CADTH Therapeutic Review Panel

Recommendations

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

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ABBREVIATIONS

A1C	glycosylated hemoglobin
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide
MTC	mixed treatment comparison
NPH	neutral protamine Hagedorn
QALY	quality-adjusted life-year
RCT	randomized controlled trial
TRP	Therapeutic Review Panel
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study

RECOMMENDATIONS

For adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea, the Therapeutic Review Panel (TRP) recommends that insulin neutral protamine Hagedorn (NPH) be added as the preferred option.

Reasons for recommendation:

- Based on the results of a Canadian Agency for Drugs and Technologies in Health (CADTH) meta-analysis of 21 randomized controlled trials (RCTs) in patients with type 2 diabetes mellitus that was inadequately controlled with metformin and a sulfonylurea, statistically significant reductions in glycosylated hemoglobin (A1C) of similar magnitude were found for all classes of antihyperglycemic drugs added to existing therapy, with the exception of alpha-glucosidase inhibitors and meglitinides.
- The addition of insulin NPH to metformin plus a sulfonylurea was associated with the most favourable cost-effectiveness estimate. Long-acting insulin analogues at prices similar to insulin NPH would also be an option for patients inadequately controlled on metformin and a sulfonylurea.

Of Note

- The available evidence regarding the comparative efficacy and safety of third-line antidiabetes drugs was considered to be of low quality. This was attributable to methodological limitations of the included clinical trials and a lack of adequately powered evidence related to impact on long-term diabetes-related complications. Clinical and methodological heterogeneity across trials was also a limitation.
- Basal insulins (i.e., insulin NPH and long-acting insulin analogues) were started as once-daily (bedtime) injections in most of the studies reviewed; which the Panel considered to be reflective of clinical practice.
- The Panel emphasized that patients initiating insulin should be supported with adequate education, follow-up, and monitoring.

Oral alternatives to insulin NPH

- The Therapeutic Review Panel (the Panel) recognized that a small proportion of patients may be unable to initiate insulin therapy (e.g., lack of access to adequate education and support). The available evidence was insufficient to recommend a specific oral alternative to insulin NPH when glycemic control is inadequate with metformin and a sulfonylurea. The Panel considered the following evidence during its deliberations on an oral alternative to insulin NPH:
  - **Clinical Effectiveness Evidence:** Dipeptidyl peptidase-4 (DPP-4) inhibitors (one RCT; 24 weeks) and thiazolidinediones (TZDs) (nine RCTs; 16 to 52 weeks) demonstrated similar reductions in hemoglobin A1C of approximately 1%. Alpha-glucosidase inhibitors (four RCTs; 14 to 24 weeks) and meglitinides (one RCT; 14 weeks) demonstrated reductions in hemoglobin A1C of –0.46% (–0.96 to 0.03) and –0.18% (–2.08 to 1.71) respectively.
  - **Cost-Effectiveness Evidence:** Insulin NPH was the most cost-effective option in the base-case economic analysis and in most sensitivity analyses. In sensitivity analyses where a high disutility was assumed for insulin use, results demonstrated that sitagliptin may be the most cost-effective alternative. TZDs (at the listed price of generic pioglitazone) were not cost-effective under any condition tested in sensitivity analyses. Meglitinides and alpha-glucosidase inhibitors were dominated by insulin NPH (i.e., they were less effective and more costly). The Panel noted a number of important limitations of the cost-effectiveness analysis (see the Additional Context and Panel Discussion Points section of this document).

- **Safety Evidence:** TZDs are associated with increased risks for congestive heart failure and fractures (in women), while the long-term safety profile of DPP-4 inhibitors is still largely unknown.

Other antidiabetes medications

- **Bolus insulin and biphasic insulin:** The Panel acknowledged that many patients who initiate therapy with basal insulin eventually require prandial or biphasic insulin to maintain glycemic control. However, initiation of basal insulin therapy was felt to be appropriate for most patients given the lack of differences in hemoglobin A1C between various third-line insulin strategies, the lower risk of hypoglycemia compared with bolus or biphasic insulins, and the convenience of once-daily dosing.
- **Glucagon-like peptide (GLP)-1 analogues/agonists:** At the time of this review, there were no drugs within this class approved by Health Canada. The Panel, therefore, did not consider GLP-1 analogues/agonists as a candidate drug class for third-line therapy.

