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CADTH Reimbursement Review

Dapagliflozin

Nonsponsored review

Therapeutic area: Chronic kidney disease

Clinical Review

Table of Contents

List of Tables

List of Figures

Abbreviations

ACE	angiotensin-converting enzyme
AE	adverse event
ARB	angiotensin II receptor blocker
CARP	Canadian Association of Retired Persons
CI	confidence interval
CKD	chronic kidney disease
CrI	credible interval
CV	cardiovascular
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FAS	full analysis set
HF	heart failure
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
KDIGO	Kidney Disease: Improving Global Outcomes50
LSM	least squares mean
MACE	major adverse cardiovascular event
MD	mean difference
MI	myocardial infarction
NE	not estimable
NMA	network meta-analysis
NOC	Notice of Compliance
NR	Not Reported
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SE	standard error

SGLT2	sodium-glucose cotransporter-2
SOC	standard of care
T2DM	type 2 diabetes mellitus
UACR	urinary albumin to creatine ratio
UTI	urinary tract infection
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Dapagliflozin propanediol monohydrate 10 mg oral tablet
Health Canada indication	To reduce the risk of sustained eGFR decline, ESKD, and cardiovascular and renal death in adults with CKD
Indication under consideration for reimbursement	As per Health Canada indication
Health Canada approval status	NOC
NOC date	August 10, 2021 (SNDS)
Requester	Formulary Working Group

CKD = chronic kidney disease; ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; NOC = Notice of Compliance; SNDS = supplement to a new drug submission.

Source: Dapagliflozin Product Monograph.[1]

Introduction

Chronic kidney disease (CKD) is characterized by abnormalities in kidney structure and/or reduction in kidney function present for at least 3 months,[2] with an overall prevalence rate of approximately 12% in Canada.[3] Patients with CKD may be asymptomatic in the early stages.[4] In later stages, CKD results in uremia characterized by a broad collection of signs and symptoms (e.g., fatigue, pain, weakness, reduced mobility, nausea).[4] Kidney failure (end-stage kidney disease [ESKD]) requires dialysis or a kidney transplant to sustain life.[2]

Treatment for CKD aims to prevent or delay progression and to address complications resulting from reduced kidney function.[2] Treatment also involves managing the underlying cause of CKD, for example obesity, type 2 diabetes mellitus (T2DM), and cardiac disorders.[4] Lifestyle modification and control of hypertension in patients with proteinuria are key components of treatment to delay progression.[2,4] Antihypertensive therapy commonly consists of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[2] Additional treatments are recommended for patients with comorbid T2DM to delay CKD progression and reduce cardiovascular (CV) risk, for example, statins and/or antiplatelet therapies.[2] Additional treatments may be used to address complications (e.g., anemia, acidosis, metabolic bone disease), as well as fluid and electrolyte abnormalities,[2] especially as patients progress to ESKD.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially developed to treat hyperglycemia in patients with T2DM; however, their beneficial effects on renal and CV outcomes have since led to the investigation of this class of drugs on cardiorenal outcomes in patients with CV disease (CVD) and CKD.[5] Of the currently available SGLT2 inhibitors believed to have renal benefit, dapagliflozin is indicated for patients with or without T2DM,[1]. In contrast, canagliflozin is indicated only for patients with T2DM.[1,6]

The Formulary Working Group requested CADTH undertake a review of dapagliflozin for CKD. The objective of this report is to perform a systematic review of the beneficial and harmful effects of dapagliflozin 10 mg oral tablets to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, ESKD, and CV and renal death in adult patients with CKD.

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH Nonsponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with dapagliflozin and comparators deemed to be appropriate based on feedback from clinical experts and public drug plans.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the Canadian Association of Retired Persons (CARP) and Kidney Foundation of Canada, provided input on patient perspectives gathered through surveys. Patients reported on the significant impact of CKD on their quality of life. Patients also described the challenges of living with CKD, such as feeling fatigue, experiencing frequent urination, having a limited ability to work and remain engaged in physical activity, undertake travel, and having to drastically change diets and lifestyles. Some challenges with existing therapies included access (lack of drug coverage under public or private plans), remembering to take medications, large number of medications, and difficulty to take time off work for treatment. Patients expected new therapies to increase their energy levels, well-being, and quality of life, reduce the number of medications they need to take, take less time away from work, and require fewer hospital visits. Patients' concerns about new therapies included interference with their other medications, side effects, impact on their mood, the duration of treatment, and cost and availability.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with experience treating patients with CKD were consulted by CADTH for this review.

According to the clinical experts consulted by CADTH, the goal of treatment is to prevent or delay disease progression to ESKD and to reduce the risk of adverse CV events and mortality. Challenges with existing treatments included the persistent risk of developing ESKD and/or CV events. Also, some patients are unable to tolerate the current standard of care (SOC) (i.e., ACE inhibitors and/or ARBs and statins).

According to the clinical experts, patients with CKD who would be most suited to dapagliflozin include those with T2DM-related CKD with an eGFR of 25 to 75 mL/min/1.73 m^2 and proteinuria, those with T2DM with high CV risk, and with heart failure (HF) irrespective of T2DM status.

The clinical experts indicated that surrogate measures of renal function, namely reduction in proteinuria, enhanced glycemia control (particularly with eGFR above 45 mL/min/1.73 m^2) and stable eGFR, are the important markers for an enhanced quality of care with the use of dapagliflozin. Clinical outcomes identified

as important by clinical experts included reduction in risk of ESKD, hospitalization for HF, all-cause mortality, and adverse CV outcomes. The clinical experts indicated that dapagliflozin could be initiated by primary care providers as well as specialists.

The clinical experts suggested that adverse events (AE) such as euglycemic diabetic ketoacidosis (DKA), amputations, and the onset of mycotic genital infections, as well as the onset of pregnancy, would require drug discontinuation. Careful consideration is required for patients of childbearing age since dapagliflozin is not recommended in pregnancy. One expert added that applying the Sick Day Medication rule (i.e., temporarily withholding dapagliflozin) should be considered in the setting of poor oral intake or fasting. The clinical experts did not recommend using dapagliflozin in patients with adult polycystic kidney disease or with autoimmune diseases who are receiving immunosuppressive therapy, given that this drug has not been studied in these patients.

Clinician Group Input

Input was submitted by 2 clinician groups: The British Columbia (BC) Renal Medical Directors (on behalf of provincial nephrologists); and a group of nephrologists, internal medicine physicians and a pharmacist at Nova Scotia Health Authority. The clinical group input generally aligned with that provided by the clinical experts. The groups added that in addition to preventing or delaying progression to ESKD, the goal of CKD therapy is to prolong dialysis-free life and improve health-related quality life (HRQoL) to enable greater life participation and maintain employment and independence. Dapagliflozin was described as a convenient daily oral therapy, which is expected to be well tolerated, accessible, simple to use, improve adherence and limit pill burden. They also noted that dapagliflozin is used in fixed doses, thereby titration and other processes are simplified for practitioners and patients.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. For the CADTH review of dapagliflozin in CKD, the drug plans provided questions pertaining to the appropriate time to initiate therapy, treatment paradigm relative to prior therapies and SOC, continuation and renewal criteria, and appropriate prescribers.

Clinical Evidence

Systematic Review

Characteristics of Included Studies

Four randomized controlled trials (RCTs) were included: Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) (N = 4,304);[7-14] Dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycemic control in patients with type 2 diabetes and CKD (DELIGHT) (N = 461);[15] Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes (DERIVE) (N = 321);[16] and Study MB102029 (Kohan et al. [2014]) (N = 252).[17-19]

All RCTs were multicentre (including centres in Canada), placebo-controlled, double-blind trials, sponsored by AstraZeneca (Kohan et al. [2014] was also sponsored by Bristol-Myers Squibb). All RCTs compared dapagliflozin 10 mg to a matched placebo once daily among patients with CKD. DAPA-CKD enrolled patients irrespective of T2DM status, while the other RCTs only enrolled patients with CKD and T2DM. The use of ACE inhibitors and ARBs was required for DAPA-CKD and DELIGHT, but not DERIVE, although most (83.8%) patients were receiving ACE inhibitors or ARBs at baseline. The proportion of patients receiving ACE inhibitors or ARBs was not reported in Kohan et al. (2014). Patients were followed for up to 38.2 months in DAPA-CKD. In DELIGHT and DERIVE, patients were followed for 27 weeks (24-week double-blind period and 3-week follow-up period). In Kohan et al. (2014), patients were followed for up to 104 weeks (double blind for 52 weeks; patient and site blind for an additional 52 weeks). The mean age ranged from 61.8 to 67.5 years across RCTs, and most patients were male (56.7% to 70.6%).

The primary outcome in DAPA-CKD was a composite of time to 50% or greater decline in eGFR, ESKD, or death from renal or CV causes. The secondary outcomes were a composite of time to 50% or greater decline in eGFR, ESKD, or death from renal causes; time to CV death or hospitalization for HF; and time to death from any cause.

Change from baseline UACR and eGFR, and mortality were the only efficacy outcomes measured consistently across all RCTs. Change from baseline UACR was an exploratory outcome in DAPA-CKD and DERIVE, the primary outcome in DELIGHT, and a safety outcome in Kohan et al. (2014). The proportion of patients experiencing at least a 30% reduction in UACR at 24 weeks was also a secondary outcome in DELIGHT. Change from baseline eGFR was an exploratory outcome in DAPA-CKD, a safety outcome in DELIGHT and DERIVE, and a secondary outcome in Kohan et al. (2014). Mortality (from any cause) was a secondary outcome on DAPA-CKD and a safety outcome in the other RCTs.

