Canadian Agency for Drugs and Technologies in Health

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CADTH Optimal Therapy Report

August 2010

Optimal Therapy Recommendations for the Prescribing and Use of Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin

Supporting Informed Decisions

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

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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1 INTRODUCTION

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

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

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

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

- The COMPUS Advisory Committee (CAC), which includes representatives from the federal, provincial, and territorial health ministries and related health organizations.
- The COMPUS Expert Review Committee (CERC), members are listed in Appendix A of this document.
- Stakeholder feedback.

1.1 COMPUS Expert Review Committee

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

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers

in implementing and using the recommendations and advice toward the promotion of optimal practices. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

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

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

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

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

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

2.1 Diabetes

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

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

2.1.1 Management of blood glucose levels in type 2 diabetes

One goal of diabetes management is to maintain control of blood glucose levels to reduce the patient's risk of developing long-term diabetes-related complications. Lifestyle modifications (i.e., weight control, proper nutrition, and adequate exercise) and use of antidiabetes drugs such as oral agents or insulin are recommended approaches for improving glycemic control.[1]

2.1.2 Technology description — Second-line antidiabetes drugs

Eleven classes of antidiabetes drugs are available as second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, basal insulins, bolus insulins, biphasic insulins, weight loss agents, and amylin analogues (Table 1). GLP-1 analogues and amylin analogues are currently not available in Canada. Agents from all classes were included in the systematic review as long as they were approved for use by Health Canada, the United States Food and Drug Administration, or the European Medicines Agency.

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Admininistration**	**Relevant Indications**
Sulfonylureas			
Gliclazide / Gliclazide MR	Range: 80 mg to 320 mg DDD: 160 mg Range for MR: 30 mg to 120 mg	Oral	Control of hyperglycemia in gliclazide-responsive type 2 diabetes, which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.[23,24]
Glimepiride	Range: 1 mg to 8 mg DDD: 2 mg	Oral	Indicated for use as follows: as an adjunct to proper dietary management, exercise, and weight reduction to lower the blood glucose in patients with type 2 diabetes who have hyperglycemia that 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 hypoglycemic agent alone.[25]
Glyburide	Range: 2.5 mg to 20 mg DDD: 10 mg	Oral	Indicated as an adjunct to proper dietary management, exercise, and weight reduction to lower blood glucose in adult patients with type 2 diabetes who have hyperglycemia that cannot be controlled by diet and exercise alone or when insulin therapy is not required.[26]
Chlorpropamide	Range: 100 mg to 500 mg DDD: 375 mg	Oral	In mild, stable type 2 diabetes to control hyperglycemia responsive to the drug. It should not be used in those patients who are prone to ketosis or who can be controlled by dietary management and exercise alone or for whom insulin therapy is more appropriate.[27]
Glipizide	Range: 5 mg to 40 mg DDD: 10 mg	Oral	Not approved in Canada
Tolbutamide	Range: 500 mg to 3,000 mg DDD: 1,500 mg	Oral	To control hyperglycemia in tolbutamide-responsive type 2 diabetes, which cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.[28]
Thiazolidinediones			
Pioglitazone	Range: 15 mg to 45 mg DDD: 30 mg	Oral	Indicated as monotherapy in patients not controlled by diet and exercise alone, to decrease insulin resistance and blood glucose levels in patients with type 2 diabetes. Also indicated for use in combination with a sulfonylurea or metformin when diet and exercise plus the single agent do not result in adequate glycemic control.[29]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Admininistration**	**Relevant Indications**
Rosiglitazone	Range: 4 mg to 8 mg DDD: 6 mg	Oral	Indicated for use as an adjunct to diet and exercise in patients with type 2 diabetes as follows: monotherapy in patients not controlled by diet and exercise alone and for whom metformin is inappropriate because of contraindications or intolerance; in combination with metformin when diet and exercise plus metformin do not result in adequate glycemic control; in combination with a sulfonylurea in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus sulfonylurea or rosiglitazone monotherapy do not result in adequate glycemic control.[30]
Meglitinides			
Nateglinide	Range: 60 mg to 120 mg DDD: 360 mg	Oral	Indicated as monotherapy to lower the blood sugar in patients with type 2 diabetes not controlled satisfactorily by diet and exercise alone. Also indicated in combination with metformin in patients whose diabetes is not controlled satisfactorily with diet, exercise, or metformin alone.[31]
Repaglinide	Range: 0.5 mg to 16 mg DDD: 4 mg	Oral	Indicated in patients with type 2 diabetes who have hyperglycemia that cannot be controlled satisfactorily by diet and exercise alone. Indicated in combination therapy with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus metformin monotherapy. Indicated in combination with rosiglitazone in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus rosiglitazone or repaglinide monotherapy do not result in adequate glycemic control.[32]
Alpha-glucosidase inhibitors			
Acarbose	Range: 150 mg to 300 mg DDD: 300 mg	Oral	Indicated for use as follows: as an adjunct to prescribed diet for the management of blood glucose levels in patients with type 2 diabetes inadequately controlled by diet alone; in combination with either a sulfonylurea, metformin or insulin to improve glycemic control in patients with type 2 diabetes inadequately controlled on diet, exercise and either a sulfonylurea, metformin or insulin alone.[33]
Miglitol	Range: 75 mg to 300 mg DDD: 300 mg	Oral	Not approved in Canada
DPP-4 inhibitors			
Sitagliptin	Dosage: 100 mg DDD: 100 mg	Oral	Indicated in combination with metformin in adult patients with type 2 diabetes inadequately controlled with metformin monotherapy.[34]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Admininistration**	**Relevant Indications**
Vildagliptin	Dosage: 100 mg DDD: 100 mg	Oral	Not approved in Canada
Saxagliptin	Dosage: 5 mg DDD: N/A	Oral	Indicated in patients with type 2 diabetes to improve glycemic control in combination with metformin or a sulfonylurea, when metformin or the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control.[35]
GLP-1 analogues			
Exenatide	Range: 10 µg to 20 µg DDD: 15 µg	SC	Not approved in Canada
Liraglutide	Range: 1.2 mg to 1.8 mg DDD: N/A	SC	Not approved in Canada
Rapid-acting insulin analogues			
Insulin aspart	Dosage is individualized	SC	Patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Insulin aspart should normally be used in regimens together with an intermediate or long-acting insulin.[36]
Insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes.[37]
Insulin glulisine	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes where treatment with insulin is required.[38]
Short-acting human insulin			
Regular human insulin	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.
Intermediate-acting insulin			
Insulin NPH	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.
Long-acting insulin analogues			
Insulin detemir	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes who require a basal insulin for the control of hyperglycemia and indicated for the treatment of type 2 diabetes in combination with oral antidiabetes drugs (metformin, sulfonylureas, or a TZD) in adult patients who are not in adequate metabolic control on oral antidiabetes drugs alone.[39]
Insulin glargine	Dosage is individualized	SC	Indicated for once-daily subcutaneous administration in the treatment of patients (> 17 years of age) with type 2 diabetes who require basal insulin for the control of hyperglycemia.[40]
Insulin NPL	Dosage is individualized	SC	Not approved in Canada
Premixed insulins			
Premixed regular NPH	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Admininistration**	**Relevant Indications**
Biphasic insulin aspart	Dosage is individualized	SC	Indicated for the treatment of adult patients with diabetes who require insulin for the maintenance of normal glucose homeostasis.[41]
Biphasic insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes.[37]
Weight loss agents			
Orlistat	Dosage: 360 mg DDD: 360 mg	Oral	Orlistat, when used in conjunction with a mildly hypocaloric diet, is indicated for obesity management, including weight loss and weight maintenance and reducing the risk of weight regain in obese patients after prior weight loss. These indications apply to obese patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia, excess visceral fat). Orlistat can be used in combination with antidiabetes drugs (sulphonylureas, metformin, insulin) to improve blood glucose control in overweight or obese type 2 diabetes patients inadequately controlled on diet, exercise, and one or more of a sulphonylurea, metformin, or insulin.[42]
Sibutramine	Range: 10 mg to 15 mg DDD: 10 mg	Oral	Indicated as adjunctive therapy within a weight management program for obese patients with an initial BMI of 30 kg/m^2 or higher and obese patients with an initial BMI of 27 kg/m^2 or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).[43]
Amylin Analogues			
Pramlintide	Range: 60 µg to 120 µg	SC	Not approved in Canada

