

Sodium-glucose cotransporter inhibitors in type 2 diabetes: thinking beyond glucose lowering

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In contemporary clinical practice, there are numerous glucose-lowering agents available for the treatment of type 2 diabetes mellitus (T2DM): from older drugs such as metformin and sulfonylureas to newer agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors. In the past decade, large-scale randomized controlled trials (RCTs) of glucose-lowering agents have shown varying benefits on cardiovascular and kidney outcomes among patients with T2DM.¹ In particular, SGLT2 inhibitors are being prescribed increasingly by physicians in a wide range of specialties² because of cardiovascular and kidney benefits reported in large RCTs, the findings of which are reflected in several major guideline updates in the past 18 months. We review the mechanism of action of SGLT2 inhibitors, summarizing data from major cardiovascular and kidney outcome trials underpinning current treatment recommendations (Box 1), and discuss the use of these agents in clinical practice, including important safety issues.

How do SGLT2 inhibitors work?

Sodium-glucose cotransporter-2 inhibitors act by blocking the paired reuptake of sodium and glucose in the proximal tubule, thereby promoting urinary glucose excretion; these agents have been shown to lower glycated hemoglobin (HbA_{1c}) by about 0.5%–0.7% in individuals with normal kidney function.³ Owing to the associated caloric losses, SGLT2 inhibitors have also been shown to reduce body weight modestly (about 2–3 kg).³ Beyond their glucosuria-mediated effects, SGLT2 inhibitors promote urinary excretion of sodium (i.e., natriuresis). The natriuretic effect of SGLT2 inhibitors contributes to intravascular volume contraction and influences intrarenal hemodynamics, yielding about 5 mmHg reductions in systolic blood pressure and 30%–50% reductions in albuminuria in patients with micro- or macroalbuminuria.^{3–5} There is accumulating evidence that these nonglycemic, pleotropic effects are at least as important as glucose lowering in explaining the observed reduction in cardiovascular morbidity and mortality and protection against progression of diabetic kidney disease with SGLT2 inhibitors, both in RCTs and routine clinical practice.^{6,7}

KEY POINTS

- New type 2 diabetes mellitus (T2DM) guidelines have moved from a glycemic-based to an outcome-based approach, recommending treatments based on patient comorbidities.
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors are now recommended as second-line treatment after metformin in patients with T2DM and prior atherosclerotic cardiovascular disease, heart failure or chronic kidney disease in American and European guidelines.
- Sodium-glucose cotransporter-2 inhibitors have been shown to reduce substantially the risk of heart failure and progression of kidney disease in a wide range of patients with T2DM in large-scale randomized controlled trials.
- Recognized adverse events with SGLT2 inhibitors include mycotic genital infections and volume depletion, but clinicians should be aware of other uncommon but potentially serious adverse effects, particularly diabetic ketoacidosis (which can occur in the presence of normal or only mildly elevated blood glucose) and possibly amputations.

What have large-scale randomized controlled trials of SGLT2 inhibitors shown?

To date, there have been 4 large RCTs of SGLT2 inhibitors involving patients with T2DM, collectively enrolling 38 723 participants across 6 continents (Table 1). Three were cardiovascular outcome trials: EMPA-REG OUTCOME (empagliflozin),⁸ the CANVAS Program (CANVAS and CANVAS-R trials; canagliflozin)⁹ and DECLARE-TIMI 58 (dapagliflozin).¹⁰ These trials assessed the effect of SGLT2 inhibition on a primary outcome of major adverse cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke or cardiovascular death. In contrast, the CREDENCE trial was specifically designed to test the effect of SGLT2 inhibition on kidney outcomes in patients with established diabetic kidney disease, with a primary outcome of doubling of serum creatinine, end-stage kidney disease or death caused by cardiovascular or kidney disease.¹¹ All 4 studies were event-driven, double-blind, randomized, placebo-controlled trials with participants receiving guideline-directed care.

Box 1: Evidence used in this review

We conducted a targeted search of MEDLINE to identify randomized, controlled, event-driven, cardiovascular or kidney outcome trials of sodium-glucose cotransporter-2 inhibitors using the medical subject heading terms “sodium-glucose transporter 2 inhibitors,” “diabetes mellitus, type 2” and “randomized controlled trial.” Our search yielded 4 randomized studies that investigated the effect of empagliflozin, canagliflozin or dapagliflozin on cardiovascular and kidney outcomes. In addition, we used evidence provided in 3 recently updated North American and European clinical practice guidelines: the 2019 American Diabetes Association standards of care, the 2018 consensus report of the American Diabetes Association and the European Association for the Study of Diabetes, and the Diabetes Canada 2018 guideline for the pharmacologic glycemic management of type 2 diabetes. These were supplemented by recent literature from our own collection.

