Comparative Efficacy and Cost-Effectiveness of Sodium-Glucose Co-Transporter 2 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists, and Nonsteroidal Mineralocorticoid Receptor Antagonists in Type 2 Diabetes and Chronic Kidney Disease

By

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Abstract

Type 2 diabetes (T2D) and chronic kidney disease (CKD) are major public health challenges. People with T2D and CKD have high risks of cardiovascular (CV) events and kidney failure. Novel drug classes, including sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and nonsteroidal mineralocorticoid receptor antagonists (nsMRA), have provided more cardiorenal protection for treatment of T2D and CKD than standard of care (SoC). This thesis examines the comparative efficacy in improving CV and renal outcomes and assesses the cost-effectiveness of these novel drugs for treatment of T2D and CKD.

This thesis has four chapters. Chapter 1 provides background information about epidemiology, disease burden, definition, and treatment of T2D and CKD. It also describes the study design and reviews the existing literature. Chapter 2 is a systematic review and network meta-analysis comparing the relative efficacy of SGLT-2i, GLP-1RA, and nsMRA in improving CV and renal outcomes in patients with T2D and CKD. We found that SGLT-2i provided better cardiorenal protection than GLP-1RA and nsMRA in patients with T2D and CKD. There were no significant differences between GLP-1RA and nsMRA in reducing CV and renal outcomes. Chapter 3 examines the cost-effectiveness of adding SGLT-2i (canagliflozin or dapagliflozin) to SoC versus SoC alone for the treatment of T2D and CKD. Our study showed that adding canagliflozin or dapagliflozin to SoC was cheaper and more effective than SoC alone. Dapagliflozin plus SoC incurred lower cost and was more effective than canagliflozin plus SoC over the 5- or 10-year horizons, but it was not cost-effective versus canagliflozin plus SoC over longer time horizon. Chapter 4 concludes and discusses implications, limitations, and future research directions in T2D and CKD treatment.

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ACD	All-cause death
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin II receptor blocker
CI	Confidence interval
CKD	Chronic kidney disease
CRO	Composite renal outcomes
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
GLP-1RA	Glucagon-like peptide 1 receptor agonists
HbA1c	Hemoglobin A1c
HFH	Heart failure hospitalization
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
KDIGO	Kidney disease: improving global outcomes
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
nsMRA	Nonsteroidal mineralocorticoid antagonists
QALYs	Quality-adjusted life years
RR	Risk ratio
SGLT-2i	Sodium-glucose co-transporter 2 inhibitors

SoC	Standard of care
SUCRA	Surface under the cumulative ranking curve
T2D	Type 2 diabetes
UACR	Urine albumin-to-creatinine ratio
WTP	Willingness-to-pay

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Chapter 1. Introduction

1.1. Epidemiology of type 2 diabetes and chronic kidney disease

Diabetes is one of the most common non-communicable diseases worldwide. In 2021, 537 million people aged 20-79 were estimated to be living with diabetes globally.[1] This number is predicted to increase to 643 million people by 2030.[1] Type 2 diabetes (T2D) accounts for more than 90% of diabetes.[1] Patients with T2D usually have hypertension, cardiovascular (CV) diseases, obesity, and especially, chronic kidney disease (CKD).

Prevalence of T2D and CKD is high in Canada. T2D affects about 3.6 million Canadians in 2022[2], with about 50% having CKD.[3] T2D is also a leading cause of end-stage kidney disease (ESKD) and accounts for approximately 40% of patients requiring kidney replacement therapy in Canada.[4] Of the 4 million Canadians living with CKD in 2020, there were 40,000 patients with ESKD, of whom 57% and 43% required dialysis and kidney transplants, respectively.[4]

1.2. Burden of type 2 diabetes and chronic kidney disease

T2D and CKD are associated with reduced quality of life and life expectancy.[5] Patients with both T2D and CKD have 23.4% higher risk of all-cause death (ACD) than those who only have T2D.[6] Additionally, T2D and CKD increase risks of kidney failure and diabetes-related complications, including diabetic ketoacidosis, hypoglycemia, retinopathy, neuropathy, amputation, and CV events.[7]

T2D and CKD impose a substantial economic burden on the healthcare system. CKD is estimated to cost more than C$40 billion per year.[8] The total direct healthcare costs of CKD were C$14,634 per patient per year (2017 Canadian dollars), of which 38% and 35% were accounted for by hospitalization and medication costs, respectively.[9] The healthcare costs were 21% greater in patients with T2D and CKD than in those with CKD alone.[9]

The health care costs for CKD increase markedly among patients with ESKD. With about C$100,000 per patient per year spent on dialysis or kidney transplants, treatment of ESKD can cost the Canadian healthcare system about C$4 billion per year, which means that 10% of total expenditure on CKD is used only to treat 1% of patients with CKD.[4,10] These costs are even higher when one accounts for productivity losses. The Canadian Pension Plan annually spends over C$200 million on patients with advanced kidney disease who cannot work.[8]

1.3. Diagnosis of type 2 diabetes and chronic kidney disease

T2D is referred to as relative insulin deficiency and peripheral insulin resistance.[11] The levels of insulin in patients with T2D can be normal or increased. However, it does not normalize glycemia because of the failure of pancreas to secrete glucose-stimulated insulin.[11] The criteria defining diabetes include a fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L), or hemoglobin A1c (HbA1C) level ≥ 6.5% (48 mmol/mol), or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test, or symptoms related to hyperglycemia or hyperglycemia with a random plasma glucose ≥200 mg/dL (11.1 mmol/L).[11]

The Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as the persistent reduction in estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or the persistent elevation of urine albumin-to-creatinine ratio (UACR) > 30 mg/g, or both, for at least 3 months.[7] Figure 1.1 shows the classification of CKD by eGFR and UACR values.[7]

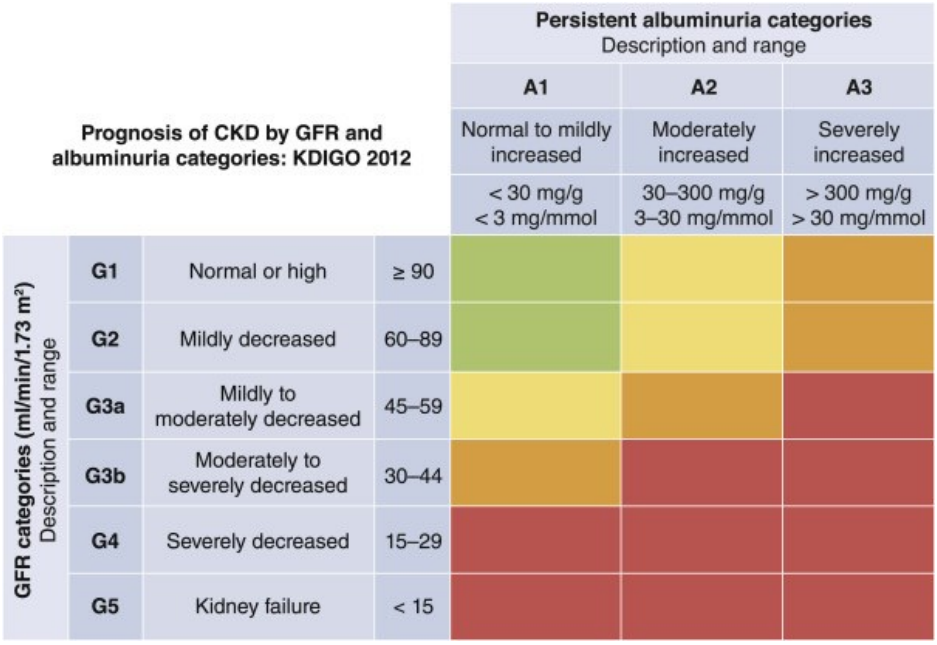

Figure 1.1. Classification of CKD based on eGFR and UACR

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

1.4. Pharmacologic interventions for type 2 diabetes and chronic kidney disease

The treatment for T2D and CKD is multifaceted and comprehensive. The treatment goal is to reduce CV events, hospitalization, ACD, and especially, progression to ESKD.[7,12] Interventions are often multipronged and include pharmacologic treatment, smoking cessation, healthy diet, weight control, and physical activity.[7]

The goal of pharmacologic interventions among T2D and CKD patients is management of glycemia, blood pressure and lipids, as well as reducing CKD progression.[7,13,14] Canadian and international guidelines recommend the use of renin-angiotensin system blockade, including an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) in patients with T2D and CKD who have hypertension and albuminuria.[12-15] The ACEi or ARB should be used with a maximally tolerated dose to reduce the risk of CKD progression.

Although these drugs are well-tolerated, it is necessary to monitor adverse events (AEs) such as hypotension, hyperkalemia, high serum creatinine levels, angioedema, and cough.

Novel glucose-lowering drugs, including sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA), are recommended alongside an ACEi or an ARB and metformin in patients with T2D and CKD.[13,15] SGLT-2i are oral drugs with effects of glucosuria and natriuresis that contribute to glycemic control, weight loss, blood pressure-lowering, and reductions in intraglomerular pressure as well as fluid overload.[16] SGLT-2i also reduce oxidative stress, fibrosis, inflammation, and glomerular damage.[16] All these mechanisms of action explain the protection of SGLT-2i against CV and renal events. However, treatment with SGLT-2i also entails higher risks of AEs, such as diabetic ketoacidosis, amputation, fracture, acute kidney injury, urinary tract infection, volume depletion, severe hypoglycemia, and genital mycotic infection.[17] Treatment with SGLT-2i in patients with T2D and CKD (eGFR $\geq$ 20 mL/min/1.73 m^2) continues until dialysis and kidney transplantation.[12,15]

GLP-1RA are used for treatment of T2D and CKD when SGLT-2i are not tolerated or contraindicated.[15] Alongside glycemic control through increases in insulin secretion and decreases in glucagon secretion, treatment with GLP-1RA can reduce HbA1c, blood pressure, lipids, and body weight.[18] GLP-1RA prevent renal damage by activating the cAMP-protein kinase A to minimize the production of reactive oxygen species.[19] GLP-1RA also suppress cardiovascular inflammation and development of atherosclerosis.[18] Therefore, GLP-1RA reduce risks of CV events and progression of CKD. There is no need for dose adjustments in patients having low eGFR treated with GLP-1RA (liraglutide, semaglutide, and dulaglutide).[13] However, treatment with GLP-1RA can be associated with higher risks of gastrointestinal symptoms, retinopathy, pancreatitis, increased heart rate, and gallbladder disease.[15]

The combination of SGLT-2i and GLP-1RA can be used in patients with T2D and CKD who are unable to attain HbA1c targets or require cardiorenal risk reduction.[15] If patients still cannot maintain the glycemic goal, other glucose-lowering drugs, including insulin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors, can be combined based on their efficacy in lowering glucose levels.[15]

A novel nonsteroidal mineralocorticoid antagonist (nsMRA), finerenone, is recommended in patients with T2D and CKD who cannot use SGLT-2i or require cardiorenal risk reduction.[20] Finerenone selectively inhibits mineralocorticoid receptors, which results in reductions in inflammation, fibrosis, and vasoconstriction in CV and kidney disease models.[21] It has been demonstrated to be efficacious in reducing risks of CV and renal events in patients with T2D and CKD in large trials.[22-24] However, it is also associated with significantly greater risk of hyperkalemia than placebo.[22]

1.5. Existing literature and current knowledge gap

1.5.1. Comparative efficacy of new drugs in type 2 diabetes and chronic kidney disease

Previous meta-analyses have compared the effect of SGLT-2i and GLP-1RA on CV and renal events in patients with CKD and/or T2D.[25-28] SGLT-2i reduced significantly risk of renal events by 21% (Risk ratio (RR), 0.79; 95% confidence interval (CI), 0.63-0.99) but were not associated with significantly lower risk of major adverse cardiovascular events (MACE) than GLP-1RA. Compared with placebo, SGLT-2i were associated with significantly lower risk of MACE (RR, 0.85; 95% CI, 0.75-0.96) and reduced risk of renal outcomes (RR, 0.68; 95% CI, 0.59-0.78). There were no significant reductions in both MACE and renal outcomes between GLP-1RA and placebo. However, these meta-analyses did not compare outcomes such as CV death, myocardial infarction (MI), stroke, heart failure hospitalization (HFH), and ACD. Furthermore,

these analyses did not include several recent large trials of SGLT-2i and GLP-1RA in patients with CKD.[29-31]

A previous meta-analysis has also examined the relative efficacy of SGLT-2i and finerenone in reduction of cardiorenal events in patients with T2D and CKD.[28] SGLT-2i significantly reduced CKD progression (Hazard ratio (HR), 0.78; 95% CI, 0.67-0.90) and HFH (HR, 0.71; 95% CI, 0.55-0.92) compared with finerenone. There were no significant differences in risks of MACE, MI, stroke, CV death and ACD between SGLT-2i and finerenone. However, this study did not include a recent large trial about the efficacy of finerenone on CV events[24] and other SGLT-2 inhibitor studies.[30,32,33]

1.5.2. Cost-effectiveness analysis of new drugs in type 2 diabetes and chronic kidney disease

International guidelines for treatment of T2D and CKD recommend SGLT-2i, such as canagliflozin or dapagliflozin, as an add-on treatment with standard of care (SoC) to reduce mortality and CKD progression.[12,34] However, differences in clinical outcomes and healthcare costs between canagliflozin and dapagliflozin raise the question of which drug is cost-effective. Compared with dapagliflozin, canagliflozin was associated with lower risk of CKD progression and stroke.[35-37] However, canagliflozin was less effective in reducing HFH, MI, dialysis, ACD, and AEs than dapagliflozin.[17,35,37,38] In Canada, treatment with SGLT-2i costs more than C$1000 per year than treatment with SoC alone.[39] Further, the cost of canagliflozin is higher than the cost of dapagliflozin. Therefore, it is unclear whether canagliflozin or dapagliflozin should be prioritized.

There are several cost-effectiveness analyses of using SGLT-2i as an add-on treatment to SoC in patients with CKD. A study showed that adding canagliflozin to SoC (canagliflozin+SoC)

yielded cost savings of €12,574 and generated additional 1.2 QALYs compared with SoC alone in patients with T2D and CKD in England.[40] Another study demonstrated that adding dapagliflozin to SoC (dapagliflozin+SoC) cost less (US$1,320) and gained 0.3 QALYs than SoC alone for treatment of CKD in Thailand.[41] In the United States, dapagliflozin+SoC was cost-effective versus SoC alone in patients with diabetic nephropathy or non-diabetic CKD, with the ICER of US$21,141 or US$60,000, respectively.[42,43]

In Canada, the reimbursment status of SGLT-2i varies markedly across provinces.[44] For example, the use of canagliflozin and dapagliflozin in patients with T2D is reimbursed without any criteria in Ontario[45], but these drugs are only eligible for reimbursement under special authorization[46]. There is no study examining the cost-effectiveness of canagliflozin+SoC versus dapagliflozin+SoC in patients with T2D and CKD. Previous cost-effectiveness analyses only compared canagliflozin+SoC or dapagliflozin+SoC individually versus SoC alone. Therefore, it is unclear which among canagliflozin+SoC, dapagliflozin+SoC, and SoC alone is the most cost-effective.

1.6. Objective of thesis

This thesis examines the comparative efficacy and cost-effectiveness of SGLT-2i, GLP-1RA, and nsMRA for treatment of T2D and CKD. First, we conducted a systematic review and network meta-analysis to assess the comparative effects of SGLT-2i, GLP-1RA, and nsMRA on CV and renal outcomes in patients with T2D and CKD. Second, we evaluated the cost-effectiveness of two SGLT-2i, namely, canagliflozin and dapagliflozin as add-on treatments to SoC versus SoC alone in patients with T2D and CKD.

1.7. Fundamental concepts of network meta-analysis and cost-effectiveness analysis

This thesis uses network meta-analysis to assess the relative efficacy of multiple pharmacologic interventions for treatment of T2D and CKD and cost-effectiveness analysis to compare the costs and health outcomes of these interventions. A brief overview of these analytical methods is presented below.

1.7.1. Network meta-analysis

In clinical practice, it is becoming increasingly common to have more than one treatment option for a clinical condition, raising the question of which treatment option is optimal. Network meta-analysis is a technique to simultaneously compare outcomes of more than two interventions for each outcome.[47,48] It overcomes the limitation of conventional meta-analysis, which only allows for comparing two interventions. Network meta-analysis also assesses and ranks multiple treatments in the network.

In network meta-analysis, a network diagram is used to visualize the connection between different interventions.[47,49] Figure 1.2 illustrates the network of four treatment groups (A, B, C, and D) for one outcome. The area of circles or nodes is weighted by the number of patients in each group. The size of lines or edges is proportional to the number of studies in each group. Direct evidence is the comparison of two groups within a study (i.e., A versus C, or A versus D), which are connected by lines. Indirect evidence is the comparison of two interventions through a common comparator (i.e., B versus C through A). Treatment effects can be estimated from direct comparisons, indirect comparisons, or both.

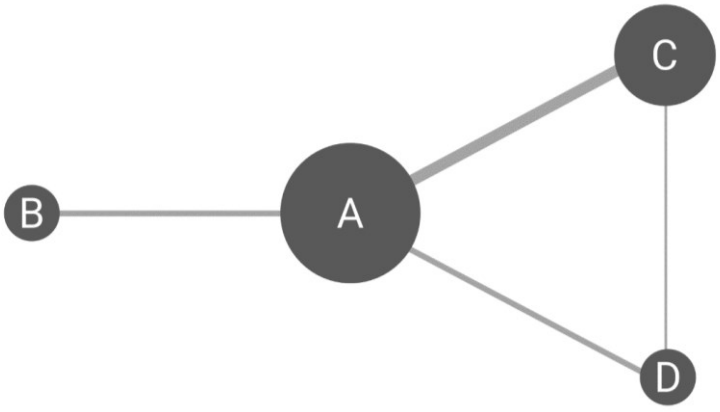

Figure 1.2. Network diagram

Treatment ranking is an important part of network meta-analysis. Depending on Frequentist or Bayesian approaches, P-scores or the surface under the cumulative ranking curve (SUCRA) are used to rank treatment, respectively. There is no difference in ranking results between these methods.[50] A higher score indicates a better ranking in the efficacy of treatment for a specific outcome. However, P-scores and SUCRA need to be interpreted with caution as these depend mainly on point estimate[50] and a small trial with low quality and significant effect can rank higher than a large trial with high quality and small effect. Therefore, the interpretation of P-scores or SUCRA should be taken into account with 95% CI or credible intervals of treatment effects, respectively.[50]

Like conventional meta-analysis, the quality of network meta-analysis also depends on search strategies, risk of bias, heterogeneity (variations in treatment effects), and publication bias. However, two important issues need to be additionally considered in conducting network meta-analyses.[51] First, the assumption of transitivity is met. That is, patient characteristics are similar across included studies. The indirect comparisons and overall results are biased if this assumption is violated. The validity of this assumption is assessed by comparing the distribution of patient characteristics across trials.[49]

Second, inconsistency between indirect and direct evidence needs to be assessed. The inconsistent assumption can be checked by statistical tests with local and global approaches. Local approaches, such as node splitting or Bucher methods, are used to examine the inconsistency in a specific comparison, while global approaches (Q-test or I^2 statistic) are performed to assess the inconsistency in a whole network.[47,49] Additionally, inconsistency is also a manifestation of intransitivity.

