Type 2 Diabetes Focused Update: SGLT2 Inhibitors and GLP1 Agonists

B.C. Provincial Academic Detailing (PAD) Service **July 2023 *updated***

Participants in this PAD session will have the opportunity to:

1. Discuss changes to available evidence and clinical practice guidelines which inform medication choices beyond HbA1c lowering.
2. Review clinical considerations which support treatment decisions, including: doses, adverse events, dosage forms, cost and coverage.
3. Specifically discuss: dapagliflozin, empagliflozin, semaglutide subcutaneous.

Wegovy (semaglutide) and Saxenda (liraglutide) have Health Canada indications for chronic weight management which is beyond the scope of this session.

Brand Name	Generic Name
SGLT2 inhibitors	
Forxiga®	dapagliflozin oral
Jardiance®	empagliflozin oral
Invokana®	canagliflozin oral
GLP1 agonists	
Ozempic® (Wegovy®)	semaglutide subcutaneous
Rybelsus®	semaglutide oral
Trulicity®	dulaglutide subcutaneous
Victoza® (Saxenda®)	liraglutide subcutaneous
Adlyxine®	lixisenatide subcutaneous

Type 2 Diabetes: BC Provincial Academic Detailing Service 2015 to 2021

2015

Systematic reviews are unable to draw conclusions that confidently inform glucose lowering medication choices in terms of their effect on diabetes related morbidity and mortality, due to insufficient, low quality or absent evidence.[1]

For many glucose lowering medications, standard or starting doses will generally yield similar HbA1c reductions compared to higher or maximum doses.[1]

2019

Contemporary guidelines reach discordant conclusions on the value of intensifying glucose-lowering medications to achieve HbA1c targets ≤ 7% in people with type 2 diabetes.[2]

2021

Systematic reviews now inform medication choices for several clinical outcomes: cardiovascular, kidney, all-cause death.

Confident conclusions cannot yet be drawn for other important outcomes: retinopathy, neuropathy, amputation, quality of life.[3-6]

Longer term clinical outcome trials with SGLT2 inhibitors and GLP1 agonists inform dosage decisions for outcomes beyond HbA1c lowering.

In people with type 2 diabetes who have atherosclerotic cardiovascular disease, guidelines prioritize the use of SGLT2 inhibitors or GLP1 agonists.

In people with type 2 diabetes and chronic kidney disease or heart failure, guidelines prioritize the use of SGLT2 inhibitors.[7,8]

These recommendations do not apply to people experiencing an acute decompensation of glycemic control.

RACE
Rapid Access to Consultative Expertise

BC 2019 CKD Guidelines
Referral Recommendations

[1]BC Provincial Academic Detailing Service 2015 Glucose Lowering Medications for Type 2 Diabetes; [2]BC Provincial Academic Detailing Service 2019 Basal Insulins for Type 2 Diabetes; [3]MCGUIRE JAMA Cardiol 2021;6:148-58; [4]KRISTENSEN Lancet Diabetes Endocrinol 2019;7:776-85; [5]SATTAR Lancet Diabetes Endocrinol 2021;9:653-62; [6]PALMER BMJ 2021;372:m4573; [7]Diabetes Canada Can J Diabetes 2020;44:575-91; [8]LI BMJ Rapid Recommendations BMJ 2021;373:n1091

Type 2 Diabetes: Non Insulin Medications Overview

Non Insulin Medications

Available in Canada

- metformin
- sulfonylureas: gliclazide, glyburide, glimepiride
- acarbose
- repaglinide
- thiazolidinediones: pioglitazone, rosiglitazone
- DPP4 inhibitors: linagliptin, sitagliptin, saxagliptin, alogliptin
- SGLT2 inhibitors: dapagliflozin, empagliflozin, canagliflozin
- GLP1 agonists: semaglutide subcut, semaglutide oral, dulaglutide subcut, liraglutide subcut, lixisenatide subcut

Annual drug cost *approx*	
metformin	< $50
gliclazide	< $150
DPP4 inhibitors	$900-$1200
SGLT2 inhibitors	$300-$1100
GLP1 agonists	$3000-$6000