ADDITIONAL CONTEXT AND PANEL DISCUSSION POINTS

Clinical outcomes

- The Panel noted that the correlation between A1C lowering and cardiovascular complications is unclear. However, A1C was not particularly useful in differentiating between the various drug classes in the third-line setting as most drugs were associated with similar reductions.
- The Panel found it difficult to compare safety profiles between older and newer antihyperglycemic drugs given the disparity in clinical experience.
- The Panel concluded that the lack of consistent definitions for mild-moderate hypoglycemia across studies limited the ability to make meaningful comparisons across drug classes with respect to this clinically important outcome.
- The Panel discussed the importance of weight change, noting that, while there is currently no universally accepted minimal clinically important difference for this outcome, a range of 5% to 10% is reported in the literature. With the exception of the weight gain observed with bolus insulins, no third-line drug was associated with a change in body weight greater than 5% (assuming a baseline body weight of 70 kg). The Panel also identified a lack of sufficient evidence regarding the relationship between weight gain/loss due to antidiabetes pharmacotherapy and either long-term clinically important outcomes or quality of life.
- The Panel discussed the importance of optimizing lifestyle and dietary practices for patients experiencing inadequate glycemic control on metformin and a sulfonylurea regardless of the pharmacotherapeutic regimen chosen.

Cost-effectiveness

- The Panel discussed the limitations of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model:
  - Older classes of antidiabetes drugs (e.g., metformin, sulfonylureas, and conventional insulins) were used in the UKPDS; the applicability of the UKPDS risk equations to patients using newer drug classes (e.g., TZDs, DPP-4 inhibitors) is uncertain.
  - The UKPDS enrolled patients with newly diagnosed diabetes; hence, it is not specific to patients using third-line therapy. The model is flexible in that it allows the user to specify the baseline risk profile, permitting its application to populations (such as candidates for third-line therapy) that differ in terms of duration of diabetes and other risk factors from the original UKPDS cohort. However, an ideal economic model for assessment of third-line therapies would be developed from long-term follow-up of patients with type 2 diabetes failing metformin and sulfonylurea.

- There was considerable uncertainty surrounding the clinical inputs used in the cost-effectiveness analysis, particularly with respect to the disutilities for insulin use, hypoglycemia, and weight gain.
- Patients in the UKPDS model were assumed to remain on the same third-line therapy over their lifetime in the reference case analysis. This approach was necessary given the lack of data on treatment regimens used after failure of third-line therapy and their clinical effects. The Panel acknowledged that treatments are unlikely to remain static in clinical practice given the progressive nature of the disease; however, this was felt to be a reasonable approach for the purposes of the economic analysis given the lack of data. Furthermore, when treatment progression beyond third-line was modelled in sensitivity analyses based on clinical assumptions about subsequent therapy, cost-effectiveness estimates were not found to differ substantially from the reference case.
- Costs related to education and support for patients initiating insulin were not included in the model because of the lack of adequate data. However, this was unlikely to have a substantial impact on the estimated cost-effectiveness of insulin as these one-time costs are likely modest compared with lifetime treatment costs.

BACKGROUND

In the CADTH therapeutic review, comparative efficacy, harms, and cost-effectiveness of third-line drugs indicated for the treatment of type 2 diabetes were evaluated.

Table 1: Drugs Included in the Therapeutic Review

Generic Name	Dosage / Administration	Relevant Health Canada Indications
Sulfonylureas		
Gliclazide / Gliclazide MR	Range: 80 mg to 320 mg DDD: 160 mg Range for MR: 30 mg to 120 mg Administered: Orally	Control of hyperglycemia in gliclazide responsive T2DM, which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.[1,2]
Glimepiride	Range: 1 mg to 8 mg DDD: 2 mg Administered: Orally	Indicated for use as follows: an adjunct to proper dietary management, exercise, and weight reduction to lower the blood glucose in patients with T2DM whose hyperglycemia cannot be controlled by diet and exercise alone; in combination with metformin when diet and exercise, and glimepiride or metformin alone do not result in adequate glycemic control; in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hyperglycemic drug alone.[3]
Glyburide	Range: 2.5 mg to 20 mg DDD: 10 mg Administered: Orally	Indicated as an adjunct to proper dietary management, exercise, and weight reduction to lower blood glucose in adult patients with T2DM whose hyperglycemia cannot be controlled by diet and exercise alone or when insulin therapy is not required.[4]
Chlorpropamide	Range: 100 mg to 500 mg DDD: 375 mg Administered: Orally	In mild, stable T2DM to control hyperglycemia that is responsive to the drug. It should not be used in those patients who are prone to ketosis or who can be controlled by dietary management and exercise alone or for whom insulin therapy is more appropriate.[5]