1.7.2. Cost-effectiveness analysis

Cost-effectiveness analysis compares two or more alternative interventions based on their costs and their effectiveness.[52] The incremental cost-effectiveness ratio (ICER) is the difference in cost of two strategies divided by their difference in effectiveness. A strategy is considered dominant if it costs less and is more effective than another strategy. After excluding the dominated strategy (which costs more and is less effective), a strategy is considered cost-effective versus another strategy if its ICER is lower than the willingness-to-pay (WTP) threshold.

Measuring costs plays a key role in the cost-effectiveness analysis. First, a perspective must be clearly defined. The cost-effectiveness analysis can adopt one or more perspectives, such as patient, payer, healthcare system, or society (including relevant costs of three previous perspectives). The choice of perspective decides what types of costs are included. For example, the healthcare system perspective only includes direct medical costs, whereas the societal perspective consists of both direct medical and non-medical costs and indirect costs. Second, a time horizon should be long enough to capture potential differences in costs and health outcomes. Multiple time horizons may be used to show the variations of ICER in different scenarios, especially when an intervention is more effective in the long term than in the short term. Third, costs and effectiveness needs to be discounted to the present year.[52,53]

The effectiveness can be measured by quality-adjusted life-years (QALYs) that are estimated by multiplying utility values and the time that patients spend in health states. Utility values reflect the quality of life of patients in specific health states. Utility values vary from 0 (dead) to 1 (perfect health condition).[52,53]

The choice of model in the cost-effectiveness analysis depends on the disease pathway and the impact of interventions on disease progression. Markov model is commonly used to model chronic conditions such as T2D and CKD. This method allows for the movement of patients through distinct health states over specific periods or cycles with equal lengths.[52] However, Markov model assumes that the risk of events is constant in each cycle, and it also ignores the impact of individual's history on both costs and effectiveness. Markov microsimulation might be used to overcome these limitations because each individual would be modeled instead of a cohort.[54] The calculation of costs and QALYs occurs within each cycle and is accumulated at the end of analysis.[52] Deterministic sensitivity analyses are conducted to assess the changes in the ICER by varying one specific parameter. In contrast, probabilistic sensitivity analyses examine the uncertainty of cost-effectiveness results by varying multiple parameters based on their distribution.[52]

1.8. Overview of the thesis

This thesis uses a manuscript style including four chapters, references, and appendices. Chapter 1 provides an introduction. I describe background information about epidemiology, disease burden, definition, and treatment of T2D and CKD. This chapter also consists of existing literature, study rationale, and main concepts of study design for chapters 2 and chapter 3.

Chapter 2 is the systematic review and network meta-analysis of novel drugs for treatment of T2D and CKD. We compare the relative effects of SGLT-2i, GLP-1RA, and nsMRA on CV

and renal outcomes. We also rank the effect of these drug classes on each outcome to guide future discussions and decisions on treatment choices for T2D and CKD.

Chapter 3 is the cost-effectiveness analysis of SGLT-2i as an add-on to SoC in patients with T2D and CKD. This study can shed light on which treatment strategy would be the most cost-effective when canagliflozin+SoC, dapagliflozin+SoC, and SoC alone are available in the real world. We conduct this study from the healthcare system perspective in Ontario, the largest population province in Canada.

Chapter 4 summarizes findings and draws a conclusion from chapter 2 and chapter 3. I also discuss important implications, limitations, and future research directions in T2D and CKD treatment.

1.9. Thesis contributions

This thesis makes several important contributions. First, findings on the relative efficacy of SGLT-2i, GLP-1RA, and nsMRA in reducing cardiorenal events in patients with T2D and CKD can be helpful in informing the development of treatment guidelines and facilitating indirect comparisons for health economic evaluations, especially when no head-to-head trials of these drugs exist. Second, as it is unclear whether canagliflozin or dapagliflozin should be prioritized because of their differences in clinical outcomes and healthcare costs, the findings from the cost-effectiveness analysis of canagliflozin+SoC, dapagliflozin+SoC, and SoC alone for treatment of T2D and CKD could guide policymakers' and clinicians' treatment choice.

Chapter 2. Comparative Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists, and Nonsteroidal Mineralocorticoid Receptor Antagonists in Type 2 Diabetes and Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis

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2.1. Abstract

Aims: This network meta-analysis compares relative efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and nonsteroidal mineralocorticoid receptor antagonists (nsMRA) in improving cardiovascular (CV) and renal outcomes in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).

Materials and methods: We searched PubMed, Embase, and Cochrane Library from inception through November 25, 2022. We selected parallel randomized controlled trials that studied patients with T2D and CKD with follow-up of at least 24 weeks and compared SGLT-2i, GLP-1RA, and nsMRA with each other and with placebo. The exclusion criteria were reviews, case studies, case series, conference abstracts, animal experiments, or in vitro studies. Primary outcomes were major adverse cardiovascular events (MACE) and composite renal outcomes (CRO). Secondary outcomes were CV death, all-cause death, stroke, myocardial infarction, and heart failure hospitalization (HFH). The risk of bias for each outcome in included studies was assessed using the Cochrane Risk of Bias 2 tool. We used fixed-effects models for low degree of heterogeneity and random-effects models for moderate or high degree of heterogeneity. A frequentist approach was used to pool risk ratios (RR) with 95% confidence intervals (CI).

Results: 29 studies with 50,938 participants for MACE and 49,965 participants for CRO were included. SGLT-2i did not significantly reduce MACE but were associated with significantly lower risks of CRO compared with GLP-1RA (RR, 0.77; 95% CI, 0.64-0.91; p = 0.003) and nsMRA (RR, 0.78; 95% CI, 0.68-0.90; p = 0.001). Compared with GLP-1RA and nsMRA, SGLT-2i significantly reduced HFH (RR, 0.69; 95% CI, 0.55-0.88; p = 0.002) and (RR, 0.78; 95% CI, 0.63-0.95; p = 0.016), respectively, but did not significantly reduce other secondary outcomes. There were no significant differences between GLP-1RA and nsMRA in lowering all outcomes.

Conclusion: SGLT-2i were associated with better cardiorenal protection than GLP-1RA and nsMRA in patients with T2D and CKD. The head-to-head trials should be conducted to provide more evidence and overcome the limitation of inconsistency in this network meta-analysis.

2.2. Introduction

Type 2 diabetes (T2D) and chronic kidney disease (CKD) place a considerable burden on healthcare systems. T2D and CKD affect approximately 130 million people globally.[55] In 2019, there were over 400,000 deaths due to T2D and CKD.[55] People with T2D and CKD face high risks of kidney failure and mortality and have other diseases, including hypertension, cardiovascular (CV) diseases, and obesity.

Treatment goals for patients with T2D and CKD are to control glycemia, blood pressure, lipids, and more importantly, to reduce CV events and progression to kidney failure.[34] Renin-angiotensin system blockers have been recommended in treating T2D and CKD for a long time, but patients treated with these drugs still have high risks of CV death and CKD progression.[56] Novel drugs, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and nonsteroidal mineralocorticoid receptor antagonists (nsMRA) have provided more cardiorenal protection for treatment of T2D and CKD.[22,57,58]

The comparisons of SGLT-2i, GLP-1RA, and nsMRA have not been explored, especially when their head-to-head trials are currently lacking. There are several existing studies comparing the relative efficacy of SGLT-2i and GLP-1RA as well as finerenone (a nsMRA) on CV and renal outcomes in patients with T2D and CKD.[25-28] However, the comparative efficacy of SGLT-2i, GLP-1RA, and nsMRA for treatment of T2D and CKD in reducing myocardial infarction (MI) and stroke is still unknown. Additionally, recent trials of SGLT-2i[30,33,59,60] and GLP-1RA[31] in patients with T2D and CKD are released and provide new evidence to inform the development of treatment guidelines. Therefore, we conduct a systematic review and network meta-analysis to compare the relative efficacy of SGLT-2i, GLP-1RA, and nsMRA in improving CV and renal outcomes in patients with T2D and CKD. Our study also compares the relative efficacy

of individual drugs to provide the results of indirect comparisons for the choice of optimal regimen and use in health economic evaluations.

2.3. Methods

This study complies with the preferred reporting items for systematic review and network meta-analysis guideline.[49] The study protocol was registered on PROSPERO (ID: CRD42021273577).

2.3.1. Search strategy

We searched articles in PubMed, EMBASE, and Cochrane Library. The search was limited to English-language publications from inception of each database to November 25, 2022. In addition, reference lists of published systematic reviews were reviewed. The search strategy was reviewed by a librarian specialist. The PICO strategy included terms and medical subject headings related to T2D and CKD, the names of SGLT-2i, GLP-1RA, nsMRA, and their individual drugs, relevant outcomes, and randomized controlled trials. Details of search strategy are presented in the Appendix 1.

2.3.2. Inclusion and exclusion criteria

We included parallel randomized controlled trials that: (i) examined at least one of the outcomes of interest (see below) in adults (18 years or older) with T2D and CKD (defined as estimated glomerular filtration rate (eGFR) $\leq$ 60 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio (UACR) $\geq$ 200 mg/g); and, (ii) compared SGLT-2i, GLP-1RA, and nsMRA with each other and with placebo; and, (iii) had a follow-up of at least 24 weeks to detect potential benefits for CV and renal outcomes. The exclusion criteria were reviews, case studies, case series, conference abstracts, animal experiments, or in vitro studies.

2.3.3. Outcomes

Primary outcomes were major adverse cardiovascular events (MACE, a composite outcome of CV death, nonfatal MI, or nonfatal stroke) and composite renal outcomes (CRO, a composite outcome of at least 40% decline in eGFR, doubling of serum creatinine, end-stage kidney disease (ESKD) or renal death). ESKD was defined as eGFR less than 15 mL/min per 1.73 m^2, hemodialysis, or kidney transplantation. Secondary outcomes were CV death, all-cause death (ACD), nonfatal/fatal stroke, nonfatal/fatal MI, and heart failure hospitalization (HFH).

2.3.4. Data collection

We used Covidence, a web-based software platform, to screen and extract data. Two reviewers independently screened titles and abstracts based on the inclusion and exclusion criteria. The full texts of potentially eligible studies were then retrieved and evaluated by each reviewer using the same criteria. Duplicate abstracts and full texts were eliminated. Any disagreement was discussed by two reviewers or a third reviewer if required. Standardized and pre-pilot forms, including study characteristics (study name, publication year, and study number), type of intervention, study population (sample size, age, gender, eGFR, HbA1c, UACR, and study duration), and relevant outcomes, were designed to collect data and assess study quality. If trials reported results from both intention-to-treat and per-protocol analyses, results from intention-to-treat analyses were used.

2.3.5. Assessment of quality

The risk of bias for each included study was assessed using the Cochrane Risk of Bias 2 tool.[61] For each outcome, the risk of bias was evaluated independently by two reviewers across five domains, including randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported outcome. For each study, a

score was assigned for each domain. Then, the overall risk of bias was the maximum risk score across the five domains. Any discrepancy was resolved by two reviewers or a third reviewer if required.

2.3.6. Data analysis

We performed the network meta-analysis using the frequentist approach. To maximize trial-level data, we used hazard ratios (HRs) and risk ratios (RRs) in order of priority. HRs from two or more subgroups such as different eGFR groups were combined using fixed-effects or random-effects model. Studies without outcomes in any arms were excluded from networks due to no effect size. The Mantel-Haenszel method was used to estimate the overall RRs and their 95% confidence intervals (95% CI) across all studies based on four groups including SGLT-2i, GLP-1RA, nsMRA, and placebo. The tau^2 and I^2 statistics were calculated to assess the degree of heterogeneity across studies. I^2 statistics of 0-25%, 25%-75%, and more than 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively. We used fixed-effects models for low degree of heterogeneity and random-effects models for moderate or high degree of heterogeneity. Visual funnel plots with Egger's tests were used to assess publication bias. Two-tailed tests were used and p-values less than 0.05 were considered for statistically significance. We used P-scores (on a scale of 0 to 1, with higher scores indicating better performance) to rank treatments for each outcome. Analyses were conducted using NetMeta package in R 4.1.2.[62] Network plots for visualizing network geometry and node connectivity were generated for each outcome using network graph package in Stata 15.2.[63]

We conducted additional sensitivity analyses in which GLP-1RA were classified into human GLP-1RA (liraglutide, dulaglutide, albiglutide, and semaglutide) and exendin-4 GLP-1RA (exenatide and lixisenatide) because of their differences in pharmacodynamics and pharmacokinetics. We then compared efficacy of these groups with SGLT-2i and nsMRA in

reductions of primary outcomes. Additionally, we excluded studies with some concerns and a high risk of bias to evaluate the robustness of results.

2.3.7. Ethics approval

Ethics approval was not required because this study only used previously published data.

2.4. Results

2.4.1. Study selection and study characteristics

A total of 5,270 titles and abstracts were screened, of which 383 full-text articles were assessed (Figure 2.1). Finally, 29 studies that met the inclusion criteria were included in the meta-analysis. All studies compared SGLT-2i, GLP-1RA, or nsMRA with placebo (Figure A.1.1, Appendix 1). There were 18 studies assessing SGLT-2i[29,30,33,35,59,60,64-75], 9 studies assessing GLP-1RA[31,76-83], and 2 studies assessing nsMRA[23,24] (Table A.1.1, Appendix 1). This network meta-analysis covered 50,938 participants for MACE and 49,965 for CRO (Figure 2.2 and Figure A.1.1, Appendix 1). The duration of follow-ups ranged from 24 weeks to 277.7 weeks. There were similarities in patient characteristics such as gender, age, and baseline HbA1c across studies. The eGFR values were consistent in trials, while UACR varied from 21.5 mg/g to 1025.5 mg/g across studies. Details of patient characteristics are shown in Table A.1.1 (Appendix 1).

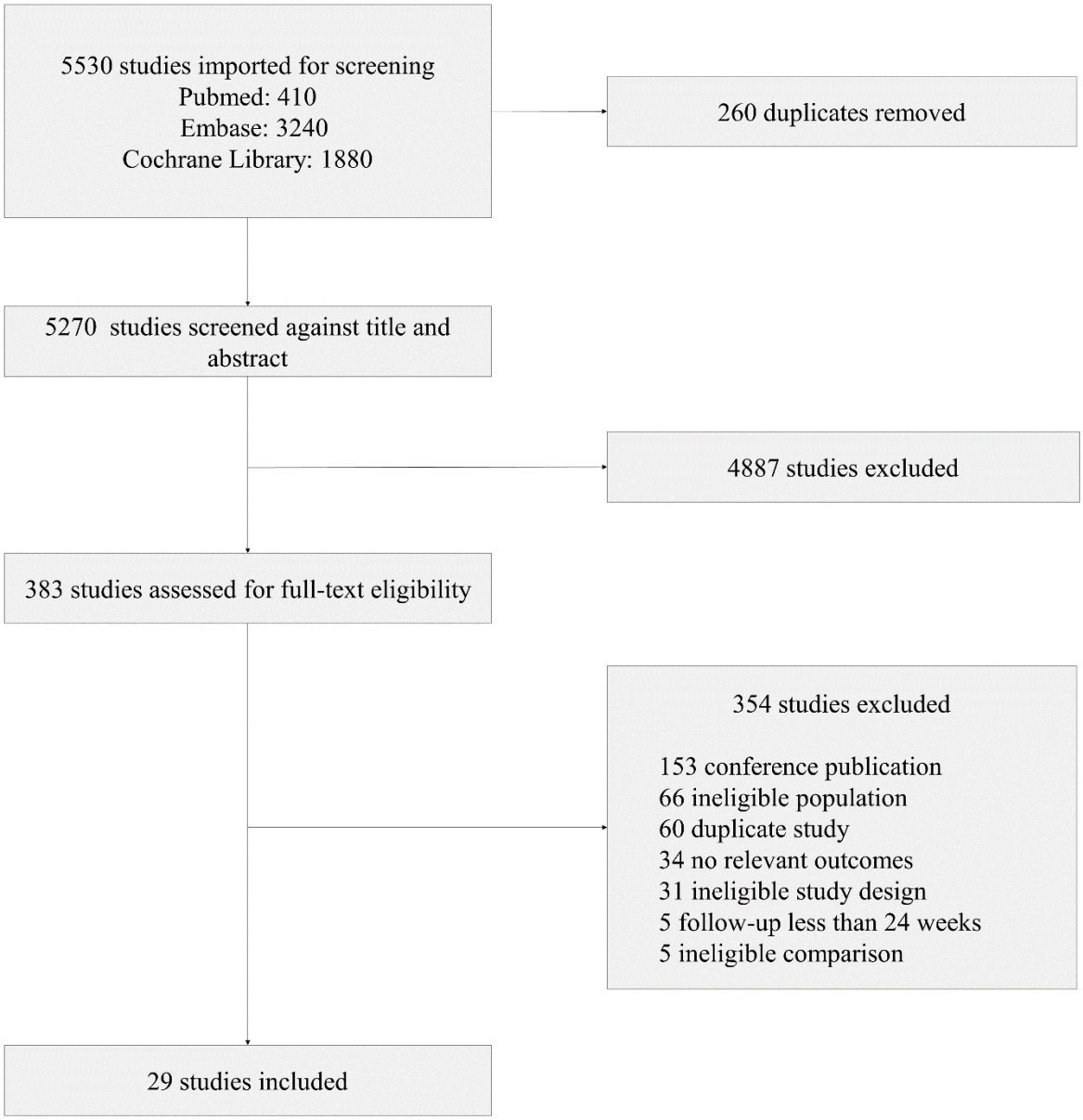

Figure 2.1. Summary of included trials for network meta-analysis

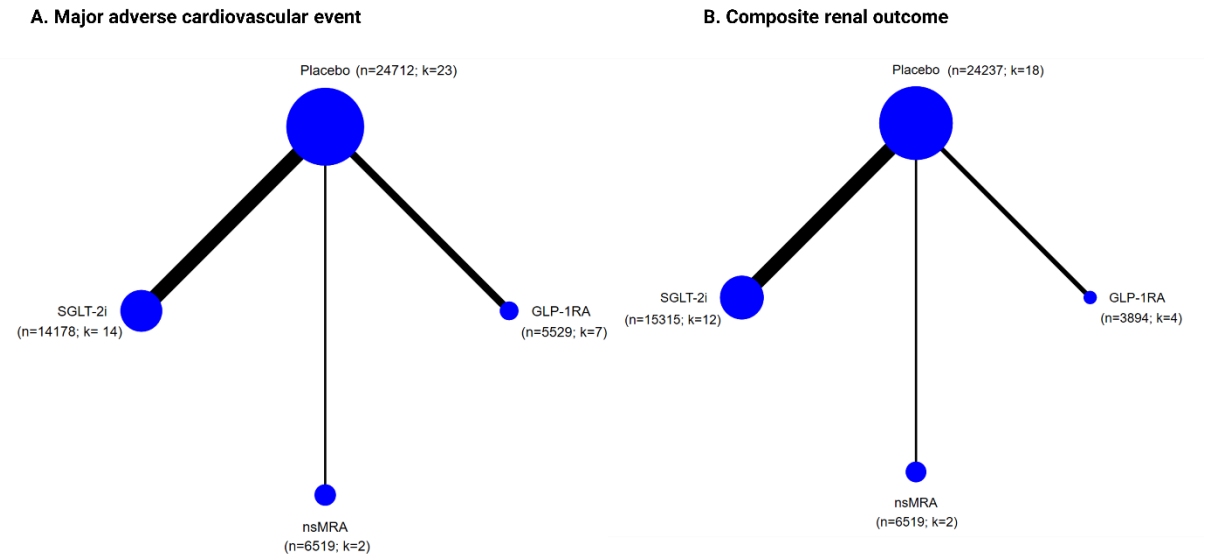

Figure 2.2. Network plots of comparisons for primary outcomes

A: Major adverse cardiovascular event was a composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

B: Composite renal outcome included at least a 40% decline in eGFR, doubling of serum creatinine, end-stage kidney disease, or renal death.

