# Type 2 Diabetes


# SGLT-2 Inhibitors and GLP-1 Agonists

## Evidence Review

## 2023

DALHOUSIE UNIVERSITY | FACULTY OF MEDICINE
Academic Detailing Service

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*"Seek simplicity, and mistrust it."*
*Alfred North Whitehead*

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# DEFINITIONS and ABBREVIATIONS

| | |
|---|---|
| A1C | Glycated hemoglobin |
| ACE | Angiotensin converting enzyme (inhibitor) |
| ACS | Acute coronary syndrome |
| ACVD | Atherosclerotic cardiovascular disease |
| Afib | Atrial fibrillation |
| ARB | Angiotensin receptor blocker |
| ARNI | Angiotensin receptor neprilysin inhibitor |
| ARR, ARI | Absolute risk reduction, absolute risk increase |
| BG | Blood glucose |
| CrCl | Creatinine clearance |
| CI | Confidence Interval |
| CKD | Chronic kidney disease |
| CV | Cardiovascular |
| CVD | Cardiovascular disease (Appendix B – definitions used in clinical trials) |
| CVOT | Cardiovascular outcome trial |
| DC | Diabetes Canada |
| DKA | Diabetic ketoacidosis |
| DM | Diabetes mellitus |
| DPP-4 | Dipeptidyl peptidase-4 (inhibitor) |
| DRP | Diabetic retinopathy |
| ECG | Electrocardiogram |
| EF | Ejection fraction |
| ER | Extended release |
| ESRD | End stage renal disease |
| GFR, eGFR | Glomerular filtration rate, estimated glomerular filtration rate |
| GLP-1 | Glucagon like peptide-1 (receptor agonist) |
| HDL | High density lipoprotein |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HHF | Hospitalization for heart failure |
| HR | Hazard Ratio |
| HUA | Hospitalization for unstable angina |
| IQR | Interquartile range |
| IV | Intravenous |
| LDL | Low density lipoprotein |
| LVEF | Left ventricular ejection fraction |
| MA | Meta-analysis |
| MACE | Major adverse cardiovascular event |
| MDRD | Modification of Diet in Renal Disease criteria |
| MEN 2 | Multiple Endocrine Neoplasia syndrome type 2 |
| MI | Myocardial infarction |

| | |
|---|---|
| MTC | Medullary thyroid cancer |
| NNT/NNH | Number needed to treat, number needed to harm (see page 20 for more information) |
| NS | Not statistically significant |
| NT-pro BNP | N-terminal pro b-type natriuretic peptide |
| NYHA HF | New York Heart Association heart failure, functional class |
| OR | Odds ratio |
| PVD | Peripheral vascular disease |
| QOE | Quality of evidence |
| RCT | Randomized controlled trial |
| RR | Relative risk |
| RRT | Renal replacement therapy |
| SC | Subcutaneous |
| SD | Standard deviation |
| SGLT-2 | Sodium glucose cotransporter 2 (inhibitor) |
| SR | Systematic review |
| SrCr | Serum creatinine |
| SU | Sulfonylurea |
| TIA | Transient ischemic attack |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TZDs | Thiazolidinediones |
| uACR | Urinary albumin-to-creatinine ratio |

# SUMMARY STATEMENTS

- The purpose of this document is to review evidence evaluating clinical efficacy and harm outcomes of sodium glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists in the treatment of adults with T2DM.

- Literature assessing the role of these agents for other indications was not reviewed.

- Metformin remains the first line pharmacological option for treatment of T2DM.[121]

## Question 1: What is the evidence for benefit of SGLT-2 inhibitors for macrovascular outcomes in the treatment of T2DM? Page 22

- SGLT-2 inhibitor use leads to small, statistically significant improvements in MACE in *some* people with T2DM.
    - Individuals with established CVD and those at high risk of developing CVD were included in the studies demonstrating this effect (EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58).[14-16]
        - Subgroup analyses evaluating MACE consistently suggest people with established CVD may be more likely to benefit than those at high risk. However, there is no high quality evidence to confirm this finding.
    - People with T2DM and low risk of CVD or newly diagnosed T2DM taking SGLT-2 inhibitors have not been evaluated for MACE in prospective RCTs. Results from the CVOTs do not apply to this group.
    - Wide confidence intervals around the primary outcome in the CVOTs reflect a lack of precision in the results, which may bring clinical relevance of these findings into question.

- SGLT-2 inhibitors were not used as monotherapy in clinical trials. The benefits observed in CVOTs occurred in people who were taking other glucose lowering drugs at baseline, including metformin (74 to 82%), insulin (43 to 48%), and SU (41 to 43%), among others.[14-16]

- Trial data do not suggest better glucose control was responsible for the beneficial outcomes. The difference in A1C reduction between groups was small, and decreased risk of CV death and all-cause mortality occurred early and continued throughout the trials, supporting an alternate mechanism of effect.[26]

- Although the evidence for use of SGLT-2 inhibitors for prevention of HF in people with T2DM is currently limited to secondary, hypothesis-generating outcomes, the beneficial effect appears to be consistent.[14-16, 27]

- Placebo controlled trials evaluating the effects of SGLT-2 inhibitors on clinical outcomes do not inform relative benefits or harms between agents within the same class.

## Question 2: What is the evidence for benefit of SGLT-2 inhibitors for microvascular outcomes in the treatment of T2DM? Page 37

### Effect on nephropathy

- The CREDENCE trial is the best available evidence evaluating renal outcomes in people with T2DM and stage 2 or 3 albuminuric CKD **(uACR >33.9 to 565.6 mg/mmol)**, treated with concomitant ACE inhibitor or ARB.[27]
    - In CREDENCE, people taking canagliflozin experienced a lower risk of a composite of ESRD, doubling of SrCr, renal or CV death compared to placebo
        - HR 0.70 (95% CI 0.59-0.82)
        - ARR 4.3%, NNT 24 over 2.62 years (95% CI 16-43)
            - NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.

- There is insufficient evidence to determine the effect of SGLT-2 inhibitors on renal outcomes in people with T2DM who do not fit the inclusion/ exclusion criteria of the CREDENCE trial, such as those with
    - eGFR < 30 or > 90 mL/min/1.73 $m^2$
    - Non-albuminuric or microalbuminuric kidney disease
    - CKD and short duration of T2DM

- SGLT-2 inhibitors appear to delay the progression of diabetic nephropathy, but do not treat it.

### Effect on diabetic retinopathy

- There are no prospective RCTs designed to evaluate the effect of SGLT-2 inhibitors on retinopathy.

- A *post hoc* analysis of the EMPA-REG OUTCOME trial suggests empagliflozin is not associated with an increased risk of retinopathy compared with standard care, but further study is required to confirm this finding.[28]

**Effect on neuropathy and peripheral vascular disease**

- There is insufficient evidence to determine the impact of SGLT-2 inhibitors on diabetic neuropathy and peripheral vascular disease (PVD).

## Question 3: What is the evidence for benefit of GLP-1 agonists for macrovascular outcomes in the treatment of T2DM? Page 49

- Evidence of benefit in MACE was observed with subcutaneous (SC) formulations of liraglutide, semaglutide, and dulaglutide, in people with established CVD or CKD and those at high risk of developing CVD.
    - Liraglutide and semaglutide have evidence of benefit for individuals with established CVD (LEADER, SUSTAIN-6).[18-19]
    - Dulaglutide has evidence of benefit for people with high risk of CVD (REWIND).[20]

- GLP-1 agonists were not used as monotherapy. The benefits observed in these trials occurred in people who were taking other glucose-lowering drugs at baseline, including biguanides (73 to 81%), insulin (24 to 58%), and SU (43 to 51%), among others.[18-20]

- The effect of GLP-1 agonists on MACE in people with T2DM and low risk of CVD, or newly diagnosed T2DM, has not been formally evaluated in prospective RCTs.

- It is not clear why some CVOTs identified improvements in MACE with GLP-1 agonists while others did not. Variable results *may* be attributed to differences in
    - Study population and design
    - Pharmacokinetics or pharmacology of individual drug therapies

- Hospitalization for HF (HHF) was evaluated as a secondary outcome in the GLP-1 agonist CVOTs, but no statistically significant differences between groups were observed.[17-21] These trials were not designed or powered to evaluate HF and should be interpreted with caution.

- Placebo controlled trials evaluating the effects of GLP-1 agonists on clinical outcomes do not inform relative benefits or harms between agents.

## Question 4: What is the evidence for benefit of GLP-1 agonists for microvascular outcomes in the treatment of T2DM? Page 66

- There are no high quality, prospective RCTs designed to evaluate the effect of GLP-1 agonists on microvascular outcomes in people with T2DM. Further study is required.

**Effects on nephropathy**

- Semaglutide (SC), liraglutide and dulaglutide may improve renal composite outcomes in people with T2DM and high baseline CV risk, based on *secondary outcomes and exploratory analyses*.[18-20]
    - Findings were driven by an improvement in macroalbuminuria, a surrogate marker.

- Results should be interpreted with *caution* because
    - The trials were not designed or powered to evaluate renal outcomes
    - There were potential confounders
    - The 95% CI around the NNTs were wide, reflecting uncertainty in the results.

**Effects on diabetic retinopathy**

- Compared to standard care, *secondary outcomes* in CVOTs showed
    - No statistically significant benefit in retinopathy with liraglutide (LEADER)[18], or a composite eye outcome with dulaglutide (REWIND)[20].
    - An *increased* risk of retinopathy with SC semaglutide in the SUSTAIN-6 study.[19]

- These findings should be interpreted with *caution* because
    - The trials were not designed or powered to evaluate retinopathy
    - Baseline rates and grading of retinopathy were not consistently reported
    - Event rates were low
    - There were potential confounders.

**Effects on neuropathy and peripheral vascular disease**

- There are no high quality clinical trials designed to evaluate the effect of GLP-1 agonists on neuropathy, PVD or amputation rates.

## Question 5: What are the potential *harms* associated with SGLT-2 inhibitors in the treatment of T2DM? Page 70

When treating people with T2DM with SGLT-2 inhibitors, it is always important to weigh the potential benefits and harms.

**Diabetic Ketoacidosis (DKA)**

- Health Canada[29] and the FDA[30] issued safety warnings regarding SGLT-2 inhibitor DKA.

- Studies report a 2-3 fold increased risk of DKA associated with SGLT-2 inhibitors compared to other glucose-lowering drugs.[31-32]

- A 2020 Canadian observational study by Douros et al. (N = 404,372) found an increased risk of DKA with SGLT-2 inhibitors compared to dipeptidyl peptidase- 4 (DPP-4) inhibitors[31]:
  - 2.03 vs 0.75 events per 1000 person-years
  - Adjusted HR 2.85 (95% CI 1.99-4.08), $I^2$ = 50%

- SGLT-2 inhibitor DKA may present with normal or near-normal BG levels.[33-36]

- People should temporarily stop taking their SGLT-2 inhibitor in situations where they are more vulnerable to developing DKA to mitigate risk.[33]
  - Acute illness
  - 3 days prior to major surgery
  - Low carbohydrate diets
  - Excessive alcohol use

- Other potential predisposing and/or precipitating factors for SGLT-2 inhibitor DKA include:[34-36]
  - Severe dehydration
  - Insulin dose reduction or omission
  - Low beta-cell function reserve
  - Pancreatic disorders causing insulin deficiency
  - History of DKA

- Careful consideration should be given to restarting SGLT-2 inhibitor following DKA to ensure the underlying cause has been addressed, is unlikely to recur, and that the potential benefits of therapy outweigh the potential risks.

**Volume-Depletion Related Adverse Effects**

- By nature of their mechanism of action, SGLT-2 inhibitors cause osmotic diuresis which may lead to hypovolemia and volume-depletion related adverse events such as postural dizziness, syncope, hypotension, and orthostatic hypotension.[34-36]

- The evidence describing these effects is limited.
  - RCTs report a mean decrease in BP of ~ 4/1 mmHg with SGLT-2 inhibitors compared to standard care.[14-16]
  - Incidence rates for hypovolemia (defined as symptomatic hypotension, orthostatic hypotension, postural dizziness, syncope) are higher in older adults, people with moderate renal impairment (eGFR < 60 mL/min/1.73m$^2$) and those taking concomitant antihypertensives, especially loop diuretics, compared to people without these risk factors.[14-16, 37-39]

**Acute Kidney Injury (AKI)**

- Despite early safety warnings[40] of AKI with SGLT-2 inhibitors, with some cases requiring hospitalization and dialysis, further investigations did not reveal an increased risk of AKI vs other glucose-lowering drugs.[14-16, 41-42]
    - Note EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58 were not designed to evaluate AKI.

- In EMPA-REG OUTCOME and the CANVAS Program a decline in eGFR of ~ 3-5 mL/min was observed in the treatment group during the first 4-8 weeks of therapy.[15, 43]
    - Upon cessation of therapy, the decrease was reversed.
    - Following initial decline, eGFR stabilized in the SGLT-2 inhibitor groups but continued to gradually decline in the standard care groups for the remainder of the trials.

- Health Canada product monographs recommend to:[34-36]
    - Avoid SGLT-2 inhibitors in people who are volume depleted or at risk of volume depletion.
    - Assess baseline renal function and monitor throughout therapy.

**Hypoglycemia**

- When used alone, SGLT- 2 inhibitors by nature of their insulin-independent mechanism of action, are not associated with hypoglycemia.[44]
    - Hypoglycemia incidence is increased with concomitant use of SGLT-2 inhibitors and insulin or SU, agents known to increase hypoglycemia risk.[34-36]
        - Insulin or SU dose reduction may help reduce hypoglycemia.

- A 2019 meta-analysis (MA) of EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58 and CREDENCE by Arnott et al. found *no associated increased risk of hypoglycemia* with SGLT-2 inhibitors compared to standard care.[32]
    - RR 0.82 (95% CI 0.65-1.03), $I^2$ = 11.7%
    - There was higher use of insulin, SU and thiazolidinediones (TZDs) in the standard care group throughout the trial to achieve BG targets in both groups, with no analysis to explore this difference as a potential confounder.

- A 2019 Cochrane Review by Madsen et al. found an increased risk of mild to moderate and serious hypoglycemia with metformin + SU vs metformin + SGLT-2 inhibitors (low-very low quality evidence).[45]
    - Absolute rates of serious hypoglycemia were low *(see Table K, page 74)*
        - 1.4% metformin + SU vs 0.3% metformin + SGLT-2 inhibitors
        - Risk ratio 6.16 (95% CI 2.92-12.97), $I^2$ = 93%

- Hypoglycemia was evaluated as a secondary outcome in this analysis. Hard outcomes (e.g., all-cause mortality, CV mortality, serious AEs, non-fatal stroke or MI) were not statistically significant for any of the groups.

**Genital Mycotic Infections (GMI)**

- Health Canada product monographs,[34-36] RCTs,[14-16] and observational studies[46-47] consistently report ~ 3 fold increased risk of GMI in people taking SGLT-2 inhibitors vs standard care, in keeping with the mechanism of increased glycosuria.

- A 2021 review of Prevention and Management of Genital Mycotic Infections in the Setting of SGLT-2 Inhibitors by Engelhardt et al. reports the following:[48]
  - Factors associated with the highest risk of GMI are female sex, prior history of chronic or recurrent GMIs (≥ 3/year) and uncircumcised males.
  - Most GMIs are mild-moderate in severity, responsive to appropriate treatment (e.g., topical or oral antifungal therapy) and do not necessitate stopping SGLT-2 inhibitor therapy.

**Fournier's Gangrene**

- There is very limited evidence to report due to low event rates of this rare but serious infection of necrotizing fasciitis of the perineum.

- Health Canada product monographs[34-36] and an FDA Safety Announcement[49] include prescribing warnings for Fournier's gangrene based on post-market case reports. When suspected, initiate prompt treatment of infection and discontinue the SGLT-2 inhibitor.

**Urinary Tract Infection (UTI)**

- Despite earlier warnings of UTI risk with SGLT-2 inhibitors use,[30] the best available evidence *did not find an associated increased risk* of severe or mild to moderate UTIs with SGLT-2 inhibitors compared to other glucose-lowering drugs.[50-51]

**Lower Limb Amputation (LLA)**

- The Health Canada product monograph for canagliflozin (Invokana®)[35] includes a serious warning regarding an associated ~ 2-fold increased risk of LLA based on findings from the CANVAS Program.
  - Canagliflozin 6.3 vs standard care 3.4 events per 1000 patient-years, $P < 0.001$[15]
  - Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events.[35]
  - Risk of amputation was highest in individuals with history of prior amputation, PVD and neuropathy.[35]

- Subsequent studies (CREDENCE, DECLARE-TIMI 58, EMPA-REG OUTCOME *post-hoc* analysis) have not replicated this finding with *any* of the SGLT-2 inhibitors;[14, 16, 27] however, these studies amended their protocols to control for risk of LLA, making it difficult to detect a difference if one truly exists.

- A Canadian observational study found no increased risk of LLA with SGLT-2 inhibitors compared to DPP-4 inhibitors;[52] however, there are limitations to this study including short duration (< 1 year), which may not be long enough to evaluate this outcome.
    - SGLT-2 inhibitors 1.3 vs DPP-4 inhibitors 1.5 events per 1000 person-years
    - Adjusted HR 0.88 (95% CI 0.71-1.09)

**Fracture**

- Health Canada product monographs warn of fracture risk with canagliflozin,[35] but not empagliflozin and dapagliflozin,[34, 36] based on one RCT.[53]

- Subsequent studies[15, 54-55] have not replicated this risk with SGLT-2 inhibitors compared to other glucose-lowering drugs.

## Question 6: What are the potential *harms* associated with GLP-1 agonists in the treatment of T2DM? Page 80

**Pancreatic Adverse Events**

- Early observational studies and pharmacovigilance data yielded conflicting reports on risk of pancreatitis and pancreatic cancer with GLP-1 agonists.[56]

**Pancreatitis**

- The product monographs for GLP-1 agonists contain similar warnings for pancreatitis. For example, the product monograph for SC semaglutide reads: “Patients should be informed of the characteristic symptoms of acute pancreatitis. After initiation of [semaglutide], observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, [semaglutide] should be discontinued; if confirmed, [semaglutide] should not be restarted. Consider anti-diabetic therapies other than [semaglutide] in patients with a history of pancreatitis.”[57]

- A large, observational study,[56] and 2 recent MAs of RCTs[58-59] have reported no increased risk of pancreatitis with GLP-1 agonist use.

**Pancreatic Cancer**

- A large observational study with median follow-up of 1.3-2.8 years reported no increased risk of pancreatic cancer with incretin-based drugs compared to users of SU. In a secondary analysis there was no increased risk with GLP-1 agonists.[60]

- A MA of RCTs with median follow up 1.3-5.4 years reported no increased risk of pancreatic cancer with GLP-1 agonist compared to standard care.[59]

- As the latency period for the development of pancreatic cancer is lengthy,[59] the above studies may not be long enough to observe a difference in rates of pancreatic cancer. Additional observational studies are required to monitor for the potential of this serious adverse event.

**Thyroid Cancer**

- GLP-1 agonists are contraindicated in people with a personal or family history of medullary thyroid cancer (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).[57, 61-64]

- The examination of this rare, but serious event is the subject of ongoing evaluation over long term observational studies.

**Gallbladder**

- A MA of RCTs[65] and an observational study[66] reported an increased risk of bile duct and gallbladder disease with GLP-1 agonist use compared to placebo and active comparators. It is difficult to accurately quantify this relationship. Limitations in these studies include:
    - Baseline rates of gallbladder disease were not evaluated
    - A composite of clinically important and surrogate outcomes was evaluated (e.g., cholecystitis and asymptomatic cholelithiasis).

- There is speculation regarding the cause of this potential association with gallbladder disease, such as drug induced weight loss or a direct effect of GLP-1 agonist on gallbladder motility; however, the exact mechanism is unknown.[65]

**Diabetic Retinopathy**

- DRP was evaluated as a secondary outcome in three CVOTs (LEADER, REWIND and SUSTAIN-6),[18-20] which compared GLP-1 agonist with standard care. The outcomes were mixed.
    - A statistically significant increase in DRP was reported with sc semaglutide in the SUSTAIN-6 trial.[19]

- This effect was not observed with liraglutide in LEADER[18] or with dulaglutide in REWIND.[20]
- It is difficult to draw conclusions comparing this outcome across different GLP-1 agonists as the event rates were low, the studies were not designed to evaluate DRP, and the severity and baseline rates of retinopathy were inconsistently reported.

➢ A large observational study comparing GLP-1 agonist use with new users of two or more oral antihyperglycemic agents reported that GLP-1 agonist use is not associated with an increased risk of DRP.[67]
  - Adjusted HR 1.0 (95% CI 0.85-1.17)

**Breast Cancer**

➢ A 2016 observational study concluded that GLP-1 agonists were not associated with an increased risk of breast cancer in women with T2DM compared with DPP-4 inhibitors.[68]

➢ A 2020 matched cohort study comparing new users of GLP-1 agonists with users of other oral antihyperglycemic agents reported no associated increased detection of breast cancer.[69]

**Acute Kidney Injury (AKI)**

➢ There are case reports of AKI in some patients treated with GLP-1 agonists.[70] There are no trials examining renal outcomes with GLP-1 agonists as a primary outcome; however CVOTs with GLP-1 agonists have explored this as secondary outcomes and suggest that there may be a beneficial effect on renal outcomes as discussed on page 65.[18-20]

**GI Adverse Events**

➢ GI effects such as nausea, vomiting and diarrhea, are well known adverse effects from GLP-1 agonists, and are the main adverse event related cause of drug discontinuation in phase 3 trials.[18-20]

➢ It is not clear whether these effects are mediated by direct effect on the GI tract such as delayed gastric emptying, or by an interaction with the central nervous system.[71]

**Hypoglycemia**

➢ GLP-1 agonists alone do not appear to increase the risk of hypoglycemia.

- Hypoglycemia incidence is increased with concomitant use of GLP-1 agonists and insulin or SU, agents known to increase hypoglycemia risk.[57,61-64]
    - Insulin or SU dose reduction may help reduce hypoglycemia.

➢ Hypoglycemia rates were similar between GLP-1 agonists and standard care in LEADER (liraglutide), REWIND (dulaglutide), PIONEER-6 (semaglutide PO), and SUSTAIN-6 (semaglutide SC).[18-21] Study protocols specified that insulin and non-investigational glucose-lowering drug doses be reduced to minimize risk of hypoglycemia, which may confound results.

➢ A 2019 Cochrane Review by Madsen et al. found no increased risk of serious hypoglycemia with metformin + SU vs metformin + GLP-1 agonist. An increased risk of mild to moderate hypoglycemia was reported with metformin + SU vs metformin + GLP-1 agonist (low-very low quality evidence).[45]
    - Hypoglycemia was evaluated as a secondary outcome in this analysis. Hard outcomes (e.g., all-cause mortality, CV mortality, serious AEs, non-fatal stroke or MI) were not statistically significant for any of the groups.

## Question 7: How do Diabetes Canada guideline recommendations align with the evidence? Page 92

➢ Diabetes Canada recommendations are based on best available evidence. Strong evidence is not always available, and in these scenarios authors rely on expert opinion and extrapolation from the literature.
    - Table N highlights how the evidence supports select Diabetes Canada pharmacotherapy recommendations pertaining to SGLT-2 inhibitors and GLP-1 agonists, and where a greater degree of extrapolation and reliance on expert opinion were required.

# INTRODUCTION

- The purpose of this document is to review evidence evaluating clinical efficacy and harm outcomes of sodium glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists in the treatment of adults with T2DM.

- Literature assessing the role of these agents for other indications aside from T2DM was not reviewed.

- Since our 2016 review on "Type 2 Diabetes: What after Metformin?"[1] there has been an abundance of new literature on these medication classes.

**Type 2 Diabetes Mellitus (T2DM)**

- Diabetes mellitus (DM) comprises two major forms which are distinctly different in their pathophysiology.[2]
  - Type 1 DM (T1DM) is an autoimmune disease in which the body destroys its pancreatic beta cells, resulting in a lack of insulin production.
  - Type 2 DM (T2DM) is primarily related to insulin resistance.

- Complications of T2DM include:[3-5]
  - Short-term
    - Hypoglycemia
    - Hyperosmolar hyperglycemic nonketotic syndrome
  - Long-term
    - Microvascular – Nephropathy, neuropathy, retinopathy, PVD
    - Macrovascular – Myocardial infarction (MI), stroke, heart failure (HF)

- Insulin resistance and inadequate insulin secretion, referred to as T2DM, is associated with an increased risk of microvascular and macrovascular disease outcomes. The increased risk of CVD in T2DM persists even after discounting smoking, hypertension and dyslipidemia, implicating dysglycemia as an independent, but not the sole contributor to risk.[5]

- CVD risk increases exponentially when insulin resistance and inadequate insulin secretion are accompanied by other metabolic derangements which collectively constitute the metabolic syndrome.[6]

- CVD is responsible for much of the associated morbidity and mortality of T2DM.
  - Care should be taken to treat all concomitant risk factors for the complications of T2DM, especially hypertension and hyperlipidemia where they have been shown to reduce CVD related events.

**Mechanism of Action**

- *SGLT-2 inhibitors* [7-9]
  - Reduce reabsorption of filtered glucose via inhibition of SGLT-2 in the proximal renal tubules, resulting in increased urinary glucose excretion and reduced plasma glucose concentration.

- *GLP-1 agonists*[10-12]
  - Increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, slow gastric emptying, and act in areas of the brain involved in regulation of appetite and caloric intake.

**Metformin is still first line**

- When lifestyle change alone is inadequate to achieve BG control, metformin is well established as the first pharmacological therapy to consider for treatment of T2DM.

- Metformin is a safe, effective, and inexpensive option with durable glycemic control.[1]

- Metformin has been evaluated in people with newly diagnosed T2DM[13], whereas RCTs evaluating CV safety of SGLT-2 inhibitors and GLP-1 agonists included people with a diagnosis of T2DM for 5 or more years.[14-21]

- In more recent RCTs demonstrating cardiorenal benefits, metformin, amongst many other glucose-lowering drugs, was included as background therapy in ~ 75% of participants.

**FDA mandated cardiovascular outcome trials (CVOTs)**

- Historically, the efficacy of diabetes drugs was defined by their ability to lower BG levels. However, in 2008, in response to concern about CV harm from rosiglitazone, the FDA and European Medicines Agency **mandated additional clinical trials to evaluate the CV safety of new diabetes drugs** as part of the approval process.
  - CVOTs were required to include participants with relatively advanced disease, older age, and some degree of renal impairment.
  - Many were designed as **non-inferiority analyses** because the FDA mandate was to provide evidence of *acceptable CV risk*, as opposed to providing evidence of improvement in rates of major adverse cardiovascular events (MACE).
    - Non-inferiority trials test the hypothesis that **new treatment is not worse than standard treatment**.
  - Most CVOTs also tested for superiority of the intervention once non-inferiority was established. Unless otherwise noted, the **superiority results are reported** in this document.

**The following CVOTs are described in this review:**

| CVOTs | |
|---|---|
| **SGLT-2 inhibitors** | **GLP-1 agonists** |
| EMPA-REG OUTCOME 2015<br>CANVAS Program 2017<br>DECLARE-TIMI 58 2019 | ELIXA 2015<br>LEADER 2016<br>SUSTAIN-6 2016<br>REWIND 2019<br>PIONEER-6 2019 |

- All participants had either established CVD or risk factors for CVD at baseline, but definitions for these conditions differed between studies (*see Appendix B).*

- In each CVOT, participants were randomized to an intervention (SGLT-2 inhibitor or GLP-1 agonist) or placebo. All subjects were permitted to continue standard care for BG management throughout the duration of the trial, including intensification of T2DM therapy as needed to achieve standard BG targets.