Table 1: Drugs Included in the Therapeutic Review		
Generic Name	**Dosage / Administration**	**Relevant Health Canada Indications**
Glipizide	Range: 5 mg to 40 mg DDD: 10 mg Administered: Orally	Not approved in Canada.
Tolbutamide	Range: 500 mg to 3,000 mg DDD: 1,500 mg Administered: Orally	To control hyperglycemia in tolbutamide responsive T2DM, which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.[6]
Thiazolidinediones		
Pioglitazone	Range: 15 mg to 45 mg DDD: 30 mg Administered: Orally	Indicated as monotherapy in patients whose diabetes is not controlled by diet and exercise alone, to decrease insulin resistance and blood glucose levels in patients with T2DM. Also indicated for use in combination with a sulfonylurea or metformin when diet and exercise plus the single drug do not result in adequate glycemic control.[7]
Rosiglitazone	Range: 4 mg to 8 mg DDD: 6 mg Administered: Orally	Indicated for use as an adjunct to diet and exercise in patients with T2DM as follows: as monotherapy in patients not controlled by diet and exercise alone and for whom metformin is inappropriate because of contraindications or intolerance; in combination with metformin when diet and exercise plus metformin do not result in adequate glycemic control; in combination with a sulfonylurea in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus sulfonylurea or rosiglitazone monotherapy do not result in adequate glycemic control.[8]
Meglitinides		
Nateglinide	Range: 180 mg to 360 mg DDD: 360 mg Administered: Orally	Indicated as monotherapy to lower the blood sugar in patients with T2DM who are not controlled satisfactorily by diet and exercise alone. Also indicated in combination with metformin in patients not controlled satisfactorily on diet, exercise, or metformin alone.[9]
Repaglinide	Range: 0.5 mg to 16 mg DDD: 4 mg Administered: Orally	Indicated in patients with T2DM whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. Indicated in combination therapy with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus metformin monotherapy. Indicated in combination with rosiglitazone in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus rosiglitazone or repaglinide monotherapy do not result in adequate glycemic control.[10]
Alpha-glucosidase inhibitors		
Acarbose	Range: 150 mg to 300 mg DDD: 300 mg Administered: Orally	Indicated for use as follows: as an adjunct to prescribed diet for the management of blood glucose levels in patients with T2DM who are inadequately controlled by diet alone; or in combination with either a sulfonylurea, metformin, or insulin to improve glycemic control in patients with T2DM that is inadequately controlled with diet, exercise, and either a sulfonylurea, metformin, or insulin alone.[11]

Table 1: Drugs Included in the Therapeutic Review		
Generic Name	**Dosage / Administration**	**Relevant Health Canada Indications**
Miglitol	Range: 75 mg to 300 mg DDD: 300 mg	Not approved in Canada at the time of this review.
DPP-4 inhibitors		
Sitagliptin	Range: 100 mg DDD: 100 mg Administered: Orally	Indicated in combination with metformin in adult patients with T2DM inadequately controlled with metformin monotherapy, in combination with metformin and a sulfonylurea when dual therapy with these drugs does not provide adequate glycemic control, or as monotherapy in patients who cannot tolerate metformin.[12]
Vildagliptin	Range: 100 mg DDD: 100 mg Administered: Orally	Not approved in Canada at the time of this review.
Saxagliptin	Range: 5 mg DDD: NA Administered: Orally	Indicated in patients with T2DM to improve glycemic control in combination with metformin or a sulfonylurea, when either drug used alone, along with diet and exercise, does not provide adequate glycemic control.[13]
GLP-1 analogues/agonists		
Exenatide	Range: 10 µg to 20 µg DDD: 15 µg Administered: SC	Not approved in Canada at the time of this review.
Liraglutide	Range: 1.2 mg to 1.8 mg DDD: NA Administered: SC	Not approved in Canada at the time of this review.
Bolus insulin		
Insulin aspart	Dosage is individualized Administered: SC	Patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin aspart should normally be used in regimens together with intermediate or long-acting insulin.[14]
Insulin lispro	Dosage is individualized Administered: SC	Indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes mellitus.[15]
Insulin glulisine	Dosage is individualized Administered: SC	Indicated for the treatment of adult patients with T2DM where treatment with insulin is required.[16]
Regular human insulin	Dosage is individualized Administered: SC	For the treatment of patients with insulin-requiring diabetes.
Basal insulin		
Insulin NPH	Dosage is individualized Administered: SC	For the treatment of patients with insulin-requiring diabetes.
Insulin detemir	Dosage is individualized Administered: SC	Indicated for the treatment of adult patients with T2DM who require a basal insulin for the control of hyperglycemia and the treatment of T2DM in combination with OADs (metformin, sulfonylureas or a TZD) in adult patients who are not in adequate metabolic control on OADs alone.[17]
Insulin glargine	Dosage is individualized Administered: SC	Indicated for once-daily subcutaneous administration in the treatment of patients (> 17 years of age) with T2DM who require basal insulin for the control of hyperglycemia.[18]
Insulin NPL	Dosage is individualized Administered: SC	Not approved in Canada at the time of this review.
Biphasic insulins		
Premixed regular NPH	Dosage is individualized Administered: SC	For the treatment of patients with insulin-requiring diabetes.