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

k, the number of studies; n, the number of participants.

2.4.2. Risk of bias and publication bias

There were four studies with some bias concerns (Figure A.1.2, Appendix 1). Two studies suffered from bias in randomization process leading to baseline imbalance.[60,75] Meanwhile, the other two studies suffered from bias in measurement of outcomes due to non-blinded outcome assessors.[73,83] There was no evidence of publication bias in all included studies (Figure A.1.3, Appendix 1).

2.4.3. Primary outcomes

Figure 2.3.A shows the network of comparisons for MACE. Although there were no significant differences in reducing risks of MACE between SGLT-2i, GLP-1RA, and nsMRA, P-score suggested that SGLT-2i were likely to be the most efficacious in reducing MACE, followed by GLP-1RA and nsMRA. SGLT-2i were associated with significantly lower risk of MACE (RR, 0.85; 95% CI, 0.76-0.96; p = 0.009) than placebo. The risks of MACE were also lower in GLP-1RA and nsMRA than in placebo, but these differences did not reach statistical significance.

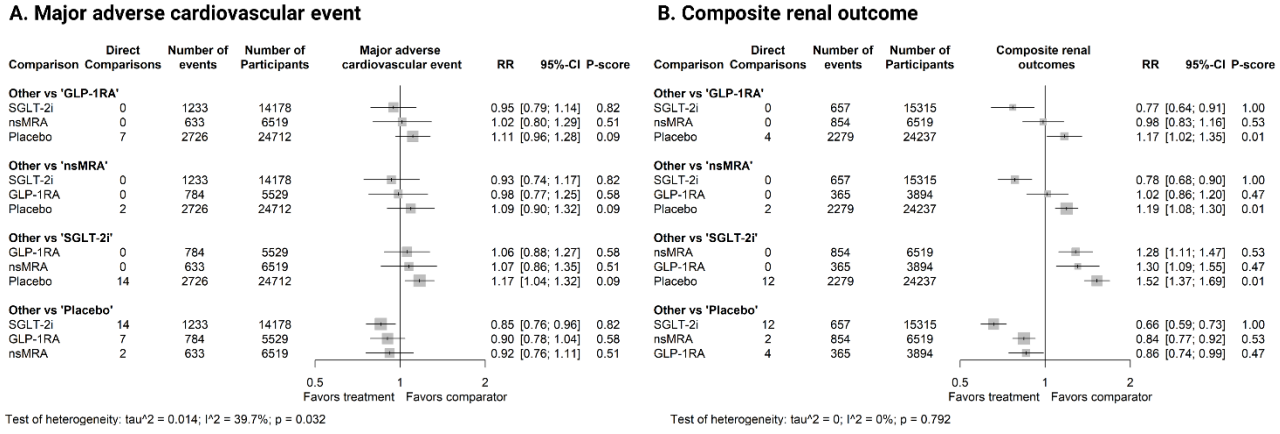

Figure 2.3. Forest plots of network meta-analysis of primary outcomes

A: *Major adverse cardiovascular event was a composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.*

B: *Composite renal outcome included at least a 40% decline in estimated glomerular filtration rate, doubling of serum creatinine, end-stage kidney disease, or renal death.*

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

The network of comparisons for CRO is presented in Figure 2.3.B. SGLT-2i were associated with significant reductions in CRO compared with GLP-1RA (RR, 0.77; 95% CI, 0.64-0.91; p = 0.003) and nsMRA (RR, 0.78; 95% CI, 0.68-0.90; p = 0.001). Therefore, SGLT-2i ranked higher than GLP-1RA and nsMRA, while nsMRA and GLP-1RA ranked equally. Compared

with placebo, SGLT-2i (RR, 0.66; 95% CI, 0.59-0.73; p < 0.001), nsMRA (RR, 0.84; 95% CI, 0.77-0.92; p < 0.001) and GLP-1RA (RR, 0.86; 95% CI, 0.74-0.99; p = 0.030) significantly lowered risks of CRO.

2.4.4. Secondary outcomes

Figure 2.4 presents the network of comparisons for secondary outcomes. Compared with GLP-1RA and nsMRA, SGLT-2i significantly reduced risks of HFH by 31% (RR, 0.69; 95% CI, 0.55-0.88; p = 0.002) and 22% (RR, 0.78; 95% CI, 0.63-0.95; p = 0.016), respectively. There were no significant differences in reductions of CV death, stroke, MI, and ACD among SGLT-2i, GLP-1RA, and nsMRA, but SGLT-2i had the highest ranking compared with the remaining treatments. nsMRA ranked higher in reducing CV death and HFH but lower in reducing stroke, MI, and ACD than GLP-1RA.

There were differences in efficacy of SGLT-2i, GLP-1RA, and nsMRA in improving secondary outcomes compared with placebo. SGLT-2i were associated with significantly lower risks of CV death (RR, 0.84; 95% CI, 0.75-0.95; p = 0.004), stroke (RR, 0.77; 95% CI, 0.60-0.99; p = 0.040), MI (RR, 0.76; 95% CI, 0.66-0.88; p < 0.001), HFH (RR, 0.61; 95% CI, 0.54-0.69; p < 0.001), and ACD (RR, 0.86; 95% CI, 0.78-0.95; p = 0.003) than placebo. Although GLP-1RA did not significantly reduce risks of all secondary outcomes compared with placebo, their point estimates were consistently below 1.00. Meanwhile, nsMRA were associated with significantly lower risk of HFH (RR, 0.78; 95% CI, 0.66-0.92; p = 0.004) but had no effect on reducing risk of stroke compared with placebo. nsMRA did not significantly reduce risks of remaining secondary outcomes compared with placebo, but their point estimates were consistently below 1.00.

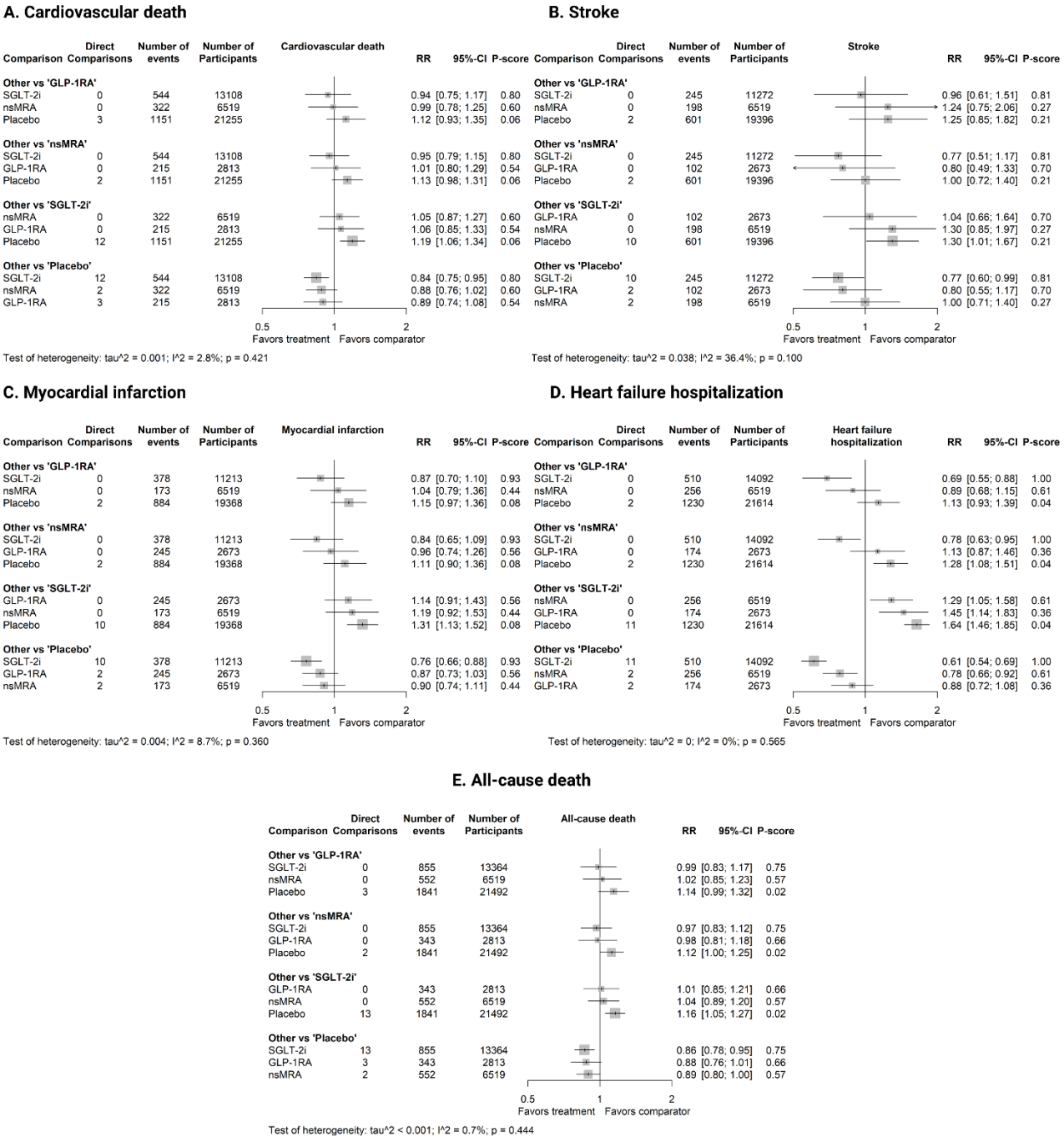

Figure 2.4. Forest plots of network meta-analysis of secondary outcomes

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

2.4.5. Individual drugs

The efficacy of individual drugs versus placebo in reductions of primary and secondary outcomes is shown in Figure 2.5. Among all drugs, liraglutide, a GLP-1RA, ranked highest in lowering MACE, CV death, stroke, and ACD. Meanwhile, canagliflozin and sotagliflozin were considered the most efficacious SGLT-2i in reductions of MACE, MI, and stroke. Dapagliflozin, followed by empagliflozin and canagliflozin, had the highest ranking in lowering CRO. Ertugliflozin ranked highest for reduction in HFH but lower for reductions in remaining outcomes than other SGLT-2i. Finerenone, a nsMRA, ranked equal or lower in reducing primary and secondary outcomes compared with liraglutide, dapagliflozin, canagliflozin, empagliflozin, and sotagliflozin.

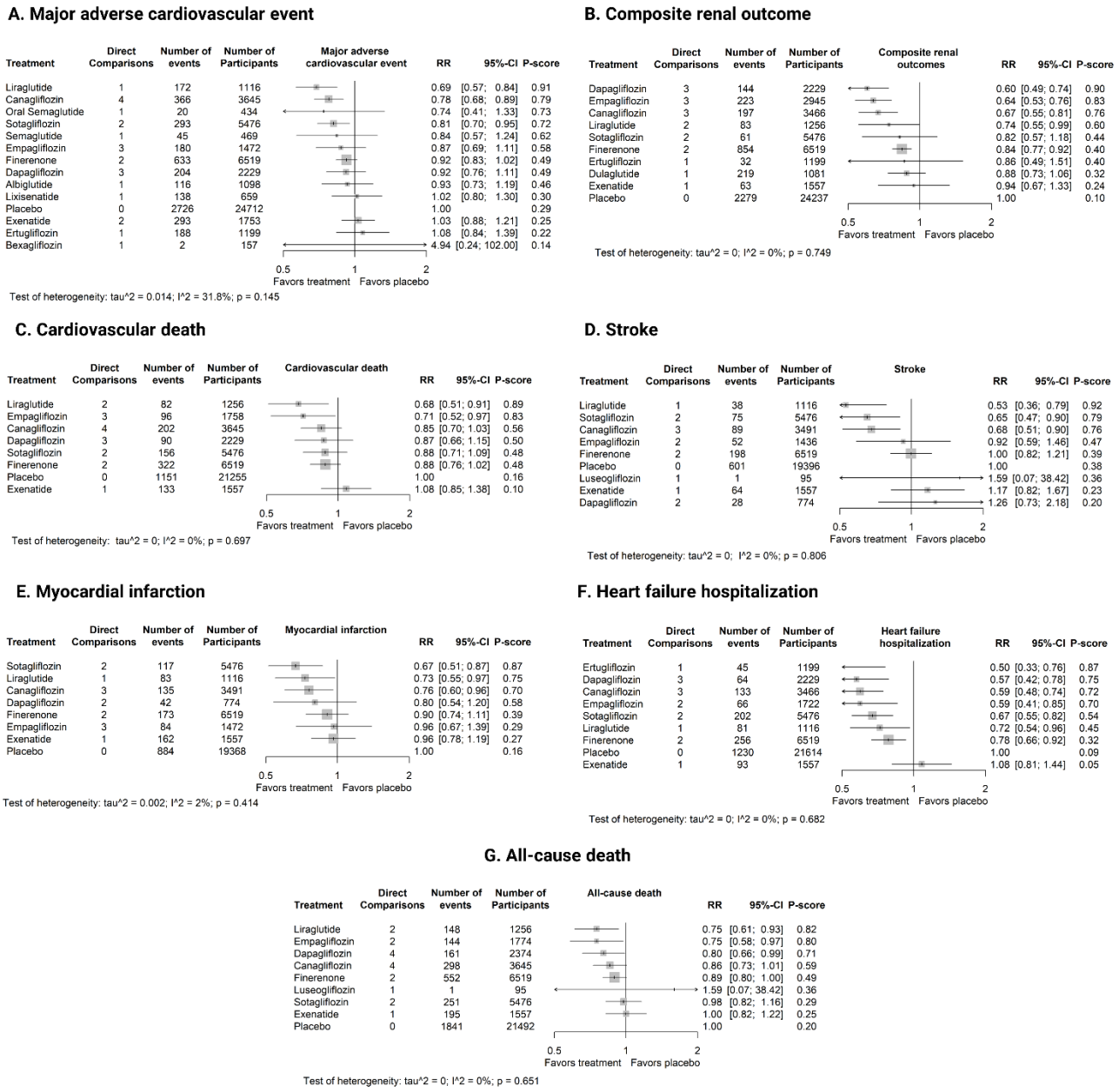

Figure 2.5. Forest plots of network meta-analysis for individual drugs

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

2.4.6. Sensitivity analysis

Our sensitivity analysis results are presented in Figure 2.6. When GLP-1RA were separated into exendin-4 and human GLP-1RA, human GLP-1RA and SGLT-2i significantly reduced

risks of MACE by 24% (RR, 0.76; 95% CI, 0.63-0.92; p = 0.005) and 17% (RR, 0.83; 95% CI, 0.71-0.97; p = 0.017), respectively, compared with exendin-4 GLP-1RA. Additionally, SGLT-2i were associated with significantly lower risks of CRO compared with exendin-4 GLP-1RA (RR, 0.70; 95% CI, 0.49-1.00; p = 0.049) and human GLP-1RA (RR, 0.78; 95% CI, 0.65-0.94; p = 0.010). However, there were no significant differences in risks of MACE and CRO among nsMRA, exendin-4 GLP-1RA, human GLP-1RA. Human GLP-1RA were associated with significantly lower risks of MACE (RR, 0.78; 95% CI, 0.68-0.90; p < 0.001) and CRO (RR, 0.84; 95% CI, 0.72-0.98; p = 0.026) than placebo. When studies with some concerns and a high risk of bias were excluded, the results were still robust.

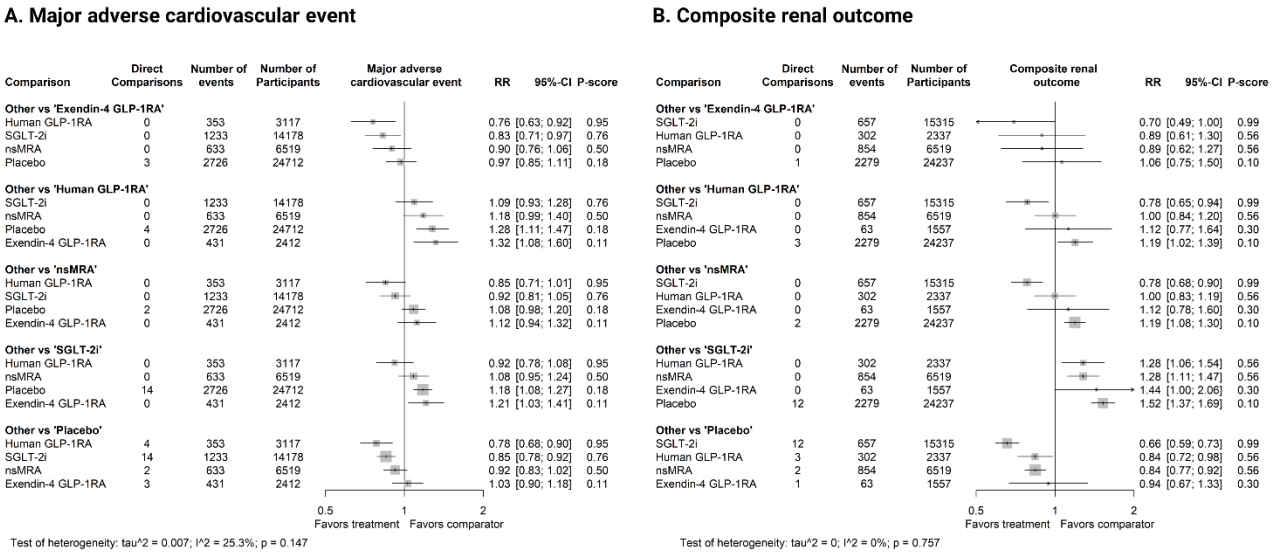

Figure 2.6. Sensitivity analyses for primary outcomes

A: *Major adverse cardiovascular event was a composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.*

B: *Composite renal outcome included at least a 40% decline in estimated glomerular filtration rate, doubling of serum creatinine, end-stage kidney disease, or renal death.*

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

2.4.7. Heterogeneity and network inconsistency

Heterogeneity across studies was low to moderate for primary and secondary outcomes (Figure 2.2 and Figure 2.3). For primary outcomes, heterogeneity was moderate for MACE (tau^2 = 0.014; I^2 = 39.7%; p = 0.032) and low for CRO (tau^2 = 0; I^2 = 0%; p = 0.792). For secondary outcomes, heterogeneity was low for CV death (tau^2 = 0.001; I^2 = 2.8%; p = 0.421), MI (tau^2 = 0.004; I^2 = 8.7%; p = 0.360), HFH (tau^2 = 0; I^2 = 0%; p = 0.565, and ACD (tau^2 < 0.001; I^2 = 0.7%; p = 0.444), and moderate for stroke (tau^2 = 0.038; I^2 = 36.4%; p = 0.100). Network consistency was not assessed in this study as no trial compared SGLT-2i, GLP-1RA, and nsMRA against each other.

2.5. Discussion

This network meta-analysis compared efficacy of SGLT-2i, GLP-1RA, and nsMRA in improving CV and renal outcomes among patients with T2D and CKD. We found that SGLT-2i did not significantly reduce risks of MACE but were associated with significantly lower risks of CRO and HFH compared with GLP-1RA and nsMRA. There were no significant differences between GLP-1RA and nsMRA in lowering primary and secondary outcomes.