- In addition, evidence describing microvascular effects of SGLT-2 inhibitors and GLP-1 agonists is reported.

**Composite outcomes in clinical trials**

- Composite primary outcomes are commonly reported in CVOTs. They represent a single measure of effect based on a combination of individual endpoints [e.g. major adverse cardiovascular event (MACE) is a composite outcome that usually includes CV death, non-fatal MI and non-fatal stroke]. When a study participant experiences any one of the components of the composite, they are considered to have experienced the composite outcome.[22]

- Advantages of composite outcomes:[23]
  - They increase event rates, which reduces sample size requirements, cost, and/or follow-up duration required to achieve adequate power to detect a statistically significant difference between groups.
  - They help investigators avoid an arbitrary choice between several important outcomes for primary analysis.

- Disadvantages of composite outcomes:[23]
  - Results may be misleading, particularly when treatment effects differ across components of variable clinical relevance.
  - The effect of the most clinically important component of a composite outcome is often the smallest, leaving results vulnerable to misinterpretation.

- It is possible to observe an increase in risk of one component of a composite outcome and a decrease in another at the same time, further complicating interpretation of results.

- Important considerations for interpretation of composite outcomes:[23]
  - Each component of the composite should be clinically important.
  - Optimally, each component should be of similar clinical importance.
  - Results for individual components of the composite outcome should be reported with confidence intervals.
  - To control for the potential of *post hoc* changes, the trial protocol should be available for review.
  - Caution should be exercised when combining results from composite outcomes in MAs and only the individual components should be used.

**Reporting and Interpretation of Numbers Needed to Treat & Numbers Needed to Harm (NNT/NNH)**

- When possible, results are reported as both absolute and relative values with 95% confidence intervals in this Evidence Review. NNTs, NNHs and 95% confidence intervals were calculated from absolute event rates using the *Dalhousie Clinical Significance Calculator*,[24] except where noted otherwise. They are provided as an estimate only and were calculated for statistically significant primary and co-primary outcomes with demonstrated superiority. NNTs were not calculated for results showing non-inferiority (in the absence of superiority data), exploratory outcomes, and non-statistically significant outcomes.

- NNT is a measure of absolute treatment *efficacy*. It describes the number of people who need to be treated with the experimental intervention versus the comparator before one person experiences benefit.[25]

- NNH is a measure of absolute treatment *safety*. It describes the number of people who need to be treated with the experimental intervention versus the comparator before one person experiences harm.[25]

- NNT and NNH should always be considered in relation to the length of the clinical trial from which they are calculated. Although sometimes reported in clinical trials, it is not appropriate to extrapolate the results over a longer period of time than the original study.[25]

- The point estimate reported for the NNT or NNH represents the best estimate of the magnitude and direction of effect.[25]

- The 95% confidence interval around the NNT or NNH describes a range of values within which we can be reasonably certain the true effect lies.[25]
    - The narrower the confidence interval, the more precise the estimate.
    - When the interval is wide it reflects imprecision. A lack of precision introduces uncertainty in the findings.

- It is important to note that NNTs should not be compared across trials to assess for comparative effectiveness because outcomes, duration and populations studied differ.[25]

**The following <u>clinical questions</u> have been reviewed for this document:**

1. What is the evidence for *benefit of SGLT-2 inhibitors for macrovascular* outcomes in the treatment of T2DM?
2. What is the evidence for *benefit of SGLT-2 inhibitors for microvascular* outcomes in the treatment of T2DM?
3. What is the evidence for *benefit of GLP-1 agonists for macrovascular* outcomes in the treatment of T2DM?
4. What is the evidence for *benefit of GLP-1 agonists for microvascular* outcomes in the treatment of T2DM?
5. What are the *potential harms* associated with *SGLT-2 inhibitors* in the treatment of T2DM?
6. What are the *potential harms* associated with *GLP-1 agonists* in the treatment of T2DM?
7. How do Diabetes Canada guideline recommendations align with the evidence?

*<u>Note:</u> The scope of this document is limited to a review of the evidence of SGLT-2 inhibitors and GLP-1 agonists, in the treatment of adults with T2DM. Literature assessing the role of these agents for other indications was not reviewed.*

**In preparing this document we reviewed the following evidence sources:**

- Cardiovascular outcome trials and other relevant RCTs
- Meta-analyses, systematic and Cochrane reviews
- Observational studies
- Diabetes Canada Guidelines
- Canadian and American drug safety reviews
- Canadian product monographs

# CLINICAL QUESTIONS

## Question 1: What is the evidence for benefit of SGLT-2 inhibitors for macrovascular outcomes in the treatment of T2DM?

- Three multicenter, randomized, double-blind, placebo-controlled trials evaluated the effects of SGLT-2 inhibitors marketed in Canada on CV morbidity and mortality.[14-16]
  - The **EMPA-REG OUTCOME trial**[14] enrolled 7,020 people with T2DM at high risk for CV events.
    - Baseline Characteristics
      - Established CVD > 99% (see Appendix B for definition)
      - HF 10%
      - T2DM for > 5 years ~82%
      - Mean A1C 8%
      - eGFR ≥ 30 mL/min/1.73 $m^2$ 100%
      - White 72%
      - Male 71%
      - Mean age ~63 years
    - Interventions
      - Empagliflozin 10 or 25 mg once daily or placebo in addition to standard care for glycemic control and CV risk management.
        - Background anti-hyperglycemic therapy was to remain unchanged during the first 12 weeks after randomization unless fasting BG levels were > 13.3 mmol/L or changes were medically necessary. Subsequently, investigators were permitted to change non-study anti-hyperglycemic drugs as needed to maintain glycemic control according to local guidelines in both study arms.
      - At baseline 30% were on 1, 50% on 2 and 20% on more than 2 anti-hyperglycemic agents.
      - Frequently prescribed co-medications at baseline included:
        - Metformin ~74%
        - Insulin ~48%
        - SU ~42%
        - Antihypertensive drugs ~95%
        - Statins ~77%
        - ASA ~83%
      - Use of DPP-4 inhibitors (~11%), TZDs (~4%), and GLP-1 agonists (~3%) was less common.
    - Follow-up

- Median 3.1 years

- Results at 3.1 years
  - Primary composite outcome:
    - People randomized to empagliflozin had a **statistically significant reduction** in CV death, non-fatal MI or non-fatal stroke relative to standard care (P = 0.04).
      - HR 0.86 (95% CI 0.74-0.99), ARR 1.6%, NNT 63 (95% CI 31-8300)
      - Note the 95% CI around the NNT is wide, reflecting a lack of precision in the result.
    - The primary composite outcome was driven by an improvement in CV death, which was not considered a statistically significant outcome on its own.
    - There was no significant difference between groups in rates of MI or stroke.
  - See Table A for further details.
  - A1C was 7.81% in the pooled empagliflozin group and 8.16% in the standard care group at week 206, a 0.35% difference.

**Table A: Results of the EMPA-REG OUTCOME trial**[14]

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR | NNT for 3.1 yr | |
|---|---|---|---|---|---|---|
| | Empagliflozin n=4,687 | Placebo n=2,333 | | | NNT | 95% CI |
| **Primary** | | | | | | |
| CV death, MI, stroke (MACE) | 10.5 | 12.1 | 0.86 (0.74-0.99) | 1.6 % | 63 | 31-8300 |
| **Secondary** | | | | | | |
| 1° outcome + HUA* | 12.8 | 14.3 | 0.89 (0.78-1.01) | 1.5 % | NS | |
| All cause death | 5.7 | 8.3 | 0.68 (0.57-0.82) | 2.6 % | NS† | |
| CV death | 3.7 | 5.9 | 0.62 (0.49-0.77) | 2.2 % | NS† | |
| HHF | 2.7 | 4.1 | 0.65 (0.50-0.85) | 1.4 % | NS† | |
| MI (nonfatal) | 4.5 | 5.2 | 0.87 (0.70-1.09) | 0.7 % | NS | |
| Stroke (nonfatal) | 3.2 | 2.6 | 1.24 (0.92-1.67) | 0.6 % | NS | |

HR, hazard ratio; ARR, absolute risk reduction; NNT, number needed to treat; CI confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
***** Key secondary outcome (where HUA = hospitalization for unstable angina)
† Note: Despite the 95% CI for the HR being below one, all cause death, CV death and HHF are not considered to be statistically significant based on the investigators' pre-specified statistical analysis plan.
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.

***Interpretation of the HR and 95% CI***:
At any point in time during the study period, people in the empagliflozin group were 14% less likely to experience CV death, nonfatal MI, or nonfatal stroke **relative** to people in the standard care (placebo) group (HR 0.86). The data show with 95% certainty, that individuals on empagliflozin were between 1% and 26% less likely to experience the primary outcome relative to those on standard care (95% CI 0.74-0.99).

***Interpretation of the ARR and NNT****:*
The overall **absolute** risk of experiencing CV death, nonfatal MI or nonfatal stroke (MACE) is 1.6% lower in the empagliflozin group compared to the standard care (placebo) group. The ARR is the difference between absolute event rates in the treatment and control groups. For every 63 people treated for 3.1 years, empagliflozin prevents one episode of MACE compared to standard care (NNT = 63). The data show with 95% certainty that the true number of people requiring treatment with empagliflozin to avoid one episode of MACE is between 31 and 8300 (95% CI around the NNT).

- Dose-response effect
  - A small dose-response effect was observed for metabolic changes; however, the **HRs for CV outcomes were similar whether a subject was taking 10 mg or 25 mg empagliflozin**.
- Strengths:
  - Large, well designed trial, with balanced treatment arms at baseline.
  - Follow-up
    - 97% completed the trial and 99% had known vital status.
- Limitations:
  - Exposure to other glucose-lowering drugs differed between groups, with greater addition of insulin, SU, and TZDs during the trial in the standard care group. This difference was necessary to achieve similar BG targets in both groups but may confound the results.
    - A pre-specified subgroup analysis showed that exposure to these drugs *at baseline* did not drive the primary outcome results; however, the analysis did not explore continued exposure or addition of anti-hyperglycemic agents throughout the trial.
    - Glucose-lowering drugs added during the trial included
      - Insulin
        - 5.8% empagliflozin vs 11.5% standard care
      - SU
        - 3.8% empagliflozin vs 7% standard care
      - TZDs
        - 1.2% empagliflozin vs 2.9% standard care

        - The reduced MACE observed in EMPA-REG OUTCOME should not be generalized to patients with T2DM without established CVD.
        - The study duration may be too short to evaluate the potential long term benefits and harms of empagliflozin.

- The **CANVAS Program**[15] pooled data from two T2DM studies, CANVAS[53] and CANVAS-R.[72]
    - N = 10,142
    - Baseline Characteristics
        - Established CVD 65% (see Appendix B for definition)
        - High risk of CVD 35%
            - High risk defined as 50 years of age or older with at least 2 CV risk factors
                - T2DM duration ≥ 10 years
                - HDL < 1 mmol/L
                - Micro- or macro-albuminuria
                - Current smoker
                - Systolic blood pressure > 140 mm Hg with ≥ 1 antihypertensive drug
        - History of HF 14%
        - Mean duration of T2DM 13.5 ± 7.8 years
        - Mean A1C 8.2 ± 0.9%
        - eGFR > 30 mL/min/1.73 $m^2$ 100%
        - White 78%
        - Male 64%
        - Mean age ~63 years
    - Interventions
        - Canagliflozin 100 mg or 300 mg once daily or placebo in addition to standard care.
        - The most commonly used anti-hyperglycemic agents at baseline were
            - Metformin 77%
            - Insulin 50%
            - SU 43%
        - Other commonly prescribed drugs included
            - Renin-angiotensin-aldosterone system inhibitors 80%
            - Statins 75%
            - Antithrombotic drugs 74%
            - Beta-blockers 54%
            - Diuretics 44%
    - Follow-up

- Median 2.4 years.

- Results at 2.4 years
  - Primary composite outcome: CV death, MI, or stroke (MACE)
    - People treated with canagliflozin experienced a **statistically significant reduction** in MACE relative to standard care (P = 0.02).
      - HR 0.86 (95% CI 0.75-0.97), P = 0.02
    - The individual components of the composite were not significantly different between groups. See Table B.

**Table B: Results of the CANVAS Program**[15]

| Outcome | # of participants per 1000 patient-years | | HR (95% CI) | P value |
|---|---|---|---|---|
| | Canagliflozin n=5,795 | Placebo n=4,347 | | |
| **Primary** | | | | |
| CV death, MI, stroke (MACE) | 26.9 | 31.5 | 0.86 (0.75-0.97) | 0.02* |
| CV death | 11.6 | 12.8 | 0.87 (0.72-1.06) | NS |
| MI (nonfatal) | 9.7 | 11.6 | 0.85 (0.69-1.05) | NS |
| Stroke (nonfatal) | 7.1 | 8.4 | 0.90 (0.71-1.15) | NS |
| **Secondary** | | | | |
| All cause death | 17.3 | 19.5 | 0.87 (0.74-1.01) | NS |

HR, hazard ratio; CI, confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
* P value reported for superiority analysis

- A pre-specified *post hoc* analysis of the CANVAS Program compared the effects of canagliflozin and standard care on MACE among participants with and without a history of CVD (secondary vs primary prevention).[73]
  - The authors concluded there was no statistical evidence of heterogeneity of canagliflozin effects between the primary and secondary prevention groups, but the power to detect differences was limited by sample size and study duration.[73] The trend in results suggests participants with history of CVD benefitted, and those without did not.
    - Primary prevention (individuals with high risk of CVD)
      - 15.8 canagliflozin vs 15.5 standard care per 1000 patient-years, HR 0.98 (95% CI 0.74-1.30)
    - Secondary prevention
      - 34.1 canagliflozin vs 41.3 standard care per 1000 patient-years, HR 0.82 (95% CI 0.72-0.95)

- By nature of their mechanism of action, the BG lowering effect of SGLT-2 inhibitors is attenuated when eGFR falls below 45 mL/min/1.73 $m^2$. However, a pre-specified subgroup analysis of the CANVAS Program by eGFR suggested that a reduction in MACE was maintained in participants with eGFR between 30 and <60 mL/min/1.73 $m^2$.[15]
- At 18 weeks, the mean difference in A1C between the canagliflozin and standard care groups was -0.58% (95% CI -0.61 to -0.56).
- Strengths:
  - Large, well designed trial, with balanced treatment arms at baseline
  - Follow-up
    - 96% completed trial
    - 99.6% had known vital status
- Limitations:
  - A dose-response relationship was not evaluated and the rationale for pooling data from 100 mg and 300 mg doses was not described.
  - Use of other glucose lowering drugs was reported at baseline, but changes to these medications during the study were not described.
  - The study duration may be too short to evaluate the potential long term benefits and harms of canagliflozin.
  - The effect of canagliflozin on MACE is unknown for individuals at low risk of developing CVD because they were not included in the study.
  - Data from the original CANVAS trial[53] was unmasked during an interim analysis for the Food and Drug Administration approval process. Subsequently, a similar study, CANVAS-R,[72] was designed for the purpose of pooling data from both studies to optimize statistical power in the CANVAS Program.[15] CANVAS-R was a pre-specified exploratory analysis focused on renal outcomes. Whether or not this change in protocol impacted the results is not clear.

- The **DECLARE-TIMI 58 trial**[16] evaluated the effects of dapagliflozin on CV and renal outcomes in people with T2DM
  - N = 17,160
  - Compared to the EMPA-REG OUTCOME and CANVAS trials, DECLARE-TIMI 58 enrolled fewer people with established CVD.
  - Baseline Characteristics
    - Established CVD ~40% (see Appendix B for definition)
    - High risk of CVD 60%
      - High risk defined as age ≥ 55 years for males or 60 years for females AND at least one of the following:
        - Hypertension

        - Dyslipidemia
        - Tobacco use
    - History of HF 10%
    - Median duration of T2DM 11 years (dapagliflozin group) & 10 years (standard care group)
    - Mean A1C 8.3 ± 1.2%
    - Mean eGFR 85 mL/min/1.73 $m^2$ (all ≥ 60 mL/min)
    - White ~80%
    - Female ~37%
    - Mean age 64 years
- Interventions
    - Dapagliflozin 10 mg once daily or matched placebo (and standard care)
    - Other glucose lowering drugs permitted in both arms at prescriber's discretion, except for open-label SGLT-2 inhibitors and TZDs.
    - Common glucose-lowering drugs used at baseline included
        - Metformin 82%
        - SU 43%
        - Insulin 41%
    - CV medication use was similar between groups
        - Antiplatelet agents ~ 61%
        - ACE inhibitor or ARB ~ 81%
        - Beta-blocker ~ 53%
        - Statin or ezetimibe ~ 75%
        - Diuretics ~ 41%.
- Follow-up
    - Median 4.2 years.
- Results at 4.2 years
    - Co-primary composite outcomes
        - CV death, non-fatal MI or non-fatal stroke
            - Dapagliflozin was *non-inferior* to standard care (P < 0.001), but there was no evidence of superiority (P = 0.17).
                - HR 0.93 (95% CI 0.84-1.03)
        - CV death or HHF
            - Participants on dapagliflozin experienced a **statistically significant reduction** compared to standard care (P = 0.005).
                - HR 0.83 (95% CI 0.73-0.95), ARR 0.9%, NNT 112 (95% CI 64-441)

        - Note the 95% CI around the NNT is wide, reflecting a lack of precision in the result.
    - This composite outcome was driven by an improvement in HHF, but HHF was an underpowered, exploratory outcome. There was no significant difference in rates of CV death between groups.
    - Subgroup analysis suggests the benefit in CV death or HHF may be limited to people with established CVD at baseline:
        - Established CVD
            - HR 0.83 (95% CI 0.71 to 0.98)
        - Multiple CV risk factors
            - HR 0.84 (95% CI 0.67 to 1.04)
- See Table C for more details.

- A1C
    - Participants taking dapagliflozin had a lower A1C throughout the study [mean absolute difference between groups, 0.42% (95% CI 0.40 to 0.45)].

**Table C: Results of the DECLARE-TIMI 58 trial[16]**

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR | NNT for 4.2 yr | |
|---|---|---|---|---|---|---|
| | Dapagliflozin n=8,582 | Placebo n=8,578 | | | NNT | 95% CI |
| **Co-Primary** | | | | | | |
| CV death or HHF | 4.9 | 5.8 | 0.83 (0.73-0.95) | 0.9% | 112 | 64-441 |
| CV death, MI, stroke | 8.8 | 9.4 | 0.93 (0.84-1.03) | 0.6% | NS | |
| **Co-Secondary** *(exploratory)* | | | | | | |
| All cause death | 6.2 | 6.6 | 0.93 (0.82-1.04) | 0.4% | NS | |
| CV death | 2.9 | 2.9 | 0.98 (0.82-1.17) | - | NS | |
| HHF | 2.5 | 3.3 | 0.73 (0.61-0.88) | 0.8% | NS* | |
| MI | 4.6 | 5.1 | 0.89 (0.77-1.01) | 0.5% | NS | |
| Ischemic stroke | 2.7 | 2.7 | 1.01 (0.84-1.21) | - | NS | |

HR, hazard ratio; ARR, absolute risk reduction; NNT, number needed to treat; CI, confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
*Note: Despite the 95% CI for the HR being below one, HHF is not considered to be statistically significant based on the investigators' pre-specified statistical analysis plan. Analyses of secondary outcomes are hypothesis-generating. Results reported here are from the superiority analyses.
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.

- Strengths:
    - Large, well designed trial, with balanced treatment arms at baseline
    - Less than 0.1% of participants lost to follow-up annually.

        - Concordance of intention to treat and per protocol analyses was observed.
            - Analysis by both methods is often favored in non-inferiority analyses to decrease risk of bias.
    - Limitations:
        - During the study the investigators and study subjects were notified of the CV benefits observed in the EMPA-REG OUTCOME trial, and the protocol was amended to evaluate additional efficacy outcomes. This change may increase the risk of surveillance or detection bias.
        - The study may be underpowered because the sample size was not increased when the protocol was amended.
        - Open label SGLT-2 inhibitor use occurred to a greater extent in the standard care group (6.1%) than in the dapagliflozin group (3.4%), despite being prohibited in the study protocol. However, a sensitivity analysis excluding people on open-label SGLT-2 inhibitors did not significantly change the results for the composite outcome of CV death or HHF.

**Do people with established CVD benefit more than people without?**

- Two MAs evaluated the effect of SGLT-2 inhibitors in people with established CVD compared to people at risk of developing CVD.[32, 74]
    - One MA by **Zelniker et al** pooled data from EMPA-REG OUTCOME, the CANVAS Program & DECLARE-TIMI 58 to perform subgroup analyses.[74]
        - N = 32,322
        - Baseline Characteristics
            - Established atherosclerotic CVD 60.2%
            - Multiple CV risk factors 39.8%
            - Female 35%
        - Results
            - MACE:
                - An overall benefit in risk of MACE with SGLT-2 inhibitors was reported (HR 0.89, 95% CI 0.83-0.96, $I^2$ = 0%).
                - Subgroup analysis of this outcome (MACE) was statistically significant for people with established CVD, whereas there was no statistical evidence of benefit for those at high risk for CVD. Therefore, people with established CVD may be more likely to benefit.
                    - Established CVD, HR 0.86 (95% CI 0.80-0.93)
                    - High risk for CVD, HR 1.00 (95% CI 0.87-1.16)

- A subsequent MA of RCTs by **Arnott et al** also described the CV benefits and safety of SGLT-2 inhibitors and performed subgroup analyses.[32]
    - N = 38,723
    - Studies included
        - EMPA-REG OUTCOME
        - The CANVAS Program
        - DECLARE-TIMI 58
        - CREDENCE

> **Note:** CREDENCE was not a traditional CVOT evaluating MACE. The purpose of CREDENCE was to assess the effects of canagliflozin on renal outcomes in people with T2DM and albuminuric CKD. The primary outcome was a composite for ESRD (defined as dialysis for at least 30 days, kidney transplant, or eGFR < 15 mL/min/1.73 $m^2$ sustained for at least 30 days), doubling of SrCr from baseline sustained for at least 30 days, or death from renal or CV disease. Neither a history of established CVD nor a presence of multiple risk factors for CVD were required for inclusion. However, all participants had T2DM and stage 2 or 3 CKD, and 50% had established CVD at baseline. CREDENCE is described in more detail on page 36.[27]

    - Baseline characteristics (% per study)
        - Established CVD: 22,870 of 38,723 total participants
            - 40.6% to 100% per study
        - History of HF 10.1% to 14.8%
        - Mean A1C 8.1% to 8.3%
        - eGFR less than 60 mL/min/1.73 $m^2$ 7.4% to 59.8%
        - Female 28.5% to 37.4%
        - Mean age 63.1 to 63.9 years
    - Follow-up
        - Median 2.4 to 4.2 years.
    - Results
        - Primary outcome: MACE
            - Total study population
                - HR 0.88 (95% CI 0.82-0.94), $I^2$ = 0%
            - Established CVD
                - HR 0.86 (95% CI 0.80-0.93)
            - High risk of CVD
                - HR 0.94 (95% CI 0.82-1.07)
            - Although the benefit in risk of MACE reported in the total study population with SGLT-2 inhibitors was similar to that reported by Zelniker et al, this study suggests a broader population, including people at high risk for CVD *may* benefit

from SGLT-2 inhibitor use. This finding is based on the point estimate for high risk participants being below one. However, the 95% CI crosses 1, so the difference is not statistically significant, and the potential for harm cannot be ruled out completely.

- The studies included in both MAs were judged to be at low risk of bias; however, there are important **limitations**:
    - There are very few RCTs of each SGLT-2 inhibitor to include in a MA (1 to 2 studies per drug), and of the trials available, there are differences in the populations studied. Inclusion of additional studies may improve generalizability of the results to the entire class and a broader patient population.
    - Results from composite outcomes were meta-analyzed by both Zelniker et al and Arnott et al, despite the recommendation from Cordoba et al that composite outcomes not be combined in MA, and that only individual components be used.[23]
        - In each MA, the findings revealed a statistically significant difference between groups for the individual outcomes of MI and CV death, but not stroke.[32, 74]
- Further study is required to determine whether or not SGLT-2 inhibitors improve MACE in the treatment of people without established CVD. At present, the individual CV outcome trials are the best available evidence to inform treatment decisions.

## Heart Failure

| |
|---|
| Although SGLT-2 inhibitors are used to treat a variety of other conditions, including HF, this document focuses on the treatment of people with T2DM. Other studies of HF including patients both with and without T2DM exist and should be considered to understand the greater role of SGLT-2 inhibitors in the treatment of HF but are beyond the scope of this review. |

- Although the primary aim of CVOTs was to evaluate MACE, improvements were also observed in HF outcomes.[14-16, 27]
    - Results from HF outcomes should be interpreted with caution because the studies were not adequately designed or powered for the purpose of evaluating HF.

- Evidence from CVOTs evaluating SGLT-2 inhibitor vs standard care:
    - EMPA-REG OUTCOME reported a secondary efficacy endpoint of HHF (empagliflozin, N = 7,020)[14]
        - 2.7% vs 4.1%, ARR 1.4%, HR 0.65 (95% CI 0.5-0.85)

    - Based on the investigators' statistical analysis plan, HHF was **not** considered to be a statistically significant outcome, despite the 95% CI for the HR being below one.
- The CANVAS Program reported a secondary endpoint of HHF (canagliflozin, N = 10,142)[15]
    - 5.5 vs 8.7 participants per 1000 patient-years, HR 0.67 (95% CI 0.52-0.87)
        - As a pre-specified exploratory outcome, a p-value was not calculated.
- DECLARE-TIMI 58 reported a co-primary endpoint of CV death and HHF (dapagliflozin, N = 17,160)[16]
    - 4.9% vs 5.8%, HR 0.83 (95% CI 0.73-0.95), ARR 0.9%, NNT 112 over 4.2 years (95% CI 64-441).
        - The composite outcome was driven by HHF (ARR 0.8%), but this finding was considered exploratory and was not statistically significant, so NNTs have not been calculated.
        - The difference in CV death alone was not statistically significant.

➢ Evidence from CREDENCE:
- CREDENCE reported several HF related secondary outcomes[27]
    - Composite CV death or HHF
        - 8.1% canagliflozin vs 11.5% placebo, HR 0.69 (95% CI 0.57-0.83)
    - HHF
        - 4.0% canagliflozin vs 6.4% placebo, HR 0.61 (95% CI 0.47-0.80)
- CREDENCE is described in more detail on page 37.

➢ A small proportion of participants had HF at baseline:
- EMPA-REG OUTCOME 10%
- The CANVAS Program 14%
- DECLARE-TIMI 58 10%
- CREDENCE 15%

➢ Whether individuals experiencing HF had reduced or preserved ejection fraction was not reported and the diagnosis of HF was not objectively defined.

➢ These exploratory findings have inspired investigators to formally evaluate SGLT-2 inhibitors in HF.

➢ Arnott et al reported a consistent reduction in HHF among participants regardless of whether or not they had HF at baseline.[32] However, a small proportion (12%) of the total study population had HF at baseline.
- Overall HHF (N = 38,723)

    - HR 0.68 (95% CI 0.60-0.76)
  - Participants with HF at baseline experiencing HHF (N = 4,543)
    - HR 0.69 (95% CI 0.57-0.83)
  - Participants without HF at baseline experiencing HHF (N = 34,180)
    - HR 0.67 (95% CI 0.58-0.77)
  - The study was not powered to detect a difference between groups.
  - See page 30 for a summary of this MA.

