Canadian Journal of Cardiology 38 (2022) 1153–1167

Society Guidelines

2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults

Primary Panel: G.B. John Mancini, MD (Co-chair),[a] Eileen O'Meara, MD (Co-chair),[b] Shelley Zieroth, MD,[c] Mathieu Bernier, MD,[d] Alice Y.Y. Cheng, MD,[e] David Z.I. Cherney, MD, PhD,[f] Kim A. Connelly, MD,[g] Justin Ezekowitz, MBBCh, MSc,[h] Ronald M. Goldenberg, MD,[i] Lawrence A. Leiter, MD,[j] Gihad Nesrallah, MD, MSc,[j,k] Breay W. Paty, MD,[l] Marie-Eve Piché, MD, PhD,[d] Peter Senior, MBBS, PhD,[m] Abhinav Sharma, MD,[n] Subodh Verma, MD, PhD,[o] Vincent Woo, MD,[c] **Secondary Panel:** Pol Darras, MD,[l] Jonathan Y. Gabor, MD,[p] Jean Grégoire, MD,[b] Eva Lonn, MD,[q] James A. Stone, MD, PhD,[r] Jean-François Yale, MD,[s] Colin Yeung, MD, MPH,[t] and Deborah Zimmerman, MD, MSc[u]

[a] Division of Cardiology, Centre for Cardiovascular Innovation, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [b] Division of Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [c] Max Rady College of Medicine, Section of Cardiology, University of Manitoba, Winnipeg, Manitoba, Canada; [d] Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Quebec, Canada; [e] Division of Endocrinology, Unity Health Toronto and Trillium Health Partners, University of Toronto, Toronto, Ontario, Canada; [f] Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada; [g] Keenan Research Center for Biomedical Science, St Michael's Hospital, Toronto, Ontario, Canada, and Division of Cardiology, University of Toronto, Toronto, Ontario, Canada; [h] Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada; [i] LMC Diabetes and Endocrinology, Vaughan, Ontario, Canada; [j] Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [k] Division of Nephrology, Department of Medicine, Humber River Hospital, North York, Ontario, Canada; [l] Division of Endocrinology, University of British Columbia, Vancouver, British Columbia, Canada; [m] Alberta Diabetes Institute, Edmonton, Alberta, Canada; [n] Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada; [o] Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [p] Department of Cardiology, Selkirk Regional Health Centre, Selkirk, Manitoba, Canada; [q] Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [r] Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada; [s] Division of Endocrinology and Metabolism, McGill University, Montreal, Quebec, Canada; [t] Division of Cardiology (Regina), Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; [u] Division of Nephrology, Department of Medicine, Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada

ABSTRACT

This guideline synthesizes clinical trial data supporting the role of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors (SGLT2i) for treatment of heart failure (HF), chronic kidney disease, and for optimizing prevention of cardiorenal morbidity and mortality in patients with type 2 diabetes. It is on the

RÉSUMÉ

La présente ligne directrice synthétise les données d'essais cliniques confirmant le rôle des agonistes des récepteurs du peptide-1 apparenté au glucagon (arGLP-1) et des inhibiteurs du cotransporteur sodium-glucose de type 2 (iSGLT2) dans le traitement de l'insuffisance cardiaque (IC) et de l'insuffisance rénale chronique ainsi que dans la

Received for publication March 16, 2022. Accepted April 21, 2022.

Corresponding author: Dr G.B. John Mancini, Rm 9111, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada. Tel.: +1-604-875-5477; fax: +1-604-875-5471.

E-mail: mancini@mail.ubc.ca

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

https://doi.org/10.1016/j.cjca.2022.04.029

basis of a companion systematic review and meta-analysis guided by a focused set of population, intervention, control, and outcomes (PICO) questions that address priority cardiorenal end points. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system and a modified Delphi process were used. We encourage comprehensive assessment of cardiovascular (CV) patients with routine measurement of estimated glomerular filtration rate, urinary albumin-creatinine ratio, glycosylated hemoglobin (A1c), and documentation of left ventricular ejection fraction (LVEF) when evaluating symptoms of HF. For patients with HF, we recommend integration of SGLT2i with other guideline-directed pharmacotherapy for the reduction of hospitalization for HF when LVEF is $>$ 40% and for the reduction of all-cause and CV mortality, hospitalization for HF, and renal protection when LVEF is $\leq$ 40%. In patients with albuminuric chronic kidney disease, we recommend integration of SGLT2i with other guideline-directed pharmacotherapy to reduce all-cause and CV mortality, nonfatal myocardial infarction, and hospitalization for HF. We provide recommendations and algorithms for the selection of glucagon-like peptide-1 receptor agonists and SGLT2i for patients with type 2 diabetes and either established atherosclerotic CV disease or risk factors for atherosclerotic CV disease to reduce all-cause and CV mortality, nonfatal stroke, and for the prevention of hospitalization for HF and decline in renal function. We offer practical advice for safe use of these diabetes-associated agents with profound cardiorenal benefits.

prévention optimisée de la morbidité et de la mortalité cardiorénales chez les patients atteints de diabète de type 2. Elle repose sur une revue systématique et une méta-analyse complémentaires utilisant un ensemble précis de questions PICO (population, intervention, comparaison, et objectifs) sur des paramètres cardiorénaux prioritaires. Le système GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) et une méthode Delphi modifiée ont été utilisés. Nous préconisons une évaluation complète des patients atteints de maladies cardiovasculaires (CV) par des mesures systématiques du débit de filtration glomérulaire estimé, du rapport albumine-créatinine urinaire et du taux d'hémoglobine glyquée (HbA_{1c}). La fraction d'éjection ventriculaire gauche (FEVG) devrait aussi être documentée lors de l'évaluation des symptômes d'IC. En présence d'IC, nous recommandons d'intégrer les iSGLT2 à d'autres pharmacothérapies fondées sur les lignes directrices pour réduire la fréquence des hospitalisations pour IC lorsque la FEVG $>$ 40 %, réduire la mortalité toutes causes confondues et la mortalité cardiovasculaire, réduire les hospitalisations pour IC ainsi que pour préserver la fonction rénale chez les patients dont la FEVG $\leq$ 40 %. En présence de néphropathie chronique avec albuminurie, nous recommandons d'intégrer les iSGLT2 à d'autres pharmacothérapies fondées sur les lignes directrices pour réduire la mortalité toutes causes confondues et la mortalité d'origine CV, réduire le risque d'infarctus du myocarde non mortel et les hospitalisations pour IC. Nous présentons des recommandations et des algorithmes pour la sélection d'arGLP-1 et d'iSGLT2 pour les patients atteints de diabète de type 2 et d'une maladie CV athéroscléreuse établie ou présentant des facteurs de risque de maladie CV athéroscléreuse afin de réduire la mortalité toutes causes confondues, la mortalité CV ainsi que les AVC non mortels et pour la prévention des hospitalisations pour IC et le déclin de la fonction rénale. Nous offrons aussi des conseils pratiques sur l'utilisation sécuritaire de ces agents associés au diabète qui ont de profonds avantages cardiorénaux.

The Canadian cardiovascular community has encouraged cardiorenal risk reduction with glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) for patients with type 2 diabetes (T2D) who have or are at risk of cardiovascular (CV) disease.[1,2] However, to date, no formal guideline has been published by the Canadian Cardiovascular Society (CCS) regarding the use of these agents. Moreover, the application of SGLT2i has expanded beyond management of T2D to include the treatment of heart failure (HF) and chronic kidney disease (CKD) in individuals with and without diabetes. The purpose of this guideline is to assist CV practitioners in the safe and effective use of these 2 drug classes while building upon and remaining concordant with the most recent, high-quality guidelines published by Diabetes Canada,[3,4] the CCS/Canadian Heart Failure Society (CHFS),[5] and the Kidney Disease Improving Global Outcomes (KDIGO).[6] Although complex patients are best managed by a shared care model, this guideline is also intended to help any CV specialist identify situations when a more proactive or even lead role might be warranted when simple and safe implementation is quite feasible. **The reader is advised to consider the specialty guidelines for comprehensive diagnosis and management of patients with T2D, HF, or CKD, including management of glycosylated hemoglobin (A1c). The recommendations in this guideline are specifically intended for cardiorenal risk reduction. Treatment recommendations for symptomatic hyperglycemia, metabolically decompensated patients with T2D, patients with type 1 diabetes, patients receiving dialysis or with severely compromised renal function (estimated glomerular filtration rate [eGFR] < 20 mL/min/1.73 m^2), or patients with acutely decompensated HF or CKD are beyond the scope of this guideline.**