This study showed that SGLT-2i were more efficacious in reducing HFH and CRO than GLP-1RA and nsMRA. Compared with GLP-1RA, the better efficacy of SGLT-2i may be explained by their ability to directly influence CV and renal outcomes beyond their effects through lowering glucose levels. For instance, the DAPA-HF and EMPEROR-Reduced trials demonstrated the efficacy of dapagliflozin and empagliflozin in lowering CV death and HFH in patients with heart failure with reduced ejection fraction regardless of diabetic and kidney status.[84,85] In addition, the DAPA-CKD and EMPA-KIDNEY trials showed evidence of renal protection with dapagliflozin and empagliflozin, which was independent of diabetes status.[29,30]

Among nsMRA, finerenone selectively inhibits mineralocorticoid receptors, which results in reductions in renal inflammation, fibrosis, and vasoconstriction.[21] However, these mechanisms could be insufficient for finerenone to have more benefits than SGLT-2i. This is because SGLT-2i not only have mechanisms similar to finerenone but also are related to glucosuria and natriuresis that contribute to glycemic control, weight loss, blood pressure-lowering, reductions in intraglomerular pressure as well as fluid overload.[16]

Our study found a moderate degree of heterogeneity for MACE and stroke. These results and existing evidence suggest specific-drug effects on MACE and stroke.[86] While canagliflozin and sotagliflozin significantly reduced risks of MACE and stroke, empagliflozin and dapagliflozin did not. However, these differences could be related to sample size because the number of patients treated with canagliflozin and sotagliflozin were higher than that of patients treated with empagliflozin and dapagliflozin. Additionally, heterogeneity for stroke can explain part of heterogeneity for MACE because MACE was a composite outcome of CV death, nonfatal MI, or nonfatal stroke. The heterogeneity for stroke could arise due to differences in stroke definitions in each trial. For example, the DECLARE-TIMI 58 trial only reported effects of dapagliflozin on ischemic stroke, while other trials for canagliflozin and sotagliflozin assessed effects of SGLT-2i on total stroke (including ischemic, hemorrhagic, and undetermined strokes).[35,64,70,71,87] The benefits of SGLT-2i on total stroke can come from reduction in hemorrhagic stroke because of lowering blood pressure of this class. High blood pressure leads to a higher risk of hemorrhagic stroke than ischemic stroke.[88,89]

Our sensitivity analyses showed that human GLP-1RA offered better cardiorenal protection than exendin-4 GLP-1RA. Several factors may explain this finding. First, from the pharmacodynamic perspective, compared to exendin-4 GLP-1RA, human GLP-1RA are compounds with endogenous structures that could easily activate GLP-1 receptors through

physiological pathways.[90] Further, exendin-4 GLP-1RA are eliminated through glomerular filtration to create inactive metabolites such as smaller peptides and amino acids, while human GLP-1RA are partially metabolized into active metabolites in target tissues through route of large proteins.[91] Second, there were differences in patient characteristics across human and exendin-4 GLP-1RA trials. For instance, the ELIXA trial evaluating efficacy of lixisenatide (an exendin-4 GLP-1RA) enrolled patients with recent acute coronary syndrome, while other trials did not.[37] The EXSCEL trial assessing the efficacy of exenatide (an exendin-4 GLP-1RA) had a high attrition rate of 40%.[81] Nevertheless, a recent trial of exendin-4 GLP-1RA of efpeglenatide suggested that this drug may be effective in reducing risks of CV and renal events in patients with T2D.[92] Unfortunately, we could not include efpeglenatide in this study because its data on efficacy in patients with T2D and CKD were not available.

Given the different mechanisms of actions of SGLT-2i, GLP-1RA, and nsMRA, combinations of these drugs may potentially enhance clinical benefits. A real-world evidence study and subgroup analyses from a trial have shown that combinations of SGLT-2i and GLP-1RA as well as finerenone and SGLT-2i or GLP-1RA may be efficacious in reducing CV events, although sample sizes of these groups are small.[22,93] Therefore, future individual trials should be conducted to assess these hypotheses. However, even if these combinations have promising results, high costs may be a barrier to their use in clinical practice.

This study has several limitations. First, inconsistency between indirect and direct comparisons could not be evaluated due to unavailability of data directly comparing SGLT-2i, GLP-1RA, and nsMRA. Second, this network meta-analysis included data from subgroup analyses in trials. There could be an imbalance between intervention and placebo groups that may bias the results. Additionally, the small number of patients in some subgroups can reduce power to detect statistical differences between intervention and placebo groups. Third, we did not compare

safety of drugs in this study. Fourth, our search strategy only included English publications, which may miss publications in other languages. Lastly, the trials included in this study varied in several aspects, including UACR values in the study sample, definitions of events, and follow-up durations.

2.6. Conclusion

This network meta-analysis found that SGLT-2i provided better cardiorenal protection than GLP-1RA and nsMRA in patients with T2D and CKD. There were no significant differences between GLP-1RA and nsMRA in reducing CV and renal outcomes.

Co-authorship Statement

I have co-authored this paper with my supervisor (Dr. Hai Nguyen), two supervisory committee members (Dr. Shweta Mital and Dr. Shawn Bugden), and Le Nguyen. I am the first author of this paper. I conceptualized the research idea, collected and analysed data, wrote the first draft, and revised the manuscript. Le Nguyen collected data. Dr. Shweta Mital and Dr. Shawn Bugden reviewed the manuscript. Dr. Hai Nguyen conceptualized the research idea and reviewed the manuscript.

Chapter 3. Cost-Effectiveness of Dapagliflozin and Canagliflozin in Patients with Type 2 Diabetes and Chronic Kidney Disease

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3.1. Abstract

Aims: This study examines the cost-effectiveness of adding canagliflozin or dapagliflozin to standard of care (SoC) versus SoC alone in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD)

Methods: We used a Markov microsimulation model to assess the cost-effectiveness of canagliflozin plus SoC (canagliflozin+SoC), dapagliflozin plus SoC (dapagliflozin+SoC), and SoC alone. Analyses were conducted from a healthcare system perspective over a lifetime horizon. Model inputs were derived from clinical trials and published literature using Canadian data. Costs were measured in 2021 Canadian dollars (C$), and effectiveness was measured in quality-adjusted life years (QALYs). All cost and QALYs were discounted at 1.5% per year.

Results: Over a patient's lifetime, canagliflozin+SoC was the most cost-effective treatment strategy. Canagliflozin+SoC yielded cost savings of C$33,460 and generated 1.38 additional QALYs compared with SoC alone. While QALY gains with dapagliflozin+SoC were higher than those with canagliflozin+SoC, this strategy was also more costly with the incremental cost-effectiveness ratio exceeding the willingness to pay threshold of C$50,000 per QALY. Dapagliflozin+SoC, however, generated cost savings and QALY gains compared with canagliflozin+SoC over shorter time horizons of 5 or 10 years. This result arose as dapagliflozin is more efficacious than canagliflozin in reducing short-term CV events and adverse events.

Conclusion: Dapagliflozin+SoC was not cost-effective versus canagliflozin+SoC in patients with T2D and CKD over the lifetime horizon. However, adding canagliflozin or dapagliflozin to SoC was less costly and more effective relative to SoC alone for treatment of T2D and CKD

3.2. Introduction

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are major public health challenges. Although there have been improvements in treatment of CKD and T2D, patients treated with standard of care (SoC), including renin-angiotensin system blockers and medications to control glycemia, blood pressure, and lipids, still have excess risks of cardiovascular (CV) events and kidney failure.[34] Sodium-glucose cotransporter 2 inhibitors (SGLT-2is), such as canagliflozin and dapagliflozin, have demonstrated cardiorenal protection in patients with CKD and T2D.[35,36] Recent guidelines for treatment of CKD and T2D recommend canagliflozin in combination with SoC (canagliflozin+SoC) or dapagliflozin in combination with SoC (dapagliflozin+SoC) to reduce mortality and CKD progression.[12]

However, given differences in clinical outcomes and healthcare costs, it is unclear whether canagliflozin or dapagliflozin should be prioritized as an add-on treatment to SoC from an economic standpoint. Compared with dapagliflozin, canagliflozin is more effective in reducing CKD progression and stroke but is less effective in reducing heart failure hospitalization (HFH), myocardial infarction (MI), dialysis, and all-cause death (ACD).[35,37,38] Patients treated with canagliflozin also have a greater risk of adverse events (AEs) than those treated with dapagliflozin.[17] Furthermore, canagliflozin+SoC costs C$1,000 more than dapagliflozin+SoC per year.[39]

There is limited evidence on the cost-effectiveness of canagliflozin+SoC, dapagliflozin+SoC, and SoC alone for treatment of CKD *and* T2D. Most previous studies examine the cost-effectiveness of these treatments for patients with either CKD or T2D.[41,42,94] To the extent that patients with both CKD and T2D face higher risks of CV and renal events as well as have greater healthcare costs than those with CKD or T2D, these studies are unable to shed light on the cost-effectiveness of these treatments for the specific group of patients with both CKD and

T2D. Only one study showed that canagliflozin+SoC was less costly and more effective than SoC alone in patients with CKD and T2D.[40] However, this study compared the cost-effectiveness of only canagliflozin+SoC versus SoC alone. No study has compared the cost-effectiveness of canagliflozin+SoC versus dapagliflozin+SoC in patients with CKD and T2D. This study fills this gap by examining the cost-effectiveness of canagliflozin+SoC, dapagliflozin+SoC, and SoC alone in patients with CKD and T2D.

3.3. Methods

3.3.1. Treatment strategies

This cost-effectiveness analysis compares three strategies. First, SoC alone is the guideline-directed medical therapy[14], including a renin-angiotensin system blocker and medications to control glycemia, blood pressure, and lipids. Second, canagliflozin+SoC is the use of canagliflozin 100 mg once daily in combination with SoC. Third, dapagliflozin+SoC is the use of dapagliflozin 100 mg once daily in combination with SoC. Treatment with canagliflozin and dapagliflozin would be permanently stopped when patients reach dialysis, or kidney transplant, or experience amputation or diabetic ketoacidosis.[20]

3.3.2. Study cohort

The study population was patients recruited in CREDENCE trial[35] for canagliflozin. The mean age and T2D duration of patients were 63 years and 15.8 years, respectively. This population had 33.9% of women and 14.5% with a history of smoking history. The percentage of patients with CVD was 10.0% for MI, 10.4% for stroke, and 14.8% for HFH. The mean estimated glomerular filtration rate (eGFR) value was 56.2 ml/minute/1.73 m2, while the median urine albumin-to-creatinine ratio (UACR) value was 927 mg/g. Details of patient characteristics are presented in Table A.2.1 (Appendix 2).

3.3.3. Model structure

We used a Markov microsimulation model to simulate a hypothetical cohort of 1,000 patients with T2D and CKD. The model comprised 8 health states that captured the CKD progression based on eGFR (mL/min/1.73 m^2): CKD 1 (eGFR ≥ 90), CKD 2 (90 > eGFR ≥ 60), CKD 3a (60 > eGFR ≥ 45), CKD 3b (45 > eGFR ≥ 30), CKD 4 (30 > eGFR ≥ 15), CKD 5 (15 > eGFR ≥ 10.5), dialysis (eGFR < 10.5), and post-kidney transplant.[34] Additionally, our model also captured the changes in UACR, including macroalbuminuria (30 ≤ UACR ≤ 300 mg/g) and microalbuminuria (UACR > 300 mg/g). In each health state, patients faced risks of MI, stroke, HFH, AEs, and ACD. ACD was further categorized into CV and non-CV death due to the effect of SGLT-2i on CV death. For each patient who remained alive, their clinical characteristics were updated before they entered the next cycle. The model used a lifetime horizon, and cycle length was 1 month. Details of the model are shown in Figure 3.1.

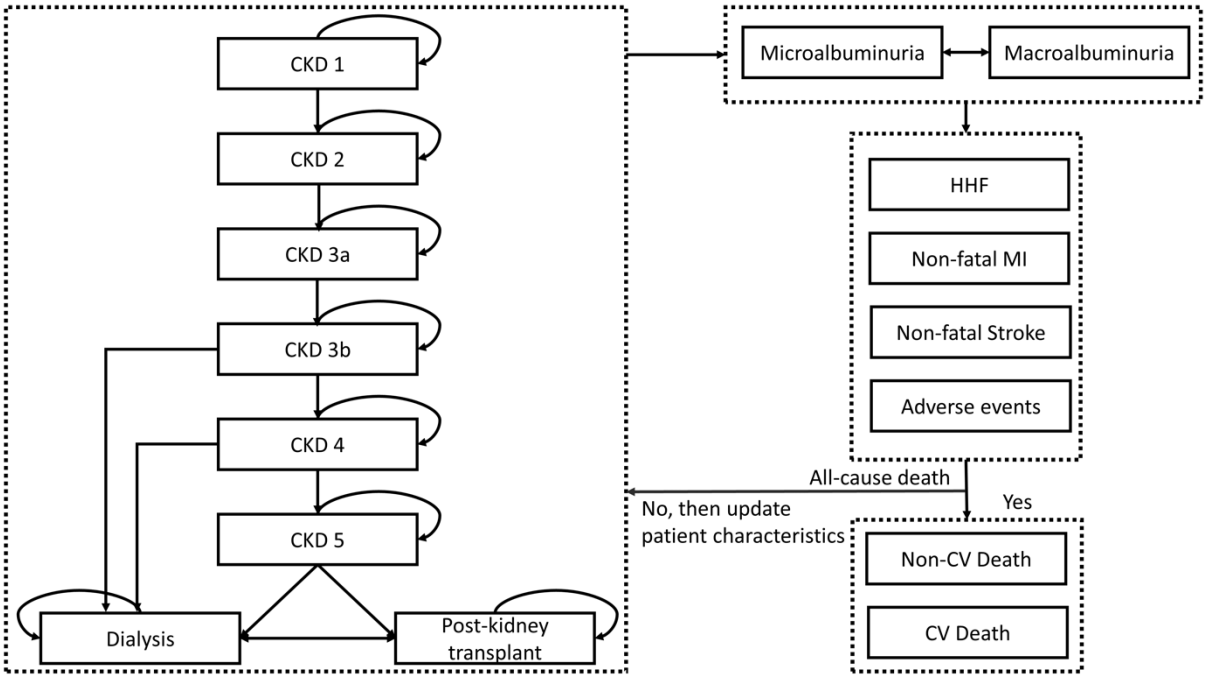

Figure 3.1. Markov model

CKD, chronic kidney disease; HFH, heart failure hospitalization; MI, myocardial infarction; CV cardiovascular.

3.3.4. Model inputs

Health state transitions and risk of events

Transitions of patients through health states were determined by eGFR values. The eGFR values in each cycle were calculated based on the rates of eGFR decline observed in the trials (Table A.2.2, Appendix 2).[35,36] Patients from CKD 3a to CKD 5 also faced risks of dialysis. Patients in CKD 5 or dialysis health states could require kidney transplants, and patients in post-kidney transplant health state could return to dialysis health state again. Additionally, patients could move between macroalbuminuria and microalbuminuria based on UACR decline. All transition probabilities were obtained from the published literature (Table A.2.3, Appendix 2).[4,95-97]

We used the validated CREDEM-DKD model[97] and other published studies[98-104] to calculate probabilities of HFH, MI, stroke, dialysis, and ACD in based on patients' characteristics in each cycle. We assumed that CV death accounted for 70% of ACD.[35] During treatment, patients also faced risks of AEs, such as diabetic ketoacidosis, severe hypoglycemia, volume depletion, acute kidney injury, fracture, amputation, urinary tract infection, and genital mycotic infection. Probabilities of AEs were obtained from the published literature (Table A.2.4, Appendix 2).[35,105]

Treatment effects

The effects of dapagliflozin and canagliflozin on eGFR, UACR, risk of CV events, dialysis, and ACD were obtained from subgroups of patients with CKD and T2D in the DAPA-CKD [38,105] and CREDENCE trials[35]. The patient characteristics of these subgroups were similar, which could contribute to the reliability of indirect comparisons. While eGFR values initially declined during the first 2-3 weeks of treatment with canagliflozin or dapagliflozin, rates of eGFR decline were subsequently lower than those with SoC alone.[35,36] Compared with

dapagliflozin, canagliflozin was associated with slower eGFR decline and lower risk of stroke.[35-37] However, canagliflozin was less effective in reducing UACR, HFH, MI, dialysis, ACD, and AEs than dapagliflozin.[17,35,37,38,106] Detailed information about treatment effects of canagliflozin and dapagliflozin is shown in Table A.2.2 and A.2.5 (Appendix 2).

In the base case analysis, we assumed that drug efficacy was maintained over the patient's lifetime. We varied this assumption in sensitivity analyses below. Treatment with SGLT-2is ceased when patients reached dialysis, or kidney transplant, or experienced amputation or diabetic ketoacidosis. The model also allowed for an annual SGLT-2i treatment discontinuation rate of 4.74%.[35]

Cost

Costs were estimated from the healthcare system perspective using Canadian data sources. Thus, only direct medical costs were considered. The model included costs of canagliflozin, dapagliflozin, SoC, healthcare management for CKD stages, CV events, and AEs (Table 3.1).[10,39,107-115] Drug costs were obtained from the Ontario Public Drug Program.[39] The cost of SoC was calculated based on the mix of drugs used by patients in the CREDENCE trial and the cost of these drugs[35] (Table A.2.6, Appendix 2). All costs were discounted at 1.5% per year[53] and inflated to 2021 Canadian dollars using the healthcare component of consumer price index.[116]

Table 3.1. The annual cost of treatment

Variable	Value	Standard error	Reference
Treatments			
Canagliflozin	1,055.94	264	[39]

Dapagliflozin	997.13	249	[39]
SoC	1,348.71	337	Appendix 2
Background management			
CKD 1/2	102	26	[107]
CKD 3a/3b	220	55	[107]
CKD 4	395	99	[107]
CKD 5 without dialysis	5,593	1,398	[107]
Diagnostic procedures for initial dialysis	621	155	[108]
Dialysis	72,436	18,109	[10]
Initial admission for kidney transplants	29,496	7,374	[109]
Post-kidney transplants			
First-year	84,076	21,019	[109]
Second year	28,636	7,159	[109]
After second year	26,131	6,533	[109]
CV events			
CV death	11,081	2,770	[110]
Nonfatal MI event	21,129	5,282	[110]
Post-MI	3,304	826	[110]
Nonfatal stroke event	28,780	7,195	[110]
Post-stroke	3,993	998	[110]
HFH event	19,329	4,832	[110]
Post-HFH	5,419	1,355	[110]
Adverse events			
Amputation	44,645	11,161	[110]

Post-amputation	6,115	1,529	[110]
Fracture	9,629	2,407	[111]
Diabetic ketoacidosis	6,829	1,707	[112]
Acute kidney injury	5,271	1,318	[113]
Severe hypoglycemia	2,324	581	[110]
Urinary tract infection	214	54	[114]
Volume depletion	69	17	[115]
Genital mycotic infection	43	11	[114]

All costs were calculated in 2021 Canadian dollars.
CKD, chronic kidney disease; CV cardiovascular; HFH, heart failure hospitalization; MI, myocardial infarction; SoC, standard of care.