Efficacy Results

Renal Events

At the conclusion of DAPA-CKD (median follow-up, 2.4 years [range = 2.0 to 2.7]), 109 (5.1%) patients in the dapagliflozin group and 161 (7.5%) patients in the placebo group experienced ESKD (HR = 0.64, 95% CI, 0.50 to 0.82). Results for outcomes that define ESKD (i.e., eGFR < 15 mL/min/1.73 m^2, long-term dialysis, or kidney transplant) were aligned with those for ESKD.[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12] Time to ESKD was not measured in the other RCTs.

At the conclusion of the DAPA-CKD, 63 (2.9%) patients in the dapagliflozin group and 91 (4.2%) in the placebo group experienced a doubling of serum creatinine (HR = 0.68, 95% CI, 0.49 to 0.94; P = 0.02). The results were consistent across prespecified subgroups of interest (i.e., T2DM status, eGFR, and UACR at baseline).[7] This outcome was not measured in the other RCTs.

The proportion of patients discontinuing treatment due to worsening renal insufficiency was reported in both DELIGHT and DERIVE, and events were infrequent in the dapagliflozin and placebo groups across the RCTs (0.0% versus 0.7%, respectively in DELIGHT and 0.6% versus 0.0%, respectively in DERIVE).[15,16] In Kohan et al.

(2014), the authors reported that the proportion of patients with marked abnormalities in serum creatinine through 104 weeks was similar across groups. Numeric results were not reported.[19]

Change in eGFR

At the conclusion of DAPA-CKD, 112 (5.2%) patients in the dapagliflozin group and 201 (9.3%) patients in the placebo group experienced a 50% or greater sustained decline in eGFR (HR = 0.53, 95% CI, 0.42 to 0.67).[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

The least squares mean (LSM) eGFR slopes from baseline to 30 months in the dapagliflozin and placebo groups were −2.86 mL/min/1.73 m^2 per year (SE = 0.11) and −3.79 (SE = 0.11) mL/min/1.73 m^2 per year, respectively. There was a decline in eGFR in the dapagliflozin group during the first 2 weeks of treatment. After this time, patients in the dapagliflozin group experienced a slower decline in eGFR (LSM difference, 1.92 mL/min/1.73 m^2; 95% CI, 1.61 to 2.24).[9] The test for subgroup interaction showed that dapagliflozin resulted in a greater attenuation of decline in eGFR relative to placebo among patients with T2DM compared to those without T2DM (interaction P value = 0.040). Dapagliflozin also resulted in a progressively greater attenuation of decline in eGFR relative to placebo in higher relative to lower UACR subgroups (interaction P value < 0.0001).[20] There were no statistically significant subgroup interactions among patients with versus without HF.[12]

Results were similar among patients with CKD and T2DM in DELIGHT and DERIVE.[15,16] After 1 week of treatment, the between-group difference in adjusted mean change from baseline was −4.8 mL/min/1.73 m^2 (95% CI, −6.3 to −3.3) in DELIGHT, favouring placebo. After 4 weeks of treatment, the between-group difference in adjusted mean change from baseline was −4.90 mL/min/1.73 m^2 (95% CI, −6.73 to −3.07) in DERIVE, favouring placebo. Three weeks following the cessation of treatment (week 27), the reduction in eGFR was reversed, with similar values observed in the dapagliflozin and placebo groups in both RCTs.

Similar to the other RCTs, the authors of Kohan et al. (2014) stated that there was an early mean decrease in eGFR after 1 week of treatment in the dapagliflozin group, followed by long-term stability, compared with a slow decline in the placebo group. Differences in change from baseline eGFR were not reported.[17] Differences in change from baseline eGFR were not reported.[17]

Change in UACR

Change from baseline UACR was a primary outcome in DELIGHT and an exploratory outcome in DAPA-CKD and DERIVE. At 2 weeks follow-up in DAPA-CKD, the difference in geometric mean percent change from baseline was −26.5% (95% CI, −22.1 to −30.9) (P < 0.0001), favouring dapagliflozin. At the conclusion of the RCT, the difference in geometric mean percent change from baseline was −29.3% (95% CI −33.1 to −25.2) (P < 0.0001), favouring dapagliflozin. The test for subgroup interaction showed that relative to placebo, dapagliflozin resulted in a greater reduction in mean UACR among patient with T2DM compared to those without (interaction P value < 0.0001). The effects of dapagliflozin on UACR were consistent across categories of baseline eGFR and UACR.[10]

In DELIGHT, the difference in the percent changes from baseline at week 4 and week 24 were −28.3% (95% CI, −36.8 to −18.7%) (P < 0.0001) and −21.0% (95% CI, −34.1 to −5.2%) (P = 0.011), respectively, both favouring dapagliflozin.[15] In DERIVE, the difference in the percent change from baseline at week 24 was 8.0% (95% CI, −14.4 to 36.3%).[16]

In Kohan et al. (2014), the change from baseline UACR was −11.69 (SE = 148.6) mg/g in the dapagliflozin group and 69.7 (SE = 80.1) mg/g in the placebo group at 104 weeks. The difference in the change from baseline was not reported. Values of more than 1,800 mg/g for 104 weeks follow-up were reported in 13.3% of patients in the placebo group compared with 9.5% of patients in the dapagliflozin group.[18]

The proportion of patients with a 30% reduction in UACR from baseline at 24 weeks was a secondary outcome in DELIGHT. The proportions of patients with a 30% reduction in UACR from baseline were 45.0% in the dapagliflozin group and 31.3% in the placebo group (OR = 1.9, 95% CI, 1.1 to 3.0; P = 0.013).[15]

CV Events

Time to first fatal or nonfatal myocardial infarction (MI) and time to first fatal or nonfatal stroke were measured but not reported in DAPA-CKD. CV events were not measured in the other RCTs.

Mortality

Time to death from any cause, time to CV death, and time to renal death were reported in DAPA-CKD. At the conclusion of the RCT, 101 (4.7%) patients in the dapagliflozin group and 146 (6.8%) patients in the placebo group had died from any cause (HR = 0.69, 95% CI, 0.53 to 0.88; P = 0.004).[9] Results among all prespecified subgroups of relevance (including T2DM status, eGFR, and UACR at baseline) were consistent with the main analysis.[20] There were no statistically significant subgroup interactions among patients with versus without T2DM, CVD, or HF.[11,12,14]

Sixty-five (0.3%) patients in the dapagliflozin group and 80 (3.7%) in the placebo group had died from CV causes (HR = 0.81, 95% CI, 0.58 to 1.12).[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

Few deaths occurred in either group due to renal causes; 2 (0.1%) patients in the dapagliflozin group and 6 (0.3%) patients in the placebo group died from renal causes. The HR and 95% CI were not estimated due to the low number of events.[9]

Mortality was a safety outcome in the other RCTs. After 27 weeks follow-up, 1 patient (0.7%) in the dapagliflozin died in DELIGHT.[15] No patient in either group died in DERIVE.[16] After 104 weeks follow-up in Kohan et al. (2014), 3 (3.5%) and 5 (6.0%) patients died in the dapagliflozin and placebo groups, respectively.[19]

Composite Outcomes (Renal and/or Cardiovascular Events)

In DAPA-CKD, time to 50% or greater eGFR decline, ESKD, CV death, or renal death was the primary outcome. After the RCT, 197 (9.2%) patients in the dapagliflozin group and 312 (14.5%) patients in the placebo group experienced a component of the composite outcome (HR = 0.61, 95% CI, 0.51 to 0.72; P < 0.001). Results for each component of the composite outcome were aligned with those for the composite. Results of sensitivity

analyses were consistent with the primary analysis. Results were also consistent across prespecified subgroups.[9] There were no statistically significant subgroup interactions among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to 50% or greater eGFR decline, ESKD, or renal death was a secondary outcome. At the conclusion of the RCT, 142 (6.6%) patients in the dapagliflozin group and 243 (11.3%) patients in the placebo group experienced a component of the composite outcome (HR = 0.56, 95% CI, 0.45 to 0.68; P < 0.001). Results for each component of the composite outcome were aligned with those for the composite.[9] There were no statistically significant subgroup interactions for this composite secondary outcome, or any components of the composite, among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to CV death or hospitalization for HF was a secondary outcome. At the conclusion of the RCT, 100 (4.6%) patients in the dapagliflozin group and 138 (6.4%) patients in the placebo group experienced a component of the composite outcome, respectively (HR = 0.71, 95% CI, 0.55 to 0.92; P = 0.009).[9] There was no statistically significant subgroup interaction for this composite secondary outcome among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to MI, stroke, or CV death was an exploratory outcome. At the conclusion of the RCT, 132 (6.1%) patients in the dapagliflozin group and 143 (6.6%) patients in the placebo group experienced a component of the composite outcome (HR = 0.92, 95% CI, 0.72 to 1.16). There was no statistically significant subgroup interaction among patients with versus without CVD.[11]

No composite outcomes were reported in the other RCTs.

