal insulin	Insulin NPH	Individualized	40 U	SC	Not specified[22]
	Insulin detemir	Individualized	40 U	SC	Yes[23]
	Insulin glargine	Individualized	40 U	SC	Not specified[24]
Biphasic insulins	Premixed regular NPH	Individualized	40 U	SC	Not specified[22]
	Biphasic insulin aspart	Individualized	40 U	SC	Not specified[25]
	Biphasic insulin lispro	Individualized	40 U	SC	Not specified[20]

AGI = alpha-glucosidase inhibitor; DDD = (World Health Organization) Defined Daily Dose; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; RoA = route of administration; SC = subcutaneous; SU = sulfonylurea; TZD = thiazolidinedione; U = units.

2 SYSTEMATIC REVIEW

2.1 Objectives

The objective of this review was to update the systematic review and NMA of third-line therapies for type 2 diabetes.

2.2 Methods

2.2.1 Research Questions

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

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 through Ovid; Embase through Ovid; The Cochrane Library through 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, 2010. 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 third-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 Third-Line Diabetes Pharmacotherapy	
Study Design	Randomized controlled trials
Population	Inadequately controlled with metformin and sulfonylurea combination therapy
Interventions/ Comparators	Metformin and a sulfonylurea plus any one of the following: placebo/no treatment, GLP-1 analogue, DPP-4 inhibitor, meglitinide, TZD, 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 the following countries: Canada, the United States (US), or the European Union (EU).

DPP-4 = dipeptidyl peptidase; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione.
Note: Inadequate control was defined as A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.[1,26]

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 since they belong to one of the drug classes listed in Table 1 and are approved in one or both of the US or the EU (Table 3).

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

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

AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; DDD = (World Health Organization) Defined Daily Dose; 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 of TRP in developing the original recommendations. These include mortality, diabetes-related complications, A1C, bodyweight, hypoglycemia, and serious adverse events (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 as in the original CADTH review.[26,27] 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 (Scottish Intercollegiate Guidelines Network [SIGN-50]).[28]

2.2.6 Statistical Analysis

The original NMAs for third-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.[1] WinBUGS[29] (MRC Biostatistics Unit, Cambridge, UK) was used for the network meta-analyses according to the routine developed at the Universities of Bristol and Leicester.[30] Metformin monotherapy (i.e., placebo) was the reference group for all network meta-analyses 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% CrIs 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[31] were assessed to ensure model convergence. Two chains were fit into WinBUGS for each analysis, each employing ≥ 20,000 iterations, with a burn-in of ≥ 20,000 iterations.

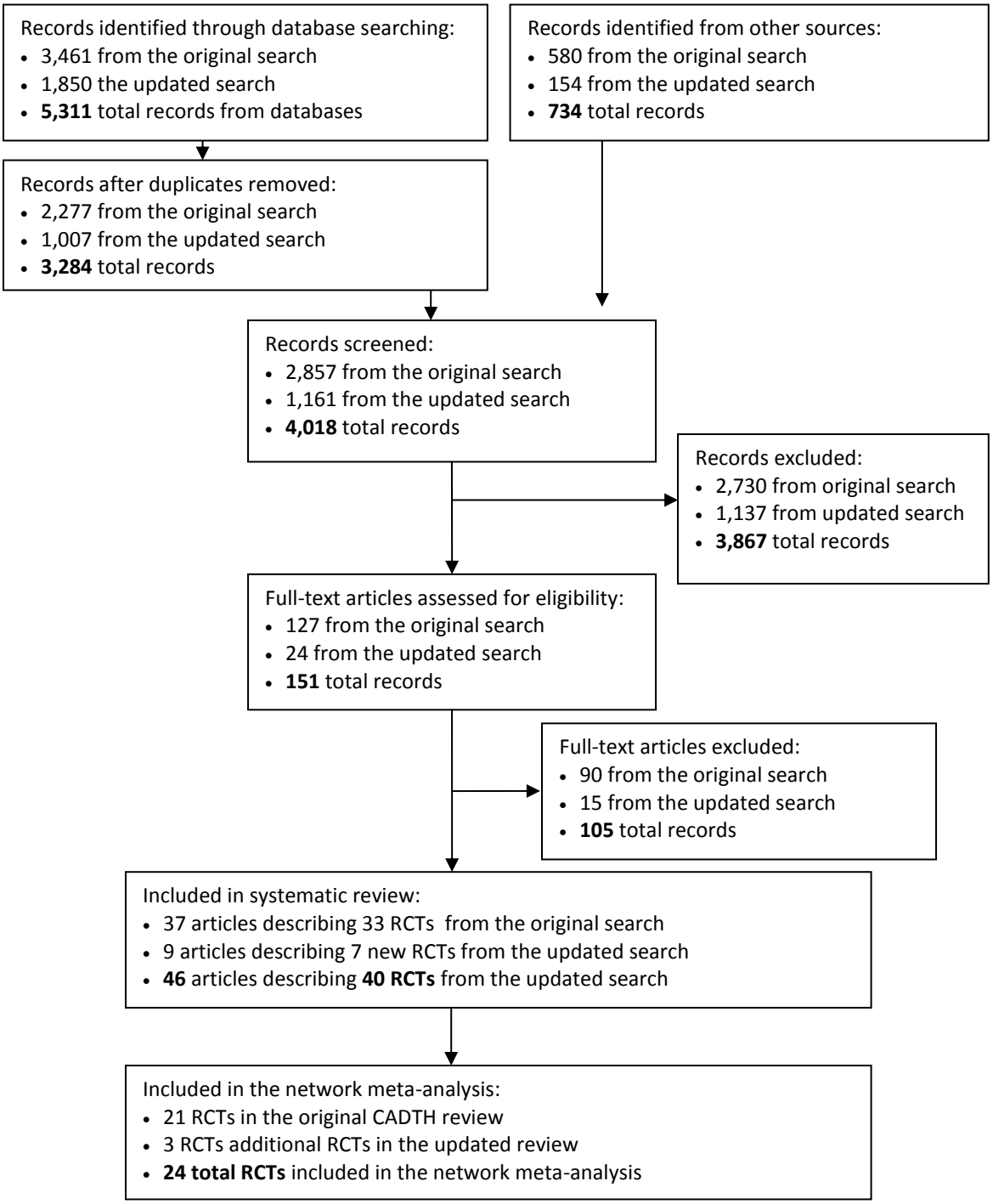
Frequentist pairwise meta-analysis was performed using R — a language and software environment for statistical computing. A random effects model was used for the reference case in all pairwise and NMAs. The robustness of the reference case for A1C was assessed using alternative modelling, sensitivity analyses, and meta-regressions.

2.3 Results

2.3.1 Literature Selection

Of the 1,161 citations identified in the updated literature search, 23 full-text articles were reviewed as full-text articles. Nine articles[32-40] reporting data from seven unique RCTs met the inclusion criteria. A PRISMA diagram showing the results of the literature selection 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 update), evidence was available for the following 8 drug classes added to metformin and a sulfonylurea: alpha-glucosidase inhibitors (5 RCTs),[37,41-44] meglitinides (1 RCT),[41] TZDs (10 RCTs),[37,45-53] DPP-4 inhibitors (3 RCTs),[36,40,54] GLP-1 analogues (7 RCTs),[39,55-60] basal insulin (21 RCTs),[32,34,39,43,45,48-50,52,53,57,60-69] bolus insulin (1 RCT),[65] and biphasic insulin (13 RCTs).[34,51,55,59,61,62,64-70] The 40 included RCTs ranged from 3 to 12 months in duration, with 6 months being the most common length. Subgroup data were extracted from three trials[34,54,56] that enrolled a mixture of patients requiring second and third-line therapy. A total of 17 distinct treatment strategies employing various combinations of third-line therapy with metformin and/or sulfonylurea were tested in the included studies. No studies compared third-line agents after discontinuation of metformin or sulfonylurea due to intolerance or contraindications.

The vast majority of RCTs used a parallel design (n = 35)[34,36,37,39,40,42,44-52,54-62,64-68,70-77] and only four employed a crossover design.[32,41,43,63] RCTs conducted in a single country[32,34,37,41-43,45-52,55,58,61-64,70,73-75] were more common than multinational trials.[36,39,40,44,54,56,57,59,60,65-69,77] Randomized sample sizes ranged from 17[51] to 734.[58] Open-label trials (27/39) were more common than double-blind trials (12/39). Twenty-eight RCTs[32,34,37,39,41,45,48-52,55,57,59,61-70,73-75,77] compared 2 active treatments, 9 RCTs[36,40,42,44,46,47,54,56,58] were placebo-controlled, and 2 RCTs[43,60] involved comparisons of active comparators as well as placebo. The majority of studies (82%) were sponsored by the pharmaceutical industry. Detailed trial characteristics are provided in Table 17.

2.3.3 Critical Appraisal

a) Internal Validity

Limitations of the newly identified RCTs were similar to those reported in the original CADTH review of third-line pharmacotherapy. Common limitations included the open-label administration of insulin and failure to conduct a true intention-to-treat analysis that included all randomized patients.[34,37,78] Study-level details regarding the internal validity assessment are reported in Table 21.

b) External Validity

Limitations that may have affected the external validity of the newly identified RCTs were 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) as opposed to more clinically meaningful end points (e.g., diabetes-related complications), and failure to report definitions for hypoglycemia. The population of interest in this review consisted of patients who were inadequately controlled with metformin and sulfonylurea combination therapy, and required a third-line agent to maintain glycemic control. However, the included studies enrolled patients who had been receiving at least a half-maximal dosage of a sulfonylurea; it is possible that patients in actual practice are tried on the maximum recommended or maximum tolerated dose. Study-level details regarding the external validity assessment are reported in Table 22. In addition, many studies were conducted exclusively in countries where health care delivery and practice patterns may differ markedly from Canada.

2.3.4 Data Synthesis

NMA and pairwise meta-analyses were conducted for A1C and body weight. Three of the newly identified RCTs[34,36,40] were eligible for inclusion in the NMAs. The remaining studies could not be pooled in the NMA because they involved intraclass comparisons,[32] or did not report changes in A1C or body weight for a relevant population or in a manner that could be pooled.[33,37,39] Evidence network diagrams

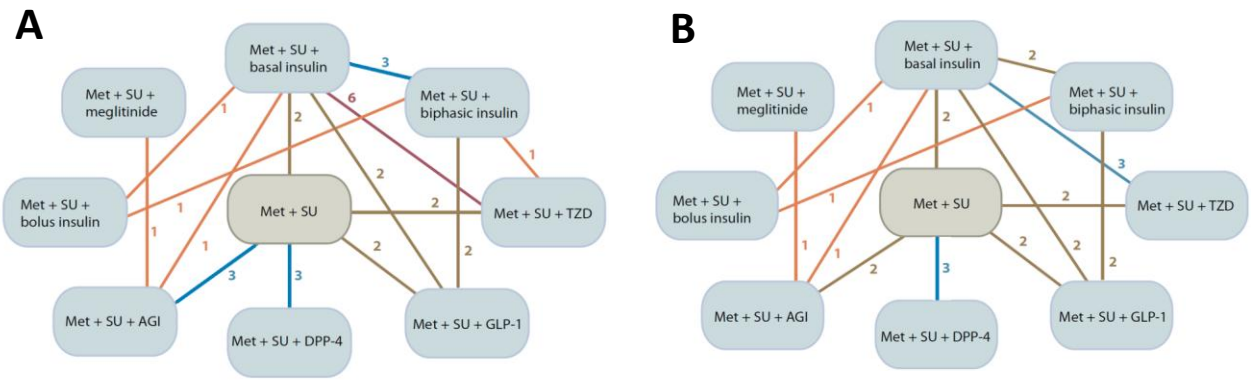
for these outcomes are shown in Figure 2. In the case of overall hypoglycemia, severe hypoglycemia and SAEs, an NMA could not be conducted because of the low event rates observed in many studies. Only pairwise direct comparisons were conducted for these outcomes.

Table 4: Overview of Evidence and Analyses Performed

Outcome	Treatment Strategies	Pairwise Comparisons	Number of Studies and Patients	Type of Analysis Conducted
A1C	9	14	24 RCTs (N = 8,517)	NMA and pairwise
Body weight	9	14	18 RCTs (N = 7,907)	NMA and pairwise
Overall hypoglycemia	9	14	28 RCTs (N = 8,553)	Pairwise
Severe hypoglycemia	9	12	25 RCTs (N = 15,111)	Pairwise
SAEs	9	10	16 RCTs (N = 6,050)	Pairwise

A1C = glycated hemoglobin; NMA = network meta-analysis; RCT = randomized controlled trial; SAE = serious adverse event.

Figure 2: Evidence Networks for Meta-Analyses of A1C (A) and Body Weight (B)



A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; GLP-1 = glucagon-like peptide-1; Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
Note: Network diagrams showing the distribution of evidence for each NMA. Numbers denote number of RCTs. (A) 24 RCTs reported the change from baseline in A1C. (B) 19 RCTs reported change from baseline in body weight.

2.3.5 Efficacy Results

a) Diabetes-Related Complications

There were no RCTs included in the original review or identified in the literature update designed to assess differences in long-term diabetes-related complications.

b) A1C

The inclusion of the newly identified RCTs increased the size of the NMA for A1C from 21 to 24 RCTs (N = 8,517).[34,36,40-52,54,55,57-60,65,69,73] The results of the updated NMA were similar to the original analysis (Figure 3). With the exception of alpha-glucosidase inhibitors and meglitinides, all classes added to metformin and a sulfonylurea achieved statistically significant reductions in A1C (range –0.72% to –1.15%) relative to metformin and sulfonylurea alone. The addition of a basal or biphasic insulin produced the largest effects, with mean differences of –1.15% (95% CrI, –1.49% to –0.83%) and –1.12% (95% CrI, –1.52% to –0.75%) respectively.

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 (40.7) was greater than that of the random effects model (6.1) suggesting that the random effects model was the better-fitting model. Model parameters indicated a 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 6.

The robustness of the reference case was assessed using alternative modelling, sensitivity analyses, and meta-regressions (Table 5). Results of the NMAs were similar when analyzed using random and fixed-effects. Sensitivity analyses were conducted to assess the impact of removing studies with the following characteristics:

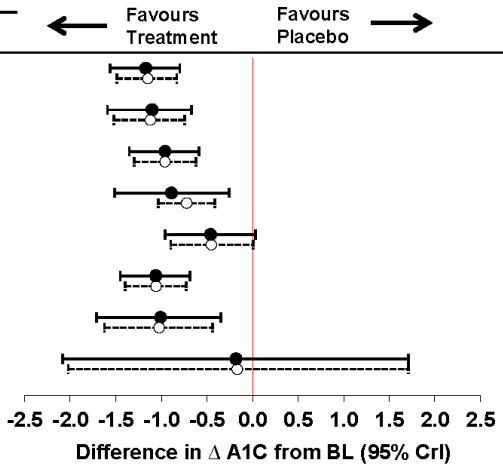
- investigated the use of rosiglitazone
- investigated the use of any thiazolidinedione (i.e., rosiglitazone or pioglitazone)
- investigated the use of an agent that were not indicated at the time of the analysis for use in combination with metformin and a sulfonylurea in Canada (i.e., pioglitazone, rosiglitazone, saxagliptin, miglitol, and repaglinide)
- specified a threshold of A1C < 7.0% in the inclusion criteria
- did not provide information for sulfonylurea dosing at baseline
- reported subgroup data for the population of interest
- crossover studies.

All of these sensitivity analyses produced 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.

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

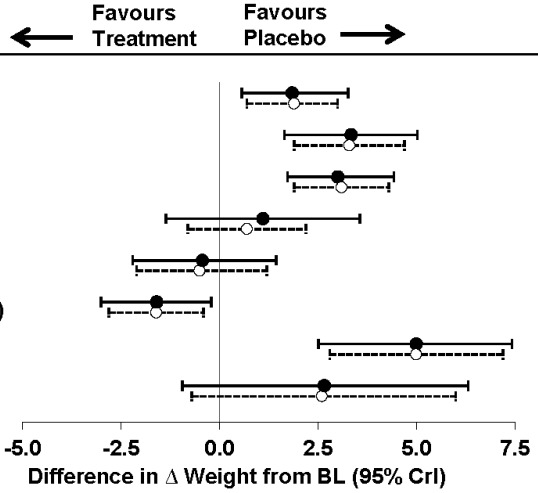
A

Treatment added-on to metformin and a sulfonylurea	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Basal Insulin	–1.17 (–1.57, –0.81)	–1.15 (–1.49, –0.83)
Biphasic Insulin	–1.10 (–1.59, –0.67)	–1.12 (–1.52, –0.75)
Thiazolidinediones	–0.96 (–1.35, –0.59)	–0.96 (–1.30, –0.62)
DPP-4 Inhibitors	–0.89 (–1.51, –0.26)	–0.72 (–1.03, -0.42)
AG Inhibitors	–0.46 (–0.96, 0.03)	–0.45 (–0.90, 0.01)
GLP-1 Analogues	–1.06 (–1.45, –0.69)	–1.06 (–1.40, –0.73)
Bolus Insulin	–1.01 (–1.71, –0.35)	–1.02 (–1.62, –0.44)
Meglitinides	–0.18 (–2.08, 1.71)	–0.17 (–2.02, 1.71)



B

Treatment added-on to metformin and a sulfonylurea	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Basal Insulin	1.9 (0.5, 3.1)	1.9 (0.7, 3.0)
Biphasic Insulin	3.4 (1.7, 5.0)	3.3 (1.9, 4.7)
Thiazolidinediones	3.0 (1.7, 4.4)	3.1 (1.9, 4.3)
DPP-4 Inhibitors	1.1 (–1.4, 3.6)	0.7 (–0.8, 2.2)
AG Inhibitors	–0.4 (–2.2, 1.4)	–0.5 (–2.1, 1.2)
GLP-1 Analogues	–1.6 (–3.0, –0.2)	–1.6 (–2.8, –0.4)
Bolus Insulin	5.0 (2.5, 7.4)	5.0 (2.8, 7.2)
Meglitinides	2.7 (–0.9, 6.3)	2.6 (–0.7, 6.0)



A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptid-1e; NMA = network meta-analysis.
Note: Forest plots comparing the results of the original (●) and updated (O) CADTH network meta-analyses for change from baseline in A1C (A) and change from baseline in body weight (B).