Overall evidence supports a moderate beneficial effect of SGLT2 inhibition on major adverse cardiovascular events, with proportional risk reductions of about 10% (Figure 1). The 3 cardiovascular outcome trials enrolled varying proportions of participants with a history of atherosclerotic cardiovascular disease (Table 1). About 60% of participants in DECLARE-TIMI 58 did not have prior cardiovascular disease and were thus at lower cardiovascular risk. In contrast, about two-thirds of those in the CANVAS Program and all participants in the EMPA-REG OUTCOME trial had a history of cardiovascular disease. A 2019 meta-analysis of these trials found that the reduction in major adverse cardiovascular events with SGLT2 inhibitors was primarily observed in those with established atherosclerotic cardiovascular disease (i.e., for the secondary prevention of cardiovascular events).⁶

Perhaps more strikingly, SGLT2 inhibitors consistently reduced the risk of admission to hospital for heart failure by about 30%, individually and overall across the completed trials (Figure 2). In contrast to their effect on major adverse cardiovascular events, the benefits for heart failure were consistent regardless of a history of heart failure or atherosclerotic cardiovascular disease,⁶ highlighting the unique kidney and systemic hemodynamic effects of these drugs.

Although these trials were not primarily designed to assess the effect of SGLT2 inhibition on progression of diabetic kidney disease, all 3 trials reported prespecified or post hoc effects on a composite kidney outcome, defined as either doubling of serum creatinine or 40% decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or death caused by kidney disease.¹²⁻¹⁴ In secondary analyses, there was clear and consistent evidence of renoprotection with proportional risk reductions of greater than 30% in each trial and overall (Figure 3).

The CREDENCE trial was reported most recently and was explicitly designed to determine the effects of SGLT2 inhibition in patients at high risk of kidney failure.¹¹ All participants had T2DM and macroalbuminuria and were required to be receiving maximum tolerated labelled dose of angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker for at least 4 weeks before being randomly assigned. The trial found that canagliflozin reduced the risk of the primary composite outcome of doubling of serum creatinine, end-stage kidney disease or death caused by cardiovascular or kidney disease (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.59–0.82) with separate evidence of benefit for end-stage kidney disease alone (HR 0.68, 95% CI 0.54–0.86). Canagliflozin also reduced the risk of major adverse cardiovascular events (HR 0.80, 95% CI 0.67–0.95) and admission to hospital for heart failure (HR 0.61, 95% CI 0.47–0.80). In absolute terms,

Table 1: Summary of the major randomized controlled trials of sodium-glucose cotransporter-2 inhibitors

Study characteristics	No. (%) of participants*			
	EMPA-REG OUTCOME ⁸ n = 7020	CANVAS program ⁹ n = 10 142	DECLARE-TIMI 58 ¹⁰ n = 17 160	CREDENCE ¹¹ n = 4401
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Dose, mg	10 or 25	100 or 300	10	100
Age, mean ± SD; yr	63.1 ± 8.7	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2
Sex, female	2004 (28.5)	3633 (35.8)	6422 (37.4)	1494 (33.9)
Follow-up time, median; yr	3.1	2.4	4.2	2.6
History of cardiovascular disease	7020 (100.0)	6656 (65.6)	6974 (40.6)	2220 (50.4)
History of heart failure	706 (10.1)	1461 (14.4)	1724 (10.0)	652 (14.8)
eGFR < 60 mL/min/1.73 m ² †	1819 (25.9)	2039 (20.1)	1265 (7.4)	2631 (59.8)
Micro- or macroalbuminuria	2782 (39.6)	3026 (29.8)	5199 (30.3)	4370 (99.3)
Primary outcome(s)	MACE	MACE	MACE and admission to hospital for heart failure or CV death	Doubling of serum creatinine level, ESKD, or CV or renal death

Note: CKD-EPI = chronic kidney disease epidemiology collaboration equation, CV = cardiovascular, eGFR = estimate glomerular filtration rate, ESKD = end-stage kidney disease, MACE = major adverse cardiovascular events (defined as nonfatal myocardial infarction, nonfatal stroke or CV death), MDRD = modification of diet in renal disease equation.