Hospitalization

Time to hospitalization for HF was an exploratory outcome in DAPA-CKD. After the RCT, 37 (1.7%) patients in the dapagliflozin group and 71 (3.3%) patients in the placebo group required hospitalization for HF (HR = 0.51, 95% CI, 0.34 to 0.76). There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

A post hoc analysis of hospitalizations (first and subsequent) was reported for DAPA-CKD.[13] At the conclusion of the RCT, 566 (26.3%) patients in the dapagliflozin group and 658 (30.6%) patients in the placebo group required any hospitalization (HR = 0.84, 95% CI, 0.75 to 0.94). Results for the additional hospitalizations outcomes, including all (first and subsequent) hospitalizations and composites including prolonged hospitalizations, deaths, and hospitalizations resulting in death were similar.

The mean number of days normalized per patient-year spent in hospital was 2.3 (SD = 7.5) in the dapagliflozin group and 2.8 (SD = 9.6) in the placebo group (P = 0.027).

Hospitalizations were not measured in the other RCTs.

Health-Related Quality of Life

Change from baseline HRQoL was measured but not reported in DAPA-CKD. HRQoL was not measured in the other RCTs.

Symptom Severity

Symptom severity was not measured in any of the included RCTs.

Functional Status

Functional status was not measured in any of the included RCTs.

Harms Results

Across all RCTs,[9,15,16,19] the number of AEs, serious AEs, or withdrawals from treatment due to AEs appeared similar across groups (Table 2). Withdrawal from treatment due to AEs were not reported in Kohan et al. (2014); however, more patients in the placebo group withdrew from the RCT due to AEs compared with the dapagliflozin group (26.2% versus 12.9%). Deaths due to AEs were not reported in any RCT. Amputations, DKA, and major hypoglycemia were infrequent in DAPA-CKD, DELIGHT, and DERIVE. In Kohan et al. (2014), amputations and DKA were not reported and major hypoglycemia was infrequent. Genital and urinary tract infections, as reported among patients with both CKD and T2DM in DELIGHT and DERIVE, were also infrequent. In Kohan et al. (2014), 14% of patients in each group experienced a urinary tract infection (UTI). Seven (8.2%) patients in the dapagliflozin group and 3 (3.6%) in the placebo group experienced a genital infection. The incidence of palpitations was not reported in any of the RCTs.

Renal AEs were balanced across groups in all RCTs. In DAPA-CKD, 155 (7.2%) and 188 (8.7%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In DELIGHT, 4 (2.8%) and 6 (4.1%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In DERIVE, 1 (0.6%) and 2 (1.2%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In Kohan et al. (2014), 8 (9.4%) and 6 (7.1%) patients in the dapagliflozin and placebo groups had a renal AE, respectively.

Volume depletion was balanced across groups in all RCTs, except Kohan et al. (2014). In DAPA-CKD, 127 (5.9%) and 90 (4.2%) patients in the dapagliflozin and placebo groups had volume depletion, respectively, In DELIGHT, 4 (2.8%) and 4 (2.7%) patients in the dapagliflozin and placebo groups had volume depletion, respectively. In DERIVE, 3 (1.9%) patients in the dapagliflozin group and none in the placebo group had volume depletion. In Kohan et al. (2014), 11 (12.9%) and 5 (6.0%) patients in the dapagliflozin and placebo groups had volume depletion, respectively.

Critical Appraisal

In all RCTs the randomization appeared successful; there were a few baseline imbalances noted in DELIGHT, DERIVE, and Kohan et al. (2014) that were compatible with chance. Background therapies were generally well-balanced across groups. Adherence to the interventions was high in DAPA-CKD (96% or higher), but this was measured only in a population subset; 12.7% and 14.4% of placebo and dapagliflozin participants, respectively, discontinued treatment during follow-up. Adherence was not reported (and therefore not known) in the other RCTs. Matched placebos were used in all RCTs to maintain blinding of participants and personnel. There were some concerns for missing outcome data in DAPA-CKD; however, sensitivity analyses yielded similar results to the primary analysis. Follow-up was nearly complete in both DELIGHT and DERIVE. In Kohan et al. (2014), there were substantial amounts of missing data (40% or more for change from baseline eGFR and UACR) at long-term follow-up, which may have introduced bias. Risk of bias in selection

of the reported result is likely low in all RCTs. Data were mostly analyzed in accordance with a prespecified analysis plan; however, data for some outcomes that were measured were not reported in DAPA-CKD (e.g., HRQoL). The statistical analysis methods appear to be acceptable in all RCTs and type I error was adequately controlled. In Kohan et al. (2014), differences in change from baseline were often not reported, limiting interpretation. Since DAPA-CKD stopped early for efficacy, it is possible that the benefits of dapagliflozin over placebo were overestimated. Subgroup analyses were defined a priori in DAPA-CKD and DELIGHT but were not powered to find significant differences. These analyses were not adjusted for multiple comparisons, resulting in an increased risk of type I error for statistically significant subgroup interactions.

Per the clinical experts consulted by CADTH, the patients, interventions, and background therapies in the RCTs were generally reflective of clinical practice in Canada. Only patients with stage IIIA CKD were included in DERIVE, which limits the generalizability to other disease stages. Use of ACE inhibitors and ARBs was not reported in Kohan et al. (2014), so it is not clear whether background therapies were similar to those used in Canada. Unlike DELIGHT, DERIVE, and Kohan et al. (2014), DAPA-CKD included patients with CKD irrespective of T2DM status, which the clinical experts consulted by CADTH considered valuable. The length of follow-up in both DELIGHT and DERIVE (27 weeks) was insufficient to inform the long-term efficacy of dapagliflozin. Outcomes that are important to patients, like HRQoL, symptoms, and functional status were not reported in any of the RCTs.

Indirect Comparisons

Description of Studies

Five network meta-analyses (NMAs) assessing dapagliflozin (10 mg) relative to canagliflozin (100 mg and/or 300 mg) or finerenone (10 and 20 mg) in patients with CKD and T2DM were included. The relevant outcomes were change in eGFR and UACR in 1 NMA;[21] MI in 1 NMA;[22] CV death in 2 NMAs;[21,23] all-cause death in 1 NMA;[23] a renal composite in 2 NMAs;[22,23] a cardiorenal composite in 1 NMA;[24] MACE in 3 NMAs;[22,23,25] hospitalization for HF in 2 NMAs;[21,23] and harms in 1 NMA (including AEs, SAEs, UTIs, and discontinuations from treatment).[22]

Efficacy Results

Change in eGFR

In the NMA by Lin et al. (2022),[22] for the comparison of dapagliflozin to canagliflozin 100 mg, the MD in the change from baseline eGFR was −4.20 (95% CI, −6.97 to −1.43) mL/min/1.73 m^2, favouring canagliflozin. For the comparison of dapagliflozin to canagliflozin 300 mg, the MD in the change from baseline eGFR was affected by imprecision, such that the 95% CI included the potential that either drug could be favoured. The authors noted funnel plot asymmetry, suggesting a risk of publication bias.

Change in UACR

In the NMA by Lin et al. (2022),[22] for the comparison of dapagliflozin to canagliflozin 100 mg, the MD in the change from baseline UACR was 99.09 (95% CI, 11.40 to 186.78) mg/g, favouring canagliflozin. The authors noted funnel plot asymmetry, suggesting a risk of publication bias.

Table 2: Summary of Harms from DAPA-CKD, DELIGHT, DERIVE, and Kohan et al. (2014) (SAS)[a]

Harms	DAPA-CKD		DELIGHT		DERIVE		Kohan et al. (2014)	
	Dapagliflozin N = 2,152	Placebo N = 2,152	Dapagliflozin N = 145	Placebo N = 148	Dapagliflozin N = 160	Placebo N = 161	Dapagliflozin N = 85	N = 84
Harms, n (%)								
Any AE	NR	NR	79 (54.5)	81 (54.7)	67 (41.9)	77 (47.8)	77 (90.6)	77 (91.7)
Any serious AEs	633 (29.5)	729 (33.9)	12 (8.3)	16 (10.8)	9 (5.6)	14 (8.7)	26 (30.6)	26 (31.0)
WDAE (from study treatment)	118 (5.5)	123 (5.7)	4 (2.8)	8 (5.4)	3 (1.9)	3 (1.9)	NR[b]	NR[b]
Deaths[c]	NR	NR	NR	NR	NR	NR	NR	NR
Notable harms, n (%)								
Amputations	35 (1.6)	39 (1.8)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR
Genital infections	NR	NR	4 (2.8)	0 (0.0)	3 (1.9)	2 (1.2)	7 (8.2)	3 (3.6)
Urinary tract infections	NR	NR	5 (3.4)	4 (2.7)	4 (2.5)	6 (3.7)	12 (14.1)	12 (14.3)
Any definite or probable DKA	0 (0.0)	2 (0.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR
Palpitations	NR	NR	NR	NR	NR	NR	NR	NR
Fractures	85 (4.0)	69 (3.2)	1 (0.7)	2 (1.4)	0 (0.0)	0 (0.0)	8 (9.4)	0 (0.0)
Renal-related AEs	155 (7.2)	188 (8.7)	4 (2.8)	6 (4.1)	1 (0.6)	2 (1.2)	8 (9.4)	6 (7.1)
Major hypoglycemia	14 (0.7)	28 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	4 (4.8)
Volume depletion	127 (5.9)	90 (4.2)	4 (2.8)	4 (2.7)	3 (1.9)	0 (0.0)	11 (12.9)	5 (6.0)

AE = adverse event; DKA = diabetic ketoacidosis; SAS = safety analysis set; WDAE = withdrawal due to adverse event.