Table 5: Sensitivity Analyses for Change from Baseline A1C (%) — NMA Estimates Versus Placebo[a]								
Analysis	**Basal Insulin**	**Biphasic Insulin**	**TZDs**	**DPP-4 Inhibitors**	**AGIs**	**GLP-1 Analogues**	**Bolus Insulin**	**Meglitinides**
Reference case	–1.15 (–1.49 to –0.83)	–1.12 (–1.52 to – 0.75)	–0.96 (–1.30 to –0.62)	–0.72 (–1.03 to –0.42)	–0.45 (–0.90 to 0.01)	–1.06 (–1.4 to, –0.73)	–1.02 (–1.62 to –0.44)	–0.17 (–2.02 to 1.71)
Modelling Assumption								
Fixed-effects (instead of random effects)	–1.05 (–1.18 to –0.93)	–1.02 (–1.17 to –0.88)	–0.98 (–1.12 to –0.84)	–0.69 (–0.78 to –0.60)	–0.42 (–0.71 to –0.14)	–1.03 (–1.16 to –0.91)	–1.12 (–1.37to –0.88)	–0.12 (–1.87 to 1.64)
Meta–Regression Adjusting for:								
Baseline A1C	–1.16 (–1.51 to –0.84)	–1.15 (–1.55 to –0.77)	–0.91 (–1.26 to –0.56)	–0.73 (–1.04 to –0.41)	–0.33 (–0.82 to 0.17)	–1.07 (–1.42 to –0.74)	–1.02 (–1.62 to –0.43)	–0.03 (–1.93 to 1.87)
Baseline duration of diabetes	–1.21 (–1.61 to –0.82)	–1.20 (–1.70 to –0.73)	–1.06 (–1.54 to –0.55)	–0.97 (–1.61 to –0.29)	–0.54 (–1.08 to 0.03)	–1.11 (–1.51 to –0.71)	–1.05 (–1.73 to –0.40)	–0.10 (–2.03 to 1.80)
Duration of RCT	–1.21 (–1.57 to –0.87)	–1.18 (–1.60 to –0.79)	–1.09 (–1.50 to –0.65)	–0.82 (–1.18 to –0.44)	–0.56 (–1.04 to –0.06)	–1.11 (–1.46 to –0.77)	–1.04 (–1.63 to –0.47)	–0.07 (–1.91 to 1.75)
Sensitivity Analyses With Removal of:								
RCTs of rosiglitazone	-1.17 (–1.61 to –0.78)	–1.14 (–1.64 to –0.69)	–0.92 (–1.39 to –0.44)	–0.72 (–1.09 to –0.35)	–0.46 (–0.97 to 0.04)	–1.07 (–1.48 to –0.68)	–1.04 (–1.77 to –0.35)	–0.12 (–2.04 to 1.74)
All TZD RCTs	–1.03 (–1.53 to –0.58)	–1.02 (–1.57 to –0.53)	————	–0.72 (–1.08 to –0.36)	–0.46 (–0.97 to 0.04)	–0.98 (–1.42 to –0.57)	–0.91 (–1.67 to –0.18)	–0.20 (–2.16 to 1.77)
RCTs with A1C < 7.0% in the inclusion criteria	–1.16 (–1.52 to –0.84)	–1.07 (–1.52 to –0.67)	–0.97 (–1.32 to –0.62)	–0.72 (–1.05 to –0.40)	–0.46 (–0.92 to 0.01)	–1.04 (–1.39 to –0.70)	–1.00 (–1.63 to –0.39)	Not applicable
RCTs not providing SU dosing at baseline	–1.30 (–1.91 to –0.76)	–1.14 (–2.02 to –0.37)	–1.08 (–1.71 to –0.51)	–0.75 (–1.33 to –0.18)	–0.46 (–1.07 to 0.14)	–1.02 (–1.75 to –0.33)	–1.09 (–2.08 to –0.16)	Not applicable
RCTs of agents not indicated for use with Met + SU in Canada[b]	–1.06 (–1.64 to –0.55)	–1.05 (–1.69 to –0.49)	————	–0.75 (–1.28 to –0.23)	–0.58 (–1.38 to 0.22)	–1.00 (–1.52 to –0.52)	–0.93 (–1.83 to –0.10)	Not applicable
RCTs of duration other than 6 months (i.e., 24 to 26 weeks)[c]	–0.97 (–1.32 to –0.63)	–1.17 (–1.60 to –0.79)	–0.74 (–1.17 to –0.27)	–0.71 (–0.93 to –0.50)	–0.43 (–0.82 to –0.07)	–0.97 (–1.31 to –0.62)	Not applicable	Not applicable

Table 5: Sensitivity Analyses for Change from Baseline A1C (%) — NMA Estimates Versus Placebo[a]								
Analysis	**Basal Insulin**	**Biphasic Insulin**	**TZDs**	**DPP-4 Inhibitors**	**AGIs**	**GLP-1 Analogues**	**Bolus Insulin**	**Meglitinides**
RCTs from which subgroup data were used	–1.16 (–1.53 to –0.83)	–1.09 (–1.55 to –0.68)	–0.97 (–1.32 to –0.61)	–0.64 (–1.05 to –0.23)	–0.46 (–0.93 to 0.00)	–1.05 (–1.42 to –0.71)	–1.01 (–1.66 to –0.40)	–0.20 (–2.08 to 1.67)
Crossover studies	–1.11 (–1.46 to –0.79)	–1.09 (–1.50 to –0.71)	–0.94 (–1.28 to –0.59)	–0.72 (–1.03 to –0.41)	–0.45 (–0.92 to 0.02)	–1.04 (–1.38 to –0.70)	–0.99 (–1.59 to –0.39)	Not applicable

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; NOC = Notice of Compliance; SU = sulfonylurea; TZDs = thiazolidinedione.

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

[b]Based on information available at the time of the analysis. Agents without a Notice of Compliance from Health Canada were also excluded in this sensitivity analysis.

[c]Includes only studies that reported treatment effects at 6 or 6.5 months (i.e., 24 or 26 weeks).

2.3.6 Safety Results

a) Body Weight

A total of 18 RCTs (N = 7,907)[34,36,41-43,45-47,49,54,55,57-60,65,69,73] were included in the NMA for change from baseline in body weight (16 from the original review and 2 from the update). Similar to A1C, the inclusion of the newly identified studies resulted in only minor changes to the NMA results. When added to metformin and sulfonylurea combination therapy, basal insulin, biphasic insulin, a rapid-acting insulin analogue, and a thiazolidinedione were associated with a significantly greater increase in body weight than occurred with metformin and sulfonylurea combination therapy alone (range 1.9 kg to 5.0 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; whereas, GLP-1 analogues were associated with statistically significant weight loss (–1.6 kg, 95% CrI, –2.8 kg to –0.4 kg). The large degree of uncertainty (i.e., wide confidence interval [CI]) for the effect of meglitinides made it difficult to draw conclusions for this drug class; however, there was a non-significant trend toward weight gain (mean difference 2.67 kg, 95% CrI, –0.94 kg to 6.32 kg).

b) Hypoglycemia

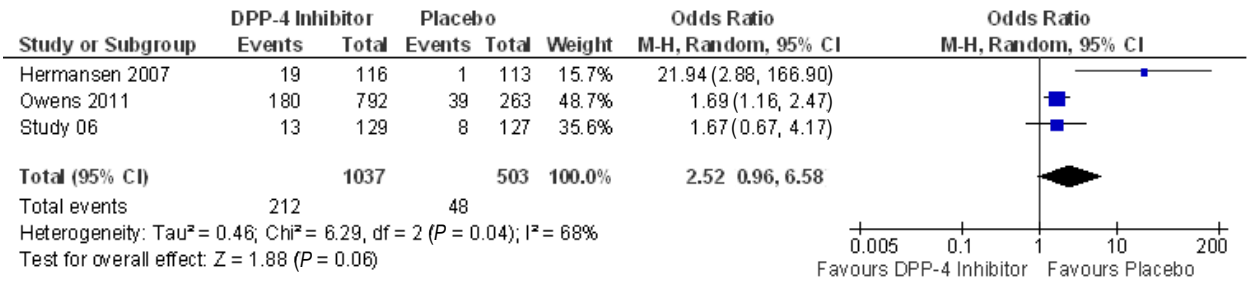
Overall Hypoglycemia

A total of 28 RCTs[36,40,43-47,49,50,52,54-60,62-70,73,75] (N = 8,553) reported the number of patients experiencing at least one event of hypoglycemia (26 from the original review and 2 from the update). 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 ≤ 3.0 mmol/L to ≤ 4.0 mmol/L), and whether or not patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose. The studies demonstrated that basal insulin, TZDs, DPP-4 inhibitors, and GLP-1 analogues were associated with a significantly greater risk of overall hypoglycemia than placebo when given in combination with metformin and a sulfonylurea. The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators. Biphasic and bolus insulins were associated with a significantly greater risk of overall hypoglycemia than basal insulin. An NMA was not performed for this outcome due to the large variation in the control group (i.e., metformin plus sulfonylurea) event rates of overall hypoglycemia. Data from the newly identified RCTs were incorporated into the direct pairwise comparisons summarized in Table 6. With the exception of the DPP-4 inhibitor class, the updated findings are similar to those of the original review with respect to hypoglycemia. Originally, only a single RCT for DPP-4 inhibitors was identified, which demonstrated a large increase in risk of hypoglycemia for patients treated with sitagliptin compared with placebo (odds ratio [OR] [95% CI], 21.9 [2.9 to 166.9]). However, the inclusion of an additional RCT for linagliptin (OR [95% CI], 1.7 [1.2 to 2.5]) suggest a much lower risk of hypoglycemia with the DPP-4 inhibitor class relative to placebo — the pooled estimate of the OR for DPP-4 inhibitors was 2.5 (95% CI, 1.0 to 6.6).

Table 6: Pairwise Comparisons of Studies Reporting Overall Hypoglycemia					
Intervention 1	**Intervention 2**	**RCTs**	**N**	**OR (95% CI)**	**I^2 (%)**
Placebo Comparisons (intervention 1 versus intervention 2)					
Basal Insulin + Met + SU	Placebo + Met + SU	1[60]	346	2.03 (1.15 to 3.58)	——
TZD + Met + SU	Placebo + Met + SU	2[46,47]	664	5.62 (2.81 to 11.25)	33
DPP-4 inhibitors + Met + SU	Placebo + Met + SU	3[36,40,54]	1,540	2.52 (0.96 to 6.58)	68
GLP-1 + Met+ SU	Placebo + Met + SU	2[58,60]	1,324	2.07 (1.54 to 2.77)	0
Active Comparisons (intervention 1 versus intervention 2)					
Biphasic insulin + Met + SU	Basal insulin + Met + SU	1[65]	469	4.01 (2.31 to 6.96)	——
		1[69]	469	1.29 (0.90 to 1.86)	——
TZD + Met + SU	Basal insulin + Met + SU	4[45,49,50,73]	413	0.40 (0.21 to 0.75)	22
GLP-1 + Met + SU	Basal insulin + Met + SU	1[60]	462	0.93 (0.62 to 1.39)	——
Bolus insulin + Met + SU	Basal insulin + Met + SU	1[65]	402	8.97 (4.34 to 18.56)	——
Biphasic insulin	Basal insulin + Met + SU	1[66]	236	1.32 (0.86 to 2.03)	——
GLP-1 + Met + SU	Biphasic insulin + Met + SU	1[55]	105	0.33 (0.19 to 0.55)	——
Bolus insulin + Met + SU	Biphasic insulin + Met + SU	1[65]	445	2.24 (0.99 to 5.05)	——
Biphasic insulin + Met	Biphasic insulin + Met + SU	1[55]	248	1.26 (0.76 to 2.09)	——
Biphasic insulin + Met	GLP-1 + Met + SU	1[55]	112	3.87 (2.28 to 6.58)	——
Biphasic insulin + Met	Basal insulin + Met	1[62]	56	1.32 (0.40 to 4.33)	——
Basal insulin + Meg + Met	Basal insulin + Met	1[62]	55	0.57 (0.15 to 2.23)	——
Basal insulin + Meg + Met	Biphasic insulin + Met	1[62]	53	0.43 (0.11 to 1.66)	——
Basal insulin	Basal insulin + Met	1[68]	174	1.08 (0.01 to 218.9)	——
Biphasic insulin	Basal insulin + Met	1[68]	173	1.12 (0.01 to 115.9)	——
Biphasic insulin	Basal insulin	1[68]	175	1.04 (0.09 to 12.34)	——

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

Figure 4: Overall Hypoglycemia Risk for DPP-4 Inhibitors Versus Placebo



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; M-H = Mantel-Haenszel.

Severe Hypoglycemia

Severe hypoglycemia was typically defined as an event requiring third-party assistance. A total of 25 RCTs (N=15,111) of third-line pharmacotherapy reported incidence of severe hypoglycemia (22 from the original review and three from the literature update).[32,34,36,42,44,45,47,49,52,54-60,62-65,67-70,73] Study-level results for the individual RCTs are presented in Table 18. Events of severe hypoglycemia were relatively rare for all drug classes including the insulins, limiting the ability to conduct comparisons across drug classes. Six RCTs[34,62,64,65,67,68] compared treatment strategies involving the use of biphasic or basal insulin. The largest was a three-arm trial that randomized patients to treatment with biphasic insulin (BiAsp30), basal insulin (determir), or bolus insulin (aspart), each in addition to continued metformin and sulfonylurea.[65] This RCT reported a statistically significant increase in risk of severe hypoglycemia with bolus insulin versus basal insulin (OR [95% CI], 4.14 (1.36 to 12.59]) and a trend toward more events with biphasic versus basal insulin (OR [95% CI], 2.82 [0.89 to 9.00]).

c) Serious Adverse Events

There were 16 RCTs (N = 6,050) for third-line pharmacotherapy identified in the update that reported SAEs.[36,40,44-47,54,58-60,65,70,73,74,76,77] Events classified as SAEs were relatively rare in the included trials, ranging from 2.3% to 5.5% of the trial populations. The proportion of patients with at least one SAE was similar between treatments. No statistical tests were conducted due to limited statistical power. Detailed results for SAEs are reported in Table 8.

Table 7: Summary of SAEs in Third-Line RCTs

Study[a]	Treatment 1	n (%)	Treatment 2	n (%)
Placebo Comparisons				
Owens et al. 2011[36]	DPP-4 inhibitor + Met + SU	25 (3)	Placebo + Met + SU	10 (4)
Study 6[40]	DPP-4 inhibitor + Met + SU	3 (2)	Placebo + Met + SU	7 (6)
Hermansen et al. 2007[54]	DPP-4 inhibitor + Met + SU	7 (6)	Placebo + Met + SU	2 (2)
Charpentier and Halimi 2009[46]	TZD + Met + SU	7 (5)	Placebo + Met + SU	5 (3)
Dailey et al. 2004[47]	TZD + Met + SU	3 (2)	Placebo + Met + SU	8 (4)
Kendall et al. 2005[58]	GLP-1 + Met + SU	12 (5)	Placebo + Met + SU	15 (6)
Russell-Jones et al. 2009[60]	GLP-1 + Met + SU	9 (4)	Placebo + Met + SU	8 (7)
Russell-Jones et al.	Basal insulin + Met + SU	16 (7)	Placebo + Met + SU	8 (7)

Table 7: Summary of SAEs in Third-Line RCTs				
Study[a]	**Treatment 1**	**n (%)**	**Treatment 2**	**n (%)**
2009[60]				
Standl et al. 2001[44]	AGI + Met + SU	5 (7)	Placebo + Met + SU	5 (7)
Berhanu et al. 2007[70]	TZD + insulin + Met	4 (4)	Placebo + insulin + Met	2 (1)
Active Comparisons				
Aljabri et al. 2004[45]	TZD + Met + SU	0 (0)	Basal insulin + Met + SU	0 (0)
Rosenstock et al. 2006[73]	TZD + Met + SU	11 (10)	Basal insulin + Met + SU	5 (5)
Vinik and Zhang 2007[76]	TZD + Met + SU	11 (10)	Basal insulin + Met + SU	5 (5)
Russell-Jones et al. 2009[60]	GLP-1 + Met + SU	9 (4)	Basal insulin + Met + SU	16 (7)
Nauck et al. 2007[59]	GLP-1 + Met + SU	19 (8)	Biphasic insulin	11/248
Holman et al. 2007[65]	Bolus insulin + Met + SU	30 (13)	Basal insulin + Met + SU	30 (13)
Holman et al. 2007[65]	Bolus insulin + Met + SU	30 (13)	Biphasic insulin + Met + SU	41 (17)
Holman et al. 2007[65]	Basal insulin + Met + SU	30 (13)	Biphasic insulin + Met + SU	41 (17)
Intraclass Comparisons				
Esposito et al. 2008[74]	Basal insulin (glargine) + Met + SU	1 (2)	Basal insulin (detemir) + Met + SU	1 (2)
Yki-Jarvinen et al. 2006[77]	Basal insulin (glargine) + Met	1 (2)	Basl (NPH) + Met	4 (7)

AGI = alpha-glucosidase inhibitor; Basl = basal insulin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; NPH = neutral protamine Hagedorn; QD = once daily; SU = sulfonylurea; TZD = thiazolidinedione.