Table 1: Drugs Included in the Therapeutic Review		
Generic Name	**Dosage / Administration**	**Relevant Health Canada Indications**
Biphasic insulin aspart	Dosage is individualized Administered: SC	Indicated for the treatment of adult patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.[19]
Biphasic insulin lispro	Dosage is individualized Administered: SC	Indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes mellitus.[15]

DDD = defined daily dose (as determined by the World Health Organization); DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; NA = not applicable; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; OAD = oral antidiabetes drug; SC = subcutaneously; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones.

SUMMARY OF APPROACH AND EVIDENCE

Clinical Effectiveness and Safety

The Panel considered a systematic review of RCTs of third-line antidiabetes drugs in adults with type 2 diabetes mellitus, treated with a combination of metformin and a sulfonylurea, where additional glucose-lowering therapy is required because of inadequate glycemic control.[20] The review included 33 unique RCTs[21-53] that provided evidence for the following eight drug classes: alpha-glucosidase inhibitors (four RCTs), meglitinides (one RCT), TZDs (nine RCTs), DPP-4 inhibitors (one RCT), GLP-1 analogues (six RCTs), basal insulin (18 RCTs), bolus insulin (one RCT), and biphasic insulin (12 RCTs). The evidence within these eight drug classes was further stratified based on the following three scenarios: addition of a third-line drug while continuing metformin and a sulfonylurea, treatment with a third-line drug upon discontinuation of metformin or a sulfonylurea (but not both), and treatment with a third-line drug upon discontinuation of both metformin and a sulfonylurea (e.g., insulin monotherapy). The first scenario was the most common among the included RCTs, with 26 RCTs reporting comparisons of interventions added-on to existing therapy with metformin and a sulfonylurea. Limited data were available regarding the discontinuation of metformin and/or a sulfonylurea when third-line pharmacotherapy was initiated. Twenty-four RCTs compared two active treatments, seven RCTs were placebo controlled, and two RCTs involved active comparators as well as placebo.

The relative effectiveness of third-line drugs was assessed according to the following outcomes: long-term diabetes-related complications, A1C, hypoglycemia (overall, severe, and nocturnal), body weight and body mass index, patient satisfaction, and health-related quality of life. Data related to the safety of third-line drugs consisted of withdrawals due to adverse events and serious adverse events. Because of the limited RCT data on the safety of these drugs, a supplemental review of safety and adverse events based on observational studies, long-term RCTs, and advisories from the US Food and Drug Administration was prepared. Mixed treatment comparison (MTC) and pairwise meta-analyses were conducted for A1C and body weight. The MTC primary analysis was restricted to RCTs using interventions added-on to metformin and sulfonylureas. A secondary MTC analysis was conducted incorporating all treatment strategies from studies considered to be sufficiently homogenous to pool. MTC analysis was not conducted for overall hypoglycemia because of large variations in event rates of the control group (i.e., metformin plus a sulfonylurea) and a lack of consistent definitions across individual RCTs. Therefore, only pairwise comparisons were performed. Study level detail is presented for the remaining outcomes for the following reasons: limited number of available studies, small number of events, and/or clinical/methodological heterogeneity between studies. Because of the paucity of data on individual insulin drugs, conventional insulins were pooled with insulin analogues into three groups (i.e., basal insulins, biphasic insulins, and bolus insulins). A sensitivity analysis was conducted to determine the effect of separating insulin NPH from long-acting insulin analogues.

The primary methodological limitations of the included RCTs were: failure to report adequate methods for allocation concealment and the use of analyses other than intention to treat. Common limitations with external validity included: short trial duration, small sample sizes, failure to report definitions for hypoglycemia and adverse events, failure to report the dose or submaximal dosing of metformin and/or the sulfonylurea at baseline, blood glucose targets that were different from those used in routine clinical practice in Canada, and a higher level of contact with health care professionals than is likely to occur in routine clinical practice.

Long-term complications of diabetes

There were no RCTs included in this review that were adequately powered to detect meaningful differences between treatments with regard to long-term diabetes-related complications (e.g., myocardial infarction, nephropathy, retinopathy, stroke or transient ischemic attack, and peripheral vascular disease). Given the paucity of data for long-term complications of diabetes, the Panel was required to use hemoglobin A1C to assess the relative efficacy of the different treatment strategies.