[a]Median follow-up time was 2.4 years in DAPA-CDK. Follow-up time for DELIGHT and DERIVE was 27 weeks. Follow-up time for Kohan et al. (2014) was 104 weeks.

[b]Withdrawal from treatment due to AEs was not reported. Eleven (12.9%) of patients in the dapagliflozin group and 22 (26.2%) in the placebo group withdrew from the RCT due to AEs.

[c]Mortality was reported in all RCTs as either an efficacy outcome or as an AE; however, deaths due to AEs were not specifically reported.

Source: Heerspink et al. (2020);[9] Pollock et al. (2019);[15] Fioretto et al. (2018);[16] Kohan et al. (2014).[19]

Cardiovascular Events

In the NMA by Li et al. (2022),[21] for the comparisons of dapagliflozin to canagliflozin as well as to finerenone, the effect estimates were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured.

Mortality

Cardiovascular death was reported in the NMAs by Li et al. (2022)[21] and Zhang et al. (2022).[23] All-cause death was also reported by Zhang et al. (2022).[23] All reported effect estimates across the comparisons were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured.

Composite Outcomes (Renal and/or Cardiovascular Events)

For the renal composite outcomes reported by Li et al. (2022)[21] (new onset of macroalbuminuria, ESKD, or decline in renal function) and Zhang et al. (2022) (sustained decrease of at least 40% in the eGFR from the baseline or a doubling of the serum creatinine level, kidney failure, or renal death),[23] the effect estimates for the comparison of dapagliflozin to canagliflozin were affected by imprecision. In the comparison of dapagliflozin to finerenone, finerenone was favoured in the analysis by Zhang et al. (2022) with RR = 0.70 (95% CI, 0.55 to 0.87),[23] however in the analysis by Li et al. (2022) the effect was imprecise.[21] For the cardiorenal composite outcome reported by Chen et al. (2022)[24] (worsening eGFR, ESKD, renal death, or CV death), for the comparison of dapagliflozin to canagliflozin the effect estimate was affected by imprecision, such that the 95% CrI included the possibility that either drug was favoured.

Across the 3 NMAs that investigated MACE (deaths from CV causes, nonfatal MI, or nonfatal stroke),[21,23,25] across comparisons (i.e., dapagliflozin versus canagliflozin in 3 NMAs and dapagliflozin versus finerenone in 2 NMAs) the effect estimates were affected by imprecision, such that the 95% CI or CrI included the possibility that either drug was favoured.

Hospitalization

Hospitalization for HF was reported in the NMAs by Li et al. (2022)[21] and Zhang et al. (2022).[23] For the comparison of dapagliflozin to canagliflozin, the effect estimates from both NMAs were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured. For the comparison of dapagliflozin to finerenone, the effect estimate from the NMA by Li et al. (2022)[21] was similarly affected by imprecision. The point estimate (RR) from the NMA by Zhang et al. (2022)[23] favoured dapagliflozin; however, the 95% CI included the possibility of little-to-no difference between the 2 drugs.

Other Efficacy Outcomes

HRQoL, symptom severity, and functional status were not reported in any of the included NMAs.

Harms Results

The NMA by Lin et al. (2021) investigated AEs, serious AEs, UTIs, and discontinuations from treatment.[22] Results for all outcomes were inconclusive for the comparison of dapagliflozin to canagliflozin (100 mg and 300 mg) due to imprecision. No NMAs were found that compared harms between dapagliflozin and finerenone.

Critical Appraisal

Four[21-23,25] of the 5 systematic reviews with NMA were informed by an a priori protocol. The search strategies relied heavily on bibliographic databases without other sources, therefore eligible studies could have been missed. In all cases, the methods for study selection and data extraction were adequate to minimize the risk of error, and risk of bias was assessed using appropriate tools. Based on the reported information, analysis methods across the NMAs generally appeared appropriate; however, model parameters (i.e., selection of priors, assessment of model fit, convergence) and assessments of heterogeneity were not always presented. In general, the majority of the contributing RCTs were identified as being at low risk of bias by the systematic review authors.

Clinical and methodological heterogeneity was noted in patient characteristics (e.g., sex distribution, disease severity), outcome definitions (particularly the composites), and length of follow-up across the included RCTs, which challenged the transitivity assumption underlying the NMAs. In many cases, there was insufficient information reported by the authors of the NMAs to judge the degree of heterogeneity in potential treatment effect modifiers. The networks were sparse (several comparisons informed by few RCTs), and all evidence for the comparisons of interest was indirect. Several comparison-outcomes were affected by important imprecision which reduced the certainty of the effect estimates. Not all of the NMA authors investigated the potential for publication bias, however Lin et al. (2022)[22] noted funnel plot asymmetry and indicated a potential that the analyses were affected by publication bias.[22] It is also notable that several of the contributing RCTs were industry-sponsored.

Across the NMAs, the included populations were directly relevant and most applicable to patients with both T2DM and CKD. Clinically relevant outcomes were considered. Notably, canagliflozin is only indicated in patients with T2DM. Several important efficacy outcomes which may be of high relevance to patients (e.g., HRQoL, symptom severity, functional status) were not reported.

Other Relevant Evidence

Description of Studies

A total of 3 RCTs were included in this section: 2 RCTs providing information specific to patients with HF, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[26,27] trial and the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial;[28,29] 1 RCT providing information specific to patients with T2DM and at increased risk of CV events the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial.[30-32] These RCTs provide subgroup-level data for patients with CKD (defined by eGFR or UACR).

DAPA-HF (N = 4,744) and DELIVER (N = 6,263) were multicentre double-blind RCTs that aimed to determine the efficacy and safety of dapagliflozin among adults with HF and either reduced (DAPA-HF) or preserved (DELIVER) ejection fraction.[27,29] In both RCTs, patients with or without T2DM were eligible. DECLARE-TIMI 58 (N = 17,160) was a multicentre double-blind RCT with T2DM and established or risk factors for atherosclerotic CVD. In all RCTs patients were randomized 1:1 to dapagliflozin 10 mg once daily or matching placebo. Patients with eGFR less than 60 mL/min/1.73m^2 was a prespecified subpopulation of interest in

DAPA-HF (n = 1,926)[26,27] and DECLARE-TIMI 58 (n = 1,265).[30-32] In DECLARE-TIMI 58 there was an additional subpopulation of patients with UACR 30 to 300 mg/g and greater than 300 mg/g (n = 5,199).[31] Patients with eGFR less than 45 mL/min/1.73m^2 and 45 to less than 60 mL/min/1.73m^2 were prespecified subpopulations of interest in DELIVER (n = 1,657).[27,29]

Results

Baseline characteristics were generally similar across treatment groups in DAPA-HF and DELIVER for the subgroups of interest, with mean age ranging from 71 to 74 years, and half of patients having T2DM.[27,29] There were some differences in the proportion male (72% in DAPA-HF and 51% in DELIVER) and ACE inhibitor or ARB use at baseline (80% in DAPA-HF and 71% in DELIVER) across the trials.[27,29] In DECLARE-TIMI 58, mean age was 64 years, 63% were male, all had T2DM, and 81% were using ACE inhibitors or ARBs at baseline.[32] The median follow-up was 18.2 (range 0 to 27.8) months in DAPA-HF,[29] 2.3 (range 1.7 to 2.8) years in DELIVER,[29] and 4.2 (range 3.9 to 4.4) years in DECLARE-TIMI 58.[32]

The composite of worsening renal function was reported in all 3 RCTs. Across the reported subgroups, dapagliflozin was favoured among the UACR subgroups in DECLARE-TIMI 58;[31] across the remaining groups few events were reported which generally resulted in wide CIs.[26,28,32] Similarly, few events were recorded for individual components of the composite in DAPA-HF and DELIVER, resulting in uncertainty in the potential benefit or harm of dapagliflozin.[26,28] Time to doubling of serum creatinine was reported only in DAPA-HF; the findings favoured dapagliflozin (HR = 0.74, 95% CI, 0.26 to 0.83).[26] The trend in change in eGFR over time was reported in all RCTs, and in general corresponded to the findings in the Systematic Review section of this report.[26,28,30] Change in UACR was reported in DECLARE-TIMI 58; in all relevant subgroups, there was an initial decline in UACR during the first 6 months that was greater in the dapagliflozin group versus placebo; the difference was sustained at all time points over the 4-year follow-up.[30]

All 3 RCTs presented results for the worsening HF composite (hospitalization or urgent visit for HF or CV death) and the composite of hospitalization or urgent visit for HF. In the DAPA-HF eGFR less than 60 mL/min/1.73m^2 subgroup and the DELIVER eGFR 45 to less than 60 mL/min/1.73m^2 subgroup, dapagliflozin was favoured, however in the remaining included groups there was a lack of clarity about the potential benefit of dapagliflozin because of wide CIs.[27,29,32] Time to MACE (CV death, MI, or ischemic stroke), MI, and ischemic stroke was reported for the DECLARE-TIMI 58 eGFR less than 60 mL/min/1.73m^2 subgroup; for each end point the CIs were wide due to a limited number of events being reported.[32]

Across all mortality outcomes, CIs were too wide to definitively show a benefit of dapagliflozin over placebo.[26,28,32] The findings related to harms in DAPA-HF[26] and DELIVER[28] appeared to align with the findings of the systematic review.

