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Challenges to managing type 2 diabetes in British Columbia: Discordant guidelines and limited treatment options

Contradictory recommendations and formulary restrictions make it difficult for BC physicians to manage their patients with diabetes using the most robust and up-to-date evidence.

ABSTRACT: Type 2 diabetes is a common metabolic condition that requires a multifaceted approach to reduce associated complications. Management is challenging because of the progressive nature of the condition and the growing availability of different classes of antihyperglycemic agents. Unfortunately, general practitioners and specialists looking for guidance in the complex pharmacological management of type 2 diabetes in BC can find themselves frustrated by contradictory recommendations from these three bodies: Diabetes Canada, the British Columbia Guidelines and Protocols Advisory Committee, and the Therapeutics Initiative. These three bodies differ in composition and the methodology that they use to prepare recommendations. Diabetes Canada is a national organization supporting a large number of volunteers from many health professions as they develop clinical practice guidelines. The Guidelines and Protocols Advisory Committee consists of representatives from the Ministry of Health and Doctors of BC who oversee working groups that develop BC-specific guidelines on important clinical topics, including diabetes care. The Therapeutics Initiative is an organization funded by the Ministry of Health and the University of British Columbia that completes assessments of drug therapy and publishes the findings in bulletin form. Receiving conflicting information is difficult for physicians and can result in a wide variability in quality of care, as well as clinical inertia, such as failure to implement or intensify a beneficial therapy. Furthermore, despite growing evidence of significant clinical benefits for many diabetes drugs, most require special authority approval or, in the case of newer agents, are not covered at all by BC Pharmacare, which makes it difficult for physicians to manage their patients with diabetes using the most up-to-date and robust evidence.

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Diabetes is a chronic metabolic disease that is becoming more common in British Columbia, with predicted prevalence rates rising from 8.3% in 2013 to 10.3% in 2020.[1] The complications of diabetes contribute significantly to morbidity and mortality, and increase the cost burden to patients, our medical system, and society as a whole.[2,3] Primary care physicians manage the majority of people living with diabetes, and more than 20% of a typical physician's caseload will likely involve caring for people with either diabetes or prediabetes.[4] Not only is the prevalence of diabetes increasing,[5] but the management of patients with diabetes is becoming more complicated as patients live longer and require additional care for frailty and comorbid conditions. There are now nine classes of antihyperglycemic agents, which often need to be used in combination owing to the progressive nature of diabetes,[6,7] a situation that increases the complexity of therapeutic decision making.

Diabetes requires a multifaceted approach to reduce both microvascular and macrovascular complications.[8] Glycemic control is an important risk factor for microvascular disease, including retinopathy, nephropathy, and peripheral neuropathy.[9-13] Early improved glucose control slows progression to these endpoints.[9,14-17] An association between macrovascular disease and aggressive glycemic control is less clear.[16,18,19] Cardiovascular (CV) benefit, most likely from better glucose control, has been seen in long-term (10- to 20-year) observational studies such as EDIC,[20] long-term follow-up of the UKPDS,[21] and a subset of VADT (although no overall survival benefit was seen in this group with established cardiovascular disease),[22] suggesting that good glycemic control achieved with less hypoglycemia, if initiated early in the course of the disease, reduces long-term CV risk.

Worldwide, clinical practice guidelines based on the best available evidence support the use of antihyperglycemic agents to reduce the risk of long-term complications of diabetes.[2,23-25] In large, randomized controlled CV safety studies, agents such as empagliflozin,[26] liraglutide,[27] semaglutide,[28] and canagliflozin[29] have demonstrated CV benefits. Conflicting information regarding appropriate use of these and other antihyperglycemic agents can confuse physicians and may result in widely variable quality of care as well as clinical inertia, which can mean physicians fail to implement or intensify a beneficial therapy.

Recommendations issued by the TI are notable for not aligning with those of other bodies.