Glycosylated Hemoglobin

There were 31 RCTs[21,22,24-45,47-52,54] (N = 7,238) that reported the change from baseline in A1C. Data were available for eight classes of drugs used as add-on therapy in combination with existing metformin and a sulfonylurea. With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in A1C (range of –0.89% to –1.17%) relative to metformin and sulfonylurea therapy alone (Table 2). However, there were no statistically significant differences between the drug classes that resulted in significant A1C reductions. Results from the secondary MTC analysis (which included all third-line treatment strategies) were similar; the addition of a basal or biphasic insulin to metformin and a sulfonylurea produced the largest effects, with mean reductions in A1C (95% credible interval [CrI]) of –1.20% (–1.66 to –0.77) and –1.13% (–1.69 to –0.60) respectively. Statistically significant improvement in A1C was also observed for patients who received biphasic insulin as monotherapy or in combination with metformin. The evidence for basal insulin as monotherapy or in combination with metformin or sulfonylureas was limited to single RCTs with important methodological limitations. Overall, the amount and quality of evidence was inadequate to draw conclusions regarding the relative efficacy of insulin add-on therapy compared with regimens in which one or both oral drugs were discontinued upon initiation of insulin. Estimates of effect derived from direct comparisons were similar in direction and magnitude as those obtained from MTC meta-analyses.

Table 2: Mean Change from Baseline in Hemoglobin A1C: Results from MTC Meta-Analysis of Add-On Therapies

Treatment versus Placebo + Metformin + Sulfonylurea	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)
Basal Insulin + Met + SU	–1.22 (–2.33 to –0.10)	–1.17 (–1.57 to –0.81)
Biphasic Insulin + Met + SU	———	–1.10 (–1.59 to –0.67)
TZD + Met + SU	–1.16 (–1.36 to –0.96)	–0.96 (–1.35 to –0.59)
DPP-4 + Met + SU	–0.89 (–1.11 to –0.66)	–0.89 (–1.51 to –0.26)
alpha-glucosidase + Met + SU	–0.43 (–0.72 to –0.14)	–0.46 (–0.96 to 0.03)
GLP-1 + Met + SU	–0.96 (–1.14 to –0.77)	–1.06 (–1.45 to –0.69)
Bolus Insulin + Met + SU	———	–1.01 (–1.71 to –0.35)
Meglitinide + Met + SU	———	–0.18 (–2.08 to 1.71)

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

Note: All values represent the difference in the change in A1C (%) from baseline between a particular third-line intervention strategy and the combination of metformin and a sulfonylurea. The MTC results are presented as the mean pooled estimate of effect (95% CrI) and the direct comparisons as the mean difference for the change in A1C from baseline (95% CI).

Body weight

There were 26 RCTs[21,23-29,31,33,34,36-39,41-45,47-50,52,54] (N = 7,011) that reported change from baseline in body weight. As with hemoglobin A1C, the primary MTC meta-analysis was restricted to studies that involved add-on therapy to metformin and a sulfonylurea. The MTC evidence network was composed of 16 RCTs[24-26,28,31,34,36-39,41-43,47,49,54] representing eight third-line drug classes in addition to placebo (Table 3). MTC analysis demonstrated that when added to metformin and a sulfonylurea, treatment with basal insulin, biphasic insulin, bolus insulin, and TZDs were all associated with a significantly greater increase in body weight than treatment with metformin and a sulfonylurea alone (range of 1.85 kg to 5.00 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; whereas, GLP-1 analogues were associated with statistically significant weight loss –1.59 kg (95% CrI: –3.01 to –0.20). The large degree of uncertainty (i.e., very wide confidence interval [CI]) for the effect of meglitinides makes it difficult to draw conclusions for this class; however, there was a trend toward weight gain (2.67 kg [95% CrI –0.94 to 6.32]). With the exception of the weight gain observed with bolus insulins, no third-line drug was associated with a change in body weight greater than 5% (assuming a baseline body weight of 70 kg). The secondary analysis, consisting of all treatment strategies, demonstrated increased weight gain for biphasic insulins used as monotherapy and for basal insulins in combination with a sulfonylurea or as monotherapy (data not shown).