Critical Appraisal

The RCTs were informed by a priori protocols. Though the RCTs were randomized, there was no stratification by baseline eGFR or UACR, therefore prognostic balance within the subgroups may not be ensured. Across the RCTs, between 11% (DAPA-HF) and 25% (DECLARE-TIMI 58) of patients discontinued treatment; in all cases discontinuations were balanced across the treatment groups. Losses to follow-up from the RCTs

were low. The patients and investigators were blinded and efficacy end points were objective and centrally adjudicated. The RCTs were not powered to detect differences between dapagliflozin and placebo in the subgroups, and event rates for some end points were low, resulting in imprecision. The analyses were not adjusted for multiple comparisons, so statistically significant findings are at increased risk of type I error. The follow-up time, particularly in DAPA-HF, may have been inadequate for longer-term outcomes. Outcomes of importance to patients (e.g., HRQoL, symptoms) were not reported.

Economic Evidence

Cost Information

As CADTH does not have access to an economic model to address the specified research question, the economic review included a comparison between the treatment costs of dapagliflozin and those of comparators deemed to be appropriate based on clinical expert consultations and drug plans.

Based on publicly available list prices, dapagliflozin is expected to have an annual cost of $996 per patient. As dapagliflozin would be used as an add-on therapy to ACE inhibitors or ARB, the reimbursement of this treatment would be more costly when compared to ACE inhibitors/ARB monotherapy in all patient subgroups. Specific to patients with T2DM, comparators further include finerenone or canagliflozin as add-on therapy to ACE inhibitors or ARB. Given this, dapagliflozin was found to be a less costly alternative in comparison to finerenone and canagliflozin at current public list price (cost savings of $223 for finerenone and $59 for canagliflozin per patient).

Conclusions

Evidence from 4 RCTs suggests that dapagliflozin as an add-on to SOC is an effective and safe treatment for adults with CKD (with or without T2DM). Evidence from DAPA-CKD suggests that among patients with CKD (with or without T2DM), dapagliflozin as an add-on to SOC therapy increases the time to CV and renal events relative to placebo. Dapagliflozin also resulted in fewer hospitalizations, reduced all-cause mortality, and reduced CV mortality or hospitalization for HF relative to placebo in DAPA-CKD. Evidence from the 4 RCTs suggests that dapagliflozin results in an initial decline in eGFR. In longer term RCTs (DAPA-CKD and Kohan et al. (2014)), the rate of eGFR decline was slowed relative to placebo thereafter (not formally tested in Kohan et al. (2014)). Abrupt declines in renal function were infrequent in all RCTs and the frequency was similar across groups. At longest follow-up in DAPA-CKD, dapagliflozin resulted in greater reduction in UACR relative to placebo; these results were supported by short-term results in DELIGHT but not DERIVE. Across all RCTs, the number of patients experiencing at least 1 AE or SAE was similar across groups. In all RCTs except for Kohan et al. (2014), most notable harms (i.e., amputations, genital infections, UTIs, DKA, palpitations, fractures, major hypoglycemia) were infrequent. No evidence was identified for HRQoL, symptom severity, or functional status, so the effect of dapagliflozin on these outcomes among patients with CKD is not known. The results of 5 NMAs suggested that canagliflozin 100 mg was favoured over dapagliflozin for change from baseline eGFR and UACR. The results of 2 NMAs suggested that dapagliflozin was favoured over finerenone for the renal composite outcome. However, due to methodological limitations, these results should be considered to be uncertain. The effect estimates were too imprecise to draw a conclusion for

other outcomes (e.g., cardiorenal composite outcomes, mortality, MACE, AEs, SAEs, UTIs, discontinuations). No NMAs were found that compared harms between dapagliflozin and finerenone.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of dapagliflozin as an add-on to SOC for the treatment of CKD could not be determined Results of the cost comparison of treatment costs demonstrate that dapagliflozin is expected to have an annual cost of $996 per patient. As dapagliflozin would be used as an add-on therapy to ACE inhibitors/ or ARB, the reimbursement of this treatment would be more costly when compared to ACE inhibitors or ARB monotherapy in all patient subgroups. Specific to patients with T2DM, comparators further include finerenone or canagliflozin as add-on therapy to ACE inhibitors or ARB. Given this, dapagliflozin was found to be a less costly alternative in comparison to finerenone and canagliflozin at current public list prices as their annual costs were $1,219 and $1,055, respectively, per patient. The potential downstream costs savings associated with adding dapagliflozin to ACE inhibitors and/or ARBs given the increased time to occurrence of sustained at least a 50% increase in eGFR, ESKD, renal or CV death when compared to ACE inhibitors and/or ARBs monotherapy were not considered as part of the cost comparison. To adequately consider the health care resource implications associated with the comparative clinical benefits reported within the clinical trials, a cost-effectiveness analysis of dapagliflozin plus ACE inhibitors and/or ARBs would be required. Given the uncertainties in the comparative clinical benefits between dapagliflozin, finerenone and canagliflozin as an add-on therapy to ACE inhibitors and/or ARBs monotherapy, it remains unclear whether and which therapy would represent the most cost-effective option in patients with CKD and T2DM.

Introduction

Disease Background

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD is defined as "abnormalities of kidney structure or function, present for at least 3 months, with implications for health."[2] CKD can be identified based on clinical context and using blood and urine tests to evaluate for declines in eGFR and loss of protein in the urine (proteinuria).[4] CKD is classified by considering the underlying cause (i.e., systemic disease affecting the kidney versus primary kidney disease), GFR category, and albuminuria category.[2] The GFR and albuminuria categories can be used to evaluate disease progression and level of risk. Stages of GFR range from 1 (normal, 90 mL/min/1.73 m^2 or higher) to 5 (kidney failure, 15 mL/min/1.73 m^2 or lower), while stages of albuminuria range from 1 (normal to mildly decreased, 30 mg/day or less) to 3 (severely increased, 300 mg/day or more).[2] At every level of GFR, increasing albuminuria results is an increased risk of adverse outcomes.[2] Kidney failure (ESKD) requires dialysis or kidney transplant to sustain life.[4]

There are multiple risk factors for developing CKD, including older age, the presence of other chronic conditions, ethnicity, lifestyle factors, prior acute kidney injury, and/or family history of CKD.[33] People affected by diabetes have an almost 2-fold increased risk of developing CKD, making it the predominant risk factor especially when combined with hypertension.[34,35] Following initial injury, the kidney can compensate via

several mechanisms including adaptive hyperfiltration, whereby the remaining healthy nephrons increase their filtration rate, however over time this results in damage to these nephrons.[4,36] In the early stages, CKD is asymptomatic, but in the later stages results in uremia which is characterized by a broad collection of signs and symptoms.[4,36] These include volume overload, metabolic alterations (e.g., anemia, mineral imbalances), hypertension, and metabolic bone disease.[2,4] These can result in symptoms including fatigue, pain, weakness, reduced mobility, and nausea, among others.[37] CKD and its associated treatments negatively impact patients' quality of life,[37] and CKD is an independent risk factor for several adverse outcomes including CVD, ESKD, and premature mortality.[4,38]

In Canada, the prevalence of stage III to V CKD in primary care was estimated as 71.9 per 1,000 individuals between 2010 and 2014.[39] This consisted of mainly individuals with stage IIIa and IIIb disease (57.0 per 1,000 individuals), followed by stage IV (11.7 per 1,000 individuals) and stage V (3.3 per 1,000 individuals).[40] Progression through the stages of CKD can be gradual (with periods of stability) or rapid, with the rate of progression being influenced by genetic and behavioural factors, as well as the presence of comorbid conditions.[4,41] Progression to ESKD occurs in only about 1% of individuals with CKD but poses a disproportionate burden on those affected and the health care system.[2] In 2021, 48,000 Canadians were affected by ESKD, about 30,000 were receiving dialysis, and about 18,000 were living with a kidney transplant.[42]

Standards of Therapy

The aim of treatment for CKD is to prevent or delay progression and to address complications associated with reduced kidney function including anemia, uricemia, acidosis, metabolic bone disease, and elevated CV risk (including risk of HF).[2] Treatment also involves managing the underlying cause of CKD, including for example obesity, T2DM, and cardiac disorders.[4]

Lifestyle modification and control of hypertension in patients with proteinuria are key components of treatment to delay progression.[4] Lifestyle modifications can include restrictions on protein and sodium intake (alterations to phosphate and potassium may also be required), being adequately physically active, attaining a healthy body weight, and not smoking.[2] Antihypertensive therapy commonly consists of ACE inhibitors or ARBs.[2] Additional treatments are recommended for patients with comorbid T2DM to delay CKD progression and reduce CV risk.[2] In these patients, glycemic control is considered part of a multifaceted approach that may also include treatment with statins and/or antiplatelet therapies.[2] Additional treatments may be used to address complications (e.g., anemia, acidosis, metabolic bone disease), as well as fluid and electrolyte abnormalities,[2] especially as patients progress to kidney failure.