[a]SAEs were not reported in Fadini et al. 2011,[32] Herman et al. 2010,[34] Al-Shaikh 2006,[61] Bergenstal et al. 2009,[55] Boye et al. 2006,[72] Davies et al. 2007,[62] De Mattia et al. 2009,[63] Derosa et al.,[41] Dorkhan et al.2009,[48] Gao et al. 2009,[56] Goudswaard et al. 2004,[64] Hartemann-Heurtier et al. 2009,[49] Heine et al. 2005,[57] Janka et al. 2005,[66] Janka et al. 2007,[71] Ko et al. 2006,[50] Lam et al. 1998,[42] Milicevic et al. 2009,[67] Ovalle and Bell 2004,[51] Reynolds et al. 2007,[52] Ross et al. 2001,[75] Stehouwer et al. 2003,[68] and Strojek et al. 2009.[69]

3 PHARMACOECONOMIC ANALYSIS

3.1 Objective

To update the 2010 CADTH pharmacoeconomic analysis of third-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 that compared alternative third-line therapies in adults with type 2 diabetes inadequately controlled with metformin and a sulfonylurea.

3.2.2 Target Population

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

3.2.3 Treatments

The following classes of drugs, added to metformin and sulfonylurea combination therapy, were considered:

- basal insulin (i.e., insulin NPH or long-acting insulin analogues)
- biphasic insulin (i.e., regular human insulin, insulin aspart, and insulin lispro)
- thiazolidinediones (TZDs)
- dipeptidyl peptidase-4 (DPP-4) inhibitors
- glucagon-like peptide-1 (GLP-1) agonists.

Alpha-glucosidase inhibitors and meglitinides, two additional classes indicated in Canada for the treatment of type 2 diabetes, were not included in the reference case in the previous analysis and this was maintained for the updated analysis as well. Based on expert opinion, they are not widely used in Canadian clinical practice in combination with metformin and a sulfonylurea.[2] TZDs were also not included in the updated analysis as they are not indicated for use in combination with metformin and sulfonylurea in Canada.[9,10]

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, and weight) for the analysis were derived from the updated systematic review investigating the use of third-line antidiabetic agents in patients inadequately controlled on metformin and a sulfonylurea. Where possible, estimates of efficacy for the economic analysis were obtained from NMAs of these RCTs.

Most RCTs included in the meta-analysis were unlikely to have had adequate sample size, or been of sufficient duration, to precisely capture incidence rates of severe hypoglycemia in patients using insulin secretagogues or insulin. 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.[79] Sensitivity analyses for this parameter were conducted using the higher rates of severe hypoglycemia reported in a study by Leese et al.[80]

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 United Kingdom Prospective Diabetes Study (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 Trial 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.[81]

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.[1,4] 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 Program (November 2012) when available. Otherwise, prices were obtained from other public drug programs (Quebec and British Columbia Drug Benefits) 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, insulin NPH for basal insulin, biphasic human insulin for biphasic insulin, exenatide for GLP-1 analogues, linagliptin for DPP-4 inhibitors) plus a 10% mark up and $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/day), it was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.[82] 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). Sensitivity analyses were conducted considering doses reported in RCTs included in the original CADTH review of second-line therapies.[4]

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, average daily utilization of blood glucose test strips for each drug class was derived from a recent utilization study in Ontario (Table 8).[83] A cost of $0.729 per test strip (as listed in the Ontario Public Drug Program) plus a pharmacy fee of $7.00 per 100 test strips was applied. No mark up was applied as test strips are not eligible for mark up in the Ontario Public Drug Program. A sensitivity analysis was conducted where the additional cost of test strips was not considered.

Table 8: Mean Daily Utilization of Blood Glucose Test Strips in 2008 by Seniors in the Ontario Public Drug Programs, by Type of Pharmacotherapy*

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

*Gomes et al[83]

Using insulin doses from clinical practice, insulin NPH had the lowest treatment cost; however, when the additional cost of test strips was included, the cost of insulin NPH was similar to that of lowest cost DPP-4 inhibitors (Table 9). However, when we applied insulin doses from RCTs, insulin NPH had the lowest treatment cost even after the additional cost of test strips was insulin.

Table 9: 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**
DPP-4 inhibitors	Linagliptin 5 mg daily	$2.88	$3.81
GLP-1 agonists	Exenatide 20 mcg daily	$5.13	$6.05
Basal human insulin	Insulin NPH 0.75 U per kg per day[b] (0.42 U per kg per day)[c]	 $1.93[b] $1.11[c]	 $3.60[b] $2.78[c]
Biphasic human insulin	Insulin NPH 30/70 1.50 U per kg per day[b] (0.76 U per kg per day)[c]	 $3.83[b] $2.88[c]	 $5.48[b] $3.63[c]
Long-acting insulin analogues	Insulin glargine 0.53 U per kg per day[b] (0.35 U per kg per day)[c]	 $3.12[b] $1.98[c]	 $4.78[b] $3.64[c]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; U = units.
[a]The cost of the lowest cost alternative was applied for each drug class, plus a 10% mark up 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. [82]
[b]Insulin doses obtained from patient sample in British Columbia (Dr. Marshall Dahl, unpublished data, 2008). This dataset reported insulin doses of 0.53U/kg, 0.75U/kg, 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 an assumed body weight of 87 kg (derived from RCTs included in systematic review).
[c]Insulin doses obtained from RCTs included in the original CADTH systematic review of second-line therapies,[4] which reported insulin doses of 0.35, 0.42, and 0.76 U/kg for long-acting insulin analogues, insulin NPH, and biphasic human insulin respectively.

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 10).[84] Inpatient, out-patient, and 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 plus a sulfonylurea was $2,070 while those using third-line therapies had an annual cost of $2,070 plus the additional cost of third-line therapy and blood glucose test strips.

Table 10: 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)[84] 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 service resource use. Resource utilization associated with managing a severe hypoglycemic episode was based on studies by Leese et al.[80] (Table 9) and National Institute for Health and Care

Excellence (NICE).[85] Management costs were based on data from the Alberta Case Costing Database [2006] [86] (Table 11). Because resource use was derived from the United Kingdom, the information for the previous analysis was presented to diabetes expert members of COMPUS Expert Review Committee 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. As such, the average cost 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 11: 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			**$2,030.91**

[a]Costs updated and inflated to 2012 Canadian dollars.
[b]Data from the United Kingdom[85]
[c]Unit cost from Alberta[86]

3.2.9 Valuing Outcomes

The primary outcome measure in the analysis was the quality-adjusted life-year (QALY), 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.[87,88] Quality weights for modelled long-term diabetes-related complications were also obtained from Sullivan et al.[87,88] when available. Otherwise, utility scores were obtained from a study by Clarke et al.,[5] who also used the EQ-5D instrument. Estimates from Clarke et al.[5] are often used in cost-effectiveness studies related to diabetes interventions. However, unlike Sullivan et al.,[87,88] Clarke et al.[5] 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 the 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 12: 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;[87,88] therefore, they were obtained from a study by Clarke et al.[5]

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 performing usual activities, thus resulting in a disutility of 0.167 during the episode.[89] 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.[90] Thus, each episode was associated with an annual decrement of 0.000004767 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 the NICE[85] 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,[91,92] which assumed a utility decrement of 0.001950135 per unit increase in body mass index (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, e.g., standard error and CI, 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 group. 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 reference case, to determine the minimal price change necessary for each of those classes to become the third-line treatment strategy with the most favourable cost-effectiveness results in comparison with other third-line treatment strategies.

3.3 Results

3.3.1 Reference Case

From the updated analysis (Table 13), the addition of basal insulin (i.e., insulin NPH) to metformin and a sulfonylurea was associated with the most favourable cost-effectiveness estimate, with an incremental cost of $68,442 per QALY gained compared with metformin and a sulfonylurea alone. Other active treatments were associated with unfavourable cost-effectiveness estimates (i.e., they were dominated or demonstrated very high incremental cost-utility ratios [ICURs]) when compared with the next least costly treatment.

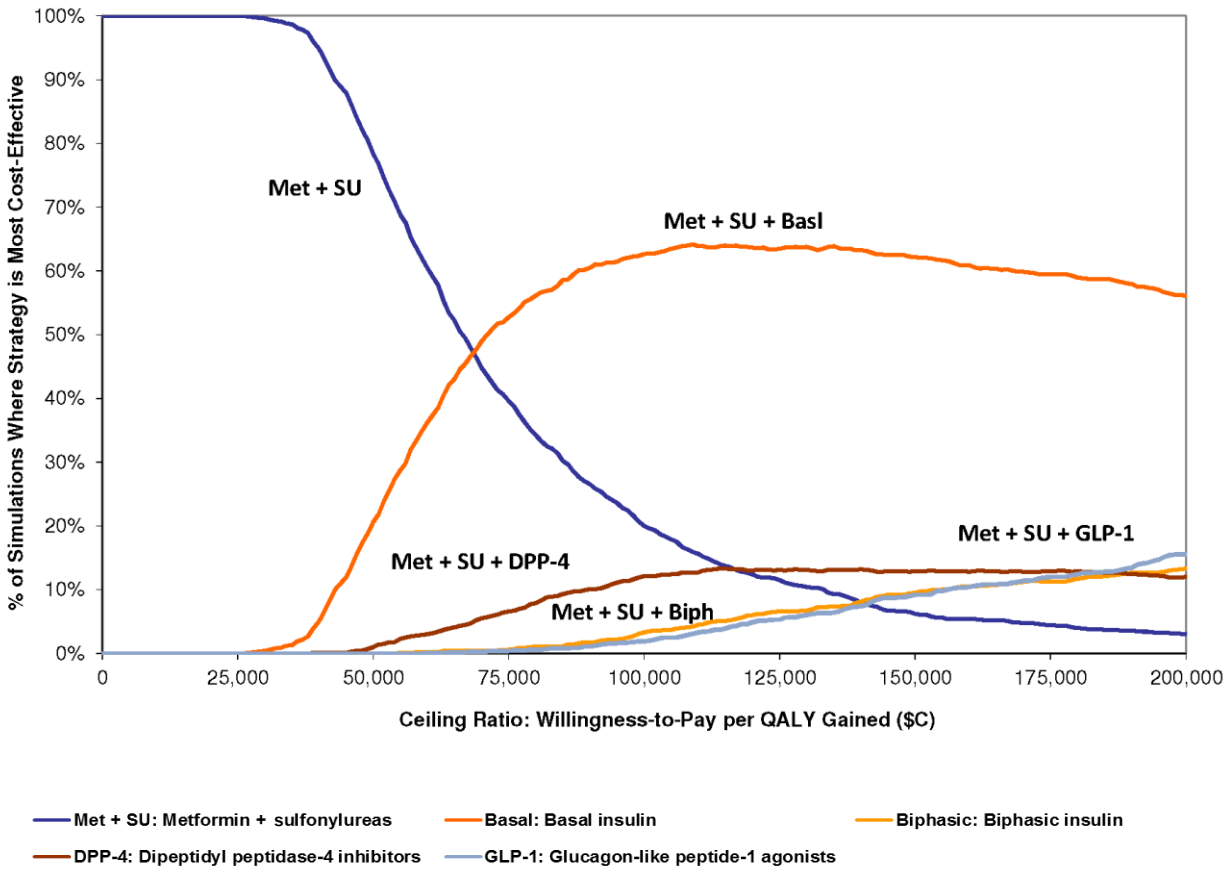
Table 13: Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results From the Updated Reference-Case Analysis

Strategy	Cost	Effectiveness (QALY)	ICUR	
			Incremental Versus Met + SU	Sequential
Met + SU	$46,746	8.2089	NA	
Met + SU + Basal insulin	$52,453	8.2923	$68,442	$68,442
Met + SU + GLP-1 analogue	$58,341	8.2957	$133,662	$1,752,233
Treatments Ruled Out by Dominance or Extended Dominance				
Met + SU + DPP-4 inhibitor	$53,097	8.2650	$113,254	**Dominated by:** Met + SU + Basal insulin
Met + SU + Biphasic insulin	$57,117	8.2875	$131,989	**Dominated by:** Met + SU + Basal insulin

DPP-4 = dipeptidyl peptidase-4; in; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; Met = metformin; NA = not applicable; QALY = quality-adjusted life-year; SU = sulfonylurea.

The cost-effectiveness acceptability curve (Figure 1) shows that basal insulin had the highest probability of being most cost-effective for willingness-to-pay thresholds above $69,000 per QALY gained.

Figure 5: 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 third-line treatments indicated that basal insulin remained the most cost-effective option in combination with metformin plus a sulfonylurea under most assumptions. The following is a summary of some of the notable results from sensitivity analyses:

- Disutility of hypoglycemia:
  - When mild to moderate hypoglycemia was assumed to impart a higher disutility than in the reference case (annual decrement of 0.0033 per episode instead of 0.000004767),[93] basal insulin remained the most cost-effective option with an ICUR of $119,288 per QALY (relative to Met + SU). Other treatments were either dominated or extendedly dominated. However, when the annual disutility for each mild to moderate hypoglycemia episode was raised further to 0.0052 (based on the value reported in a NICE appraisal[94]) DPP-4-inhibitors emerged as the most cost-effective option, with an ICUR of $135,366 per QALY (relative to metformin and a sulfonylurea alone). Other treatments, excluding GLP-1 agonists, were either dominated or extendedly dominated.
  - When an annual decrement of 0.047 was applied for each severe hypoglycemic event as suggested by Currie et al.[95] (instead of 0.01 as in the reference case), basal insulin remained the most favourable option with an ICUR of $99,918 per QALY gained.
- Disutility of increase in BMI: When a utility decrement of 0.001950135 per unit increase in BMI (based on data from NICE Obesity Guidelines[91,92]) was applied, basal insulin remained the most cost-

effective option, although the ICUR increased from $68,442 to $90,225 per QALY gained relative to metformin and sulfonylurea (Table 14).

Table 14: Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results from a Sensitivity Analysis Assuming a Utility Decrement of 0.001950135 per Unit Increase in BMI

Strategy	Cost	Effectiveness	Incremental Versus Met + SU	Sequential
Met + SU	$46,746	8.2089	Not applicable	Not applicable
Met + SU + Basal insulin	$52,453	8.2722	$90,225	$90,225
Met + SU + GLP-1	$58,341	8.3039	$122,064	$185,526
Dominance and Extended Dominance				
Met + SU + DPP-4	$53,097	8.2545	$139,351	Dominated by: Met + SU + basal insulin Not dominated by: Met + SU + GLP-1
Met + SU + Biphasic insulin	$57,117	8.2570	$215,819	Dominated by: Met + SU + basal insulin Not dominated by: Met + SU + GLP-1 and Met + SU + DPP-4

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucaon-like peptide-1; Met = metformin; QALY = quality-adjusted life-year; SU = sulfonylurea.

- Dose of insulin: The doses of insulin NPH (0.75 U/kg/day) and biphasic human insulin (1.5 U/kg/day) were based upon a dataset from patients with type 2 diabetes in British Columbia. A sensitivity analysis was conducted where the dose of insulin was instead based on data from RCTs included in the systematic review. The ICUR for basal insulin decreased from $68,442 to $44,636 per QALY gained relative to metformin and a sulfonylurea alone.
- To address the limitation of the reference-case analysis with respect to the absence of therapy progression over time, it was assumed in a sensitivity analysis that when A1C increased over time to ≥ 9%, insulin NPH (0.75 U/kg/day) would be added as a fourth-line treatment in non-insulin groups. The insulin doses in the basal and biphasic insulin groups were kept constant. The results showed that basal insulin remained the most favourable option, but the ICUR increased from $68,442 to $126,151 per QALY gained relative to metformin and a sulfonylurea alone.
- Cost of treatments: The primary economic analysis applied the lowest cost comparator within each class and assumed treatment effects at the class level. When the treatment cost for long-acting insulin analogues (insulin glargine) was applied for the basal insulin option rather than insulin NPH, the resulting ICUR was $103,159 per QALY gained relative to metformin and a sulfonylurea.
- Test strips: Results were sensitive to inclusion of the cost of test strips in the analysis, as well as the time horizon. When the cost of test strips was excluded, cost-effectiveness estimates for basal insulin became more favourable — the ICUR decreased from $68,442 to $46,986 per QALY gained relative to metformin and a sulfonylurea. When a time horizon of 10 years was used rather than 40 years, the ICUR for basal insulin increased from $68,442 to $116,113 per QALY gained relative to metformin and a sulfonylurea.
- Impact of Insulin Injections on HRQoL: We did not apply a utility decrement for insulin use in the reference-case analysis. Some studies have reported that insulin use is itself associated with a reduction in quality of life;[96-98] therefore, we ran a sensitivity analysis where we assumed a one-time

decrement of –0.06 based on data from a trial by Maddigan et al.[97] Because this estimate exceeded the disutilities for even some serious complications (e.g., myocardial infarction),[87,88] we ran a subsequent analysis using the lower limit of the CI (–0.03). Decrements were only applied in year one, based on expert opinion.[2] When the larger decrement was applied, basal insulin became less favourable than in the reference case but remained the most cost-effective option, with an ICUR of $85,716 per QALY gained relative to metformin and a sulfonylurea alone.