Sources of recommendations

British Columbia physicians' management of diabetes is guided by recommendations from three principle sources:

- Diabetes Canada (DC), formerly known as the Canadian Diabetes Association, which publishes clinical practice guidelines for the prevention and management of diabetes in Canada[2,3] and updates these as necessary.[23]
- The Guidelines and Protocols Advisory Committee (GPAC), which publishes clinical practice guidelines for use in BC on many topics, including diabetes care.[30]
- The Therapeutics Initiative (TI), which publishes recommendations regarding drug therapy for managing diabetes in their regular Therapeutics Letters.[31]

Table 1 summarizes the composition and methodology of the bodies and shows how they vary in their guideline development and publishing processes. The recommendations produced by all three are widely disseminated.

Diabetes Canada

In 1998 the Canadian Diabetes Association published one of the first evidence-based guidelines for the management of diabetes in Canada.[32] In this and subsequent publications an independent expert committee developed and graded recommendations based on the quality of evidence from key studies. Updates were published in 2003, 2008, 2013, and 2018.[3] These guidelines are ranked among the best in the world with respect to quality, rigor, and process[33] as assessed using the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation).[34] Each recommendation addresses a clinically important question related to the management of diabetes and its sequelae. Health benefits of interventions as well as risks and side effects are considered in formulating the recommendations. Patient preferences and values are considered by consulting people with diabetes and reviewing the literature. Each recommendation is justified using the strongest clinically relevant, empirical evidence that can be identified. Sources of evidence are cited and the strength of this evidence is indicated based on criteria from the epidemiological

	Diabetes Canada (DC)	Guidelines and Protocols Advisory Committee (GPAC)	Therapeutics Initiative (TI)
Composition of body	• The 2013 clinical practice guidelines were developed with the active participation of 120 volunteers. • Authors and reviewers of DC guidelines include health professionals from family medicine, endocrinology, internal medicine, and other specialties, nursing, dietetics, pharmacy, and exercise physiology, as well as people with diabetes.	• The 2015 diabetes care guideline was developed by a working group led by a physician chair and supported by a Ministry of Health research officer. • GPAC working groups include general practitioners, specialists, and other subject matter experts, as well as a government-employed pharmacist.	• Since 1994 Therapeutics Letters have been published regularly to identify "problematic" issues and provide "brief, simple, practical messages."[31] • Working groups have authored these letters under the guidance of the TI executive, which includes five physicians and five nonphysicians, including academics specializing in pharmacology.
Scope of recommend-ations	• Prevention and management of type 1 diabetes, type 2 diabetes, gestational diabetes mellitus. • Macrovascular and microvascular complications. • Organization of care and self-management education. • Diabetes in special populations.	• Epidemiology and prevention. • Management of type 1 and type 2 diabetes in adults, including complications. • BC-specific topics (e.g., Pharmacare coverage, Pharmacare special authority process).	• Prescription drug therapies. • Laboratory testing considered on occasion.
Authors identified	• Yes.	• No. • In future, "lists of contributors may be published on the website."[36]	• No.
Disclosures published	• Yes.	• Conflict of interest must be disclosed, but is not published. • In future, disclosures will be published (personal conversation between Dr Clement and Ministry of Health).	• Yes for TI members in general. • No for authors of Therapeutics Letters.
Committee members remunerated	• No, except for the hourly stipend paid to members of the Independent Methods Review Committee, who are physicians with expertise in appraising evidence and have no conflicts of interest.	• Committee and working group members receive payment through the Ministry of Health and Doctors of BC for the hours they spend performing GPAC business.	• Employed TI members receive a salary from the University of British Columbia supported by a Ministry of Health grant.
Literature review conducted	• Yes. • Full systematic literature review conducted based on clinically relevant questions.	• No. • Although a full systematic literature review is not conducted, guideline authors quote extensively from DC recommendations, which are based on a literature review.	• Yes. • The TI publication process "involves a literature review,"[31] but no details are provided. • Previous Therapeutics Letters and review articles are often cited.
Recommend-ations graded	• Yes. • Each recommendation is assigned a grade based on the available evidence, its methodological strength, and its applicability to the Canadian population. • Each recommendation is approved by the Steering Committee and Executive Committee, with 100% consensus required.	• No statement is provided about levels of evidence or grading of recommendations. • References are provided.	• No process for assessing evidence and grading recommendations is identified or declared. • References are provided for some statements.
Frequency of publication and methodology for updates	• A major rewrite is scheduled every 5 years. • Interim updates with independent medical review are completed when important new trial evidence is published.	• Each guideline is reviewed every 3 to 5 years.	• Therapeutics Letters tend to be published in response to a topic of discussion or controversy and when there is a potential for cost to the medical system. • No schedule of topics is published.
Independent methodological review conducted	• Yes.	• No.	• No.
Peer review conducted	• Clinical practice guidelines are sent to national and international reviewers by the publisher, Elsevier, as part of a standard peer-review process.	• Guidelines are sent for review, but not as part of a true peer-review process.	• Therapeutics Letters are sent for review, but not as part of a true peer-review process since the authors are the editor and the reviewers do not have the ability to request rewrites.