- A MA of two HF trials (DAPA-HF & EMPEROR-Reduced)[75-76] comparing SGLT-2 inhibitors to placebo found a benefit in a *secondary composite outcome* of **HHF or CV death in subgroups with and without T2DM**.[77]
  - N = 8,474
  - Studies included
    - DAPA-HF
    - EMPEROR-Reduced
  - Baseline characteristics
    - Symptomatic HFrEF with LVEF ≤ 40% and elevated natriuretic peptides 100%
    - NYHA functional class II 67 to 75%
    - Treated with appropriate therapies for HF, as available and tolerated (i.e. ACE inhibitor, ARB, mineralocorticoid receptor antagonist, and ARNI)
    - T2DM 45 to 50%
    - Male ~76%
  - Follow-up
    - DAPA-HF, median 18.2 months
    - EMPEROR-Reduced, median 16 months
  - Results by subgroup
    - Composite of first HHF or CV death
      - T2DM, HR 0.74 (95% CI 0.65–0.84), ARR 6.2%, p<0.0001
      - No T2DM, HR 0.75 (95% CI 0.65–0.87), ARR 4.2%, p<0.0001
  - Limitations:
    - Not designed to assess this secondary outcome.
    - No statistical adjustment for multiple comparisons in subgroup analysis.
      - The more statistical tests performed on the data, the greater the risk of concluding there is a difference between groups when there truly is not (type 1 error or false positive).

- These findings are important because clinical outcomes are worse in people with T2DM and HF, likely as a result of high CV risk and the direct toxic effects of diabetes on cardiac myocytes.[78] However, **EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58 were not adequately designed or powered to assess HF outcomes.**

- Studies have already been completed, and others are ongoing, to evaluate the role of SGLT-2 inhibitors for the management of HF in people with and without T2DM, but these trials are beyond the scope of this review.[75-76, 79-82]

- The mechanism of benefit of SGLT-2 inhibitors in HF is not fully understood and may be multifactorial. A detailed review of the mechanism is described here:
  - *Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart Br Card Soc. 2021 Feb 26;107(13):1032–8.*[83]

- Dapagliflozin is currently the only SGLT-2 inhibitor formally indicated as an adjunct to diet, exercise, and standard of care therapy *to reduce the risk of HHF* in adults with T2DM and CV risk factors or established CV disease.[36]
  - This indication is based on a HF study, DAPA-HF, in which 42% of participants had T2DM at baseline.[75]

**Academic Detailing Comments**

- SGLT-2 inhibitor use leads to small, statistically significant improvements in MACE in *some* people with T2DM.
  - Individuals with established CVD and those at high risk of developing CVD were included in the studies demonstrating this effect (EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58).[14-16]
    - Subgroup analyses evaluating MACE consistently suggest people with established CVD may be more likely to benefit than those at high risk.[15, 32, 74] However, there is no high quality evidence to confirm this finding.
  - People with T2DM and low risk of CVD or newly diagnosed T2DM taking SGLT-2 inhibitors have not been evaluated for MACE in prospective RCTs. Results from the CVOTs do not apply to this group.
  - Wide confidence intervals around the primary outcome in the CVOTs reflect a lack of precision in the results, which may bring clinical relevance of these findings into question.

- SGLT-2 inhibitors were not used as monotherapy in these clinical trials. The benefits observed occurred in people who were taking other glucose lowering drugs at baseline, including metformin (74 to 82%), insulin (43 to 48%), and SU (41 to 43%), among others.[14-16]

- Major adverse CV events develop over many years, but the CVOTs were short by comparison (2.4 to 4.2 years). One cannot meaningfully describe the magnitude of benefits from SGLT-2 inhibitors over the long term in these relatively short studies.

- Trial data do not suggest better glucose control was responsible for the beneficial outcomes. The difference in A1C reduction between groups was small, and decreased risk of CV death and all-cause mortality occurred early and continued throughout the trials, supporting an alternate mechanism of effect.[26]

- Although the evidence for use of SGLT-2 inhibitors for prevention of HF in people with T2DM is currently limited to secondary, hypothesis-generating outcomes, the beneficial effect appears to be consistent.[14-16, 27]

- Although the BG lowering effect of SGLT-2 inhibitors is attenuated when eGFR falls below 45 mL/min/1.73 $m^2$, it is less clear whether or not improvements in MACE persist with lower eGFR.
    - Subgroup analyses did not compare results in people with eGFR below 45 mL/min/1.73 $m^2$ to those with eGFR above 45 mL/min/1.73 $m^2$ in the CVOTs.
    - Results were inconsistent in subgroup analyses between studies. The CANVAS Program[15] suggests benefit in those with eGFR < 60 mL/min/1.73 $m^2$ whereas the same effect was not observed in EMPA-REG OUTCOME.[14]
    - People with baseline CrCl < 60 mL/min were excluded from DECLARE-TIMI 58. There was no statistically significant difference in subgroup analysis of MACE by eGFR.[16] Subgroup analysis showed that people with an eGFR between 60 and < 90 mL/min/1.73 $m^2$ benefitted in a composite of CV death or HHF whereas those with eGFR outside this range did not (MACE and CV death/HHF were co-primary outcomes in DECLARE-TIMI 58).[16]

- It is not clear whether or not potential benefits in HF are maintained if eGFR is less than 45 mL/min/1.73 $m^2$.

- **Placebo controlled** trials evaluating the effects of SGLT-2 inhibitors on clinical outcomes **do not inform relative benefits or harms between agents within the same class.**

- To optimize use of SGLT-2 inhibitors, one must weigh the benefits of therapy against the potential harms (see page 69).

## Question 2: What is the evidence for benefit of SGLT-2 inhibitors for microvascular outcomes in the treatment of T2DM?

- Microvascular complications of T2DM include nephropathy, retinopathy, neuropathy and PVD.

- The indirect effect of BG lowering on microvascular outcomes has been described in a previous Academic Detailing Program document (Type 2 Diabetes What after Metformin? 2016)[1] and will not be readdressed at this time.

**Effects of SGLT-2 inhibitors on nephropathy**

- Secondary and exploratory analyses of CVOTs identified potential renal benefits with SGLT-2 inhibitors.[15-16, 43, 84]
    - Event rates were low as most participants were at low risk of advanced kidney disease.
        - In addition to previously described inclusion and exclusion criteria, baseline eGFR requirements were
            - ≥ 30 mL/min/1.73 $m^2$ in the CANVAS Program and EMPA-REG OUTCOME
            - ≥ 60 mL/min in DECLARE-TIMI 58
        - uACR was
            - Not evaluated to determine study eligibility
            - Below 3.4 mg/mmol at baseline for ~ 60% of EMPA-REG OUTCOME and ~ 70% of DECLARE-TIMI 58 subjects.
            - Below 3.5 mg/mmol at baseline in 70% of the CANVAS Program subjects.
        - Approximately 80% were on a renin-angiotensin system blocker.

- In response to these signals of potential benefit, the **CREDENCE trial** sought to evaluate effects of canagliflozin on renal outcomes in people with T2DM and *albuminuric* CKD.[27]
    - CREDENCE was a multicenter, international, double-blind, placebo-controlled, randomized trial.
    - N = 4,401
    - Inclusion criteria
        - T2DM and A1C 6.5 to 12%
        - Stage 2 or 3 CKD, defined as
            - eGFR 30 to < 90 ml/min/1.73 $m^2$ and
            - uACR > 33.9 to 565.6 mg/mmol
        - Stable and maximum tolerated dose of ACE inhibitor or ARB
        - Age 30 years or older

- Exclusion criteria
  - Type 1 diabetes
  - Suspected nondiabetic kidney disease
  - Immunosuppression for kidney disease
  - History of dialysis or kidney transplantation
- Baseline characteristics were similar between groups
  - Established CVD 50% (see Appendix B for definition)
  - Mean eGFR 56.2 ± 18.2 mL/min/1.73 $m^2$
  - Median uACR (IQR) 104.9 (52.4-207.4) mg/mmol
  - HF 15%
  - Duration T2DM 15.8 ± 8.6 years
  - Mean A1C 8.3 ± 1.3%
  - White 67%
  - Female 34%
  - Mean age 63 ± 9.2 years
- Interventions
  - Canagliflozin 100 mg once daily or placebo *plus*
    - Standard care for glucose control and CV risk factor management
    - ACE inhibitor or ARB continued throughout trial
  - At baseline, frequently prescribed medications included
    - Insulin 65.5%
    - Biguanides 57.8%
    - SU 28.8%
- Follow-up
  - Median 2.6 years.
- Results
  - Primary composite outcome
    - At any point in time during the study period, the canagliflozin group was 30% less likely to experience the primary composite outcome (ESRD, doubling of SrCr, renal or CV death) relative to the placebo group [HR 0.70 (95% CI 0.59-0.82)].
      - Result was driven by reductions in ESRD and doubling of SrCr. There is no evidence of a statistically significant benefit in renal or CV death.
      - *Exploratory* subgroup analyses revealed that individuals with eGFR between 45 and 59 mL/min/1.73 $m^2$ benefited most with respect to the primary outcome, and beneficial effects were observed in people with eGFR as low as 30 mL/min/1.73 $m^2$.

- As pre-specified, 60% of the study population had eGFR < 60 mL/min/1.73 $m^2$ at baseline and this subgroup drove the positive kidney outcomes.
- Key findings are reported in Table D.

**Table D: Results of the CREDENCE trial**[27]

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR | NNT for 2.62 yr | |
|---|---|---|---|---|---|---|
| | Canagliflozin n=2,202 | Placebo n=2,199 | | | NNT | 95% CI |
| **Primary** | | | | | | |
| ESRD*, doubling of SrCr, renal or CV death | 11.1 | 15.5 | 0.70 (0.59-0.82) | 4.3% | 24 | 16-43 |
| ESRD* | 5.3 | 7.5 | 0.68 (0.54-0.86) | 2.2% | 45 | 28-127 |
| Doubling SrCr | 5.4 | 8.5 | 0.60 (0.48-0.76) | 3.2% | 32 | 22-60 |
| Renal death | 0.1 | 0.2 | Not calculated† | 0.1% | | |
| CV death | 5.0 | 6.4 | 0.78 (0.61-1.00) | 1.4% | NS | |
| **Secondary** | | | | | | |
| ESRD*, doubling of SrCr, or renal death | 6.9 | 10.2 | 0.66 (0.53-0.81) | 3.2% | 31 | 21-63 |
| All cause death | 7.6 | 9.1 | 0.83 (0.68-1.02) | 1.5% | NS | |

HR, hazard ratio; ARR, absolute risk reduction; NNT, number needed to treat; CI, confidence interval; NS, not significant
Participants were treated with ACE inhibitor or ARB and standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
* ESRD defined as eGFR < 15 mL/min, dialysis or kidney transplant.
† HR was not calculated because there were fewer than 10 events reported.
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only

- A1C
  - Overall mean difference in **A1C** was 0.25% lower with canagliflozin vs placebo throughout the trial (95% CI -0.31 to -0.20) and 0.11% lower at the end of the trial (95% CI -0.28 to -0.06).
- eGFR
  - During the first 3 weeks, a greater reduction in **eGFR** was observed in the canagliflozin group compared to the placebo group (-3.72±0.25 vs –0.55±0.25 mL/min/1.73 $m^2$). Subsequently, the eGFR decreased at a slower rate in the canagliflozin group than in the placebo group (–1.85±0.13 vs –4.59±0.14 mL/min/1.73 $m^2$ per year).

- Strengths
  - Loss to follow-up 0.9%
  - Adherence to study protocol 84%
  - Blinded adjudication of efficacy and safety endpoints
  - Concomitant ACE inhibitor or ARB required, in keeping with current best practice.

- Limitations
    - Numerous composite outcomes evaluated, which makes interpretation of findings challenging.
        - Not powered to evaluate individual components of composite outcomes.
    - CKD is a slowly progressing disease with ESRD typically developing over at least five years, but trial was stopped early in response to beneficial interim analysis results. Early study cessation may have:
        - Reduced power to detect differences between groups.
        - Increased chance of overestimating effect sizes.
        - Hindered evaluation of rare outcomes, like renal death.
    - A reduction in doubling of SrCr represents the largest absolute risk reduction of all components evaluated in the primary composite outcome. However, SrCr is a surrogate marker that is less clinically important compared to ESRD, CV and renal death. Ideally, when a composite outcome is included in a trial, the individual components should be of similar clinical importance.[23]
    - Results are not generalizable to people with
        - eGFR less than 30 mL/min/1.73 $m^2$
        - eGFR greater than 90 mL/min/1.73 $m^2$
        - Non-albuminuric or microalbuminuric renal disease
        - Non diabetes-related kidney disease.
        - CKD and short duration of T2DM

➢ A systematic review (SR) and MA by **Neuen BL *et al*** sought to evaluate the impact of SGLT-2 inhibitors on renal outcomes in people with T2DM and a broader range of renal impairment.[85]

- N = 38,723
- Studies included 4 placebo controlled RCTs and secondary analyses
    - EMPA-REG OUTCOME (N = 7,020)
    - The CANVAS Program (N = 10,142)
    - CREDENCE (N = 4,401)
    - DECLARE-TIMI 58 (N = 17,160)
- Results for primary outcome
    - Composite of dialysis, transplantation, or death from kidney disease
        - RR 0.67 (95% CI 0.52 – 0.86), $I^2$ = 0%
        - The result was heavily weighted by the CREDENCE trial, which differed from other studies because
            - All subjects had uACR > 34 mg/mmol, whereas the majority of participants (~90%) in other studies did not.

- 60% of the CREDENCE population had baseline eGFR < 60 mL/min/1.73 $m^2$, compared to 7% (DECLARE-TIMI 58), 20% (the CANVAS Program) and 26% (EMPA-REG OUTCOME).
- All subjects in CREDENCE were receiving renin-angiotensin system blockers compared to 80% in the remaining trials.

- Risk of bias in the individual studies was low, but there are important **limitations** to consider:
  - 1 RCT each for empagliflozin and dapagliflozin, and 2 RCTs for canagliflozin included in the analysis.
  - Patient populations varied between individual trials.
  - Definitions of outcome measures varied between trials.
  - Some renal outcomes were evaluated post-hoc in the original studies; others were secondary, exploratory outcomes.
  - Does not evaluate effect of SGLT-2 inhibitors on renal outcomes in people with eGFR < 30 mL/min.

➢ The mechanism of renal effects of SGLT-2 inhibitors is described here:
*Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovasc Diabetol. 2020 Jun 26;19(1):98.*[86]

➢ Health Canada approved indications and contraindications related to renal function:
- Canagliflozin is the only Health Canada approved SGLT-2 inhibitor indicated for individuals with T2DM *and* diabetic nephropathy, as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of ESRD, doubling of SrCr, and CV death in adult patients with T2DM and diabetic nephropathy with albuminuria (>33.9 mg/mmol).[35]
- Empagliflozin is contraindicated in patients treated for T2DM with severe renal impairment (eGFR < 20 mL/min/1.73 $m^2$) and ESRD.[34]
- Empagliflozin, canagliflozin and dapagliflozin are contraindicated in patients on dialysis. [34-36]
- Dapagliflozin is indicated to reduce the risk of sustained eGFR decline, ESRD, and CV and renal death in adults with CKD. [36]
  - This indication is based on a CKD trial, DAPA-CKD.[87]
    - Two thirds of participants had T2DM at baseline.

➢ Overall, the strongest evidence for renal outcomes is from the CREDENCE trial, which included people with T2DM and albuminuric CKD. The effect of SGLT-2 inhibitors in T2DM and *non-albuminuric* kidney disease has not been adequately studied to draw firm conclusions.

**Are renal benefits of SGLT-2 inhibitors maintained at lower eGFR despite an attenuated effect on BG concentration?**

- SGLT-2 inhibitors reduce reabsorption of filtered glucose in the proximal renal tubules. When eGFR falls below 45 mL/min/1.73 $m^2$, their ability to reduce BG concentration is impaired.[88]

- SGLT-2 inhibitors also have multiple proposed renal mechanisms beyond reduction in BG levels, which provides an explanation why these agents may continue to be beneficial despite lower GFR.[86]

- ***Proposed* protective effects** of SGLT-2 inhibitors on the kidney include[86]
  - Direct effects
    - Improve glomerular hyper-filtration
    - Reduce renal oxygen consumption
    - Reduce renal inflammatory reactions
    - Restore the mode of cellular energy metabolism
  - Indirect effects
    - Improve BG
    - Improve blood pressure
    - Decrease uric acid levels
    - Promote weight loss
    - Increase glucagon levels
    - Reduce insulin levels
    - Promote diuresis

- Evidence:
  - An exploratory subgroup analysis of CREDENCE suggests that participants with lower *baseline* eGFR may be more likely to benefit in the primary composite outcome (ESRD, doubling of SrCr, renal death or CV death) than those with higher *baseline* eGFR:[27]
    - eGFR 30 to < 45 mL/min/1.73 $m^2$ – HR 0.75 (95% CI 0.59 – 0.95), n = 1,313
    - eGFR 45 to < 60 mL/min/1.73 $m^2$ – HR 0.52 (95% CI 0.38 – 0.72), n = 1,279
    - eGFR 60 to < 90 mL/min/1.73 $m^2$ – HR 0.82 (95% CI 0.60 – 1.12), n = 1,809
      - Although participants with declining eGFR were permitted to continue in the trial until dialysis or renal transplant were required, the proportion of people discontinuing therapy for this reason was small (0.8% and 1.3% in the canagliflozin and standard care groups, respectively).
      - To what degree eGFR changed in participants during the study is unclear.

        - Generalizability of results is limited to people with T2DM and macroscopic albuminuria.

- A pre-specified subgroup analysis of the DAPA-CKD trial[87] (dapagliflozin vs placebo) suggests benefit in the primary composite renal outcome (sustained decline in eGFR ≥ 50%, ESRD, or death from renal or CV disease) may be maintained in those with *baseline* eGFR less than 45 mL/min/1.73 $m^2$ .
    - eGFR < 45 mL/min/1.73 $m^2$, HR 0.63 (95% CI 0.51 – 0.78), n = 2,522
    - eGFR ≥ 45 mL/min/1.73 $m^2$, HR 0.49 (95% CI 0.34 – 0.69), n = 1,782
        - Note: DAPA-CKD was NOT a T2DM trial. Sixty-seven percent of participants had T2DM and 37% had CVD at baseline.
        - Several important questions remain unanswered in DAPA-CKD:
            - To what extent did participants' eGFR change during the study?
            - How many people had eGFR less than but close to 45 mL/min/1.73 $m^2$ vs nearing requirement for renal replacement therapy?

- A pre-specified subgroup analysis of the EMPA-KIDNEY trial (empagliflozin vs placebo) suggests benefit in the primary composite outcome [progression of kidney disease (ESRD, sustained ↓ eGFR to < 10 ml/min/1.73 $m^2$, sustained ↓ eGFR of ≥ 40% from baseline, or death from renal causes) or CV death] may be maintained across a wide range of baseline eGFR.
    - eGFR ≥ 20 to < 30 mL/min/1.73 $m^2$, HR 0.73 (95% CI 0.62-0.86), n = 2,282
    - eGFR ≥ 30 to < 45 ml/min/1.73 $m^2$, HR 0.78 (95% CI 0.62-0.97), n = 2,928
    - eGFR ≥ 45 mL/min/1.73 $m^2$, HR 0.64 (95% CI 0.44-0.93), n = 1,399
    - *Note: EMPA-KIDNEY was NOT a T2DM trial. Approximately 46% of participants had history of diabetes and ~27% had CVD at baseline. Subgroup analysis suggests participants benefited in the primary outcome whether they had diabetes or not.

➢ Based on this evidence, renal benefits of SGLT-2 inhibitors may persist as eGFR falls below 45 mL/min/1.73 $m^2$. The findings described above should be interpreted with caution because subgroup analyses represent low quality evidence.

➢ These outcomes support the Health Canada approved indications and contraindications related to renal function as described on page 41.

**Effects of SGLT-2 inhibitors on diabetic retinopathy**

- There is limited evidence evaluating the effect of SGLT-2 inhibitors on diabetic retinopathy (DRP).
  - EMPA-REG OUTCOME[14]
    - For a detailed description of EMPA-REG OUTCOME (N = 7,020), see page 21.
    - A separate analysis of the EMPA-REG OUTCOME dataset focused on secondary, pre-specified microvascular outcomes.[43]
      - Outcome
        - Composite of first occurrence of any of the following: initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or *incident or worsening nephropathy* (defined as progression to macroalbuminuria, doubling of SrCr and eGFR ≤ 45 mL/min/1.73 $m^2$, initiation of RRT, or death from renal disease).
      - Results
        - Empagliflozin 14% vs standard care 20.5%
        - HR 0.62 (95% CI 0.54-0.70), P-value <0.001
          - Finding was driven by difference in incident or worsening nephropathy
          - See page 41 for additional results from studies designed to assess diabetic nephropathy.
    - A separate post-hoc analysis of the same dataset by **Inzucchi et al** focused specifically on ocular findings.[28]
      - Outcome
        - Composite of time to first initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness or administration of intravitreal agents
      - Results
        - Empagliflozin 1.6% vs placebo 2.1%, ARR 0.5%
        - HR 0.78 (95% CI 0.54-1.12), P = 0.1732
        - Results did not vary by empagliflozin dose or presence of DRP at baseline.
        - Differences in individual components of the composite outcome were not statistically significant.
      - Limitations
        - Post hoc, secondary outcome
        - Not designed or powered to assess for DRP

- Retinopathy at baseline coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA), but nature and severity of retinopathy not reported.
- Retinal evaluations and photography not performed routinely but captured as adverse effects during each study visit or between visits if the subject notified the investigators.
- Components of composite outcome vary in severity of clinical relevance.

▪ Authors' conclusion[28]
- "In the EMPA-REG OUTCOME trial in patients with type 2 diabetes and CV disease, empagliflozin was not associated with an increased risk of retinopathy compared with placebo."

- A SR and MA of placebo-controlled randomized trials by **Li et al** evaluated the effect of SGLT-2 inhibitors on ocular events in adults with T2DM, including a **secondary** analysis of retinopathy.[89]
  - 6 studies were included in the retinopathy evaluation (N = 22,398)
    - EMPA-REG OUTCOME (N = 7,020)
    - CANVAS Program (N = 10,142)
    - CREDENCE (N = 4,401)
    - EMIT (ipragliflozin; not available in Canada, N = 245)[90]
    - 2 other small RCTs [1 canagliflozin (N = 146), 1 dapagliflozin (N = 444)][91-92]
  - Baseline Characteristics
    - Mean age 54 to 63 years
    - Women 28.5% to 45.7%
    - Mean A1C 8.1% to 8.9%
    - History of retinopathy 21% to 42.8% (not reported in 2 retinopathy trials)
  - In addition to SGLT-2 inhibitor or placebo, participants were taking a variety of other anti-hyperglycemic and cardio-protective drugs.
  - Median follow-up duration
    - 16 to 161.8 weeks
  - Outcome
    - DRP was reported as a **secondary outcome**, defined as a composite of
      - Blindness not clearly attributable to non-diabetic cause
      - Retinopathy comprising non-proliferative retinopathy, proliferative retinopathy, retinal edema, hemorrhage, or detachment
      - Macular edema

- Vitreous abnormality comprising hemorrhage or detachment
- Requirement of retinal photocoagulation therapy, intravitreal treatment, vitrectomy, or other eye-related surgery

- Results
  - No statistically significant effect of SGLT-2 inhibitors on retinopathy
    - SGLT-2 inhibitor 380 vs placebo 244 events/ 1000 patient-years
    - Risk ratio 0.98 (95% CI 0.84-1.16), $I^2$ = 0%
- Limitations
  - No relevant primary outcome reported.
  - Original trials not designed to evaluate DRP.
    - Ocular events were reported as *adverse events* in all but one study.
    - Inconsistent diagnostic and reporting criteria between trials reported to be likely.[89]
    - No grading of retinopathy.
    - Inconsistent reporting of baseline retinopathy.
  - Three of 6 studies were ≤ 24 weeks duration.
  - Limitations in statistical analysis
    - HRs were treated as risk ratios in the analyses when risk ratios were not reported in the original study.
    - Median values describing baseline patient characteristics were treated as means in the analyses when means were not reported in the original study.
    - Per protocol analysis of data (intention to treat analysis preferred).

**Effects of SGLT-2 inhibitors on neuropathy**

- There are no known studies evaluating the effects of SGLT-2 inhibitors on neuropathy.

**Effects of SGLT-2 inhibitors on peripheral vascular disease**

- PVD outcomes were rarely reported in the CVOTs. However, rate of amputation is an outcome of interest since it occurred more frequently in individuals taking canagliflozin compared to placebo in the CANVAS Program.[15] For more information, see page 24.

- A SR and MA by **Dorsey-Trevino et al** reported on the effect of SGLT-2 inhibitors on microvascular complications, including PVD, in adults with T2DM.[93]
  - Outcome
    - Limb amputation

  - N = 31,674
- Studies included
  - CANVAS, CREDENCE, DECLARE-TIMI 58
- Results
  - No statistically significant effect of SGLT-2 inhibitors on limb amputation compared to placebo
    - SGLT-2 inhibitor 1.96% vs placebo 1.52%, ARI 0.44%
    - OR 1.30 (95% CI 0.93-1.83), $I^2$ = 73%
- Limitations
  - Limited data, with only 2 studies of canagliflozin and 1 of dapagliflozin
  - Amputation was reported as a secondary safety outcome
  - Heterogeneity for the outcome was high
  - Of the 3 studies included, CANVAS was the only one to independently demonstrate an increased risk of amputation. Differences in study design and patient population may have contributed to the variable results:
    - CREDENCE
      - In response to the increased risk of amputation detected in CANVAS, the CREDENCE investigators amended their protocol during the trial to control for this potential risk. The amendments required examination of participants' feet at each study visit and temporary interruption of study drug in people with any active condition that could lead to amputation.
      - In addition, exclusion criteria were modified to preclude enrollment of people with a history of atraumatic amputation within 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.
    - DECLARE-TIMI 58
      - The protocol was amended during the trial to evaluate risk of amputation. Amputations were documented both retroactively and prospectively from the time of amendment and evaluated as adverse effects.

## Academic Detailing Comments

- The CREDENCE trial is the best available evidence evaluating renal outcomes in people with T2DM and stage 2 or 3 albuminuric CKD (uACR >33.9 to 565.6 mg/mmol), treated with concomitant ACE inhibitor or ARB.
    - In CREDENCE, people taking canagliflozin experienced a lower risk of a composite of ESRD, doubling of SrCr, renal or CV death compared to placebo.[27]
        - HR 0.70 (95% CI 0.59-0.82)
        - ARR 4.3%, NNT = 24 over 2.62 years (95% CI 16-43)
            - NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.
        - Subgroup analysis showed that people with eGFR < 60 mL/min/1.73 $m^2$ at baseline drove the positive kidney outcomes.
            - Approximately 30% of the study population had a baseline eGFR between 30 and < 45 mL/min/1.73 $m^2$

- There is insufficient evidence to determine the effect of SGLT-2 inhibitors on renal outcomes in people with T2DM who do not fit the inclusion/ exclusion criteria of the CREDENCE trial, such as those with
    - eGFR < 30 or > 90 mL/min/1.73 $m^2$
    - Non-albuminuric or microalbuminuric kidney disease
    - CKD and short duration of T2DM

- SGLT-2 inhibitors appear to delay the progression of diabetic nephropathy, but do not treat it.

- There are no prospective RCTs designed to evaluate the effect of SGLT-2 inhibitors on DRP. A post hoc analysis of the EMPA-REG OUTCOME trial suggests empagliflozin is not associated with an increased risk of retinopathy compared with standard care, but further study is required to confirm this finding.[43]

- There is insufficient evidence to determine the impact of SGLT-2 inhibitors on DRP and PVD.