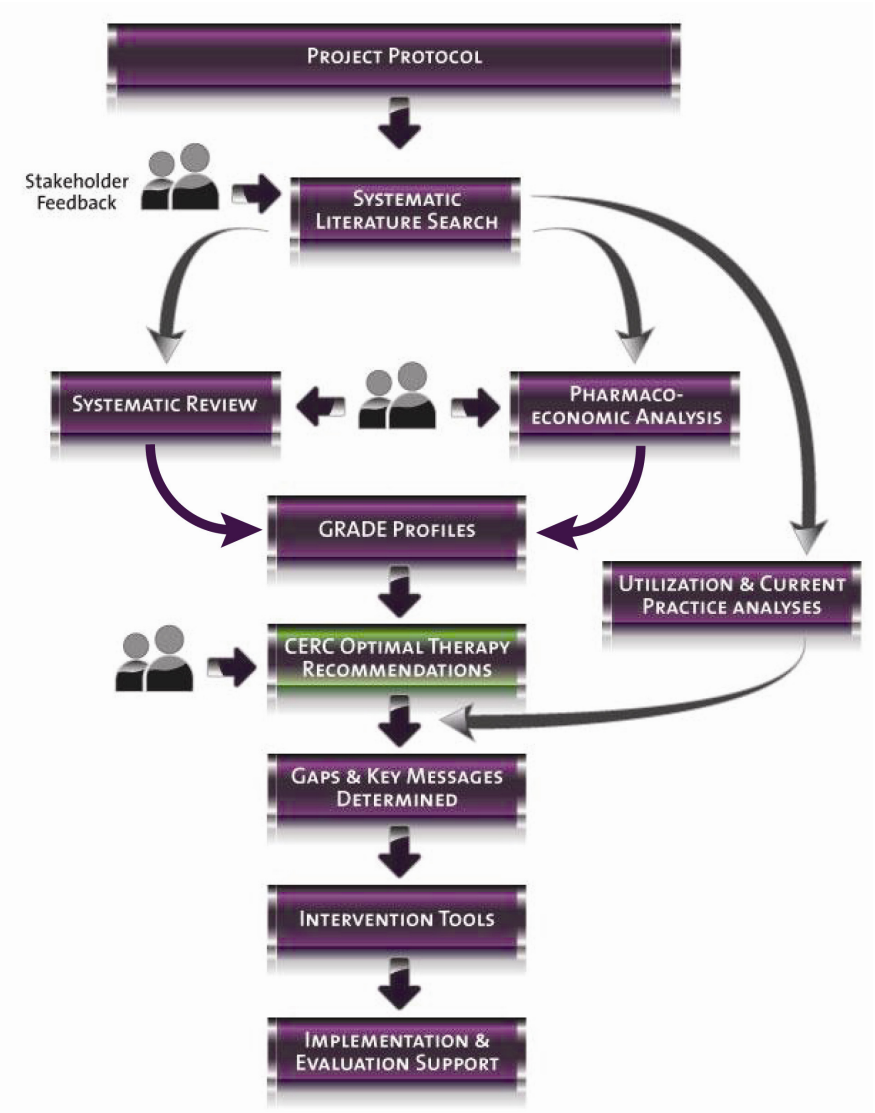
BMI = body mass index; DDD = defined daily dose (as per the World Health Organization); DPP = dipeptidyl peptidase-4; GLP = glucagon-like peptide-1; N/A = not applicable; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; SC = subcutaneous; TZD = thiazolidinediones.