*Unless specified otherwise.

†eGFR based on the MDRD equation in the EMPA-REG OUTCOME trial⁸ and the CANVAS Program,⁹ and the CKD-EPI equation in DECLARE-TIMI 58¹⁰ and CREDENCE¹¹ trials.

treatment with canagliflozin would be expected to prevent 47 primary composite outcomes and 24 end-stage kidney disease events for every 1000 “CREDESCENCE-like” patients treated over 2.5 years, translating into numbers needed to treat of 21 and 42, respectively.

By what mechanisms do SGLT2 inhibitors achieve their varied effects?

The glycemic effect of SGLT2 inhibitors is dependent on glomerular filtration and substantially diminishes as kidney function declines.^{15,16} This is their hallmark feature. In contrast, the effect of SGLT2 inhibitors on major adverse cardiovascular events does

not appear to be influenced by kidney function, and relative (and absolute) effects on heart failure may even be greater in patients with an eGFR below 60 mL/min/1.73 m².^{6,17} In the CREDESCENCE trial, canagliflozin provided renoprotection down to an eGFR of 30 mL/min/1.73 m², despite markedly attenuated glycemic efficacy at lower ranges of eGFR,¹¹ an observation reinforced by previous data showing that benefits for kidney outcomes are independent of HbA_{1c} before and during therapy or by degree of reduction in HbA_{1c}.¹⁸ Collectively, these data in patients with reduced kidney function raise an important question: To what extent are the cardiovascular and kidney benefits of SGLT2 inhibitors due to glucose lowering?

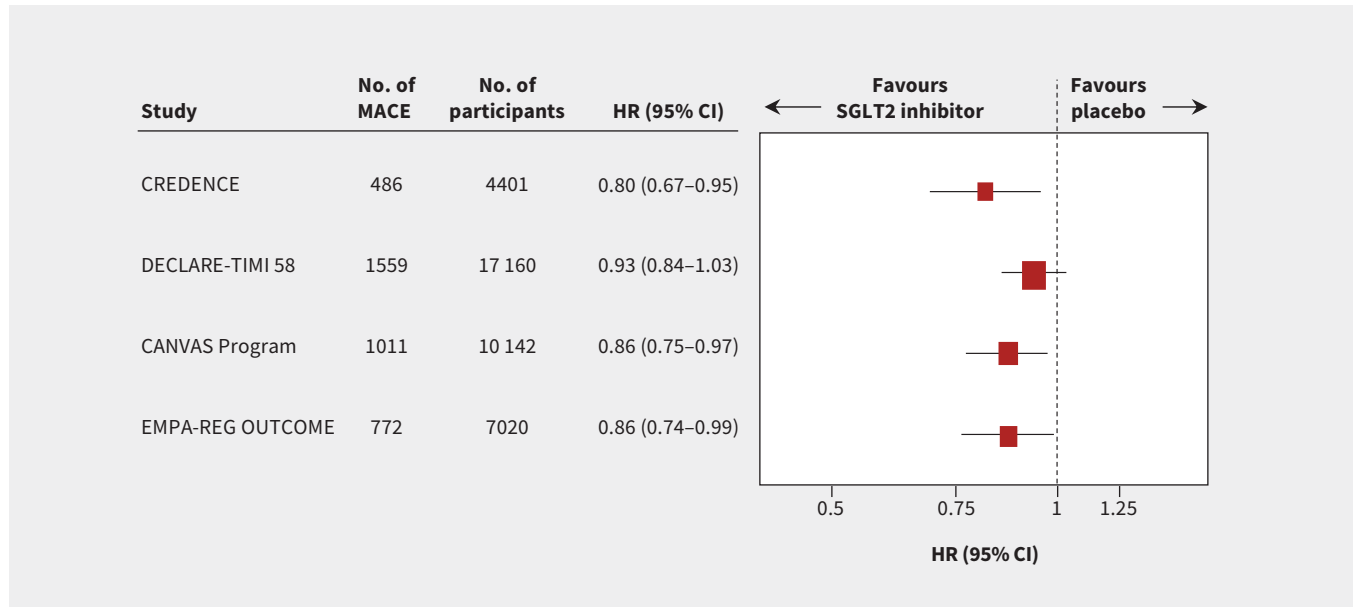


Figure 1: Major adverse cardiovascular events (MACE), defined as nonfatal myocardial infarction, nonfatal stroke or cardiovascular death (the size of each box is weighted using the inverse variance method). Note: CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose cotransporter-2.