- Cost of mild to moderate hypoglycemia: In the reference-case analysis, patients experiencing a mild to moderate hypoglycemic event did not incur health care resource use. A study by Brod et al. found that non-severe hypoglycemia events were associated with substantial economic consequences for patients and employers, with extra blood glucose tests and lost productivity at a cost ranging from US$15.26 to US$93.47 per non-severe event.[99] In a scenario where mild to moderate hypoglycemia events were assumed to incur a cost of $93, basal insulin became less favourable but remained the most cost-effective option with an ICUR of $75,603 per QALY gained relative to metformin and sulfonylurea alone.
- TZDs were not modelled in the reference-case analysis as they are not indicated for combination use with metformin and a sulfonylurea. However, a sensitivity analysis was performed in which pioglitazone was included as a treatment option in order to model potential off-label use in the third-line setting. TZDs are associated with an increased risk of congestive heart failure (CHF) (HR 2.10 [95% CI, 1.35 to 3.27]).[100] To model CHF risk in the UKPDS Outcomes Model is challenging as it is predicted by a number of surrogates (e.g., A1C, cholesterol), all of which influence multiple outcomes within the model. The increased risk of CHF in patients using TZDs was therefore incorporated by artificially increasing body weight by 30 kg since CHF is the only sub-model in the UKPDS Outcomes Model that is influenced by body weight. Results of this sensitivity analysis showed that TZDs were dominated by basal insulin (Table 15).

Table 15: Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results from the Sensitivity Analysis Including TZDs

Strategy	Cost	Effectiveness	Incremental Versus Met + SU	Sequential
Met + SU	$46,746	8.2089	Not applicable	Not applicable
Met + SU + AGI	$49,342	8.2519	$60,375	$60,375
Met + SU + Basal insulin	$52,453	8.2923	$68,442	$77,029
Met + SU + GLP-1	$58,341	8.2957	$133,662	$1,752,233
Dominance and Extended Dominance				
Met + SU + DPP-4	$53,097	8.2650	$113,254	Dominated by: Met + SU + Basal insulin Not dominated by: Met + SU + AGI; and Met + SU + GLP-1.
Met + SU + Biphasic insulin	$57,117	8.2875	$131,989	Dominated by: Met + SU + Basal insulin Not dominated by: Met + SU + AGI; Met + SU + GLP-1; and Met + SU + DPP-4.
Met + SU + TZD	$51,450	8.1880	Dominated	Dominated by: Met + SU + Basal insulin Not dominated by: Met + SU + AGI; Met + SU + GLP-1; Met + SU + DPP-4; and Met + SU + Biphasic insulin.

AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1; Met = metformin; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione.

3.3.3 Threshold Analysis

In the reference case, GLP-1 agonists and DPP-4 inhibitors were dominated or extendedly dominated compared with other treatments. The results of varying the unit price showed that in order to become the most cost-effective third-line treatment strategy, the unit cost of the modelled DPP-4 inhibitor (linagliptin) would have to be 40% lower (resulting in an ICUR of $64,926 per QALY gained compared with metformin and a sulfonylurea alone). When lesser reductions were modelled, the DPP-4 inhibitor remained extendedly dominated by basal insulin. For GLP-1 agonists, a 50% reduction in unit price would be necessary for this class to be the most cost-effective option, resulting in an ICUR of $62,629 per QALY gained compared with metformin and a sulfonylurea alone. Price reductions less than 50% resulted in basal insulin being the most cost-effective option, although ICURs for GLP-1 analogues relative to basal insulin were lower compared with the reference case. The results of the threshold analysis are presented in Table 16.

Table 16: Threshold Analysis of DPP-4 Inhibitors and GLP-1 Agonists as Third-Line Treatments

Class	Price Reduction	New Unit Price	ICUR (versus Met + SU)	Sequential ICUR	Rank
DPP-4 (linagliptin 5 mg)	Reference case	$2.55	$113,254 per QALY	Dominated by Met + SU + Basal Insulin	3
	25%	$1.913	$83,049 per QALY	Extendedly dominated by Met + SU + Basal Insulin	2
	35%	$1.658	$70,967 per QALY	Extendedly dominated by Met + SU + Basal Insulin	2
	40%	$1.530	$64,926 per QALY	$64,926 per QALY (relative to Met + SU)	1
	50%	$1.275	$52,845 per QALY	$52,845 per QALY (relative to Met + SU)	1
GLP-1 (exenatide 20 mcg)	Reference case	$2.295	$133,662 per QALY	$1,752,233 per QALY (relative to Met + SU + Basal insulin)	5
	25%	$1.721	$98,146 per QALY	$835,300 per QALY (relative to Met + SU + Basal insulin)	2
	35%	$1.492	$83,939 per QALY	$468,523 per QALY (relative to Met + SU + Basal insulin)	2
	40%	$1.377	$76,836 per QALY	$285,144 per QALY (relative to Met + SU + Basal insulin)	2
	50%	$1.148	$62,629 per QALY	$62,629 per QALY (relative to Met + SU)	1

DPP-4 = dipeptidyl peptidase-4; ICUR = incremental cost-utility ratio; GLP-1 = glucagon-like peptide-1; Met = metformin.
QALY = quality-adjusted life-year; SU = sulfonylurea.

4 DISCUSSION

4.1 Interpretation of Systematic Review Results

The objective of this review was to conduct an update of CADTH's systematic review and NMAs of diabetes pharmacotherapy for patients inadequately controlled with metformin and a sulfonylurea. The original review included a total of 33 unique RCTs. We identified an additional 8 RCTs that met the inclusion for the CADTH review, bringing the total to 41 RCTs conducted in patients inadequately controlled with metformin and a sulfonylurea. Three of the newly identified RCTs were incorporated into the updated network meta-analyses of agents added on to metformin and a sulfonylurea. Overall, the inclusion of these RCTs resulted in only minor changes to the estimates of effect and did not alter the interpretation of the original review.

The original review only included a single placebo-controlled RCT[54] that investigated the use of a DPP-4 inhibitor in combination with metformin and a sulfonylurea. The updated literature search identified two additional 24-week, placebo-controlled RCTs[36,40] investigating linagliptin and saxagliptin in combination with metformin and a sulfonylurea. The inclusion of these studies in the NMAs resulted in a slight reduction in the improvement in A1C associated with DPP-4 inhibitors (from –0.89% to –0.72%). The class-level effect size was reduced because sitagliptin was associated with a mean difference of –0.89% relative to placebo; whereas, linagliptin and saxagliptin were associated with mean differences of –0.62% and –0.66% relative to placebo respectively. The larger effect size for sitagliptin appears to be driven by a deterioration of 0.3% in the placebo group of that trial, compared with an improvement of 0.05% and 0.1% in the placebo groups of the saxagliptin and linagliptin trials respectively. Overall, the within group change from baseline was similar for each DPP-4 inhibitor.

When added to metformin and sulfonylurea therapy, treatment with basal insulin, biphasic insulin, rapid-acting insulin analogues, or TZDs resulted in statistically significantly greater increases in body weight than treatment with metformin and a sulfonylurea alone. Meglitinides appeared to be trending toward an increase in body weight; however, the wide CIs indicate considerable uncertainty in the effect estimate (2.6 kg [95% CI, –0.7 to 6.0]). NMA results demonstrated that DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral and that GLP-1 analogues were associated with statistically significant weight loss. There is no universally accepted minimal clinically important difference for body weight, although 5% is the smallest change cited as being of clinical importance in the literature.[101-104] Based on the overall weight of the patients included in the NMA (weighted mean 87.0 kg), the only drug class that exceeded a change of 5% relative to placebo was bolus insulin (5.7%). However, comparisons of GLP-1 analogues with TZDs (5.4%), biphasic insulins (5.7%), and bolus insulin (7.6%) also exceeded the 5% threshold. 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 insulins continues over the long-term, or whether stabilization occurs at some point.

Given the large differences in baseline overall hypoglycemia event rates in the control groups (i.e., metformin plus a sulfonylurea) across studies, NMA was not conducted for this outcome. Furthermore, definitions of hypoglycemia were variable and often not reported in the included clinical trials. These issues, which are commonly encountered in diabetes studies, make it difficult to accurately compare hypoglycemia data across trials.[105] The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators, and biphasic and bolus insulins were associated with a significantly greater risk of hypoglycemia than basal insulin. When given in combination with metformin and sulfonylureas, TZDs, GLP-1 analogues, and DPP-4 inhibitors were

associated with a significantly greater number of patients experiencing hypoglycemia than placebo. In contrast, CADTH's analysis of second-line therapy found no increased risk of hypoglycemia when these agents are administered in combination with metformin alone, suggesting that combined use with sulfonylureas may potentiate risk.[4] Events of severe hypoglycemia were relatively rare for all drug classes including the insulins, limiting the statistical power to make comparisons across drug classes. Bolus insulin was shown to be associated with more events of severe hypoglycemia than basal insulin.

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 agents compared with drugs from 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.[106-110] 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.[14,16-18,111] 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 with non-users (OR, 2.24 [95% CI, 1.36 to 3.68]).[112]

4.2 Pharmacoeconomic Considerations

The 2010 CADTH report on the cost-effectiveness of third-line antidiabetic treatments indicated that basal insulin was associated with the lowest total lifetime costs ($44,206) and the most favourable incremental cost-effectiveness estimates ($60,049 per QALY gained).[2] Total lifetime costs and QALYs, as well as incremental cost-effectiveness results from the primary economic analysis reported in the original CADTH report, are presented in Appendix 9. The updated cost-effectiveness analysis based on the results of the updated NMA indicated that insulin NPH (basal insulin) remains the most cost-effective third-line therapy in patients inadequately controlled on metformin plus a sulfonylurea, despite higher rates of overall and severe hypoglycemia relative to other oral antidiabetic drugs, and despite the introduction of GLP-1 analogues into the model. The main driver of this result was the difference in treatment costs, since differences in complication rates and QALYs gained between treatments were small.

Cost-effectiveness results were sensitive to variation in model inputs and assumptions, in particular, assumptions regarding the disutility associated with hypoglycemic episodes. In the reference case, patients experiencing mild to moderate hypoglycemia were assumed to have a transient reduction in HRQoL. 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. Thus, each episode was associated with an annual decrement of 0.000004767 QALYs. This estimate differs from an estimate by Levy et al.[93] that states that each mild to moderate hypoglycemia episode is associated with a disutility of 0.0033, which is equivalent to spending 1.2 days in a state of death. When this disutility was considered in a sensitivity analysis, DPP-4-inhibitors (linagliptin) became the most cost-effective option with an ICUR of $90,007 per QALY gained relative to metformin and a sulfonylurea alone. Other treatments were either dominated or extendedly dominated. The marked difference between the reference case disutility and the disutility reported by Levy et al.[93] are indicative of the high degree of uncertainty regarding the true impact of hypoglycemia on quality of life, although the notion that an episode of mild to moderate hypoglycemia results in a death-like state for 1.2 days probably has limited face validity.

In the primary analysis, 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.[85] An annual decrement of 0.01 was applied for each severe hypoglycemic event; the same decrement that was applied in a recently published report[85] by NICE. The estimates used by NICE[85] are less pronounced than those reported in an industry-sponsored study by Currie et al.,[113] in which they suggest a utility decrement of 0.047 associated with severe hypoglycemic episodes and state that this should be applied over one year. By applying this disutility, they are assuming that each severe hypoglycemic episode is equivalent to spending 17 days in a state of death. This disutility estimate is greater than for other more severe complications such as myocardial infarction (–0.041); [87,88] hence, its validity is questionable. Nevertheless, we ran a sensitivity analysis using the estimate by Currie et al.[95], and found a negligible impact on cost-effectiveness results. Insulin NPH remained the most favourable among active comparisons, with an ICUR of $99,918 per QALY gained.

The impact of weight gain on HRQoL is another area of uncertainty that has the potential to impact the cost-effectiveness results given the propensity of insulins to increase weight, and the weight neutrality or modest weight loss associated with the incretins. Assuming a utility decrement of 0.001950135 per unit increase in BMI in a sensitivity analysis based on NICE obesity guidelines,[91] cost-effectiveness estimates for insulin NPH became less favourable — the ICUR increased from $68,442 to $90,225 per QALY gained relative to metformin and a sulfonylurea. No increase in utility was assigned to the modest weight loss associated with GLP-1 analogues in either the reference-case or sensitivity analyses, as the impact of such weight loss on HRQoL remains uncertain. If evidence of benefit becomes available in the future, it is possible that the relative cost-effectiveness of GLP-1 analogues may improve.

Apart from the concerns surrounding hypoglycemia and weight gain, patients may be reticent about initiating insulin therapy due to concerns about administering injections.[114] It is therefore possible that this route of administration is associated with reduced quality of life, especially in patients newly initiated on insulin. However, we were unable to identify any evidence related the disutility related to the injectable route of administration. Should future studies report such data, then the cost-effectiveness of insulin NPH may be reduced.

The primary economic analysis applied the lowest cost comparator within each class and assumed treatment effects at the class level. For example, the pooled treatment effects from all basal insulin products (e.g., insulin glargine, insulin NPH, and insulin detemir) were applied and assumed the treatment cost of insulin NPH. The basis for this was the lack of sufficient evidence in the updated NMAs to differentiate between insulin NPH and long-acting analogues, and previous research showing that the long-acting analogues have minimal or no benefit compared with insulin NPH in terms of glycemic control, and modest benefit at best in terms of hypoglycemia risk.[115] When the treatment cost for long-acting insulin analogues (insulin glargine) was considered in a sensitivity analysis (assuming all outcomes were identical to those for insulin NPH), the ICUR increased to $103,159 per QALY gained relative to metformin and a sulfonylurea. Had a reduced risk for hypoglycemia been assumed, the ICUR for insulin glargine may have been somewhat lower. However, it is worth noting that in a previous cost-effectiveness analysis, long-acting insulin analogues were not cost-effective compared with insulin NPH in patients with type 2 diabetes even when reduced hypoglycemia risk was factored into the model.[116]

For the newer, more expensive oral antidiabetic agents, GLP-1 agonist and DPP-4 inhibitors, the results showed they were among the classes with the least favourable cost-effectiveness results, largely driven by their high cost and similar gains in glycemic control compared with less expensive agents. Threshold

analyses indicated that significant unit price reductions would be required to displace basal insulin as the third-line treatment of choice.

4.3 Strengths and Limitations

The systematic review was conducted according to a protocol specified in advance, using standardized, reproducible methods for identification of evidence, data abstraction, quality assessment, and analysis. 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. NMAs involve pooling of trials within and between pairwise contrasts. To avoid the introduction of bias, it is imperative that clinical and methodological variation across studies is minimized. If variability does exist, assessment of its effects on NMA results is required. We observed variability in study and patient characteristics that may be important predictors of treatment effect including baseline A1C, baseline body weight, duration of diabetes, and study length. To address these, we performed alternative modelling, meta-regression analyses, and sensitivity analyses. Results from these analyses were consistent with each other and with the reference case; hence, the observed variability across included studies did not appear to introduce an appreciable degree of bias. Furthermore, direct and indirect estimates were in close alignment. As well, the findings reported by CADTH with respect to the efficacy of third-line treatments added on to metformin have been independently confirmed in another published NMAs.[117]

Despite the aforementioned strengths, a number of limitations related to the available evidence warrant discussion. There was little evidence for the effect of third-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 prediction of macrovascular outcomes.[118,119] As well, the evidence on hypoglycemia was primarily related to overall hypoglycemia, an outcome of uncertain clinical significance that was inconsistently defined across studies. Further study is required to determine whether differences exist between third-line agents regarding the risk for clinically meaningful hypoglycemia events. Finally, due to the relatively short duration of most included trials, it was impossible to determine whether there were differences in the durability of antihyperglycemic effects across drug classes.

A majority of RCTs were assessed as having significant methodological limitations (e.g., improper reporting of allocation concealment or failure to provide an intention-to-treat analysis) and were less than one year in duration. There was significant variability in the reporting of metformin and sulfonylurea dosing at baseline, with most RCTs failing to report this information. Furthermore, several studies only required half-maximal dosing of sulfonylureas before patients were considered to have failed therapy. These limitations could affect the relative efficacy of third-line treatment strategies, and even compromise the generalizability of results. For example, patients who are inadequately controlled on maximally tolerated doses of metformin and a sulfonylurea may experience a lesser response to third-line therapy than those that receive submaximal therapy, since the former may have more long-standing, treatment-resistant disease. It is also noteworthy that most included trials included patients who may have received various antidiabetes drugs before metformin and sulfonylurea combination therapy, which may impact generalizability to the clinical population of interest to a certain degree. However, this concern is somewhat mitigated by the robustness of the results in meta-regression analyses to adjust for differences in duration of diabetes and baseline A1C, both of which are likely the most important predictors of treatment efficacy.

The reference case for the NMAs was conducted by grouping agents into classes (e.g., DPP-4 inhibitors, GLP-1 analogues, and basal insulins); an approach that requires the important assumption that agents within a particular drug class are similar enough to pool. The individual agent NMAs 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 pharmacodynamic 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%]).[115,120] These findings suggest that it is appropriate to pool these agents into a single basal insulin class for the purposes of this NMA.