3 OBJECTIVE

This report provides recommendations for the optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.

4 PROJECT OVERVIEW

Once a topic is selected, staff undertakes activities related to key areas in the CADTH procedure. The CAC provides advice and guidance throughout the process, from topic identification through to supporting intervention and evaluation tools. CERC, as described in Section 1.1, provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of medications. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.



To identify and promote the implementation of evidence-based and cost-effective therapy in the prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy, CADTH follows the process outlined in the flow chart to the right.

This report represents the Optimal Therapy Recommendations (green box).

5 RESULTS

5.1 Optimal Therapy Recommendations

Through careful evaluation of the evidence (Section 6) and significant deliberation of the issues (Section 7), CERC produced one recommendation on the use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.

CERC applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for developing recommendations (Section 7). As stipulated by the GRADE method, the strength of a recommendation is reflected by the use of the words "suggests" or "recommends," (i.e., for a weak recommendation, "CERC **suggests** that …," and for a strong recommendation, "CERC **recommends** that …").

Table 2: Summary of CERC Recommendation for Second-Line Antidiabetes Drugs

- CERC recommends that a **sulfonylurea** be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone.

Detailed information regarding this recommendation (i.e., vote results, the rating of overall quality of clinical evidence, underlying values and preferences related to the recommendations and suggestions, clinical notes, and context) is provided in Appendix B.

5.2 Research Gaps

An important aspect of CADTH's mandate includes the identification and dissemination of research gaps; that is, areas in which there is insufficient evidence to guide optimal prescribing and use. The following sections outline gaps in research related to second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy. Identification of these gaps will assist researchers and research funding organizations in planning future clinical research. The knowledge that results from such research will lead to improved clinical practice and better outcomes for patients with diabetes.

5.2.1 Populations, interventions, comparators, and outcomes with insufficient evidence

No studies addressed any of the following subgroups specified in the protocol: children, First Nations people, ethnic minorities, or the elderly (≥ 65 years of age). First Nations populations are of special interest given the high prevalence of diabetes among them.[44] There was also no evidence for patients requiring a switch in therapy due to metformin intolerance or contraindication. Further research is also required in populations at higher risk of severe hypoglycemia or its consequences, so that the real-world benefits of agents associated with lower hypoglycemia risk can be better quantified.

There was insufficient evidence for a number of outcomes considered important for making recommendations on the use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy. In particular, sparse evidence was available for long-term complications of diabetes, mortality, health-related quality of life, and

patient satisfaction. Longer trials powered to detect these outcomes are required to provide more definitive information regarding the comparative clinical and economic benefits of the available second-line agents.

In terms of the comparisons conducted in studies, the majority consisted of placebo-controlled trials. There were few direct comparisons of newer drug classes such as the DPP-4 inhibitors and GLP-1 analogues versus older agents such as sulfonylureas. As well, evidence regarding the effects of insulins as second-line therapy was sparse. The research gaps identified in this review are summarized in Table 3.

Table 3: Populations, Interventions, and Outcomes Requiring Further Research

Category	Research Gap
Populations	• Patients < 18 years of age • First Nations • Patients ≥ 65 or ≥ 75 years old
Interventions and Comparators	• Insulins • Comparisons between DPP-4 inhibitors and GLP-1 analogues with older agents
Outcomes	• Long-term complications of diabetes • Mortality • Health-related quality of life • Patient satisfaction with diabetes care

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

6 THE EVIDENCE

The clinical and cost-effectiveness evidence for the use of second-line antidiabetes drugs for patients with type 2 diabetes was derived from the CADTH Optimal Therapy Report: *Second-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis*.[45]

7 CONSIDERATION OF THE EVIDENCE

7.1 COMPUS Expert Review Committee Process and Perspective

CERC members consider clinical effectiveness (i.e., benefits and harms), burdens, and cost and cost-effectiveness data, when formulating Optimal Therapy Recommendations. Committee members bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, consumers, members of the public) and draw upon their own values and preferences to discuss the evidence and reach conclusions.

CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendations and advice toward the promotion of optimal practices. To assist in knowledge transfer to intended audiences, CERC also develops Clinical Notes (where appropriate) to provide guidance based on clinical judgment where there is insufficient evidence. Context statements also accompany the recommendations to provide commentary relating to the evidence.

An important component of each Optimal Therapy Recommendation is a clear statement regarding the values and preferences that supported CERC member's choice of one alternative over another. These serve as a guide for patients, clinicians, and decision-makers in interpreting the appropriateness of recommendations based on their own values and preferences.

CADTH applied the GRADE approach to summarize the available evidence and facilitate the generation of Optimal Therapy Recommendations by CERC.[46] The GRADE methodology was developed by the GRADE Working Group, an international collaboration of methodologists, to provide committees charged with formulating recommendations with a framework for evaluating evidence. GRADE provides a systematic and transparent approach to appraise quality of evidence, weigh the balance of benefits versus harms, identify underlying values and preferences, and rate the overall strength of recommendations.[47] The GRADE methodology is used by a number of organizations worldwide, including the World Health Organization[48] and the American Thoracic Society.[49]

The process by which CERC used the GRADE evidence profiles and economic data to generate Optimal Therapy Recommendations for second-line antidiabetes therapy consisted of five steps. Each of these steps is described in further detail in Appendix C.

- Individual review of GRADE evidence profiles and provision of feedback
- Preparatory work prior to the identification of draft Optimal Therapy Recommendations
- Identification of draft Optimal Therapy Recommendations
- Grading strength of recommendations
- Identification of research gaps

7.2 Specific Considerations

Prior to the initiation of the systematic review by CADTH, members of CERC identified the outcomes for which evidence was required to make recommendations for the use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy. These included:

- long-term complications of diabetes (e.g., mortality, cardiovascular disease, nephropathy, retinopathy)
- surrogate outcomes related to glycemic control (i.e., A1C)
- hypoglycemia
- body weight and body mass index
- quality of life and patient satisfaction
- resource use and costs.

7.2.1 Hemoglobin A1C

A1C was the most frequently reported measure of glycemic control in the studies included in the CADTH systematic review of second-line antidiabetes drugs. During the development of Optimal Therapy Recommendations for the prescribing and use of insulin analogues,[50] (a previous CADTH topic), CERC deliberated extensively on the evidence available to support the validity of A1C as a surrogate outcome for clinically relevant complications of diabetes[7,20,21,51-72] and the minimal difference in this outcome that could be considered clinically relevant.[73-75] Committee members believed there were important limitations associated with the use of A1C as a surrogate outcome, particularly with regard to cardiovascular outcomes. CERC recognized that the widespread implementation in clinical practice of A1C as a parameter to

monitor treatment efficacy in patients with either type 1 or type 2 diabetes has revolutionized diabetes care by allowing for the measurement of long-term glycemic control. Furthermore, diabetes treatment guidelines define optimum glycemic control based on A1C targets.

7.2.2 Hypoglycemia

CERC recognized that hypoglycemia, particularly severe and nocturnal episodes, pose a substantial barrier to achieving optimal glycemic control in patients with diabetes. CERC noted that the risk of hypoglycemia varied across patients, as well as within an individual patient over time, depending upon a number of clinical circumstances. In the systematic review of second-line agents, insulin and insulin secretagogues were associated with a higher risk of overall hypoglycemia than other agents. However, events of severe and nocturnal hypglycemia were exceedingly rare across all drug classes. CERC noted the methodological limitations associated with the outcome of overall hypoglycemia (e.g., the lack of consistent definitions across studies) as well as its uncertain clinical significance. In light of the sparse data on severe hypoglycemia, CERC considered evidence from observational studies to provide information regarding the absolute risk of this outcome.[76,77] Both mild-moderate and severe hypoglycemia were considered in the cost-effectiveness analysis.

7.2.3 Weight gain

CERC discussed the importance of weight change at length, particularly with respect to the magnitudes of weight gain or loss observed with different classes of antidiabetes drugs. The evidence regarding clinically meaningful reductions in body weight was reviewed and discussed during the recommendation process.[78-85] CERC noted that there is currently no universally accepted minimal clinically important difference for weight change. The committee also identified a lack of sufficient evidence regarding the relationship between weight gain or loss due to antidiabetes pharmacotherapy and either long-term clinically important outcomes or quality of life. It was further noted that net weight change alone does not capture the possible clinical consequences of weight gain, since weight distribution may also play an important role. For example, the TZDs tend to cause subcutaneous fat deposition, while insulins and insulin secretagogues are associated with visceral deposition.[86-88]

7.2.4 Direct and indirect comparisons

Because of the large number of drug classes available for use as second-line therapy for type 2 diabetes, pair-wise treatment comparisons alone would not have been readily interpretable. Mixed treatment comparison (MTC) meta-analysis offered an approach to simultaneously compare the relative safety and efficacy of multiple treatments using both direct and indirect evidence. The limitations of indirect comparisons were discussed at length by CERC. In rating the overall quality of evidence using the GRADE criteria, the limitations of using evidence from indirect comparisons was clearly noted. Furthermore, CERC considered both direct and indirect estimates of effect in their deliberations whenever possible. The fact that there was very good alignment in both the direction and magnitude of effects between the direct and indirect comparisons added to the CERC members' confidence in the results from the MTC meta-analysis.