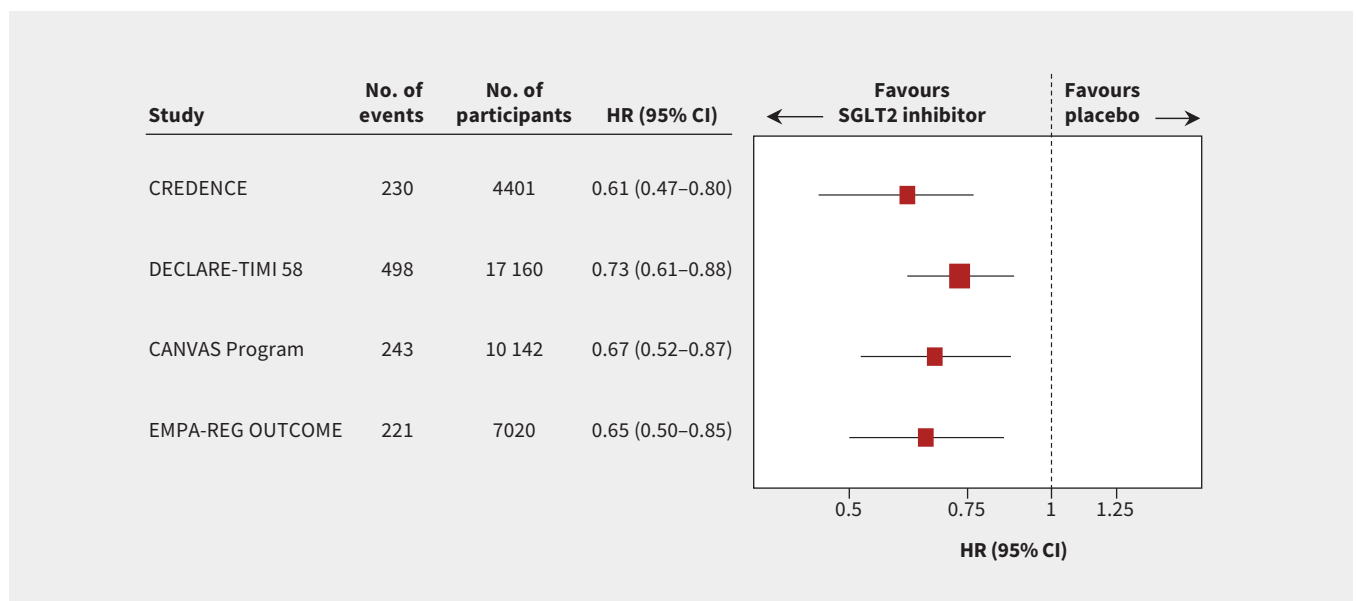


Figure 2: Admission to hospital for heart failure (the size of each box is weighted using the inverse variance method). Note: CI = confidence interval, HR = hazard ratio, SGLT2 = sodium-glucose cotransporter-2.