SGLT2 inhibitors were initially developed for patients with T2DM and aimed at treating hyperglycemia; however, their beneficial effects on renal and CV outcomes in these patients have since led to the investigation of this class of drugs on cardiorenal outcomes in patients with CVD and CKD.[5] Of currently available SGLT2 inhibitors believed to have renal benefit, dapagliflozin is indicated for patients with or without T2DM,[1]. In contrast, canagliflozin is indicated only for patients with T2DM.[1,6]

Drug

The key characteristics of dapagliflozin are shown in Table 3. Dapagliflozin is a SGLT2 inhibitor that was granted Notice of Compliance (NOC) status in August 2021 for CKD.[1] The indication under review is for reducing the risk of sustained eGFR decline, ESKD, and CV and renal death in adult patients with CKD.[1]

SGLT2 inhibitors function by reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release.[43] In addition to reducing blood glucose, dapagliflozin reduces sodium reabsorption and increases the delivery of sodium to the distal tubule, which may in turn influence lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure.[43]

The drug has been previously reviewed by CADTH 3 times, for indications in T2DM and HF. In November 2015, CADTH's Canadian Drug Expert Committee (CDEC) recommended to reimburse dapagliflozin with conditions, in combination with metformin, a sulfonylurea, or insulin (alone or with metformin) to improve glycemic control in patients with T2DM.[44] In April 2016, CDEC did not recommend reimbursing dapagliflozin in combination with metformin and a sulfonylurea in patients with T2DM.[44,45] In April 2016, CDEC did not recommend reimbursing dapagliflozin in combination with metformin and a sulfonylurea in patients with T2DM.[45] In December 2020, CDEC recommended reimbursing dapagliflozin with conditions as an adjunct to SOC therapy for patients with HF with reduced ejection fraction.[46]

Table 3: Key Characteristics of Dapagliflozin, Canagliflozin, and Finerenone

Criteria	Dapagliflozin	Canagliflozin	Finerenone
Mechanism of action	Blocking reabsorption of glucose in the proximal tubule through SGLT2, which lowers the renal glucose threshold and leads to substantial glycosuria.	Blocking reabsorption of glucose in the proximal tubule through SGLT2, which lowers the renal glucose threshold and leads to substantial glycosuria.	Nonsteroidal, selective mineralocorticoid receptor antagonist
Indication[a]	To reduce the risk of sustained eGFR decline, ESKD, and CV and renal death in adults with CKD.	As an adjunct to diet, exercise, and SOC therapy to reduce the risk of ESKD, doubling of serum creatinine, and CV death among patients with T2DM and diabetic nephropathy with albuminuria (> 33.9 mg/mmol).	As an adjunct to SOC therapy in adults with CKD and T2D to reduce the risk of: • end-stage kidney disease and a sustained decrease in eGFR • CV death, nonfatal MI, and hospitalization for HF.
Route of administration	Oral	Oral	Oral
Recommended dose	10 mg once daily	• eGFR ≥ 60 mL/min/1.73 m^2: 100 mg once daily • eGFR 30 to < 60 mL/min/1.73 m^2: 100 mg once daily (can be increased to 300 mg once daily for additional glycemic control)	• 20 mg once daily for patients with eGFR ≥ 60 mL/min/1.73 m^2 • 10 mg once daily for patients with eGFR ≥ 25 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2

Criteria	Dapagliflozin	Canagliflozin	Finerenone
Serious adverse effects or safety issues	• Contraindicated in patients on dialysis • Should not be used in patients with T1DM, in the treatment of diabetic ketoacidosis or in patients with a history of diabetic ketoacidosis • Not recommended in CKD patients with polycystic kidney disease, lupus nephritis, antineutrophil cytoplasmic antibody-associated vasculitis, or patients requiring or having recent history of immunosuppressive therapy for the treatment of kidney disease	• Contraindicated in patients on dialysis • Should not be used in patients with T1DM, in the treatment of diabetic ketoacidosis, or in patients with a history of diabetic ketoacidosis • Increased risk of nephropathy • Increased risk of lower limb amputations	• Contraindicated in patients with Addison's disease or who are receiving concomitant systemic treatment with medications that are strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) • Hyperkalemia

CKD = chronic kidney disease; ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; SGLT2 = sodium-glucose cotransporter-2; MI = myocardial infarction; SOC = standard of care; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Health Canada–approved indication.

Source: dapagliflozin product monograph;[1] canagliflozin product monograph;[6] finerenone product monograph.[47]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient input(s) received by CADTH have been included in the stakeholder section at the end of this report.

Two patient groups, CARP and Kidney Foundation of Canada, submitted input for this review. Both patient groups collected patient and caregiver perspectives through surveys. CARP collected survey responses from August 15 to August 19, 2022. Of 2,044 respondents, a subset reported living with CKD (16%, n = 321); 2% (n = 40) reported being caregivers, 9% (n = 176) being family or friends of people living with CKD, and 39% (n = 792) being concerned about kidney health. The Kidney Foundation of Canada collected survey responses in July and August 2022, promoted through the organization's social media channels and website. Of 36 respondents, 53% (n = 19) were patients with CKD and 6% (n = 2) were caregivers.

Respondents to both surveys described their experience living with CKD. Most respondents indicated that CKD had a significant effect on their quality of life, reporting symptoms such as fatigue, frequent urination, itchiness, swelling, dizziness and nausea or vomiting, frequent hospitalization, insomnia, depression, and low morale. Patients described limitations in their ability to work and engage in physical activity and travel, with a financial burden due to loss of income.

Respondents highlighted their challenges with existing treatments and their expectations for new CKD therapies. Challenges with existing treatment included difficulty in access (e.g., lack of drug coverage),

difficulty in remembering to take medications, high number of medications, and difficulty to take time off work for treatment (e.g., for dialysis). Expectations for new therapies included improvements in energy levels, well-being, and quality of life. Other important expectations were having to use less medication overall, take less time away from work, and make fewer hospital visits. Patients were also concerned with concomitant medication use, their mood, duration of treatment, its cost and availability, and side effects.

Respondents also shared their experience with the drug under review. In the CARP survey, 9 respondents indicated they had experience with dapagliflozin. In the Kidney Foundation survey, 2 respondents reported experience with dapagliflozin. Both respondents reported improved potassium and sodium levels since undergoing treatment. One respondent reported an improvement in their symptoms of tiredness and weakness, high blood pressure, nausea, and vomiting. One patient each reported worsening tiredness/ weakness, high blood pressure, and low blood pressure.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of CKD at tertiary centres.

Unmet Needs

Per the clinical experts, CKD is currently managed with lifestyle modification and therapeutic interventions including renin angiotensin system inhibitors (e.g., ACE inhibitors and ARBs) to manage hypertension, statins, and drugs to manage hyperglycemia (in patients with CKD and T2DM). The current goal of CKD treatment is to prevent or delay progression of CKD to kidney failure, and to reduce the risk of adverse CV events (e.g., MI, stroke, peripheral vascular disease, and mortality). The clinical experts noted that current treatments do not address the persistent residual risk of developing kidney failure and/or CV events in some patients.

Place in Therapy

The clinical experts indicated that dapagliflozin would be used as an add-on therapy to the current SOC, which is ACE inhibitors and/or ARBs and statins.

Patient Population

According to the clinical experts, patients with CKD who would be most suited to dapagliflozin include those with T2DM-related CKD with eGFR of 25 to 75 mL/min and proteinuria. The clinical experts also indicated that patients with T2DM, eGFR above 25 mL/min mL/min, and albuminuria above 3 mg/mmol could use dapagliflozin in combination with finerenone.

Assessing Response to Treatment

Clinical outcomes identified as important by clinical experts include reduction in risk of kidney failure requiring dialysis or transplant, hospitalization for HF, all-cause mortality, and adverse CV outcomes. The clinical experts indicated that surrogate measures of renal function such as reduction in proteinuria, enhanced glycemia control in patients with T2DM (particularly with eGFR above 45 mL/min/1.73 m^2), and stable eGFR are process measures used to assess response to treatment and quality of care.

Discontinuing Treatment

The clinical experts suggested that the following would determine if the treatment should be discontinued: AEs such as DKA or amputation risk, the onset of mycotic genital infections, and/or the onset of pregnancy. The clinical experts noted that the use of dapagliflozin in people of childbearing age will require careful consideration as the drug is not recommended in pregnancy. One expert added that Sick Day Medication rule (i.e., temporarily withholding dapagliflozin) should be considered in the setting of poor oral intake or fasting to minimize the risk of euglycemic DKA, and bone health should be regularly monitored to mitigate the risk of fractures.

Prescribing Conditions

The clinical experts indicated that dapagliflozin can be safely initiated by primary care providers in the community setting, and could also be prescribed by specialists in nephrology, cardiology, endocrinology, or general internal medicine.

Additional Considerations

The clinical experts did not recommend dapagliflozin for patients with adult polycystic kidney disease and patients with autoimmune diseases (e.g., lupus nephritis, vasculitis, Antiglomerular Basement Membrane disease) who are receiving immunosuppressive therapy, given this drug has not been studied in these patients and is not yet indicated.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. The full original clinician group inputs received by CADTH have been included in the stakeholder section at the end of this report.

Clinical group input aligned with the input provided by the clinical experts. Clinician group input was submitted by 2 groups: BC Renal Medical Directors and a group of nephrologists, internal medicine physicians and a pharmacist at the Nova Scotia Health Authority. The BCR Medical Directors represent nephrologists within the province of BC. The Medical Directors are physician leads for the 5 geographical health authorities and responsible for ensuring that the principles, practice, and policies of BC Renal are implemented.