Table 1. Comparison of three bodies issuing diabetes management recommendations.

literature and other guidelines processes. Recommendations based on biological or mechanistic reasoning, expert opinion, or consensus are explicitly identified and graded as such. Finally, harmonization is sought with guidelines issued by other bodies, including the Canadian Cardiovascular Society, the Canadian Hypertension Education Program, the Canadian Cardiovascular Harmonization of National Guidelines Endeavour, and the Society of Obstetricians and Gynecologists of Canada.

Guidelines and Protocols Advisory Committee

The Guidelines and Protocols Advisory Committee consists of representatives from the BC Ministry of Health and Doctors of BC. The committee advises the Medical Services Commission regarding both the effective utilization of medical services and high-quality, appropriate patient care,[35,36] and oversees a number of working groups responsible for developing guidelines and protocols on almost 100 topics (see www.bcguidelines.ca). The diabetes care guideline does not include an independent literature review but instead relies heavily on existing documents, including the Diabetes Canada clinical practice guidelines. The diabetes care guideline also addresses circumstances in BC and includes BC-specific information such as Medical Service Plan billing rules and incentive fees, lab test availability, Pharmacare coverage, referral pathways, and local resources. A handbook outlining the process for guideline development indicates that "For guidelines published after 2014, lists of contributors may be published on the website."[36]

Therapeutics Initiative

The Therapeutics Initiative was established in 1994 by the Department of Pharmacology and Therapeutics in cooperation with the Department of Family Practice at the University of British Columbia "to provide physicians, pharmacists, allied health professionals and the public with up-to-date, evidence-based, practical information on prescription drug therapy."[31] Funding is provided by the BC Ministry of Health through a grant to UBC. Four TI working groups are engaged in the development of recommendations that are published bimonthly in Therapeutics Letters and distributed as unsolicited mail to physicians and pharmacists in BC. Each letter commonly focuses on adverse outcomes found in trials as opposed to the primary or secondary objectives of the trials reviewed. Authors of the letters are not named and there is no stated methodology for literature selection or review or grading of recommendations, nor a predefined schedule for discussion of specific therapeutic areas. Since 2010, 18 drugs or classes of drugs have been reviewed in detail in 27 Therapeutics Letters and only one drug has been given a full recommendation (intravenous iron in appropriately selected people with chronic severe iron deficiency).[37]

Recommendations compared

Both Diabetes Canada and the Guidelines and Protocols Advisory Committee identify a process, structure, and timeline for their work in advance. The recommendations produced by both are more comprehensive in scope than those of the Therapeutics Initiative, which focuses mainly on drug therapies and aims to "improve prescription habits."