7.2.5 Therapeutic agents not available in Canada

Evidence regarding second-line therapeutic agents not available in Canada was included in the systematic review (i.e., exenatide, liraglutide, vildagliptin, miglitol, and glipizide). However, CERC was presented with sensitivity analyses in which these studies were removed from the overall evidence pool. These results were similar to the reference case analysis that included all available evidence. Since there are currently no GLP-1 analogues approved for use in Canada, this class was not considered a candidate for the Optimal Therapy Recommendation on second-line therapy. However, the clinical evidence available for this class was deliberated upon by CERC.

8 NEXT STEPS

The Optimal Therapy Recommendation will be widely disseminated to encourage uptake and implementation by decision-makers at various levels (e.g., policy decision-makers, health care professionals, and patients). Gaps in practice and knowledge related to the use of second-line antidiabetes drugs will be identified by comparing the final recommendations with information on current practice (*Current Practice Analysis of Health Care Providers and Patients on Second-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled on Metformin*[89]) and utilization (*Current Utilization of Second-Line Therapies in Patients with Type 2 Diabetes Inadequately Controlled on Metformin*[90]) of these products in Canada.

Key messages to promote the optimal prescribing and use of second-line antidiabetes drugs will be developed to address identified gaps in practice and knowledge. Intervention tools will be populated with the key messages and related evidence for implementation across Canada.

APPENDIX A: EXPERT COMMITTEE AND CONTRIBUTORS

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Conflicts of Interest

Dr. Michael Evans has received grant support from AstraZeneca Canada Inc. to offset the cost of Mini-Med School, an educational program for the public.

Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant from Amgen Canada Inc. 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 Inc., 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. Marshall Dahl has received an honorarium for less than $5,000 from Eli Lilly for his work related to workshops. He has also received an arms-length grant for a diabetes study in coronary artery patients from GlaxoSmithKline Inc. In addition, Dr. Dahl has received an honorarium for less than $5,000 from sanofi-aventis Canada Inc. for a lecture.

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 Inc.

Dr. Robyn Houlden has received honoraria for educational lectures from Merck Frosst, Eli Lilly, AstraZeneca, Novo Nordisk Canada Inc., sanofi-aventis, Pfizer, and Boehringer Ingelheim. She has also received research grants from GlaxoSmithKline, Medtronic Inc., Pfizer Canada Inc., AstraZeneca Canada Inc., and Eli Lilly Canada Inc.

None of the other CERC members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

APPENDIX B: DETAILED RECOMMENDATION AND SUPPORTING EVIDENCE

Background

The detailed recommendation tables offer the following information:

- **Vote results** — Indicates the number of CERC members voting in favour of the proposed recommendation statement.

- **CERC rating of overall quality of clinical evidence** — Indicates results of the vote by CERC on the overall quality of the evidence available for a recommendation. Possible ratings of quality were "low," "moderate," or "high," and were based on criteria developed by the GRADE Working Group.

- **Strength of recommendation** — Indicates the results of the vote by CERC on the strength of the recommendation, based on criteria developed by the GRADE working group. Possible ratings are "strong" or "weak,"

- **Underlying values and preferences** — Indicates the values and preferences that CERC members identified as most important in guiding the recommendation.

- **Clinical notes** — Provides guidance from CERC regarding specific clinical considerations that may assist patients, policy decision-makers, and clinicians in selecting optimal therapy, especially in areas where there is a lack of sufficient evidence.

- **Context** — Lists key points arising from CERC members' deliberation of the clinical and economic evidence pertaining to the recommendation. This information is provided to assist patients, clinicians, and policy decision-makers with the interpretation and application of the recommendation and underlying evidence.

- **Evidence** — The most pertinent evidence used in generating the recommendations is presented following each recommendation. A detailed description of the evidence is presented in the CADTH Optimal Therapy Report: *Second-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis.*[45]

Optimal Therapy Recommendation

CERC recommends that a **sulfonylurea** be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone.

(Voting: agree 12, disagree 0; strong recommendation; low-quality evidence)

Underlying Values and Preferences

CERC placed a high value on:

- efficient use of limited resources (i.e., cost-effectiveness of the various agents)
- evidence demonstrating a lack of clinically meaningful differences in glycemic control, hypoglycemia, and weight gain among the various classes of agents
- greater availability of long-term safety data for older drug classes (e.g., sulfonylureas) compared with newer classes.