To ensure homogeneity in the NMAs, the overall patient population was restricted to patients who were inadequately controlled with both metformin and a sulfonylurea. Trials that enrolled mixed patient populations, such as patients experiencing inadequate control with metformin monotherapy or combination therapy, were not included in our review unless they reported subgroup data for the population of interest. Ensuring a homogenous population is essential for performing meta-analyses; however, this approach may have led to the exclusion of potentially relevant RCTs. One example is the LEAD-6 trial that compared liraglutide and exenatide in patients treated with maximally tolerated doses of metformin, sulfonylurea, or both.[121] This RCT reported a treatment difference in A1C favouring liraglutide compared with exenatide of –0.33% (95% CI, –0.47 to –0.18) and could not be incorporated into our agent-level analysis in the absence of subgroup data. The indirect comparison from our NMAs also favoured liraglutide compared with exenatide by a similar margin (–0.19%; 95% CrI: –0.87 to 0.47); however, the width of the CrI demonstrates considerable uncertainty with this estimate.

With respect to 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. Since a reduced incidence of these outcomes and the resulting benefits in terms 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 that were included in the pharmacoeconomic model.

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 subsequent treatments. Due to these considerations, it was assumed in the reference case that patients remained on their respective third-line therapy during 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 insulin NPH as fourth-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. As such, some elements of the sensitivity analysis results could not be discounted appropriately. In the future, if the UKPDS model is updated to enable more seamless integration of changes in treatment sequences over time, reanalysis may be warranted.

With respect to the inputs used in the analysis, there was considerable uncertainty regarding 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 sensitivity analyses.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Based on the updated systematic review, there was insufficient evidence to evaluate the comparative efficacy of third-line treatments added to metformin and a sulfonylurea in terms of clinically important long-term complications of diabetes. Compared with continued treatment with metformin and a sulfonylurea, addition of DPP-4 inhibitors, GLP-1 analogues, TZDs, and insulins produced statistically significant reductions in A1C; whereas, meglitinides and alpha-glucosidase inhibitors did not. Insulins and TZDs were all associated with an increase in body weight, DPP-4 inhibitors and alpha-glucosidase inhibitors were not associated with significant weight gain, and GLP-1 analogues were associated with weight loss. The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators, although the risk of severe hypoglycemia was low across all drug classes. Further studies of adequate size and duration are required to assess comparative efficacy in terms of durability of antihyperglycemic effect, long-term complications of diabetes, and quality of life.

The results of the updated cost-effectiveness analysis comparing third-line treatments were congruent with those of the original analysis. The addition of insulin NPH to metformin and sulfonylurea combination therapy represented the most cost-effective third-line therapy. GLP-1 analogues, which could not be considered in the original analysis since 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 insulin NPH as the most cost-effective third-line therapy, reductions in cost of 40% 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 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 onward 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.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
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.
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

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
	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.
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.

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
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.
131	or/124-130
132	116 and 123 and 131
133	132 use emef
134	62 or 133

Ovid MEDLINE & Embase Strategy	
#	**Strategy**
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.

Ovid Cochrane Strategy	
#	**Searches**
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.
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/

Ovid Cochrane Strategy	
#	**Searches**
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	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 anti-diabetes drugs
Limits:	Publication years 2009 to 2012

The following sections of the CADTH grey literature checklist, *Grey Matters: A Practical 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
- Open Access Journals.

APPENDIX 2: STUDY CHARACTERISTICS

Table 17: Detailed Study Characteristics of RCTs Included in the Systematic Review of Third-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author and Year	Countries	Sponsor	Interventions/Comparators	Glycemic Target	Treatment Duration	Criteria for Defining Combination Therapy Failure	Sample Size	Blinding
Herman et al. 2010[34]	US	Lilly US	• Biphasic insulin lispro + Met + SU • Insulin glargine + Met + SU	A1C < 7.0%	6 months	A1C >7.0%	1,274[a]	OL
Owens et al. 2011[36]	Multinational (Europe, North America, South America, Asia)	Boehringer Ingelheim	• Linagliptin + Met + SU • Placebo + Met + SU	A1C < 6.5% or 7.0%	24 weeks	A1C 7.0 to 10.0%	1,058	DB
Study 6[40]	Multinational (Australia, North America, Asia)	AstraZenec, Bristol-Myers Squibb	• Saxagliptin + Met + SU • Placebo + Met + SU	NR	6 months	A1C 7.0% to10.0%	257	DB
DURATION [33,39]	Multinational (Europe, Australia, North America, Asia)	Amylin, Eli Lilly	• Exenatide (QW) + Met + SU • Insulin glargine + Met + SU	A1C < 7.0 and < 6.5%	26 weeks	A1C 7.1% to 11.0%	135	OL
Fadini et al 2011 [32]	Italy	Novo Nordisk	• Insulin detemir + Met + SU • Insulin glargine + Met + SU	NR	6 months	NR	43	OL
Derosa et al. 2010 [37]	Italy	Not reported	• Pioglitazone + Met + SU • Acarbose + Met + SU	NR	9 months	A1C ≥ 6.5%	350	DB
Aljabri et al. 2004[45]	Canada	Eli Lilly	• Pioglitazone (30 mg to 45 mg) + Met + SU • NPH insulin + Met + SU	FG < 6.0 mmol/L	4 months	A1C >8.0%	62	OL
Al-Shaikh 2006[61]	Saudi Arabia	Not reported	• Insulin glargine (HS) + Met + SU • Biphasic insulin	FBG < 7.7 mmol/L	6 months	A1C c > 8.0%	221	OL
Bergenstal et al. 2009[55]	US	Novo Nordisk	• Exenatide + Met + SU • BIAsp30 (QD) + Met + SU • BIAsp30 (BID) + Met + SU	FBG 5.0-6.1 mmol/L	6 months	A1C ≥ 8.0%	372	OL
Berhanu et al. 2007[70]	US	Takeda	• Insulin + Pioglitazone + Met • Insulin + Placebo + Met	FPG < 7.8 mmol/L	20 weeks	A1C > 8.0%	222	DB
Boye et al. 2006[72]	Multinational	Takeda	• Exenatide (BID) + Met + SU • Insulin glargine + Met + SU	FBG < 5.5 mmol/L	26 weeks	A1C 7.0% to 10.0%	NR	OL
Charpentier et al. 2009[46]	France	Eli Lilly	• Pioglitazone (30mg to 45 mg) + Met + SU • Placebo + Met + SU	A1C < 6.5%	7 months	A1C 7.0% to 9.5%	299	DB

Table 17: Detailed Study Characteristics of RCTs Included in the Systematic Review of Third-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author and Year	Countries	Sponsor	Interventions/Comparators	Glycemic Target	Treatment Duration	Criteria for Defining Combination Therapy Failure	Sample Size	Blinding
Dailey et al. 2004[47]	US	Takeda	• Rosiglitazone (4 mg to 8 mg) + Met + SU • Placebo + Met + SU	A1C <7.0%	4 months	A1C 7.0% to 10.0%	365	DB
Davies et al. 2007[62]	UK	Bristol-Myers Squibb	• Biphasic insulin (BID) + Met • NPH insulin (HS) + Repaglinide (AC) + Met • NPH Insulin (HS) + Met	FBG < 6.0 mmol/L	4 months	A1C > 7.0%	82	OL
De Mattia et al. 2009[63]	Italy	Sanofi-aventis	• Insulin glargine + Met + SU • NPH Insulin + Met + SU	FBG < 5.5 mmol/L	3 months	A1C ≥ 8.0%	20	OL
Derosa et al. 2009[41]	Italy	University of Pavia, Italy	• Acarbose + Met + SU • Repaglinide + Met + SU	Not reported	3.5 months	A1C ≥ 6.5%	103	DB
Dorkhan et al. 2009[48]	Sweden	Sanofi-aventis	• Pioglitazone + Met + SU • Insulin glargine + Met + SU	FBG < 6.0 mmol/L or A1C < 6.2%	6.5 months	A1C > 6.2%	30	DB
Esposito et al. 2008[74]	Italy	Second University of Naples	• NPL insulin (HS) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.6 mmol/L	9 months	A1C 7.5% to 10%	116	OL
Gao et al. 2009[56a]	Multinational (Asia)	Eli Lilly, Amylin	• Exenatide (10 mcg BID) + Met + SU • Placebo (BID) + Met + SU	Fixed dose	4 months	A1C > 7.0%	472	DB
Goudswaard et al. 2004[64]	Netherlands	Not reported	• NPH insulin (QD) + Met + SU • Biphasic insulin (70/30) (BID)	FBG 4.0 mmol/L to 7.0 mmol/L	12 months	A1C ≥ 7.0%	69	OL
Hartemann-Heurtier et al. 2009[49]	France	Takeda	• Pioglitazone + Met + SU • NPH insulin + Met + SU	FPG 6.1 mmol/L	6 months	A1C > 7.5%	28	OL
Heine et al. 2005[57]	Multinational	Eli Lilly, Amylin	• Exenatide (10 µg BID) + Met + SU • Insulin glargine + Met +SU	FBG < 5.5 mmol/L	26 weeks	A1C 7.0% to 10.0%	551	OL
Hermansen et al. 2007[54a]	US and Denmark	Merck	• Sitagliptin (100 mg/day) + Met + SU • Placebo + Met + SU	Not reported	6 months	A1C ≥ 7.5%	441	DB
Holman et al. 2007[65]	Ireland, UK	Novo Nordisk and Diabetes UK	• Insulin aspart (TID) + Met + SU • Insulin detemir (HS/BID) + Met + SU • Biphasic insulin (BID) + Met + SU	FBG 4.0 mmol/L to 5.5 mmol/L	12 months	A1C 7.0% to 10.0%	708	DB
Janka et al. 2005[66]	Multinational (Europe)	Aventis	• Insulin glargine + Met + SU • 30/70 NPH + placebo	FBG < 5.5 mmol/L	6 months	A1C > 7.5%	364	OL
Janka et al. 2007[71]	Multinational (Europe)	Sanofi-aventis	• Insulin glargine (QD) + Met + SU • Biphasic insulin (BID)	FBG < 5.5 mmol/L	6 months	A1C 7.5% to 10.5%	130	OL

Table 17: Detailed Study Characteristics of RCTs Included in the Systematic Review of Third-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author and Year	Countries	Sponsor	Interventions/Comparators	Glycemic Target	Treatment Duration	Criteria for Defining Combination Therapy Failure	Sample Size	Blinding
Kendall et al. 2005[58]	US	Not reported	• Exenatide (5 mcg BID) + Met + SU • Exenatide (10 mcg BID) + Met + SU • Placebo + Met + SU	Not reported	7.5 months	A1C 7.5% to11.0%	734	DB
Ko et al. 2006[50]	Hong Kong	Nethersole Hospital	• Rosiglitazone + Met + SU • NPH Insulin (HS) + Met + SU	A1C < 7.5%	52 weeks	A1C ≥ 8.5%	112	OL
Lam et al. 1998[42]	Hong Kong	Bayer	• Acarbose (150 mg to 300 mg) + Met + SU • Placebo + Met + SU	Not reported	24 weeks	A1C 8.4% to 10.8%	90	DB
Lopez-Alvarenga et al. 1999[43a]	Mexico	Bayer	• Acarbose (100 mg TID) + Met + SU • Insulin NPH + Met + SU • Placebo + Met + SU	FPG < 7.7 mmol/L	3 months	FBG > 8.8 mmol/L	37	OL
Milicevic et al. 2009[67]	Multinational	Eli Lilly	• Insulin NPH (HS) + SU • Biphasic insulin lispro	FBG < 6.7 mmol/L	6 months	A1C > 20% ULN	135	OL
Nauck et al. 2007[59]	Multinational	Eli Lilly, Amylin	• Exenatide (10 mcg BID) + M+S • Biphasic insulin aspart 30/70	FBG < 7.0 mmol/L	12 months	A1C ≥ 7.0%	505	OL
Ovalle and Bell 2004[51]	US	GlaxoSmith Kline	• Rosiglitazone (8 mg) + Met + SU • Biphasic insulin 70/30	FBG < 6.7 mmol/L	6 months	Not reported	17	OL
Reynolds et al. 2007[52]	US	GlaxoSmith Kline	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FBG < 6.7 mmol/L	6 months	A1C 8% to12%	40	OL
Rosenstock et al. 2006[73]	US	Aventis	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.5 mmol/L	6 months	A1C 7.5% to 11%	219	OL
Ross et al. 2001[75]	Canada	Eli Lilly	• Insulin lispro + Insulin NPH • Human insulin + Insulin NPH	2 hour PPG < 8.9 mmol/L	5.5 months	A1C < 130% above ULN	148	OL
Russell-Jones et al. 2009[60]	Multinational	Novo Nordisk	• Liraglutide (1.8 mg) + Met + SU • Insulin glargine + Met + SU • Placebo + Met + SU	FPG < 5.5 mmol/L	26 weeks	FPG 7.5% to12.8 mmol/L	581	OL
Standl et al. 2001[44]	Multinational	Bayer and Sanofi-Synthélabo	• Miglitol (50mg to 100 mg TID) + Met + SU • Placebo + Met + SU	Not reported	24 weeks	A1C 7.5% to 10.5%	154	DB
Stehouwer et al. 2003[68]	Multinational	Aventis	• NPH insulin + SU • NPH insulin + 30/70 insulin NPH • NPH insulin	FPG 4.0 mmol/L to 7.0 mmol/L or A1C ≤ 6.5%	9 months	A1C > 6.5%	261	OL
Strojek et al. 2009[69]	Multinational	Novo Nordisk	• Insulin glargine + Met + SU • BIAsp30 + Met + SU	FPG 5.0 mmol/L to 6.1 mmol/L	6.5 months	A1C 7.0% to 11%	480	OL

Table 17: Detailed Study Characteristics of RCTs Included in the Systematic Review of Third-Line Pharmacotherapies for Type 2 Diabetes (Original Review and Update)

Author and Year	Countries	Sponsor	Interventions/Comparators	Glycemic Target	Treatment Duration	Criteria for Defining Combination Therapy Failure	Sample Size	Blinding
Vinik and Zhang 2007[76]	US	Sanofi-aventis	• Rosiglitazone (QD) + Met + SU • Insulin glargine (HS) + Met + SU	FPG < 5.5 mmol/L	6 months	A1C 7.5% to 11%	219	OL
Yki-Jarvinen et al. 2006[77]	Finland and UK	Aventis	• Insulin glargine + Met • NPH Insulin + Met	FPG 4.0 mmol/L to 5.5 mmol/L	9 months	A1C ≥ 8.0%	110	OL

A1C = glycated hemoglobin; AC = with meals; BIAsp = biphasic insulin aspart; BID = twice daily; DB = double-blind;FBG = fasting blood glucose; FPG = fasting plasma glucose; HRQoL = health-related quality of life; HS = at bedtime; Met = metformin; NGSP = National Glycohemoglobin Standardization Program; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; OL = open label; QD = once daily; SU=sulfonylurea; TZD = thiazolidinedione; ULN = upper limit of normal.

[a]Subgroup of patients who were inadequately controlled on metformin and a sulfonylurea.