The composition of DC guidelines committees is broad-based and interprofessional, including people with diabetes as well as experts in various specialties from across Canada. The GPAC working groups responsible for developing guidelines are smaller than the DC committees, but also include medical experts and a Pharmacare pharmacist. The members of TI working groups include salaried employees and other health care professionals and academics who are identified on the organization's website. While the authors of DC guidelines are named, authors of GPAC guidelines and Therapeutics Letters are not.

Recommendations issued by the TI are notable for not aligning with those of other bodies, while recommendations issued by DC and GPAC align closely with American and European guidelines for diabetes management[24,25] and those of the United Kingdom's National Institute for Health and Care Excellence (NICE), which produces the only guidelines to receive a higher rating than the DC diabetes guidelines[33] and is cited in one Therapeutics Letter as a source of "independent information."[38]

DC, GPAC, and these international bodies recommend monitoring patients with diabetes using a glycated hemoglobin (HbA1c) level, and that the target A1c should be individualized, with a reasonable level for most adults being less than 7.0% and a target for those who are younger being 6.5% so they may benefit from more years of excellent glycemic control to avoid microvascular complications. Algorithms in DC, GPAC, and other international guidelines provide diabetes care teams with direction for management. No such direction is provided by the TI other than a preference for lifestyle intervention: "While we await the trial evidence, it is rational to emphasize lifestyle measures in these patients: weight loss, low carbohydrate diets and exercise."[39] This recommendation is made despite the statement in another

Therapeutics Letter that "weight loss is difficult to maintain"[40] and a lack of any references to support emphasizing "low carbohydrate diets," which a literature review by Diabetes Canada found no evidence to support.[3] In the comments section of the TI website, a request for clarification regarding exactly what kind of carbohydrates such a diet would include is answered as follows: "We [the TI] are not experts on evidence about diet" (reply to Dr Virendra Sharma by Thomas L. Perry, MD, FRCPC, Chair, TI Education Working Group, 21 March 2017, 9:05 p.m.).

BC Pharmacare coverage

The most recent Diabetes Canada clinical practice guidelines recommend that antihyperglycemic agents should be chosen based on both patient and agent characteristics.[2,3] While all agents named by DC have been evaluated and approved for use in Canada, in BC only a few (generally older and less-expensive agents such as glyburide, metformin, and human insulins) are fully covered under the provincial formulary.[41] This makes it much more difficult for physicians to use up-to-date evidence when managing their patients with diabetes.

Table 2 and **Table 3** illustrate the extent to which BC restricts Pharmacare coverage compared with three other provinces: Alberta and Ontario (each historically considered a have province) and Nova Scotia (considered

Clinical priority	Therapy recommended by Diabetes Canada	British Columbia	Alberta	Ontario	Nova Scotia
At diagnosis					
A1c < 8.5%	Lifestyle intervention	n/a	n/a	n/a	n/a
First-line agents to consider based on clinical priority and patient characteristics					
A1c ≥ 8.5%	Metformin (Glucophage, Glumetza)	L	L	L	L
A1c ≥ 8.5%	Metformin + another agent	See second-line options below			
Symptomatic hyperglycemia with metabolic decompensation	Insulin ± metformin	See listings for insulin in Table 3			
Second-line options to consider based on clinical priority and patient characteristics when glycemic target is not reached after 2–3 months					
Clinical cardiovascular disease	Empagliflozin (Jardiance)	NL	R	L	R
	Liraglutide (Victoza)	NL	NL	NL	NL
Hypoglycemia risk	**DPP-4 inhibitors**				
	Alogliptin (Nesina)	NL	NL	NL	NL
	Linagliptin (Trajenta)	R	R	L	R
	Sitagliptin (Januvia)	DL	R	L	R
	Saxagliptin (Onglyza)	R	R	L	R
	GLP-1 receptor agonists				
	Albiglutide (Eperzan)	NL	NL	NL	NL
	Exenatide (Byetta)	NL	NL	NL	NL
	Liraglutide (Victoza)	NL	NL	NL	NL
	Dulaglutide (Trulicity)	NL	NL	NL	NL
	Semaglutide (Ozempic)	NL	NL	NL	NL
	SGLT2 inhibitors				
	Canagliflozin (Invokana)	NL	R	L	R
	Dapagliflozin (Forxiga)	NL	R	L	R
	Empagliflozin (Jardiance)	NL	R	L	R
	TZDs				
	Pioglitazone (Actos)	R	R	L	R
	Rosiglitazone (Avandia)	DL	R	NL	NL