## Question 3: What is the evidence for benefit of GLP-1 agonists for macrovascular outcomes in the treatment of T2DM?

➢ Five multicenter, randomized, double-blind, placebo-controlled trials evaluated the effects of GLP-1 agonists marketed in Canada on CV morbidity and mortality in T2DM.

- The **ELIXA trial** compared the effect of lixisenatide and standard care in people with T2DM and recent acute coronary syndrome (ACS).[17]
  - N = 6,068
  - Inclusion criteria
    - T2DM
    - Acute coronary event within 180 days
  - Exclusion criteria
    - Age < 30 years
    - Percutaneous coronary intervention within previous 15 days
    - Coronary artery bypass graft surgery for qualifying event
    - Planned coronary revascularization procedure within 90 days after screening
    - eGFR < 30 mL/min/1.73 $m^2$
    - A1C < 5.5% or > 11%
  - Baseline Characteristics
    - Established CVD 100% (see Appendix B for definition)
    - Qualifying ACS event
      - NSTEMI ~39%
      - STEMI ~44%
      - Unstable angina ~17%
    - HF ~22%
    - Mean duration T2DM ~9 years
    - Mean A1C 7.6%
    - Mean eGFR ~76 mL/min/1.73 $m^2$
    - Mean BMI ~30 $kg/m^2$
    - White ~75%
    - Male ~70%
    - Mean age ~60 years
  - Interventions
    - Lixisenatide 10 mcg or placebo SC injection once daily
      - May increase to 20 mcg daily at investigator's discretion after 2 weeks
        - 85.5% of lixisenatide subjects were taking 20 mcg at the time of last dose.

        - Additional anti-hyperglycemic agents permitted at prescriber's discretion, except for open-label incretin therapies (standard care).
        - Frequently prescribed medications at baseline included:
            - Metformin ~66%
            - Insulin ~39%
            - SU ~33%
            - ACE inhibitor or ARB ~85%
            - Statin ~93%
            - Anti-platelet ~97%
            - Beta-blocker ~84%
    - Follow up
        - Median 2.1 years
    - Results at 2.1 years
        - Primary composite outcome
            - **Lixisenatide was *non-inferior* to standard care** for the primary composite outcome of CV death, nonfatal stroke, nonfatal MI, or unstable angina ($P < 0.001$), but there was no evidence of superiority ($P = 0.81$).
                - HR 1.02 (95% CI 0.89-1.17), ARI 0.2%
        - Mean difference in A1C across all visits -0.27% with lixisenatide vs placebo and standard care (95% CI -0.31 to -0.22, $P < 0.001$)
    - Strengths:
        - Independent, blinded adjudication of efficacy and safety endpoints.
        - 96.3% and 96.1% of lixisenatide and standard care groups, respectively, completed the trial.
    - Limitations:
        - Baseline differences in age, eGFR, A1C and prior stroke history between groups
            - Note: Post hoc sensitivity analysis adjusting for these differences did not significantly change results.
        - Use of additional anti-hyperglycemic drugs during study permitted but not described; potential differences may confound results.
        - Study drug discontinued in a higher proportion of the lixisenatide group compared to the standard care group (27.5% vs 24%, $P = 0.002$).
        - Relatively short duration for evaluation of long term effects.
        - Not powered to evaluate rare outcomes (e.g. cancer).
    - Observations:
        - Lixisenatide has a short half-life (~3 hours) compared to other GLP-1 agonists, which may explain the lack of CV benefit observed.[123]

        - Of all the GLP-1 agonist CVOTs, ELIXA included people with the highest risk of subsequent CV events as all the participants had an ACS within 180 days of enrollment.[123]

- The **LEADER trial** compared the effect of liraglutide vs placebo plus standard care in people with T2DM at high risk for CVD. LEADER was designed as a non-inferiority trial, with subsequent analysis for superiority. The superiority results are reported below.[18]
    - N = 9,340
    - Inclusion criteria
        - T2DM
        - A1C ≥ 7%
        - Age ≥ 50 years with established CVD or CKD, defined as at least one of the following:
            - Coronary heart disease
            - Cerebrovascular disease
            - PVD
            - Chronic HF (NYHA class II or III)
            - CKD stage 3 or greater (eGFR < 60 mL/min/1.73 $m^2$)
        - Age ≥ 60 years with at least one CV risk factor:
            - Microalbuminuria or proteinuria
            - Hypertension **and** left ventricular hypertrophy
            - Left ventricular systolic or diastolic dysfunction
            - Ankle-brachial index <0.9
    - Exclusion criteria
        - T1DM
        - Use of GLP-1 agonists, DPP-4 inhibitors, pramlintide*, or rapid-acting insulin (*Pramlintide is an anti-hyperglycemic drug and synthetic analog of the peptide hormone, amylin. It slows gastric emptying, suppresses glucagon secretion, and regulates appetite, but is not available in Canada).
        - Familial or personal history of MEN 2 or MTC
        - Occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomization
    - Baseline characteristics similar between groups
        - Established CVD (see Appendix B for definition) or CKD stage 3 or greater ~81%
        - HF NYHA class I, II or III ~18%
        - Mean duration T2DM 12.8 years
        - Mean A1C 8.7%

        - eGFR
            - ≥ 90 mL/min/1.73 $m^2$ ~35%
            - 60-89 mL/min/1.73 $m^2$ ~42%
            - 30-59 mL/min/1.73 $m^2$ ~20%
            - <30 mL/min/1.73 $m^2$ ~3%
        - Microalbuminuria 26.3%, macroalbuminuria 10.5%[102]
        - Mean BMI 32.5 $kg/m^2$
        - North American ~30%
        - Male ~64%
        - Mean age ~64 years
    - Interventions
        - Liraglutide 1.8 mg (or maximum tolerated dose) or matching placebo SC once daily *plus* standard care.
            - Addition of glucose-lowering drugs permitted except for GLP-1 agonists, DPP-4 inhibitors, and pramlintide.
                - Pramlintide is an anti-hyperglycemic drug and synthetic analog of the peptide hormone, amylin. It slows gastric emptying, suppresses glucagon secretion, and regulates appetite, but is not available in Canada.
        - Use of frequently prescribed medications similar between groups at baseline:
            - Metformin ~76%
            - Insulin ~44%
            - SU ~51%
            - ASA ~63%, Other anti-platelet ~15.7%
            - Beta-blocker ~55%
            - ACE inhibitor ~51%, ARB ~32%
            - Statin ~72%
    - Follow-up
        - Median 3.8 years
    - Results at 3.8 years
        - Primary outcome: MACE
            - Individuals randomized to liraglutide experienced a **statistically significant reduction** in MACE relative to standard care (P = 0.01).
                - HR 0.87 (95% CI 0.78-0.97), ARR 1.9%, NNT 53 (95% CI 31-202)
                    - Note the 95% CI around the NNT is wide, reflecting a lack of precision in the result.
                - Outcome driven by an improvement in CV death.

        - HR 0.78 (95% CI 0.66-0.93), ARR 1.3%, NNT 77 (95% CI 46-258)
    - The individual outcomes of nonfatal MI and nonfatal stroke were not statistically significant.
- A benefit in the secondary composite outcome (CV death, MI, stroke, coronary revascularization, HUA, and HHF) was also driven by an improvement in CV death.
- Select findings are reported in Table E.

**Table E: Results of the LEADER Trial**[18]

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR | NNT for 3.8 yrs | |
|---|---|---|---|---|---|---|
| | Liraglutide n=4,668 | Placebo n=4,672 | | | NNT | 95% CI |
| **Primary** | | | | | | |
| CV death, MI, stroke (MACE) | 13 | 14.9 | 0.87 (0.78-0.97) | 1.9% | 53 | 31-202 |
| **Secondary** | | | | | | |
| CV death | 4.7 | 6 | 0.78 (0.66-0.93) | 1.3% | 77 | 46-258 |
| Nonfatal MI | 6 | 6.8 | 0.88 (0.75-1.03) | 0.8% | NS | |
| Nonfatal stroke* | 3.4 | 3.8 | 0.89 (0.72-1.11) | 0.4% | NS | |
| CV death, MI, stroke, coronary revascularization, HUA, HHF | 20.3 | 22.7 | 0.88 (0.81-0.96) | 2.4% | 42 | 25-137 |
| All cause death | 8.2 | 9.6 | 0.85 (0.74-0.97) | 1.4% | 72 | 40-408 |

HR, hazard ratio; ARR, absolute risk reduction; NNT, number needed to treat; CI confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
*Analysis not pre-specified
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only

        - Pre-specified exploratory subgroup analyses suggest greater benefit in MACE with liraglutide vs standard care in people with eGFR < 60 mL/min/1.73 $m^2$ and history of CVD.
            - Note: Very few people with eGFR < 30 mL/min/1.73 $m^2$ were included, so findings apply to people with eGFR between 30 and < 60 mL/min/1.73 $m^2$.
        - Mean difference in A1C at 36 months -0.40% between liraglutide and standard care (95% CI -0.45 to -0.34).
    - Strengths
        - Well-designed trial with balanced treatment arms at baseline
        - Outcome events adjudicated by a blinded, external, independent committee
        - Loss to follow-up 0.2%

- Limitations
  - Exposure to other glucose-lowering drugs during the trial differed between groups, with greater use in the standard care group. This difference was necessary to target similar BG concentrations in both groups but may confound results.
    - Insulin
      - Liraglutide 28.8% vs standard care 43.2%
    - SU
      - Liraglutide 7.5% vs standard care 10.8%
    - TZDs
      - Liraglutide 2.1% vs standard care 3.4%
    - SGLT-2 inhibitors
      - Liraglutide 2.1% vs standard care 2.8%
  - A greater use of beta-blockers at baseline in the liraglutide arm may confound results (56.8% liraglutide vs 54.1% standard care, P = 0.009).
  - Open label GLP-1 agonist use occurred to a greater extent in the standard care group (3%) than in the liraglutide group (1.9%), despite being prohibited by the study protocol.
  - Cause of CV death not clear[94]
    - 219/4,668 subjects on liraglutide experienced CV death, but only 17 had a fatal MI and 16 had a fatal stroke. 278/4,762 subjects on standard care experienced CV death, but only 28 had a fatal MI and 25 had a fatal stroke. What caused the majority of CV deaths?
  - It is unknown if a lower risk population would achieve the same benefits as the subjects in the LEADER trial.

- The **SUSTAIN-6 trial** evaluated the CV safety of SC semaglutide vs placebo plus standard care in people with T2DM.[19]
  - N = 3,297
  - Inclusion criteria
    - T2DM
    - A1C ≥ 7% (on zero to two oral glucose-lowering drugs, with or without basal or premixed insulin)
    - Age ≥ 50 years and established CVD or CKD, defined as at least one of the following:
      - CVD (see Appendix B for definition)
      - Cerebrovascular disease
      - PVD

- Chronic HF (NYHA class II or III)
- CKD stage 3 or greater (eGFR < 60 mL/min/1.73 $m^2$)

▪ Age ≥ 60 years and at least one CV risk factor:
- Persistent microalbuminuria (3.4 to 33.8 mg/mmol) or proteinuria
- Hypertension **and** left ventricular hypertrophy
- Left ventricular systolic or diastolic dysfunction
- Ankle-brachial index <0.9

○ Key exclusion criteria
▪ DPP-4 inhibitor use within 30 days before screening
▪ GLP-1 agonist or insulin other than basal or premixed within 90 days before screening
▪ History of acute coronary or cerebrovascular event within 90 days before randomization
▪ Planned revascularization of a coronary, carotid, or peripheral artery
▪ Long-term dialysis

○ Baseline characteristics similar between groups
▪ Established CVD or CKD stage 3 or higher 83%
▪ Established CVD 58.8%
▪ HF 23.6%
▪ Mean duration T2DM 13.9 years
▪ Mean A1C 8.7%
▪ eGFR
- ≥ 90 mL/min/1.73 $m^2$ 30%
- 60 to < 90 mL/min/1.73 $m^2$ 41.5%
- 30 to < 60 mL/min/1.73 $m^2$ 25.2%
- 15 to < 30 mL/min/1.73 $m^2$ 2.9%
- < 15 mL/min/1.73 $m^2$ 0.4%

▪ Mean BMI 32.8 kg/$m^2$
▪ White 83%
▪ Male 60.7%
▪ Mean age 64.6 ± 7.4 years

○ Interventions
▪ Semaglutide 0.5 mg or 1 mg SC once weekly or matched placebo (randomized 1:1:1:1) plus standard care for BG management.
- Addition of glucose-lowering drugs permitted except for GLP-1 agonists and DPP-4 inhibitors.

▪ Glucose-lowering drug use at baseline 98.4%
▪ Use of frequently prescribed medications similar between groups at baseline:

- Biguanides 73.2%
- Insulin 58%
- SU 42.8%
- ASA ~ 64%, anti-thrombotic agents ~76%
- Beta-blockers ~57%
- ACE inhibitors ~50%, ARB ~34%
- Diuretics ~38%
- Statins ~73%

- Follow up
  - Median 2.1 years
- Results at 2.1 years
  - Primary composite outcome
    - **Semaglutide was *non-inferior* to placebo** for the primary composite outcome of CV death, non-fatal MI or non-fatal stroke (P < 0.001).
      - HR 0.74 (95% CI 0.58-0.95), ARR 2.3%, NNT 44 (95% CI 25-210).
      - Note the 95% CI around the NNT is wide, reflecting a lack of precision in the result.
      - The primary composite outcome was driven by a reduction in rate of non-fatal stroke. The individual outcomes of nonfatal MI and CV death were not statistically significant.
    - ***Post hoc*** testing for superiority was also statistically significant for MACE (P = 0.02), but there were no statistical adjustments for multiple comparisons.
      - May increase risk of type 1 error or false positive
    - Select findings are reported in Table F.

**Table F: Results of the SUSTAIN-6 Trial**[19]

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR (ARI) | NNT for 2.1 yrs | |
|---|---|---|---|---|---|---|
| | Pooled Semaglutide n=1,648 | Pooled Placebo n=1,649 | | | NNT | 95% CI |
| **Primary** | | | | | | |
| CV death, MI, stroke (MACE) | 6.6 | 8.9 | 0.74 (0.58-0.95)* | 2.3% | 44 | 25-210 |
| **Secondary** | | | | | | |
| CV death | 2.7 | 2.8 | 0.98 (0.65-1.48) | 0.1% | NS | |
| Nonfatal MI | 2.9 | 3.9 | 0.74 (0.51-1.08) | 1.0% | NS | |
| Nonfatal stroke | 1.6 | 2.7 | 0.61 (0.38-0.99) | 1.1% | 91 | 48-905 |
| All cause death | 3.8 | 3.6 | 1.05 (0.74-1.50) | (0.2%) | NS | |

HR, hazard ratio; ARR, absolute risk reduction; ARI, absolute risk increase; NNT, number needed to treat; CI confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
*P-value for non-inferiority <0.001; *Post hoc* P-value for superiority 0.02
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.

        - Primary outcome results were similar between semaglutide 0.5 mg and 1 mg dosing.
            - Semaglutide 0.5 mg, HR 0.77 (95% CI 0.55-1.08), P = 0.13
            - Semaglutide 1 mg, HR 0.71 (95% CI 0.49-1.02), P = 0.06
    - A1C
        - At 104 weeks, A1C was 0.7% and 1% lower than baseline with semaglutide 0.5 mg and 1 mg, respectively compared to placebo (P < 0.001).
    - Strengths
        - Outcomes adjudicated by a blinded, independent, external committee (Exception: peripheral revascularization).
        - Follow-up 98%
    - Limitations
        - Superiority testing was not pre-specified and there was no statistical adjustment for multiple comparisons (may increase risk of type 1 error or false positive).
        - Exposure to other glucose-lowering drugs differed between groups, with greater use in the standard care group. This difference was necessary to target similar BG levels in both groups but may confound the results. Introduction of glucose-lowering drugs during the trial:
            - Insulin
                - Semaglutide ~9% vs standard care ~24%

        - SU
            - Semaglutide ~4% vs standard care ~7.5%
        - TZD
            - Semaglutide ~0.8% vs standard care ~3.5%
        - SGLT-2 inhibitors
            - Semaglutide ~2.5% vs standard care ~5.5%
    - Unknown if greater A1C reduction in semaglutide arm improved outcomes compared to standard care.
    - Relatively short duration for evaluation of long term effects.
    - Effect of semaglutide on MACE unknown for individuals at low risk of developing CVD because they were not included in the study.

- The **REWIND trial** evaluated the CV impact of dulaglutide vs standard care in T2DM.[20]
    - N = 9,901
    - Inclusion criteria
        - T2DM
        - A1C ≤ 9.5%
        - Taking up to 2 glucose-lowering drugs with or without basal insulin
        - BMI ≥ 23 kg/$m^2$
        - One of the following:
            - Age ≥ 50 years with established vascular disease (MI, ischemic stroke, revascularization, HUA, or imaging evidence of myocardial ischemia)
            - Age ≥ 55 years and myocardial ischemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, eGFR < 60 mL/min/1.73 $m^2$, or albuminuria
            - Age ≥ 60 years and at least two of the following
                - Tobacco use
                - Dyslipidemia
                - Hypertension
                - Abdominal obesity
    - Exclusion criteria
        - eGFR < 15 mL/min/1.73 $m^2$
        - Cancer in previous 5 years
        - Severe hypoglycemia in previous year
        - Life expectancy < 1 year
        - Coronary or cerebrovascular event within previous 2 months
        - Plans for revascularization
    - Baseline characteristics similar between groups

- CVD **~31%** (low compared to other CVOTs)
  - Defined as MI, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or coronary, carotid, or peripheral revascularization (see Appendix B for definition).
- CV event (MI or ischemic stroke) ~20%
- HF ~8.6%
- Median duration T2DM 9.5 years
- Median A1C 7.2%
- Median eGFR ~75 mL/min/1.73 $m^2$
  - eGFR ≥ 60 mL/min/1.73 $m^2$ ~78%
  - Albuminuria (uACR ≥ 3.39 mg/mmol) ~35%
    - Microalbuminuria (uACR 3.39-33.9 mg/mmol) ~27%
    - Macroalbuminuria (uACR > 33.9 mg/mmol) ~8%
- Mean BMI 32.3 kg/$m^2$
- White ~76%
- Male ~54%
- Mean age 66 years

- Interventions
  - Dulaglutide 1.5 mg SC once weekly or placebo plus standard care for BG control and CV risk management.
    - Addition of other glucose-lowering drugs permitted except for GLP-1 agonists and pramlintide.
      - Pramlintide is an anti-hyperglycemic drug and synthetic analog of the peptide hormone, amylin. It slows gastric emptying, suppresses glucagon secretion, and regulates appetite, but is not available in Canada.
  - Use of frequently prescribed medications similar between groups at baseline:
    - Metformin ~81%
    - Insulin ~24%
    - SU ~46%
    - Antiplatelet ~54%
    - Beta-blockers ~46%
    - ACE inhibitor or ARB ~81%
    - Diuretics ~44%
    - Statins ~66%
- Follow up
  - Median 5.4 years
- Results at 5.4 years

- Primary composite outcome
  - Participants randomized to dulaglutide experienced a **statistically significant reduction** in the primary composite outcome of CV (or unknown cause of) death, nonfatal MI or nonfatal stroke relative to standard care.
    - HR 0.88 (95% CI 0.79-0.99), ARR 1.4%, NNT 72 (95% CI 37-1130), P = 0.026
      - Note the 95% CI around the NNT is wide, reflecting a lack of precision in the result.
  - The primary composite outcome was driven by an improvement in nonfatal stroke, whereas other components were not statistically significant.
- Select findings are presented in Table G.

**Table G: Results of the REWIND Trial**[20]

| Efficacy Outcome | Event Rate % | | HR (95% CI) | ARR (ARI) | NNT for 5.4 yr | |
|---|---|---|---|---|---|---|
| | Dulaglutide n=4,949 | Placebo n=4,952 | | | NNT | 95% CI |
| **Primary** | | | | | | |
| CV or unknown cause of death, MI, stroke | 12.0 | 13.4 | 0.88 (0.79-0.99) | 1.4% | 72 | 37-1130 |
| **Secondary** | | | | | | |
| CV or unknown cause of death | 6.4 | 7.0 | 0.91 (0.78-1.06) | 0.6% | NS | |
| Nonfatal MI | 4.1 | 4.3 | 0.96 (0.79-1.16) | 0.2% | NS | |
| Nonfatal stroke | 2.7 | 3.5 | 0.76 (0.61-0.95) | 0.8% | 125 | 68-852 |
| HHF (or urgent visit) | 4.3 | 4.6 | 0.93 (0.77-1.12) | 0.3% | NS | |
| HUA | 1.8 | 1.6 | 1.14 (0.84-1.54) | (0.2%) | NS | |
| All cause death | 10.8 | 12.0 | 0.90 (0.80-1.01) | 1.2% | NS | |

HR, hazard ratio; ARR, absolute risk reduction; ARI, absolute risk increase; NNT, number needed to treat; CI confidence interval; NS, not significant
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.
NNTs were calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. They are provided as an estimate only.

  - Compared to standard care, subjects on dulaglutide had a lower mean A1C by 0.61% (95% CI 0.58-0.65).
- Strengths
  - REWIND was designed as a superiority trial, whereas other CVOTs tested for non-inferiority, with or without a superiority analysis.
  - Compared to other CVOTs, REWIND enrolled a higher proportion of women (~47%) and people without established CVD (~69%).

        - Longest duration of the GLP-1 agonist CVOTs.
    - Limitations
        - Insulin use increased throughout the course of the study, to a greater extent in the standard care group, which may confound results.
            - Use of insulin at baseline: dulaglutide 24% vs standard care 23.7%
            - Use of insulin at last visit: dulaglutide 27.1% vs standard care 35.9%
        - More than 25% of subjects not taking study drug at time of last visit.
    - Observations
        - Participants had the lowest baseline A1C and CV risk in REWIND compared to subjects in other GLP-1 agonist CVOTs.

- The **PIONEER-6 study**[21] aimed to rule out an increase in CV risk with oral semaglutide compared to standard care in people with T2DM.
    - N = 3,183
    - Inclusion criteria
        - T2DM
        - Age ≥ 50 years and at least one of following:
            - Established CVD
                - Prior MI, stroke, or TIA
                - Prior coronary, carotid, or peripheral arterial revascularization
                - > 50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries
                - History of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging or unstable angina pectoris with ECG changes
                - Asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging
                - HF NYHA class II-III
            - Moderate CKD
                - eGFR 30-59 mL/min/1.73 $m^2$
        - Age ≥ 60 years and at least one CV risk factor:
            - Microalbuminuria or proteinuria
            - Hypertension and left ventricular hypertrophy
            - Left ventricular systolic or diastolic dysfunction
            - Ankle-brachial index < 0.9

- Key exclusion criteria
  - Treatment with any GLP-1 agonist, DPP-4 inhibitor, or pramlintide* within 90 days before screening (*Pramlintide is an anti-hyperglycemic drug and synthetic analog of the peptide hormone, amylin. It slows gastric emptying, suppresses glucagon secretion, and regulates appetite, but is not available in Canada.)
  - HF NYHA class IV
  - Planned coronary, carotid, or peripheral artery revascularization
  - MI, stroke, HUA or TIA within 60 days of screening
  - Long-term or intermittent hemodialysis or peritoneal dialysis, or severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$)
  - Proliferative retinopathy or maculopathy resulting in active treatment
- Baseline characteristics similar between groups
  - Established CVD or CKD ~85% (as defined in inclusion criteria)
  - Moderate CKD (eGFR 30-59 mL/min/1.73 $m^2$) 28.2%
  - HF (NYHA class II-III) 12.2%
  - Mean duration T2DM 14.9 years
  - Mean A1C 8.2%
  - Mean eGFR 74 mL/min/1.73 $m^2$
    - eGFR ≥ 60 mL/min/1.73 $m^2$ ~72.5%
    - Microalbuminuria or proteinuria 33%
  - Mean BMI 32.3 kg/$m^2$
  - White ~72%
  - Male ~68%
  - Mean age 66 years
- Interventions
  - Oral semaglutide titrated to target dose 14 mg once daily or placebo plus standard care for BG control and CV risk management.
    - Semaglutide 3 mg once daily for 4 weeks, then 7 mg once daily for 4 weeks, then 14 mg daily as tolerated.
    - Medication taken in the morning, swallowed whole, at least 30 minutes before eating, with 120 mL water or less. Other oral medication not permitted within 30 minutes of study drug.
    - Addition of other glucose-lowering drugs permitted except for GLP-1 agonists, DPP-4 inhibitors, and pramlintide.
      - Pramlintide is an anti-hyperglycemic drug and synthetic analog of the peptide hormone, amylin. It slows gastric emptying, suppresses glucagon secretion, and regulates appetite, but is not available in Canada.

- Use of frequently prescribed medications similar between groups at baseline:
  - Biguanides ~77%
  - Insulin ~60%
  - SU ~32%
  - Antiplatelet/ antithrombotic drugs ~79%
  - Antihypertensive drugs ~94%
  - Diuretics ~40%
  - Lipid-lowering drugs ~85%

- Follow up
  - Median 1.3 years
  - Received study drug for more than a year ~75%
- Results at 1.3 years
  - Primary composite outcome
    - **Oral semaglutide was *non-inferior* to standard care** for the primary composite outcome of CV (or cause undetermined) death, nonfatal MI, or nonfatal stroke ($P < 0.001$), but there was no evidence of superiority ($P = 0.17$).
      - HR 0.79 (95% CI 0.57-1.11), ARR 1%
  - Mean change in A1C from baseline to study end -1.0% (semaglutide) vs -0.3% (standard care).
- Strengths
  - CV and other selected events adjudicated by blinded, independent external committee.
- Limitations
  - Exposure to other glucose-lowering drugs differed between groups, with greater use in the standard care group. This difference was necessary to target similar BG levels in both groups but may confound results.
    - Insulin, semaglutide 11.2% vs standard care 23.6%
    - SU, semaglutide 3.5% vs standard care 7.8%
    - TZD, semaglutide 0.5% vs standard care 1.5%
    - SGLT-2 inhibitors, semaglutide 3.1% vs standard care 7%
  - Use of beta-blockers, ACE inhibitors, ARBs, and statins not reported at baseline (reported only as “anti-hypertensives” and “lipid-lowering drugs”).
  - Short duration for evaluation of long term effects.
- Observations
  - To maximize absorption, oral semaglutide must be taken on an empty stomach at least 30 minutes before the first food, beverage or other

oral medications of the day, with no more than 120 mL of water. Despite optimal administration technique, bioavailability is approximately 1%. Individuals may struggle to adhere to this regimen, particularly outside the structured environment of a clinical trial, which could impact generalizability of results.

- A longer, prospective RCT comparing the effect of PO and SC semaglutide would be useful to determine whether or not these formulations can be used interchangeably.
- A larger CVOT comparing the effect of oral semaglutide vs placebo on MACE in people with T2DM and established CVD is currently in progress (SOUL Study) with estimated completion in 2024.[95]

- Despite the overall benefit in MACE observed in REWIND, LEADER and SUSTAIN-6, available data suggest the benefit derived from people in North America did not appear to be as great as in participants from other geographic regions.[18-20, 96]
  - Interpretation of this finding is limited by subgroup analyses that were neither designed nor powered to evaluate this particular population.
  - Confirmation in a North American trial is required, although such a study is not likely to be pursued by manufacturers.