Drug Class Indications Beyond HbA1c Lowering

Health Canada
US FDA

	DPP4 inhibitors	SGLT2 inhibitors	GLP1 agonists	Clinical Outcome Trial Doses
Type 2 Diabetes with Cardiovascular Disease		+	+	dapagliflozin 10 mg PO once a day* empagliflozin 10 or 25 mg PO once a day* canagliflozin 100 or 300 mg PO once a day* semaglutide 0.5 or 1 mg subcut once a week semaglutide 14 mg PO once a day dulaglutide 1.5 mg subcut once a week* liraglutide 1.8 mg subcut once a day*
Type 2 Diabetes with Multiple Cardiovascular Risk Factors		+	+	
Diabetic Nephropathy		+		canagliflozin 100 mg PO once a day*
Chronic Kidney Disease		+		dapagliflozin 10 mg PO once a day* empagliflozin 10 mg PO once a day
Heart Failure		+		dapagliflozin 10 mg PO once a day* empagliflozin 10 mg PO once a day*
Chronic Weight Management			+	semaglutide 2.4 mg subcut once a week* liraglutide 3 mg subcut once a day*

PharmaCare Coverage
British Columbia

regular benefit	metformin	dapagliflozin	glyburide			
limited coverage	semaglutide subcutaneous	empagliflozin	gliclazide	linagliptin	saxagliptin	pioglitazone

* Denotes which SGLT2i or GLP1a has a Health Canada indication as of July 2023

SGLT2 inhibitors, GLP1 agonists: meta-analyses & systematic reviews

SGLT2 inhibitors versus placebo added to usual care[1]

4 RCTs; 42,568 participants; followed median 2.4-4.2 years
68% T2DM with CVD; 32% T2DM with multiple CVD risk factors
mean age 63-64, HbA1c 8.1-8.3%, T2DM diagnosis duration 12-14 yrs

Major adverse cardiovascular events	HR 0.91 (95%CI 0.86, 0.97)
Death from any cause	HR 0.87 (95%CI 0.81, 0.94)
Hospitalization for heart failure*	HR 0.70 (95%CI 0.62, 0.78)
Kidney related outcome*	HR 0.61 (95%CI 0.54, 0.69)

GLP1 agonists versus placebo added to usual care[2,3]

8 RCTs; 60,080 participants; followed median 1.3-5.4 years
77% T2DM with CVD; 23% T2DM with multiple CVD risk factors
mean age 60-66, HbA1c 7.3-8.9%, T2DM diagnosis duration 9-15 yrs

Major adverse cardiovascular events	HR 0.86 (95%CI 0.80, 0.93)
Death from any cause	HR 0.88 (95%CI 0.82, 0.94)
Hospitalization for heart failure*	HR 0.89 (95%CI 0.82, 0.98)
Kidney related outcome*	HR 0.79 (95%CI 0.73, 0.87)

* In these T2DM cardiovascular trials, hospitalization for heart failure and kidney related outcomes were often secondary or exploratory outcomes. Kidney outcome definitions varied across trials. For example, macroalbuminuria (a surrogate outcome) was excluded from SGLT2i trial definitions of kidney related outcomes but was included in GLP1a trials. Not represented in the tables above, additional SGLT2i trials have enrolled participants specifically with diabetic nephropathy, CKD, HFrEF, HFpEF and examine patient-important kidney and heart failure outcomes.