Table 2. Formulary listings in BC and selected provinces for therapy recommended by Diabetes Canada. *(Table continued on next page.)*

See next page for legend.

(Table continued from previous page.)

Clinical priority	Therapy recommended by Diabetes Canada	British Columbia	Alberta	Ontario	Nova Scotia
Second-line options to consider based on clinical priority and patient characteristics when glycemic target is not reached after 2–3 months (Continued)					
Weight gain risk	**GLP-1 receptor agonists**				
	Albiglutide (Eperzan)	NL	NL	NL	NL
	Exenatide (Byetta)	NL	NL	NL	NL
	Liraglutide (Victoza)	NL	NL	NL	NL
	Semaglutide (Ozempic)	NL	NL	NL	NL
	SGLT2 inhibitors				
	Canagliflozin (Invokana)	NL	R	L	R
	Dapagliflozin (Forxiga)	NL	R	L	R
	Empagliflozin (Jardiance)	NL	R	L	R
	Alpha-glucosidase inhibitor				
	Acarbose (Glucobay)	DL	L	R	L
Relative A1c lowering	**DPP-4 inhibitors**				
	Alogliptin (Nesina)	NL	NL	NL	NL
	Linagliptin (Trajenta)	R	R	L	R
	Sitagliptin (Januvia)	DL	R	L	R
	Saxagliptin (Onglyza)	R	R	L	R
	GLP-1 receptor agonists				
	Albiglutide (Eperzan)	NL	NL	NL	NL
	Exenatide (Byetta)	NL	NL	NL	NL
	Liraglutide (Victoza)	NL	NL	NL	NL
	Dulaglutide (Trulicity)	NL	NL	NL	NL
	Semaglutide (Ozempic)	NL	NL	NL	NL
	Insulin (see Table 3)				
	Insulin secretagogues				
	Gliclazide (Diamicron, Diamicron MR)	R	L	L	L
	Glimperide (Amaryl)	NL	NL	L	NL
	Glyburide (Diabeta, Euglucon)	L	L	L	L
	Repaglinide (GlucoNorm)	NL	L	L	NL
	SGLT2 inhibitors				
	Canagliflozin (Invokana)	NL	R	L	R
	Dapagliflozin (Forxiga)	NL	R	L	R
	Empagliflozin (Jardiance)	NL	R	L	R
	TZDs				
	Pioglitazone (Actos)	R	R	L	R
	Rosiglitazone (Avandia)	DL	R	NL	NL

Table 2 (Continued). Formulary listings in BC and selected provinces for therapy recommended by Diabetes Canada.

Adapted from Diabetes Canada. Formulary listings for diabetes medications in Canada. April 2018[41]

L = listed. Can be prescribed by any doctor. Cost will be fully or partially covered according to the terms of the public drug plan.
R = restricted. Only available to those who meet eligibility criteria and received prior approval from the drug benefit plan. Cost will be fully or partially covered according to the terms of the public drug plan.
NL = not listed. Not available through the public drug plan.
DL = delisted. Product has been removed from the formulary and is no longer available.