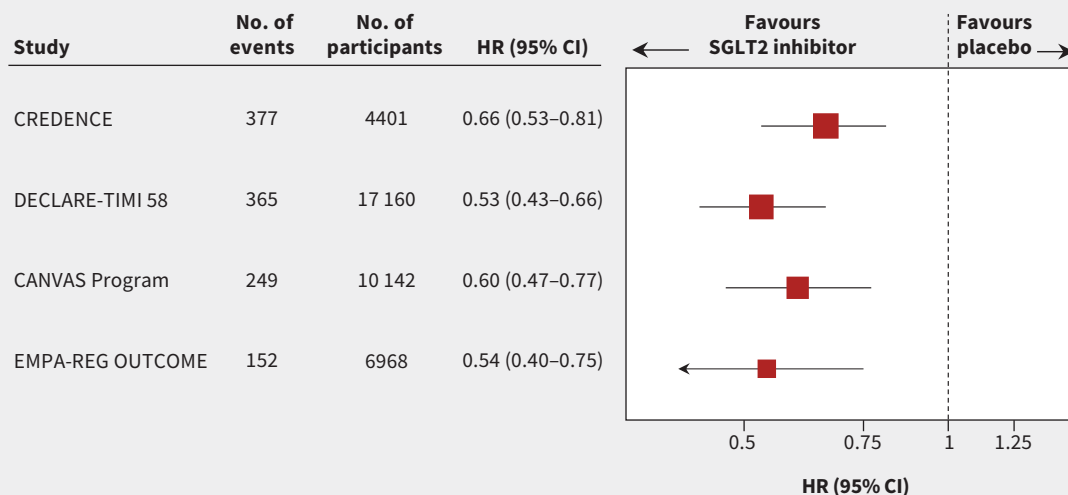


Figure 3: Substantial loss of kidney function, ESKD or death from kidney disease. Substantial loss of kidney function was defined as doubling of serum creatinine level in the CREDESCENCE¹¹ and EMPA-REG OUTCOME⁸ trials and sustained 40% decline in estimated glomerular filtration rate in the CANVAS Program⁹ and DECLARE-TIMI 58 trial.¹⁰ The size of each box is weighted using the inverse variance method. Note: CI = confidence interval, ESKD = end-stage kidney disease, HR = hazard ratio, SGLT2 = sodium-glucose cotransporter-2.

It is likely that several mechanisms (e.g., reduction in body weight, blood pressure and albuminuria) contribute to the observed reduction in cardiovascular and kidney outcomes with SGLT2 inhibitors. However, one of the most intriguing physiologic explanations is that SGLT2 inhibitors improve glomerular and systemic hemodynamics. It is well-established that chronic hyperglycemia promotes afferent arteriolar vasodilatation, which increases intraglomerular pressure — a crucial process in the pathogenesis of diabetic kidney disease.¹⁹ Sodium-glucose cotransporter-2 inhibitors are thought to lower intraglomerular pressure.^{20,21} By blocking proximal tubular sodium reuptake, these drugs increase distal sodium delivery to the macula densa, leading to afferent arteriolar vasoconstriction through a process called “tubuloglomerular feedback.” Clinically, this reduction in intraglomerular pressure is reflected in an acute “dip” in eGFR of about 5 mL/min/1.73 m², followed by stabilization and preservation of kidney function, and a reduction in albuminuria over time.³

This characteristic acute eGFR response with SGLT2 inhibitors is similar to that seen with the only other drugs approved by regulatory agencies for the treatment of diabetic kidney disease — ACE inhibitors and angiotensin II receptor blockers. Although SGLT2 inhibitors reduce intraglomerular pressure by possibly enhancing afferent arteriolar vasoconstriction, ACE inhibitors and angiotensin II receptor blockers do so by promoting efferent arteriolar vasodilatation.²² Importantly, the parallel and complementary mechanisms of SGLT2 inhibitors and ACE inhibitors or angiotensin II receptor blockers appear to be additive, with no signal toward increased risk of acute kidney injury in any of the completed trials. Most participants (99.9%) in the CREDESCENCE and about 80% of participants in the 3 cardiovascular outcome trials were receiving ACE inhibitors or angiotensin II

receptor blockers at baseline. The trials’ findings collectively suggest that these drugs might also reduce the risk of acute kidney injury, underscoring the importance of further mechanistic work to understand these drugs better.^{23,24}

What are the adverse effects of SGLT2 inhibitors?

Safety data suggest that SGLT2 inhibitors are generally well tolerated, with some important caveats.

Osmotic diuresis and symptomatic volume depletion because of glucosuric and natriuretic effects can occur, but are generally of modest severity.²⁵

There is about a threefold increased risk of mycotic genital infections, but not urinary tract infections,²⁶ which in most cases does not require permanent discontinuation of the drug. Men and women are both at increased risk, but the absolute risk may be greater in women, given the greater frequency of mycotic infections.

Although the absolute risk is extremely low, the US Food and Drug Administration (FDA) recently issued a warning about the risk of Fournier gangrene, based on 12 cases involving patients taking SGLT2 inhibitors in postmarketing surveillance analyses.²⁷ While this concern has been corroborated in a recent case series also using data from the FDA’s Adverse Event Reporting System,²⁸ more cases occurred in participants treated with placebo than in the dapagliflozin arm in the DECLARE-TIMI 58 trial,¹⁰ underscoring the challenges of interpreting routinely collected data because of confounding by indication and variably quality of reports. Notwithstanding the extremely low incidence and limitations of current data, prescribers should be aware of this uncommon outcome, especially given the importance of early recognition and treatment.