Context

- Most included studies defined inadequate control with metformin monotherapy as a hemoglobin A1C value of greater than 7% after at least two months of treatment with stable doses of metformin, although some studies used a threshold as low as 6.5% and others as high as 7.5%.
- The "low" rating for the quality of evidence was attributed to the lack of data on long-term, clinically important outcomes, the inclusion in trials of patients with variable treatment histories before metformin monotherapy, and methodological limitations of the available studies.
- There was insufficient evidence to determine whether clinically important differences existed between drug classes for long-term complications of diabetes.
- Each of the eight drug classes significantly reduced hemoglobin A1C relative to placebo; however, there were no significant differences between any of the active treatments.
- Despite the statistically significant increase in risk of overall hypoglycemia, CERC concluded that sulfonylureas were a safe therapeutic option for most patients given the rarity of severe hypoglycemia events across all drug classes. These findings are corroborated by large observational studies reporting the incidence of severe hypoglycemia. For example, approximately 0.06 events of severe hypoglycemia per 100 patient-years were observed with metformin alone in one study,[91] versus 0.24 events per 100 patient-years with insulin secretagogues (i.e., sulfonylureas and meglitinides) (Number needed to harm = 550).
- The average weight gain associated with sulfonylureas (approximately 2 kg compared with metformin alone) was neither considered to be clinically meaningful for most patients, nor was it felt to outweigh the advantages of these agents.
- The evidence for the cost-effectiveness of sulfonylureas was robust across numerous sensitivity analyses.
- It was CERC members' clinical opinion that within the sulfonylurea class, gliclazide may be associated with less weight gain and a reduced risk of hypoglycemia relative to glyburide, although there was a lack of sufficient comparative evidence.
- CERC noted that the unique mechanisms of action of DPP-4 inhibitors and GLP-1 analogues may provide theoretical advantages in terms of efficacy and safety. However, the available evidence indicates that these classes have only modest benefits in terms of hypoglycemia risk and weight gain, and that they are not cost-effective compared with sulfonylureas. Furthermore, long-term data on clinically important outcomes are lacking.
- The risk of heart failure and possible risk of other adverse outcomes (e.g., fractures) were considered to limit the utility of TZDs for most patients requiring second-line therapy. The high rates of gastrointestinal adverse effects observed with acarbose in clinical practice were considered to limit the usefulness of this agent.

Summary of Clinical Evidence

Table A1: Results for Hemoglobin A1C, Overall Hypoglycemia, and Body Weight			
Hemoglobin A1C (change from baseline, %) (as a surrogate for long-term complications of diabetes)			
Treatment versus Metformin Monotherapy	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Quality of Evidence**
Sulfonylureas	-0.80 (-1.00 to -0.59)	-0.79 (-0.95 to -0.63)	Very low
Meglitinides	-0.71 (-1.24 to -0.18)	-0.64 (-0.93 to -0.37)	
TZDs	-0.96 (-1.18 to -0.75)	-0.82 (-1.00 to -0.66)	
DPP-4 inhibitors	-0.78 (-0.96 to -0.60)	-0.80 (-0.95 to -0.65)	
alpha-glucosidase inhibitors	-0.74 (-0.94 to -0.53)	-0.74 (-0.98 to -0.50)	
GLP-1 analogues	-0.75 (-0.96 to -0.53)	-0.82 (-1.05 to -0.59)	
Basal insulin	NA	-0.82 (-1.16 to -0.47)	
Biphasic insulin	NA	-0.97 (-1.33 to -0.61)	
Overall Hypoglycemia (odds ratio)			
Treatment versus Metformin Monotherapy	**Direct Estimates WMD (95% CI)**	**MTC Estimates Median OR (95% CrI)**	**Quality of Evidence**
Sulfonylureas	4.64 (1.27 to 16.97)	8.22 (4.52 to 16.63)	Very low
Meglitinides	6.59 (1.53 to 28.29)	8.59 (3.47 to 25.20)	
TZDs	1.56 (0.56 to 4.33)	1.10 (0.54 to 2.27)	
DPP-4 inhibitors	1.07 (0.59 to 1.93)	1.05 (0.56 to 2.21)	
alpha-glucosidase inhibitors	0.49 (0.04 to 5.55)	0.39 (0.01 to 6.67)	
GLP-1 analogues	1.00 (0.31 to 3.20)	1.12 (0.33 to 3.90)	
Basal insulin	NA	5.20 (1.48 to 21.46)	
Biphasic insulin	NA	11.01 (3.48 to 40.43)	
Body Weight (change from baseline, kg)			
Treatment versus Metformin Monotherapy	**Direct Estimates WMD (95% CI)**	**MTC Estimates (95% CrI)**	**Quality of Evidence**
Sulfonylureas	1.79 (1.29 to 2.28)	2.01 (1.09 to 2.94)	Very low
Meglitinides	2.01 (-0.31 to 4.32)	1.80 (0.35 to 3.29)	
TZDs	2.30 (1.93 to 2.66)	2.59 (1.66 to 3.51)	
DPP-4 inhibitors	0.70 (0.20 to 1.21)	0.57 (-0.45 to 1.60)	
alpha-glucosidase inhibitors	-0.90 (-1.92 to 0.13)	-0.92 (-2.35 to 0.51)	
GLP-1 analogues	-1.58 (-3.53 to 0.37)	-1.79 (-3.43 to -0.14)	
Basal insulin	NA	1.56 (-0.46 to 3.63)	
Biphasic insulin	NA	2.96 (0.96 to 5.00)	

CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; MTC = mixed treatment comparison; NA = not available; OR = odds ratio; TZD = thiazolidinediones; WMD = weighted mean difference.