Insulin (Brand name)	British Columbia	Alberta	Ontario	Nova Scotia
Bolus (prandial) insulins				
Aspart (NovoRapid/Novolog)	L*	L	R	L
Glulisine (Apidra)	L*	L	L	L
Lispro (Humalog)	L*	L	L	R†
Short-acting insulins				
Regular (Humulin-R, Novolin ge Toronto)	L	L	L	L
Pork regular insulin (Hyperpurin Regular)	R	NL	NL	NL
Basal insulins: Intermediate-acting regular				
NPH (Humulin-N, Novolin ge NPH)	L	L	L	L
Basal insulins: Long-acting analogues				
Detemir (Levemir)	R	L	L	R
Glargine (Lantus)	R‡	L	L	R
Glargine 300 (Toujeo)	NL	NL	NL	NL
Glargine SEB (Basaglar)	R‡	L	L	L
Degludec (Tresiba)	NL	NL	NL	NL
Pork isophane insulin (Hypurin NPH)	R	NL	NL	NL
Premixed insulins				
Premixed regular-NPH (Humulin 30/70, Novolin 30/70, 40/60, 50/50)	L	L	L	L
Biphasic insulin aspart (NovoMix 30)	L*	NL	L	NL
Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix 50)	L*	L	L	NL

Table 3. Formulary listings in BC and selected provinces for insulin.

Adapted from Diabetes Canada. Formulary listings for diabetes medications in Canada. April 2018.[41]

L = listed. Can be prescribed by any doctor. Cost will be fully or partially covered according to the terms of the public drug plan.
R = restricted. Only available to those who meet eligibility criteria and received prior approval from the drug benefit plan. Cost will be fully or partially covered according to the terms of the public drug plan.
NL = not listed. Not available through the public drug plan.
SEB = subsequent-entry biologic.

*Partial reimbursement provided for rapid-acting insulins; patients must pay the difference.
†Full benefit provided for children 18 years and younger.
‡As of 21 August 2018, Pharmacare offers restricted coverage for Basaglar brand of insulin glargine only. Patients starting insulin glargine will no longer be provided coverage for Lantus (www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/newsletters/news18-011.pdf).

a have-not province). Although drug evaluation is now performed nationally by the Common Drug Review and the Canadian Agency for Drugs and Technologies in Health (CADTH), it appears that recommendations from the TI rather than those from the much more robust DC guidelines are determining BC Pharmacare policy. BC is the only province to require special authority for gliclazide (for use after hypoglycemia with glyburide),[41,42] and is the only province to not list empagliflozin. The rejection of empagliflozin appears to be influenced largely by cost and supported by the TI's criticisms of the EMPA-REG OUTCOME trial.[43] These criticisms, however, do not accord with most interpretations of the trial and other recent CV safety trials[26-29] such as the LEADER trial of liraglutide,[27] which demonstrated benefit for people with type 2 diabetes and clinical cardiovascular disease.

As a result of TI conclusions, BC residents with diabetes are at a disadvantage when compared with Canadians in other jurisdictions. Essentially, BC has become a have-not province for people with diabetes, a problem likely to worsen as the rates of diabetes in BC continue to rise.[44]

Key recommendations considered

Clear, high-quality, evidence-based recommendations are the cornerstone of medical training and subsequent decision making for health care providers. Physicians and patients expect and deserve the best care possible based on transparent processes and unbiased sources.

In BC, comparing key recommendations on important clinical issues such as A1c targets and pharmacological therapy[45-55] reveals significant discord. The TI is at odds with DC and GPAC on a number of topics, as shown in **Table 4**. In an example regarding cardiovascular outcomes and the use of empagliflozin, the Therapeutics Letter of July/August 2017 disputes the conclusions of the EMPA-REG OUTCOME trial.[43] The TI authors question the design of the trial, which is one mandated by the FDA, and the "aggressive" use of insulin, sulfonylureas, and DPP4s in the control group, which are the very medications BC Pharmacare covers. The TI authors also focus on genital infections experienced by some study subjects, and emphasize these harms in a table. Despite these concerns, the Therapeutics Letter of September/October 2017 names canagliflozin and dapagliflozin as "drugs to avoid"[55] but does not name empagliflozin.