- A number of SRs and MAs [97-98] have pooled data from the GLP-1 CVOTs for analysis, but results will not be included in this document and should be interpreted with caution due to
  - Heterogeneity in the study population
  - Differences in pharmacokinetics between drugs
  - Availability of only 1 study per drug/route
  - Lack of evidence of a class effect

**Heart Failure**

- Hospitalization for HF (HHF) was evaluated as a secondary outcome in the GLP-1 agonist CVOTs, but no statistically significant differences between groups were observed.[17-19, 21, 99]
  - These studies were not designed or powered to evaluate HHF and results should be interpreted with caution.

**Mechanism of CV Benefit**

- The mechanism of CV benefit with GLP-1 agonists is unknown, but likely multifactorial. It has been hypothesized to be different from SGLT-2 inhibitors, given the variability in time to benefit observed on Kaplan-Meier curves from CVOT trials.[100] For example:
  - LEADER (liraglutide)[18]
    - >12 months for CV death

  - >18 months for all cause death and HHF
- EMPA-REG OUTCOME (empagliflozin)[14]
  - < 3 months for CV death, all cause death, and HHF

## Academic Detailing Comments

- Evidence of benefit in MACE was observed with SC formulations of liraglutide, semaglutide, and dulaglutide, in people with established CVD or CKD and those at high risk of developing CVD.
  - Liraglutide and semaglutide have evidence for individuals with established CVD (LEADER, SUSTAIN-6).[18-19]
  - Dulaglutide has evidence for people with high risk of CVD (REWIND).[20]

- GLP-1 agonists were not used as monotherapy in these clinical trials.[18-20] The benefits observed occurred in people who were taking other glucose-lowering drugs at baseline, including biguanides (73 to 81%), insulin (24 to 58%), and SU (43 to 51%), among others.[18-20]

- The effect of GLP-1 agonists on MACE in people with T2DM and low risk of CVD, or newly diagnosed T2DM, has not been formally evaluated in prospective RCTs.

- It is not clear why some CVOTs identified improvements in MACE with GLP-1 agonists while others did not. Variable results *may* be attributed to differences in
  - Study population and design
  - Pharmacokinetics or pharmacology of individual drug therapies

- **Placebo controlled** trials evaluating the effects of GLP-1 agonists on clinical outcomes **do not inform relative benefits or harms between agents.**

- To optimize use of GLP-1 agonists, one must weigh the benefits of therapy against the potential harms (see page 79).

## Question 4: What is the evidence for benefit of GLP-1 agonists for microvascular outcomes in the treatment of T2DM?

- Microvascular complications of T2DM include nephropathy, retinopathy, neuropathy and PVD.

- The indirect effect of BG lowering on microvascular outcomes has been described in a previous Academic Detailing Program document (Type 2 Diabetes What after Metformin? 2016)[1] and will not be readdressed at this time.

**Effects of GLP-1 agonists on nephropathy**

- There are no published prospective RCTs designed to evaluate the effect of GLP-1 agonists on nephropathy. The available evidence is **limited to secondary outcomes and exploratory analyses**.

- Evidence suggests GLP-1 agonists (SC semaglutide, liraglutide and dulaglutide) may improve renal outcomes in people with T2DM and high baseline CV risk.
  - Results are summarized in Table H (page 66).
  - See page 53 (SUSTAIN-6),[19] 50 (LEADER),[18] and 57 (REWIND)[20] for study details.

- In general, positive findings are driven by a decrease in macroalbuminuria, a **surrogate marker**.
  - Macroalbuminuria has been shown to be an independent predictor of renal insufficiency; however that outcome was not observed in these trials.

- Interpret results with **caution** because
  - The original trials were not designed or powered to evaluate renal outcomes.
  - There are potential confounders, including use of other drugs, glycemic control, changes in weight and blood pressure.
  - 95% CI around the NNTs are wide, reflecting uncertainty in the results.

- Future studies are required to determine the effect of GLP-1 agonists on renal outcomes in people with T2DM more definitively.
  - The **FLOW** semaglutide RCT started in June 2019 and is scheduled to be complete in August 2024.[101] Results will be helpful to further evaluate this relationship.

**Table H: Evidence Summary – Effect of GLP-1 Agonists on Nephropathy (*Secondary Outcomes*)**

| Study (Intervention) | Outcome | Event Rate % | | HR (95% CI) | ARR | Comments |
|---|---|---|---|---|---|---|
| | | GLP-1 | Placebo | | | |
| SUSTAIN-6[19] (Semaglutide) | New or worsening nephropathy[a] or need for continuous RRT | 3.8 | 6.1 | 0.64 (0.46-0.88) | 2.3% | Result driven by ↓ macroalbuminuria |
| MANN et al[102] (Liraglutide) *Pre-specified 2º analysis of LEADER* | Renal composite outcome[b] | 5.7 | 7.2 | 0.78 (0.67-0.92) | 1.5% | Result driven by ↓ macroalbuminuria |
| GERSTEIN et al[103] (Dulaglutide) *Exploratory analysis of REWIND* | Renal composite outcome[c] | 17.1 | 19.6 | 0.85 (0.77-0.93) | 2.5% | Result driven by ↓ macroalbuminuria |

HR, hazard ratio; ARR, absolute risk reduction; CI, confidence interval; RRT, renal replacement therapy;
a) Persistent macroalbuminuria, persistent doubling of SrCr and a CrCl < 45 mL/min/1.73 $m^2$ (MDRD)
b) New onset macroalbuminuria or doubling of SrCr and eGFR ≤ 45 mL/min/1.73 $m^2$, need for continuous RRT, or death from renal disease
c) New macroalbuminuria (uACR > 33.9 mg/mmol), sustained decline in eGFR ≥ 30%, or chronic RRT
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.

**Effects of GLP-1 inhibitors on diabetic retinopathy**

- There are no published prospective RCTs designed to evaluate the effect of GLP-1 agonists on DRP.

- The available evidence is **limited to secondary outcomes** in the GLP-1 agonist CVOTs, which are summarized in Table I (page 67).
    - No statistically significant difference in retinopathy with liraglutide (LEADER)[18] or a composite eye outcome with dulaglutide (REWIND).[20]
    - Increased risk of retinopathy with semaglutide compared to placebo and standard care in the SUSTAIN-6 study.[19]
        - The investigators observed a difference in retinopathy rates early in the study period, and stated the following:
            - "An association between rapid glucose lowering and worsening of retinopathy has been reported in patients with type 1 diabetes. The applicability of such an association to our finding is unclear, and a direct effect of semaglutide cannot be ruled out."

- The CVOTs are described on page 53 (SUSTAIN-6), [19] 50 (LEADER),[18] and 57 (REWIND).[20]

➢ Interpret results with **caution** because
- The original trials were not designed or powered to evaluate DRP, and event rates were low.
  - Eye examinations were only included in the protocol of SUSTAIN-6, not LEADER, or REWIND.
  - Baseline rates of retinopathy were reported inconsistently.
- There are potential confounders, including use of other drugs, glycemic control, changes in weight and blood pressure.
- 95% CI around the NNTs are wide, reflecting uncertainty in the results.

➢ Future studies are required to clarify the effect of GLP-1 agonists on DRP in people with T2DM.
- The **FOCUS** semaglutide RCT started in May 2019 and is scheduled to be complete in September 2027. Results will be helpful to further evaluate this relationship.[104]

**Table I: Evidence Summary – Effect of GLP-1 Agonists on Diabetic Retinopathy (*Secondary Outcomes*)**

| Study (Intervention) | Outcome | Event Rate % | | HR (95% CI) | ARI | Comments |
|---|---|---|---|---|---|---|
| | | GLP-1 | Placebo | | | |
| SUSTAIN-6[19] (Semaglutide) | Retinopathy[a] | 3.0 | 1.8 | 1.76 (1.11-2.78) | 1.2% | Driven by ↑ retinal photocoagulation. See page 53 for more info. |
| LEADER[18] (Liraglutide) | Retinopathy[a] | 2.3 | 2.0 | 1.15 (0.87-1.52) | 0.3% | |
| REWIND[20] (Dulaglutide) | Composite eye outcome[b] | 1.9 | 1.5 | 1.24 (0.92-1.68) | 0.4% | Analysis performed *post hoc* |

HR, hazard ratio; ARI, absolute risk increase; CI, confidence interval
a) Vitreous hemorrhage, onset of diabetes-related blindness, and need for treatment with an intravitreal agent or retinal photocoagulation
b) Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy.
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.

**Effects of GLP-1 agonists on neuropathy**

➢ There are no known studies evaluating the effect of GLP-1 agonists on neuropathy.

**Effects of GLP-1 agonists on peripheral vascular disease**

- There are no high quality clinical trials evaluating the effect of GLP-1 agonists on PVD or amputation rates.

- The available evidence is limited to a single **post hoc exploratory analysis** of the LEADER trial by Dhatariya et al, designed to assess the impact of liraglutide on the incidence of diabetes-related foot ulcers and sequelae in people with T2DM and high baseline CV risk.[105]
  - LEADER[18] is described on page 50.
  - Results
    - No statistically significant difference in time to first diabetes-related foot ulcer event
      - Liraglutide 3.8% vs standard care 4.1%, ARR 0.3%
      - HR 0.92 (95% CI 0.75-1.13), P = 0.41
    - Decreased risk of amputation as a complication of diabetes-related foot ulcer events with liraglutide compared to standard care
      - Liraglutide 0.9% vs standard care 1.4%, ARR 0.5%
      - HR 0.65 (95% CI 0.45-0.95), P = 0.03
  - Limitations
    - Study not designed or powered to evaluate these outcomes. Interpret findings with caution.

- The body of **evidence is insufficient** to confidently determine the effect of GLP-1 agonists on PVD.

## Question 5: What are the potential *harms* associated with SGLT-2 inhibitors in the treatment of T2DM?

- In this section, data from RCTs, MAs and observational studies are reported.
- Observational studies are useful in evaluating real-world effects of an intervention in a broader patient population.
- When possible, Canadian data is reported to improve generalizability of results.

**Diabetic Ketoacidosis (DKA)**

This section has been adapted with permission from British Columbia's Provincial Academic Detailing Service "Type 2 Diabetes: SGLT2 Inhibitors and Diabetic Ketoacidosis" document.[106]

- In 2016, Health Canada issued a warning that SGLT-2 inhibitors increase the risk of DKA.[29] The FDA updated a similar warning in 2022.[30] Newer trials support these warnings:
  - A 2019 MA of four large RCTs (EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58, & CREDENCE; N = 38,723) by Arnott et al. revealed a higher risk of DKA with SGLT-2 inhibitors compared to standard care.[32]
    - RR 2.46 (95% CI 1.43 – 4.24), $I^2$ = 0%
  - A 2020 Canadian observational trial by Douros et al. (N = 404,372; mean follow-up 0.9 years) found an increased risk of DKA with SGLT-2 inhibitors compared to DPP-4 inhibitors.[31]
    - 2.03 vs 0.75 events per 1000 person-years
    - Adjusted HR 2.85 (95% CI 1.99 – 4.08), $I^2$ = 50%
- Although rare, SGLT-2 inhibitor DKA is a medical emergency requiring immediate treatment, including SGLT-2 inhibitor discontinuation when its use is implicated.
  - Upon resolution of DKA, SGLT-2 inhibitor use should be re-evaluated.
    - Health Canada product monographs warn that SGLT-2 inhibitors "*should not be used* in patients with a history of DKA".[34-36]
    - Our **expert content reviewer** suggests clinical judgement is required and clinicians should:
      - Verify the type of diabetes diagnosed (type 1 vs type 2 vs other).
      - Identify the underlying cause of DKA and assess the likelihood of a recurrent episode.
      - Determine whether or not the potential benefits of therapy outweigh the risks.
- For a more comprehensive review of DKA management please see:
  - Goguen J et al. Hyperglycemic Emergencies in Adults: 2018 Clinical Practice Guidelines. Can J Diabetes 2018.[107] https://doi.org/10.1016/j.jcjd.2017.10.013

- Gosmanov AR et al. Management of adult diabetic ketoacidosis. *Diabetes Metab Syndr Obes*. 2014;7: 255-264[108] https://doi.org/10.2147/DMSO.S50516

- People with SGLT-2 inhibitor DKA may present with normal or near-normal BG levels. Upon initiation of SGLT-2 inhibitor therapy, Health Canada product monographs advise people with T2DM to seek immediate medical attention, **regardless of BG level**, if they experience symptoms of DKA, which may include:[34-36]
  - Difficulty breathing
  - Nausea, vomiting, or stomach pain
  - Loss of appetite or excessive thirst
  - Unusual fatigue
  - Confusion

- Advise people to temporarily stop taking their SGLT-2 inhibitor in situations where they are more vulnerable to developing DKA to mitigate risk. See Table J.

**Table J: Proposed strategies to minimize risk of DKA**[33]

| Risk Factor | Mitigation Strategy |
|---|---|
| Acute serious illness | • Hold SGLT-2 inhibitor at onset of illness<br>• Restart when feeling well and able to eat and drink |
| Major surgery | • Hold SGLT-2 inhibitor 3 days before surgery*<br>• Restart once physiological stress has resolved, feeling well and able to eat and drink |
| Bariatric surgery | • Hold SGLT-2 inhibitor during preoperative low-carbohydrate diet**<br>• Reassess postoperatively |
| Low intake of carbohydrates (CHO)** | • Hold SGLT-2 inhibitor<br>• Restart if low CHO diet** is discontinued |
| Excess intake of alcohol*** | • Stop SGLT-2 inhibitor immediately<br>• Reassess if alcohol intake is reduced*** |
| **Empirical based on 5 half-lives; **Not consistently defined in the literature; Diabetes Canada acknowledges low-CHO intake as 50-130 g/day and very low-CHO intake as < 50 g/day,[109] ***No threshold defined in the literature Adapted from Clin Ther 2016;38:2654–64.* | |

- Other potential predisposing/precipitating factors for SGLT-2 inhibitor DKA include:[34-35]
  - Severe dehydration
  - Insulin dose reduction or omission
  - Low beta-cell function reserve (e.g. latent autoimmune diabetes in adults)
  - Pancreatic disorders causing insulin deficiency (e.g. T1DM, pancreatitis, pancreatic surgery)
  - History of DKA

**Volume-Depletion Related Adverse Effects**

- By nature of their mechanism of action, SGLT-2 inhibitors cause osmotic diuresis, which may lead to hypovolemia and volume depletion-related adverse events such as postural dizziness, syncope, orthostatic hypotension, or hypotension.[34-36]

- The evidence describing these adverse effects associated with SGLT-2 inhibitor use is very limited.

- Clinical trials report a greater mean decrease in blood pressure by ≈ 4/1 mm Hg in patients on SGLT-2 inhibitors compared to standard care.[14-16]

- Micromedex reports the following incidence rates for hypovolemia (defined as symptomatic hypotension, orthostatic hypotension, postural dizziness, syncope):[37-39]
    - Empagliflozin:
        - 0.3% (25 mg) to 0.5% (10 mg) vs 0.3% with placebo (all patients)
        - 2.3% (10 mg) to 4.4% (25 mg) vs 2.1% with placebo (≥ 75 years)
    - Canagliflozin:
        - 2.3% (100 mg) to 3.4% (300 mg) vs 1.5% with comparator
        - In general, factors associated with the largest increased incidence of events were concomitant use of loop diuretics, moderate renal impairment (eGFR <60 mL/min/1.73 $m^2$), and age 75 years or older.
    - Dapagliflozin:
        - 0.6% (5 mg) to 0.8% (10 mg) vs 0.4% with placebo (all patients)
        - 0.5% (5 mg) to 1.5% (10 mg) vs 0.4% with placebo (≥ 65 years)
        - 2.5% (10 mg) vs 1.5% with placebo (concomitant loop diuretic use)

- Health Canada product monographs recommend[34-36]
    - Assess volume status and correct any deficit prior to starting an SGLT-2 inhibitor.
    - Cautious use in people with pre-existing hypotension and older age.
    - Temporary discontinuation of SGLT-2 inhibitors during times of acute illness due to risk of hypovolemia.
    - Cautious use and monitoring of volume status during therapy, particularly in individuals taking concomitant loop diuretics.
        - Note: Canagliflozin is not recommended in combination with loop diuretics.
        - Our **expert content reviewer** suggests if hypotension is due to concomitant SGLT-2 inhibitor and diuretic use, a dose reduction or withholding of diuretic may be considered, *if clinically appropriate*.

**Acute Kidney Injury (AKI)**

- A 2015 Health Canada safety review identified a link between SGLT-2 inhibitors and AKI.[40]
  - This link was established based on case reports of dapagliflozin and canagliflozin provided by the manufacturers, some of which required admission to hospital and dialysis.
    - A review of literature at that time provided limited additional evidence.
    - Empagliflozin was not yet marketed, therefore not included in the review.
  - Based on this information, Health Canada product monographs were updated with stronger warning statements regarding risk of AKI.[34-36]

- Subsequent RCTs observed *numerically lower rates of AKI with SGLT-2 inhibitors* compared to standard care, but these trials were not specifically designed to evaluate this outcome.[14-16]
  - EMPA-REG OUTCOME[14] (N = 7,020)
    - Empagliflozin 1% vs standard care 1.6%, P < 0.05
  - CANVAS[15] (N = 10,142)
    - Canagliflozin 3 vs standard care 4.1 events per 1000 patient-years, P = 0.33
  - DECLARE-TIMI 58[16] (N = 17,160)
    - Dapagliflozin 1.5% vs standard care 2%, HR 0.69 (95% CI 0.55-0.87), P = 0.002

- A decrease in eGFR of ~3 to 5 mL/min was observed in the treatment groups during the first four to eight weeks of therapy in the CVOTs, which may be confused with AKI.[15, 43]
  - Upon cessation of therapy, the decrease was reversed.
  - Following initial decline, eGFR stabilized in the SGLT-2 inhibitor groups while it continued to gradually decline in the standard care groups for the remainder of the trials.

- A 2020 Canadian retrospective cohort study by Rampersad et al. (N = 9,556) designed to evaluate renal effects of SGLT-2 inhibitors in a broader patient population with T2DM found new start SGLT-2 inhibitors are *not associated with increased risk of incident AKI* compared to other glucose-lowering drugs:[41]
  - SGLT-2 inhibitors (n = 4,778; mean follow-up 0.9 ± 0.7 year)
    - 1.11 events per 100 patient-years (95% CI 0.79-1.43)
  - Other glucose-lowering drugs (n = 4,778; mean follow-up 0.7 ± 0.6 year)
    - 1.99 events per 100 patient-years (95% CI 1.52-2.46)
  - HR 0.64 (95% CI 0.40-1.03), P = 0.06
    - No effect modification observed by renin-angiotensin-aldosterone system inhibitor (P = 0.9) or diuretic use (P = 0.8).

- A 2020 Canadian observational trial by Iskander et al. (N = 39,094) in people aged 66 years or older found that new use of SGLT-2 inhibitors was associated with a *lower 90-day risk of a hospital encounter with AKI* compared to DPP-4 inhibitors.[42]

- SGLT-2 inhibitors 1.10% vs DPP-4 inhibitors 1.99%
- Weighted risk ratio 0.79 (95% CI 0.64-0.98)

➢ Health Canada product monographs recommend to:[34-36]
- Avoid SGLT-2 inhibitors in people who are volume depleted or at risk of volume depletion.
- Assess baseline renal function and monitor throughout therapy.

**Hypoglycemia**

➢ Given the insulin-independent mechanism of action of SGLT-2 inhibitors, these agents, when used alone, are not associated with an increased risk of hypoglycemia.[44]

➢ When SGLT-2 inhibitors are used concomitantly with insulin or SU, the incidence of hypoglycemia is increased, and dose reduction of insulin or SU may be required.[34-36, 44]
- The 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults recommend that upon initiation of SGLT-2 inhibitor, in addition to insulin or SU, in patients with:[110]
  - A1c > 8.0%, consider:
    - Continuing insulin or SU at current dose due to low risk of hypoglycemia
  - A1c ≤ 8.0%, consider:
    - Insulin dose reduction of 10-20%; counsel on hypoglycemia.
    - SU dose reduction by 50% or stop SU.
  - Hypoglycemia, consider:
    - Stopping SU and reducing insulin dose
  - These recommendations are based on expert opinion of guideline panel members.
- Our **expert content reviewer** suggests the long-acting insulin dose be reduced 12-24 hours prior to starting the SGLT-2 inhibitor, when dose reduction is indicated.

➢ Currently, no observational studies exist assessing hypoglycemia risk with SGLT-2 inhibitors; however, findings across RCTs are consistent. A 2019 MA of four large RCTs (EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58, & CREDENCE; N = 38,723) by Arnott et al. found *no associated risk of hypoglycemia* with SGLT-2 inhibitors compared to standard care.[32]
- RR 0.82 (95% CI 0.65 – 1.03), $I^2$ = 11.7%
- At baseline, exposure to other glucose-lowering medications was balanced in both groups, however, throughout the duration of included trials, the standard care group required a greater addition of insulin, SU and TZDs to achieve similar BG targets in both groups. There was no analysis to explore this difference as a potential confounder of results.

- A 2019 Cochrane Review of RCTs by Madsen et al. investigated the effects of metformin plus SU compared with metformin plus other glucose-lowering drugs, including SGLT-2 inhibitors, in people with T2DM.[45] Since most patients will start and remain on metformin, these groups represent realistic options in clinical practice. Mild or moderate and serious hypoglycemia were assessed as *secondary* outcomes.
    - Results (see Table K)

**Table K: Hypoglycemia Rates: Metformin + SU compared to Metformin + SGLT-2 Inhibitor**[45]

| | Metformin + SU* | Metformin + SGLT-2 inhibitor | # trials | Risk Ratio (95% CI) | $I^2$** |
|---|---|---|---|---|---|
| | Event Rates | | | | |
| **Mild-moderate hypoglycemia** | 30.8% (n=1670) | 5.4% (n=1639) | 3 | 5.60 (2.38-13.14) | $I^2$=93% |
| **Serious hypoglycemia** | 1.4% (n=2907) | 0.3% (n=3027) | 4 | 6.16 (2.92-12.97) | $I^2$=93% |

*Analysis included 2nd and 3rd generation SU (e.g. glyburide, gliclazide, glimepiride)
**$I^2$ is a measure of percentage of variation (heterogeneity) across studies. An $I^2$ of 75%-100% represents considerable heterogeneity.

    - *Mild to moderate hypoglycemia* rates with SU (analyses include glyburide, glimepiride and gliclazide) were *significantly increased* compared with SGLT-2 inhibitors; however, **rates of severe hypoglycemia were low.**
- Limitations:
    - Definitions of hypoglycemia varied across included studies, making interpretation of clinical outcomes difficult.
    - Hypoglycemia was evaluated as a secondary outcome in this MA. Hard outcomes of all-cause mortality, CV mortality, serious AEs, non-fatal stroke or MI were not different amongst any of the groups.
    - The evidence is low to very low quality with high rates of heterogeneity ($I^2$) between studies in the MA. In addition, the risk ratio for the comparisons with SGLT-2 inhibitors are high and the confidence intervals wide, reflecting small absolute differences and a lack of precision in the result.

**Genital Mycotic Infection (GMI)**

- Health Canada product monographs[34-36], RCTs,[14-16] and observational studies[46-47] consistently report ~ 3 fold increased risk of GMI in people taking SGLT-2 inhibitors compared to DPP-4 inhibitors or standard care, in keeping with the mechanism of increased glycosuria.

- A 2021 review of Prevention and Management of Genital Mycotic Infections in the Setting of SGLT-2 Inhibitors by Engelhardt et al. reports the following:[48]

- Factors associated with the highest risk of GMI are female sex, prior history of chronic or recurrent GMIs (≥ 3/year) and uncircumcised males.
- Most GMIs are mild-moderate in severity, responsive to appropriate treatment (e.g., topical or oral antifungal therapy) and do not necessitate stopping SGLT-2 inhibitor therapy.

**Fournier's Gangrene**

- Fournier's gangrene is a rare but serious infection of necrotizing fasciitis of the perineum.

- The FDA issued a Safety Announcement in 2018, identifying 12 cases of Fournier's gangrene in patients on SGLT-2 inhibitors.[49] Both men and women with T2DM and SGLT-2 inhibitor exposure were affected.

- Health Canada product monographs include warnings of this risk and recommend SGLT-2 inhibitors be discontinued and prompt treatment of infection initiated when Fournier's gangrene is suspected.[34-36]

- There is limited evidence to report due to low event rates. RCTs have not demonstrated an increased risk of Fournier's gangrene with SGLT-2 inhibitor use.[14-16] These studies were not designed or adequately powered to evaluate risk of extremely rare events.

- A 2020 matched cohort study from Canada and the U.K. by Fisher et al. evaluating the rate of Fournier's gangrene with SGLT-2 inhibitors and DPP-4 inhibitors as a *secondary outcome* reported the following (N = 416,488; mean follow-up 0.9 years):[50]
  - SGLT-2 inhibitors 0.08 events per 1000 person-years (95% CI 0.05-0.13)
  - DPP-4 inhibitors 0.14 events per 1000 person-years (95% CI 0.09-0.21)
  - A statistical comparison between groups was not reported.
  - The number of events was low overall and statistical adjustments were not performed for this secondary outcome.

**Urinary Tract Infection (UTI)**

- In response to post-marketing case reports, both Health Canada and the FDA have updated product monographs and issued warnings to highlight risk of serious UTI, including urosepsis and pyelonephritis, in people taking SGLT-2 inhibitors.[30, 34-36]

- Subsequent RCTs[14-16] and observational studies[50-51] have not replicated this associated risk.

- Although other studies exist, the best available evidence comes from two observational trials reporting *no increased risk of UTI* associated with SGLT-2 inhibitors compared to alternative glucose-lowering drugs.[50-51]

- *Severe UTI*
  - A 2020 matched cohort study from Canada and the UK (N = 416,488; mean follow-up 0.9 years) by Fisher et al. evaluated the risk of severe UTI in adults with T2DM using SGLT-2 inhibitors vs DPP-4 inhibitors.[50]
    - Primary outcome
      - Urosepsis, defined as hospitalization for either acute pyelonephritis, UTI or acute cystitis
    - Results: SGLT- 2 inhibitor vs DPP-4 inhibitor
      - 1.00 (95% CI 0.87-1.16) vs 2.03 (95% CI 0.83-2.24) per 1000 person-years
      - Pooled adjusted HR 0.58 (95% CI 0.42-0.80), $I^2$ = 56%
      - A subgroup analysis found risk of severe UTI to be similar for women and men.
  - A 2019 American population-based cohort study by Dave et al. compared adults with T2DM starting treatment with SGLT-2 inhibitors vs DPP-4 inhibitors or GLP-1 agonists.[51]
    - Primary outcome
      - Severe UTI, defined as hospitalization for either primary UTI, sepsis with UTI or pyelonephritis
    - Results
      - SGLT-2 inhibitors vs DPP-4 inhibitors (n = 123,752)
        - 1.76 vs 1.77 events per 1,000 person-years
        - Adjusted HR 0.98 (95% CI 0.68-1.41)
      - SGLT-2 inhibitor vs GLP-1 agonist (n = 111,978)
        - 2.15 vs 2.96 events per 1,000 person-years
        - Adjusted HR 0.72 (95% CI 0.53-0.99)
      - Subgroup analyses found risk of severe UTI to be similar for women and men for both comparisons (SGLT-2 inhibitors vs DPP-4 inhibitors and SGLT-2 inhibitors vs GLP-1 agonists).
- *Mild to Moderate UTI*
  - A 2019 American population-based cohort study by Dave et al. compared adults with T2DM starting treatment with SGLT-2 inhibitors vs DPP-4 inhibitors or GLP-1 agonists.[51]
    - *Secondary* outcome
      - Outpatient UTI treated with antibiotics
    - Results
      - SGLT-2 inhibitor vs DPP-4 inhibitor (n = 123,752)
        - 34.5 vs 36.05 events per 1,000 person-years
        - Adjusted HR 0.96 (95% CI 0.89-1.04)
      - SGLT-2 inhibitor vs GLP-1 agonist (n = 111,978)
        - 36.65 vs 41.04 events per 1,000 person-years
        - Adjusted HR 0.91 (95% CI 0.84-0.99)

- Based on best available evidence from observational studies, SGLT-2 inhibitors do not appear to increase risk of severe or non-severe UTI events vs other antihyperglycemics.