Table 3: Mean Change from Baseline in Body Weight: Results from MTC Meta-Analysis of Add-On Therapies

Treatment versus Placebo + Metformin + Sulfonylurea	Direct Estimates (kg) WMD (95% CI)	MTC Estimates (kg) (95% CrI)
Basal Insulin + Met + SU	0.88 (–1.39 to 3.15)	1.85 (0.54 to 3.09)
Biphasic Insulin + Met + SU	———	3.35 (1.65 to 5.03)
TZD + Met + SU	3.54 (2.43 to 4.64)	3.10 (1.73 to 4.43)
DPP-4 + Met + SU	1.10 (0.28 to 1.29)	1.11 (–1.36 to 3.57)
alpha-glucosidase + Met + SU	–0.88 (–1.63 to –0.14)	–0.43 (–2.20 to 1.44)
GLP-1 + Met + SU	–0.88 (–1.29 to –0.47)	–1.59 (–3.01 to –0.20)
Bolus Insulin + Met + SU	———	5.00 (2.52 to 7.43)
Meglitinide + Met + SU	———	2.67 (–0.94 to 6.32)

CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP = glucagon-like peptide; Met = metformin; MTC = mixed treatment comparison; SU = sulfonylurea; TZD = thiazolidinedione; WMD = weighted mean difference.
Note: All values represent the difference in the change in body weight (kg) from baseline between a particular third-line intervention strategy and the combination of metformin and a sulfonylurea. The MTC results are presented as the mean pooled estimate of effect (95% CrI) and the direct comparisons as the mean difference for the change in A1C from baseline (95% CI).

Severe hypoglycemia

Twenty-two RCTs[24-27,29,32-34,36-38,41-47,49-51,54] (n = 6,368) reporting the number of patients experiencing severe hypoglycemia (typically defined as an event requiring third-party assistance) were identified in the systematic review. Events of severe hypoglycemia were relatively rare for all drug-classes including the insulins. Overall, there were no events reported in 35 out of 52 treatment groups. One RCT[41] reported a statistically significant increase in the number of patients experiencing severe hypoglycemia with bolus insulin (16/238) compared with basal insulin (4/234) when added to metformin and a sulfonylurea (odds ratio [95% CI] 4.14 [1.36 to 12.59]). This trial also reported a trend toward more events with biphasic insulin compared with basal insulin (odds ratio [95% CI] 2.82 [0.89 to 9.00]).

Overall hypoglycemia

There were 26 RCTs[21,24-34,36-38,41,42,44-51,54] (N = 7,238) that reported overall hypoglycemia, 15 of which did not provide a definition of it.[25,27-33,35,39,40,42,43,47,52] MTC meta-analysis was not performed for this outcome because of the large variation in control group event rates (i.e., metformin plus a sulfonylurea) and the lack of consistency in definitions. When given in combination with metformin and sulfonylureas, TZDs,

GLP-1 analogues, and DPP-4 inhibitors were associated with a significantly higher risk of overall hypoglycemia than placebo. 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.

Cost and Cost-Effectiveness

The clinical results from the systematic review were used to perform a class-level cost-effectiveness analysis.[55] The analysis compared five treatment classes added to metformin and a sulfonylurea as third-line therapy (basal insulin, biphasic insulin, TZDs, DPP-4 inhibitors (sitagliptin), and placebo). The lowest cost alternative for each class of drugs (e.g., pioglitazone for TZDs) was used in the primary economic analysis. GLP-1 analogues were not included in the analysis as they were not approved for sale in Canada at the time of this review. The average daily costs of treatments were estimated with and without the additional cost of blood glucose test strips (Table 4). Average test strip use, by pharmacotherapy, was obtained from the Ontario Public Drug Program in 2009.[56] A cost of $0.72 per test strip plus a pharmacy fee of $7.00 per 100 test strips was applied. The UKPDS Outcomes Model[57] was used to forecast the cumulative incidence of diabetes-related complications over a 40-year time horizon as well as associated costs. For each treatment strategy, inputs for predictive risk factors in the model, such as A1C, body mass index, and body weight were informed by the results of the systematic review and MTC meta-analysis.[20] Overall hypoglycemia, severe hypoglycemia, and congestive heart failure (with respect to TZDs) were also considered in the model.

In the primary economic analysis, the addition of insulin NPH to metformin plus a sulfonylurea was associated with the most favorable cost-effectiveness estimates among active treatments with an incremental cost per quality-adjusted life-year (QALY) gained of $60,800 relative to metformin plus a sulfonylurea alone (Table 6). Other active treatments were more costly and less effective in terms of QALYs gained compared with insulin NPH, although the differences for both costs and QALYs among classes were small (range in QALYs of 8.2190 with TZDs to 8.3251 with basal insulin). Cost-effectiveness results were sensitive to variation in model inputs and assumptions. In some circumstances DPP-4 inhibitors became the most cost-effective therapeutic option. For example, this occurred when DPP-4 inhibitors were compared with long-acting insulin analogues rather than insulin NPH, if insulin was considered undesirable by patients (i.e., high disutility was applied for insulin injections), or if higher rates of hypoglycemia were assumed among patients using insulin than in the primary analysis. Results from sensitivity analyses should be interpreted with caution, however, as the clinical data informing model inputs are limited, especially data related to the impact of insulin use and hypoglycemia on quality of life and the incidence of hypoglycemia across various treatments. Furthermore, the clinical evidence of DPP-4 inhibitors at third-line is limited to one RCT of sitagliptin[47] and their long-term clinical effectiveness and safety profile is largely unknown due to limited clinical experience. Well-designed studies, which explore these noted key issues, are needed to more accurately assess the cost-effectiveness of competing third-line therapies.