APPENDIX 3: RESULTS FROM NMA (BLACK) AND DIRECT PAIRWISE (BLUE) META-ANALYSES FOR A1C (%) (A) AND BODY WEIGHT (KG) (B)

A

Placebo ← Vs.	Basal Insulin	Biphasic Insulin	TZDs	DPP-4 Inhibitors	AGIs	GLP–1 Analogues	Bolus Insulin	Meglitinides
–1.2 (–1.5 to –0.8) *–1.2 (–2.3 to –0.1)*								
–1.1 (–1.5 to –0.8) *NA*	0.0 (–0.2 to 0.3) *–0.3 (–0.7 to 0.0)*							
–1.0 (–1.3 to –0.6) *–1.2 (–1.4 to –1.0)*	0.2 (–0.1 to 0.5) *0.2 (0.04 to 0.4)*	0.2 (–0.2 to 0.6) *0.3 (–1.0 to 1.6)*						
–0.7 (–1.0 to –0.4) *–0.7 (–0.9 to –0.6)*	0.4 (–0.0 to 0.9) *NA*	0.4 (–0.1 to 0.9) *NA*	0.2 (–0.2 to 0.7) *NA*					
–0.5 (–0.9, 0.0) *–0.4 (–0.7 to –0.1)*	0.7 (0.2 to 1.3) *1.5 (–1.5 to 3.5)*	0.7 (0.1 to 1.3) *NA*	0.5 (–0.1 to 1.1) *NA*	0.3 (–0.3 to 0.8) *NA*				
–1.1 (–1.4 to –0.7) *–1.0 (–1.1 to –0.9)*	0.1 (–0.2 to 0.4) *–0.1 (–0.4 to 0.2)*	0.1 (–0.2 to 0.4) *0.2 (–0.5 to 0.9)*	–0.1 (–0.5 to 0.3) *NA*	–0.3 (–0.8 to 0.1) *NA*	–0.6 (–1.2 to –0.1) *NA*			
–1.0 (–1.6 to –0.4) *NA*	0.1 (–0.4 to 0.7) *–0.6 (–0.8 to –0.4)*	0.1 (–0.4 to 0.6) *–0.1 (–0.3 to 0.1)*	–0.1 (–0.7 to 0.5) *NA*	–0.3 (–1.0 to 0.4) *NA*	–0.6 (–1.3 to 0.2) *NA*	0.0 (–0.5 to 0.6) *NA*		
–0.2 (–2.0 to 1.7) *NA*	1.0 (–0.9 to 2.9) *NA*	1.0 (–0.9 to 2.9) *NA*	0.8 (–1.1 to 2.7) *NA*	0.6 (–1.3 to 2.5) *NA*	0.3 (–1.5 to 2.1) *0.3 (–1.4 to 2.0)*	0.9 (–1.0 to 2.8) *NA*	0.9 (–1.1 to 2.8) *NA*	

B

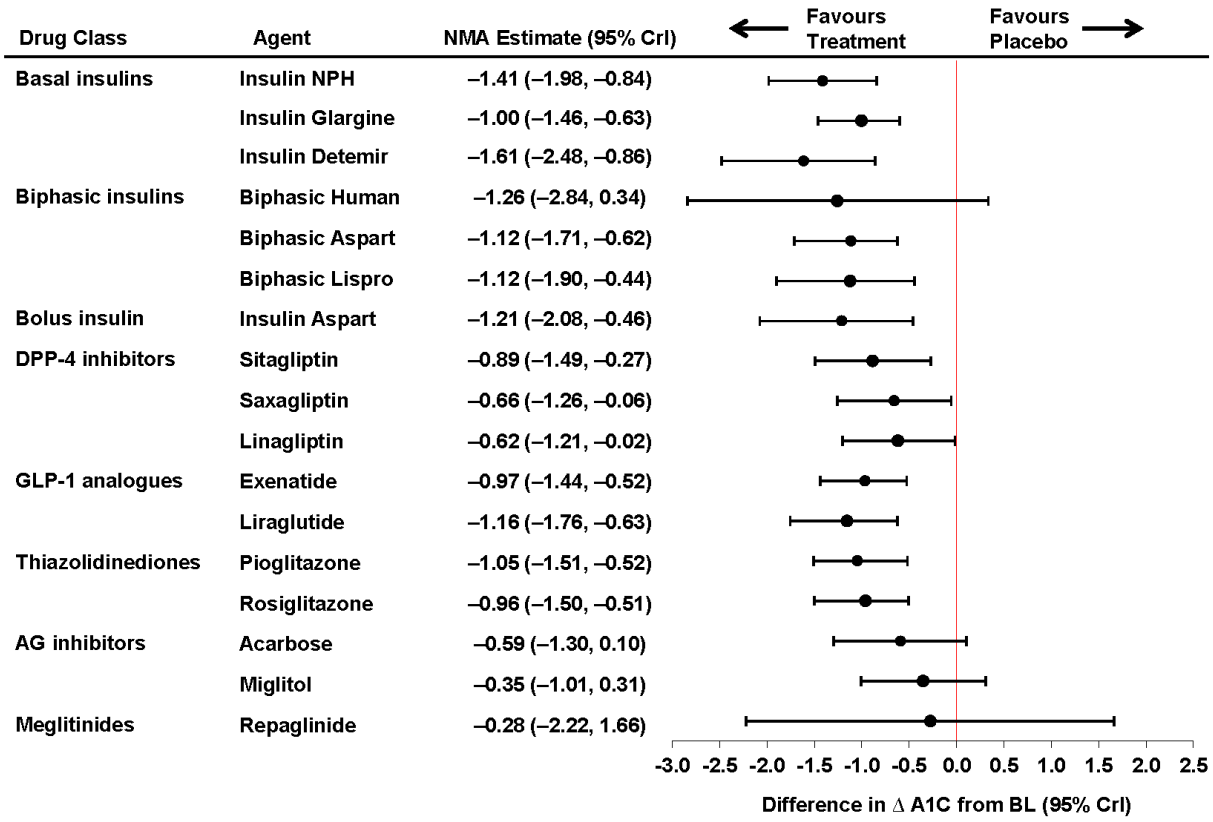
Placebo ← Vs.	Basal Insulin	Biphasic Insulin	TZDs	DPP-4 Inhibitors	AGI	GLP-1 Analogues	Bolus Insulin	Meglitinides
1.9 (0.7 to 3.0) *0.9 (–1.4 to 3.2)*								
3.3 (1.9 to 4.7) *NA*	1.4 (0.4 to 2.5) *1.4 (–1.3 to 4.1)*							
3.1 (1.9 to 4.3) *3.5 (2.4 to 4.6)*	1.2 (0.1 to 2.4) *0.9 (0.1 to 1.7)*	–0.2 (–1.7 to 1.3) *NA*						
0.7 (–0.8 to 2.2) *1.1 (0.3 to 1.3)*	–1.2 (-3.0 to 0.7) *NA*	–2.6 (–4.7 to –0.6) *NA*	–2.4 (–4.3 to –0.5) *NA*					
–0.5 (–2.1 to 1.2) *–0.9 (–1.6 to –0.1)*	–2.4 (-4.2 to –0.4) *–0.3 (–2.1 to 1.5)*	-3.8 (–5.8 to –1.6) *NA*	–3.6 (–5.5 to –1.5) *NA*	–1.2 (-3.3 to 1.1) *NA*				
–1.6 (–2.8 to –0.4) *–0.9 (–1.3 to –0.5)*	-3.5 (–4.6 to –2.3) *-3.9 (–4.3 to –2.2)*	–4.9 (–6.1 to -3.7) *–5.2 (–6.0 to –4.5)*	–4.7 (–6.2 to –3.2) *NA*	–2.3 (-4.3 to –0.4) *NA*	–1.1 (–3.1 to 0.8) *NA*			
5.0 (2.8 to 7.2) *2.0 (1.0 to 3.0)*	3.1 (1.2 to 5.1) *3.8 (3.0 to 4.6)*	1.7 (–0.3 to 3.6) *1.0 (0.2 to 1.8)*	1.9 (–0.4 to 4.1) *NA*	4.3 (1.7 to 6.9) *NA*	5.5 (2.7 to 8.1) *NA*	6.6 (4.5 to 8.7) *NA*		
2.6 (–0.7 to 6.0) *NA*	0.7 (–2.7 to 4.3) *NA*	–0.7 (–4.3 to 2.9) *NA*	–0.5 (-4.0 to 3.1) *NA*	1.9 (–1.7 to 5.7) *NA*	3.1 (0.1 to 6.0) *3.1 (1.0 to 5.3)*	4.2 (0.7 to 7.8) *NA*	–2.4 (–6.3 to 1.6) *NA*	

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NA = not applicable; TZDs = thiazolidinedione; Vs. = versus.

APPENDIX 4: NETWORK META-ANALYSIS OF INDIVIDUAL AGENTS

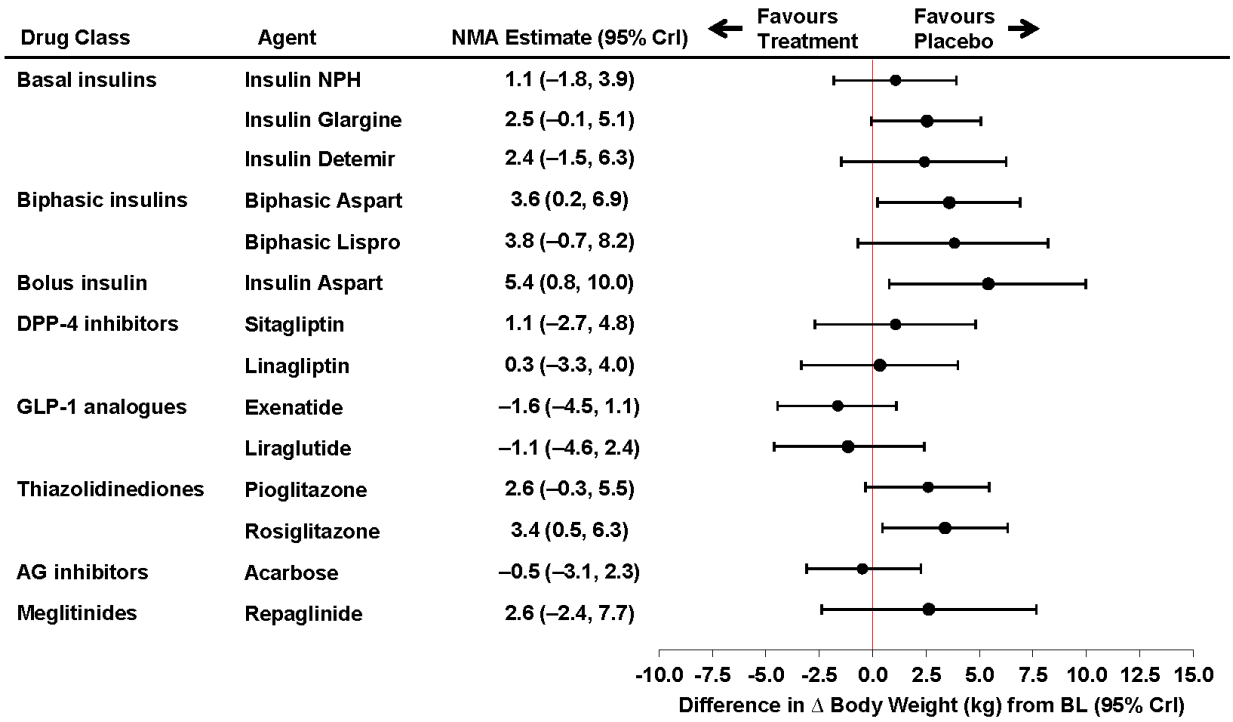
Figure 6 shows the results of a sensitivity analysis conducted at the level of individual agents as opposed to the class-level analysis used in the reference case. The effect sizes observed with the individual agents are generally similar to the overall effect size reported for the drug classes. There is considerable uncertainty with the effect sizes of agents used in only a single RCT (e.g., insulin detemir, biphasic human, repaglinide); therefore, the results of this sensitivity analysis should be interpreted with caution. A similar sensitivity analysis for body weight is shown in Figure 7.

Figure 6: Sensitivity Analysis for A1C — Individual Agent-Level NMAs



A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; TZD = thiazolidinedione.
Note: All active treatments and placebo were provided in combination with metformin and a sulfonylurea.

Figure 7: Sensitivity Analysis for A1C — Individual Agent-Level NMAs



A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; TZD = thiazolidinedione.
Note: All active treatments and placebo were provided in combination with metformin and a sulfonylurea.

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

Table 18: Severe Hypoglycemia for Third-Line Pharmacotherapy

Study[a]	Treatment 1	n/N	Treatment 2	n/N	OR (95% CI)
Placebo Comparisons					
Dailey et al. 2004[47]	TZD + Met + SU	0/181	Placebo + Met + SU	0/184	No events
Hermansen et al. 2007[54]	DPP-4 + Met + SU	0/116	Placebo + Met + SU	0/113	No events
Owens et al. 2011[36]	DPP-4 + Met + SU	21/792	Placebo + Met + SU	13/263	0.52 (0.26 to 1.06)
Lam et al. 1998[42]	AGI + Met + SU	1/41	Placebo + Met + SU	0/40	3.0 (0.1 to 75.9)
Kendall et al. 2005[58]	GLP-1 + Met + SU	1/486	Placebo + Met + SU	0/247	1.5 (0.1 to 37.7)
Gao et al. 2009[56]	GLP-1 + Met + SU	2/189	Placebo + Met + SU	0/186	5.0 (0.2 to 104.3)
Russell-Jones et al. 2009[60]	GLP-1 + Met + SU	5/230	Placebo + Met + SU	0/114	5.6 (0.3 to 101.9)
Russell-Jones et al. 2009[60]	Basal insulin + Met	0/232	Placebo + Met + SU	0/114	No events
Standl et al. 2001[44]	AGI + Met + SU	0/65	Placebo + Met + SU	0/68	No events
Active Comparisons					
Aljabri et al. 2004[45]	TZD + Met + SU	0/30	Basal insulin + Met	0/28	No events
Bergenstal et al. 2009[55]	GLP-1 + Met + SU	0/124	Biphasic insulin QD + Met + SU	4/124	0.1 (0.01 to 2.0)
	Biphasic insulin BID + Met	6/124	GLP-1 + Met + SU	0/124	13.7 (0.8 to 245.1)
	Biphasic insulin BID + Met	6/124	Biphasic insulin QD + Met + SU	4/124	1.5 (0.4 to 5.5)
Berhanu et al. 2007[70]	Insulin + TZD + Met	4/110	Insulin + Placebo + Met	0/112	9.5 (0.5 to 178.7)
Davies et al. 2007[62]	Biphasic insulin + Met	0/27	Basal insulin + Met	0/29	No events
	NPH + Meg + Met	1/26	Basal insulin + Met	0/29	3.5 (0.1 to 89.0)
	NPH + Meg + Met	1/26	Biphasic insulin + Met	0/27	3.2 (0.1 to 83.1)
Goudswaard et al. 2004[64]	Biphasic insulin	1/31	Basal insulin + Met + SU	0/33	3.3 (0.1 to 84.0)
Hartemann et al. 2009[49]	TZD + Met + SU	0/14	Basal insulin + Met + SU	0/13	No events
Heine et al. 2005[57]	GLP-1 + Met + SU	4/282	Basal insulin + Met + SU	4/267	1.0 (0.2 to 3.8)
Herman et al. 2010[34]	Biphasic insulin + Met + SU	12/632	Basal insulin + Met + SU	8/615	1.47 (0.60 to 3.62)
Holman et al. 2007[65]	Bolus insulin + Met + SU	16/238	Basal insulin + Met + SU	4/234	4.1 (1.4 to 12.6)
	Bolus insulin + Met + SU	16/238	Biphasic insulin + Met + SU	11/235	1.5 (0.67 to 3.23)
	Biphasic insulin + Met + SU	11/235	Basal insulin + Met + SU	4/234	2.8 (0.9 tp 9.0)
Milicevic et al. 2009[67]	Biphasic insulin	2/68	Basal insulin + Met + SU	0/67	5.1 (0.2 to 107.7)
Nauck et al. 2007[59]	GLP-1 + Met + SU	0/253	Biphasic insulin + Met + SU	0/248	No events
Reynolds et al. 2007[52]	Basal insulin + Met + SU	0/18	TZD + Met + SU	0/17	No events
Rosenstock et al. 2006[73]	TZD + Met + SU	6/112	Basal insulin + Met + SU	3/104	1.9 (0.5 to 7.8)
Russell-Jones et al. 2009[60]	GLP-1 + Met + SU	5/230	Basal insulin + Met + SU	0/232	11.3 (0.6 to 206.3)
Stehouwer et al. 2003[68]	Basal insulin	0/88	Basal insulin + SU	0/86	No events
	Biphasic Insulin	0/87	Basal insulin + SU	0/88	No events

Table 18: Severe Hypoglycemia for Third-Line Pharmacotherapy					
Study[a]	**Treatment 1**	**n/N**	**Treatment 2**	**n/N**	**OR (95% CI)**
	Basal insulin	0/88	Biphasic insulin	0/87	No events
Strojek et al. 2009[69]	Biphasic insulin + Met + SU	3/231	Basal insulin + Met + SU	2/238	1.55 (0.26 to 9.38)
Intraclass Comparisons					
De Mattia et al. 2009[63]	Basal (Glargine) + Met + SU	0/20	Basal (NPH) + Met + SU	0/20	No events

AGI = alpha-glucosidase inhibitor; BID = twice daily; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Meg = meglitinide; Met = metformin; n = number of patients with an event; N = total number of patients; NPH = neutral protamine Hagedorn; OR = odds ratio; QD = once daily; SU = sulfonylurea; TZD = thiazolidinedione.

[a]Severe hypoglycemia was not reported in Derosa et al. 2009, [41] Derosa et al. 2010,[37] Diamant et al. 2010,[39] Dorkhan et al. 2009,[48] Al-Shaikh 2006,[61] Janka et al. 2005,[66] Janka et al. 2007,[71] Ko et al. 2006,[50] Lopez-Alvarenga et al. 1999,[43] Study 6,[40] Charpentier 2009 and Halimi,[46] Ovalle and Bell 2004,[51] Ross et al. 2009.[75]

APPENDIX 6: SUMMARY OF RCTS THAT WERE NOT POOLED

Study	Comparators	Description	Summary of Key Results	
			Glycemic Control	Body Weight
Mixed Patient Population				
DURATION [33,39]	• Exenatide (2 mg QW) • Insulin glargine	• 26 weeks • Open label • N = 456	Mean change in A1C was greater with exenatide (MD = –0.16%, –0.29 to –0.03).	Mean change in weight favoured exenatide (MD = –4.0 kg; –4.6 kg to –3.5 kg)
Data Reported in a Manner That Could be Pooled				
Derosa et al. 2010[37]	• Pioglitazone • Acarbose	• 6 month • Double blind • N = 473	Mean change in A1C was greater with pioglitazone (< 0.05; mean difference not reported).	No significant difference between groups in weight at 6 months.
Treatments That Are Contraindicated or With Low Clinical Utility				
Davies et al. 2007[62]	• Biphasic insulin (b.i.d.) + Met • NPH insulin (HS) + repaglinide (AC) + Met • NPH Insulin (HS) + Met	• 4 month • Open label • N = 82	Change in A1C was –1.9% (–1.0 to –2.8) with NPH + repaglinide + Met; –1.1% (–0.5 to –1.7) with biphasic insulin + Met; –0.8% (0.15 to –1.8) with NPH + Met.	No significant differences in change in body weight from baseline between groups (P = 0.06).
Berhanu et al. 2007[70]	• Insulin + pioglitazone + Met • Insulin + placebo + Met	• 20 weeks • Double blind • N = 222	No statistically significant difference between groups.	
Intraclass comparisons				
Fadini et al. 2011[32]	• Insulin detemir • Insulin glargine	• 6 month • Open label • N = 43	No significant difference between groups in A1C at 3 months.	More weight gain with insulin glargine compared with insulin determir (2.8 kg versus –1.1 kg; P < 0.001)
Yki-Jarvinen et al. 2006[77]	• Insulin glargine + Met • NPH insulin + Met	• 9 months • Open label • N = 110	No statistically significant difference between groups.	No statistically significant difference between groups.
Esposito 2008 et al. [74]	• NPL insulin (HS) + Met + SU • Insulin glargine (HS) + Met + SU	• 9 months • Open label • N = 116	No statistically significant difference between groups.	No statistically significant difference between groups.
Ross et al. 2001[75]	• Insulin lispro + insulin NPH • Human insulin + insulin NPH	• 5.5 months • Open label • N = 148	No statistically significant difference between groups.	No statistically significant difference between groups.