**Lower Limb Amputation (LLA)**

- The Health Canada product monograph for canagliflozin (Invokana®) includes a serious warning regarding an associated ≈ 2-fold increased risk of LLA based on observations from the CANVAS Program.[35]
  - Canagliflozin 6.3 vs standard care 3.4 events per 1000 patient-years, $P < 0.001$[15]
  - Amputation of the toe and midfoot were most common, but above and below knee amputations also occurred.[35]
  - Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events.[35]
  - Risk of amputation was highest in individuals with history of prior amputation, PVD and neuropathy.[35]

- To control for this risk, the canagliflozin Health Canada product monograph recommends prescribers provide patient education on routine preventative foot care, maintaining adequate hydration, and monitoring for signs and symptoms of infection and to stop canagliflozin if infection symptoms occur.[35]

- Diabetes Canada offers guidance on preventative foot care for patients:[111]
  - https://guidelines.diabetes.ca/docs/patient-resources/foot-care.pdf

- In response to the increased risk of amputation detected in the CANVAS Program, other investigators amended their protocols mid-study to control for this potential risk.
  - CREDENCE[27]
    - Additional requirement to examine participants' feet at each study visit and temporarily interrupt study drug in people with any active condition that could lead to amputation.
    - Exclusion criteria modified to preclude enrollment of people with a history of atraumatic amputation within 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.
  - DECLARE-TIMI 58[16]
    - Additional outcome added to evaluate amputation risk as an adverse effect both retroactively and prospectively from the time of amendment.
  - Neither CREDENCE[27] nor DECLARE-TIMI 58[16] reported an increased risk of amputation with SGLT-2 inhibitor over standard care, but these protocol changes may have made it harder to detect a difference compared to the CANVAS Program, if one truly exists.

- EMPA-REG OUTCOME was published prior to CANVAS and was not designed to evaluate amputations; however, a *post hoc* analysis of study data did not identify an increased risk with empagliflozin compared to standard care.[28]

- Health Canada product monographs for empagliflozin (Jardiance®)[34] and dapagliflozin (Forxiga®)[36] do not include warnings regarding LLA.

- In light of the conflicting findings from RCTs, larger observational trials were undertaken to evaluate the real-world risk of amputation with these drugs.
    - A 2020 matched pair cohort study from Canada and the U.K. by Yu et al. (N = 415,634; mean follow-up 11 ± 9 months) found no difference in rates of below-knee amputation with new SGLT-2 inhibitor use vs DPP-4 inhibitor use.[52]
        - Results: SGLT-2 inhibitors vs DPP-4 inhibitors
            - 1.3 vs 1.5 events per 1,000 person-years
            - Adjusted HR 0.88 (95% CI 0.71-1.09)
            - No statistically significant differences were observed when data was analyzed by drug molecule.
        - Limitations:
            - Patients with a prior history of amputation were excluded.
            - Study follow-up duration may not have been long enough for people to develop this outcome.
            - People in the SGLT-2 inhibitor cohort were permitted to continue pre-existing DPP-4 inhibitor use during the study.

- Overall, evidence is conflicting and there are limitations to the interpretation of the data. Longer observational trials are needed to evaluate the potential association of LLA with SGLT-2 inhibitors. In the meantime, a cautious approach may be warranted, especially in people with risk factors for LLA.

**Fracture**

- The canagliflozin (Invokana®) Health Canada product monograph[35] warns of increased risk of bone fracture, occurring as early as 12 weeks after initiation of therapy, based on adverse event reports from one RCT.[53] However, product monographs for empagliflozin (Jardiance®) and dapagliflozin (Forxiga®) do not include similar warnings.[34, 36]

- Risk of low-trauma fracture, not defined in the study protocol, was numerically higher in the canagliflozin group compared to standard care, but the difference was not statistically significant.[15]
    - Canagliflozin 11.58 vs standard care 9.17 events per 1000 patient-years
    - HR 1.23 (95% CI 0.99-1.52)

- A MA of RCTs[54] and an observational trial[55] did not show an increased risk of bone fracture with SGLT-2 inhibitors compared to other glucose-lowering drugs.

## Question 6: What are the potential *harms* associated with GLP-1 agonists in the treatment of T2DM?

- In this section data from RCTs, MAs and observational studies are reported.
- Observational studies are useful in evaluating real-world effects of an intervention in a broader patient population.
- When possible, Canadian data is reported to improve generalizability of results.

**Pancreatic Adverse Events**

- Within years of the introduction of GLP-1 agonists on the market, post marketing reports emerged raising concern of pancreatitis and pancreatic cancer in users of these medications, prompting calls from regulatory agencies for further studies regarding this potential association.[112]
- Prior to 2015, observational studies and pharmacovigilance data yielded conflicting results on risk of pancreatic adverse events.[56]
    - These older studies may have been limited by small sample size and confounding by indication: people with diabetes who have an indication for a GLP-1 agonist may also have concomitant risk for pancreatitis, such as obesity, longer diabetes duration, and co-medication.[56]
- Based on these concerns of potential increased risk of pancreatic adverse events, pancreatitis and pancreatic neoplasms were defined as events of special interest in the CVOTs of GLP-1 agonists.[58]
- The Health Canada product monographs for GLP-1 agonists contain similar warnings for pancreatitis. The monograph for semaglutide states: "Patients should be informed of the characteristic symptoms of acute pancreatitis. After initiation of [semaglutide], observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, [semaglutide] should be discontinued; if confirmed, [semaglutide] should not be restarted. Consider anti-diabetic therapies other than [semaglutide] in patients with a history of pancreatitis."[57]

**Pancreatitis**

- A large observational study from 2016 by Azoulay et al looked at the potential association between incretin-based drugs (DPP-4 inhibitors and GLP-1 agonists) and risk of acute pancreatitis.[60]
    - Multicenter, population-based cohort study conducted in Canada, the US and the UK

- 5,165 cases of hospitalization for pancreatitis and 96,654 controls
- Mean follow up 2.3 years
- Results
    - Incretin-based drugs were not associated with increased risk of pancreatitis compared with the use of 2 or more oral anti-hyperglycemic agents
        - Pooled adjusted HR 1.03 (95% CI 0.87 to 1.22)
    - In a secondary analysis, the risk did not vary by class
        - DPP-4 inhibitors pooled adjusted HR 1.09 (95% CI 0.86 to 1.22)
        - GLP-1 agonists pooled adjusted HR 1.04 (95% CI 0.81 to 1.35)

➢ Two recently published MAs of GLP-1 agonist CVOTs also reported no increased risk of pancreatitis with this class of medication.[58-59] While the original RCTs were not designed or powered to evaluate pancreatitis, this was an adverse outcome of interest that was independently adjudicated in LEADER, SUSTAIN-6, REWIND and PIONEER-6 in an attempt to minimize misclassification of diagnosis.

➢ The similar findings in a large observational study[60] and two recent MA of RCTs[58-59] strengthen the conclusion that GLP-1 agonists are not associated with increased risk of pancreatitis. While the observational study provides real-world evidence, there is the possibility for misclassification of events in this type of study. As pancreatic adverse events were independently adjudicated in 4 of 5 GLP-1 agonist CVOTs, the potential for misclassification is less.[18-21]

**Pancreatic Cancer**

➢ A large observational study from 2016 looked at incretin-based drugs compared to SU and risk of pancreatic cancer.[56]
- Multicenter, population-based cohort study conducted in Canada, US and the UK
- 1,221 cases of pancreatic cancer and 22,298 controls
- Median follow-up 1.3 to 2.8 years
- Results
    - Incretin-based drugs were not associated with an increased risk of pancreatic cancer compared with SU
        - Pooled adjusted HR 1.02 (95% CI 0.84 to 1.23)
    - In a secondary analysis, the risk did not vary by class
        - GLP-1 agonist pooled adjusted HR 1.13 (95% CI 0.38 to 3.38)
        - DPP-4 inhibitor pooled adjusted HR 1.02 (95% CI 0.84 to 1.24)

➢ A MA reported on pancreatic adverse events from data in CVOTs of GLP-1 agonists and found similar results.[59]
- 56 000 patients (7 RCTs)

- Median follow up 1.3-5.4 years.
    - No statistically significant difference between the rates of pancreatic cancer in the GLP-1 agonist group compared to standard care
        - OR 1.12 (95% CI 0.77-1.63)
        - The authors of this study point out that individuals in RCTs may not be representative of the general population as participants with history of alcohol use disorder (and therefore at higher risk for pancreatic adverse events) may have been excluded from RCTs, thus creating a selection bias.

➢ As the latency period for the development of pancreatic cancer is long,[59] the length of follow up in the CVOTs (1.3-5.4 years) and the above discussed observational study (1.3-2.8 years) may not have been enough for patients to develop pancreatic cancer.

➢ Additional observational studies are required to continue to evaluate a potential association with pancreatic cancer and GLP-1 agonists.

**Thyroid Cancer**

➢ Establishing a potential increase in risk of MTC and duration of GLP-1 agonist use is challenging due to the low rate of MTC (estimated incidence of 0.2 cases per 100,000 patient-years).[71]

➢ All GLP-1 agonists are contraindicated in people with a personal or family history of MTC or MEN 2. For example, the product monograph for semaglutide states: "Semaglutide causes treatment-dependent thyroid C-cell tumours at clinically relevant exposures in both sexes of rats and mice. It is unknown whether semaglutide causes thyroid C-cell tumors, including MTC, in humans, as human relevance could not be ruled out by clinical or nonclinical studies. [Semaglutide] is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)."[57]

➢ Pharmacovigilance
    - The examination of this rare, but serious event is the subject of ongoing evaluation.
        - Collection and analysis of pharmacovigilance data has been mandated by US Regulatory authorities, who are currently monitoring the annual incidence of MTC and will continue to do so for at least 15 years.
        - The Medullary Thyroid Carcinoma Surveillance Study: A Case Series Registry began in 2012, with estimated completion date in 2035. (https://clinicaltrials.gov/ct2/show/NCT01511393)

**Gallbladder**

- The product monograph for 3 of 4 GLP-1 agonists marketed in Canada (exception: lixisenatide) cite a possible increase in gallbladder related events.[57, 62-63]

- A 2020 MA of 43 RCTs by Nreu et al. comparing GLP-1 agonists with either placebo or active comparator reported an increased risk of cholelithiasis with GLP-1 agonist exposure (N = 74,846).[65] Studies included had a minimum follow-up duration of 52 weeks.
  - Results
    - GLP-1 agonist 1.17% vs placebo or active comparator 0.97%
    - OR 1.28 (95% CI 1.11 to 1.48)
  - Limitations
    - Some trials enrolled people without T2DM using GLP-1 agonists for other indications, e.g., weight management. Generally higher doses of GLP-1 agonists are used in trials of weight management and this may confound results.
    - The majority of participants were from the CVOTs and these trials were not designed to evaluate cholelithiasis.
    - The determination of gallbladder events was not independently adjudicated, which could have led to misclassification.
    - Pre-screening for gallbladder disease was not generally required prior to enrollment in a trial, so participants may have been identified during the trial if they presented with GI side effects, and required diagnostic tests which may have identified pre-existing, but previously unknown cases of cholelithiasis.[113]
    - A composite of clinically important and surrogate outcomes was evaluated (e.g., cholecystitis and asymptomatic cholelithiasis).

- Data from observational studies are limited. A 2016 population cohort study based in the UK by Faillie et al looked at incretin-based drugs and risk of gallbladder diseases in adults with T2DM.[66] This study examined current use of DPP-4 inhibitors and GLP-1 agonists (alone or in combination) compared with current use of at least 2 oral anti-hyperglycemic agents in people initiating therapy between 2007 and 2014.
  - Sample size by exposure group
    - GLP-1 agonists, n = 693
    - DPP-4 inhibitors, n = 3,270
    - Other anti-hyperglycemic drugs, n = 67,406
  - Mean follow up 3.2 years
  - Results

- Primary outcome
  - GLP-1 agonists were associated with increased risk of bile duct and gallbladder disease compared with current use of at least 2 oral anti-hyperglycemic drugs
    - 6.1 (95% CI 4.1 to 8.7) vs 3.3 (95% CI 2.8 to 3.9) events per 1000 person-years
    - Adjusted HR 1.79 (95% CI 1.21 to 2.67)
  - DPP-4 inhibitor use was not associated with increased risk of gallbladder disease compared with current use of at least 2 oral anti-hyperglycemic drugs
    - 3.6 (95% CI 2.8-4.6) vs 3.3 (95% CI 2.8-3.9) per 1000 person years
    - Adjusted HR 0.99 (95% CI 0.75 to 1.32)
- Secondary outcome
  - GLP-1 agonists were also associated with increased risk of cholecystectomy
    - Event rates not reported
    - Adjusted HR 2.08 (95% CI 1.08 to 4.02)

➢ There are speculations regarding the cause of this association with gallbladder disease, such as drug induced weight loss or a direct effect of GLP-1 agonist on gallbladder motility; however, the exact mechanism is unknown.[65]

**Diabetic Retinopathy (DRP)**

➢ Diabetic retinopathy was evaluated as a secondary outcome in 3 of the GLP-1 agonist CVOTs (LEADER, REWIND, and SUSTAIN-6).[18-20] In PIONEER-6, DRP was reported as an AE.[21]

**Table L: Diabetic Retinopathy – Results from LEADER, SUSTAIN-6 and REWIND Trials**

| Study (Intervention) | Outcome | Event rate % | | HR (95% CI) | ARI | Comments |
|---|---|---|---|---|---|---|
| | | GLP-1 | Placebo | | | |
| SUSTAIN-6[19] (Semaglutide) | Retinopathy[a] | 3.0 | 1.8 | 1.76 (1.11-2.78) | 1.2% | Driven by ↑ retinal photocoagulation. See page 53 for more info. |
| LEADER[18] (Liraglutide) | Retinopathy[a] | 2.3 | 2.0 | 1.15 (0.87-1.52) | 0.3% | |
| REWIND[20] (Dulaglutide) | Composite eye outcome[b] | 1.9 | 1.5 | 1.24 (0.92-1.68) | 0.4% | Analysis performed *post hoc* |

HR, hazard ratio; ARI, absolute risk increase; CI, confidence interval;
[a] Vitreous hemorrhage, onset of diabetes-related blindness, and need for treatment with an intravitreal agent or retinal photocoagulation
[b] Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy
Participants were treated with standard care for diabetes, including other glucose-lowering drugs, in both the intervention and control groups.

- A statistically significant increase in DRP complications (defined as requirement for retinal photocoagulation, use of an intravitreal agent, vitreous hemorrhage, or onset of diabetes related blindness) was reported with SC semaglutide vs standard care in SUSTAIN-6 [3.0% vs 1.8%, HR 1.76 (1.11 to 2.78), N = 3,297].[19]

- In the PIONEER-6 trial (N = 3,183), the reported rate of DRP (as defined by the *Medical Dictionary for Regulatory Activities*, version 20.1) for oral semaglutide vs standard care was 7.1% vs 6.3%.[21]
    - Participants with proliferative retinopathy or maculopathy requiring treatment were excluded at baseline.

- It is difficult to draw any comparisons or conclusions regarding the event rates of DRP for the individual GLP-1 agonists as:
    - These studies were not designed or powered to evaluate DRP, and event rates were low.
    - The 95% CI are wide, reflecting uncertainty in the results
    - The baseline rates of retinopathy were inconsistently reported.
    - Severity of baseline retinopathy was not graded.

- It remains unclear whether any association between GLP-1 agonists and DRP is due to an independent drug effect, or due to glycemic lowering.[114]

- In a *post-hoc* analysis of the SUSTAIN-6 clinical program, Vilsbol et al. observed that in those who experienced a DRP complication there was a trend towards a larger and faster A1C reduction in the first 16 weeks of treatment, regardless of randomization to sc semaglutide or standard care.[115]

- Previous studies of people with T2DM[116] and people undergoing bariatric surgery[117] have suggested that early and rapid glucose lowering may result in an initial increase in DRP yet prevent or delay the development of this complication over longer periods of time.[71]

- A 2018 observational cohort study from the UK by Douros et al. examined risk of newly diagnosed DRP with exposure to GLP-1 agonist compared with new users of two or more oral antihyperglycemic medications.[67]
    - Participants with previous DRP and insulin use before first ever non-insulin anti-hyperglycemic drug were excluded.
    - 77,115 new users of antihyperglycemic medications
    - 3047 participants received GLP-1 agonist (97% in combination therapy)
    - Median 2.8 years follow up
    - Results

- Primary outcome
  - Use of GLP-1 agonist compared with new use of two or more oral antihyperglycemic drugs was not associated with an increased risk of newly diagnosed DRP
    - 40.4 (95% CI 34.6-46.9) vs 49.0 (95% CI 47.1-51.0) events per 1000 person-years
    - Adjusted HR 1.0 (0.85-1.17)
- Secondary outcome
  - In a prespecified secondary outcome, heterogeneity was observed across duration of GLP-1 agonist use, classified as <6 months, 6.1-12 months, and > 12 months.
    - DRP incidence rates were higher for 6.1-12 months of GLP-1 agonist use compared with the control group over the same time frame
      - 56.6 (95% CI 41.6-75.2) vs 45.9 per 1000 person years (95% CI 41.5-50.7)
      - Adjusted HR 1.44 (95% CI 1.06-1.95).
      - This association was not observed for shorter (<6 months) and longer duration (>12 months) of use.
      - The authors of this study write that "the results of our duration-response analyses suggest a potential transient increased risk in this outcome," and "the fact that the association decreased with longer durations of use may relate to the depletion of susceptible phenomenon, where patients susceptible of developing retinopathy selected themselves out of the exposure group in the early phase of treatment."[67]

- The following strategies may potentially mitigate the development or worsening of DRP upon initiation of a GLP-1 agonist:[71]
  - Consider a slower dose titration of GLP-1 agonist
  - Decrease insulin to prevent rapid decreases in glucose concentrations, if GLP-1 agonist and insulin are co-prescribed

- As discussed previously on page 66, future studies are required to clarify the effect of GLP-1 agonists on DRP in people with T2DM. The **FOCUS** semaglutide RCT started in May 2019 and is scheduled to be complete in September 2027.[104] This RCT will evaluate SC semaglutide vs placebo in people with T2DM.

**Breast Cancer**

- RCTs with liraglutide have yielded conflicting results in reported breast cancer events compared with placebo. In a study of liraglutide for weight management, there were reported imbalances in the incidence of breast neoplasms in the treatment group compared with placebo (4.36 liraglutide vs 1.8 placebo per 1000 person years).[118] In contrast, this imbalance was not observed in the LEADER trial in breast cancer events observed in those randomized to liraglutide vs standard care (21 events in treatment arm vs 20 events in standard care group, N = 9340).[18] Neither of these trials were powered or designed to evaluate breast cancer as an outcome, and doses of GLP-1 agonist used in trials examining weight management were generally higher than in those examining T2DM.

- A 2016 population-based cohort study conducted in the UK by Hicks et al compared the rate of breast cancer with the use of GLP-1 agonists vs DPP-4 inhibitors.[68]
    - N = 44 984 women
    - Follow up mean 3.5 years
    - GLP-1 agonists were not associated with increased risk of breast cancer compared with DPP-4 inhibitors
        - 4.4 vs 3.4 per 1000 person-years
        - Adjusted HR 1.4 (95% CI 0.91 to 2.16)

- Although a potential association between GLP-1 agonists and breast cancer remains controversial, it has been speculated that weight loss with this class of agents may lead to improved detection of breast cancer.[69]

- A 2020 matched cohort study conducted in the UK followed female obese people with T2DM newly treated with antihyperglycemic agents, to examine this potential association.[69]
    - Included participants: Female, > 40 years, BMI > 30
    - Exclusions: Insulin use, prior history of breast cancer, prior history of polycystic ovarian syndrome
    - 5510 cases of breast cancer and 5510 controls
    - Median follow up 2.4 years
    - Participants in GLP-1 agonist exposed group were assigned to one of five categories: <5% decrease in baseline body weight, 5-10% decrease, >10% decrease, no change and weight gain.
    - Potential confounders such as age, alcohol-related disorders, smoking and prior malignancy history were considered.
    - Results
        - Primary outcome
            - GLP-1 agonists were not associated with an increased detection of breast cancer

        - HR 1.3 (95% CI 0.9-1.9)
    - Secondary outcome
        - An increased association with breast cancer detection was observed in participants experiencing >10% weight loss
        - HR 1.8 (95% CI 1.1-2.8)

- Although weight loss may be associated with decreased risk of breast cancer in the long term,[119] the results of the above study suggest that shorter term weight loss with GLP-1 agonists may be associated with increased detection of breast cancer. Replicating these findings in a larger, multisite study would improve generalizability.

**Acute Kidney Injury (AKI)**

- There are case reports of AKI in some people treated with GLP-1 agonists.[70] There are no trials examining renal outcomes with GLP-1 agonists as a primary outcome; however CVOTs with GLP-1 agonists have explored this in secondary analyses and suggest that there may be a beneficial effect, as discussed on page 65.

**GI Adverse Events**

- GI effects such as nausea, vomiting and diarrhea, are well known adverse effects from GLP-1 agonists.

- GI complaints are the main adverse-event related cause of drug discontinuation in phase 3 trials. For example:
    - SUSTAIN-6 (N=3297):[19] Rate of discontinuation due to GI events
        - Semaglutide 0.5 mg (and standard care) 5.6%
        - Semaglutide 1 mg (and standard care) 9.7%
        - Placebo 0.5 mg (and standard care) 1.2%
        - Placebo 1.0 mg (and standard care) 0.6%
    - LEADER (N=9340):[18] Rate of discontinuation due to GI events
        - Liraglutide 1.8 mg (and standard care) 2.8%
        - Placebo (and standard care) 0.5%
    - REWIND (N=9901):[20] Rate of discontinuation due to GI adverse events not reported. Rate of serious GI events (not defined):
        - Dulaglutide (and standard care) 1.5 mg 2.4 %
        - Placebo (and standard care) 2.4%

- It is not clear whether these effects are mediated by direct effect on the GI tract such as delayed gastric emptying, or by an interaction with the central nervous system.[71]

- Gradual dose titration is suggested for all GLP-1 agonists. Data on how to prevent or treat GI disturbances with GLP-1 agonists are limited.[71] Suggestions include:
  - Eat slowly with reduced portion size per meal
  - Stop eating when satiety is experienced
  - Avoid or minimize high fat foods

**Hypoglycemia**

- GLP-1 agonists alone do not appear to increase the risk of hypoglycemia.

- When GLP-1 agonists are used concomitantly with insulin or SU, the incidence of hypoglycemia is increased, and dose reduction of insulin or SU may be required.[57,61-64]
  - The 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults recommend that upon initiation of GLP-1 agonist, in addition to insulin or SU, in patients with:[110]
    - A1c > 8.0%, consider:
      - Continuing insulin or SU at current dose due to low risk of hypoglycemia
    - A1c ≤ 8.0%, consider:
      - Insulin dose reduction of 10-20%; counsel on hypoglycemia.
      - SU dose reduction by 50% or stop SU.
    - Hypoglycemia, consider:
      - Stopping SU and reducing insulin dose
    - These recommendations are based on expert opinion of guideline panel members.
  - Our **expert clinical reviewer** suggests:
    - If A1C 6.5-8.5%, decrease basal insulin by 10-20%.
    - If A1C < 6.5%, consider a greater decrease in basal insulin.
    - Consider decreasing prandial insulin by 50%.
    - Reassess and adjust therapy as needed.

- An RCT of GLP-1 agonists for weight management compared SC semaglutide 2.4 mg weekly, SC liraglutide 3.0 mg daily and placebo in people without diabetes.[120]
  - N=338
  - 68 weeks follow up
  - Reported rates of hypoglycemia
    - Semaglutide 0 participants
    - Liraglutide 1 participant
    - Placebo 1 participant

- As GLP-1 agonists would be add-on therapy to existing antihyperglycemic agents for the majority of people with T2DM, it is relevant to examine the rates of hypoglycemia in this population.

- The CVOTs examined the effect of GLP-1 agonists in addition to standard care. Participants in these trials were on a background of oral antihyperglycemic agents and insulin, as previously discussed (page 48). The reported rates of hypoglycemia in these trials are:
    - SUSTAIN-6 (SC semaglutide, N = 3297)[19]
        - Severe (defined according to American Diabetes Association criteria) or symptomatic hypoglycemia with BG < 3.1 mmol/L
            - 0.5 mg semaglutide 23.1%, 1.0 mg semaglutide 21.7%, 0.5 mg placebo 21.5%, 1.0 mg placebo 21%
    - LEADER (liraglutide, N = 9340)[18]
        - Confirmed hypoglycemia (BG<3.1 mmol/L)
            - liraglutide 43.7%, standard care 45.6%
        - Serious hypoglycemia (hypoglycemia for which the patient required assistance from a third party)
            - liraglutide 2.4%, standard care 3.3%
    - REWIND (dulaglutide, N = 9901)[20]
        - Severe hypoglycemia (not defined)
            - dulaglutide 1.3%, standard care 1.5%
    - PIONEER-6 (semaglutide PO, N = 3183)[21]
        - Serious hypoglycemia (as defined by the American Diabetes Association, per study protocol)
            - semaglutide PO 1.4%, standard care 0.8%
    - Although rates of hypoglycemia were similar between groups in the CVOTS, it is important to note that the study protocols specified that insulin and non-investigational drugs be reduced to minimize risk of hypoglycemia. This is a reasonable clinical approach but may confound interpretation of hypoglycemia rates.

- A 2019 Cochrane Review of RCTs by Madsen et al. investigated the effects of metformin plus SU compared with metformin plus other antihyperglycemic agents, including GLP-1 agonists, in people with T2DM.[45] Since most people will start and remain on metformin, these groups represent realistic options in clinical practice. Mild or moderate and serious hypoglycemia were assessed as *secondary* outcomes.
    - Results (see table M)
    - *Mild to moderate hypoglycemia* rates with SU (analyses include glyburide, glimepiride and gliclazide) were *significantly increased* compared with GLP-1 agonists; however, **rates of severe hypoglycemia were low.**

- There was **no difference in the rates of serious hypoglycemia** for Metformin + SU compared with Metformin + GLP-1 agonist.

**Table M: Metformin + SU compared to Metformin + GLP-1 agonist**[45]

| | Metformin + SU* | Metformin + GLP-1 | # trials | Risk Ratio (95% CI) | $I^2$** |
|---|---|---|---|---|---|
| | Event Rates | | | | |
| **Mild-moderate hypoglycemia** | 37.8% (n=1057) | 11% (n=1537) | 3 | 3.24 (2.05-5.13) | $I^2$ = 84.6% |
| **Serious hypoglycemia** | 0.1% (n=1057) | 0.1% (n=1537) | 3 | 1.0 (0.16-6.30) | $I^2$ = 0% |

*Analysis included 2nd and 3rd generation SU (e.g., glyburide, gliclazide, glimepiride)
**$I^2$ is a measure of percentage of variation (heterogeneity) across studies. An $I^2$ of 75%-100% represents considerable heterogeneity.

- Limitations:
  - Definitions of hypoglycemia varied across included studies, making interpretation of clinical outcomes difficult.
  - Hypoglycemia was evaluated as a secondary outcome in this MA. Hard outcomes of all-cause mortality, CV mortality, serious AEs, non-fatal stroke or MI were not different amongst any of the groups.
  - The evidence is low to very low quality with high rates of heterogeneity ($I^2$) between studies in the MA.