We assembled a panel of content and methods experts with representation from key Canadian partner organizations including Diabetes Canada, the CHFS, and the Canadian Society of Nephrology, drawing from community and academic practice settings, with broad geographic representation and considering equity and diversity. We conducted a *de novo* systematic review and meta-analysis on the basis of a series of focused Population, Intervention, Comparison, Outcome (PICO) questions in which the interventions were SGLT2i and GLP-1RA, and in which the comparator was standard care. The meta-analysis was specifically commissioned by the CCS to support this guideline.[7] This guideline focused on the critical outcomes of total mortality, CV mortality, nonfatal myocardial infarction (MI), nonfatal stroke, major adverse cardiac events (MACE: CV death, nonfatal MI, or nonfatal stroke),

hospitalization for HF, and composite kidney outcomes with emphasis on significant decline in eGFR, progression to end-stage kidney disease, or death from kidney disease. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, we derived pooled estimates for each PICO question and appraised evidence certainty on an outcome-by-outcome basis. With GRADE, evidence certainty is appraised across 5 domains: risk of bias, indirectness, imprecision, inconsistency, and publication bias. This extensive and detailed analysis is provided in the companion article.[7] We used a modified Delphi process in which panelists voted on and suggested refinements to draft statements to derive the final statements. All conflicts of interest were declared. For recommendations to go forward a two-thirds voting majority was required. It should be emphasized that the voting was primarily an evaluation of the commissioned meta-analysis which, by design, included all available data and not just trial-specific data. Practical points were identified through surveying the panel members, and through examining other published guidelines.[3-6] The primary writing group also submitted a draft for peer-review by a secondary panel, after which peer-review was undertaken by the CCS Guideline Committee. Simultaneously but separately, the *de novo* systematic review and meta-analysis supporting this guideline was peer-reviewed.[7] The overall goal of the process was to produce guidelines on the basis of the best, most comprehensive, and most up to date evidence that would allow clinicians and patients to make collaborative treatment decisions. These guidelines were undertaken under the auspices of the Guideline Committee of the CCS without representation or funding from the pharmaceutical or device industry.

Evidence Synthesis and Recommendations at a Glance

As indicated previously, the recommendations are on the basis of a companion, systematic review and meta-analysis to which the reader is referred for details of data synthesis and GRADE tables summarizing evidence quality.[7] Table 1 herein is a summary of the relative benefits (hazard ratios [HRs]) and event reductions per 1000 treated patients. The resulting recommendations are provided in Table 2. A summary of the specific trials, the medications used, and the cardiorenal outcomes that were significantly improved are provided in Table 3. A general approach to the integration of GLP-1RA and SGLT2i as cardiorenal agents into cardiovascular practice is provided in Figure 1.

Screening

The opportunity to help reduce cardiorenal morbidity and mortality through the use of diabetes-related drugs requires vigilance in identification of appropriate patients for therapy. Assessment of HF symptoms is commonplace and fosters appropriate use of imaging and biomarker tests to identify HF and its phenotype. Serum creatinine and eGFR are often measured to ensure appropriate CV drug dosing or in anticipation of diagnostic tests using contrast media. But measures of A1c and urine albumin-creatinine ratio (UACR) are often not included to identify patients who might well benefit from use of cardiorenal risk-reduction drugs. Consequently, we have included a general recommendation to undertake these tests as part of a comprehensive CV risk assessment. Moreover, digital health technologies might further facilitate

Table 1. Summary of relative (hazard ratios) and absolute event reductions per 1000 treated patients for cardiorenal outcomes in study populations with heart failure, chronic kidney disease, or type 2 diabetes

Study patient population		T2D	Class	MACE	All-cause mortality	CV death	Nonfatal MI	Nonfatal 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 per 1000 pts			−22 (−38 to −4)	−17 (−32 to −2)			−46 (−54 to −37)	−52 (−65 to −39)	−9 (−13 to −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 per 1000 pts							−31 (−40 to −19)	−35 (−49 to −20)	
CKD	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 per 1000 pts		−17 (−25 to −9)	−17 (−24 to −9)	−9 (−13 to −3)	−12 (−19 to −3)		−32 (−37 to −26)	−35 (−41 to −28)	−19 (−23 to −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 per 1000 pts		−13 (−19 to −7)	−11 (−15 to −6)	−7 (−11 to −4)	−8 (−8 to −1)		−20 (−23 to −16)	−25 (−29 to −21)	−17 (−20 to −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 per 1000 pts		−16 (−22 to −8)	−9 (−13 to −4)	−6 (−9 to −3)		−4 (−7 to −2)		−6 (−11 to −1)	−21 (−29 to −13)

Numbers in parentheses represent 95% confidence intervals.[7] Cells shaded in green represent statistically significant hazard ratios for which data pertaining to absolute events per 1000 patients are provided.

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not applicable; pts, patients; SGLT2i, sodium-glucose co-transporter 2 inhibitors; T2D, type 2 diabetes; +/−, with/without.

* Hazard ratios are on the basis of the composite kidney outcomes defined in the primary trials (see Supplemental Table S1).

† Darker green shading indicates differences between heart failure with left ventricular ejection fraction ≤ 40% vs > 40%.

‡ Darker green shading indicates differences between classes of medications.

Table 2. Practice recommendations for use of GLP-1RA or SGLT2i 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, nonfatal 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 nonfatal stroke.	Strong	Moderate

According to current Canadian product monographs, initiation of dapagliflozin is not recommended for eGFR < 25 mL/min/1.73 m^2, empagliflozin and canagliflozin are not recommended for eGFR < 30 mL/min/1.73 m^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; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; SGLT2i, sodium-glucose co-transporter 2 inhibitors; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio.

identification of appropriate patients.[27] The reader is referred to the major society guidelines for more detailed recommendations regarding screening and symptom evaluation processes.[3-6]

GOOD PRACTICE STATEMENT

Cardiovascular specialists are encouraged to assess kidney and glycemic status through measurement of eGFR, UACR, and A1c and to document left ventricular ejection fraction (LVEF) when evaluating symptoms of HF.

SGLT2i for the Treatment of HF

PICO 1: In patients with HF and reduced ejection fraction (HFrEF; ≤ 40%) what is the role of SGLT2i and GLP-1RA compared with placebo for reduction of CV disease or hospitalization for HF?

Our systematic review did not identify any large randomized clinical trials of GLP-1RA for the management of HF. Accordingly, our discussion and recommendations are on the basis of evidence from clinical trials of SGLT2i. The results of the **D**apagliflozin **a**nd **P**revention of **A**dverse Outcomes in **H**eart **F**ailure (DAPA-HF) trial[18] were described in the previous CCS/CHFS guideline update.[5] During a median 18-month follow-up of 4744 patients with HFrEF, treatment with dapagliflozin 10 mg daily significantly reduced the composite primary end point of time to first worsening of HF or death from CV causes (HR, 0.74; 95% confidence interval [CI], 0.65-0.85]; $P < 0.001$), as well as hospitalization for HF (HR, 0.70; 95% CI, 0.59-0.83) and CV death (HR, 0.82; 95% CI, 0.69-0.98). Importantly, 55% of patients did not have T2D, and the effect of dapagliflozin was similar at any A1c level.[18] Ancillary studies have shown that benefits were seen as early as 30 days after treatment initiation.[28] Additionally, diuretic dose was not modified during the trial for most patients,[29] quality of life was improved,[30] and blood pressure (BP) was reduced by an average of approximately 2 mm Hg.[31] Outcomes were not modified by baseline kidney

Table 3. Summary of medications associated with statistically significant cardiorenal outcome reductions in major randomized clinical trials* (class and medication listed in alphabetical order)

Class	Medication	Major adverse cardiac events	All-cause mortality	Cardiovascular mortality	Nonfatal stroke	Hospitalization for HF	Cardiovascular death or hospitalization for HF	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-TIMI 58,[19] DAPA-CKD,[17] DAPA-HF[18]	DECLARE-TIMI 58,[19] DAPA-CKD,[17] DAPA-HF[18]	DECLARE-TIMI 58,[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]	

AMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes; CANVAS, **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy; CREDENCE, **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation; DAPA-CKD, **D**apagliflozin **a**nd **P**revention of **A**dverse Outcomes in **C**hronic **K**idney **D**isease; DAPA-HF, **D**apagliflozin **a**nd **P**revention of **A**dverse Outcomes in **H**eart **F**ailure; DECLARE-TIMI 58, **D**apagliflozin **E**ffect on **C**ardiovascu**l**ar **E**vents-**T**hrombolysis **i**n **M**yocardial **I**nfarction; EMPA-REG OUTCOME, **Empa**gliflozin Cardiovascular **Outcome** Event Trial in Type 2 Diabetes Mellitus Patients—**R**emoving **E**xcess **G**lucose; EMPEROR-Preserved, **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Preserved** Ejection Fraction; EMPEROR-Reduced, **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Reduced** Ejection Fraction; ER, extended release; EXSCEL, **Ex**enatide Study of **C**ardiovascular **E**vent **L**owering; GLP-1, glucagon-like peptide-1; Harmony Outcomes, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; HF, heart failure; LEADER, **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults; PIONEER 6, **P**eptide **Inn**ovatio**n** for **E**arly Diab**e**tes T**r**eatment 6; REWIND, **R**esearching Cardiovascular **E**vents With a **W**eekly **In**cretin in **D**iabetes; SCORED, Effect of **S**otagliflozin on **C**ardi**o**vascular and **R**enal **E**vents in Patients With Type 2 **D**iabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SGLT2, sodium-glucose co-transporter 2; SOLOIST-WHF, Effect of **So**tagli**flo**zin on Cardio**v**as**c**ular Events in Patients With **T**ype 2 Diabetes Post **W**orsening **H**eart **F**ailure; SUSTAIN 6, **S**emaglutide **U**nabated **Sust**ain**a**bility in Treatment of Type 2 Diabetes 6; VERTIS-CV, E**v**aluation or **Ert**ugliflozin Eff**i**cacy and **S**afety **C**ardio**v**ascular Outcomes Trial.

