CARDIORENAL RISK REDUCTION IN ADULTS

Canadian Cardiovascular Society

2022 EDITION

Cardiorenal Risk Reduction in Adults

GUIDELINES POCKET GUIDE

This pocket guide is a quick-reference tool that features diagnostic and management recommendations based on the 2022 Canadian Cardiovascular Society (CCS) Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults.

These recommendations are intended to provide a reasonable and practical approach to care for physicians, pharmacists, nurses and other healthcare providers. They are subject to change as scientific knowledge/technology advance and practice patterns evolve, and are not intended to be a substitute for clinical judgement. Adherence to these these recommendations will not necessarily produce successful outcomes in every case.

For information about the GRADE approach for rating the strength of recommendations and quality of evidence, visit **www.ccs.ca**.

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Co-Chairs

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CCS Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults Primary Panel

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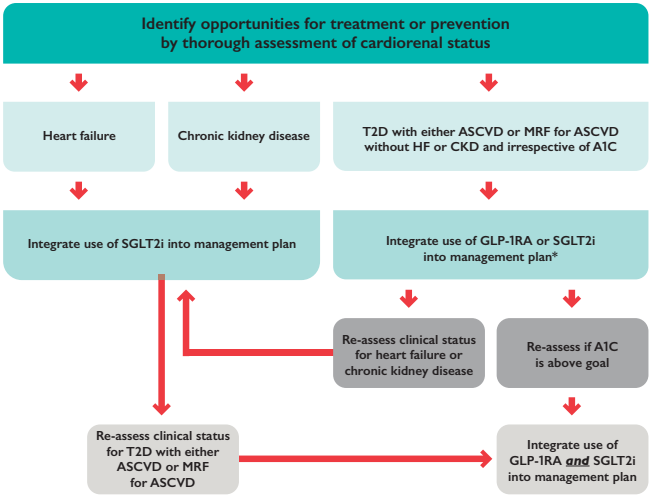
Formal recommendations from the 2022 CCS Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults

Process	Practice Statement	Strength of Recommendation	Quality of Evidence
Screening[1]	CV specialists are encouraged to assess kidney and glycemic status through measurement of eGFR, UACR, and A1C and to document LVEF when evaluating symptoms of HF.	-	-
Recommendations			
Treatment of HF	In adults with HF and LVEF ≤ 40%, we recommend use of SGLT2i to reduce all-cause and CV mortality, hospitalization for HF and the composite end-point of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease.	Strong	Moderate
	In adults with HF and LVEF > 40%, we recommend use of SGLT2i to reduce hospitalization for HF.	Strong	Moderate
Treatment of CKD	In adults with CKD (UACR > 20 mg/mmol, eGFR ≥ 25 mL/min/1.73m^2), we recommend use of SGLT2i to reduce the composite of significant decline in eGFR, progression to end stage kidney disease or death due to kidney disease, all-cause and CV mortality, non-fatal MI, and hospitalization for HF.	Strong	Moderate
Prevention of cardiorenal events in adults with either T2D and ASCVD or multiple risk factors for ASCVD	In adults with T2D and either ASCVD or multiple risk factors for ASCVD, we recommend use of: a. GLP-1RA or SGLT2i to reduce the risk of all-cause, or CV mortality or MACE.	Strong	Moderate
	b. SGLT2i to reduce the risk of hospitalization for HF or the composite of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease.	Strong	Moderate
	c. GLP-1RA to reduce the risk of non-fatal stroke.	Strong	Moderate