## Question 7: How do Diabetes Canada guideline recommendations align with the evidence?

- The Diabetes Canada (DC) guidelines for pharmacotherapy in T2DM were updated in 2020 and provide recommendations for the use of GLP-1 agonists and SGLT-2 inhibitors in adults with T2DM, according to the following comorbid conditions:[121]
    - Established atherosclerotic CVD
    - History of HF (EF < 40%)
    - History of CKD with eGFR > 30 mL/min/1.73 $m^2$
    - Age 60 years or older with at least 2 CV risk factors

- For the complete guidelines, please see here:
    - Diabetes Canada | Clinical Practice Guidelines - Full Guidelines (guidelines.diabetes.ca/cpg)

- For a summary of Academic Detailing comments on *select* DC recommendations pertaining to advancement of therapy with SGLT-2 inhibitors and GLP-1 agonists, see Table N. Table N is formatted to reflect the place in therapy for these agents based on the comorbid conditions described above, and the clinical trial evidence to support targeted outcomes cited in the guidelines.

- Relevant studies referenced in the DC guidelines are described in greater detail elsewhere in this document (see Questions 1, 2, 3 & 4).
    - Populations studied include more males than females, and the majority had established T2DM for ten years or longer.
    - Interventions were not evaluated as monotherapy. Participants in both arms took a variety of other glucose-lowering drugs at baseline and throughout the trials, including metformin, insulin, SU, and more, as well as a variety of other medications for CV risk management.
    - The definitions for CVD and CV risk factor varied between trials and are summarized in Appendix B.

- In general, the guidelines support selecting and adjusting glucose-lowering drugs based on individualized patient priorities, comorbidities and treatment goals. However, little guidance is provided to direct management of people with T2DM and *multiple* co-morbidities and treatment goals. The authors acknowledge that they are "unable to provide guidance in all circumstances and for all people with diabetes."[122]

- It is important to note that guideline authors focused on clinical practices that were thought to be potentially beneficial, but did **not include an assessment of possible harms**.[122] In

selecting appropriate therapy for a person with T2DM, evaluation of both efficacy and safety is pertinent.

- Each reference for guideline recommendations was critically appraised by the guideline authors and assigned a level of evidence based on pre-specified criteria, including assessment of the study objective(s), methodological rigor, susceptibility to bias and generalizability.

- Criteria for assigning levels of evidence in DC guidelines for studies of treatment and prevention:[122]

| Level | Criteria |
|---|---|
| 1A | Systematic overview or meta-analysis of high-quality RCTs<br>a) Comprehensive search for evidence<br>b) Authors avoided bias in selecting articles for inclusion<br>c) Authors assessed each article for validity<br>d) Reports clear conclusions that are supported by the data and appropriate analyses.<br>OR<br>Appropriately designed RCT with adequate power to answer the question posed by the investigators<br>a) Patients were randomly allocated to treatment groups<br>b) Follow up at least 80% complete<br>c) Patients and investigators were blinded to the treatment<br>d) Patients were analyzed in the treatment groups to which they were assigned<br>e) The sample size was large enough to detect the outcome of interest |
| 1B | Non-randomized clinical trial or cohort study with indisputable results |
| 2 | RCT or systematic overview that does not meet Level 1 criteria |
| 3 | Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies |
| 4 | Other |

- Criteria for assigning grade of recommendations for clinical practice in DC guidelines:[122]

| Grade | Criteria |
|---|---|
| A | The best evidence was at Level 1 |
| B | The best evidence was at Level 2 |
| C | The best evidence was at Level 3 |
| D | The best evidence was at Level 4 or consensus |

- The assigned grade was lowered in the following situations:
  - The evidence was deemed not applicable to the Canadian population

- Based on Steering and Executive Committee member consensus, there were additional concerns regarding the recommendation
- Subgroups were not well represented in the study or the beneficial effect of an intervention was less clear in certain subgroups
- Findings from relevant (and equally rigorous) studies on the topic were conflicting

- Guideline recommendations are based on best available evidence; however, strong evidence is not always available, and in these scenarios authors rely on expert opinion and extrapolation from the literature.
  - Table N highlights how the evidence supports select DC pharmacotherapy recommendations, and where a greater degree of extrapolation and reliance on expert opinion were required.
  - In some cases, a guideline recommendation is supported by a high quality study of a similar patient population [e.g. empagliflozin for reduction of MACE in people with established CVD (EMPA-REG)], but the magnitude of effect is small and results lack precision despite statistical significance [e.g. EMPA-REG: NNT for MACE 63 (95%CI 31-***8300***) at 3.1 years].[14] Nonetheless, the quality of evidence for the recommendation is reported to be Grade A, Level 1A.
  - In other cases, studies of a different patient population and results that are not statistically significant are cited to support a recommendation [e.g. dapagliflozin for reduction of progression of nephropathy in patients with CVD (DECLARE-TIMI 58)]. DECLARE-TIMI 58 was not designed to evaluate nephropathy, did not find a statistically significant difference in a secondary renal outcome between groups, and only 40% of the patient population had CVD at baseline. The quality of evidence was reported as Grade B, Level 2.
  - These examples are highlighted in yellow in Table N.

- Table N includes NNTs for statistically significant outcomes for quick reference; however a thorough interpretation of the results requires consideration of event rates and absolute and relative differences between groups. Please refer to Questions 1, 2, 3 & 4 or the original trial for a more detailed description of study results.

| Table N: Academic Detailing Comments on Select Diabetes Canada (DC) GLP-1 agonist & SGLT-2 inhibitor Recommendations for Adults with T2DM (2020) & Supporting Evidence | | | | |
|---|---|---|---|---|
| **DC Recommendations for Advancement or Adjustment of Treatment** | | | | **Academic Detailing Comments** |
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **History of CVD** | **DC Recommendation: *A GLP-1 agonist or SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | GLP-1 agonists | | |
| | | Grade A Level 1A | Liraglutide (LEADER[18]) | • 1° outcome, MACE – NNT 53 (95% CI 31-202)[†] at 3.8 years<br>○ Driven by ↓ CV death, not MI or stroke<br>• ~81% had established CVD *or CKD stage 3 or greater*<br>○ # participants with CVD but no CKD not reported |
| | | | Dulaglutide (REWIND[20]) | • 1° outcome, MACE – NNT 72 (95% CI 37-*1130*)[†] at 5.4 year<br>○ Driven by ↓ nonfatal stroke; other components NS<br>• ~31% of participants had CVD at baseline |
| | | Grade B Level 2 | Semaglutide SC (SUSTAIN-6[19]) | • 1° outcome, MACE – NNT 44 (95% CI 25-210)[†] at 2.1 years<br>○ Driven by ↓ nonfatal stroke; other components NS<br>• Testing for superiority performed post hoc<br>• 58.8% of participants had established CVD at baseline |
| | | SGLT-2 inhibitors | | |
| | | Grade A Level 1A | Empagliflozin (EMPA-REG[14]) | • 1° outcome, MACE – NNT 63 (95% CI 31-***8300***)[†] at 3.1 year<br>○ Driven by ↓ CV death, not MI or stroke; however, CV death alone NS<br>• >99% of population had CVD at baseline |
| | | Grade B Level 2 | Canagliflozin (CANVAS[15]) | • 1° outcome, MACE – NNT 83 (95% CI 47-***388***)[‡] at 3.6 years<br>○ Individual components of composite NS<br>• 65% had CVD & 35% were at high risk of CVD at baseline |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **History of CVD** | **DC Recommendation: *A GLP-1 agonist or SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ HHF<br><br>(See section below for guidelines specific to people who already have a HF diagnosis) | Grade B Level 2 | Empagliflozin (EMPA-REG[14]) | • HHF was a secondary outcome & results were NS based on investigators' pre-specified statistical analysis plan<br>• Study not designed to evaluate HF<br>• >99% of population had CVD at baseline |
| | | | Canagliflozin (CANVAS[15]) | • HHF was an exploratory outcome & results were NS based on investigators' pre-specified statistical analysis plan<br>• Study not designed to evaluate HF<br>• 65% had CVD & 35% were at high risk of CVD at baseline. |
| | | | Dapagliflozin (DECLARE-TIMI 58[16]) | • HHF was an exploratory outcome & results were NS based on investigators' pre-specified statistical analysis plan<br>• Study not designed to evaluate HF alone. A composite of CV death and HHF was evaluated as a co-primary outcome.<br>○ NNT 112 (95% CI 64-***441***)[†] at 4.2 years<br>▪ Driven by ↓ HHF; difference in CV death NS<br>• 40% had CVD at baseline; remainder had CV risk factors |
| | ↓ progression of nephropathy | Grade B Level 2 | Empagliflozin (Wanner et al[43]) | • Pre-specified secondary analysis of EMPA-REG; original trial not designed to evaluate renal outcomes.<br>• Exploratory finding: Incident or worsening nephropathy 12.7% empagliflozin vs 18.8% placebo, HR 0.61 (95% CI 0.53-0.70), ARR 6.1%<br>• >99% of population had CVD at baseline<br>• Mean baseline eGFR 74.2 ± 21.6 mL/min/1.73 $m^2$<br>• 29% microalbuminuric & 11% macroalbuminuric at baseline |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **History of CVD** | **DC Recommendation: *A GLP-1 agonist or SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ progression of nephropathy | Grade B Level 2 | Canagliflozin (CANVAS[15]) | • Study not designed to evaluate renal outcomes.<br>• Progression of albuminuria and renal composite (40% ↓ eGFR, RRT or renal death) NS based on the investigators' pre-specified statistical analysis plan.<br>• 65% had CVD & 35% were at high risk of CVD at baseline.<br>• eGFR ≥ 30 mL/min/1.73 $m^2$ 100%<br>• Mean baseline eGFR 76.5 ± 20.5 mL/min/1.73 $m^2$ |
| | | | Dapagliflozin (DECLARE-TIMI 58[16]) | • Study not designed to evaluate renal outcomes.<br>• Secondary composite renal outcome (≥ 40% decrease in eGFR to < 60 mL/min/1.73 $m^2$, ESRD, or death from renal cause) NS based on the investigators' pre-specified statistical analysis plan.<br>• 40% had CVD at baseline; remainder had CV risk factors<br>• Mean baseline eGFR 85 mL/min/1.73 $m^2$ (all ≥ 60 mL/min) |
| **History of HF (EF ≤ 40%) and eGFR > 30 mL/min/ 1.73 $m^2$** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ HHF or CV death | Grade A Level 1A | Dapagliflozin (DAPA-HF[75]) | DAPA-HF (N = 4,744)<br>• Multicenter, double-blind, randomized, placebo controlled trial<br>• Subjects with and without T2DM randomized to dapagliflozin 10 mg daily or placebo plus standard care & stratified by T2DM.<br>• Key inclusion criteria: EF ≤ 40%, NYHA HF class II-IV, eGFR > 30 mL/min/1.73 $m^2$, NT-proBNP ≥ 600 pg/mL (or ≥ 400 mg/mL if HHF within previous 12 months or ≥ 900 pg/mL in presence of afib or flutter)<br>• Key characteristics of baseline population<br>○ NYHA class II 67%<br>○ **T2DM 42%**, remainder did not have diabetes<br>○ Male 77% (continued next page) |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **History of HF (EF ≤ 40%) and eGFR > 30 mL/min/ 1.73 m²** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ HHF or CV death | Grade A Level 1A | Dapagliflozin (DAPA-HF[75]) | (continued from previous page)<br>• 1º composite outcome: CV death or worsening HF (unplanned HHF or urgent visit resulting in IV med for HF)<br>  ○ Dapagliflozin 16.3% vs placebo 21.2%<br>  ○ HR 0.74 (95% CI 0.65 -0.85), ARR 4.9%<br>  ○ **NNT 21 (95% CI 15-38)**† at median 18.2 months<br>  ○ Results were similar in subgroup analysis whether people had T2DM or not. |
| | | Grade A Level 1 | Empagliflozin Canagliflozin (Zelniker et al SR & MA[74]) | Zelniker et al (N = 34,322)<br>• MA of EMPA-REG, CANVAS & DECLARE-TIMI 58<br>• 50% of participants were on empagliflozin or canagliflozin<br>• Composite HHF/CV death: HR 0.77 (95% CI 0.71-0.84)<br>• At baseline,<br>  ○ 10% had HF & >99% had ACVD in EMPA-REG<br>  ○ 14% had HF & 65% had ACVD in CANVAS<br><br>Note: EMPEROR REDUCED[76], a HF trial that included people with and without T2DM, was published too recently to be considered in the guideline update. Please see Question 1 for more information about HF outcomes. |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **CKD with eGFR > 30 mL/min/1.73 $m^2$** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ progression of nephropathy | Grade A Level 1A | Canagliflozin (CREDENCE[27]) | 1º composite outcome: ESRD, doubling of SrCr, renal/CV death<br>• NNT 24 (95% CI 16-43)† at 2.6 years<br>• Result driven by ↓ ESRD & doubling of SrCr; difference in renal/CV death NS<br>Key characteristics of baseline population:<br>• CVD ~50%<br>• Albuminuric CKD 100%<br>  ○ Mean eGFR ~56 mL/min/1.73 $m^2$<br>  ○ eGFR ≥ 90 mL/min/1.73 $m^2$ 4.8%<br>  ○ eGFR < 30 mL/min/1.73 $m^2$ ~3.9%<br>  ○ Median uACR 105 mg/mmol |
| | | Grade A Level 1 | Empagliflozin Dapagliflozin (Zelniker et al SR & MA[74]) | Zelniker et al (N = 34,322)<br>• Meta-analysis of EMPA-REG, CANVAS & DECLARE-TIMI 58, but none of these trials were designed to evaluate nephropathy<br>• 70% of participants were on empagliflozin or dapagliflozin<br>• Composite worsening renal function, ESRD, or renal death: HR 0.55 (95% CI 0.48-0.64)<br>  ○ Subgroup analysis showed no significant difference whether participants had established CVD or not, but ~100% & 65% on empagliflozin & canagliflozin, respectively, had established CVD at baseline.<br>• Baseline eGFR criteria in EMPA-REG was ≥30 mL/min/1.73 $m^2$ & mean eGFR was ~74 mL/min/1.73 $m^2$<br>• Baseline CrCl criteria in DECLARE-TIMI 58 was ≥60 mL/min & mean eGFR was ~85 mL/min/1.73 $m^2$ |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **CKD with eGFR > 30 mL/min/1.73 m²** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ HHF | Grade A Level 1 | Canagliflozin Dapagliflozin Empagliflozin (Zelniker et al SR & MA[74]) | Zelniker et al (N = 34,322)<br>• MA of EMPA-REG, CANVAS & DECLARE-TIMI 58<br>  ○ HHF: HR 0.69 (95% CI 0.61-0.79)<br>• EMPA-REG and CANVAS were not designed to evaluate HF<br>• DECLARE-TIMI 58 evaluated a co-primary composite outcome of CV death and HHF<br>Key baseline characteristics of study population:<br>• Mean eGFR<br>  ○ EMPA-REG & CANVAS ~75 mL/min/1.73 m²<br>  ○ DECLARE-TIMI 58 ~85 mL/min/1.73 m²<br>• eGFR inclusion criteria<br>  ○ EMPA-REG & CANVAS ≥30 mL/min/1.73 m²<br>  ○ DECLARE-TIMI 58 **≥60 mL/min**<br>• Established CVD<br>  ○ EMPA-REG >99%<br>  ○ CANVAS 65% (35% were at high risk of CVD)<br>  ○ DECLARE-TIMI 58 40% (60% had CVD risk factors)<br>• HHF<br>  ○ EMPA-REG 10.1%, CANVAS 14.4%, DECLARE-TIMI 58 10% |
| **CKD with eGFR > 30 mL/min/1.73 m²** | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade B Level 2 | Canagliflozin (CREDENCE[27]) | 2° outcome, MACE: Canagliflozin 9.9% vs placebo 12.2%<br>• HR 0.80 (95% CI 0.68-0.95), ARR 2.3%<br>• NNT 42 (95% CI 24-*190*)[+] at 2.6 years<br>Key baseline characteristics of study population:<br>• Albuminuric CKD stage 2-3, 100%<br>• Established CVD at baseline 50% |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **CKD with eGFR > 30 mL/min/1.73 m²** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE USED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade C Level 3 | Empagliflozin (EMPA-REG[14]) | 1º outcome, MACE<br>• NNT 63 (95% CI 31-***8300***)† at 3.1 years<br>• Greatest benefit in the composite outcome was in CV death, however none of the individual components were statistically significant.<br>Key baseline characteristics of study population:<br>• CVD >99%<br>• Mean eGFR 74.2 ± 21.6 mL/min/1.73 m²<br>• eGFR ≥ 90 mL/min/1.73 m² ~20%<br>• eGFR < 30 mL/min/1.73 m² excluded from trial<br>• Microalbuminuria 29% & macroalbuminuria 11% |
| **CKD with eGFR > 30 mL/min/1.73 m²** | **DC Recommendation: *A GLP-1 agonist "MAY BE CONSIDERED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade B Level 2 | Liraglutide (LEADER[18]) | 1º outcome, MACE:<br>• NNT 53 (95% CI 31-*202*)† at 3.8 years<br>Key baseline characteristics of study population:<br>• **CVD or CKD stage 3 or greater** ~81%<br>  ○ % with CVD alone not reported<br>• eGFR ≥ 90 mL/min/1.73 m² ~35%<br>• eGFR < 30 mL/min/1.73 m² ~3%<br>• Microalbuminuria 26.3% & macroalbuminuria 10.5% |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **CKD with eGFR > 30 mL/min/1.73 $m^2$** | **DC Recommendation: *A GLP-1 agonist "MAY BE CONSIDERED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade B Level 2 | Semaglutide (SUSTAIN-6[19]) | 1° outcome, MACE:<br>• NNT 44 (95% CI 25-*210*)† at 2.1 years<br>• Superiority of outcome tested post-hoc<br>Key baseline characteristics of study population:<br>• CVD 58.8%<br>• CVD or CKD stage 3 or higher 83%<br>• eGFR ≥ 90 mL/min/1.73 $m^2$ 30%<br>• eGFR < 30 mL/min/1.73 $m^2$ 3.3% |
| **Age > 60 years ≥ 2 CV risk factors**** | **DC Recommendation: *A GLP-1 agonist "SHOULD BE CONSIDERED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade A Level 1A | Dulaglutide (REWIND[20]) | 1° outcome, MACE:<br>• NNT 72 (95% CI 37-***1130***)† at 5.4 years<br>• Result driven by ↓ nonfatal stroke; difference in CV death and nonfatal MI NS<br>Key baseline characteristics of study population:<br>• Mean (SD) age 66 (6.5) years<br>• Established vascular disease 31.5%<br>• An unknown proportion of participants qualified for the study based on **age ≥ 55 years** and myocardial ischemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, eGFR < 60 mL/min/1.73 $m^2$, or albuminuria. Alternatively, individuals may have qualified based on age ≥ 50 years with established vascular disease, or age ≥ 60 years and at least 2 CV risk factors. |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **Age > 60 years ≥ 2 CV risk factors**** | **DC Recommendation: *A GLP-1 agonist "SHOULD BE CONSIDERED"*** | | | |
| | ↓ MACE<br><br>(composite of nonfatal MI, stroke, or CV death) | Grade B Level 2 | Liraglutide (LEADER[18]) | 1° outcome, MACE:<br>• NNT 53 (95% CI 31-*202*)† at 3.8 years<br>• Result driven by ↓ CV death; difference in nonfatal MI and stroke NS<br>Inclusion criteria: T2DM, A1C ≥ 7%, and one of<br>• **Age ≥ 50 years** with established CVD or CKD ≥ stage 3 or greater<br>• Age ≥ 60 years with at least **1 CV risk factor**<br>Key baseline characteristics of study population:<br>• Established CVD or CKD stage 3 or greater ~81% |
| | | Grade C Level 2 | Semaglutide (SC) (SUSTAIN-6[19]) | 1° outcome, MACE:<br>• NNT 44 (95% CI 25-*210*)† at 2.1 years<br>• Result driven by ↓ nonfatal stroke; difference in CV death and nonfatal MI NS<br>• Superiority of outcome tested post-hoc<br>Inclusion criteria: T2DM, A1C ≥ 7%, and one of following<br>• **Age ≥ 50 years** and established CVD or CKD stage 3 or greater<br>• Age ≥ 60 years and **at least 1 CV risk factor**<br>Key baseline characteristics of study population:<br>• CVD 58.8%<br>• CVD or CKD stage 3 or higher 83% |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **Age > 60 years ≥ 2 CV risk factors** eGFR > 30 mL/min/1.73 m$^2$** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE CONSIDERED"*** | | | |
| | ↓ HHF | Grade B Level 2 | Canagliflozin (CANVAS[15]) | 2$^o$ exploratory outcome, HHF:<br>• **NS** based on investigators' pre-specified statistical analysis plan.<br>Key baseline characteristics of study population:<br>• **Established CVD 65%**<br>• High risk of CVD 35% (defined as **age ≥ 50 years** and at least 2 CV risk factors)<br>Study not designed to evaluate HF. |
| | | | Dapagliflozin (DECLARE-TIMI 58[16]) | • HHF was a secondary outcome & results were **NS** based on investigators' pre-specified statistical analysis plan.<br>• Study not designed to evaluate HF.<br>Key baseline characteristics of study population:<br>• Established CVD ~40%<br>• **High risk of CVD 60%** (defined as age **≥ 55 years for males** or 60 years for females & at least **1 CV risk factor**. |
| **Age > 60 years ≥ 2 CV risk factors** eGFR > 30 mL/min/1.73 m$^2$** | ↓ progression of nephropathy | Grade C Level 3 | Canagliflozin (CANVAS[15]) | Results for the following secondary renal outcomes NS based on investigators' pre-specified statistical analysis plan:<br>• Composite ↓ 40% eGFR, RRT, or renal death<br>• Progression of albuminuria<br>Study not designed to evaluate renal outcomes.<br>Key baseline characteristics of study population:<br>• **Established CVD 65%**<br>• High risk of CVD 35% (defined as **age ≥ 50 years** and at least 2 CV risk factors)<br>• eGFR ≥ 30 mL/min/1.73 m$^2$ required for inclusion |

| DC Recommendations for Advancement or Adjustment of Treatment | | | | Academic Detailing Comments |
|---|---|---|---|---|
| **Comorbid Condition(s)** | **Targeted Outcome*** | **QOE per DC** | **Drug (DC Reference)** | **Internal & external validity of supporting references and magnitude of effect** |
| **Age > 60 years ≥ 2 CV risk factors** eGFR > 30 mL/min/1.73 m²** | **DC Recommendation: *An SGLT-2 inhibitor "SHOULD BE CONSIDERED"*** | | | |
| | ↓ progression of nephropathy | Grade C Level 3 | Dapagliflozin (DECLARE-TIMI 58[16]) | Results for the following secondary exploratory outcomes NS based on investigators' pre-specified statistical analysis plan:<br>• Composite sustained ↓ in eGFR ≥40% to < 60 ml/min/1.73 m², new ESRD or death from renal or CV causes<br>• Composite sustained ↓ in eGFR ≥40% to < 60 ml/min/1.73 m², new ESRD or death from renal causes<br>Study not designed to evaluate renal outcomes.<br>Key baseline characteristics of study population:<br>• Established CVD ~40%<br>• **High risk of CVD 60%** (defined as age **≥ 55 years for males** or 60 years for females & at least **1 CV risk factor**.<br>• **eGFR ≥ 60 mL/min** required for inclusion |

* Based on studies comparing SGLT-2 inhibitors or GLP-1 agonists to placebo and both groups receiving standard care for BG management.
** CV risk factors: Smoking (tobacco use), hypertension (untreated BP ≥ 140/95 or current antihypertensive therapy), dyslipidemia (untreated LDL > 3.4 mmol/L or HDL < 1 mmol/L for men or < 1.3 mmol/L for women, or triglyceride > 2.3 mmol/L or current lipid-lowering therapy), central obesity.
† NNT calculated from absolute event rates in the RCT using the Dalhousie Clinical Significance Calculator. Provided as an estimate only.
‡ NNT calculated from the Kaplan-Meier curve[15] using the Dalhousie Academic Detailing Clinical Significance Calculator.[24] Provided as an estimate only.
See page 93 for explanation of yellow shading.
A1C = Glycated hemoglobin, ACVD = Atherosclerotic cardiovascular disease, Afib = Atrial fibrillation, ARR = Absolute risk reduction, CKD = Chronic kidney disease, CV = Cardiovascular, CVD = Cardiovascular disease, DC = Diabetes Canada, EF = Ejection fraction, eGFR = Estimated glomerular filtration rate, ESRD = End stage renal disease, HF = Heart failure, HHF = Hospitalization for heart failure, HfpEF = Heart failure with preserved ejection fraction, HR = Hazard ratio, IV = Intravenous, MA = Meta-analysis, MACE = Major adverse cardiovascular event (nonfatal MI, stroke, or CV death), MI = Myocardial infarction, NNT = Number needed to treat, NS = Not statistically significant, NT-pro BNP = N-terminal pro b-type natriuretic peptide, NYHA HF = New York Heart Association heart failure functional class, QOE = Quality of evidence, RRT = Renal replacement therapy, SD = standard deviation, SR = systematic review, SrCr = Serum creatinine, T2DM = Type 2 diabetes mellitus, uACR = Urinary albumin to creatinine ratio

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## Appendix A: Select Health Canada Approved Indications for SGLT-2 Inhibitors & GLP-1 Agonists in T2DM

| Drug | Monotherapy[1] | Combination with MET | Combination with PIO +/- MET | Combination with SU | Combination with insulin | Combination with MET + SU | Combination with MET + Sitagliptin | Additional Indications for Specific Comorbidities | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD | Nephro-pathy |
| **GLP-1 AGONISTS** | | | | | | | | | |
| Dulaglutide (Trulicity) | ✓ | ✓ +/- SGLT2 | X | X | ✓ (basal/prandial) + MET | ✓ | X | ✓ (non-fatal stroke) [2] | X |
| Liraglutide (Victoza) | ✓ | ✓ +/- SGLT2 | X | X | ✓ (basal) + MET | ✓ | X | ✓[3] | X |
| Lixisenatide (Adlyxine) | X | ✓ | ✓ | ✓ | ✓ (basal) +/- MET | ✓ | X | X | X |
| Semaglutide SC (Ozempic) | ✓ | ✓ +/- SGLT2 | X | X SEMA + SU<br>✓ SEMA + SU + SGLT2 | ✓ (basal) + MET | ✓ | X | X | X |
| Semaglutide PO (Rybelsus) | ✓ | Approved for use in combination with other glucose-lowering drugs based on clinical trials, but specific products not listed in product monograph indications | | | | | | X | X |
| **SGLT-2 INHIBITORS** | | | | | | | | | |
| Canagliflozin (Invokana) | ✓ | ✓ | ✓ | ✓ | ✓ +/- MET | ✓ | ✓ | ✓[4] | ✓[5] |
| Dapagliflozin (Forxiga) | ✓ | ✓ | X | ✓ | ✓ +/- MET | ✓ | ✓ +/- MET | ✓ + HF[6] | ✓[7] |
| Empaglifozin (Jardiance) | ✓ | ✓ +/- LIN | ✓ | X | ✓ (basal/prandial) +/- MET | ✓ | X | ✓ + HF[8] | X |

1. Most indications listed are adjuncts to proper dietary management, exercise, and weight reduction.
2. Dulaglutide is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of nonfatal stroke in adults with T2DM who have multiple CV risk factors or established CVD.
3. Liraglutide is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the incidence of CV death in patients with T2DM and established CVD.
4. Canagliflozin is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of MACE (CV death, nonfatal MI and nonfatal stroke) in adults with T2DM and established CVD.
5. Canagliflozin is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of ESRD, doubling of SrCr, and CV death in adult patients with T2DM and diabetic nephropathy with albuminuria (>33.9 mg/mmol).
6. Dapagliflozin is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of HHF in adults with T2DM and CV risk factors or established CVD and as an adjunct to standard of care therapy, for the treatment of HF with reduced ejection fraction to reduce the risk of CV death, HHF and urgent HF visit.
7. Dapagliflozin is indicated to reduce the risk of sustained eGFR decline, ESRD, and CV and renal death in adults with CKD.
8. Empagliflozin is indicated as an adjunct to diet, exercise and standard care therapy to reduce the incidence of CV death in patients with T2DM and established CVD and in adults as an adjunct to standard of care therapy for the treatment of chronic HF.