*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.[7] On the basis of those criteria, a study using lixisenatide[26] 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 nonfatal myocardial infarction.

†Kidney composite outcome definitions are provided in Supplemental Table S1.

‡Not available or approved in Canada.

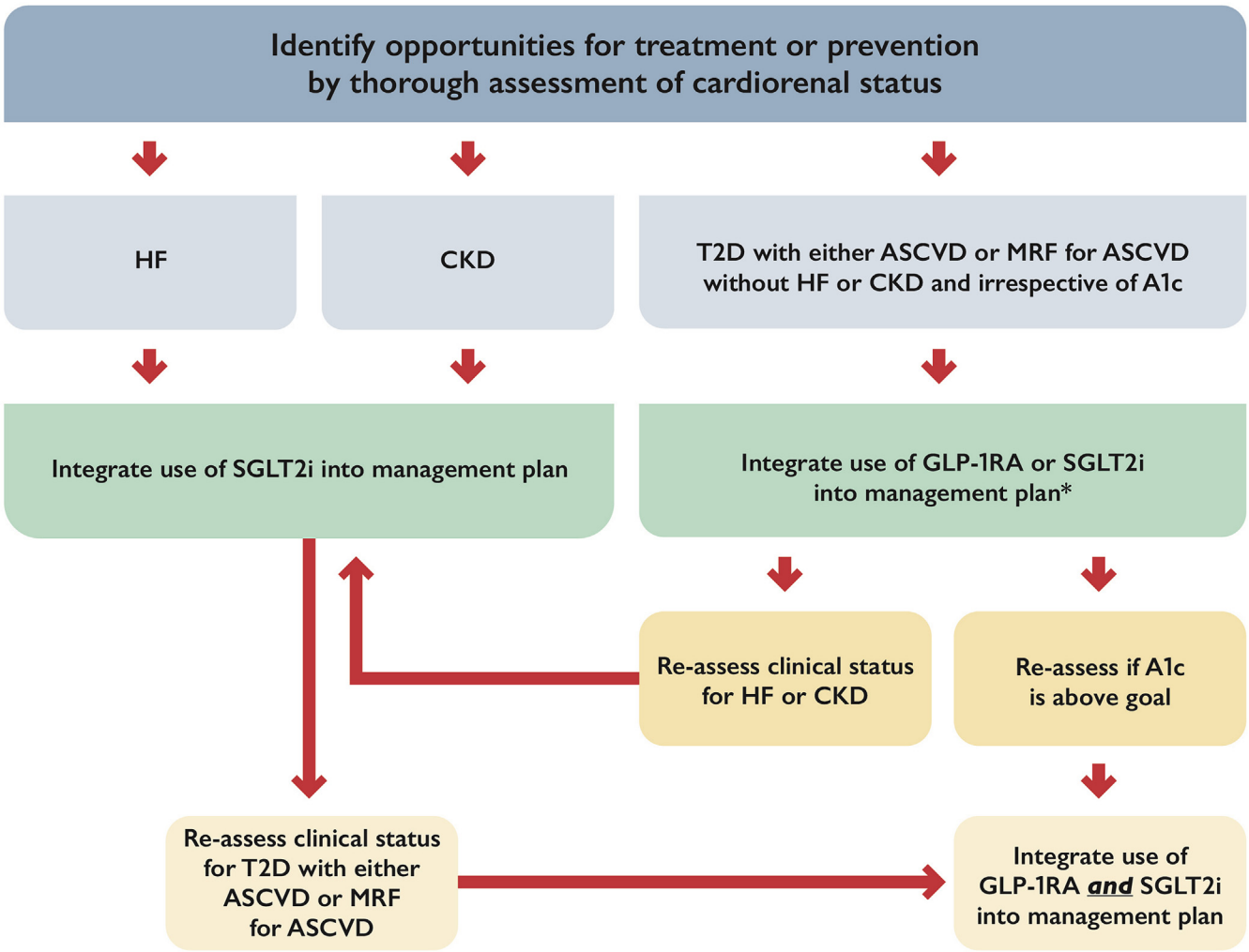

Figure 1. Integration of glucagon-like peptide-1 receptor antagonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) into cardiovascular practice. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; MRF, multiple risk factors; T2D, type 2 diabetes. * In patients with high stroke risk, or history of transient ischemic attack/stroke, consider initial integration of GLP-1RA into management plan followed by integration of SGLT2i on the basis of changes in heart failure or kidney status or for further glycosylated hemoglobin (A1c)-lowering.

function and dapagliflozin was associated with a slower eGFR decline compared with placebo in diabetes and nondiabetes cohorts.[32] The **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Reduced** Ejection Fraction (EMPEROR-Reduced) trial,[21] which compared empagliflozin 10 mg daily with placebo in patients with symptomatic HFrEF, showed results concordant with the DAPA-HF study. Participants had an LVEF $\leq$ 40% and elevated N-terminal pro hormone brain natriuretic peptide levels that varied according to LVEF and atrial fibrillation status. Enrollment could occur with an eGFR as low as 20 mL/min/1.73 m^2. During a median follow-up of 16 months, CV death or hospitalization for HF occurred in 19.4% of participants in the empagliflozin group and in 24.7% of the placebo group (HR, 0.75; 95% CI, 0.65-0.86; $P < 0.001$) and the benefit was comparable in those with or without diabetes. The total number of hospitalizations for HF was lower in the empagliflozin group (HR, 0.70; 95% CI, 0.58-0.85; $P < 0.001$), as was the annual rate of decline in eGFR (-0.55 vs -2.28 mL/min/1.73 m^2 per year; $P < 0.001$). Use of background therapy for HFrEF was excellent in both trials. Notably, sacubitril-valsartan served as a renin-angiotensin inhibitor in approximately 11% of patients in DAPA-HF and approximately 19% in EMPEROR-Reduced at baseline (concordant with clinical practice at the time of recruitment for these trials). Cardiac resynchronization therapy was used in 7.5% of patients in DAPA-HF and in 12% in EMPEROR-Reduced. Implantable cardioverter defibrillators, with or without cardiac resynchronization therapy, were used in 26% and 31%, respectively. No treatment interactions were noted among SGLT2i and these baseline therapies.[21] Treatment with SGLT2i showed no excess in hypovolemia, hypoglycemia, or renal side effects compared with placebo. A meta-analysis of the 2 trials shows that SGLT2i reduce morbidity and mortality in patients with symptomatic HFrEF, whether T2D is present or not.[33] The CCS/CHFS guideline was one of the first worldwide to endorse SGLT2i as foundational therapy for patients with HFrEF in concert with angiotensin receptor neprilysin inhibitor (ARNI), or angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), β-blocker, and mineralocorticoid receptor antagonist (MRA).[5]

Our systematic review and meta-analysis (Table 1) indicates that use of SGLT2i in patients with LVEF ≤ 40% is associated with a 16% reduction in all-cause mortality or CV mortality, a 31% reduction in hospitalization for HF, and a 41% reduction in the composite kidney outcome of significant decline in eGFR, progression to end-stage kidney disease, or death due to kidney disease.[7]

RECOMMENDATION

1. 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 Recommendation; Moderate-Quality Evidence).

Practical tip. SGLT2i can be considered in stabilized HF patients. They are not indicated for the treatment of type 1 diabetes, or for patients receiving dialysis or with severely compromised renal function (eGFR < 20 mL/min/1.73 m^2). Clinicians should refer to the appropriate guidelines for conditions such as symptomatic hyperglycemia, metabolically decompensated patients with T2D, as well as for acute renal failure. Consider temporary discontinuation of SGLT2i therapy in the context of acute events (see Figs. 2 and 3), and permanent discontinuation if eGFR remains < 20 mL/min/1.73 m^2.

PICO 2: In patients with HF and preserved ejection fraction (HFpEF; > 40%) what is the role of novel antihyperglycemic agents compared with placebo for reduction of CV death or hospitalization for HF?