Table A2: Results for Long-Term Complications of Diabetes			
Comparison	**Number of Trials (total N)**	**OR (95% CI)**	**Quality of Evidence**
Ischemic Heart Disease			
TZDs versus sulfonylureas	1 RCT[92] (N = 630)	2.97 (0.12 to 73.22)	Very Low
alpha-glucosidase inhibitors versus placebo	1 RCT[93] (N = 153)	0.32 (0.01 to 7.89)	Low
Sulfonylureas versus meglitinides	1 RCT[94] (N = 213)	0.18 (0.01 to 3.73)	Low
Sulfonylureas versus DPP-4 inhibitors	1 RCT[95] (N = 1,135)	0.14 (0.01 to 2.68)	Very Low
DPP-4 inhibitors versus placebo	1 RCT[96] (N = 190)	3.10 (0.12 to 76.97)	Very Low
DPP-4 inhibitors versus TZDs	1 RCT[97] (N = 575)	1.05 (0.07 to 16.93)	Very Low
Congestive Heart Failure			
TZDs versus sulfonylureas	1 RCT[98] (N = 630)	2.49 (0.48 to 12.94)	Low
DPP-4 inhibitors versus sulfonylureas	1 RCT[99] (N = 2,789)	1.00 (0.14 to 7.09)	Very Low
DPP-4 inhibitors versus TZDs	1 RCT[100] (N = 575)	No events	Very Low
alpha-glucosidase inhibitors versus Placebo	1 RCT[93] (N = 153)	0.32 (0.01 to 7.89)	Low
Macular Edema			
TZDs versus sulfonylureas	1 RCT[101] (N = 2,222)	No events	Very Low
Mortality			
TZD versus sulfonylureas	1 RCT[92] (N = 630)	0.20 (0.01 to 4.10)	Very Low
DPP-4 inhibitors versus placebo	3 RCTs[96,102,103] (N = 1,117)	0.22 (0.02 to 2.16)	Very Low
DPP-4 inhibitors versus sulfonylureas	2 RCTs[95,99] (N = 3,924)	0.59 (0.14 to 2.50)	Very Low
TZD versus placebo	1 RCT[104] (N = 223)	No events	Low
alpha-glucosidase inhibitors versus placebo	1 RCT[105] (N = 152)	No events	Very Low
Meglitinides versus sulfonylureas	1 RCT[94] (N = 213)	No events	Low
BIAsp 30 versus Sulfonylureas	1 RCT[106] (N = 222)	3.20 (0.13 to 79.29)	Low
TZD versus DPP-4 inhibitors	1 RCT[107] (N = 2,627)	6.05 (0.25 to 148.75)	Very Low
Neuropathy			
DPP-4 inhibitors versus placebo	1 RCT[96] (N = 190)	2.00 (0.36 to 11.19)	Very Low
Peripheral vascular disease			
Sulfonylureas versus DPP-4 inhibitors	1 RCT[99] (N = 2,789)	0.33 (0.01 to 8.17)	Very Low
Stroke/Transient Ischemic Attack			
Sulfonylureas versus DPP-4 inhibitors	1 RCT[99] (N = 2,789)	0.07 (0.00 to 1.16)	Very Low
TZDs versus DPP-4 inhibitors	1 RCT[97] (N = 575)	3.18 (0.33 to 30.79)	Very Low

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; OR = odds ratio; PVD = peripheral vascular disease; RCT = randomized controlled trial; TIA = transient ischemic attack; TZD = thiazolidinediones.

Summary of Cost-Effectiveness Evidence

Table A3: Comparison of Prices of Treatments with and without the Cost of Blood Glucose Test Strips				
Class	**Agent**	**Dose**	**Estimated Price per Day**	
			Without Test Strips ($)	**With Test Strips ($)**
Metformin	Apo-metformin	500 mg four times daily	0.50	1.24
Sulfonylurea	Apo-glyburide	5 mg twice daily	0.73	1.64
Meglitinides	Rapeglinide	2 mg twice daily	1.28	2.20
Thiazolidinediones	Apo-pioglitazone	30 mg once daily	3.00	3.74
DPP-4 inhibitors	Sitagliptin	100 mg once daily	3.38	4.13
alpha-glucosidase inhibitors	Acarbose	100 mg three times daily	1.76	2.50
Basal insulin	Humulin N	0.75 U per kg per day	1.95	3.60
Biphasic insulin	Novolin ge 30/70 penfill	1.50 U per kg per day	3.81	5.45

DPP-4 = dipeptidyl peptidase-4.