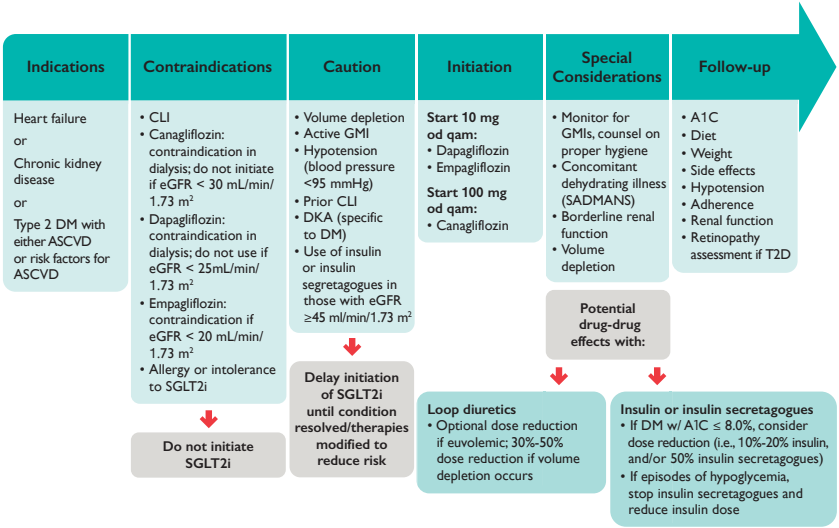
According to current Canadian product monographs, initiation of dapagliflozin is not recommended for eGFR < 25 mL/min/1.73m^2, empagliflozin and canagliflozin eGFR < 30 mL/min/1.73m^2. Conversion of UACR 200 mg/g = 22.6 mg/mmol, which was rounded to 20 mg/mmol for clinical translation in Canada. [1] The screening recommendation is a "good practice statement" which was not derived from a PICO question or extensive literature review but which, nevertheless, was considered by the panel through the same modified Delphi process used to evaluate the other recommendations.

A1C, glycosylated hemoglobin; ASCVD, atherosclerotic cardiovascular disease, CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SGLT2i, sodium-glucose co-transporter 2 inhibitors; T2D, type 2 diabetes; UACR, urine albumin creatinine ratio; +/- = with or without.

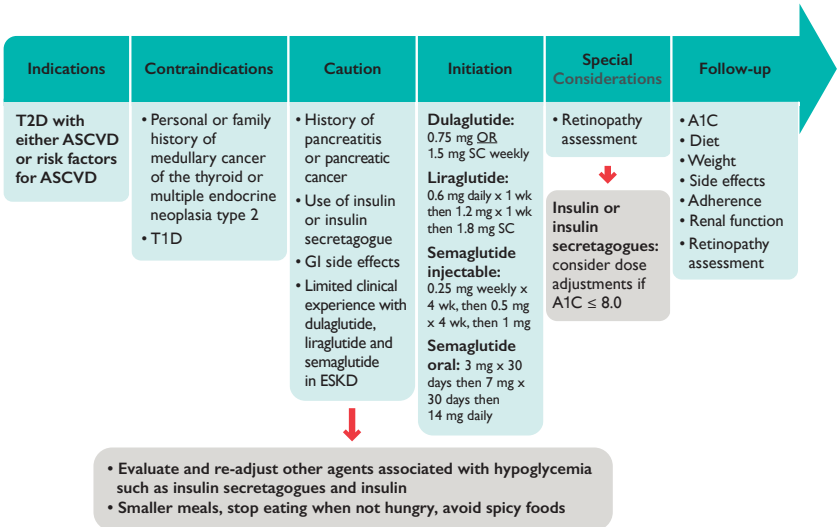


*In patient with high stroke risk, or history of TIA/stroke, consider initial integration of GLP-1RA into management plan followed by integration of SGLT2i based on changes in heart failure or kidney status or for further A1C lowering.