Effectiveness

Effectiveness was measured by quality-adjusted life-years (QALYs). QALYs were estimated by multiplying utility values for each health state by the time patients spent in those health states. Utility and disutility values were obtained from studies, which directly elicited health state utilities from patients as well as published cost-effectiveness analyses. A baseline utility for patients with T2D was used; disutility values were then applied for CKD stages, CV events, and AEs (Table 3.2).[115,117-125] Given the long-term impacts of MI, stroke, HFH, and amputations, patients who experienced these events had a lower utility for the remainder of their lives.[110] All utility values were discounted at 1.5% per year.[53]

Table 3.2. Health state utility and event-specific disutility

Variable	Value	Standard error	Reference
Utility for diabetes	0.792	0.002	[117]
Disutility for CKD stages			
CKD 1/2	0	0	[118]
CKD 3a/3b	0.0300	0.0075	[118,119]
CKD 4	0.0500	0.0125	[118,119]
CKD 5	0.0600	0.0150	[118,119]
Dialysis	0.1800	0.0450	[118]
Transplant	0.0300	0.0075	[120]
Disutility for CV events			
Nonfatal MI event	0.0409	0.0002	[121]
Post-MI	0.0120	0.0003	[110]
Nonfatal stroke event	0.0524	0.0001	[121]
Post-stroke	0.0400	0.0002	[110]
HFH event	0.0635	0.0002	[121]
Post-HFH	0.0180	0.0002	[110]
Disutility for adverse events	**Value**	**Standard error**	**Reference**
Amputation[a]	0.2800	0.0700	[120]
Fracture	0.0390	0.0098	[117]
Diabetic ketoacidosis	0.0091	0.0023	[122]
Acute kidney injury	0.0240	0.0060	[123]
Severe hypoglycemia	0.0100	0.0025	[124]
Urinary tract infection	0.0043	0.0011	[125]

Volume depletion	0.0043	0.0011	[115]
Genital mycotic infection	0.0046	0.0012	[125]

[a]*Permanent disutility was applied for this event.*
CKD, chronic kidney disease; CV cardiovascular; HFH, heart failure hospitalization; MI, myocardial infarction.

3.3.5. Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) between two strategies is calculated by dividing their difference in cost by their difference in QALYs. A dominated strategy – one that is more expensive and produces fewer QALYs than another strategy – is excluded from the analysis. Among the remaining strategies, we considered a strategy to be cost-effective versus another strategy if its ICER was lower than the widely accepted willingness-to-pay (WTP) threshold of C$50,000 per QALY.[126]

To evaluate the robustness of our results, we conducted one-way sensitivity analyses in which we varied key variables over a range of ± 25%, including costs of canagliflozin, dapagliflozin, SoC, CV events, ACD, amputation, dialysis, and rates of eGFR decline. We also conducted threshold analyses to identify values of key inputs that would influence our results. Additionally, probabilistic sensitivity analyses were conducted with 1,000 iterations to assess the uncertainty of all parameters.

As the long-term efficacy of canagliflozin and dapagliflozin is unknown, we considered alternative scenarios for long-term efficacy of these drugs. First, we assumed that their efficacy in lowering MI, stroke, HFH, ACD, dialysis, eGFR and UACR declines would reduce by 3.5% each year after the first 2.5 years (the median follow-up duration of DAPA-CKD[29] and CREDENCE trials[35]) based on the impact of increase in age on the efficacy of SGLT-2is.[127,128] Second, we assessed the cost-effectiveness over shorter time horizons of 5, 10, and 20 years (instead of lifetime horizon in the base case). As SGLT-2is reduce CKD progression over time,

the use of alternative time horizons could influence the cost-effectiveness of treatment strategies under comparison.

All analyses were conducted using TreeAge Pro Healthcare 2022 R1.2.[129]

3.3.6. Ethics approval

This study used published data from the literature, so no ethics approval was required.

3.4. Results

3.4.1. Base case analysis

The cost-effectiveness results in base case are presented in Table 3.3. Panel A compares the cost-effectiveness of all treatment strategies. SoC alone was dominated by dapagliflozin+SoC as it cost more and yielded fewer QALYs. After excluding SoC alone, dapagliflozin+SoC cost more (C$216,770 versus C$210,073) and generated more QALYs (8.24 versus 8.18) compared with canagliflozin+SoC. However, dapagliflozin+SoC was not cost-effective versus canagliflozin+SoC, with an ICER of C$113,290 per QALY. Panel B shows that, compared with SoC alone, adding canagliflozin or dapagliflozin to SoC generated cost savings of C$33,460 and C$26,764 and yielded 1.38 and 1.44 more QALYs, respectively. These cost savings and QALYs gains arose primarily due to the efficacy of these SGLT-2is in delaying dialysis compared with SoC alone.

Table 3.3. Base case cost-effectiveness results

Strategy	Cost (C$)	Incremental costs (C$)	QALY	Incremental QALY	ICER
Panel A: All strategies					
Canagliflozin+SoC	210,073	-	8.18	-	-
Dapagliflozin+SoC	216,770	6,697	8.24	0.06	113,290
SoC	243,533	26,764	6.81	-1.44	Dominated
Panel B: SGLT-2 inhibitor+SoC versus SoC alone					
SoC	243,533	-	6.81	-	-
Canagliflozin+SoC	210,073	-33,460	8.18	1.38	Dominant
Dapagliflozin+SoC	216,770	-26,764	8.24	1.44	Dominant

All costs were calculated in 2021 Canadian dollars.
Base case analysis was conducted under the lifetime horizon.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; SoC, standard of care; SGLT-2, sodium-glucose cotransporter 2.

3.4.2. Sensitivity analyses

One-way sensitivity analysis results are illustrated in Figure 3.2. SoC alone continued to be dominated by canagliflozin+SoC and dapagliflozin+SoC when the values of key parameters were varied between +/- 25% of their base case values (Figure 3.2.A, 3.2.B). Furthermore, the ICER of dapagliflozin+SoC versus canagliflozin+SoC was most sensitive to drug efficacy in reducing eGFR decline, maintenance cost of dialysis, and costs of SGLT-2is (Figure 3.2.C). Especially, dapagliflozin+SoC would be cost-effective or dominant versus canagliflozin+SoC if the difference in eGFR decline between canagliflozin+SoC and dapagliflozin+SoC was less than 0.46 mL/min/1.73 m2/year.

Figure 3.2. Tornado diagram for one-way sensitivity analyses

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; MI, myocardial infarction; SoC, standard of care.
Blue bar is lower bound. Red bar is upper bound.

The results of probabilistic sensitivity analyses are shown in Figure 3.3. At the WTP threshold of C$50,000 per QALY, canagliflozin+SoC was cost-effective in 59% of iterations, while dapagliflozin+SoC was cost-effective in 41% of iterations. Additionally, the probabilities of being cost saving were 60.8% for canagliflozin+SoC and 38.9% for dapagliflozin+SoC.

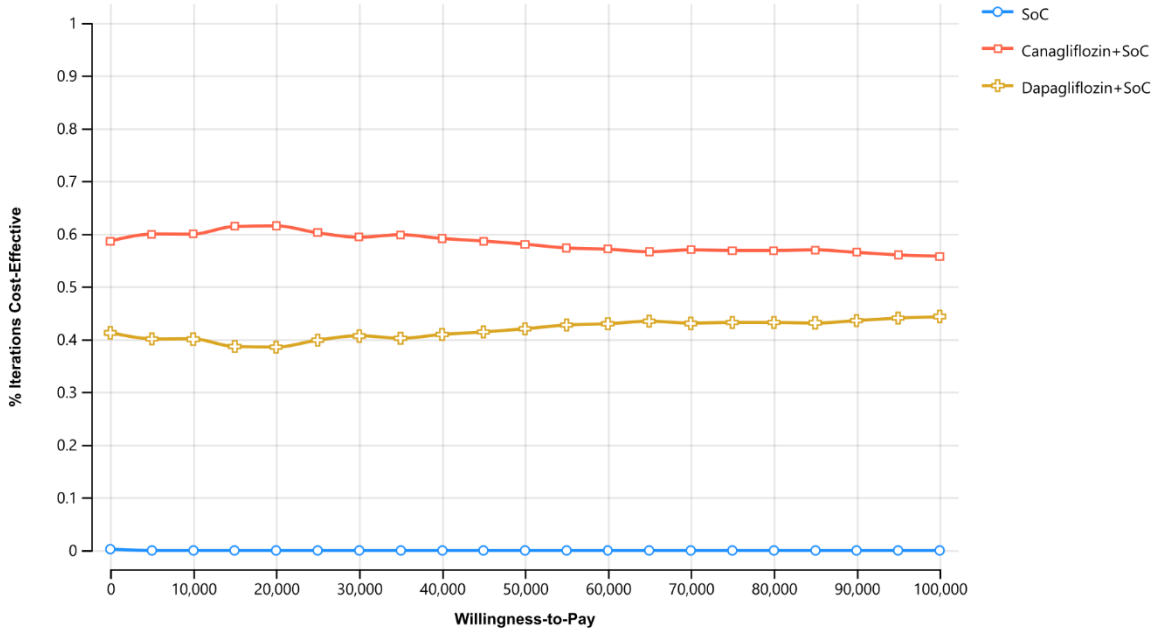

Figure 3.3. Cost-effectiveness acceptability curve of base case analysis

SoC, standard of care.

Results for scenario analyses are presented in Table A.2.7 (Appendix 2). If the efficacy of SGLT-2is in lowering MI, stroke, HFH, ACD, dialysis, eGFR and UACR declines was reduced by 3.5% per year after the first 2.5 years, the results remained similar in the base case. While the ICER was lower (C$76,087/QALY versus C$113,290/QALY in the base case), it still exceeded the WTP threshold of C$50,000/QALY. Over shorter time horizons of 5 and 10 years, dapagliflozin+SoC dominated canagliflozin+SoC. This result arose due to dapagliflozin's higher efficacy in reducing short-term CV events and AEs (Table A.2.8, Appendix 2). However, when the time horizon was extended to 20 years or lifetime, the higher efficacy of canagliflozin in slowing CKD progression (and thereby, lower dialysis costs) dominated the shorter-term benefits of dapagliflozin.

3.5. Discussion

This is the first study examining the cost-effectiveness of canagliflozin+SoC, dapagliflozin+SoC, and SoC for treatment of T2D and CKD. We found that adding canagliflozin or dapagliflozin to SoC yielded cost savings and gained more QALYs than SoC alone. Compared with canagliflozin+SoC, dapagliflozin+SoC cost less and was more effective over 5- and 10-year horizons but was not cost-effective over a lifetime horizon.

There are several studies evaluating the cost-effectiveness of SGLT-2i added to SoC in patients with CKD. Our study drew consistent conclusions with studies in England[40] and Thailand[41] demonstrating that canagliflozin+SoC and dapagliflozin+SoC were less costly and more effective than SoC in patients with CKD. However, another study showed that dapagliflozin+SoC was very cost-effective versus SoC alone in US patients with diabetic nephropathy, with the ICER of US$19,023 per QALY.[43] Our model included the effect of SGLT-2i on multiple AEs and CV events, dialysis, and high-risk population, which leads to differences in results between our study and cost-effectiveness analysis in US[43]. Generally, differences in model structure, assumptions, and inputs in different contexts make it difficult to directly compare the results of cost-effectiveness analyses.

Our finding of cost-savings of SGLT-2i compared with SoC alone highlights the economic benefits of adding these drugs for the treatment of T2D and CKD. With the annual incidence of approximately 17,000 patients with diabetic kidney disease and macroalbuminuria in Canada[3,130], treatment with canagliflozin or dapagliflozin could save C$512 million over the lifetime horizon. The economic benefits will become larger when lower-priced generic drugs are launched.

Aside from canagliflozin and dapagliflozin, empagliflozin is used for treatment of T2D and CKD. EMPA-REG OUTCOME and EMPA-KIDNEY trials showed that empagliflozin reduced CV events and CKD progression compared with SoC in patients with T2D and CKD.[30,131,132] However, we could not compare empagliflozin with canagliflozin and dapagliflozin as an add-on treatment in our study as patients with T2D and CKD in EMPA-REG OUTCOME trial[52,53] had different baseline characteristics from patients in the DAPA-CKD[38,105] and CREDENCE trials[35] and data for patients with T2D and CKD from the EMPA-KIDNEY trial[30] were unavailable. Future research should be conducted to shed light on the cost-effectiveness of canagliflozin, dapagliflozin, and empagliflozin in treating patients with T2D and CKD.

There are several limitations of our study. First, data from head-to-head trials of canagliflozin and dapagliflozin were not available. Furthermore, we had to rely on data from subgroups of patients with T2D and CKD in the DAPA-CKD[38,105] and CREDENCE trials[35]. Additionally, CREDENCE trial was stopped early at a planned analysis. Therefore, the efficacy of the drugs could therefore be underestimated or overestimated due to the small sample sizes of these patient subgroups. Second, baseline characteristics were randomly selected from separate distributions in the trial, ignoring possible correlations of these parameters. However, we note that no significant correlations were found in baseline characteristics in CREDENCE trial[97]. Third, long-term efficacy of canagliflozin and dapagliflozin is unknown and we had to assume that the efficacy of these drugs would be maintained beyond the trial duration. While we considered alternative scenarios in additional analyses, similar cost-effectiveness analyses utilizing long-term efficacy data may be conducted when such data become available in the future. Fourth, although our cost-effectiveness analysis was conducted in Canadian context, the study cohort was simulated based the population in CREDENCE trial[35] that recruited patients in several countries including Canada. Therefore, results of post-hoc analyses for Canadian population may be used to update our results.

Last, due to a lack of data, this study could not examine the cost-effectiveness of SGLT-2i in patients with T2D and CKD and microalbuminuria. This may be an area for further research.

3.6. Conclusion

Adding canagliflozin or dapagliflozin to SoC dominated SoC alone for treatment of T2D and CKD. While dapagliflozin+SoC was not cost-effective versus canagliflozin+SoC over a lifetime horizon, it was cost-effective over shorter time horizons of 5-10 years

Co-authorship Statement

I have co-authored this paper with my supervisor, Dr. Hai Nguyen, two supervisory committee members, Dr. Shweta Mital and Dr. Shawn Bugden. I am the first author of this paper. I conceptualized the research idea, collected and analysed data, wrote the first draft, and revised the manuscript. Dr. Shweta Mital and Dr. Shawn Bugden reviewed the manuscript. Dr. Hai Nguyen conceptualized the research idea and reviewed the manuscript.

Chapter 4. Summary and conclusion

4.1. Main findings

In Chapter 2, we conducted a systematic review and network meta-analysis to compare the relative effect of SGLT-2i, GLP-1RA, and nsMRA on CV and renal outcomes in patients with T2D and CKD. We found that SGLT-2i did not significantly reduce risks of MACE but were associated with significantly lower risks of CRO and HFH compared with GLP-1RA and nsMRA. There were no significant differences between GLP-1RA and nsMRA in lowering MACE, CRO, CV death, ACD, HFH, stroke, and MI.

In Chapter 3, we examined the cost-effectiveness of canagliflozin+SoC, dapagliflozin+SoC, and SoC alone in patients with T2D and CKD. We found that adding canagliflozin or dapagliflozin to SoC yielded cost savings and gained more QALYs than SoC alone. The cost savings were driven primarily by the efficacy of canagliflozin and dapagliflozin in delaying dialysis. The time horizon affected the cost-effectiveness result of dapagliflozin+SoC versus canagliflozin+SoC. Compared with canagliflozin+SoC, dapagliflozin+SoC was less costly and more effective over 5- and 10-year horizons but was not cost-effective over 20-year or lifetime horizons.

4.2. Limitations

Our network meta-analysis has several limitations. First, although all included studies were trials, most of them were only designed to examine the efficacy of drugs for treatment of CKD or T2D instead of both T2D and CKD. Therefore, our data were mainly obtained from subgroup analyses, which resulted in some outcomes with small sample sizes. It is possible that our network meta-analysis did not have sufficient statistical power to detect significant differences between interventions with a small number of participants. Second, we found several

differences in UACR values, definition of events, and follow-up durations, whereas other patient characteristics were similar across trials. However, there was no clear evidence that the transitivity assumption was violated, and the heterogeneity in the network was only low to moderate. Third, inconsistency was not examined in this network meta-analysis because of lack of head-to-head trials. Last, our network meta-analysis only focused on CV and renal events and did not compare AEs of treatments.

There are several limitations in our cost-effectiveness analysis. First, we assumed that efficacy of canagliflozin and dapagliflozin would be constant and maintained over lifetime horizon in the base case. This assumption is inevitable because long-term data about the efficacy of SGLT-2i is not available. However, sensitivity analyses with alternative scenarios showed that our results still hold. Second, data about efficacy of dapagliflozin were obtained from subgroup analyses, which could reduce statistical power to find small differences. Additionally, no head-to-head trials exist, so we used cross-trial comparisons to evaluate the relative efficacy of canagliflozin and dapagliflozin. Last, our study did not consider correlations between patient characteristics when they were assigned from their distributions in the trial. Nonetheless, the impact of these correlations on the results of model can be small because no significant correlations were found in baseline characteristics in CREDENCE trial.[97]

4.3. Implications of study findings

This thesis conducted different analyses (the systematic review and network meta-analysis and the cost-effectiveness analysis) to assess SGLT-2i, GLP-1RA, and nsMRA for treatment of T2D and CKD with the goal to inform clinical and policy decisions on these drugs based on the balance of costs and health outcomes. Our network meta-analysis filled the gap in the relative efficacy of SGLT-2i, GLP-1RA, and nsMRA in reducing CV and renal events in patients with T2D and CKD. Additionally, comparisons between individual drugs were also reported.

Clinical practitioners can use our results to develop treatment guidelines and personalize treatment plans. Our findings also provide valuable data on indirect comparisons of efficacy of SGLT-2i, GLP-1RA, and nsMRA in treating T2D and CKD to be used in health economic evaluations.

The findings from our cost-effectiveness analysis can be helpful for clinicians, policymakers, and other stakeholders to guide decisions on optimal regimen and design market access strategy. The cost savings and better effectiveness of SGLT-2i highlight their benefits compared with SoC alone for treatment of T2D and CKD. This finding is important because SGLT-2i have been under-prescribed. Only 14.9% of diabetic patients with CVD or CKD were treated with SGLT-2i in Canada.[133] Currently, SGLT-2i have been primarily used to improve glycemic control instead of reducing risks of CV and renal events.[3] The knowledge gap among clinicians and high costs of SGLT-2i are possible reasons for underuse of these drugs.[133] Therefore, our findings can help to promote the use of SGLT-2i for treatment of T2D and CKD. Our study also sheds light on the choice between canagliflozin and dapagliflozin in terms of cost and effectiveness, which can help inform clinicians' and patients' treatment decisions.

There are several recommendations in terms of clinical practice and policy in Canada. First, it is important to update treatment guidelines for management of T2D and CKD, especially when many new evidence and trials have been published recently. The latest guideline for this specific population was conducted in 2018 in Canada.[14] Second, health economic reports of SGLT-2i in patients with T2D and CKD should be re-examined because of new benefits of this drug class. Last, the reimbursement status of SGLT-2i varies markedly across provinces.[44] Therefore, it is necessary to understand the reasons for this situation to improve the national health equity.

4.4. Future research

The network meta-analysis and cost-effectiveness analysis conducted in this thesis revealed several important dimensions for further research. First, future studies could examine the efficacy of combinations of SGLT-2i, GLP-1RA, and nsMRA. These three classes have different mechanisms of action and no drug-drug interactions, so their combinations might potentially increase the efficacy in reducing CV and renal events. Subgroup analyses of existing trials have suggested additive effects of these drugs in reducing MACE and HFH, but these results did not reach statistical differences due to small sample size.[22,93] Furthermore, as these drug combinations may be potentially expensive, cost-effectiveness analyses could be conducted to identify the population that can benefit most from the combination of these drugs.

Second, there is limited evidence on the efficacy of SGLT-2i, GLP-1RA, and nsMRA in CKD patients without albuminuria or with microalbuminuria. Most trials recruited CKD participants with macroalbuminuria.[23,30,35] Additionally, a majority of evidence on the efficacy of SGLT-2i and GLP-1RA in CKD patients in reduction of renal outcomes comes from subgroup analyses of trials that have MACE as the primary endpoint in patients with T2D.