Another uncommon but potentially serious adverse effect of SGLT2 inhibitors is ketoacidosis, which can occur even in the presence of normal or only mildly elevated blood glucose levels.²⁹ This is because SGLT2 inhibitors stimulate lipolysis; the increased delivery of free fatty acids to the liver modestly increases circulating ketones.³⁰ In most patients, this effect is not clinically significant. It may, however, contribute to an increased risk of ketoacidosis in those with pancreatic insufficiency requiring long-term treatment with insulin. In many instances, ketoacidosis has occurred in the context of a precipitating factor, such as infection, omitted insulin or prolonged fasting.³¹ Although only 74 cases occurred in 38 723 participants in the completed trials (event rates of 0.1–2.2 per 1000 patient-years),^{6,11} it is possible that the incidence might be higher as the use of these agents in wider clinical practice becomes more common. Thus, it is important to have a high index of suspicion for this uncommon but potentially life-threatening adverse effect.

An increased risk of amputation of the lower extremities, mainly at the level of the metatarsals, and a small increased risk of fracture were unexpected and concerning findings in the CANVAS Program.⁹ The amputation rates across the CANVAS Program were 6.3 and 3.4 per 1000 person-years with canagliflozin and placebo, respectively (HR 1.97, 95% CI 1.41–2.75). In light of data from the CANVAS Program, the US FDA issued a Drug Safety Communication for canagliflozin about the risk of amputation.³² The risk of amputations has not been observed in trials of empagliflozin or dapagliflozin, or in CREDENCE, despite these patients being at much higher risk of amputation. Additionally, the risk of fracture was observed only in 1 of the 2 companion trials in the CANVAS Program (CANVAS but not CANVAS-R), and not in any other SGLT2 trials, including CREDENCE. It remains unclear whether these differences are related to patient characteristics, trial protocols or chance.

How has the evidence on SGLT2 inhibitors influenced updated guidelines?

In 2018, several clinical practice guidelines for the treatment of T2DM were updated with new algorithms to reflect the latest evidence for cardiovascular and kidney protection with specific glucose-lowering agents. Major guideline updates included the American Diabetes Association standards of care,³³ a consensus report by the American Diabetes Association and the European Association for the Study of Diabetes,³⁴ the American College of Cardiology's Expert Consensus Decision Pathway³⁵ and Diabetes Canada's clinical practice guideline.³⁶ The American Diabetes Association's standards of care were updated further in 2019 after the publication of findings from the CREDENCE trial.³⁷

Largely because of its cost, tolerability and safety, metformin remains first-line pharmacotherapy, alongside comprehensive lifestyle management. However, there is limited evidence that metformin reduces the risk of cardiovascular outcomes or progression of kidney disease, with unclear effect on all-cause mortality.³⁸ Because SGLT2 inhibitors and GLP-1 receptor agonists have been shown to reduce the risk of major adverse cardiovas-

cular events in large trials of cardiovascular outcomes, both are now recommended as second-line agents in patients with T2DM and established cardiovascular disease (Figure 4).^{33–36}

The 2018 consensus report by the American Diabetes Association and European Association for the Study of Diabetes and the American Diabetes Association's 2019 standards of care make additional specific recommendations on the use of SGLT2 inhibitors in patients with heart failure and chronic kidney disease.^{34,37} Because of the evidence that these drugs reduce the risk of admission to hospital for heart failure and clinically important kidney outcomes (Figures 2 and 3), SGLT2 inhibitors are now recommended as second-line treatment in people with T2DM and heart failure or chronic kidney disease in the American Diabetes Association and European Association for the Study of Diabetes guideline (Figure 4). In light of data from CREDENCE trial, the 2019 standards of care specifically recommended SGLT2 inhibitors for the prevention of kidney failure and cardiovascular events in patients with T2DM and an eGFR down to 30 mL/min/1.73 m², particularly in those with macroalbuminuria.³⁷

How should SGLT2 inhibitors be used in practice?

Based on current guideline recommendations,³⁴ SGLT2 inhibitors should be considered as second-line treatment after metformin in patients with T2DM and atherosclerotic cardiovascular disease, heart failure or chronic kidney disease (Figure 4).

We suggest they be avoided in patients with a history of ketoacidosis, because this may identify a subgroup of patients with relative insulin deficiency or other physiologic predisposition to this condition. Dapagliflozin has been approved recently for the treatment of type 1 diabetes;³⁹ however, treatment should be avoided generally outside RCTs other than after close consultation with specialist endocrinologists and a clear sick-day management plan, because of the much greater risk of ketoacidosis. Notwithstanding that no amputation signal was observed in CREDENCE, it would seem prudent to avoid these agents in patients with critical limb ischemia or a history of amputation while awaiting data from ongoing trials, given the adverse-effect profile observed in the CANVAS Program.