The **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Preserved** Ejection Fraction (EMPEROR-Preserved)[22] trial was the first phase III randomized double-blind placebo-controlled trial to achieve its primary end point in patients with symptomatic HFpEF (> 40%). In this landmark trial the composite of CV death or HF hospitalization was significantly reduced in patients who were randomized to empagliflozin 10 mg vs placebo and standard of care therapy (HR, 0.79; 95% CI, 0.69-0.90; $P < 0.0003$). A total of 5988 patients were randomized with a median follow-up of 26 months. Standard of care therapy included 80% of patients receiving renin angiotensin inhibitor or ARNI, 38% receiving MRA, 86% receiving β-blocker, and 70% receiving statins in the placebo arm, which was not significantly different from the empagliflozin randomized group. The reduction in the primary composite end point was driven predominantly by a reduction in first hospitalization for HF (HR, 0.71; 95% CI, 0.60-0.83). The first hierarchical secondary end point of total (first and recurrent) HF hospitalization was significantly reduced (HR, 0.73; 95% CI, 0.61-0.88; $P < 0.001$) as was the second secondary end point, which was the slope of decline in glomerular filtration rate (−3.3 mL/min/1.73 m^2 for those receiving empagliflozin vs −5.7 mL/min/1.73 m^2 for those receiving placebo; $P < 0.0001$). This aligned with findings in the EMPEROR-Reduced trial. In contrast to **P**rospective Comparison of **AR**NI With **A**RB **G**lobal **O**utcomes in **HF** With Preserved Ejectio**n** Fraction (PARAGON-HF)[34] there was no heterogeneity for treatment effect for the primary end point relevant to sex or baseline LVEF on the basis of predefined tertiles of LVEF. There was also no heterogeneity for treatment benefit on the basis of the presence or absence of diabetes.[35] The safety profile was similar to that previously recognized in HFrEF patient cohorts. Additional data presented with an alpha protected pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved suggest that empagliflozin is an agent that will be beneficial across a continuum of ejection fraction although benefit was not seen with ejection fraction > 65%.[36,37]

The role of GLP-1RA and related agents in HFpEF might be clarified by ongoing studies.[30,38,39] On the basis of our meta-analysis (Table 1), use of SGLT2i is associated with a 29% reduction in hospitalization for HF. In contrast to the results in patients with HFrEF, the results in patients with HFpEF do not support a significant reduction in either all-cause or CV mortality or in reducing the composite kidney outcome.[7]

RECOMMENDATION

2. In adults with HF and LVEF > 40%, we recommend use of SGLT2i to reduce hospitalization for HF (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. This recommendation is on the basis of the results of the EMPEROR-Preserved trial (empagliflozin 10 mg daily vs placebo in addition to recommended HF therapy) but trials using other SGLT2i are pending. The recommendation is intended for stabilized patients. SGLT2i are not indicated for the treatment of type 1 diabetes, or for patients receiving dialysis or with severely compromised renal function (eGFR < 20 mL/min/1.73 m^2).

General discussion

High value is placed on use of therapies that reduce CV mortality and hospitalization for HF in well conducted randomized controlled trials. Medications such as ARNI and SGLT2i have clinical benefits in patients treated with ACEi or ARB, β-blockers, and MRA as background therapy. The mechanisms of action are complementary in patients with HFrEF and underscore a multidrug approach.

Preference is given to the use of pharmacotherapy in patients with symptomatic HFrEF regardless of New York Heart Association functional class. The writing group acknowledges lack of data that have directly compared dapagliflozin and empagliflozin in the management of HFrEF. Local accessibility to these agents and eGFR might provide guidance as to which agent is selected as a component of the 4 standard therapies for HFrEF. The writing group also acknowledges lack of evidence that has compared different strategies for the

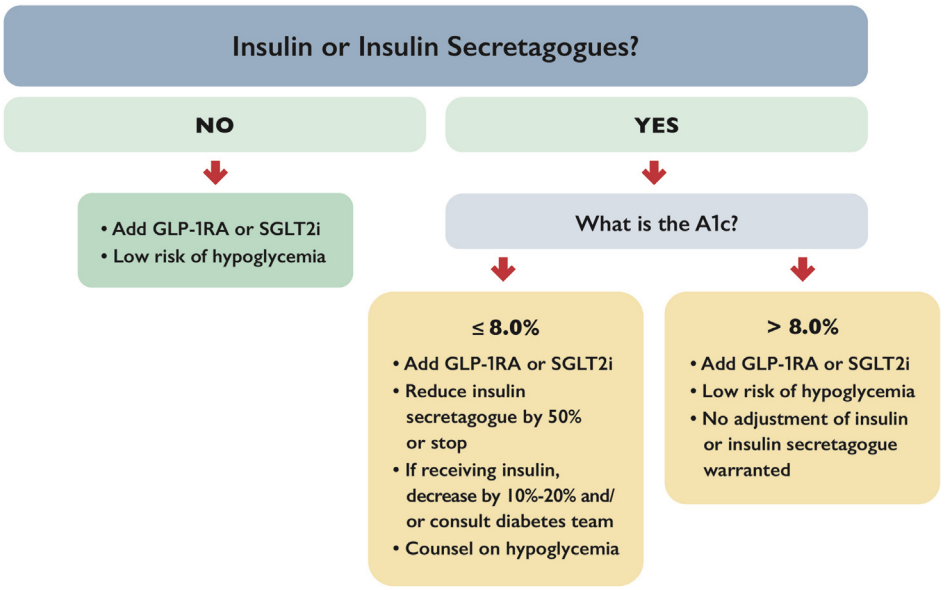

Figure 2. Management of antihyperglycemic medications when adding SGLT2i (eGFR $\geq$ 45 mL/min/1.73 m^2) or glucagon-like peptide-1 receptor antagonists (GLP-1RA). A1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter 2 inhibitors.* SGLT2i have markedly reduced glycemic-lowering efficacy when eGFR < 45 mL/min/1.72 m^2, so there is less concern about hypoglycemia with insulin or insulin secretagogues (meglitinides or sulfonylureas).

sequence in which guideline-directed medical therapies are prescribed.

Evidence from the recent Effect of **So**tagli**flo**zin on Cardi**o**vas**c**ular Events in Patients With **T**ype 2 Diabetes Post **W**orsening **H**eart **F**ailure (SOLOIST-WHF) trial[25] suggests that sotagliflozin (a sodium-glucose co-transporter 1/2 inhibitor, not yet available in Canada) could be used safely before discharge or shortly thereafter in patients with T2D who were hemodynamically stabilized after hospitalization for HF. Sotagliflozin significantly reduced the risk of achieving the primary end point of CV death, hospitalization for HF, or urgent visit for HF (51.0 vs 76.3 events per 100 patient-years; HR, 0.67; 95% CI, 0.52-0.85). The value of early initiation is a primary focus of 1 ongoing and 1 completed trial.[40,41] The **Emp**agliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for Ac**u**te Heart Fai**l**ure (de Novo or Decompensated Chronic HF) Who Have Been **S**tabilise**d** (EMPULSE) trial had not been published at the time of the final draft of this report and is not included in our meta-analysis.[41] It included fewer than 600 patients, but using the win ratio approach (a new approach to the analysis of composite end points in clinical trials on the basis of the clinical priority attached to each component), it suggests that the use of SGLT2i in patients hospitalized for acute HF (HFrEF or HFpEF) can provide significant net clinical benefit, including reduced rates of rehospitalization and death within 90 days compared with placebo and regardless of the type of HF or diabetes status. In addition, improvements in quality of life metrics were seen and therapy was well tolerated compared with placebo with no cases of diabetic ketoacidosis (DKA) in either group. Although it would not have met our criteria for meta-analysis, another novel trial showed that patient-centred quality of life outcomes were improved with canagliflozin with similar results for patients with HFrEF and HFpEF, and for patients with and without T2D.[42]

Integration of SGLT2i in the Management of Patients With CKD

PICO 3: In patients with CKD what is the role of novel antihyperglycemic agents compared with placebo for reduction of the composite of kidney death, progression to dialysis, or reduction of eGFR?