Both clinician groups' input on unmet needs aligned with that of the clinical experts, and additionally noted improving HRQoL to enable greater life participation and maintaining employment and independence. They

agreed that current therapies do not reliably delay progression in all individuals and highlighted the need for more effective therapies that are well tolerated.

The input of the clinician groups on populations suitable for treatment with dapagliflozin agreed with that of the clinical experts, indicating it to be those meeting the inclusion criteria of the DAPA-CKD trial (with or without T2DM). Both clinician groups noted that the drug would be used in addition to current medications and in some instances would permit reduction or cessation of other medications, which may be valued by patients.

Similar to the input of the clinical experts, the BC Renal Medical Directors group indicated that plateauing of kidney function within 4 to 8 months of treatment, usually with a reduction in proteinuria is a clinically meaningful response. In addition to the discontinuation criteria mentioned by the clinical experts, the Nova Scotia Health Authority group added that additional evaluation, and reassessment of SGLT2 therapy may be needed if there is a greater than 25% decline in eGFR upon initiation of dapagliflozin.

Both clinician groups advocated for the availability of dapagliflozin to all who would benefit.

Industry Input

CADTH prepared this section based on industry-provided input.

Industry input was submitted by 1 organization, AstraZeneca Canada Inc., 1 of the manufacturers of dapagliflozin in Canada at the time of this review. They agreed with the project scope posted on the CADTH website and commented on the burden of CKD on patients and caregivers.

The manufacturer noted that CKD is associated with a significant clinical burden in patients, encompassing substantial morbidity and mortality, even in the early stages of disease, and this risk increases as CKD progresses. Per the manufacturer, CKD has significant physical, social, emotional, work, and financial impacts on both patients and caregivers. The manufacturer suggested that it is important to protect patients from cardiorenal outcomes, and access to dapagliflozin will improve patient and caregiver quality of life.[48] They also suggested that access to dapagliflozin will have limited budget impact to drug plans as generics enter the market following dapagliflozin's loss of exclusivity in May 2023.

The manufacturer shared that ESKD, especially dialysis, are among the costliest complications encountered by any health care system; with the annual per patient cost rising exponentially between CKD stage III and dialysis.[49] Further, the manufacturer added that the burden of CKD and renal replacement therapy increased considerably during the COVID-19 pandemic, which strained nephrology services through an increased incidence of acute kidney injuries, higher need for dialysis treatment and fewer renal transplants being performed.[50]

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review process by identifying issues that may impact their ability to implement a recommendation. The

implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Policy considerations	
At what point in therapy would dapagliflozin be appropriate to initiate in patients with CKD to reduce the risk of declined eGFR, CV and renal death?	As per the clinical experts consulted by CADTH for this review, dapagliflozin would be appropriate for any patients with eGFR of 25 mL/min to 60 mL/min, and as an add-on therapy with ACE inhibitors or ARBs.
Are there other drugs (i.e., ACE or ARB) in the treatment of CKD that would be required before initiating dapagliflozin?	Per the experts, aligning with the DAPA-CKD protocol, patients would ideally be on a maximal tolerated dose of ACE inhibitors or ARBs and remain with residual risk (albuminuria) and kidney function represented by an eGFR of at least 20 mL/min and UACR of 200 mg/g to 5,000 mg/g before dapagliflozin is initiated. The clinical experts noted there may be situations where ACE inhibitors or ARBs are not tolerated, or significant hyperkalemia limits their effective use. In such situations, dapagliflozin can be used without meeting the requirement for initial use of ACE inhibitors or ARBs.
If patients are not able to tolerate either an ACE or ARB can dapagliflozin still be initiated?	Per the clinical experts, dapagliflozin can be initiated in patients who are unable to tolerate ACE inhibitors or ARBs or when significant hyperkalemia limits their effective use.
Based on the evidence of the DAPA-CKD trial would CDEC now include dapagliflozin in the SOC for the treatment of patients with CKD?	Per the clinical experts, dapagliflozin should be included in the SOC along with ACE inhibitors or ARBs for the treatment of patients with CKD. The clinical experts cited the KDIGO guidelines for patients with diabetes and CKD, which have added dapagliflozin to the SOC with ACE inhibitors and ARBs.[51] The experts expect updated guidelines pertaining to CKD patients with or without T2DM to reflect the same advice in the future.
Will the patient have to show a specific percentage of improvement in eGFR or stabilization as a renewal criteria?	Per the clinical experts, patients would not have to show a percentage of improvement in eGFR or stabilization to continue receiving the drug. The clinical experts stated that the benefits of this drug extend beyond renal outcomes (reducing the progression of CKD and/or prevention of ESKD), to include mortality (renal and CV causes). Per the experts, irrespective of changes in eGFR, this drug is recommended to be continued until renal replacement therapy (dialysis or transplant) is initiated. Per the clinical experts, episodes of acute illness (dehydration, urine infection) would put dapagliflozin on hold. Per the experts, it is important to continue to monitor eGFR at regular intervals (3 to 6 months depending on stability) to assess the progression of CKD and risk for acute AEs (acute insults, Acute kidney injuries), particularly with acute illnesses.
Would a nephrologist be the only specialist to prescribe and manage this medication in patients with CKD?	Per the clinical experts, a nephrologist would not be the only specialist to prescribe dapagliflozin. Dapagliflozin can be safely initiated by primary care providers (in community settings), and

Drug program implementation questions	Clinical expert response
	prescribed by specialists in nephrology, cardiology, endocrinology and general internal medicine.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BIA = budget impact analysis; CKD = chronic kidney disease; CDEC = Canadian Drug Expert Committee; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; SOC = standard of care; T2DM = type 2 diabetes mellitus.

Note: The clinical expert response in this table may be different than those reflected by the clinical specialist as part of the Formulary Management Expert Committee.

Clinical Evidence

The clinical evidence included in the review of dapagliflozin is presented in 3 sections. The first section, the Systematic Review, includes studies that were selected according to a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes other studies that were perceived to address gaps in the evidence from the Systematic Review.

Systematic Review

Objectives

To perform a systematic review of the beneficial and harmful effects of dapagliflozin 10 mg oral tablets to reduce the risk of sustained eGFR decline, ESKD, and CV and renal death in adults with CKD.

Methods

Studies selected for inclusion in the systematic review were those meeting the selection criteria in Table 5. Outcomes included in the CADTH review protocol reflect those considered to be important to patients, clinicians, and drug plans.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adults with CKD, with or without T2DM[a] Subgroups: • T2DM status (yes vs. no) • CVD status • CKD risk category • Albuminuria at baseline • Proteinuria at baseline • eGFR at baseline • Prior use of ACE inhibitors and/or ARB
Intervention	Dapagliflozin 10 mg oral tablets alone or as an add on to SOC (e.g., ACE inhibitors or ARBs)
Comparators	• Placebo with or without SOC (e.g., ACE inhibitors or ARBs) • Canagliflozin 100 mg or 300 mg oral tablets (patients with T2DM) with or without SOC (e.g., ACE inhibitors or ARBs) • Finerenone 10mg or 20mg with or without SOC

Criteria	Description
Outcomes[b]	• Renal events (e.g., kidney failure defined as eGFR < 15 mL/min/1.73m ^{2}, initiation of dialysis or transplant) • Change in eGFR from baseline • Change in UACR from baseline • Cardiovascular events (e.g., MI) • Mortality (i.e., renal, CV, and all cause) • Hospitalization (i.e., renal, CV, and all cause) • HRQoL • Symptom severity • Functional status **Harms outcomes:** AEs, SAEs, WDAEs, deaths due to AEs, and notable harms (i.e., amputations, genital infections, DKA, palpitations, fractures, renal AEs, major hypoglycemia, volume depletion)
Study design	Published and unpublished Phase III and IV RCTs[c]

AE = adverse event; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CVD = cardiovascular disease; CKD = chronic kidney disease; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; MI = myocardial infarction; RCT = randomized controlled trial; SAE = serious adverse events; SOC = standard of care; T2DM = type 2 diabetes mellitus; UACR = urine albumin-to-creatinine ratio; WDAE = withdrawal due to adverse events.

[a]RCTs where patients received background SOC (e.g., ACE inhibitors, ARBs) were eligible, so long as the same SOC therapies were available to all randomized groups.

[b]Composites of individual outcomes in the list were also considered relevant (e.g., renal and CV composites; cardiorenal composites).

[c]When the phase of the RCT was not reported, we assumed it is phase II and excluded the RCT if the sample size was smaller than 50.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[52]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dapagliflozin and CKD. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on August 5, 2022. Regular alerts updated the search until CADTH's FMEC meeting on June 29, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist.[53].[53] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Additional information on the grey literature search

strategy is in Appendix 1. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

Two CADTH clinical reviewers independently screened titles and abstracts. Full-text articles of all records considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies and differences were resolved through discussion.

Characteristics of Included Studies

Four studies were included in the systematic review (Appendix 2, Figure 1): DAPA-CKD, DELIGHT, DERIVE, and Kohan et al. (2014).[7-20] The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 3.

Study Design

All RCTs were multicentre (including centres in Canada), placebo-controlled, double-blind trials, sponsored by AstraZeneca (Kohan et al. (2014) was also sponsored by Bristol-Myers Squibb). DAPA-CKD and DERIVE were phase III while DELIGHT and Kohan et al. (2014) were phase II/III.