Contradictory recommendations serve to confuse medical care providers, and restrictive Pharmacare coverage only adds to this confusion and promotes clinical inertia. A recent evidence-based review of formulary coverage for diabetes and cardiovascular disease concluded that glucose-lowering agents that reduce mortality in patients at very high cardiovascular risk are now available, and that empagliflozin has been shown to be highly cost-effective. The authors urge all provincial formularies to "re-examine their access requirements

	Diabetes Canada (DC)	Guidelines and Protocols Advisory Committee (GPAC)	Therapeutics Initiative (TI)
A1c targets	• Target levels for A1c should be individualized. • A1c ≤ 7.0% recommended for most individuals. • A1c ≤ 6.5 in some patients with type 2 diabetes may further lower the risk of nephropathy[16] (Grade A, Level 1 recommendation) and retinopathy[17] (Grade A, Level 1), but this must be balanced against the risk of hypoglycemia[16] (Grade A, Level 1). • Less-stringent A1c targets of 7.1%–8.5% may be appropriate in patients with limited life expectancy; high level of functional dependency; extensive coronary artery disease at high risk of ischemic events; multiple comorbidities; history of recurrent severe hypoglycemia; hypoglycemia unawareness; longstanding diabetes for whom it is difficult to achieve an A1c ≤ 7.0% despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy (Grade D, Consensus for all).	• Recommendations for A1c align with DC.	• No upper or suggested A1c level for treatment recommended: "The optimal glycemic target in patients with type 2 diabetes is unknown."[49] • "A glycemic target of < 6.0% compared to a target of 7.0% to 7.9% caused increased mortality in type 2 diabetics who were at high risk of cardiovascular events."[49] • "Most commonly used surrogate markers have not been proven to be consistently predictive of morbidity or mortality risk thus their use in risk calculators is questionable."[50] • "Relying on surrogate markers to assess effectiveness of drug therapy has not been proven to yield clinically meaningful benefits and there are important examples where that strategy was harmful."[50] • "Additional RCTs that test specific glycemic targets are needed for the full spectrum of patients with type 2 diabetes."[49] • "The current regulatory framework for glucose lowering drugs that bases benefit on lowering HbA1c and bases harms on not increasing specific cardiovascular outcomes requires rethinking."[54]
Lifestyle intervention	• Recommends starting lifestyle intervention at the time of diagnosis and continuing alongside pharmacological management. • Guidelines include 5 physical activity recommendations and 13 nutrition recommendations.	• Recommendations for lifestyle intervention align with DC.	• Recommends lifestyle intervention as opposed to pharmacological management: "Type 2 diabetes management should focus on weight management, appropriate nutrition, regular physical activity and blood pressure control, rather than intensive glucose lowering treatment."[51] • "Exercise and weight loss are effective in treating type 2 diabetes."[40]

Table 4. Key recommendations issued by three bodies for the management of type 2 diabetes. *(Table continued on next page.)*

(Table continued from previous page.)