Last, head-to-head trials or indirect comparisons with individual patient-level data should be conducted to overcome limitations around transitivity assumptions. Further, real-world evidence studies are necessary to assess the long-term effectiveness and safety of SGLT-2i, GLP-1RA, and nsMRA beyond trials.

4.5. Conclusion

The systematic review and network meta-analysis is a comprehensive approach to making direct and indirect comparisons between multiple interventions, especially when no head-to-

head trial exists. Combined with network meta-analysis, cost-effectiveness analysis may guide optimal treatment based on the balance between clinical outcomes and costs.

The network meta-analysis in this thesis demonstrated that SGLT-2i provided better cardiorenal protection than GLP-1RA and nsMRA in patients with T2D and CKD. There were no significant differences between GLP-1RA and nsMRA in reducing MACE, CRO, CV death, ACD, HFH, stroke, and MI.

Treatment with canagliflozin or dapagliflozin as an add-on to SoC cost less and was more effective than SoC alone for treatment of T2D and CKD. The cost savings were driven primarily by the efficacy of canagliflozin and dapagliflozin in delaying dialysis. Dapagliflozin+SoC was less costly and more effective than canagliflozin+SoC over the short-term horizon, but it was not cost-effective versus canagliflozin+SoC over the long-term horizon.

References

1. International Diabetes Federation. IDF Diabetes Atlas—10th Edition. 2021; https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf.

2. Canada OD. Diabetes in Canada: Backgrounder. 2022; https://www.diabetes.ca/DiabetesCanadaWebsite/media/Advocacy-and-Policy/Backgrounder/2022_Backgrounder_Canada_English_1.pdf.

3. Chu L, Fuller M, Jervis K, Ciaccia A, Abitbol A. Prevalence of Chronic Kidney Disease in Type 2 Diabetes: The Canadian REgistry of Chronic Kidney Disease in Diabetes Outcomes (CREDO) Study. *Clinical therapeutics.* 2021;43(9):1558-1573.

4. Canadian Institute for Health Information. Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register, 2010 to 2019: End-Stage Kidney Disease and Kidney Transplants. 2020; https://www.cihi.ca/en.

5. Wyld MLR, Morton RL, Aouad L, Magliano D, Polkinghorne KR, Chadban S. The impact of comorbid chronic kidney disease and diabetes on health-related quality-of-life: a 12-year community cohort study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2021;36(6):1048-1056.

6. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *Journal of the American Society of Nephrology : JASN.* 2013;24(2):302-308.

7. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney international.* 2020;98(4s):s1-s115.

8. Manns B, McKenzie SQ, Au F, Gignac PM, Geller LI. The Financial Impact of Advanced Kidney Disease on Canada Pension Plan and Private Disability Insurance Costs. *Can J Kidney Health Dis.* 2017;4:2054358117703986.

9. Manns B, Hemmelgarn B, Tonelli M, et al. The Cost of Care for People With Chronic Kidney Disease. *Can J Kidney Health Dis.* 2019;6:2054358119835521.

10. Beaudry A, Ferguson TW, Rigatto C, Tangri N, Dumanski S, Komenda P. Cost of Dialysis Therapy by Modality in Manitoba. *Clinical journal of the American Society of Nephrology : CJASN.* 2018;13(8):1197-1203.

11. Committee ADAPP. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes care.* 2021;45(Supplement_1):S17-S38.

12. de Boer IH, Khunti K, Sadusky T, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes care.* 2022;45(12):3075-3090.

13. Mottl AK, Alicic R, Argyropoulos C, et al. KDOQI US Commentary on the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD. *American Journal of Kidney Diseases.* 2022;79(4):457-479.

14. Philip McFarlane MD P, FRCPC, David Cherney MD, PhD, FRCPC, Richard E. Gilbert MBBS, PhD, FACP, FRACP, FRCPC, Peter Senior MBBS, PhD, FRCP. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Chronic Kidney Disease in Diabetes. *Can J Diabetes.* 2018(42):S201–S209.

15. Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care.* 2022. https://doi.org/10.2337/dci22-0034.

16. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2020;75(4):422-434.

17. Qiu M, Ding L-L, Zhang M, Zhou H-R. Safety of four SGLT2 inhibitors in three chronic diseases: A meta-analysis of large randomized trials of SGLT2 inhibitors. *Diabetes & vascular disease research.* 2021;18(2):14791641211011016.

18. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell metabolism.* 2018;27(4):740-756.

19. Yang S, Lin C, Zhuo X, et al. Glucagon-like peptide-1 alleviates diabetic kidney disease through activation of autophagy by regulating AMP-activated protein kinase-mammalian target of rapamycin pathway. *Am J Physiol Endocrinol Metab.* 2020;319(6):E1019-E1030.

20. American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes—2022. *Diabetes care.* 2021;45(Supplement_1):S175-S184.

21. Yang P, Huang T, Xu G. The novel mineralocorticoid receptor antagonist finerenone in diabetic kidney disease: Progress and challenges. *Metabolism: clinical and experimental.* 2016;65(9):1342-1349.

22. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *European heart journal.* 2021;43(6):474-484.

23. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *The New England journal of medicine.* 2020;383(23):2219-2229.

24. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *The New England journal of medicine.* 2021;385(24):2252-2263.

25. Zhang Y, Jiang L, Wang J, et al. Network meta-analysis on the effects of finerenone versus SGLT2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus and chronic kidney disease. *Cardiovascular diabetology.* 2022;21(1):232.

26. Giugliano D, Longo M, Signoriello S, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. *Cardiovascular diabetology.* 2022;21(1):42.

27. Yamada T, Wakabayashi M, Bhalla A, et al. Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. *Cardiovascular diabetology.* 2021;20(1):14.

28. Zhao LM, Zhan ZL, Ning J, Qiu M. Network Meta-Analysis on the Effects of SGLT2 Inhibitors Versus Finerenone on Cardiorenal Outcomes in Patients With Type 2 Diabetes and Chronic Kidney Disease. *Frontiers in pharmacology.* 2021;12:751496.

29. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *The New England journal of medicine.* 2020;383(15):1436-1446.

30. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine.* 2022;388(2):117-127.

31. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. *Nature Medicine.* 2022;28(1):89-95.

32. Haneda M, Seino Y, Inagaki N, et al. Influence of Renal Function on the 52-Week Efficacy and Safety of the Sodium Glucose Cotransporter 2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus. *Clinical therapeutics.* 2016;38(1):66-88.e20.

33. Allegretti AS, Zhang W, Zhou W, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2019;74(3):328-337.

34. de Boer IH, Caramori ML, Chan JCN, et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney international.* 2020;98(4):S1-S115.

35. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *The New England journal of medicine.* 2019;380(24):2295-2306.

36. Heerspink HJL, Jongs N, Chertow GM, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *The lancet Diabetes & endocrinology.* 2021;9(11):743-754.

37. Nguyen BN, Nguyen L, Mital S, Bugden S, Nguyen HV. Comparative Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists, and Nonsteroidal Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease and Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. *Diabetes, obesity & metabolism.* 2023. doi: 10.1111/dom.15009.

38. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *The lancet Diabetes & endocrinology.* 2021;9(1):22-31.

39. Ontario Ministry of Health Long-term Care. Ontario Drug Benefit Formulary/Comparative Drug Index, effective from May 31, 2022. 2022; https://www.formulary.health.gov.on.ca/formulary/.

40. Willis M, Nilsson A, Kellerborg K, et al. Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2021;12(1):313-328.

41. Vareesangthip K, Deerochanawong C, Thongsuk D, Pojchaijongdee N, Permsuwan U. Cost–Utility Analysis of Dapagliflozin as an Add-on to Standard of Care for Patients with Chronic Kidney Disease in Thailand. *Advances in therapy.* 2022;39(3):1279-1292.

42. Tisdale RL, Cusick MM, Aluri KZ, et al. Cost-Effectiveness of Dapagliflozin for Non-diabetic Chronic Kidney Disease. *Journal of general internal medicine.* 2022;37(13):3380-3387.

43. Abegaz TM, Diaby V, Sherbeny F, Ali AA. Cost Effectiveness of Dapagliflozin Added to Standard of Care for the Management of Diabetic Nephropathy in the USA. *Clinical drug investigation.* 2022;42(6):501-511.

44. Ottawa: CADTH. Reimbursement of Newer Drugs for Type 2 Diabetes in Canada: An Environmental Scan. 2019; https://www.cadth.ca/sites/default/files/pdf/es0337-reimbursement-t2d-drugs.pdf.

45. Ontario Ministry of Health Long-term Care. Ontario Drug Benefit Formulary/Comparative Drug Index, effective from March 17, 2023. 2023; https://www.formulary.health.gov.on.ca/formulary/.

46. Newfoundland and Labrador Prescription Drug Program. NLPDP Coverage Status Table. 2023; https://www.health.gov.nl.ca/health/prescription/coverage_status_table.pdf.

47. Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Undertaking network meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions.*2019:285-320.

48. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Internal and Emergency Medicine.* 2017;12(1):103-111.

49. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.

50. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology.* 2015;15(1):58.

51. Phillips MR, Steel DH, Wykoff CC, et al. A clinician's guide to network meta-analysis. *Eye.* 2022;36(8):1523-1526.

52. Gray A, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Healthcare.* Oxford University Press; 2010.

53. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 2017; https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

54. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health.* 2012;15(6):812-820.

55. Deng Y, Li N, Wu Y, et al. Global, Regional, and National Burden of Diabetes-Related Chronic Kidney Disease From 1990 to 2019. *Frontiers in endocrinology.* 2021;12:672350.

56. American Diabetes Association Professional Practice Committee. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2022. *Diabetes care.* 2021;45(Supplement_1):S125-S143.

57. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet Diabetes & Endocrinology.* 2019;7(10):776-785.

58. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet.* 2019;393(10166):31-39.

59. Wada T, Mori-Anai K, Takahashi A, et al. Effect of canagliflozin on the decline of estimated glomerular filtration rate in chronic kidney disease patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study in Japan. *Journal of diabetes investigation.* 2022;13(12):1981-1989.

60. Haneda M, Seino Y, Inagaki N, et al. Influence of Renal Function on the 52-Week Efficacy and Safety of the Sodium Glucose Cotransporter 2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus. *Clinical therapeutics.* 2016;38(1):66-88.e20.

61. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.

62. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2022; https://www.R-project.org/.

63. Chaimani A, Salanti G. Visualizing Assumptions and Results in Network Meta-analysis: The Network Graphs Package. *The Stata Journal.* 2015;15(4):905-950.

64. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *The New England journal of medicine.* 2021;384(2):129-139.

65. Cherney DZI, Ferrannini E, Umpierrez GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. *Diabetes, Obesity and Metabolism.* 2021;23(12):2632-2642.

66. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *The New England journal of medicine.* 2020;383(15):1425-1435.

67. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *The lancet diabetes & endocrinology.* 2014;2(5):369-384.

68. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *The New England journal of medicine.* 2016;375(4):323-334.

69. Pollock C, Stefánsson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *The Lancet Diabetes & Endocrinology.* 2019;7(6):429-441.

70. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2019;380(4):347-357.

71. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England journal of medicine.* 2017;377(7):644-657.

72. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes, Obesity and Metabolism.* 2014;16(10):1016-1027.

73. Häring H-U, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes care.* 2013;36(11):3396-3404.

74. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney international.* 2018;93(1):231-244.

75. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney international.* 2014;85(4):962-971.

76. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *The Lancet.* 2019;394(10193):131-138.

77. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *The New England journal of medicine.* 2015;373(23):2247-2257.

78. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *The Lancet.* 2018;392(10157):1519-1529.

79. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine.* 2019;381(9):841-851.

80. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *The New England journal of medicine.* 2016;375(19):1834-1844.

81. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2017;377(13):1228-1239.

82. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2017;377(9):839-848.

83. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): a Randomized Clinical Trial. *Diabetes care.* 2016;39(2):222-230.

84. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *The New England journal of medicine.* 2020;383(15):1413-1424.

85. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *The New England journal of medicine.* 2019;381(21):1995-2008.

86. Giugliano D, Esposito K. Class effect for SGLT-2 inhibitors: a tale of 9 drugs. *Cardiovascular diabetology.* 2019;18(1):94.

87. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine.* 2015;373(22):2117-2128.

88. Zhou Z, Jardine MJ, Li Q, et al. Effect of SGLT2 Inhibitors on Stroke and Atrial Fibrillation in Diabetic Kidney Disease. *Stroke.* 2021;52(5):1545-1556.

89. Tsai W-H, Chuang S-M, Liu S-C, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. *Scientific reports.* 2021;11(1):15364.

90. Longato E, Di Camillo B, Sparacino G, Tramontan L, Avogaro A, Fadini GP. Cardiovascular effectiveness of human-based vs. exendin-based glucagon like peptide-1 receptor agonists: a retrospective study in patients with type 2 diabetes. *European journal of preventive cardiology.* 2020;28(1):22-29.

91. Górriz JL, Soler MJ, Navarro-González JF, et al. GLP-1 Receptor Agonists and Diabetic Kidney Disease: A Call of Attention to Nephrologists. *J Clin Med.* 2020;9(4):947.

92. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *The New England journal of medicine.* 2021;385(10):896-907.

93. Wright AK, Carr MJ, Kontopantelis E, et al. Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes. *Diabetes care.* 2022;45(4):909-918.

94. Reifsnider OS, Kansal AR, Gandhi PK, et al. Cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or standard of care in patients with type 2 diabetes and established cardiovascular disease. *BMJ open diabetes research & care.* 2021;9(1):e001313.

95. Elbasha E, Greaves W, Roth D, Nwankwo C. Cost-effectiveness of elbasvir/grazoprevir use in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease in the United States. *J Viral Hepat.* 2017;24(4):268-279.

96. Manns B, Hemmelgarn B, Tonelli M, et al. Population based screening for chronic kidney disease: cost effectiveness study. *BMJ.* 2010;341:c5869.

97. Willis M, Asseburg C, Slee A, Nilsson A, Neslusan C. Development and Internal Validation of a Discrete Event Simulation Model of Diabetic Kidney Disease Using CREDENCE Trial Data. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2020;11(11):2657-2676.

98. Abbott KC, Hypolite IO, Hshieh P, Cruess D, Taylor AJ, Agodoa LY. Hospitalized Congestive Heart Failure after Renal Transplantation in the United States. *Annals of Epidemiology.* 2002;12(2):115-122.

99. Ribic CM, Holland D, Howell J, et al. Study of Cardiovascular Outcomes in Renal Transplantation: A Prospective, Multicenter Study to Determine the Incidence of

Cardiovascular Events in Renal Transplant Recipients in Ontario, Canada. *Can J Kidney Health Dis.* 2017;4:2054358117713729.

100. Abedini S, Holme I, Fellström B, et al. Cerebrovascular Events in Renal Transplant Recipients. *Transplantation.* 2009;87(1):112-117.

101. Tonelli M, Klarenbach S, Manns B, et al. Residence location and likelihood of kidney transplantation. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2006;175(5):478-482.

102. United States Renal Data System. 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. 2021; https://adr.usrds.org/2021.

103. Sun CY, Sung JM, Wang JD, et al. A comparison of the risk of congestive heart failure-related hospitalizations in patients receiving hemodialysis and peritoneal dialysis - A retrospective propensity score-matched study. *PLOS ONE.* 2019;14(10):e0223336.

104. Winkelmayer WC, Hurley MP, Liu J, Brookhart MA. Altitude and the risk of cardiovascular events in incident US dialysis patients. *Nephrology Dialysis Transplantation.* 2012;27(6):2411-2417.

105. Persson F, Rossing P, Vart P, et al. Efficacy and Safety of Dapagliflozin by Baseline Glycemic Status: A Prespecified Analysis From the DAPA-CKD Trial. *Diabetes care.* 2021;44(8):1894-1897.

106. Jongs N, Greene T, Chertow GM, et al. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *The lancet Diabetes & endocrinology.* 2021;9(11):755-766.

107. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Review Report: Sodium Zirconium Cyclosilicate (Lokelma). 2020; https://www.ncbi.nlm.nih.gov/books/NBK563722/.

108. Ontario Ministry of Health Long-term Care. Schedule of Benefits Physician Services Under the Health Insurance Act (Effective November 1, 2021). 2022; https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master.pdf.

109. Barnieh L, Yilmaz S, McLaughlin K, Hemmelgarn BR, Klarenbach S, Manns BJ. The Cost of Kidney Transplant over Time. *Progress in Transplantation.* 2014;24(3):257-262.

110. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. New drugs for type 2 diabetes: second-line therapy – science report. 2017; https://www.cadth.ca/sites/default/files/pdf/TR0012_T2D_Science_Report.pdf.

111. Blackhouse G, Gaebel K, Xie F, et al. Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Canada. *Cost Effectiveness and Resource Allocation.* 2010;8(1):14.

112. Fernando SM, Bagshaw SM, Rochwerg B, et al. Comparison of outcomes and costs between adult diabetic ketoacidosis patients admitted to the ICU and step-down unit. *Journal of Critical Care.* 2019;50:257-261.

113. Silver SA, Harel Z, McArthur E, et al. 30-Day Readmissions After an Acute Kidney Injury Hospitalization. *The American journal of medicine.* 2017;130(2):163-172.e164.

114. Sabapathy S, Neslusan C, Yoong K, Teschemaker A, Johansen P, Willis M. Cost-effectiveness of Canagliflozin versus Sitagliptin When Added to Metformin and Sulfonylurea in Type 2 Diabetes in Canada. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharmacologie clinique.* 2016;23(2):e151-168.

115. McEwan P, Darlington O, McMurray JJV, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *European journal of heart failure.* 2020;22(11):2147-2156.

116. Statistics Canada. Table 18-10-0005-01 Consumer Price Index, annual average, not seasonally adjusted. 2022; https://doi.org/10.25318/1810000501-eng.

117. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. *Value in Health.* 2016;19(8):1002-1008.

118. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney international.* 2005;68(6):2801-2808.

119. Jesky MD, Dutton M, Dasgupta I, et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. *PLOS ONE.* 2016;11(11):e0165675.

120. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of Utility Values for Economic Modeling in Type 2 Diabetes. *Value in Health.* 2014;17(4):462-470.

121. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.

122. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. *Med Decis Making.* 2016;36(8):1020-1033.

123. Nisula S, Vaara ST, Kaukonen K-M, et al. Six-month survival and quality of life of intensive care patients with acute kidney injury. *Crit Care.* 2013;17(5):1-8.

124. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Third-Line Pharmacotherapy for Type 2 Diabetes. 2013; https://www.ncbi.nlm.nih.gov/books/NBK361974/.

125. Shingler S, Fordham B, Evans M, et al. Utilities for treatment-related adverse events in type 2 diabetes. *Journal of medical economics.* 2015;18(1):45-55.

126. Griffiths EA, Vadlamudi NK. Cadth's $50,000 Cost-Effectiveness Threshold: Fact or Fiction? *Value in Health.* 2016;19(7):A488-A489.

127. Chan GC-K, Ng JK-C, Chow K-M, Szeto C-C. SGLT2 inhibitors reduce adverse kidney and cardiovascular events in patients with advanced diabetic kidney disease: A population-based propensity score-matched cohort study. *Diabetes research and clinical practice.* 2023;195:110200.

128. Scheen AJ. Cardiovascular and renal outcomes with SGLT2 inhibitors: Real-life observational studies in older patients with type 2 diabetes: SGLT2 inhibitors in elderly and real life. *Diabetes Epidemiology and Management.* 2023;10:100135.