An ongoing study is evaluating the role of GLP-1RA in patients with established CKD[43] but completed trials pertain solely to SGLT2i. The first trial in the setting of CKD was the **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation (CREDENCE) trial undertaken in patients with T2D, eGFR 30 to < 90 mL/min/1.73 m^2 and UACR 33.9-565 mg/mmol.[16] All patients were receiving baseline ACEi or ARB, and were assigned to treatment with canagliflozin at a dose of 100 mg daily or placebo. The trial was stopped early (with 4401 patients randomized and a median follow-up of 2.6 years) because of overwhelming benefit: the composite of end-stage kidney disease, doubling of serum creatinine, and kidney or CV death was reduced in subjects who received canagliflozin compared with placebo (43.2 vs 61.2 events per 1000 patient-years; $P < 0.00001$). Beneficial effects were noted irrespective of baseline A1c, including among patients with A1c between 6.5% and 7%. The **D**apagliflozin **a**nd **P**revention of **A**dverse Outcomes in **C**hronic **K**idney **D**isease (DAPA-CKD) trial[17] showed that dapagliflozin, used in addition to standard therapy, also reduced kidney and CV outcomes in patients with established CKD. In 4304 participants, with or without T2D, with an eGFR between 25 and 75 mL/min/1.73 m^2 and albuminuria (a UACR of 22.6-565.6 mg/mmol) who were randomized to dapagliflozin 10 mg daily or placebo, the primary composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from kidney or CV causes was

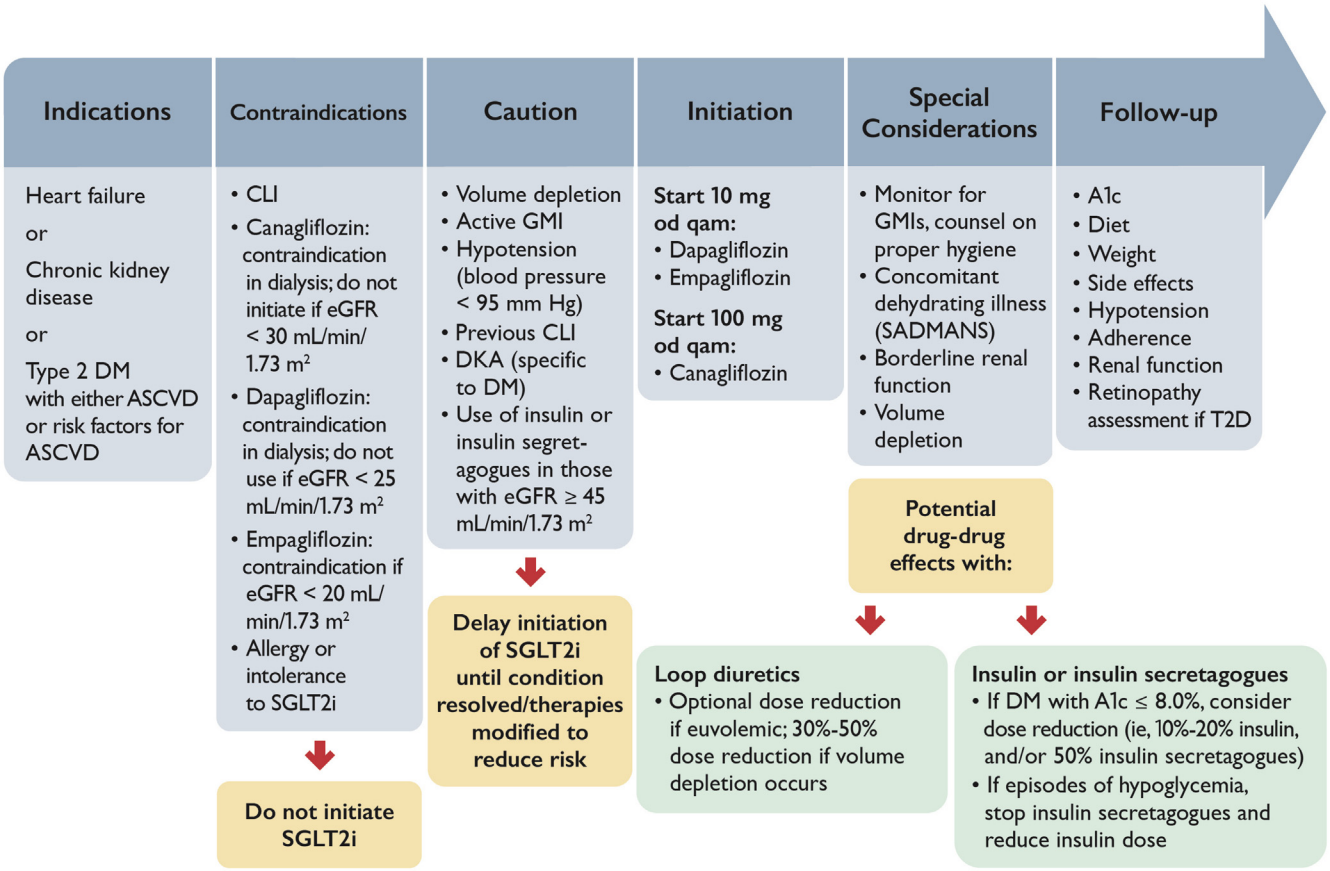

Figure 3. Practical approach to the use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) for treatment of cardiovascular disease. A1c, glycosylated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; CLI, critical limb ischemia; DKA, diabetic ketoacidosis; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GMI, genital mycotic infection; od qam, once daily every morning; SADMANS, sulfonylureas, angiotensin-converting enzyme inhibitors, diuretics and direct renin inhibitors, metformin, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, sodium-glucose co-transporter 2 inhibitors; T2D, type 2 diabetes.

reduced by 44% (HR, 0.56; 95% CI, 0.45-0.68; $P < 0.001$). The HR for composite of death from CV causes or hospitalization for HF was 0.71 (95% CI, 0.55-0.92; $P < 0.009$). All-cause mortality was also significantly reduced (HR, 0.69; 95% CI, 0.53-0.88; $P < .004$) and the excellent safety profile of dapagliflozin was confirmed in this group. Not available at the time of data synthesis and publication of this guideline, the **Empa**gliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic **Kidney** Disease (EMPA-KIDNEY) study, undertaken in patients with established CKD, which compared empagliflozin 10 mg with placebo, was stopped early after achieving positive efficacy on the basis of the primary end point (a composite of kidney disease progression or cardiovascular death) thereby further supporting the role of SGLT2i for cardiorenal protection.[44]

On the basis of our meta-analysis of the available data, Table 1 shows substantial benefit in all critical end points of interest except for reduction of nonfatal stroke.[7] The 36% reduction in the composite kidney outcome was also associated with all-cause (18%) and CV mortality (15%) reductions, a 23% reduction in nonfatal MI, and a 37% reduction in hospitalization for HF.[7]

RECOMMENDATION

3. In adults with CKD (UACR > 20 mg/mmol and eGFR ≥ 25 mL/min/1.73 m^2), we recommend use of SGLT2i to reduce the composite of significant decline in eGFR, progression to end stage kidney disease, or kidney death, all-cause and CV mortality, nonfatal MI, and hospitalization for HF (Strong recommendation, Moderate-Quality Evidence).

Practical tip. Referral to a specialist with expertise in CKD should be considered in the following situations: progressive loss of kidney function, urine UACR persistently > 60 mg/mmol, or progressive rise in UACR despite appropriate therapy, eGFR < 30 mL/min/1.73 m^2, inability to continue kidney-protective therapies because of adverse effects, such as hyperkalemia or a > 30% increase in serum creatinine within 3 months of starting SGLT2i, ACEi, or ARB, inability to achieve target BP, or signs/symptoms of another underlying kidney disease, such as glomerulonephritis.

General discussion

Because of the close inter-relationship of CKD and CV disease, recognizing these clinical entities and their prognostic effect is of great importance. A diagnosis of CKD is made in people with an eGFR < 60 mL/min/1.73 m^2 and/or random UACR ≥ 2.0 mg/mmol on at least 2 of 3 samples over a 3-month period.[6] Measuring eGFR and UACR on an annual basis (at a minimum) is recommended for patients with CV disease or multiple risk factors. The reviewed trials indicate cardiorenal benefits of SGLT2i in patients regardless of diabetes status. Among those living with CKD and T2D, it should be emphasized that reduction in the onset and progression of CKD can also be enhanced by attaining optimal A1c and BP goals. For the latter, incorporation of an ACEi or an ARB is warranted. Moreover, even when patients with T2D and CKD have achieved A1c goals, one of the SGLT2i should be included to reduce risks of CKD progression, HF, and MACE. In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[6] recommend long-acting GLP-1RA. This is further supported by secondary analyses of some of the GLP-1RA trials in patients with T2D.[45] Although this guideline supports this recommendation, we have not made an explicit recommendation in this regard because no dedicated CKD trials using this class are currently complete. The available evidence from other trials is summarized in the accompanying *de novo* meta-analysis[7] but the kidney outcomes definitions have varied among trials (Supplemental Table S1). Moreover, because of our focus on cardiorenal benefits, and considering that SGLT2i have been studied in clinical trials dedicated to patients with CKD, we believe that SGLT2i should be part of first-line treatment in patients with CKD and T2D and that the inclusion of drugs with proven cardiorenal benefits should be independent of whether the patient is taking metformin or not. It should be emphasized, however, that the A1c-lowering effect of SGLT2i is diminished in the presence of CKD, and is minor at eGFR 30-45 mL/min/1.73 m^2 and absent at an eGFR of < 30 mL/min/1.73 m^2.