AC = before meals; b.i.d. = twice daily; HR = hazard ratio; HS = bedtime; Met = metformin; MD = mean difference; MTD = maximum tolerated dose; N = total number of patients; NPH = neutral protamine Hagedorn; QW = once weekly; RCT = randomized controlled trial; SU = sulfonylurea.

APPENDIX 7: SUMMARY OF MODEL-FIT PARAMETERS AND RANKING

Table 19: Model-Fit Parameters for All Network Meta-Analyses

Outcome	Analysis	Mean Residual Deviance	Unconstrained Data Points	DIC
A1C	Random effects	24.14	28	6.099
	Fixed effects	69.34	28	40.648
	Remove RCTs with agents not indicated for use with metformin and a sulfonylurea	15.31	16	–2.143
	Remove crossover RCTs	21.71	24	–2.080
	Remove RCTs with A1C < 7.0% in the inclusion criteria	22.01	24	2.194
	Remove RCTs with TZDs	18.53	18	0.495
	Remove RCTs with rosiglitazone	21.20	22	2.851
	Remove RCTs not providing SU dosage at baseline	13.97	17	6.640
	Six-month RCTs only	15.64	16	–1.224
	Agent-level NMAs	25.76	27	10.840
Body weight	Random effects	21.48	21	43.056
	Agent-level NMAs	20.92	21	44.280

A1C = glycated hemoglobin; DIC = deviance information criterion; NMA = network meta-analysis; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione.

Table 20: Probability Best and Ranking from Reference Case

Analysis	Treatment	Probability and Ranks — Mean (SD)	
		Probability Best	Ranking
A1C	Placebo	0.00 (0.00)	8.5 (0.5)
	Basal insulin	0.29 (0.45)	2.3 (1.1)
	Biphasic insulin	0.20 (0.40)	2.7 (1.3)
	TZD	0.04 (0.19)	4.4 (1.4)
	DPP-4 inhibitors	0.01 (0.10)	6.0 (1.2)
	AGIs	0.00 (0.04)	7.1 (0.9)
	GLP-1 analogues	0.11 (0.32)	3.4 (1.4)
	Bolus insulin	0.21 (0.40)	3.7 (2.0)
	Meglitinides	0.14 (0.34)	6.8 (2.8)
Body weight	Placebo	0.00 (0.05)	2.9 (0.7)
	Basal insulin	0.00 (0.00)	5.3 (0.6)
	Biphasic insulin	0.00 (0.00)	7.3 (0.8)
	TZD	0.00 (0.00)	7.0 (0.8)
	DPP-4 inhibitors	0.01 (0.09)	3.9 (0.9)
	AGIs	0.11 (0.32)	2.3 (0.9)
	GLP-1 analogues	0.87 (0.34)	1.1 (0.4)
	Bolus insulin	0.00 (0.01)	8.8 (0.6)
	Meglitinides	0.01 (0.08)	6.3 (1.8)

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidly peptidase-4; GLP-1 = glucagon-like peptide-1; SD = standard deviation; TZD = thiazolidinedione.

APPENDIX 8: CRITICAL APPRAISAL OF INCLUDED RCTS (ORIGINAL REVIEW AND UPDATE)

Table 21: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Patients and Investigators**	**Groups are similar at baseline**	**Only Difference 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**
Aljabri et al.2004[45]	AA	WC	AA	NAd	AA	AA	AA	Yes	PA	N/A
Al-Shaikh 2006[61]	WC	AA	NAd	NAd	PA	WC	PA	Yes	AA	N/A
Bergenstal et al. 2009[55]	WC	WC	WC	NAd	AA	AA	AA	No	PA	NAd
Berhanu et al. 2007[70]	AA	WC	WC	AA	AA	AA	AA	Yes	WC	NAd
Blevins et al.2011[78]	AA	AA	AA	NAd	AA	PA	AA	No	PA	NAd
BMS 2012[40]	No full-text publication; therefore, critical appraisal could not be performed									
Charpentier and Halimi 2009[46]	WC	NR	NAd	AA	WC	WC	WC	Yes	PA	NAd
Dailey et al. 2004[47]	AA	NR	PA	AA	AA	AA	PA	No	AA	NAd
Davies et al. 2007[62]	AA	WC	NAd	PA	PA	AA	AA	Yes	PA	N/A
De Mattia et al. 2009[63]	AA	AA	NAd	NAd	AA	AA	AA	Yes	AA	NAd
Derosa et al. 2010[37]	AA	PA	AA	AA	AA	PA	AA	No	PA	NAd
Derosa et al.[41]	AA	WC	WC	AA	AA	AA	WC	Yes	AA	NAd
Diamant et al. 2010[39]	AA	AA	AA	NAd	AA	PA	AA	Yes	AA	NAd
Diamant et al. 2012[33]	AA	AA	AA	NAd	AA	PA	AA	Yes	AA	NAd
Dorkhan et al. 2009[48]	AA	AA	NAd	NAd	PA	AA	AA	Yes	WC	N/A
Esposito et al. 2008[74]	WC	WC	WC	NAd	AA	AA	AA	Yes	PA	NAd
Fadini et al. 2011[32]	AA	NR	NAd	NAd	AA	AA	AA	Yes	AA	NAd
Farmer et al. 2011[35]	WC	WC	WC	AA	AA	WC	WC	Yes	PA	NAd
Gao et al. 2009[56]	AA	AA	PA	AA	WC	AA	AA	Yes	AA	NAd
Goudswaard et al. 2004[64]	WC	WC	WC	NAd	PA	WC	WC	No	WC	N/A
Hartemann-Heurtier et al. 2009[49]	AA	WC	WC	PA	AA	AA	PA	No	AA	N/A
Heine et al. 2005[57]	WC	AA	NAd	NAd	WC	WC	WC	Yes	AA	NAd
Herman et al. 2011[34]	AA	NR	NAd	NAd	AA	AA	AA	NR	NR	NAd
Hermansen et al. 2007[54]	WC	WC	WC	AA	AA	WC	WC	Yes	PA	NAd
Holman et al. 2007[65]	AA	WC	WC	NAd	WC	AA	WC	Yes	WC	AA

Table 21: Assessment of Interval Validity (Modified SIGN-50 Checklist for RCTs)										
Study	**Appropriate and Clearly Focused Question**	**Randomized Assignment**	**Adequate Concealment**	**Blinding of Patients and Investigators**	**Groups are similar at baseline**	**Only Difference 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**
Janka et al. 2005[66]	AA	WC	AA	NAd	WC	WC	WC	No	AA	NAd
Kalra et al. 2010[38]	AA	NR	NAd	NAd	AA	PA	AA	Yes	AA	NAd
Kendall et al. 2005[58]	AA	AA	PA	AA	AA	AA	AA	No	WC	PA
Ko et al. 2006[50]	AA	AA	NAd	NAd	PA	AA	AA	Yes	PA	N/A
Lam et al. 1998[42]	AA	AA	NAd	AA	AA	AA	AA	Yes	PA	NAd
Lopez-Alvarenga et al. 1999[43]	AA	AA	NR	NAd	AA	AA	PA	No	PA	N/A
Milicevic et al. 2009[67]	WC	AA	NAd	NAd	WC	WC	WC	No	AA	AA
Nauck et al. 2007[59]	AA	WC	WC	NAd	AA	AA	AA	Yes	WC	PA
Ovalle and Bell 2004[51]	AA	AA	NAd	NAd	PA	AA	AA	Yes	WC	N/A
Owens et al. 2011[36]	AA	NR	NAd	AA	AA	AA	AA	Yes	AA	NAd
Reynolds et al. 2007[52]	WC	AA	NAd	NAd	AA	AA	WC	Yes	PA	N/A
Rosenstock et al. 2006[73]	WC	AA	NAd	NAd	WC	WC	PA	Yes	AA	NAd
Ross et al. 2001[75]	WC	AA	NAd	NAd	AA	AA	AA	NR	AA	NAd
Russell-Jones et al. 2009[60]	AA	WC	AA	AA	AA	AA	AA	Yes	AA	NAd
Standl et al. 2001[44]	AA	AA	PA	AA	AA	AA	AA	No	PA	PA
Stehouwer et al. 2003[68]	WC	WC	NAd	NAd	AA	AA	AA	NR	AA	NAd
Yki-Jarvinen et al. 2006[77]	AA	WC	NR	NAd	WC	AA	WC	Yes	AA	AA

AA = adequately addressed; ITT = intention to treat; NAd = not addressed; NR = not reported; PA = poorly addressed; QA = quality assessment; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; WC = well-covered.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
Aljabri et al. 2004[45]	• Power likely limited (n = 58). Sample size calculated for hypoglycemia outcome. • Metformin and a sulfonylurea doses at baseline were not reported. • Only 16 weeks in duration — may not be indicative of long-term efficacy. • Fasting glucose target (< 6 mmol/L) was lower than recommended in Canada.
Al-Shaikh 2006[61]	• Conducted in Saudi Arabia —population and care patterns may not be reflective of Canada. • 6 months duration —may not be indicative of long-term efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (< 7.7 mmol/L) was higher than recommended in Canada.
Bergenstal et al. 2009[55]	• 24-week duration — may not be indicative of long-term relative efficacy. • Patients were only required to take half-maximal doses of a sulfonylurea before being classified as inadequately controlled — may not be reflective of clinical practice, where higher doses of a sulfonylurea are likely to be tried before considering alternative therapy. • Disproportionate number of withdrawals between treatment groups (BIAsp 30 QD: 16%, BIAsp 30 BID: 19%, exenatide: 30%). • Fasting glucose target (5.0 mmol/L to 6.1 mmol/L) was lower than recommended in Canada.
Berhanu et al. 2007[70]	• Baseline demographic data not reported. • Sample size calculated for primary outcome of insulin dose change — not a relevant outcome for systematic review. • Patients were only required to take half-maximal doses of a sulfonylurea before being classified as inadequately controlled — may not be reflective of clinical practice, where higher doses of a sulfonylurea are likely to be tried before considering alternative therapy. • Treatment sequence does not reflect usual clinical practice, i.e., sulfonylurea discontinued, insulin added, and then TZD added. • Primary outcome of insulin dose change not as clinically relevant as standard measures of efficacy and safety. • Hypoglycemia definitions not reported. • Fasting glucose target (< 7.8 mmol/L) was higher than recommended in Canada.
Blevins et al. 2011[78]	• 24 weeks in duration — may not be indicative of long-term efficacy. • Exenatide QW not available in Canada.
BMS 2012[40]	• 24 weeks in duration — may not be indicative of long-term efficacy. • A1C criteria for determining metformin and sulfonylureas failure were not reported.
Charpentier and Halimi 2009[46]	• 7 months duration — may not be indicative of long-term efficacy. • Hypoglycemia definitions not reported. • A1C target < 6.5% is lower than that recommended in Canada. • Excluded patients with BMI > 35 kg/m2 — results may not be applicable to morbidly obese individuals.
Dailey et al. 2004[47]	• 24-week duration — may not be indicative of long-term relative efficacy. • Differential drop out between groups: 20% in active group versus 37% in placebo group. • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved.
Davies et al. 2007[62]	• Power likely limited (< 30 per treatment group). No sample size calculation described. • 4 months duration — may not be indicative of long-term efficacy. • Sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • Fasting glucose target (< 6.0 mmol/L) was lower than recommended in Canada.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
De Mattia et al. 2009[63]	• Very little information provided concerning the baseline characteristics of each group. • No sample size calculations. Power likely very low given sample size (n = 20). • Combined formulation of metformin and glyburide not available in Canada. • Metformin and sulfonylurea doses at baseline were only 400 mg/day and 2.5 mg/day respectively. Higher doses are usually tried in clinical practice before adding third-line agents. • Study designed primarily to detect differences in glycemic variability; other clinical outcomes were secondary. • 12-week duration — may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (< 5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m2 — results may not be applicable to morbidly obese individuals.
Derosa et al. 2010[37]	• 24 weeks in duration — may not be indicative of long-term efficacy. • A1C criteria for determining metformin failure were not reported. • Employed forced titration of trial medications independent of glycemic control, which is not reflective of clinical practice. • All patients were overweight (BMI 26 kg/m2 to 27 kg/m2).
Derosa et al.[41]	• Diabetes duration substantially lower than most studies (mean = 3.3 years to 3.7 years) — may limit generalizability of results since diabetes duration is related to pancreatic reserve. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • BMI lower than most studies (mean 27 kg/m2). • No hypoglycemia data reported. • 12-week duration — may not be indicative of long-term relative efficacy. • Employed forced titration of trial medications independent of glycemic control, which is not reflective of clinical practice.
Diamant et al. 2010,[39] 2012[33]	• A1C target (lower end) (< 6.5%) was lower than recommended in Canada. • Exenatide QW not available in Canada.
Dorkhan et al. 2009[48]	• No sample size calculations. Power likely limited due to very small sample (n = 30). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • Hypoglycemia data not reported. • Trial was designed to test differences between treatments in measures of fluid retention, an outcome that is of less clinical relevance than those of interest in the systematic review. • 26-week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 6.0 mmol/L) and A1C target (< 6.2%) were lower than recommended in Canada.
Esposito et al. 2008[74]	• Powered to detect a difference in A1C of 0.25%. • NPL insulin not available in Canada. • Metformin and sulfonylurea doses at baseline were not reported. • Only statistical significance considered. • 36-week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 5.6 mmol/L) was lower than recommended in Canada.
Fadini et al. 2011[32]	• Limited statistical power (N = 42). • A1C criteria for determining metformin failure were not reported. • Specialized population: 65-year-old and overweight patients with macroangiopathy.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
Gao et al. 2009[56]	• Study conducted in Asian countries — may be less generalizable to Canada. e.g., baseline BMI was lower than in European or North American studies. • Care patterns in Asian countries may differ from Canada, but no obvious issues. • Sulfonylurea doses at baseline were not reported. • Disproportionate number of withdrawals (17.5% for add-on exenatide versus 10.3% for add-on placebo). • Only 16 weeks in duration — may not be indicative of long-term efficacy.
Goudswaard 2004 et al. [64]	• Power likely limited for most outcomes due to small sample (n = 64), although sample size was calculated for a minimal detectable difference of 0.8% in A1C. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • The overall proportion of withdrawals exceeded 20%. • Biweekly calls by nurse during insulin titration unrealistic in routine clinical care.
Hartemann-Heurtier et al. 2009[49]	• Power likely very limited due to small sample size (n = 28). • Study designed to measure surrogates such as abdominal fat distribution. The only reported outcome of interest to systematic review was A1C. • 24-week duration — may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Fasting glucose target (< 6.1 mmol/L) was lower than recommended in Canada.
Heine 2005 et al.;[57] Boye et al. 2006[72]	• Non-inferiority study — powered to detect difference of 0.4% in A1C. Likely adequately powered for other outcomes also given large sample size (n = 551). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • 26-week duration — may not be indicative of long-term relative efficacy. • Higher dropout in exenatide group (19% versus 9%), mostly due to adverse effects. • Hypoglycemia definitions not reported. • Fasting glucose target (< 5 .5 mmol/L) was lower than recommended in Canada.
Herman et al. 2011[34]	• 24 weeks in duration — may not be indicative of long-term efficacy.
Hermansen et al. 2007[54]	• 24-week duration — may not be indicative of long-term relative efficacy. • Minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • Hypoglycemia definitions not reported.
Holman et al. 2007[65]	• Powered to detect 0.4% difference in A1C. Large sample size (n = 708); therefore, power was likely adequate for most outcomes. • Interim telephone contacts with patients — unrealistic in clinical practice. • Fasting (< 5.5 mmol/L) and post-prandial (< 7.0 mmol/L) glucose targets were lower than recommended in Canada.
Janka et al. 2005[66]	• Large study (n = 384), so power likely adequate for most outcomes. • Unequal dropout rate (4% for glargine + OADs versus 15% for premixed insulin). • Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. Also, minimum metformin dose required at baseline was only 850 mg/day. • 24-week duration — may not be indicative of long-term relative efficacy. • Dropout rate higher in NPH 30/70 group versus glargine. • Fasting glucose target (< 5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m2 — results may not be applicable to morbidly obese individuals.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
Janka et al. 2007[71]	• Patients 65 years and older only (mean age 67 and 63 in the 2 groups) — unlikely to affect results substantially. • Minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. Also, minimum metformin dose required at baseline was only 850 mg/day. • No sample size calculation. • 24-week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (<5.5 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 — results may not be applicable to morbidly obese individuals.
Kendall et al. 2005[58]	• Large sample size (n = 733), therefore likely adequate power for most outcomes. • Metformin and sulfonylurea doses at baseline were not reported. • 30-week duration — may not be indicative of long-term relative efficacy. • Proportion of dropouts exceeded 20%. • Effects observed in fixed low-dose group of exenatide are of limited generalizability since doses are likely to be titrated based on level of glycemic control in clinical practice.
Ko et al. 2006[50]	• Study conducted in Hong Kong — population and treatment patterns may not be representative. • Mean BMI 25 kg/m^2 — lower than most other studies. • Likely limited power for rarer outcomes such as severe hypoglycemia due to small sample size (n = 112). • Target A1C was < 7.5%, which is higher than recommended in Canada. • Hypoglycemia was not assessed.
Lam et al. 1998[42]	• Chinese patients — may be less generalizable to Canada. • Excluded patients with BMI ≥ 30 (mean BMI was 24 kg/m^2 to 25 kg/m^2) — results may not be applicable to obese individuals. • Power likely limited due to small sample size (n = 89). No sample size calculation. • 6-week "dietary reinforcement" likely not realistic. • 24-week duration — may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported.
Lopez-Alvarenga et al. 1999[43]	• Study conducted in Mexico — may limit generalizability to Canada. • BMI seems lower than most other studies (mean about 27 kg/m^2), while A1C at baseline was much higher (> 11%). • Sulfonylurea used was chlorpropamide, which is rarely used in Canada. • Insulin titration protocol appears to differ from other studies in that increments are not based on degree of hyperglycemia. • Hypoglycemia not defined. • 3 months duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 7.7 mmol/L) was higher than recommended in Canada. • Excluded patients with BMI > 35 kg/m^2 — results may not be applicable to morbidly obese individuals.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
Milicevic et al. 2009[67]	• Power likely limited for rarer outcomes such as severe hypoglycemia due to relatively small sample size (n = 135). • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • Clinic visits every 4 weeks likely exceeds visit frequency in routine care. • Disproportionate number of withdrawals in the Glib/NPH group (17.9%) in comparison with the biphasic lispro group (5.9%). • Frequent SMBG (9-point profiles) not reflective of usual care. • 24-week duration — may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Post-prandial glucose target (< 8.0 mmol/L) was lower than recommended in Canada. • Excluded patients with BMI > 32 kg/m^2 — results may not be applicable to morbidly obese individuals.
Nauck et al. 2007[59]	• Somewhat lower insulin doses at endpoint than in past studies. • Metformin and sulfonylurea doses at baseline were not reported. • The proportion of withdrawals was twice as high in the exenatide group (21%) than in the insulin group (10%). • Clinical relevance of 0.4% A1C margin was considered, although clinical relevance of observed weight loss not considered.
Ovalle and Bell 2004[51]	• Likely underpowered (n = 17). No sample size calculations presented. • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • Study designed to detect differences in measures of pancreatic beta-cell function, not clinical outcomes. No data reported on hypoglycemia. • 6 month duration — may not be indicative of long-term relative efficacy.
Owens et al. 2011[36]	• 24 weeks in duration — may not be indicative of long-term efficacy. • A1C target (< 6.5%) was lower than recommended in Canada.
Reynolds et al. 2007[52]	• Baseline demographic data not reported. • Limited power (n = 40), no sample size calculations. • Only half-maximal doses required for both metformin and a sulfonylurea at baseline.
Rosenstock et al. 2006,[73] Vinik and Zhang 2007[76]	• No sample size calculations. • Patients were only required to take half-maximal doses of a sulfonylurea before being classified as inadequately controlled — may not be reflective of clinical practice, where higher doses of a sulfonylurea are likely to be tried before considering alternative therapy. • Central supervision of insulin titration — may not be realistic for usual care. • The proportion of withdrawals was twice as high in the rosiglitazone group (10.7%) than in the insulin glargine group 5.8%). • 24-week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 5.5 mmol/L) was lower than recommended in Canada.
Ross et al. 2001[75]	• Baseline A1C quite high compared with other studies (10.6%). • Metformin and sulfonylurea doses at baseline were not reported. Also, the duration of stable metformin and sulfonylurea combination therapy was not reported. • No sample size calculations presented.
Russell-Jones et al. 2009[60]	• Extensive patient contact (9 visits plus 2 phone calls) — likely not reflective of routine care. • 26 week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 5.5 mmol/L) was lower than recommended in Canada.