129. TreeAge Software. TreeAge Pro Healthcare 2021, R1. 2022; https://www.treeage.com/.

130. LeBlanc AG, Jun Gao Y, McRae L, Pelletier C. At-a-glance - Twenty years of diabetes surveillance using the Canadian Chronic Disease Surveillance System. *Health promotion and chronic disease prevention in Canada : research, policy and practice.* 2019;39(11):306-309.

131. Wanner C, Heerspink HJL, Zinman B, et al. Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial. *Journal of the American Society of Nephrology : JASN.* 2018;29(11):2755-2769.

132. Wanner C, Lachin JM, Inzucchi SE, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. *Circulation.* 2018;137(2):119-129.

133. Hao R, Myroniuk T, McGuckin T, et al. Underuse of cardiorenal protective agents in high-risk diabetes patients in primary care: a cross-sectional study. *BMC Primary Care.* 2022;23(1):124.

134. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2016;375(4):311-322.

135. United States Renal Data System. *2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021.

136. McIntosh B, Cameron C, Singh SR, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. *Open medicine : a peer-reviewed, independent, open-access journal.* 2011;5(1):e35-48.

137. BC Guidelines. Diabetes Care. 2021; https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/diabetescare_guideline_full_2021.pdf.

138. BC Guidelines. Cardiovascular Disease - Primary Prevention. 2021; https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/gpac_cardiovasculardisease_appendixd_dec2021.pdf.

139. Sakaan SA, Hudson JQ, Oliphant CS, et al. Evaluation of Warfarin Dose Requirements in Patients with Chronic Kidney Disease and End-Stage Renal Disease. *Pharmacotherapy.* 2014;34(7):695-702.

140. Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. *Clinical cardiology.* 2019;42(8):774-782.

141. BC Guidelines. Hypertension – Diagnosis and Management 2021; https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/htn-full-guideline.pdf.

142. BC Guidelines. Heart Failure. 2021; https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/bc-guidelines/heart_failure_appendix_a.pdf.

143. Cameron C, Virani A, Dean H, Evans M, Dolovich L, Dahl M. Utilization and Expenditure on Blood Glucose Test Strips in Canada. *Canadian Journal of Diabetes.* 2010;34(1):34-40.

Appendices

Appendix 1: Appendix to Chapter 2

A1.1. Search strategies

Pubmed:

Population:

("diabetes mellitus, type 2"[MeSH] OR "diabetes mellitus type 2"[tiab] OR "type 2 diabetes mellitus"[tiab] OR "T2D"[tiab] OR "T2DM" OR “renal insufficiency, chronic”[MeSH] OR “chronic kidney disease”[tiab] OR “CKD”[tiab] OR “kidney disease”[tiab] OR “kidney failure”[tiab] OR “chronic kidney failure”[tiab] OR “renal failure”[tiab] OR “chronic renal disease”[tiab])

Intervention and comparison

((“Sodium-Glucose Transporter 2 Inhibitor*”[MeSH] OR “SGLT-2*”[tiab] OR “SGLT2*”[tiab] OR “canagliflozin”[tiab] OR “dapagliflozin”[tiab] OR “empagliflozin”[tiab] OR “ipragliflozin”[tiab] OR “tofogliflozin”[tiab] OR “luseogliflozin”[tiab] OR “remogliflozin”[tiab] OR “ertugliflozin”[tiab] OR “sotagliflozin”[tiab] OR “bexagliflozin”[tiab]) OR

(“Glucagon-Like Peptide-1 Receptor”[MeSH] OR “GLP-1*”[tiab] OR “GLP1*”[tiab] OR “Efpeglenatide”[tiab] OR “Dulaglutide”[tiab] OR “Semaglutide”[tiab] OR “Taspoglutide”[tiab] OR “Albiglutide”[tiab] OR “tirzepatide”[tiab] OR “Liraglutide”[tiab] OR “Lixisenatide”[tiab] OR “Exenatide”) OR

("Mineralocorticoid Receptor Antagonists"[MeSH] OR "nonsteroidal mineralocorticoid receptor antagonists"[tiab] OR "non-steroidal mineralocorticoid receptor antagonists"[tiab] OR "Nonsteroidal MRA*"[tiab] OR "MRA"[tiab] OR "finerenone" OR "esaxerenone" OR "apararenone"[tiab]))

Outcomes

(“cardiovascular death”[tiab] OR “cardiovascular events”[tiab] OR “major adverse cardiovascular event*”[tw] OR “MACE*”[tiab] OR “cardiac events”[tiab] OR “all-cause death”[tiab] OR “stroke”[tiab] OR “myocardial infarction”[tiab] OR “heart failure”[tiab] OR “renal death”[tiab], OR “renal outcomes”[tiab] OR “kidney outcomes”[tiab] OR “decline in eGFR”[tiab] OR “end-stage kidney disease”[tiab] OR “ESKD”[tiab] OR “end stage renal disease”[tiab] OR “ESRD”[tiab] OR “acute kidney injury”[tiab] OR “acute kidney failure”[tiab] OR “kidney transplantation”[tiab])

Study design:

(randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh] OR randomly [tiab] OR trial [ti] NOT (animals [mh] NOT humans [mh]))

EMBASE

#105 #37 AND #50 AND #82 AND #105 AND [english]/lim AND [embase]/lim AND [31-7-1900]/sd NOT [25-11-2022]/sd

#104 #37 AND #50 AND #82 AND #105

#103 #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102

#102 'kidney transplantation':ab,ti

#101 'acute kidney failure':ab,ti

#100 'acute kidney injury':ab,ti

#99 'eskd':ab,ti

#98 'end stage renal disease':ab,ti

#97 'end-stage kidney disease':ab,ti

#96 'loss of kidney function':ab,ti

#95 'decline in egfr':ab,ti

#94 'kidney outcomes':ab,ti

#93 'renal outcomes':ab,ti

#92 'renal death':ab,ti

#91 'cardiac events':ab,ti

#90 'heart failure':ab,ti

#89 'myocardial infarction':ab,ti

#88 'stroke':ab,ti

#87 'all-cause death':ab,ti

#86 'mace':ab,ti

#85 'major adverse cardiovascular event'/exp OR 'major adverse cardiovascular events':ab,ti

#84 'cardiovascular events':ab,ti

#83 'cardiovascular death':ab,ti

#82 #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81

#81 'apararenone':ab,ti

#80 'esaxerenone':ab,ti

#79 'finerenone':ab,ti

#78 'mra':ab,ti

#77 'nonsteroidal mra':ti,ab

#76 'non-steroidal mineralocorticoid receptor antagonists':ab,ti

#75 'nonsteroidal mineralocorticoid receptor antagonists':ab,ti

#74 'mineralocorticoid antagonist'/exp OR 'mineralocorticoid antagonist'

#73 'exenatide':ab,ti OR 'tirzepatide':ab,ti

#72 'lixisenatide':ab,ti

#71 'liraglutide':ab,ti

#70 'semaglutide':ab,ti

#69 'dulaglutide':ab,ti

#68 'efpeglenatide':ab,ti OR 'albiglutide':ab,ti OR 'taspoglutide':ab,ti

#67 'glp1':ab,ti

#66 'glp-1':ab,ti

#65 'glucagon like peptide 1'/exp OR 'glucagon like peptide 1'

#64 'glucagon like peptide 1 receptor agonist'/exp OR 'glucagon like peptide 1 receptor agonist'

#63 'bexagliflozin':ab,ti

#62 'sotagliflozin':ab,ti

#61 'ertugliflozin':ab,ti

#60 'remogliflozin':ab,ti

#59 'luseogliflozin':ab,ti

#58 'tofogliflozin':ab,ti

#57 'ipragliflozin':ab,ti

#56 'empagliflozin':ab,ti

#55 'dapagliflozin':ab,ti

#54 'canagliflozin':ab,ti

#53 'sglt-2*':ab,ti

#52 'sglt2':ab,ti

#51 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose transporter 2 inhibitor'

#50 #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49

#49 'chronic renal disease':ab,ti

#48 'ckd':ab,ti

#47 'renal failure':ab,ti

#46 'chronic kidney failure':ab,ti

#45 'kidney failure':ab,ti

#44 'kidney disease':ab,ti

#43 'chronic kidney disease':ab,ti

#42 'chronic kidney failure'/exp OR 'chronic kidney failure'

#41 't2d*':ab,ti

#40 'type 2 diabetes mellitus':ti,ab

#39 'diabetes mellitus type 2':ti,ab

#38 'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'

#37 #22 NOT #36

#36 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35

#35 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)

#34 (rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de

#33 (databases NEAR/5 searched):ab

#32 'update review':ab

#31 'we searched':ab AND (review:ti,tt OR review:it)

#30 review:ab AND review:it NOT trial:ti,tt

#29 ('random cluster' NEAR/4 sampl*):ti,ab,tt

#28 'random field*':ti,ab,tt

#27 nonrandom*:ti,ab,tt NOT random*:ti,ab,tt

#26 'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)

#25 'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)

#24 'cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)

#23 ((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)

#22 #21 NOT #3

#21 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 trial:ti,tt

#19 'human experiment'/de

#18 volunteer:ti,ab,tt OR volunteers:ti,ab,tt

#17 (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt

#16 assigned:ti,ab,tt OR allocated:ti,ab,tt

#15 ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt

#14 crossover:ti,ab,tt OR 'cross over':ti,ab,tt

#13 (parallel NEXT/1 group*):ti,ab,tt

#12 'double blind procedure'/de

#11 ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt

#10 (open NEXT/1 label):ti,ab,tt

#9 (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)

#8 compare:ti,tt OR compared:ti,tt OR comparison:ti,tt

#7 placebo:ti,ab,tt

#6 'intermethod comparison'/de

#5 'randomization'/de

#4 random*:ti,ab,tt

#3 #1 OR #2

#2 'controlled clinical study'/de

#1 'randomized controlled trial'/de

CENTRAL

ID	Search
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2	(diabetes mellitus type 2):ti,ab,kw
#3	(T2D):ti,ab,kw
#4	(T2DM):ti,ab,kw
#5	MeSH descriptor: [Renal Insufficiency, Chronic] 2 tree(s) exploded
#6	(chronic kidney disease):ti,ab,kw
#7	(CKD):ti,ab,kw
#8	(kidney disease):ti,ab,kw
#9	(kidney failure):ti,ab,kw
#10	(chronic kidney failure):ti,ab,kw
#11	(renal failure):ti,ab,kw
#12	(chronic renal disease):ti,ab,kw
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees
#15	(SGLT-2):ti,ab,kw
#16	(SGLT2):ti,ab,kw
#17	(canagliflozin):ti,ab,kw
#18	(dapagliflozin):ti,ab,kw

#19 (empagliflozin):ti,ab,kw

#20 (ipragliflozin):ti,ab,kw

#21 (tofogliflozin):ti,ab,kw

#22 (luseogliflozin):ti,ab,kw

#23 (remogliflozin):ti,ab,kw

#24 (ertugliflozin):ti,ab,kw

#25 (sotagliflozin):ti,ab,kw

#26 (bexagliflozin):ti,ab,kw

#27 MeSH descriptor: [Glucagon-Like Peptide-1 Receptor] explode all trees

#28 (GLP-1):ti,ab,kw

#29 (GLP1):ti,ab,kw

#30 (Efpeglenatide):ti,ab,kw

#31 (tirzepatide):ti,ab,kw

#32 (Dulaglutide):ti,ab,kw

#33 (Semaglutide):ti,ab,kw

#34 (Liraglutide):ti,ab,kw

#35 (Lixisenatide):ti,ab,kw

#36 (Exenatide):ti,ab,kw

#37 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees

#38 (nonsteroidal mineralocorticoid receptor antagonists):ti,ab,kw

#39 (non-steroidal mineralocorticoid receptor antagonists):ti,ab,kw

#40 (Nonsteroidal MRA):ti,ab,kw

#41 (finerenone):ti,ab,kw

#42 (esaxerenone):ti,ab,kw

#43 (apararenone):ti,ab,kw

#44 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #32 OR #33 OR #34 OR #35 OR #36 OR #38 OR #39 OR #40 #41 OR #42 OR #43

#45 (cardiovascular death):ti,ab,kw

#46 (cardiovascular events):ti,ab,kw

#47 (major adverse cardiovascular event*):ti,ab,kw

#48 (MACE*):ti,ab,kw

#49 (cardiac events):ti,ab,kw

#50 (all-cause death):ti,ab,kw

#51 (stroke):ti,ab,kw

#52 (myocardial infarction):ti,ab,kw

#53 (heart failure):ti,ab,kw

#54 (renal death):ti,ab,kw

#55 (renal outcomes):ti,ab,kw

#56 (kidney outcomes):ti,ab,kw

#57 (decline in eGFR):ti,ab,kw

#58 (end-stage kidney disease):ti,ab,kw

#59 (ESKD):ti,ab,kw

#60 (end stage renal disease):ti,ab,kw

#61 (acute kidney injury):ti,ab,kw

#62 (acute kidney failure):ti,ab,kw

#63 (kidney transplantation):ti,ab,kw

#64 #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 #63

#65 #13 AND #44 AND #64

#66 ("randomized-controlled trial"):pt

#67 ("randomized-controlled trials"):pt

#68 (controlled clinical trial):pt

#69 (randomized):ti,ab,kw

#70 MeSH descriptor: [Placebos] explode all trees

#71 (placebo*):ti,ab,kw

#72 (placebo):ti,ab,kw

#73 MeSH descriptor: [Clinical Trials as Topic] explode all trees

#74 (randomly):ti,ab,kw

#75 (trial):ti,ab,kw

#76 #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75

#77 #65 AND #76

Table A.1.1. Baseline Characteristics (All studies)

Study name	Year	Study number	Group	Drug class	Follow-up (week)	CKD definition	Male (%)	Age	eGFR (mL/min /1.73 m^2)	HbA1c %	UACR (mg/g)	Sample size
FIDELIO-DKD[23]	2020	NCT02540993	Finerenone 10/20 mg	nsMRA	135.7	UCAR 30-300 & eGFR 25-60; or UCAR 300-5000 & eGFR 25-75	68.9	65.4	44.4	7.7	833.0	2833
			Placebo				71.5	65.7	44.3	7.7	867.0	2841
FIGARO-DKD[24]	2021	NCT02545049	Finerenone 10/20 mg	nsMRA	177.4	UCAR 30-300 & eGFR 25-90; or UCAR 300-5000 & eGFR>60	68.6	64.1	67.6	7.7	302.0	3686
			Placebo				70.3	64.1	68.0	7.7	315.0	3666
REWIND[76]	2019	NCT01394952	dulaglutide 1·5 mg	GLP-1RA	277.7	eGFR<60	NA	NA	NA	NA	NA	1081
			Placebo									1118
ELIXA[77]	2015	NCT01147250	Lixisenatide 10/20 µg	GLP-1RA	108.0	eGFR<60	NA	NA	NA	NA	NA	659
			Placebo									748
Harmony Outcomes[78]	2018	NCT02465515	albiglutide 30-50 mg	GLP-1RA	82.3	eGFR<60	NA	NA	NA	NA	NA	1098
			Placebo									1124
SUSTAIN-6[80]	2016	NCT01720446	Semaglutide 0.5/1.0 mg	GLP-1RA	108.0	eGFR<60	NA	NA	NA	NA	NA	469
			Placebo									470
PIONEER-6[79]	2019	NCT02692716	Oral Semaglutide 14 mg	GLP-1RA	68.1	eGFR<60	NA	NA	NA	NA	NA	434
			Placebo				NA	NA	NA	NA	NA	422

Study name	Year	Study number	Group	Drug class	Follow-up (week)	CKD definition	Male (%)	Age	eGFR (mL/min /1.73 m^2)	HbA1c %	UACR (mg/g)	Sample size
EXSCEL[81]	2017	NCT01144338	Exenatide 2 mg	GLP-1RA	166.9	eGFR<60	NA	NA	NA	8.1	NA	1557
			Placebo				NA	NA	NA	8.1	NA	1620
LEADER[82,134]	2016	NCT01179048	liraglutide 1.8 mg	GLP-1RA	198.1	eGFR<60	60.6	67.3	45.5	8.7	47.3	1116
			Placebo				65.3	67.3	45.8	8.6	51.8	1042
LIRA-RENAL[83]	2016	NCT01620489	liraglutide 1.8 mg	GLP-1RA	26.0	eGFR 30–59	53.6	68.0	45.4	8.1	55.5	140
			Placebo				47.4	66.3	45.5	8.0	69.8	137
SCORED[64]	2021	NCT03315143	sotagliflozin 200/400 mg	SGLT-2i	68.6	eGFR<60	55.7	69.0	44.4	8.3	74.0	5292
			Placebo				54.5	69.0	44.7	8.3	75.0	5292
SOTA-CKD4[65]	2021	NCT03242018	sotagliflozin 200/400 mg	SGLT-2i	26.0	eGFR<30	50.5	67.0	23.9	8.3	NA	184
			Placebo				45.2	68.0	24.1	8.4	NA	93
VERTIS CV[66]	2020	NCT03242018	ertugliflozin 5/15 mg	SGLT-2i	154.3	eGFR<60	63.3	68.3	49.1	8.2	30.0	1199
			Placebo									608
Bexagliflozin [33]	2019	NCT02836873	Bexagliflozin 20 mg	SGLT-2i	24.0	eGFR<60	58.6	69.3	45.4	8.0	NA	157
			Placebo				67.1	69.9	44.8	8.0	NA	155
EMPA-REG RENAL[67]	2014	NCT01164501	empagliflozin 25 mg daily	SGLT-2i	52.0	eGFR<60	57.1	64.7	34.9	8.0	NA	224
			Placebo				55.8	64.8	33.1	8.1	NA	224
EMPA-REG OUTCOME[68, 87]	2015	NCT01131676	empagliflozin 10/25 mg	SGLT-2i	159.4	eGFR<60	67.3	67.1	48.4	8.1	NA	1212
			Placebo				68.9	67.1	48.6	8.0	NA	607

Study name	Year	Study number	Group	Drug class	Follow-up (week)	CKD definition	Male (%)	Age	eGFR (mL/min /1.73 m^2)	HbA1c %	UACR (mg/g)	Sample size
MB102029[75]	2014	NCT00663260	dapagliflozin 10 mg	SGLT-2i	104.0	eGFR<60	66.1	67.0	44.1	8.3	76.0	168
			Placebo				63.1	67.0	45.6	8.5	67.0	84
Delight[69]	2019	NCT02547935	dapagliflozin 10 mg	SGLT-2i	24.0	UACR 30 - 3500 mg/g & eGFR 25-75	29.7	64.7	50.2	8.4	270.0	145
			Placebo				29.1	64.7	47.7	8.6	257.5	148
DECLARE-TIMI 58[70]	2019	NCT01730534	dapagliflozin 10 mg	SGLT-2i	219.0	eGFR<60	63.5	67.5	51.1	8.2	NA	606
			Placebo				65.1	67.1	51.6	8.3	NA	659
DAPA-CKD[29]	2020	NCT03036150	dapagliflozin 10 mg	SGLT-2i	125.1	eGFR 25-75 & UACR>=200 mg/g	66.1	64.1	44.0	7.8	1,025.0	1455
			Placebo				67.6	64.7	43.6	7.8	1,005.0	1451
CANVAS Program[71]	2017	NCT01032629 NCT01989754	Canagliflozin 100/300 mg	SGLT-2i	188.2	eGFR<60	59·4	67.6	49·2	8·3	21·5	1110
			Placebo				56·7	67.6	49.0	8·3	21·7	929
CREDENCE[35]	2019	NCT02065791	Canagliflozin 100 mg	SGLT-2i	135.6	eGFR 30 to <90 & UCAR >300 to 5000	65.4	62.9	56.3	8.3	923.0	2202
			Placebo				66.7	63.2	56.0	8.3	931.0	2199
DIA3004[72]	2014	NCT01064414	Canagliflozin 100/300 mg	SGLT-2i	52.0	GFR 30-50	59.2	68.7	39.1	8.0	26.9	179
			Placebo				63.3	68.2	40.1	8.0	31.3	90
TS071-03-4[60]	2016	JapicCTI-111543	Luseogliflozin 2.5 mg	SGLT-2i	52.0	eGFR<60	75.8	67.9	52.0	7.7	335.7	95
			Placebo				78.0	68.4	52.4	7.7	231.9	50
EMPA-REG METSU[73]	2013	NCT01159600	empagliflozin 10/25 mg	SGLT-2i	24.0	eGFR<60	NA	NA	NA	NA	NA	36
			Placebo				NA	NA	NA	NA	NA	22