Integration of GLP-1RA or SGLT2i in Patients With T2D With or at Risk of atherosclerotic CVD

PICO 4: In patients with T2D and either atherosclerotic CVD (ASCVD) or high CV risk, what is the role of novel antihyperglycemic agents compared with placebo for reduction of a composite of CV death, nonfatal MI, or nonfatal stroke?

The initial trial that used empagliflozin published in 2015, through to the most recent trial that used efpeglenatide published in 2021 were evaluated in detail in the accompanying systematic review and meta-analysis.[7] Table 1 shows that MACE was reduced similarly by both classes with a relative risk reduction of 12%-14%. These classes were also associated with similar relative risk reductions in all-cause (12%-15%) and CV mortality (13%-15%). Reduction in nonfatal MI was noted only with SGLT2i but the effect was modest (10% relative risk reduction). Because this effect was not statistically different from the neutral effects on nonfatal MI associated with the GLP-1RA class, we make no recommendation on the basis of this end point. The SGLT2i class showed significant relative risk reduction for the prevention of the composite kidney outcomes (35%) and for hospitalization for HF (32%) compared with placebo and superior to GLP-1RA. As noted previously, currently we do not have any large clinical trials for the treatment of HF or CKD in patients with or without T2D using GLP-1RA. Finally, the important but less common outcome of nonfatal stroke was reduced with GLP-1RA, particularly in the **S**emaglutide **U**nabated **S**us**tain**ability in Treatment of Type 2 Diabetes (SUSTAIN) 6 trial (semaglutide once weekly injection) and **R**esearching Cardiovascular **E**vents With a **W**eekly **In**cretin in **D**iabetes (REWIND; dulaglutide) trials.[9,46,47] The systematic review and meta-analysis (Table 1) indicates a relative risk reduction of nonfatal stroke of 16% associated with use of GLP-1RA.

RECOMMENDATION

4. In adults with T2D and either established 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 Recommendation; Moderate-Quality Evidence),
   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 kidney death (Strong Recommendation; Moderate-Quality Evidence),
   c. GLP-1RA to reduce the risk of nonfatal stroke (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. A combination of SGLT2i and GLP-1RA might theoretically improve cardiorenal benefits in patients with T2D and either ASCVD or multiple risk factors for ASCVD whose A1c remains suboptimal despite initial treatment with only one of these agents or if clinical status changes (eg, new onset HF or CKD; Fig. 1).

General discussion

The principles of pharmacotherapy for patients with T2D have been thoroughly reviewed by Diabetes Canada.[3,4] Achievement of target glucose levels, especially in the early years after T2D diagnosis, reduces the incidence and progression of microvascular complications and, in the long term (more than 10 years), is associated with reduced CV outcomes.[48-51] In parallel with achieving the A1c goal, it is also recommended that GLP-1RA or SGLT2i be included for patients with T2D with or at high risk of ASCVD to reduce cardiorenal risk, irrespective of A1c. Thus, substitution of (replacing rather than adding) an

agent with cardiorenal benefit might be appropriate if people are at or near A1c target.

The choice of initial pharmacotherapy has emerged as an area of uncertainty in patients with newly diagnosed T2D who have or are at risk of ASCVD. Although most guidelines continue to recommend metformin as first-line anti-hyperglycemic therapy, the European Society of Cardiology diabetes guideline[52] recommends that GLP-1RA or SGLT2i should be first-line therapy in individuals with ASCVD or at high or very high CV risk. Although there have been no specific trials to show cardiorenal benefit for GLP-1RA or SGLT2i when used as first-line therapy or as monotherapy or in newly diagnosed T2D, the benefit seen in the CV outcome trials has not been found to vary with the duration of diabetes, suggesting that similar benefits might be seen early in the course of disease.[4] The benefits are also not dependent on the presence of metformin.[8,53-55] Therefore, the inclusion of GLP-1RA or SGLT2i at the time of diagnosis of T2D in patients with ASCVD or multiple risk factors is a reasonable option and aligns with the views of Diabetes Canada.[3,4] In addition, the traditional role of metformin in the early management of T2D is not always appropriate if not tolerated or contraindicated (eg, eGFR < 30 mL/min/1.73 m^2). In HF, including HFrEF and HFpEF, SGLT2i used in addition to other evidence-based HF therapies but without treatment with metformin were shown to improve major HF-related outcomes and quality of life within a short period of time after initiation of therapy. Moreover, benefit was seen in patients with and those without T2D.[8,53-55]

SGLT2i reduce hospitalization for HF[15,20] and reduce progression of nephropathy[15,19] in persons with T2D and CV risk factors only; benefits to reduce MACE or mortality, at least within the short-term duration of the trials to date, are less certain.[56,57] Conversely, in such patients, GLP-1RA seem to reduce MACE,[9,12,13] a factor that might help selection between SGLT2i or GLP-1RA for A1c reduction. Our analyses (Table 1) indicate that the reduction of nonfatal stroke is strongest for GLP-1RA, which might also factor into the initial choice of classes.

Opinions vary about whether beneficial effects are general to a class or specific to individual agents. Although network meta-analyses have attempted to provide comparisons of specific SGLT2i or GLP-1RA, no head-to-head trials are currently available that help differentiate between medications within either of these 2 classes.[56,58] Consequently, the writing group consensus emphasizes class effects but recognizes that some outcomes have been associated with specific agents (Table 3). Using both classes together to achieve glycemic targets when needed appears to be a reasonable option. However, it is not known whether additional cardiorenal benefit can be expected by combining both classes, although the potential mechanisms might be complementary. The most recent GLP-1RA CV outcome trial showed similar benefit whether the patient was using SGLT2i or not.[10,59] Finally, an individualized approach to therapy should also weigh the individual's preferences, costs and coverage, side effect profile, consideration of kidney function and glucose-lowering efficacy, desire for weight loss, and comorbidities such as frailty. Although diminished kidney function attenuates the glucose-lowering effects of SGLT2i, cardiorenal protection is maintained with an eGFR $>$ 20-25 mL/min/1.73 m^2.[21,22,36]

Table 4. Side effects and mitigation strategies

	Mitigation strategies
Side effects of SGLT2 inhibitor use	
Genital mycotic infections	• Explain mechanism of action • Maintain genital hygiene (rinse, wipe; advise that episodes rarely recur after treatment) • Consider prescription of anti-mycotic 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 $\geq$ 45 mL/min/1.73 m^2. See Figure 2 for mitigation strategies
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 SGLT2i in acute illness • Hold 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	
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

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

Practical Considerations for Integrating GLP-1RA and SGLT2i Into Practice

When using these classes for cardiorenal benefit, one must consider potential side effects and advise on strategies to minimize them (Table 4 and Fig. 2).[3-5,60-65]

The most common side effects of GLP-1RA are gastrointestinal (nausea, vomiting, diarrhea). These side effects are most prominent at initiation of treatment and usually improve over time. Mitigation strategies are shown in Table 4. Note that a dipeptidyl peptidase 4 (DPP-4) inhibitor can be discontinued when adding GLP-1RA because they are both incretin-based therapies and the DPP-4 inhibitor is redundant