Practical approach for use of SGLT2i



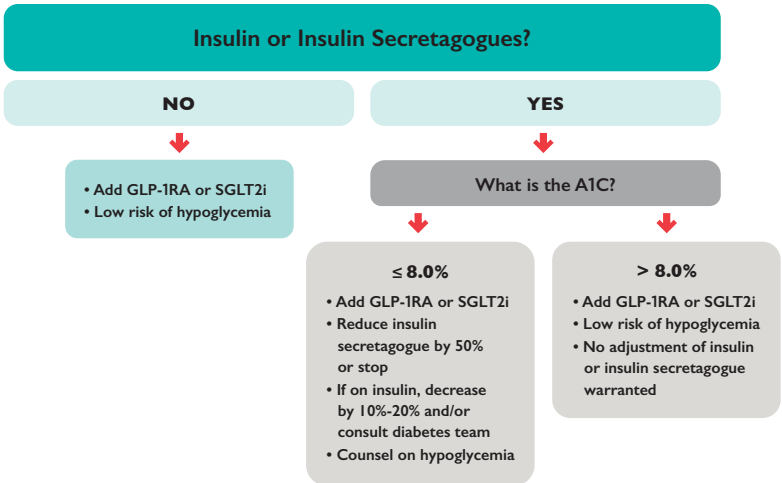
Practical approach for use of GLP-1RA



How to mitigate the main side effects of SGLT2i and GLP-1RA

Side Effects of SGLT2 Inhibitors	Mitigation Strategies
Genital mycotic infections	Explain mechanism of action Maintain genital hygiene (rinse, wipe; advise that episodes rarely recur after treatment) Consider prescription of antimycotic agent at time of initiation to be used if infection occurs
Volume depletion	Adequate hydration Hold in acute illness or preoperative
Hypoglycemia	Potential exists if used in combination with insulin secretagogues or insulin and eGFR ≥ 45 ml/min/1.73m^2
Diabetic ketoacidosis	**Do not use in type 1 diabetes** Do not discontinue insulin without the advice of a diabetes specialist; cautiously reduce insulin by 10 – 20% at a time Hold the SGLT2i in acute illness Hold the SGLT2i for 2 – 3 days before scheduled surgery or procedures Patients without diabetes not at risk
Amputation	Uncertain risk with canagliflozin but increased risk not seen with other SGLT2i Emphasis on preventative foot care (monitor for new pain, tenderness, sores, ulcers, and infections in the legs and feet) Risk factors that predispose to the need for amputation should be considered when choosing medication Hold during active foot ulcer
Side Effects of GLP-1 Receptor Agonists	**Mitigation Strategies**
Gastrointestinal (nausea, vomiting, diarrhea)	Usually transient Slow titration of dose Smaller meals; stop eating when no longer hungry Avoid spicy foods Maintain adequate hydration May use antiemetics if required
Hypoglycemia	Potential exists if used in combination with insulin secretagogues or insulin. See Figure 2 for mitigation strategies.

Integration of SGLT2i and GLP-1RA in patients with type 2 diabetes already being treated with other antihyperglycemic agents



**SGLT2i have markedly reduced glycemic lowering efficacy when eGFR < 45 mL/min/1.73m^2, so there is less concern about hypoglycemia with insulin or insulin secretagogues.*

Quantitative summary of the relative and absolute benefits of SGLT2i and GLP-1RA for the reduction of cardiorenal outcomes

Study Patient Population		T2D	Class	Major Adverse Cardiac Events	All-cause mortality	CV death	Non-fatal Myocardial Infarction	Non-fatal Stroke	Hospitalization for HF	CV Death or Hospitalization for HF	Composite Kidney Outcome*
HF	LVEF ≤ 40%	+/-	SGLT2i	NA	0.84† (0.72, 0.97)	0.84 (0.71, 0.98)	NA	NA	0.69 (0.64, 0.75)	0.75 (0.69, 0.81)	0.59† (0.42, 0.83)
		Events/1000 pts			-22 (-38, -4)	-17 (-32, -2)			-46 (-54, -37)	-52 (-65, -39)	-9 (-13, -4)
	LVEF > 40%	+/-	SGLT2i	NA	1.00 (0.89, 1.13)	1.06 (0.80, 1.40)	NA	NA	0.71 (0.62, 0.82)	0.77 (0.68, 0.87)	0.95 (0.73, 1.24)
		Events/1000 pts							-31 (-40, -19)	-35 (-49, -20)	
Chronic Kidney Disease	Any LVEF	+/-	SGLT2i	0.83 (0.75, 0.91)	0.82 (0.74, 0.90)	0.85 (0.77, 0.94)	0.77 (0.62, 0.95)	0.78 (0.49, 1.25)	0.63 (0.58, 0.70)	0.73 (0.68, 0.78)	0.64 (0.57, 0.73)
		Events/1000 pts		-17 (-25, -9)	-17 (-24, -9)	-9 (-13, -3)	-12 (-19, -3)		-32 (-37, -26)	-35 (-41, -28)	-19 (-23, -14)
T2D with either ASCVD or multiple risk factors	Any LVEF or eGFR	+	SGLT2i	0.88 (0.82, 0.93)	0.85 (0.79, 0.92)	0.85 (0.78, 0.92)	0.90 (0.83, 0.98)	0.99 (0.88, 1.11)	0.68‡ (0.63, 0.74)	0.76‡ (0.72, 0.80)	0.65‡ (0.57, 0.74)
		Events/1000 pts		-13 (-19, -7)	-11 (-15, -6)	-7 (-11, -4)	-8 (-8, -1)		-20 (-23, -16)	-25 (-29, -21)	-17 (-20, -12)
		+	GLP-1 RA	0.86 (0.80, 0.93)	0.88 (0.82, 0.94)	0.87 (0.80, 0.94)	0.94 (0.88, 1.02)	0.84‡ (0.76, 0.94)	0.91 (0.83, 1.002)	0.89 (0.81, 0.98)	0.78 (0.70, 0.87)
		Events/1000 pts		-16 (-22, -8)	-9 (-13, -4)	-6 (-9, -3)		-4 (-7, -2)		-6 (-11, -1)	-21 (-29, -13)