Study name	Year	Study number	Group	Drug class	Follow-up (week)	CKD definition	Male (%)	Age	eGFR (mL/min /1.73 m^2)	HbA1c %	UACR (mg/g)	Sample size
Pooled analysis[74]	2018	NCT01159600 NCT01210001 NCT01177813 NCT01164501	empagliflozin 10/25 mg	SGLT-2i	24.0	eGFR<60	56.2	64.3	35.4	8.0	NA	276
			Placebo				55.8	64.9	36.3	8.0	NA	285
EMPA-KIDNEY[30]	2022	NCT03594110	empagliflozin 10 mg	SGLT-2i	104.4	eGFR 20-45 or eGFR<90 & UACR>200	NA	NA	NA	NA	NA	1525
			Placebo				NA	NA	NA	NA	NA	1515
TA-7284[59]	2022	NCT03436693	Canagliflozin 100 mg	SGLT-2i	104.0	eGFR 30-90 & UCAR 300-5000	74.7	62.5	56.3	7.8	712.0	154
			Placebo				83.8	62.4	55.2	7.8	630.0	154
FREEDOM CVO[31]	2021	NCT01455896	Exenatide 2 mg	GLP-1RA	480.0	eGFR<60	NA	NA	NA	NA	NA	196
			Placebo				NA	NA	NA	NA	NA	212

GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

CKD, chronic kidney disease; NA, not available; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

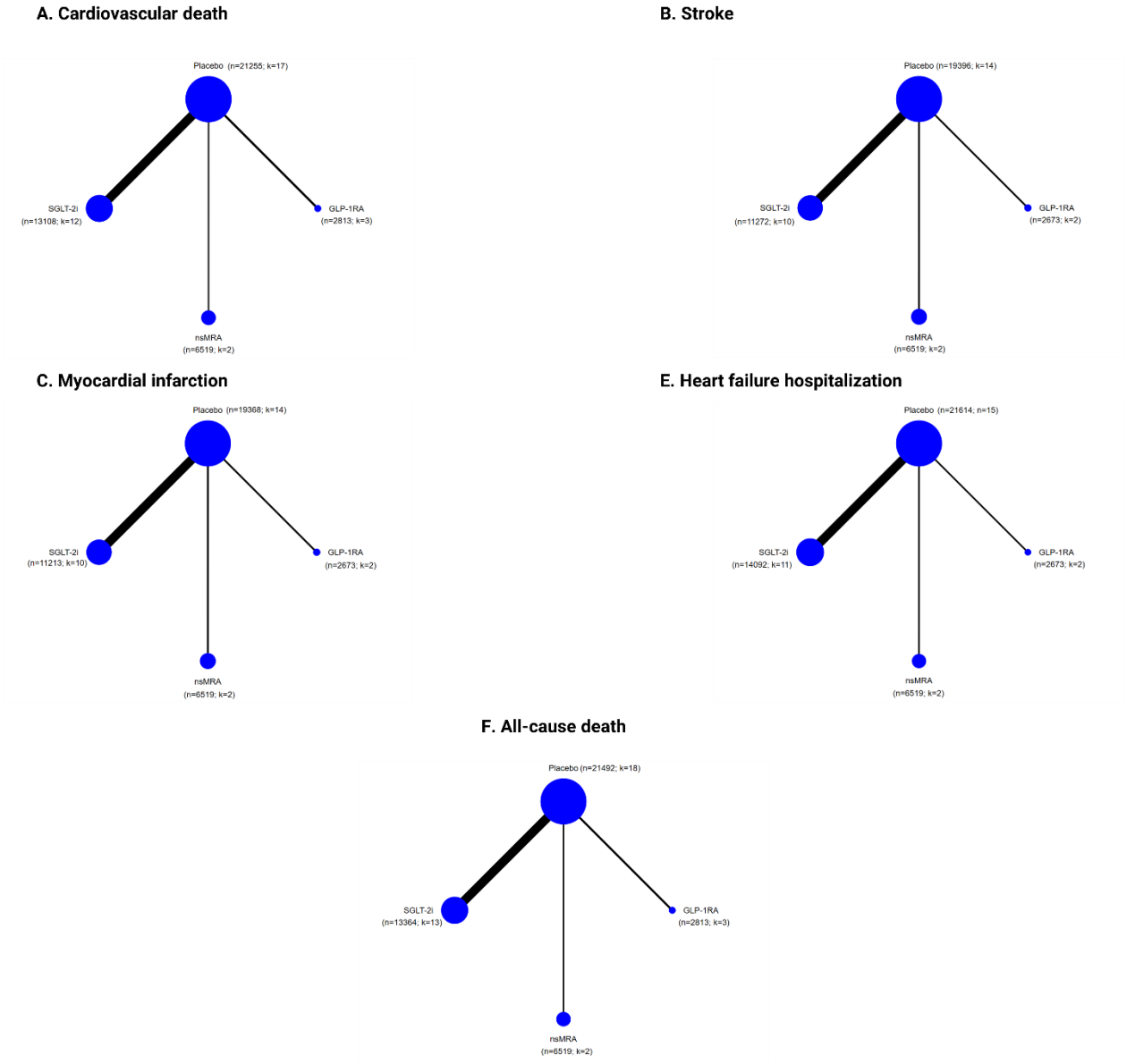

Figure A.1.1. Network plots of comparisons for secondary outcomes*GLP-1, glucagon-like peptide 1 agonists; k, the number of studies; n, the number of participants; MRA, nonsteroidal mineralocorticoid receptor antagonists; SGLT-2, sodium-glucose cotransporter 2 inhibitors. The size of the nodes is proportional to the number of participants. The thickness of lines is proportional to the number of trials.*

Figure A.1.2. Risk of bias of individual trials for each outcome

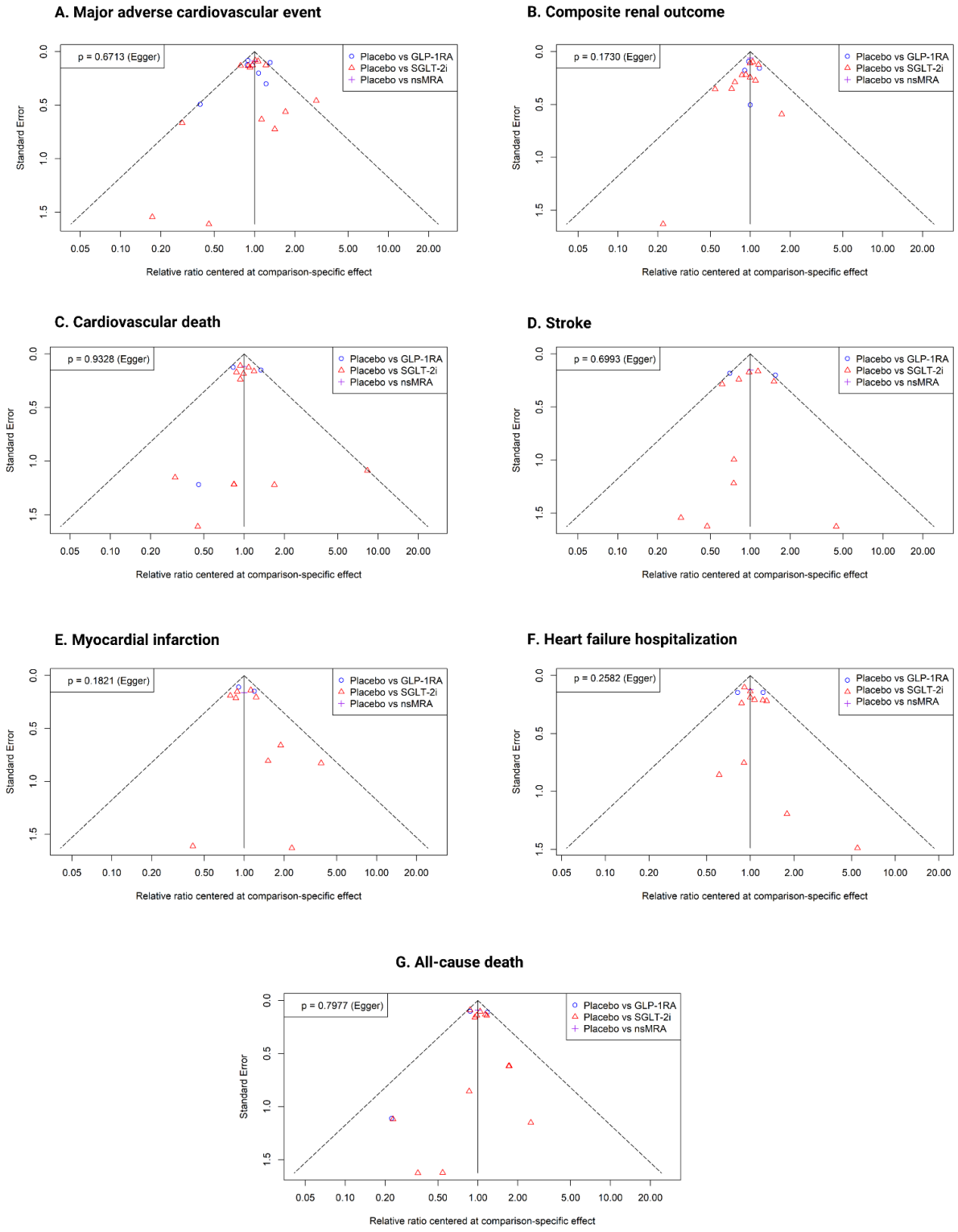

Figure A.1.3. Funnel plots for publication bias

Appendix 2: Appendix to Chapter 3

A.2.1. Detailed parameters in the model

Table A.2.1. Baseline patient characteristics for the model

Patient characteristics	Units	Mean	Standard deviation	Reference
Age	Years	63.02	9.20	[35]
Female	Proportion	0.339	0.47	[35]
Smoking status	Proportion	0.145	0.35	[35]
T2D duration	Years	15.78	8.63	[35]
eGFR	mL/min/1.73 m^2	56.18	18.24	[35]
ln(UACR)	mg/dL	6.79	1.02	[35]
MI history	Proportion	0.100	0.30	[35]
Stroke history	Proportion	0.104	0.31	[35]
HF history	Proportion	0.148	0.36	[35]

T2D, type 2 diabetes; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; MI, myocardial infarction; HF, heart failure.

Table A.2.2. The decline of eGFR and UACR

Strategy	Initial eGFR (mL/min/1.73 m^2)	Follow-up eGFR (mL/min/1.73 m^2/year)	UACR (%)	Reference
SoC	-0.55 ± 0.25	-4.59 ± 0.14	-0.17 (-0.22; 0.13)	[35,106]
Canagliflozin+SoC versus SoC	-3.17 (-3.87; -2.47) (First 3 weeks)	2.74 (2.37; 3.11)	0.31 (0.26; 0.35)	[35]
Dapagliflozin+SoC versus SoC	-2.61 (-2.16; -3.06) (First 2 week)	2.26 (1.88; 2.64)	0.35 (0.39; 0.31)	[36,106]

eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; SoC, standard of care

Table A.2.3. Transition probability in patients with end-stage kidney disease

Health state	Monthly probability	Reference
CKD5 to transplant	0.0007	[95]
Transplant to dialysis	0.0033	[96]
Transplant to HFH	0.0016	[98]
Transplant to MI	0.0009	[99]
Transplant to stroke	0.0011	[100]
Transplant to all-cause death		[101,135]
18–44	0.0024	
45–54	0.0022	
55–64	0.0036	
65-69	0.0055	
70-74	0.0079	
75-79	0.0117	
80-84	0.0166	
85+	0.0164	
Dialysis to HFH	0.0028	[103]
Dialysis to MI	0.0019	[104]
Dialysis to stroke	0.0018	[104]
Dialysis to transplant	0.0030	[4]
Dialysis to all-cause death		[4]
18–44	0.0051	
45–54	0.0079	
55–64	0.0115	
65–74	0.0158	
75+	0.0233	

CKD, chronic kidney disease; HFH, heart failure hospitalization, MI, myocardial infarction

Table A.2.4. Monthly probability of adverse events in SoC

Adverse events	Value (%)	Reference
Diabetic ketoacidosis	0.0017	[35]
Severe hypoglycemia	0.0666	[105]
Volume depletion	0.1956	[35]
Acute kidney injury	0.1665	[35]
Fracture	0.1008	[35]
Amputation	0.0933	[35]
Urinary tract infection	0.3751	[35]
Genital mycotic infection	0.0189	[35]

Table A.2.5. Relative treatment effects of SGLT-2 inhibitors compared SoC

Outcome	Canagliflozin	Ref	Dapagliflozin	Ref
	HR (95% CI)		HR (95% CI)	
All-cause death	0.83 (0.68-1.02)	[35]	0.74 (0.56-0.98)	[38]
HFH	0.61 (0.47-0.80)	[35]	0.47 (0.31-0.73)	[38]
MI	0.86 (0.64-1.16)	[35]	0.80 (0.54-1.2)	[37]
Stroke	0.77 (0.55-1.08)	[35]	1.26 (0.73-2.18)	[37]
Dialysis	0.74 (0.55-1.00)	[35]	0.68 (0.47-0.98)	[38]
Amputation	1.59 (1.26-2.01)	[17]	1.04 (0.84-1.29)	[17]
Fracture	1.19 (1.01-1.40)	[17]	1.06 (0.94-1.18)	[17]
Diabetic ketoacidosis	3.07 (1.13-8.34)	[17]	2.13 (1.11-4.06)	[17]
Acute kidney injury	0.86 (0.67-1.10)	[17]	0.69 (0.57-0.83)	[17]
Severe hypoglycemia	1.40 (0.88-2.24)	[17]	0.66 (0.50-0.88)	[17]
Urinary tract infection	1.10 (0.97-1.26)	[17]	0.96 (0.77-1.19)	[17]
Volume depletion	1.33 (1.11-1.59)	[17]	1.13 (1.00-1.28)	[17]
Genital mycotic infection	3.88 (3.17-4.76)	[17]	6.21 (3.25-11.86)	[17]

HFH, heart failure hospitalization, MI, myocardial infarction; SGLT-2, Sodium-glucose cotransporter 2.

Table A.2.6. Cost of SoC

Treatment	The most common drug	Price, C$	Recommended/ average daily usage	Daily cost	Annual cost	% Patients in trial	Ref
Insulin	Novolin ge NPH 1000U/10mL Inj Susp-10mL Pk	24.8300	Insulin NPH 0.75 U per kg per day	1.6202	591.37	65.5	[136]
Sulfonylurea	Sandoz Gliclazide MR 60mg ER Tab	0.0632	120 mg	0.1264	46.17	28.8	[137]
Biguanides	Metformin 500mg Tab	0.0247	2000 mg	0.0988	36.06	57.8	[110]
GLP-1 receptor agonist	Exenatide Byetta 5 mcg/dose (250 mcg/mL) 2.4 mL injection	143.67	10 mcg twice daily	4.7900	1,748.35	4.2	[110]
DPP-4 inhibitor	Sitagliptin Phosphate Monohydrate 100 mg (Januvia)	3.2787	100 mg	3.2787	1,196.73	17.1	[110]
Statin	Atorvastatin 80mg Tab	0.2342	80 mg	0.2342	85.48	69.0	[138]
Antithrombotic	Warfarin 5 mg Tab	0.0675	5 mg	0.0675	24.64	59.6	[139,140]
RAAS inhibitor	Lisinopril 20mg Tab	0.1945	40 mg	0.3890	141.99	99.9	[34]
Beta blocker	Bisoprolol 10mg Tab	0.0885	10 mg	0.0885	32.30	40.2	[141]
Diuretic	Furosemide 40mg Tab	0.0327	40 mg	0.0327	11.94	46.7	[142]
Diabetic Testing Agent	Contour Next Blood Glucose Test Strips Strip	0.7290	1.56 test	1.1372	415.08	100	[143]
Total						**1,348.71**	

A.2.2. Results

Table A.2.7. Cost-effectiveness results for waning of treatment effects

Strategy	Cost (C$)	Incremental costs (C$)	QALY	Incremental QALY	ICER
All strategies					
Canagliflozin+SoC	214,122	-	7.87	-	-
Dapagliflozin+SoC	221,916	7,794	7.97	0.10	76,087
SoC	243,533	21,617	6.81	-1.16	Dominated
SGLT-2is +SoC versus SoC					
SoC	243,533	-	6.81	-	-
Canagliflozin+SoC	214,122	-29,411	7.87	1.06	Dominant
Dapagliflozin+SoC	221,916	-21,617	7.97	1.16	Dominant

All costs were calculated in 2021 Canadian dollars.

This analysis is conducted under the lifetime horizon.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; SoC, standard of care; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

Table A.2.8. Cost-effectiveness results with different time horizon

Strategy	Cost (C$)	Incremental costs (C$)	QALY	Incremental QALY	ICER
Panel A: Time horizon: 5 years					
All strategies					
Dapagliflozin+SoC	27,809		3.38		-
Canagliflozin+SoC	30,308	2,499	3.35	-0.03	Dominated
SoC	30,409	2,599	3.28	-0.11	Dominated
SGLT-2i +SoC versus SoC					
SoC	30,409	-	3.28	-	-
Dapagliflozin+SoC	27,809	-2,599	3.38	0.11	Dominant
Canagliflozin+SoC	30,308	-100	3.35	0.08	Dominant

Strategy	Cost (C$)	Incremental costs (C$)	QALY	Incremental QALY	ICER
Panel B: Time horizon: 10 years					
All strategies					
Dapagliflozin+SoC	75,328	-	5.78	-	-
Canagliflozin+SoC	78,774	3,447	5.70	-0.08	Dominated
SoC	106,281	30,953	5.32	-0.46	Dominated
SGLT-2i +SoC versus SoC					
SoC	106,281	-	5.32	-	-
Dapagliflozin+SoC	75,328	-30,953	5.78	0.46	Dominant
Canagliflozin+SoC	78,774	-27,506	5.70	0.38	Dominant
Panel C: Time horizon: 20 years					
All strategies					
Canagliflozin+SoC	177,725	-	7.75	-	-
Dapagliflozin+SoC	186,449	8,724	7.90	0.15	57,964
SoC	226,828	40,378	6.65	-1.25	Dominated
SGLT-2i +SoC versus SoC					
SoC	226,828	-	6.65	-	-
Canagliflozin+SoC	177,725	-49,102	7.75	1.10	Dominant
Dapagliflozin+SoC	186,449	-40,378	7.90	1.25	Dominant

All costs were calculated in 2021 Canadian dollars.

This analysis is conducted under the lifetime horizon.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; SoC, standard of care; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.