Table 4: Daily Cost of Treatments with and without the Cost of Blood Glucose Test Strips

Treatment	Insulin Dose from Canadian Clinical Practice*		Insulin Dose from RCTs[†]	
	Daily Treatment Cost without Test Strips[‡] ($)	Daily Treatment Cost with Test Strips[§] ($)	Daily Treatment Cost without Test Strips ($)	Daily Treatment Cost with Test Strips ($)
Insulin NPH	1.95	3.60	1.08	2.72
Pioglitazone[¶]	2.50	3.41	2.50	3.41
Rosiglitazone	5.00	5.92	5.00	5.92
Biphasic human insulin	3.81	5.45	1.88	3.52
DPP-4 inhibitors	2.88	3.80	2.88	3.80
Long-acting insulin analogues	3.04	4.69	2.04	3.68
Biphasic insulin analogues	4.34	5.98	1.88	3.51

DPP-4 = dipeptidyl peptidase-4, NPH = neutral protamine Hagedorn; RCT = randomized controlled trial.
* Insulin doses obtained from patient sample in British Columbia. This dataset reported insulin doses of 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.
† Insulin doses obtained from RCTs included in systematic review. RCTs reported insulin doses of 0.35 U/kg, 0.42 U/kg, 0.53 U/kg, and 0.76 U/kg for long-acting insulin analogues, insulin NPH, biphasic insulin analogues, and biphasic human insulin respectively.
‡ The cost of the lowest cost alternative was applied for each drug class plus a 10% 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.
§ Patients using insulin were assumed to use 2.1 test strips per day, while those using oral drugs in combination with sulfonylureas used 1.16 test strips per day, based on data from the Ontario Public Drug Program.
¶ Based on the cost of 30 mg generic pioglitazone in Saskatchewan, Alberta, and the Non-Insured Health Benefits (NIHB) program; in Ontario, generic pioglitazone costs less ($1.57) under the ministry's Exceptional Access Program.

Table 5: Estimated Cumulative Incidence of Long-Term Diabetes-Related Complications Over a 40-year Period, Primary Economic Analysis

Outcome	Treatments Strategies				
	Met + SU (%)	Basl + Met + SU (%)	Bipl + Met + SU (%)	TZD* + Met + SU (%)	DPP-4 + Met + SU (%)
Ischemic heart disease	8.9	8.4	8.5	8.3	8.5
Myocardial infarction	25.5	24.4	24.5	26.7	24.5
Congestive heart failure	11.3	11.1	11.6	20.7*	11.0
Stroke	11.4	10.8	10.9	12.2	11.1
Amputation	5.8	4.6	4.7	4.7	5.0
Blindness	5.7	5.2	5.1	5.0	5.3
Renal failure	3.4	3.3	3.3	3.1	3.3

Basl = basal insulin, Bipl = biphasic insulin; DPP-4 = dipeptidyl peptidase-4, Met = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
*The reference case assumes that TZDs are associated with an increased risk of chronic heart failure based on evidence from the RECORD trial.

Table 6: Estimated Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results from the Reference Case Analysis

Treatment	Average Costs Incurred Over Lifetime ($)	Average QALYs Gained Over Lifetime	Incremental Cost-Effectiveness Results
Met + SU	39,128	8.2405	NA
Met + SU + basal insulin	44,206	8.3251	$60,049 per QALY (relative to Met + SU)
Met + SU + DPP-4 inhibitor	44,717	8.3059	Dominated by Met + SU + basal insulin
Met + SU + TZD*	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; NA = not applicable; QALY = quality-adjusted life-years; SU = sulfonylurea; TZD = thiazolidinedione.
*The reference case assumes that TZDs are associated with an increased risk of chronic heart failure based on evidence from the RECORD trial.

KNOWLEDGE GAPS RELATED TO THIRD-LINE THERAPY FOR TYPE 2 DIABETES AND SECONDARY RESEARCH QUESTIONS

- The Panel concluded that there was insufficient evidence to make a recommendation regarding whether the usage of metformin and sulfonylureas should be continued or discontinued on the initiation of basal insulin.
- The Panel concluded that there was insufficient evidence to provide recommendations on the following secondary research questions that were included in the CADTH therapeutic review:
  - What is the evidence regarding the safety and efficacy of increased doses of metformin versus the addition of second-line drugs after inadequate control on metformin monotherapy?
  - What constitutes an adequate trial of first- and second-line therapy (i.e., metformin and sulfonylureas) before the decision to increase doses or to add or switch to third-line drug(s) is made?
  - What is the clinical evidence related to increased doses of first- and second-line therapy (i.e., metformin and/or sulfonylureas) versus addition or switch to a third-line drug(s)?
- There was no RCT evidence to conduct the subgroup analyses specified in the project protocol (e.g., including First Nations people and ethnic minorities). Furthermore, the only RCT evidence available for elderly patients was a subgroup analysis from a single study.