- SGLT2 inhibitors decrease the risk of death when added to usual care (high certainty evidence)[4,5]
- SGLT2 inhibitors decrease the risk of hospitalization for heart failure compared with GLP1 agonists (indirect comparison)[4,5]
- Absolute benefits are estimated to vary by baseline risk[4,5]

- GLP1 agonists decrease the risk of death when added to usual care (high certainty evidence)[4,5]
- GLP1 agonists decrease the risk of non-fatal stroke compared with SGLT2 inhibitors (indirect comparison)[4,5]
- Absolute benefits are estimated to vary by baseline risk[4,5]

	with CKD and CVD		with CKD		with CVD		with ≥ 3 CVD risk factors	
Baseline risk of death per 1000 people with T2DM over 5 years[4,5]	265		170		120		70	
Change in risk of death if 1000 people receive treatment for 5 years[4,5]	SGLT2i	GLP1a	SGLT2i	GLP1a	SGLT2i	GLP1a	SGLT2i	GLP1a
	30 fewer	**24 fewer**	**22 fewer**	**17 fewer**	**16 fewer**	**13 fewer**	**10 fewer**	**8 fewer**

Major Adverse Cardiovascular Events cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; HR ratio of hazard rates in treated versus placebo group over time; 95%CI 95% confidence interval

[1]MCGUIRE JAMA Cardiol 2021;6:148-58; [2]SATTAR Lancet Diabetes Endocrinol 2021;9:653-62; [3]KRISTENSEN Lancet Diabetes Endocrinol 2019;7:776-85; [4]PALMER BMJ 2021;372:m4573;
[5]PALMER BMJ 2022;376:o109 correction to estimates for SGLT2 inhibitors

Dapagliflozin, Empagliflozin, Semaglutide subcut: trials, dose, cost

	Type 2 Diabetes Clinical Outcome Trials		HbA1c, Body Weight	Some Ongoing Trials
Dapagliflozin Forxiga ~$300 per year (5 mg & 10 mg)	**T2DM Cardiovascular Trial** 17160 people, median follow up 4.2 years (DECLARE 2019)[1] **41% CVD**, mean age 64, mean HbA1c 8.3%, CrCl ≥ 60 10 mg PO once a day added to usual care		When added to metformin[4] ▼ HbA1c ~0.5% 10 mg vs 5 mg[5] ▼ HbA1c additional 0.08-0.19% Body Weight[1,6] ▼ ~2 kg	Acute Myocardial Infarction[9] dapagliflozin 10 mg Early Type 2 Diabetes[10] dapagliflozin 10 mg versus metformin
	Major Adverse Cardiovascular Events: ▼ HR 0.93, 95%CI 0.84 to 1.03 **~2 fewer** people per 1000/year	Death from any cause: ▼ HR 0.93, 95%CI 0.82 to 1.04 **~1 fewer** death per 1000/year		
Empagliflozin Jardiance ~$1100 per year (10 mg & 25 mg)	**T2DM Cardiovascular Trial** 7020 people, median follow up 3.1 years (EMPA REG 2015)[2] **100% CVD**, mean age 63, mean HbA1c 8.1%, eGFR ≥ 30 10 or 25 mg PO once a day added to usual care		When added to metformin[4] ▼ HbA1c ~0.6% 25 mg vs 10 mg[7] ▼ HbA1c additional 0.06-0.13% Body Weight[2,6] ▼ ~2 kg	Acute Myocardial Infarction[11] empagliflozin 10 mg
	Major Adverse Cardiovascular Events: ▼ HR 0.86, 95%CI 0.74 to 0.99 **~7 fewer** people per 1000/year	Death from any cause: ▼ HR 0.68, 95%CI 0.57 to 0.82 **~9 fewer** deaths per 1000/year		
Semaglutide subcutaneous Ozempic ~$3000 per year (1 mg) ~$6000 per year (2 mg)	**T2DM Cardiovascular Trial** 3297 people, median follow up 2.1 years (SUSTAIN-6 2016)[3] **83% CVD or CKD**, mean age 65, mean HbA1c 8.7% 0.5 or 1 mg subcut once a week added to usual care		When added to metformin[4] ▼ HbA1c ~1.3% 1 mg vs 0.5 mg[8] ▼ HbA1c additional 0.1-0.4% Body Weight[3,6] ▼ ~4 kg (0.5 mg) ▼ ~5 kg (1 mg)	Diabetic Nephropathy[12] semaglutide 1 mg subcut Diabetic Retinopathy[13] semaglutide 1 mg subcut T2DM Cardiovascular[14] semaglutide 14 mg oral Overweight & Obesity CVD[15] semaglutide 2.4 mg subcut
	Major Adverse Cardiovascular Events: ▼ HR 0.74, 95%CI 0.58 to 0.95 **~12 fewer** people per 1000/year	Death from any cause: **?** HR 1.05, 95%CI 0.74 to 1.50 indeterminate result, wide 95%CI		