In Canada, there are 4 SGLT2 inhibitors approved for use in patients with T2DM: empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. Both empagliflozin and canagliflozin have label indications for the prevention of cardiovascular events in patients with established cardiovascular disease.^{40,41} Because glycemic efficacy is tied to glomerular filtration, their use has been limited in patients with reduced kidney function; however, in Canada, these restrictions have been revised recently. Empagliflozin is now permitted for use in patients with an eGFR down to 30 mL/min/1.73 m².⁴⁰ Guidelines also recommend that canagliflozin may be considered for use down to the same eGFR threshold for cardiovascular and kidney protection.^{36,40} These recommendations are reinforced by the 2019 updates to the American Diabetes Association's standards of care.³⁷

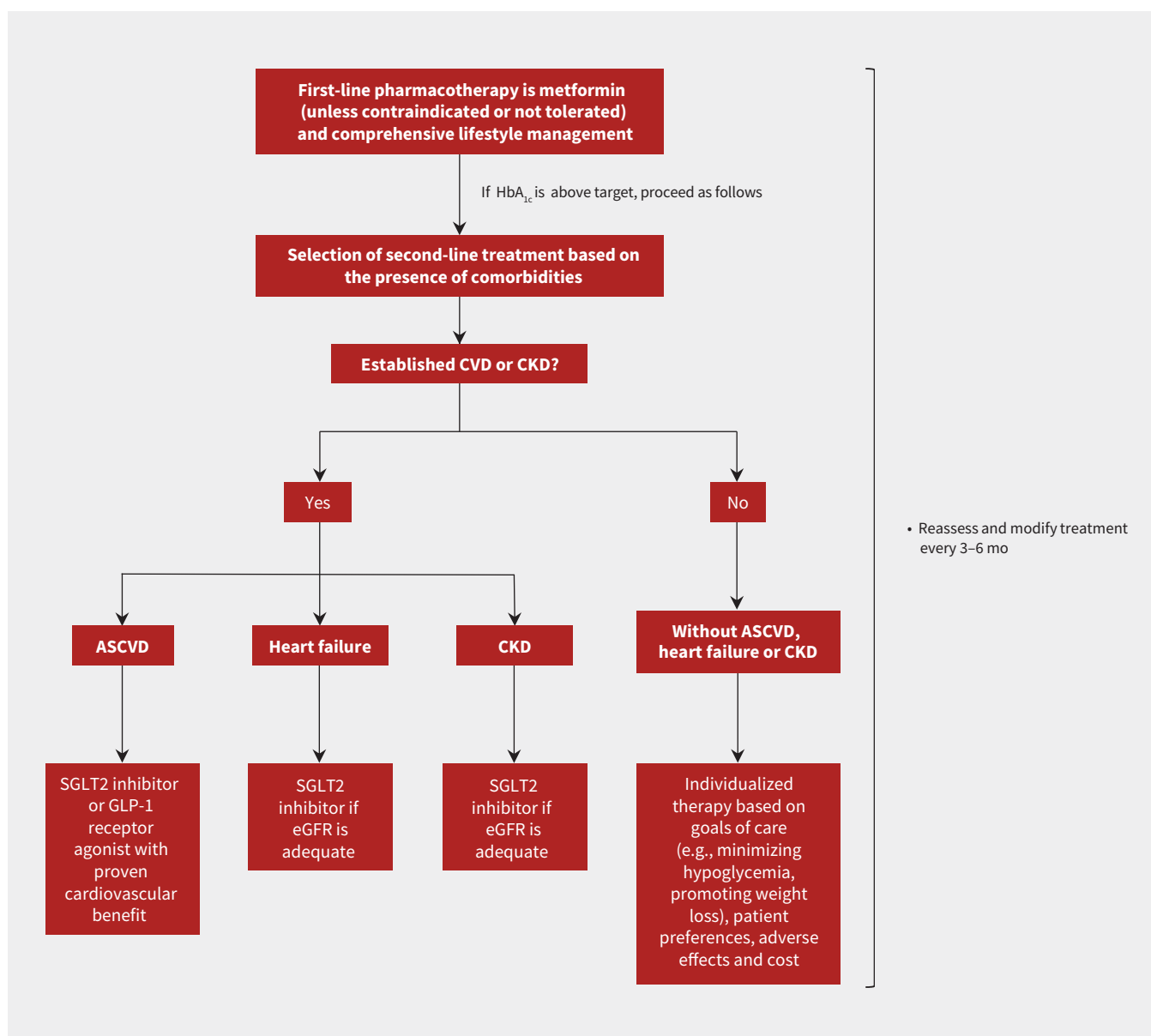


Figure 4: Summary of the overall approach to glucose-lowering medications in type 2 diabetes as recommended by the 2018 consensus report of the American Diabetes Association and European Association for the Study of Diabetes.³⁴ Note: ASCVD = atherosclerotic cardiovascular disease, CKD = chronic kidney disease, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, GLP-1 = glucagon-like peptide-1, HbA_{1c} = glycated hemoglobin, SGLT2 = sodium-glucose cotransporter-2.

Some other practical considerations are worth noting (Box 2). Patients taking concomitant diuretics may require dose adjustment to reduce the risk of volume depletion.⁴² Sodium-glucose cotransporter-2 inhibitors are insulin sparing and thus insulin doses should also be adjusted appropriately. At each consultation, patients should be carefully examined for any evidence of substantial ischemia in the lower extremities such as skin ulceration, and discontinuation of the drug in such cases may be prudent. Patients should be instructed to hold treatment if they are unable to tolerate oral intake, for example, owing to vomiting or diarrhea. These agents should also be withheld in the perioperative period to minimize the risk of ketoacidosis.⁴³

What research questions remain unanswered?

As these agents become increasingly used in a wider range of patients in routine practice, it will be important to continue to assess the generalizability of results from completed trials. A holistic assessment of absolute benefits, cost considerations, patient preferences and presence of multiple comorbidities is important to minimize harms and maximize benefits. These considerations might be particularly important in older, frail patients in whom the adverse effect profile may be prohibitive.