Table A4: Total Costs, QALYs, and Incremental Cost-Effectiveness Results (reference case analysis)			
Treatment	**Average Costs Incurred During Lifetime ($)**	**Average QALYs Gained During Lifetime**	**Incremental Cost-Effectiveness Results**
Metformin	39,924	8.7194	NA (reference category)
Sulfonylurea	40,669	8.7777	$12,757 per QALY (relative to metformin)
alpha-glucosidase inhibitors	42,797	8.7800	$939,479 per QALY (relative to sulfonylureas)
Thiazolidinediones	46,202	8.7807	$4,621,828 per QALY (relative to α-glucosidase inhibitors)
Meglitinides	42,269	8.7682	Dominated by sulfonylureas
DPP-4 inhibitors	47,191	8.7795	Dominated by thiazolidinediones
Basal insulin	47,348	8.7686	
Biphasic insulin	52,367	8.7761	

DPP-4 = dipeptidyl peptidase-4; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX C: DETAILED CERC PROCESS

The steps that CERC followed for generating Optimal Therapy Recommendations are presented here.

1. Individual review of GRADE evidence profiles and provision of initial feedback

CERC members were provided with the GRADE evidence profiles in an online format. Members completed a form designed to elicit feedback on the available evidence and its quality, values and preferences, and possible Clinical Notes and Context statements. Feedback was collated and provided to the committee.

2. Preparatory work prior to the identification of draft Optimal Therapy Recommendations

CERC members discussed through teleconference the clinical and cost-effectiveness evidence presented in the GRADE evidence profiles as well as the collated feedback from individual members. After the teleconference, and the face-to-face meeting to develop recommendations, members were asked to complete a second feedback form. This form was populated based on the results of individual feedback and committee discussion at the teleconference. It contained draft versions of the recommendation, values and preferences, Clinical Notes, and Context. Members were asked to indicate the level of agreement with the items in the form and to suggest any additional considerations. Individual feedback was collated and provided to CERC before the face-to-face meeting.

3. Identification of draft Optimal Therapy Recommendations

At the face-to-face meeting to develop draft Optimal Therapy Recommendations, CERC discussed collated comments from the second round of feedback. Any outstanding issues with respect to the evidence, values and preferences, or other considerations were clarified. CERC then proceeded to vote on the following items (in the order presented):

1) *Overall quality of the available evidence (clinical and economic):* Possible ratings were "high," "moderate," and "low." This rating was based on an assessment of evidence quality across all outcomes considered "important" or "critical" by CERC. Where evidence was lacking for such outcomes, an overall rating of "low" was more likely, regardless of the quality of evidence for outcomes reported in studies.

2) *Identification of values and preferences:* Members were asked to identify the two most important values and preferences underlying their selection of the optimal second-line therapy for most patients with type 2 diabetes inadequately controlled on metformin.

Voting on the draft Optimal Therapy Recommendation:
After discussion and refinement of the draft recommendation presented in the second feedback form, CERC members voted on the recommendation.

Voting was conducted by secret ballot. Quorum consisted of a minimum of five core CERC members and 50% of the committee members appointed as clinical experts in the management of diabetes. A majority vote was sufficient for a draft recommendation to be accepted. Each vote concluded with a committee discussion on the vote results in which members were given an opportunity to discuss factors behind their individual votes. Draft

recommendations could be edited by CERC during these deliberations, however, a revote was required for substantive changes.

4. Grading strength of recommendations

The final step in the GRADE methodology is assigning a strength of either "strong" or "weak" to each recommendation. This rating is intended to convey the degree of confidence the committee has that adherence to the recommendation will result in the desired outcome.[49] As stipulated by the GRADE process, recommendation strength is reflected by use of the words "suggests" or "recommends" (i.e., for weak recommendations, "CERC suggests that …" and for strong recommendations, "CERC recommends that …").

According to the GRADE Working Group, the rating of strength has implications for how users interpret a recommendation.[49]

A "strong" recommendation:

- is likely to be followed by most well-informed patients
- is unlikely to require decision aids to elicit patient values and preferences
- can often be implemented as policy.

A "weak" recommendation:

- is likely to be followed by the majority of well-informed patients; however, a significant minority would choose not to follow the recommendation
- requires careful consideration of patient values and preferences; decision aids may be helpful in determining the course of action
- is likely to require debate and the involvement of multiple stakeholders before policy can be determined.

Once draft Optimal Therapy Recommendations were identified, a proposed rating of strength (i.e., either "strong" or "weak") was assigned to each recommendation. Four questions put forward by the GRADE Working Group as points of consideration when evaluating recommendation strength were used as a guide:

- Is the available evidence of lower quality?
- Is there uncertainty regarding the balance of benefits versus harms and burdens?
- Is there uncertainty or are there differences in values and preferences?
- Is there uncertainty about whether or not the net benefits are worth the costs?

An affirmative answer to one or more of these questions increased the likelihood that a recommendation was downgraded to "weak."

CERC members discussed their agreement with the proposed strength and rationale for the rating and voted on their level of agreement.

5. Identification of research gaps

Where there was insufficient information upon which to produce Optimal Therapy Recommendations, CERC identified "gaps" in research and knowledge. These consisted of populations, treatment comparisons, and outcomes of clinical interest for which evidence was insufficient.

APPENDIX D: ABBREVIATIONS

A1C	glycosylated hemoglobin
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MTC	mixed treatment comparison
TZD	thiazolidinediones

APPENDIX E: GLOSSARY

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

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

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

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

Diabetes: A group of common metabolic disorders characterized by hyperglycemia and caused by insufficient insulin secretion, reduced insulin sensitivity of target tissues, or both.

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

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

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

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

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

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

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

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

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

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

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