Table 22: Assessment of External Validity for RCTs Included in the Update	
Study	**Key Limitations with the External Validity of the Studies**
Standl et al. 2001[44]	• BMI at baseline somewhat lower than in other studies (mean 28 kg/m^2). • Metformin and sulfonylurea doses at baseline were not reported. • Miglitol not available in Canada. • 24-week duration — may not be indicative of long-term relative efficacy. • Hypoglycemia definitions not reported. • Excluded patients with BMI > 35 kg/m^2 — results may not be applicable to morbidly obese individuals.
Stehouwer et al. 2003[68]	• No power calculations presented. Likely adequate power for most outcomes given sample size (n = 261). • Minimum dose of metformin at baseline was only 1,000 mg/day — higher doses likely used in clinical practice. • Twice weekly adjustment by diabetes educator or diabetologist of insulin doses until targets reached is not realistic in clinical practice. • Hypoglycemia not defined. • 9 month duration — may not be indicative of long-term relative efficacy.
Strojek et al. 2009[69]	• Patients were only required to take half-maximal doses of a sulfonylurea before being classified as inadequately controlled — may not be reflective of clinical practice, where higher doses of a sulfonylurea are likely to be tried before considering alternative therapy. • 26-week duration — may not be indicative of long-term relative efficacy.
Yki-Jarvinen et al. 2006[77]	• A1C mean 9.5% at baseline is higher than most other studies. • Metformin and sulfonylurea doses at baseline were not reported. Also, minimum duration of stable metformin and sulfonylurea combination therapy was less than 3 months, which is likely insufficient to determine whether adequate glycemic control was achieved. • SMBG results sent to treatment centre by modem, and numerous phone calls by care providers — not reflective of actual practice. • 36 week duration — may not be indicative of long-term relative efficacy. • Fasting glucose target (< 5.5 mmol/L) was lower than recommended in Canada.

BID = twice daily; BMI = body mass index; Glib = glibenclamide; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drugs; QD = at bedtime; SMBG = self-monitoring of blood glucose.

APPENDIX 9: RESULTS OF PHARMACOECONOMIC SENSITIVITY ANALYSES

Scenario	Result
Reference-case analysis	Met + SU + basal insulin versus Met + SU: $68,442 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,752,233 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Price of a long-acting insulin analogue used rather than insulin NPH	Met + SU + basal insulin versus Met + SU : $103,159 Met + SU+ DPP-4 versus Met + SU + basal insulin: $82,432 Met + SU+ GLP-1 versus Met + SU + basal insulin: $170,975 Met + SU + biphasic insulin is dominated by Met + SU + basal insulin (but not by any other therapy)
Effect estimates from pairwise meta-analyses of RCTs	Met + SU + basal insulin versus Met + SU: $64,316 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + GLP-1 is dominated by Met + SU + basal insulin and Met + SU + biphasic insulin
Patients add-on insulin NPH (0.75 U/kg/day) added to non-insulin groups when A1C ≥ 9%	Met + SU + basal insulin versus Met + SU : $79,376 Met + SU + GLP-1[a] , Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Insulins are removed as treatment options (third line)	Met + SU + DPP-4 versus Met + SU: $113,254 Met + SU + GLP-1 versus Met + SU + DPP-4L: $170,975
Inclusion of TZD (pioglitazone) as comparator (TZD is dominated by Met + SU + Basal insulin)	Met + SU + basal insulin versus Met + SU: $68,442 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,752,233 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
AGI included as comparator (AGI result in $60,375 per QALY relative to Met + SU)	Met + SU + AGI versus Met + SU: $60,375 Met + SU + basal insulin versus Met + SU + AGI: $77,029 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,752,233 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + TZD is dominated by a blend of Met + SU and Met + SU + AGI
Insulin dose for basal human insulin and biphasic human insulin from RCTs (rather than doses from BC dataset)	Met + SU + basal insulin versus Met + SU: $44,636 Met + SU + GLP-1 versus Met + SU + basal insulin: $2,343,031 Met + SU + biphasic insulin is dominated by Met + SU + basal insulin Met + SU + DPP-4 is dominated by Met + SU + basal insulin and Met + SU + biphasic insulin
Higher disutility associated with severe hypoglycemia (from Currie et al.[122])	Met + SU + basal insulin versus Met + SU: $99,918 Met + SU + DPP-4 versus Met + SU + Basal insulin: $51,432 Met + SU + GLP-1 versus Met + SU + DPP-4: $170,975 Met + SU + biphasic insulin is dominated by Met + SU + Ba basal insulin and Met + SU + GLP-1
Higher disutility associated with mild to moderate hypoglycemia (from Levy et al.[93])	Met + SU + basal insulin versus Met + SU: $119,288 Met + SU + DPP-4 versus Met + SU + basal insulin: $265,738 Met + SU + GLP-1 versus Met + SU + DPP-4: $171,090 Met + SU + biphasic insulin is dominated by Met + SU + basal insulin, Met + SU + DPP-4 and Met + SU + GLP-1

Scenario	Result
Higher disutility associated with mild to moderate hypoglycemia (0.0052) (from NICE study)[94]	Met + SU + DPP-4 versus Met + SU: $135,366 Met + SU + basal insulin is extendedly dominated by Met + SU + DPP-4 Met + SU + GLP-1 versus Met + SU + DPP-4: $117,262 Met + SU + biphasic insulin is dominated by Met + SU + DPP-4
Disutility of 0.030 associated with insulin use in year one (rather than no disutility)	Met + SU + basal insulin versus Met + SU : $76,111 Met + SU + GLP-1 versus Met + SU + basal insulin : $500,545 Met + SU + DPP-4 is dominated by Met + SU + basal insulin Met + SU + biphasic insulin is dominated by Met + SU + basal insulin
Disutility of 0.060 associated with insulin use in year one (rather than no disutility)	Met + SU + basal insulin versus Met + SU : $85,716 Met + SU + GLP-1 versus Met + SU + basal insulin : $291,976 Met + SU + DPP-4 is dominated by Met + SU + basal insulin Met + SU + Biphasic insulin is dominated by Met + SU + basal insulin
Model incorporates reduced quality of life associated with weight gain (NICE Guidelines)[91]	Met + SU + basal insulin versus Met + SU: $90,225 Met + SU + GLP-1 versus Met + SU + basal insulin: $185,526 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Price of test strips not included in cost-effectiveness analysis (as opposed to included, as per published utilization data)	Met + SU + basal insulin versus Met + SU: $46,986 Met + SU + GLP-1 versus Met + SU + basal insulin: $2,284,707 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Price of test strips reduced by 50%	Met + SU + basal insulin versus Met + SU: $58,654 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,995,149 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Cost of mild to moderate hypoglycemia event set at C$93 as per Brod et al.[99]	Met + SU + basal insulin versus Met + SU: $75,603 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,603,735 Met + SU + DPP-4 is dominated by Met + SU + Basal insulin Met + SU + biphasic insulin is dominated by Met + SU + basal insulin
Use of gliclazide as SU instead of glyburide	Met + SU + basal insulin versus Met + SU: $68,494 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,752,394 Met + SU + DPP-4 is dominated by Met + SU + basal insulin Met + SU + biphasic insulin is dominated by Met + SU + basal insulin
Cost of DPP-4 inhibitors is $2.25 instead of $2.55	Met + SU + basal insulin versus Met + SU: $68,442 Met + SU + DPP-4 versus Met + SU: $99,040 Met + SU + DPP-4 versus Met + SU + basal insulin: $5,616 Met + SU + GLP-1 versus Met + SU + DPP-4: $196,962 Met + SU + biphasic insulin is dominated by Met + SU + basal insulin (but not by any other therapy)
Time horizon of 10 years (rather than 40 years)	Met + SU + basal insulin versus Met + SU: $116,133 Met + SU + GLP-1 versus Met + SU + basal insulin: $8,059,040 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin

Scenario	Result
Time horizon of 5 years (rather than 40 years)	Met + SU + basal insulin versus Met + SU: $193,974 Met + SU + biphasic insulin versus Met + SU + basal insulin: $506,725,586 Met + SU + GLP-1 versus Met + SU + biphasic insulin: $4,469,150 Met + SU + DPP-4 is dominated by Met + SU + basal insulin (but not by any other therapy)
Disutilities in patients with diabetes from Clarke et al.[5]	Met + SU + basal insulin versus Met + SU: $60,187 Met + SU + GLP-1 versus Met + SU + basal insulin: $1,176,925 Met + SU + biphasic insulin and Met + SU + DPP-4 are dominated by Met + SU + basal insulin (but not by any other therapy)

A1C = glycated hemoglobin; AGI = alpha-glucosidade inhibitor; BC = British Columbia; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; NICE = National Institute for Health and Care Excellence; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione.

[a]BYETTA (exenatide) is indicated in combination with insulin glargine (with or without metformin) to improve glycemic control in patients with type 2 diabetes when insulin glargine (with or without metformin) in addition to diet and exercise, does not provide adequate glycemic control.

APPENDIX 10: REFERENCE-CASE RESULTS FROM 2010 CADTH PHARMACOECONOMIC REVIEW

Treatment	Average Costs Incurred During a Lifetime	Average QALYs Gained During a Lifetime	Incremental Cost-Effectiveness Results
Met + SU	$39,128	8.2405	NA
Met + SU + Basal insulin	$44,206	8.3251	$60,049 per QALY gained (versus Met + SU)
Met + SU + DPP-4	$44,717	8.3059	Dominated by Met + SU + Basal insulin
Met + SU + TZD[a]	$45,936	8.2191	Dominated by Met + SU + Basal insulin
Met + SU + biphasic insulin	$48,317	8.3198	Dominated by Met + SU + Basal insulin

DPP-4 = dipeptidyl peptidase-4; Met = metformin; NA = not applicable; QALY = quality-adjusted life-year; SU = sulfonylurea; TZD = thiazolidinedione.

[a]The updated reference case analysis excluded TZDs as they are not approved as third-line treatments in Canada.

APPENDIX 11: SENSITIVITY ANALYSES FROM 2010 CADTH PHARMACOECONOMIC REPORT

Scenario	Result
Reference-case analysis	Met + SU + basal insulin versus Met + SU: $60,049 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Price of a long-acting insulin analogue used rather than insulin NPH	Met + SU + DPP-4 versus Met + SU: $85,561 Met + SU + basal insulin versus Met + SU + DPP-4: $175,037 Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Effect estimates from pairwise meta-analyses of RCTs	Met + SU + basal insulin versus Met + SU: $59,951 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Patients add-on insulin NPH when A1C ≥ 9% (rather than static third-line therapy over lifetime)	Met + SU + basal insulin versus Met +SU: $63,245 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Model assumes that patients use Met + TZD rather than Met + SU + TZD (since Met + SU + TZD is not indicated for use in Canada)	Met + SU + basal insulin versus Met + SU: $60,049 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
AGIs included as comparator	Met + SU + basal insulin versus Met + SU: $60,049 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + TZD is dominated by a blend of Met + SU and Met + SU + basal insulin
Insulin dose for basal human insulin and biphasic human insulin from RCTs (rather than doses from BC dataset)	Met + SU + basal insulin versus Met + SU: $37,797 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Higher disutility associated with severe hypoglycemia (from Currie et al. rather than NICE)[95]	Met + SU + basal insulin versus Met + SU: $69,892 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Higher disutility associated with mild to moderate hypoglycemia (from Levy et al. rather than COMPUS IA Report)[93]	Met + SU + DPP-4 versus Met + SU: $90,007 Met + SU + basal insulin is dominated by a blend of Met + SU and Met + SU + DPP-4 Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + DPP-4
Model incorporates reduced quality of life associated with weight gain (NICE Guidelines)[94]	Met + SU + basal insulin versus Met + SU: $75,537 Met + SU + TZD is dominated by a blend of Met + SU and Met + SU + DPP-4 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + DPP-4
Price of test strips not included in cost-effectiveness analysis (as opposed to included, as per published utilization data)	Met + SU + basal insulin versus Met + SU: $41,414 Met + SU + DPP-4, Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin
Cost of DPP-4 inhibitors is $2.30 rather than $2.55	Met + SU + basal insulin versus Met + SU: $60,049 Met + SU + TZD and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + DPP-4 is dominated by a blend of Met + SU and Met + SU + basal insulin

Scenario	Result
Time horizon of 10 years (rather than 40 years)	Met + SU + basal insulin versus Met + SU: $104,568 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + TZD is dominated by a blend of Met + SU and Met + SU + basal insulin
Time horizon of 5 years (rather than 40 years)	Met + SU + basal insulin versus Met + SU: $182,885 Met + SU + DPP-4 and Met + SU + biphasic insulin are dominated by Met + SU + basal insulin Met + SU + TZD is dominated by a blend of Met + SU and Met + SU + basal insulin

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BC = British Columbia; COMPUS = Canadian Optimal Medication Prescribing and Utilization Service; DPP-4 = dipeptidyl peptidase-4; IA = insulin analogue; Met = metformin; NICE = National Institute for Health and Care Excellence; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; SU = sulfonylurea; TZD = thiazolidinedione.