CVD cardiovascular disease; **CrCl** mL/min Cockroft-Gault equation
Major Adverse Cardiovascular Events cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; **HR** ratio of hazard rates in treated versus placebo group over time; **95%CI** 95% confidence interval
Per 1000/year estimate of absolute difference between treatment and placebo if 1000 people receive the medication for one year
eGFR mL/min/1.73 m^2; **CKD** chronic kidney disease

[1]DECLARE-TIMI 58 NEJM 2019;380:347-57; [2]EMPA REG OUTCOME NEJM 2015;373:2117-28; [3]SUSTAIN 6 NEJM 2016;375:1834-44; [4]TSAPAS Ann Int Med 2020;173:278-86; [5]FDA 2014 Review Dapagliflozin; [6]TSAPAS Diabetes Obes Metab 2021;23:2116-24; [7]FDA 2014 Review Empagliflozin; [8]FDA 2017 Review Semaglutide Subcutaneous; [9]DAPA-MI 2023; [10]SMARTEST 2026; [11]EMPACT-MI 2023; [12]FLOW 2024; [13]FOCUS 2027; [14]SOUL 2024; [15]SELECT 2023

SGLT2i Clinical Considerations: dapagliflozin, empagliflozin, canagliflozin

Health Canada and US FDA Prescribing Information plus recent Canadian observational drug safety studies

Contraindications Precautions[1-6]	▪ Type 1 diabetes ▪ Pregnancy & lactation ▪ History of diabetic ketoacidosis ▪ Dialysis
Kidney [1-10]	▪ Glycemic efficacy decreases with declining renal function however SGLT2i clinical outcome trials enroll participants with eGFR down to 20-30 mL/min and demonstrate improvements in patient important outcomes (CVD, CKD, HF) ▪ Health Canada (current): do not initiate empagliflozin, canagliflozin if eGFR < 30 mL/min; dapagliflozin if eGFR < 25 mL/min ▪ Diabetic nephropathy (canagliflozin 100 mg): can be continued if eGFR < 30 mL/min until dialysis ▪ eGFR may decrease upon initiation (on average, a 3 mL/min/1.73 m^2 decrease); an eGFR decrease > 30% from baseline warrants careful evaluation, which occurred in 4% of participants with diabetic nephropathy by 3 weeks ▪ Lower risk of hospitalization for acute kidney injury in older adults with SGLT2i compared to DPP4i (2020 cohort study)
Diabetic Ketoacidosis (Euglycemic or Hyperglycemic) [1-6,11-17]	▪ Increased risk of DKA compared to DPP4i: rate ~2 per 1000 patient years (2020 cohort study) ▪ Risk factors: sudden reduction or omission of insulin; pancreatic disorders causing insulin deficiency (eg, type 1 diabetes, pancreatitis, pancreatic surgery); long standing type 2 diabetes; latent autoimmune diabetes; acute serious illness or infection; major surgery or hospitalization; reduced caloric intake due to illness, surgery, ketogenic diet; high alcohol intake ▪ Surgery: discontinue SGLT2i 3 days prior, restart when feeling well and able to eat and drink ▪ Acute illness: hold SGLT2i ▪ BC PAD 2019 SGLT2i Diabetic Ketoacidosis
Hypoglycemia [1-6,18-20]	▪ Concomitant sulfonylurea or insulin increases hypoglycemia risk: when initiating an SGLT2i, consider current level of glycemic control and hypoglycemia history to inform need to reduce or continue sulfonylurea or insulin; use glucose self monitoring to further inform sulfonylurea and insulin dose adjustment ▪ Caution: rapid reduction or discontinuation of insulin identified as a risk factor for diabetic ketoacidosis
Hypovolemia [1-6,20,21]	▪ Assess for volume depletion and correct before initiating an SGLT2i (counsel that urine volume may increase) ▪ Caution: older adults, hypotension, loop diuretics (consider dose decrease), hold for intercurrent illness leading to volume depletion ▪ RxFiles Type 2 Diabetes Sick Days ▪ Diabetes Canada Sick Day Medication List
Infection [1-6,22-26]	▪ Increased risk of genital mycotic infection but not urinary tract infections compared to DPP4i (2019 cohort study) ▪ Genital infection risk factors: women, prior mycotic genital infection, uncircumcised men; educate on signs and symptoms of serious infection ▪ Compared to DPP4i, no observed increase in below-knee amputations or urosepsis and Fournier's gangrene was numerically similar (2020 cohort studies) ▪ Canagliflozin: discontinue if active foot ulcer, lower extremity infection, ischemic limb and consider risk factors that may increase risk of amputation before initiating (prior amputation, peripheral vascular disease, neuropathy, foot ulcers)