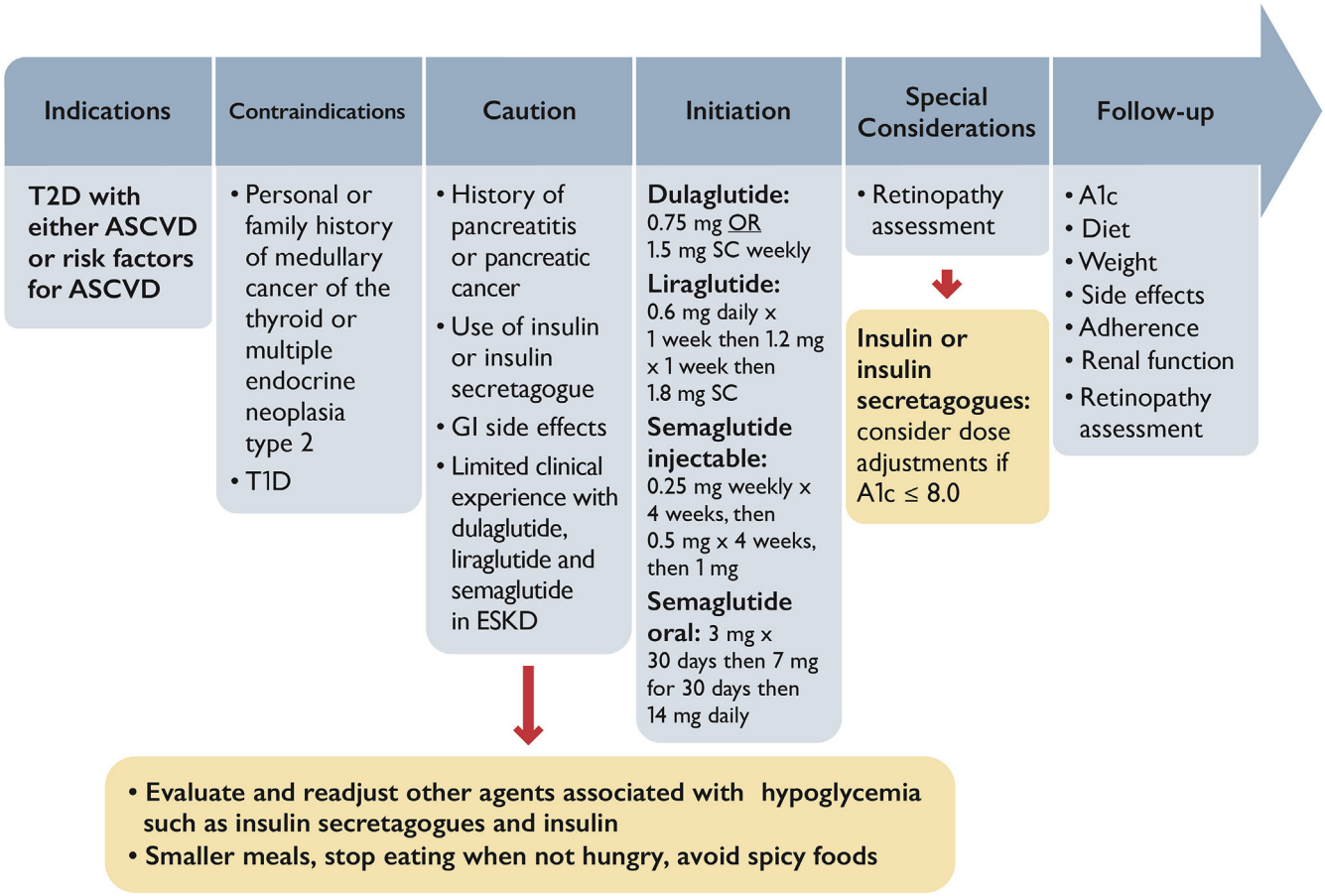

Figure 4. Practical approach to the use of glucagon-like peptide-1 receptor antagonists (GLP-1RA) for cardiorenal risk reduction. A1c, glycosylated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; ESKD, end-stage kidney disease; GI, gastrointestinal; T1D, type 1 diabetes; T2D, type 2 diabetes; SC, subcutaneously.

in that situation. In the SUSTAIN 6 trial of subcutaneous once weekly semaglutide, more retinopathy events occurred in the semaglutide group. However, this increase appears to be due to the rapid and robust glucose-lowering in people with marked hyperglycemia and preexisting retinopathy—a phenomenon previously observed in studies of insulin. In those patients, glucose-lowering is still desired but simultaneous regular examinations by an eye care professional is critical so that any changes can be addressed in a timely fashion. The long-term benefits of glucose control on the eyes far outweigh any acute risk.

The most common adverse effect of SGLT2i is genital mycotic infections (GMIs). Women (10%-15% risk), those with previous GMI, and uncircumcised men are at highest risk. GMI risk can be reduced with appropriate genital hygiene strategies and when they occur, can typically be managed with antifungal drugs and do not require discontinuation of therapy.

The risk of hypoglycemia is an important consideration if patients are using insulin secretagogues (meglitinides and sulfonylureas) and/or insulin (Fig. 2). The risk of hypoglycemia is greater if the eGFR is > 45 mL/min/m^2 or the A1c is close to target in which case a reduced dose of insulin secretagogues and/or insulin should be considered and additional self-blood glucose monitoring and counselling around hypoglycemia symptoms and treatment are recommended. The risk of hypoglycemia is lower if A1c is $> 8\%$. If SGLT2i are used in those with eGFR < 45 mL/min/1.73 m^2 the risk is lower because the glycemic-lowering effect of SGLT2i is minimal. In contrast, for GLP-1RA, the potential for glucose-lowering is present across the eGFR spectrum. To decide if adjustment of existing insulin secretagogues and/or insulin is needed, consider the current A1c. If A1c is $> 8\%$, then the addition of these agents is less likely to cause hypoglycemia but the patient should be counselled about the potential for hypoglycemia. However, if the A1c is $\leq 8\%$, then a reduction in the dose or discontinuation of the insulin secretagogue is warranted to avoid hypoglycemia. In the case of insulin, dose reduction by 10%-20% or more might be required to avoid hypoglycemia. Communication with the patient's diabetes team is critical when any such changes to therapy are being considered, especially for SGLT2i, as aggressive reduction of insulin is a risk factor for DKA.

SGLT2i have been associated with DKA (incidence 0.1%) among patients with diabetes. Patients with SGLT2i-associated DKA might present with normal or only modestly elevated blood glucose level (< 14 mmol/L). Inadequate insulin remains the cause of DKA and therefore, mitigation strategies shown in Table 4 can reduce the risk. Nonspecific symptoms associated with DKA include:

shortness of breath, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and lethargy. Patients without diabetes are not at risk of DKA when these agents are used.[64]

SGLT2i use might result in a temporary decrease in eGFR of up to 15%-25%, which generally resolves in 1-3 months and is not usually a sign of acute kidney injury. The decrease in eGFR is expected and results from a decrease in intraglomerular pressure induced by these agents, conceptually similar to what is seen with ACEi and ARB. In fact, trial evidence suggests that there is no increase or even a reduction in acute kidney injury.[61] Accordingly, this eGFR reduction should not result in premature discontinuation of SGLT2i, which favourably modifies kidney outcomes. Despite this reassurance, attention to volume status is always required, especially when SGLT2i, ARNIs, and loop diuretics are used in combination because of their additive effects to promote diuresis. SGLT2i should be stopped temporarily in the setting of concomitant dehydrating illness as part of "sick day" management.[62] Caution is warranted in patients with very low and variable BP or when kidney function is already extremely compromised. Currently, canagliflozin and dapagliflozin are contraindicated in patients undergoing dialysis and empagliflozin is contraindicated in patients with an eGFR < 20 mL/min/1.73 m^2. As indicated previously, referral to a specialist with expertise in CKD should be considered in the following situations: progressive loss of kidney function, urine UACR persistently > 60 mg/mmol, or progressive increase in UACR despite appropriate therapy, eGFR < 30 mL/min/1.73 m^2, inability to continue kidney-protective therapies because of adverse effects, such as hyperkalemia or a $> 30\%$ increase in serum creatinine within 3 months of starting SGLT2i, ACEi, or ARB, inability to achieve target BP, or signs/symptoms of another underlying kidney disease, such as glomerulonephritis.

The increased risk of amputation seen in the large, long-term **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) trial for canagliflozin, and select observational studies, merits further research but overall, there is currently no consistent evidence of SGLT2i exposure and increased risk of amputation.[65]

Summary and Conclusions

A remarkable paradigm shift has occurred with the availability of diabetes-related drugs with proven cardiorenal benefits in patients with and without T2D. We summarize our overview for appropriate, safe, and effective use of SGLT2i in Figure 3 and for GLP-1RA in Figure 4. CV medicine continues to progress with numerous new interventions shown to be clearly superior to historical standards of care and requiring practitioners to balance the proven benefits with administrative, economic, and access issues. These factors can complicate physician-patient decisions in the early stages of implementation but ultimately, evidence shows that more general incorporation of these treatments in appropriate patients will alter the natural course of disease. Achieving A1c targets continues to be an important goal for T2D. Also critical is the expeditious reduction of cardiorenal risk, thereby mandating a paradigm shift in prioritization of therapies. The profound benefits noted in the treatment of established HF or CKD or in the prevention of cardiorenal morbidity or mortality are not strongly tied to A1c-lowering. Accordingly, their initiation should not be predicated on the need for additional A1c-lowering. While upholding the principle of judicious stewardship of health care resources, it is imperative to advocate for lowering all hurdles to access of these classes of agents. Accordingly, the recommendations put forward can be considered ideal and aspirational, requiring tailoring to the specific and changing clinical environment faced by individuals with T2D, CKD, or HF and their health care professionals. This will require shared decision-making with the patient that reflects interdisciplinary collaboration from cardiologists, nephrologists, endocrinologists, primary care physicians, and pharmacists who should make every effort to integrate these diabetes-related agents with cardiorenal benefits into an overall and individualized treatment plan.