* Hazard ratios are based on the composite kidney outcomes as defined in the primary trials (See Supplemental Table S1). Cells shaded in green represent statistically significant hazard ratios for which data pertaining to absolute events/1000 patients are provided. Darker green shading indicates differences between heart failure with left ventricular ejection fraction ≤ 40% vs > 40%† or between classes of medications.‡ ASCVD = atherosclerotic cardiovascular disease, CV = Cardiovascular, eGFR = estimated glomerular filtration rate, GLP-1RA = glucagon-like peptide-1 receptor agonists, LVEF = left ventricular ejection fraction, pts = patients, SGLT2i = sodium-glucose co-transporter 2 inhibitors, T2D = type 2 diabetes, +/- = with or without.

Studies used to develop the 2022 CCS Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults

Class	Medication	Major Adverse Cardiac Events	All-cause Mortality	Cardiovascular Mortality	Non-fatal Stroke	Hospitalization for Heart Failure	Cardiovascular Death or Hospitalization for Heart Failure	Kidney Composite Outcome*
GLP-1 Receptor Agonist	Albiglutide#	Harmony Outcomes[8]						
	Dulaglutide	REWIND[9]			REWIND[9]			REWIND[9]
	Efpeglenatide#	AMPLITUDE-O[10]				AMPLITUDE-O[10]		AMPLITUDE-O[10]
	Exenatide ER		EXSCEL[11]					
	Liraglutide	LEADER[12]	LEADER[12]	LEADER[12]				LEADER[12]
	Semaglutide	SUSTAIN-6[13]	PIONEER 6[14]	PIONEER 6[14]	SUSTAIN-6[13]			SUSTAIN-6[13]
SGLT2 Inhibitor	Canagliflozin	CANVAS Program[15], CREDENCE[16]				CANVAS Program[15], CREDENCE[16]	CANVAS Program[15], CREDENCE[16]	CANVAS Program[15], CREDENCE[16]
	Dapagliflozin		DAPA-CKD[17], DAPA-HF[18]	DAPA-HF[18]		DECLARE[19], DAPA-CKD[17], DAPA-HF[18]	DECLARE[19], DAPA-CKD[17], DAPA-HF[18]	DECLARE[19], DAPA-CKD[17]
	Empagliflozin	EMPA-REG OUTCOME[20]	EMPA-REG OUTCOME[20]	EMPA-REG OUTCOME[20]		EMPA-REG OUTCOME[20], EMPEROR-Reduced[21], EMPEROR-Preserved[22]	EMPA-REG OUTCOME[20], EMPEROR-Reduced[21], EMPEROR-Preserved[22]	EMPA-REG OUTCOME[20], EMPEROR-Reduced[21]
	Ertugliflozin#					VERTIS-CV[23]		
	Sotagliflozin#	SCORED[24], SOLOIST-WHF[25]				SCORED[24], SOLOIST-WHF[25]	SCORED[24], SOLOIST-WHF[25]	

'This table reflects data considered suitable for the systematic review and meta-analysis which used hazard ratios-time to event data, adjusted for other covariates'. Based on those criteria, a study using lixisenatide[56] showed neutral results for all critical end-points of interest for this guideline and is not shown. Similarly, no individual trial showed significant reduction in non-fatal MI. + Kidney composite outcome definitions are provided in Supplemental Table S1. # Not available or approved in Canada. AMPLITUDE-O = Effect of Efpeglenatide on Cardiovascular Outcomes; CANVAS Program = Canagliflozin Cardiovascular Assessment Study; CREDENCE = Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD = Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; DAPA-HF = Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure; DECLARE = Dapagliflozin Effect on Cardiovascular Events; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) Outcome Trial; EMPEROR-Preserved = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; EMPEROR-Reduced = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; EXSCEL = Exenatide Study of Cardiovascular Event Lowering Trial; Harmony Outcomes = Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; PIONEER 6 = Peptide Innovation for Early Diabetes Treatment 6; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SCORED = Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; VERTIS-CV = eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial.

Selected references for page 10

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Notes:

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