	Diabetes Canada (DC)	Guidelines and Protocols Advisory Committee (GPAC)	Therapeutics Initiative (TI)
Pharmacological therapy	• Treatment algorithm provided. • Individualized therapy recommended. • Recommends adding second- and third-line agents to metformin according to agent and patient characteristics and continuing until A1c target reached.[23] • Lists each class of medication with effect on A1c lowering, hypoglycemia, weight, cardiovascular outcome, and cost. **Sulfonylureas** • Gliclazide reported to cause less hypoglycemia than glyburide, especially in the elderly. In general, initial doses of sulfonylureas in the elderly should be half of those used for younger people, and doses should be increased more slowly (Grade D, Consensus). • Gliclazide[45] and gliclazide[46] MR (Grade B, Level 2) and glimepiride[47] (Grade C, Level 3) should be used instead of glyburide, as they are associated with a reduced frequency of hypoglycemic events. • No specific preferred second-line agents are recommended except in cases of clinical cardiovascular disease, where the preferred second-line agent is empagliflozin or liraglutide.[23]	• Treatment algorithm provided. • Recommendations for treatment align with DC 2013 guidelines published prior to the November 2016 update.[23] **Sulfonylureas** • Risk of hypoglycemia depends on agent (more risk with glyburide). • "Controversies in Care" section mentions data linking sulfonylureas with cardiovascular harm, but concludes that "At present, there is a lack of evidence clearly demonstrating cardiovascular harm."[30]	• No treatment algorithm provided. • No recommendations regarding which medications to use, when to use them, and in which patient populations. • Therapeutics Letter of March 2017 states that "glucocentric" approach to type 2 diabetes "may be misguided" and quotes from a study questioning "the likelihood that an individual will benefit from treatment of DM2 over an expected life span"[39] and concluding that "there is a potential epidemic of overtreatment with antihyperglycemic therapies."[39] **Sulfonylureas** • Despite citing study findings that the incidence of hypoglycemic reactions was significantly greater with glibenclamide than with gliclazide,[45] the TI states "There is insufficient evidence from double-blind randomized trials that gliclazide provides a therapeutic advantage over other sulfonylurea drugs."[53] • "Sulfonylureas, metformin, and insulin are equally efficacious in improving glucose control in type 2 diabetes" and "are better than diet alone."[40] **Intensive insulin** • "The effectiveness of intensive insulin treatment in delaying the onset of complications of diabetes has been established for type 1 and, to a lesser extent, for type 2 diabetes."[40] **Acarbose** • "Acarbose can be used as an adjunct to diet and other oral agents to achieve glucose control in patients with NIDDM. Its main disadvantages are cost and the high incidence of gastrointestinal side effects."[52] **Antihyperglycemics** • "Widely prescribed glucose lowering drugs for people with type 2 diabetes have been approved in Canada without evidence that they reduce mortality or major morbidity."[54]
Cardiovascular outcomes	• Based on publications from the EMPA-REG OUTCOME[26] and LEADER[27] trials, the November 2016 DC update to the 2013 guidelines[23] recommends using an antihyperglycemic agent with demonstrated cardiovascular outcome benefit (empagliflozin,[26] liraglutide[27]) in patients with clinical cardiovascular disease not meeting glycemic targets after lifestyle intervention and metformin. Based on the CANVAS[29] program, the 2018 DC guidelines added canagliflozin to this recommendation.	• Latest guideline was issued before publication of EMPA-REG OUTCOME and LEADER trials and DC update. • Guideline links to Canadian Agency for Drugs and Technology in Health and Common Drug Review statement that empagliflozin "was superior to placebo for improving glycemic control, reducing body weight, and lowering systolic blood pressure," supporting use in patients with type 2 diabetes at high risk for cardiovascular disease.[48]	• "Phase 4 trials have been published for saxagliptin, alogliptin, sitagliptin, empagliflozin, and liraglutide... These trials must be interpreted cautiously considering the current uncertainty regarding the effects of standard of care on cardiovascular outcomes."[54] • Question design and benefit of EMPA-REG trial (see text).

Table 4 (Continued). Key recommendations issued by three bodies for the management of type 2 diabetes.

for SGLT-2 inhibitors and to consider adding GLP-1 agonists to reflect current evidence and clinical guideline recommendations."[56]

Patients in BC living with type 2 diabetes deserve care that meets nationally vetted standards and provincial support for the most up-to-date evidence-based approach to diabetes management.

Summary

Type 2 diabetes is a common disease and its management is becoming increasingly complex. Management recommendations used in BC come primarily from Diabetes Canada, the Guidelines and Protocols Advisory Committee, and the Therapeutics Initiative.

The use of antihyperglycemic therapy has been shown to reduce complications and save lives. Physicians in BC are receiving contradictory information and facing formulary restrictions not seen in other provinces. Better alignment of evidence-based recommendations and appropriate drug coverage is needed to improve clinical outcomes and the lives of people in BC living with diabetes, and to make the management of diabetes less challenging for physicians and patients alike. BCMJ

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Competing interests

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