References

1. Mancini GBJ, Cheng AY, Connelly K, et al. Diabetes for cardiologists: practical issues in diagnosis and management. Can J Cardiol 2017;33:366-77.
2. Mancini GBJ, Cheng AY, Connelly K, et al. CardioDiabetes: core competencies for cardiovascular clinicians in a rapidly evolving era of type 2 diabetes management. Can J Cardiol 2018;34:1350-61.
3. Lipscombe L, Butalia S, Dasgupta K, et al. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update. Can J Diabetes 2020;44:575-91.
4. Senior PA, Houlden RL, Kim J, et al. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update - the user's guide. Can J Diabetes 2020;44:592-6.
5. O'Meara E, McDonald M, Chan M, et al. CCS/CHFS heart failure guidelines: clinical trial update on functional mitral regurgitation, SGLT2 inhibitors, ARNI in HFpEF, and tafamidis in amyloidosis. Can J Cardiol 2020;36:159-69.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98:S1-115.
7. Ali MU, Mancini GBJ, Fitzpatrick-Lewis D, et al. The effectiveness of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists on cardiorenal outcomes: systematic review and meta-analysis. Can J Cardiol 2022;38:1201-10.
8. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519-29.
9. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121-30.
10. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med 2021;385:896-907.
11. Holman RR, Bethel MA, Hernandez AF. Once-weekly exenatide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:2502.
12. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.

13. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.

14. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51.

15. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

16. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.

17. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.

18. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

19. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

21. Packer M, Anker SD, Butler J, et al. Empagliflozin in patients with heart failure, reduced ejection fraction, and volume overload: EMPEROR-Reduced Trial. J Am Coll Cardiol 2021;77:1381-92.

22. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-61.

23. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35.

24. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384:129-39.

25. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117-28.

26. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.

27. Whitelaw S, Pellegrini DM, Mamas MA, Cowie M, Van Spall HGC. Barriers and facilitators of the uptake of digital health technology in cardiovascular care: a systematic scoping review. Eur Heart J Digit Health 2021;2:62-74.

28. Martinez FA, Serenelli M, Nicolau JC, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation 2020;141:100-11.

29. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. Circulation 2020;142:1040-54.

30. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation 2020;141:90-9.

31. Serenelli M, Böhm M, Inzucchi SE, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). Eur Heart J 2020;41:3402-18.

32. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. Circulation 2021;143:298-309.

33. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020;396:819-29.

34. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.

35. Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-Reduced trial. Circulation 2021;143:337-49.

36. Packer M, Butler J, Zannad F, et al. Empagliflozin and major renal outcomes in heart failure. N Engl J Med 2021;385:1531-3.

37. Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. Eur Heart J 2022;43:416-26.

38. ClinicalTrials.gov. A study of tirzepatide (LY3298176) in participants with heart failure with preserved ejection fraction and obesity (SUMMIT). Available at: https://clinicaltrials.gov/ct2/show/NCT04847557. Accessed November 29, 2021.

39. ClinicalTrials.gov. Research study to investigate how well semaglutide works in people living with heart failure and obesity (STEP-HFpEF). Available at: https://clinicaltrials.gov/ct2/show/NCT04788511. Accessed November 15, 2021.

40. ClinicalTrials.gov. Dapagliflozin and effect on cardiovascular events in acute heart failure - thrombolysis in myocardial infarction 68 (DAPA ACT HF-TIMI 68). Available at: https://clinicaltrials.gov/ct2/show/NCT04363697. Accessed November 8, 2021.

41. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28:568-74.

42. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med 2022;28:809-13.

43. ClinicalTrials.gov. A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW). Available at: https://clinicaltrials.gov/ct2/show/NCT03819153. Accessed November 29, 2021.

44. EMPA-Kidney Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transplant 2022;37:1317-29.

45. Shaman AM, Bain SC, Bakris GL, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: a pooled analysis of SUSTAIN 6 and LEADER trials. Circulation 2022;145:575-85.

46. Leiter LA, Bain SC, Hramiak I, et al. Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. Cardiovasc Diabetol 2019;18:73.

47. Goldenberg RM, Cheng AYY, Fitzpatrick T, Gilbert JD, Verma S, Hopyan JJ. Benefits of GLP-1 (glucagon-like peptide 1) receptor agonists for stroke reduction in type 2 diabetes: a call to action for neurologists. Stroke 2022;53:1813-22.

48. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with

conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

49. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.

50. ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39:701-8.

51. Mancini GBJ, Maron DJ, Hartigan PM, et al. Lifestyle, glycosylated hemoglobin A1c, and survival among patients with stable ischemic heart disease and diabetes. J Am Coll Cardiol 2019;73:2049-58.

52. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255-323.

53. Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? Diabetes Obes Metab 2020;22:631-9.

54. Ferrannini G, Gerstein H, Colhoun HM, et al. Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. Eur Heart J 2021;42:2565-73.

55. Crowley MJ, McGuire DK, Alexopoulos AS, et al. Effects of liraglutide on cardiovascular outcomes in type 2 diabetes patients with and without baseline metformin use: post hoc analyses of the LEADER trial. Diabetes Care 2020;43:e108-10.

56. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ 2021;372:m4573.

57. Wright AK, Carr MJ, Kontopantelis E, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care 2022;45:909-18.

58. Duan XY, Liu SY, Yin DG. Comparative efficacy of 5 sodium glucose cotransporter 2 inhibitor and 7 glucagon-like peptide 1 receptor agonists interventions on cardiorenal outcomes in type 2 diabetes patients: a network meta-analysis based on cardiovascular or renal outcome trials. Medicine (Baltimore) 2021;100:e26431.

59. Lam CSP, Ramasundarahettige C, Branch KRH, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose co-transporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. Circulation 2022;145:565-74.

60. Lingvay I, Leiter LA. Use of GLP-1 RAs in cardiovascular disease prevention: a practical guide. Circulation 2018;137:2200-2.

61. Lin DS, Lee JK, Chen WJ. Clinical adverse events associated with sodium-glucose cotransporter 2 inhibitors: a meta-analysis involving 10 randomized clinical trials and 71 553 individuals. J Clin Endocrinol Metab 2021;106:2133-45.

62. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in canada: sick-day medication list. Can J Diabetes 2018;42:S316.

63. Canadian Heart Failure Society. Practical approach to SGLT2 inhibitors for treatment of cardiovascular disease. Available at: https://heartfailure.ca/sites/default/files/chfs_practical_approach_algorithm_sglt2i.pdf. Accessed November 8, 2021.

64. Goldenberg RM. Sodium-glucose cotransporter-2 inhibitors increase the risk of diabetic ketoacidosis in adults with type 2 diabetes: should we be concerned in people without diabetes? Can J Diabetes 2022;46:109.

65. Fralick M, Kim SC, Schneeweiss S, Everett BM, Glynn RJ, Patorno E. Risk of amputation with canagliflozin across categories of age and cardiovascular risk in three US nationwide databases: cohort study. BMJ 2020;370:m2812.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.04.029.

Update

Canadian Journal of Cardiology
Volume 38, Issue 12, December 2022, Page 1979

DOI: https://doi.org/10.1016/j.cjca.2022.10.008

Canadian Journal of Cardiology 38 (2022) 1979–1980

Errata

Erratum to "Syncope in Patients With Severe Aortic Stenosis: More Than Just an Obstruction Issue" [Can J Cardiol (2021):284-291].

In the article, "Syncope in Patients With Severe Aortic Stenosis: More Than Just an Obstruction Issue" by Francisco-Pascual et al., published in the February 2021 issue (Can J Cardiol 202;37:284-291), an incomplete affiliation was assigned to 2 of the authors, Jaume Francisco-Pascual and Ignacio Ferreira González. These authors were incorrectly assigned the affiliation "Universitat Autònoma de Barcelona, Bellaterra, Spain," but the correct affiliation for these authors should have been listed as "**Department of Medicine,** Universitat Autònoma de Barcelona, Bellaterra, Spain."

Erratum to "2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults" [Can J Cardiol (2022):1153-1167].

In the article, "2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults" by Mancini et al., published in the August 2022 issue (Can J Cardiol 2022;38:1153-67), an author was accidentally omitted from the author list. Jonathan Y. Gabor, MD, should have been listed as the second author in the Secondary Panel section. Dr Gabor is affiliated with the Department of Cardiology, Selkirk Regional Health Centre, Selkirk, Manitoba, Canada. This information has been corrected in the online version of the article.

Erratum to "Evaluation of Saline-Enhanced Radiofrequency Needle-Tip Ablation for Ventricular Tachycardia (SERF VT CANADA Trial)" [Can J Cardiol (2022):1277-1285].

In the article, "Evaluation of Saline-Enhanced Radiofrequency Needle-Tip Ablation for Ventricular Tachycardia (SERF VT CANADA Trial)" by Sanchez-Somonte et al., published in the August 2022 issue (Can J Cardiol 2022;38:1277-1285), the second author's surname was misspelled as Dryda. The correct spelling is **Dyrda**. This information has been corrected in the online version of the article.

https://doi.org/10.1016/j.cjca.2022.10.007