GLP1a Clinical Considerations: semaglutide, dulaglutide, liraglutide

Health Canada and US FDA Prescribing Information plus recent Canadian observational drug safety studies

Contraindications Precautions[27-34]	▪ Type 1 diabetes ▪ Pregnancy & lactation ▪ History of pancreatitis ▪ Concurrent DPP4 inhibitors ▪ Personal or family history of medullary thyroid cancer, Multiple Endocrine Neoplasia syndrome type 2
Kidney[27-34]	▪ No dosage adjustment required in renal impairment; limited efficacy and safety data if eGFR < 15 mL/min or dialysis
Subcutaneous Injection [27-29]	▪ Weekly: semaglutide (steady state 4-5 weeks), dulaglutide (steady state 2-4 weeks) ▪ Daily: liraglutide (steady state 3 days) ▪ Site: abdomen, thigh, upper arm; site can be changed without dosage adjustment ▪ Timing: any time of day, without regard to meals ▪ Multidose disposable prefilled pen: semaglutide, liraglutide (requires pen needle change and dose selection using dose counter on pen) ▪ Single dose disposable prefilled pen: dulaglutide
Semaglutide Oral[30]	▪ Low oral bioavailability: dosed once a day on an empty stomach with maximum 120 mL of water (approx half a cup); presence of multiple tablets in the stomach decreases semaglutide absorption (wait 30 minutes before taking other oral medications)
Hypoglycemia [27-36]	▪ Concomitant sulfonylurea or insulin increases risk: when initiating a GLP1a, consider current level of glycemic control and hypoglycemia history to inform need to reduce or continue sulfonylurea or insulin (insulin dose was decreased by 20% in semaglutide subcut trials); use glucose self monitoring to further inform sulfonylurea and insulin dose adjustment ▪ Caution: rapid reduction or discontinuation of insulin identified as a risk factor for diabetic ketoacidosis (2019 UK Government)
Gastrointestinal [27-34,37,38]	▪ Dose related: slow dose titration is intended to improve tolerability ▪ Nausea, diarrhea >> vomiting, abdominal pain > decreased appetite > constipation, dyspepsia ▪ Monitor for deterioration in renal function if severe adverse gastrointestinal reaction ▪ Acute pancreatitis: discontinue GLP1a ▪ Acute gallbladder disease: gallbladder studies if cholelithiasis suspected ▪ No observed increase in hospitalization for acute pancreatitis with incretin-based drugs (DPP4 inhibitors, GLP1 agonists) (2016 case-control study)
Retinopathy [27,30,31,34,38,39]	▪ Increased risk in semaglutide clinical trials: monitor for progression of diabetic retinopathy in patients with retinopathy
Heart Rate [27-34,38]	▪ Dose related increase in heart rate (mean increase 1-6 BPM in clinical trials); PR interval prolongation ▪ Caution: history of tachyarrhythmias, atrioventricular block, other sympathomimetic drugs or drugs that prolong PR interval

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Reference list is available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.
For more information, or to schedule an academic detailing session, please contact:

BC Provincial Academic Detailing Service

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