CVD: cardiovascular disease, HF: heart failure, LIN: linagliptin, MET: metformin, PIO: pioglitazone, SEMA: semaglutide, SC: subcutaneous, SGLT2: sodium glucose co-transporter 2 inhibitor, SU: sulfonylurea

**Appendix B: Definitions Used to Describe CVOT Populations**

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **EMPA-REG Outcome** | **High risk of (*recurrent*) CV events**, defined as the presence of ≥ 1 of the following:<br>• History of MI >2 months prior to informed consent<br>• Evidence of multi-vessel coronary artery disease i.e. in ≥ 2 major coronary arteries or the left main coronary artery, documented by any of the following:<br>– Presence of significant stenosis: ≥ 50% luminal narrowing during angiography (coronary or multi-slice computed tomography)<br>– Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft > 2 months prior to consent)<br>– The combination of revascularization in one major coronary artery and significant stenosis (≥ 50% luminal narrowing) in another major coronary artery<br>• Evidence of single-vessel coronary artery disease, ≥ 50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:<br>– A positive non-invasive stress test for ischemia<br>– Hospital discharge for unstable angina ≤12 months prior to consent<br>• Unstable angina >2 months prior to consent with evidence of single- or multi-vessel coronary artery disease<br>• History of stroke (ischemic or hemorrhagic) >2 months prior to consent<br>• Occlusive peripheral artery disease documented by any of the following:<br>– Limb angioplasty, stenting, or bypass surgery<br>– Limb or foot amputation due to circulatory insufficiency<br>– Evidence of significant peripheral artery stenosis (> 50% on angiography, or > 50% or hemodynamically significant via non-invasive methods) in 1 limb<br>– Ankle brachial index < 0.9 in ≥ 1 ankle |
| **CANVAS Program** | **History of CVD**:<br>• Age ≥ 30 years with documented symptomatic atherosclerotic CVD (e.g. stroke, MI, HUA, coronary artery bypass graft, percutaneous coronary intervention with or without stenting, peripheral revascularization (angioplasty or surgery), symptomatic with documented hemodynamically significant carotid or PVD, or amputation secondary to vascular disease.<br>**OR**<br>**High Risk of CVD**:<br>• Age ≥ 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure > 140 mmHg (average of 3 readings) recorded at the screening visit, while the subject is on at least one blood pressure–lowering treatment, current daily cigarette smoker, documented microalbuminuria or macroalbuminuria, or documented high-density lipoprotein cholesterol of < 1 mmol/l (< 39 mg/dl). |

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **DECLARE-TIMI 58** | **Established CVD**, defined as any of the following:<br>• Ischemic heart disease (any of the following):<br>– Documented MI<br>– Percutaneous Coronary Intervention<br>– Coronary Artery Bypass Grafting<br>– Objective Findings of Coronary Stenosis (≥ 50%) in at least 2 coronary artery territories (ie, left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving the main vessel, a major branch, or a bypass graft<br>• Cerebrovascular disease (any of the following):<br>– Documented ischemic stroke (known TIA, primary intracerebral haemorrhage or sub-arachnoid hemorrhage do not qualify.)<br>– Carotid stenting or endarterectomy<br>• Peripheral Arterial Disease (any of the following):<br>– Peripheral arterial intervention, stenting or surgical revascularization<br>– Lower extremity amputation as a result of peripheral arterial obstructive disease<br>– Current symptoms of intermittent claudication AND ankle/brachial index (ABI) < 0.90 documented within last 12 months<br>**OR**<br>**No known CVD AND at least two CV risk factors in addition to T2DM**, defined as:<br>○ Age ≥ 55 years in men and ≥ 60 in women **AND**<br>○ Presence of at least 1 of the following additional risk factors<br>– Dyslipidemia (at least one of the following)<br>▪ Low-density lipoprotein cholesterol (LDL-C) > 130 mg/dl (3.36 mmol/L) within last 12 months<br>▪ On lipid lowering therapy prescribed by a physician for hypercholesterolemia (ie LDL-C > 130 mg/dl (3.36 mmol/L)) for greater than 12 months. This should be verified by documentation of lab value LDL-C > 130 mg/dl (3.36 mmol/L).<br>– Hypertension (at least one of the following)<br>▪ BP > 140/90 mm Hg at enrollment visit. The patient must have both an elevated systolic BP (> 140 mmHg) and an elevated diastolic BP (> 90 mmHg) on both measurements<br>▪ On anti-hypertensive therapy prescribed by a physician for blood pressure lowering<br>– Current Tobacco use (≥ 5 cigarettes/day for at least 1 year at randomization) |

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **ELIXA** | **Recent hospitalization for ACS**<br>• Men and women who experienced a spontaneous ACS event (i.e., ST-segment elevation myocardial infarction or non ST-segment elevation myocardial infarction or unstable angina) with the following requirements:<br>○ There must have been a documented elevation above the normal reference range of a cardiac biomarker (Troponin or CK-MB),<br>**AND**<br>○ The presentation of the event must be consistent with an ACS which leads to admission to an acute care facility (eg, ER, CCU, Cath Lab, hospital). If the qualifying ACS event follows a revascularization procedure, it must have occurred more than 15 days after a percutaneous coronary intervention and more than 45 days after a coronary artery bypass graft,<br>**AND**<br>○ Patients should be approached about the study as soon as possible following their admission for the qualifying ACS event, including signing of the informed consent form, where permitted by local regulations. However, the screening visit must occur only after the patient is discharged from the acute care facility and must take place within 180 days following the date of admission for the qualifying ACS event.<br><br>Note: In cases where emergent coronary angiography is performed during the ACS event, which demonstrates occlusion of at least one epicardial coronary artery, and which is accompanied by an attempt at reperfusion, the biomarker requirement may be waived. |
| **LEADER** | **Prior CVD (or CKD)**: age ≥ 50 and ≥ 1 of the following criteria:<br>• Prior MI<br>• Prior stroke or TIA<br>• Prior coronary, carotid or peripheral arterial revascularization<br>• > 50% stenosis of coronary, carotid, or lower extremity arteries<br>• History of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes<br>• Asymptomatic cardiac ischemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo<br>• Chronic heart failure NYHA class II-III<br>• Chronic renal failure:<br>• eGFR < 60 ml/min/1.73 $m^2$ (MDRD formula)<br>• eGFR < 60 ml/min/1.73 $m^2$ (Cockcroft-Gault formula)<br>**OR**<br>(continued on next page) |

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **LEADER** (continued from previous page) | **At Risk of CVD**: Age ≥ 60 years and ≥ 1 of the following criteria:<br>• Microalbuminuria or proteinuria<br>• Hypertension and left ventricular hypertrophy by ECG or imaging<br>• Left ventricular systolic or diastolic dysfunction by imaging<br>Ankle-brachial index < 0.9 |
| **SUSTAIN-6** | **Established CVD**<br>Aged 50 years or older with documented clinical evidence of CVD, defined as meeting at least one of the below criteria*:<br>○ prior MI<br>○ prior stroke or prior TIA<br>○ prior coronary, carotid or peripheral arterial revascularization<br>○ more than 50% stenosis on angiography or imaging of coronary, carotid or lower extremities arteries<br>○ history of symptomatic coronary heart disease documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina with ECG changes<br>○ asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging<br>○ chronic HF NYHA class II-III<br>○ chronic renal impairment, documented (prior to screening) by eGFR below 60 ml/min/1.73 $m^2$ per MDRD<br>**OR**<br>**CV Risk Factor**<br>Aged 60 years or older with subclinical evidence of CVD, defined as meeting at least one of the below criteria*:<br>○ persistent microalbuminuria (30–299 mg/g) or proteinuria<br>○ hypertension and left ventricular hypertrophy by electrocardiogram or imaging<br>○ left ventricular systolic or diastolic dysfunction by imaging<br>○ ankle/brachial index less than 0.9<br><br>*As determined by the investigator. |
| **REWIND** | **Age ≥ 50 years & established clinical vascular disease** defined as ≥ 1 of the following:<br>○ a history of MI<br>○ a history of ischemic stroke<br>○ a history of coronary, carotid, or peripheral artery revascularization. If prior coronary artery bypass grafting (CABG), the CABG should have been performed > 2 years prior to randomization.<br>○ hospitalization for unstable angina with ECG changes (new or worsening ST or T wave changes), or myocardial ischemia on imaging, or need for percutaneous coronary intervention (PCI);<br>(continued on next page) |

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **REWIND** (continued from previous page) | **OR**<br>**Age ≥ 55 years and subclinical vascular disease** defined as 1 or more of the following:<br>○ a history of myocardial ischemia by a stress test or with cardiac imaging, with or without history of exertional angina<br>○ > 50% vascular stenosis with imaging of the coronary, carotid, or lower extremity arteries, with or without claudication history<br>○ ankle-brachial index < 0.9<br>○ eGFR < 60 ml/min/1.73 $m^2$<br>○ a history of hypertension with documented left ventricular hypertrophy on an ECG or echocardiogram<br>○ microalbuminuria or macroalbuminuria;<br>**OR**<br>**Age ≥ 60 years and at least 2 or more of the following risk factors for CV outcomes**:<br>○ current tobacco use (any form of tobacco)<br>○ documented low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L (130 mg/dL) within the past 6 months<br>○ documented high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L (40 mg/dL) for men and < 1.3 mmol/L (50 mg/dL) for women within the past 6 months<br>○ use of at least 1 blood pressure medication to treat hypertension or untreated systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 95 mmHg<br>○ measured waist-to-hip ratio > 1.0 for men and > 0.8 for women |
| **PIONEER-6** | **Established CVD**<br>Age ≥ 50 years at screening and at least one of the following conditions:<br>○ prior MI<br>○ prior stroke or TIA<br>○ prior coronary, carotid, or peripheral arterial revascularization<br>○ > 50% stenosis on angiography or imaging of coronary, carotid, or lower extremity arteries<br>○ history of symptomatic coronary heart disease documented by e.g., positive exercise stress test or any cardiac imaging or unstable angina pectoris with ECG changes<br>○ asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging<br>○ chronic HF New York Heart Association (NYHA) class 2–3<br>○ moderate renal impairment (eGFR 30 to 59 ml/min/1.73 $m^2$)<br>(continued on next page) |

| Clinical Trial | Definitions Used to Describe Study Populations |
|---|---|
| **PIONEER-6** (continued from previous page) | **OR**<br>**CV Risk Factor**<br>Age ≥ 60 years at screening and at least one of the following risk factors:<br>○ microalbuminuria or proteinuria<br>○ hypertension and left ventricular hypertrophy by electrocardiogram or imaging<br>○ left ventricular systolic or diastolic dysfunction by imaging<br>○ ankle–brachial index < 0.9 |

## Appendix C: Drug Tables – SGLT-2 Inhibitor and SGLT-2 Inhibitor Combination Products

| SGLT-2 Inhibitors | | | | | |
|---|---|---|---|---|---|
| **Name** Generic, *Trade* | **Strengths** | **Adult Dose** (Product Monographs)[34-36] | **Dose Adjustments** (Product Monographs)[34-36] | **Nova Scotia Pharmacare Status** | **McKesson Cost (Supply)** |
| **SGLT-2 Inhibitors (MOA: inhibit SGLT-2, reducing reabsorption of glucose from the renal tubular lumen)** | | | | | |
| **Canagliflozin** *Invokana* | 100 mg<br>300 mg | 100-300 mg PO daily<br><br>Take before first meal of day.<br>Swallow whole. | <u>Hepatic</u><br>• Severe impairment: Use not recommended (not studied)<br><br><u>Renal</u><br>• eGFR 30 to < 60 mL/min/1.73 $m^2$: 100 mg daily<br>• eGFR < 30 mL/min/1.73 $m^2$: Do not *initiate* therapy<br>• eGFR < 30 mL/min/1.73 $m^2$, albuminuria > 33.9 mg/mmol, and on *established* therapy: May continue at 100 mg daily<br>• CI if on dialysis | Exception status* | $94† (30 days) |
| **Dapagliflozin** *Forxiga* | 5 mg<br>10 mg | 5-10 mg PO daily<br><br>HF: 10 mg PO daily<br><br>CKD: 10 mg PO daily<br><br>Swallow whole. | <u>Hepatic</u>:<br>• Severe impairment: Use not recommended<br><br><u>Renal</u><br>• eGFR ≥ 25 mL/min/1.73 $m^2$: No change in dose<br>• eGFR < 25 mL/min/1.73 $m^2$: Initiation of therapy not recommended<br>• CI if on dialysis | Exception status* | $89† (30 days) |
| **Empagliflozin** *Jardiance* | 10 mg<br>25 mg | 10-25 mg PO daily<br><br>HF: 10 mg PO daily<br><br>Swallow whole. | <u>Hepatic:</u><br>• Severe impairment: Use not recommended<br><br><u>Renal:</u><br>• Not recommended if eGFR < 30 mL/min/1.73 $m^2$<br>• CI if eGFR < 20 mL/min/1.73 $m^2$ | Exception status* | $90† (30 days) |

BG: blood glucose, CI: contraindicated, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, HF: heart failure, MOA: mechanism of action, PO: by mouth, SGLT-2: sodium glucose co-transporter 2
*See Exception Status Criteria in Appendix E.
†Cost for one tablet daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs. Last updated: February 2023

## Appendix C: Drug Tables - continued

| **Name** Generic, *Trade* | **Strengths** | **Adult Dose** (Product Monographs)[124-125] | **Dose Adjustments** (Product Monographs[124-125] & Lexi-comp) | **Nova Scotia Pharmacare Status** | **McKesson Cost (Supply)** |
|---|---|---|---|---|---|
| **Combined Formulations: SGLT-2 Inhibitors + Biguanides** | | | | | |
| **Empagliflozin + Metformin** *Synjardy* | 5/500 mg<br>5/850 mg<br>5/1000 mg<br><br>12.5/500 mg<br>12.5/850 mg<br>12.5/1000 mg | 1 tablet PO BID with meals<br><br>In patients already taking metformin, start empagliflozin at 5 mg BID and continue metformin at a similar total daily dose<br><br>**MAX:** Total daily dose 25/2000 mg | <u>Hepatic:</u><br>• CI in patients with clinical or laboratory evidence of hepatic disease.<br><br><u>Renal:</u><br>PM: CI in people with renal impairment, e.g. CrCl < 60 mL/min (due to metformin component)<br>Lexi-comp[126]:<br>• eGFR ≥ 45 mL/min/1.73 $m^2$ – no adjustment; monitor renal function<br>• eGFR 30 to 45 mL/min/1.73 $m^2$ – US manufacturer does not recommend initiating therapy<br>• eGFR < 30 mL/min/1.73 $m^2$ – CI<br>• ESRD/ dialysis - CI | Exception status* | $93† (30 days) |
| **Dapagliflozin + Metformin** *Xigduo* | 5/850 mg<br>5/1000 mg | 1 tablet PO BID with meals<br><br>**MAX:** Total daily dose 10/2000 mg | <u>Hepatic:</u><br>• CI in patients with clinical or laboratory evidence of hepatic disease.<br><br><u>Renal:</u><br>PM: CI in people with renal impairment, e.g. CrCl < 60 mL/min<br>Lexi-comp[127]:<br>• eGFR ≥ 45 mL/min/1.73 $m^2$ – no change<br>• eGFR 30 to < 45 mL/min/1.73 $m^2$ – initiation of therapy not recommended<br>• eGFR < 30 mL/min/1.73 $m^2$/dialysis – CI | Exception status* | $80† (30 days) |

BID: twice daily, CI: contraindicated, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, PM: product monograph, PO: by mouth, SGLT-2: sodium glucose co-transporter 2, US: United States
*See Exception Status Criteria in Appendix E.
†Cost for one tablet twice daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs. Last updated: February 2023

## Appendix C: Drug Tables - continued

| **Name** Generic, *Trade* | **Strengths** | **Adult Dose** (Product Monograph)[128] | **Dose Adjustments** (Product Monograph[128] & Lexi-comp) | **Nova Scotia Pharmacare Status** | **McKesson Cost (Supply)** |
|---|---|---|---|---|---|
| **Combined Formulations Continued: SGLT-2 Inhibitors + Biguanides** | | | | | |
| **Canagliflozin + Metformin** *Invokamet* | 50/500 mg<br>50/1000 mg<br>150/500 mg<br>150/1000 mg | 1 tablet PO BID with meals<br>In patients already taking metformin, start canagliflozin at 50 mg BID and continue metformin at a similar total daily dose<br>**MAX:** Total daily dose 300/2000 mg<br>Swallow whole. | Hepatic:<br>• CI in patients with clinical or laboratory evidence of hepatic disease.<br>Renal:<br>PM:<br>• CI in people with renal impairment, e.g. CrCl < 60 mL/min<br>• No dose adjustment required provided eGFR > 60 mL/min/1.73 $m^2$<br>Lexi-comp[129]:<br>• eGFR ≥ 60 mL/min/1.73 $m^2$ – no change<br>• eGFR 45 to < 60 mL/min/1.73 $m^2$ – Max dose canagliflozin 100 mg/day; no dose adjustment for metformin required<br>• eGFR 30 to <45 mL/min/1.73 $m^2$ – Initiation of therapy not recommended; continuation of existing therapy permitted at canagliflozin dose of 100 mg/day max and metformin dose 500 mg BID max; monitor renal function closely<br>• eGFR < 30 mL/min/1.73 $m^2$ or dialysis – CI | Not a benefit | $108† (30 days) |
| | Note: XR formulation approved by Health Canada but not yet available. | | | | |

BID: two times daily, CI: contraindicated, CrCl: creatinine clearance, eGFR: estimated glomerular filtration rate, PM: Product monograph, PO: by mouth, SGLT-2: sodium glucose co-transporter 2, XR: extended release.
†Cost for one tablet twice daily, regardless of strength. Pricing is approximate.
For additional prescribing information, see product monographs.

Updated February 2023.

## Appendix D: Drug Tables – GLP-1 Agonist and GLP-1 Agonist Combination Products

| GLP-1 Agonists | | | | | |
|---|---|---|---|---|---|
| **Name** Generic, *Trade* | **Strength(s)** | **Adult Dose** (Product Monographs)[57,61-63] | **Dose Adjustments** (Product Monographs)[57,61-63] | **Nova Scotia Pharmacare Status** | **McKesson Cost† (Supply)** |
| **GLP-1 Receptor Agonists (MOA: mimic actions of GLP-1, thereby ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying, and ↑ satiety)** | | | | | |
| **Liraglutide** *Victoza* | Prefilled pen:<br>6 mg/mL | 0.6 mg SC daily x 7 days, then 1.2 mg SC daily. May ↑ to 1.8 mg SC daily after 7 days if additional BG control required.<br><br>MAX: 1.8 mg SC daily | Hepatic:<br>• No dose adjustment; limited clinical experience<br>Renal:<br>• Use in ESRD not recommended<br>• Otherwise, no dose change required for ↓ CrCl | Not a benefit | $210-$316 (30 days @ 1.2-1.8 mg/day) |
| **Dulaglutide** *Trulicity* | Prefilled pens:<br>0.75 mg/0.5 mL<br>1.5 mg/0.5 mL<br>3 mg/0.5 mL<br>4.5 mg/0.5 mL | Start at 0.75 mg SC once weekly. May ↑ dose every 4 weeks or more prn for BG control as follows:<br>1.5 mg → 3 mg → 4.5 mg<br><br>MAX: 4.5 mg SC once weekly | Hepatic:<br>• No dose adjustment; caution - limited clinical experience<br>Renal:<br>• No dose adjustment | Not a benefit | $230 (28 days @ 0.75-1.5 mg/ week) |
| **Lixisenatide** *Adlyxine* | Prefilled pens (3 mL):<br>10 mcg/dose (0.05 mg/mL)<br>20 mcg/dose (0.1 mg/mL) | 10 mcg SC daily x 14 days, then 20 mcg SC daily starting day 15<br><br>Administer 60 minutes before any meal of the day | Hepatic:<br>• No dose adjustment<br>Renal:<br>• CrCl 30-90 mL/min: no dose adjustment<br>• ESRD, dialysis, severe renal impairment: not recommended | Exception status* | $124 (28 days @ 20 mcg/d) |
| **Semaglutide** *Ozempic* | Prefilled pens:<br>2 mg/pen (1.34 mg/mL)<br><br>4 mg/pen (1.34 mg/mL) | 0.25 mg SC weekly x 4 weeks, then 0.5 mg SC weekly.<br>May ↑ dose every 4 weeks for BG control as follows:<br>1 mg → 2 mg<br><br>MAX: 2 mg SC weekly | Hepatic:<br>• Use with caution (not studied)<br>Renal:<br>• No dose adjustment<br>• Not recommended in ESRD | Exception status* | $221 (28 days @ 0.5-1 mg/ week) |
| | Note: 8 mg/pen (2.68 mg/mL) approved by Health Canada but not yet available. | | | | |

BG: blood glucose, CrCl: creatinine clearance, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, GLP-1: glucagon-like peptide-1, MOA: mechanism of action, PRN: as needed, SC: subcutaneous.
*See Exception Status Criteria in Appendix E.
†Pricing is approximate.
For additional prescribing information, see product monographs. Updated February 2023

## Appendix D: Drug Tables – continued

| **Name** Generic, *Trade* | **Strength(s)** | **Adult Dose** (Product Monographs)[64,130-131] | **Dose Adjustments** (Product Monographs)[64,130-131] | **Nova Scotia Pharmacare Status** | **McKesson Cost† (Supply)** |
|---|---|---|---|---|---|
| **GLP-1 Receptor Agonists – Continued** | | | | | |
| **Semaglutide** *Rybelsus* | 3 mg<br>7 mg<br>14 mg | 3 mg PO daily x 30 days, then<br>7 mg PO daily x 30 days, then<br>may ↑ to 14 mg daily for greater BG control<br><br>Take 30 minutes before first food, beverage, or other PO drugs of the day. Take with ≤ 120 mL water. Swallow whole. | Hepatic:<br>• No dose adjustment<br><br>Renal:<br>• No dose adjustment | Not a benefit | $227<br>(30 days @ 7-14 mg/day) |
| **Combination Formulations: Long acting BASAL insulin + GLP-1 Agonist** | | | | | |
| **Insulin degludec/ liraglutide** *Xultophy* | Prefilled pen:<br>100 units/mL + 3.6 mg/mL | GLP-1 agonist or basal insulin naïve patients: 10 units/0.36 mg SC daily start for<br><br>Already on basal insulin/GLP-1: discontinue single agents; start 16 units/ 0.58 mg SC daily<br><br>Titrate by 2 units once or twice weekly until fasting plasma glucose within target range.<br><br>MAX: 50 units/1.8 mg daily | Hepatic:<br>• No dose adjustment<br>• Intensify BG monitoring to titrate dose prn.<br><br>Renal:<br>• No dose adjustments for mild to moderate impairment; intensify BG monitoring to titrate dose prn<br>• Severe renal impairment or ESRD: use is not recommended | Not a benefit | $ 107- 335<br>(30 days @ 16 to 50 units/0.58 to 1.8 mg daily) |
| **Insulin glargline/ lixisenatide** *Soliqua* | Prefilled pen:<br>100 units/mL + 33 mcg/mL | <30 units basal insulin/day:<br>Starting dose 15 units/ 5 mcg SC daily<br><br>30–60 units basal insulin/day:<br>Starting dose 30 units/10 mcg SC daily<br><br>Titrate by 2–4 units weekly prn<br><br>MAX: 60 units/20 mcg SC daily | Hepatic:<br>• No dose adjustment; not studied<br><br>Renal:<br>• No dose adjustments for mild to moderate impairment (CrCl 30-90 mL/minute)<br>• Severe renal impairment or ESRD: use is not recommended | Not a benefit | $63-250<br>(30 days @ 15 to 60 units/ 5 to 20 mcg daily) |

BG: blood glucose, CrCl: creatinine clearance, ESRD: end-stage renal disease, GLP-1: glucagon-like peptide-1, PO: by mouth, PRN: as needed, SC: subcutaneous
†Pricing is approximate.
For additional prescribing information, see product monographs. Last updated: February 2023

# Appendix E: Nova Scotia Pharmacare EXCEPTION STATUS CRITERIA

*June 2022*

### Canagliflozin (Invokana):

- For the treatment of type 2 diabetes (T2DM) for patients with:
  - Inadequate glycemic control on metformin and a sulfonylurea (SU); and
  - For whom insulin is not an option.

Note:

- 200 mg is not a recognized dose; as such a dose of two 100 mg tablets will not be funded.

### Dapagliflozin (Forxiga):

- For the treatment of T2DM when:
  - Added on to metformin for patients:
    - who have inadequate glycemic control on metformin; and
    - who have a contraindication or intolerance to a SU; and
    - for whom insulin is not an option.
- Added on to a SU for patients:
  - Who have inadequate glycemic control on a SU; and
    - who have a contraindication or intolerance to metformin; and
    - for whom insulin is not an option.

### Dapagliflozin + metformin (Xigduo):

- For the treatment of T2DM for patients:
  - who are already stabilized on therapy with dapagliflozin and metformin to replace the individual components of dapagliflozin and metformin; and
  - for whom insulin is not an option

Claim Note:

- Must have met criteria for dapagliflozin.

### Empagliflozin (Jardiance):

- For treatment of T2DM for patients with:
  - inadequate glycemic control on metformin and a SU; and
  - for whom insulin is not an option

OR

- As an adjunct to diet, exercise, and standard care therapy to reduce the incidence of cardiovascular (CV) death in patients with T2DM and established CV disease (details must be provided as per clinical note below) who have:
  - inadequate glycemic control despite an adequate trial of metformin

Clinical Notes:

- Established CV disease is defined as one of the following (details must be provided):
  - History of myocardial infarction (MI)
  - Multi-vessel coronary artery disease in two or more major coronary arteries (irrespective of revascularization status)
  - Single-vessel coronary artery disease with significant stenosis & either a positive non-invasive stress test or discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection.
  - Last episode unstable angina >2 months prior with confirmed evidence of coronary multi- or single-vessel disease
  - History of ischemic/ hemorrhagic stroke.
  - Occlusive peripheral artery disease.

### Empagliflozin + metformin (Synjardy):

- For the treatment of T2DM in patients who are already stabilized on therapy with empagliflozin and metformin, to replace the individual components of empagliflozin and metformin. Patients must meet coverage criteria for empagliflozin.

### Lixisenatide (Adlyxine):

- For treatment of T2DM when added to:
  - Basal insulin for patients who have inadequate BG control on basal insulin; or
  - Basal insulin and metformin for patients who have inadequate glycemic control on metformin and basal insulin

### Semaglutide (Ozempic):

- For the treatment of T2DM in combination with metformin & a SU, when diet and exercise plus dual therapy with metformin & a SU do not achieve adequate BG control