Several RCTs of SGLT2 inhibitors are expected to be completed and reported over the next 3–4 years and will provide additional important data. These include kidney outcome trials

Box 2: Practical suggestions for the use of sodium-glucose cotransporter-2 inhibitors

- Ensure patients are clinically stable and volume replete when commencing an sodium-glucose cotransporter-2 inhibitor.⁴²
- Consider reducing the dose of any concurrent loop diuretic (if euvolemic) and adjusting insulin dose appropriately.⁴²
- Emphasize the importance of personal hygiene to reduce the risk of mycotic infections.²⁵
- At each consultation, examine patients for signs of substantial lower extremity ischemia and consider drug withdrawal in such cases.³⁷
- Provide advice about withholding treatment if the patient is unable to eat or drink, such as during an acute illness.²⁹
- Temporarily withhold treatment before and after major surgery to reduce the risk of ketoacidosis.²⁵

for empagliflozin (EMPA-KIDNEY, ClinicalTrials.gov No. NCT03594110)⁴⁴ and dapagliflozin (DAPA-CKD, ClinicalTrials.gov No. NCT03036150), as well as trials of heart failure enrolling participants with reduced and preserved ejection fraction (i.e., EMPEROR-Reduced, ClinicalTrials.gov No. NCT03057977; EMPEROR-Preserved, ClinicalTrials.gov No. NCT03057951; and DELIVER, ClinicalTrials.gov No. NCT03619213). Because of the proposed nonglycemic mechanism of benefit, these trials are recruiting participants with and without diabetes. The recently completed DAPA-HF trial showed that dapagliflozin reduced the risk of heart failure in people with heart failure and reduced ejection fraction irrespective of diabetes status, providing further evidence that these drugs may benefit people without diabetes.⁴⁵

Conclusion

Sodium-glucose cotransporter-2 inhibitors are a practice-changing development in the treatment of T2DM, and data to date from completed trials support their ability to provide cardiovascular and kidney protection in addition to current standard of care. In combination with ongoing trials, this class of medication is shifting the therapeutic paradigm in T2DM from a glycemic-based to an outcome-based approach, as shown by the number and scope of recent updates to treatment guidelines for T2DM. Treatments should be selected based on end-organ protection and patient comorbidities rather than focusing on lowering of glucose levels alone.

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Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier and Vitae; and has received personal fees for consulting and scientific presentations related to canagliflozin from Mitsubishi Tanabe and Mundipharma.

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