Participating TRP Members:

TRP Co-Chairs: Dr. Robert Peterson and Dr. Lisa Dolovich

TRP Members: Dr. G. Michael Allan, Dr. Michael Allen, Dr. Bruce Carleton, Dr. Scott Klarenbach, Dr. Laurie Mallery, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

TRP Public Members: Mrs. Cathy MacNutt and Mr. Brad Neubauer

TRP Specialist Expert Members: Dr. Robyn Houlden, Dr. Ehud Ur, and Dr. Ann Colbourne

Conflict of Interest:

- Dr. Robert Peterson received unrestricted funding from Celgene Corporation to lecture on drug safety in China.
- Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant from Amgen Canada and Merck Frosst Canada Ltd. to the Alberta Kidney Disease Network.
- Dr. Ann Colbourne has received honoraria for educational lectures for Novo Nordisk Canada Inc., Lifescan, Sanofi-aventis Canada Inc., AstraZeneca Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Ltd. of $5,000 or less. She was involved in a community-based interprofessional collaborative chronic disease management program, funded by AstraZeneca Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Ltd.
- Dr. Robyn Houlden has received honoraria for educational lectures from Merck Frosst Canada Ltd., Eli Lilly Canada Inc., AstraZeneca Canada Inc., Novo Nordisk Canada Inc., Sanofi-aventis Canada Inc., Pfizer Canada Inc., and Boehringer Ingelheim. She has also received research grants from GlaxoSmithKline Inc., Medtronic, Pfizer Canada Inc., AstraZeneca Canada Inc., and Eli Lilly Canada Inc.
- Dr. Ehud Ur has received honoraria for educational lectures, honoraria for organizing conferences, or other honoraria for $5,000 or less from GlaxoSmithKline Inc., Novo Nordisk Canada Inc., Sanofi-aventis Canada Inc., Merck Frosst Canada Ltd., and Novartis Pharmaceuticals Canada Inc. He has received funding for consultant or advisory services from GlaxoSmithKline Inc., and Novo Nordisk Canada Inc., and has received research grants through the Queen Elizabeth II Foundation (Halifax) from GlaxoSmithKline Inc., Novo Nordisk Canada Inc., and Lifescan.
- Dr. Bruce Carleton has received research support for a national program to improve adverse drug reaction reporting and identification of genetic determinants of drug risk in children, known as the Canadian Pharmacogenomics Network for Drug Safety project. Funding has been provided by the Canadian Institutes of Health Research (CIHR) and Canada Foundation for Innovation (CFI) from January 2009 to 2013. The University of British Columbia has also received funds from Pfizer Canada Inc. that will be used as part of the grant provided by CIHR and CFI. Research funding for the period 2004-2008 was primarily provided by Genome Canada, with some support from Genome British Columbia, Merck Frosst Canada Ltd., Pfizer Canada Inc., Eli Lilly Canada Inc., and Janssen-Ortho Inc., which provide pooled funds matching government funds for this grant. The pharmaceutical industry has no formal or informal role in this program of research.
- Dr. Lindsay Nicolle has received payment for consulting services from Pfizer Canada Inc. and Leo Pharma Inc.
- Dr. Yvonne Shevchuk has received financial support from Institut Rosell Inc. for work on probiotics.
- Dr. Lisa Dolovich, Dr. Michael Allen, Dr. Adil Virani, Dr. James Silvius, Dr. G. Michael Allan, Dr. Laurie Mallery, Mr. Brad Neubauer, and Mrs. Cathy MacNutt report no conflict of interest.

About This Document:

This Therapeutic Review Panel Recommendation or Advice is the official record, which comprises a recommendation and the reasons for the recommendation or advice, for use by Canadian jurisdictions in making well-informed decisions. Recommendations or advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its

cost-effectiveness. Therapeutic review clinical and economic reports are based on published information available up to the time that TRP made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

The TRP is a panel of the Canadian Agency for Drugs and Technologies in Health (CADTH), established to make recommendations and provide advice based on therapeutic reviews completed as part of the therapeutic review pilot project. It is made up of experts in drug evaluation and drug therapy as well as public members.

The Therapeutic Review Panel Recommendation or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

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