DAPA-CKD (N = 4,304) aimed to assess whether dapagliflozin compared with placebo reduced the composite end point of worsening of renal function or CV death in patients with CKD.[54] Patients were randomized 1:1, stratified by T2DM status and UACR ratio (≤ 1,000 or > 1,000).[9]

The objective of DELIGHT (N = 461) was to evaluate the effect of dapagliflozin with and without saxagliptin on lowering albumin and improving glycemic control in patients with T2DM and moderate-to-severe CKD. Patients were randomized 1:1:1, stratified according to pre-enrolment glucose-lowering therapy. Dietary advice was provided in a 4-week single-blind placebo run in period.[15]

The objective of DERIVE (n = 321) was to evaluate the efficacy and safety of dapagliflozin in patients with T2DM and CKD stage IIIA. Patients were randomized 1:1, stratified by pre-enrolment glucose-lowering therapy.[16]

The objective of Kohan et al. (2014) (n = 252) was to examine the efficacy and safety of dapagliflozin 5 mg and 10 mg compared with placebo among patients with T2DM and moderate renal impairment. Patients were randomized 1:1:1, stratified by pre-enrolment glucose-lowering therapy. Diet and exercise counselling was provided during a 7-day lead-in period. All patients received placebo during a single-blind, 1-week lead-in period before randomization.

Eligibility Criteria

All RCTs enrolled adults with CKD, though the CKD-related eligibility criteria varied by trial.[9,15,16,19] Criteria were similar for DAPA-CKD, DELIGHT, and Kohan et al. (2014), enrolling patients with moderate CKD, while DERIVE enrolled patients with CKD stage IIIA. In DAPA-CKD, patients were enrolled regardless of T2DM status, while in the other RCTs patients had to have T2DM with inadequate glycemic control. Stable antidiabetic treatment was required in these RCTs. The use of ACE inhibitors or ARBs was required for DAPA-CKD and DELIGHT, but not DERIVE or Kohan et al. (2014).

In all RCTs, patients were excluded if they had certain CV events (e.g., MI, transient ischemic attack, stroke, unstable angina) within a certain time frame before enrolment (varied by RCT). In all RCTs but Kohan et al. (2014), patients were excluded if they received therapy with an SGLT2 inhibitor or were previously intolerant to 1. Additionally, ongoing treatment with a GLP-1 agonist, or DPP4 inhibitors was an exclusion criterion in DELIGHT. Ongoing treatment with a GLP-1 analogue, or rapid acting insulins was an exclusion criterion in DERIVE.

Interventions

In DAPA-CKD, patients received tablets of dapagliflozin 10 mg or matching placebo once daily. Dapagliflozin 5 mg could be used if clinically indicated; however, the dose was to be increased to 10 mg as soon as possible.[55] Concomitant medications were permitted.[55] Patients were to be treated based on regional SOC for CV risk factors, diabetes, and CKD complications.[55] The use of open-label SGLT2 inhibitors was prohibited. Among approximately 84% of patients with data available, adherence was high in both groups (96 to 99%).[56] The mean duration of treatment was 24.8 (SD = 9.4) months in the dapagliflozin group and 24.3 (SD = 24.3) months in the placebo group.

In DELIGHT, patients received dapagliflozin 10 mg, dapagliflozin 10 mg and saxagliptin 2.5 mg, or matching placebo once daily for 24 weeks. The use of antiviral drugs, long-term treatment with glucocorticoids, and weight loss medication was prohibited.[15]

In DERIVE, patients received dapagliflozin 10 mg or matching placebo once daily for 24 weeks. The use of antiviral drugs, long-term treatment with glucocorticoids, and weight loss medication was prohibited.[16]

In Kohan et al. (2014), patients received dapagliflozin 5 mg, dapagliflozin 10 mg, or matching placebo for up to 104 weeks (double-blind for 52 weeks, followed by patient and site-blind for 52 weeks). Patients with a lack of glycemic control were eligible to receive open-label rescue medication, except for metformin, added or substituted per investigator judgment.[19]

No information about adherence was reported for DELIGHT, DERIVE, or Kohan et al. (2014).

Outcomes

A list of efficacy outcomes identified in the CADTH review protocol that were assessed in the RCTs are provided in Table 7.

The primary outcome in DAPA-CKD was a composite of time to 50% or greater decline in eGFR (confirmed by a second serum creatinine measurement after at least 28 days), the onset of ESKD, or death from renal or CV causes. The sponsor chose the composite end point to align with other studies and meet European Medicines Agency requirements.[55] Cardiovascular death was added to the composite by the sponsor, citing a correlation between CV death and risk of developing ESKD.[55] The secondary outcomes were a composite of time to 50% or greater decline in eGFR, the onset of ESKD, or death from renal causes; time to CV death or hospitalization for HF; and time to death from any cause.[55]. All other outcomes, including those contributing to each composite outcome, were exploratory.[54]

The primary and secondary outcomes in DELIGHT were not relevant to the current review. Change from baseline UACR, eGFR, and mortality were the only outcomes measured consistently across all RCTs. Change from baseline UACR was an exploratory outcome in DAPA-CKD and DERIVE, the primary outcome in DELIGHT, and a safety outcome in Kohan et al. (2014).[9,15,16,19] The proportion of patients experiencing a greater than 30% reduction in UACR at 24 weeks was also a secondary outcome in DELIGHT.[15] Change from baseline eGFR was an exploratory outcome in DAPA-CKD, a safety outcome in DELIGHT and DERIVE, and a secondary outcome in Kohan et al. (2014).[9,15,16,19] Mortality was a secondary outcome in DAPA-CKD and a safety outcome in the other RCTs.[9,15,16,19]

Potential events in DAPA-CKD were identified through laboratory data, questioning patients about their overall health, and/or information obtained through standard medical practice. Data for eGFR were collected through a central laboratory. All remaining primary and secondary outcomes were adjudicated by an independent committee.[54] All deaths, renal events, and CV events were adjudicated centrally and blindly. All clinical laboratory tests in DELIGHT, DERIVE, and Kohan et al. (2014) were performed by a central laboratory or designated reference laboratory.[15,19,57]

Table 6: Characteristics of Included RCTs

Trial name and design[a]	Participants		Intervention and comparator	Follow-up
	Key inclusion criteria	Key exclusion criteria		
DAPA-CKD[9] Multicentre phase III DB RCT sponsored by AstraZeneca	• 4,304 adults aged ≥ 18 years • With or without T2DM • CKD (eGFR 25 to 75 mL/min/1.73 m^2 and UACR 200 to 5000 mg/g) • Stable dose of ACE inhibitors or ARBs ≥ 4 weeks	• Certain nondiabetic kidney diseases • Recent CVD event, CHF • Hepatic disease • Recent immunotherapy, treatment with SLGT2 inhibitors	For up to 38.2 months: • dapagliflozin 10 mg, oral, once daily • matched placebo	2 weeks; 2, 4, 8 months, then at 4-month intervals
DELIGHT[15] Multicentre phase II/III DB RCT sponsored by AstraZeneca	• 461 adults aged ≥ 18 years • T2DM with inadequate glycemic control (hemoglobin A1C 7.0 to 11.0%) • CKD (eGFR 25 to 75 mL/min/1.73 m^2 and UACR 30 to 3500 mg/g) • Stable glucose-lowering regimen and ACE inhibitors or ARBs ≥ 12 weeks	• Nondiabetic CKD • Severe CVD or hypertension • Recent major hypoglycemia, low Hgb, hepatic disease • Treatment with SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, glucocorticoids	For 24 weeks: • dapagliflozin 10 mg, oral, once daily • saxagliptin 2.5 mg, oral, once daily • matched placebo	Every 4 weeks and 3 weeks post-treatment
DERIVE[16] Multicentre phase III	• 321 adults aged ≥ 18 to < 75 years • T2DM with inadequate	• Certain nondiabetic kidney diseases • Recent CVD event, severe	For 24 weeks: • dapagliflozin 10 mg, oral, once	Weeks 1, 4-, 12-, 24-, and 3-weeks post-treatment

Trial name and design[a]	Participants		Intervention and comparator	Follow-up
	Key inclusion criteria	Key exclusion criteria		
DB RCT sponsored by AstraZeneca	glycemic control (hemoglobin A1C 7.0 to 11.0%) • CKD stage IIIA (eGFR 45 to 59 mL/min/1.73 m^2) • Stable glucose-lowering regimen ≥ 12 weeks	hypertension • Increased serum potassium, decrease calcium, low Hgb • Hepatic disease • Treatment with SGLT2 inhibitors, GLP-1 analogue, short-acting insulin	daily • matched placebo	
Kohan et al. (2014)[19] Multicentre phase II/ III DB RCT sponsored by Bristol-Myers Squibb and AstraZeneca	• 252 adults aged ≥ 18 years • T2DM with inadequate glycemic control (hemoglobin A1C 7.0 to 11.0%) • CKD (eGFR 30 to 59 mL/min/1.73 m^2) • Stable glucose-lowering regimen ≥ 6 weeks	• Certain nondiabetic kidney diseases • History of diabetes insipidus or DKA or hyperosmolar nonketotic coma • Uncontrolled hypertension • Specified CVD/vascular diseases • Hepatic disease	For 104 weeks: • dapagliflozin 10 mg, oral, once daily • dapagliflozin 5 mg, oral, once daily • matched placebo	Weeks 1, 12, 24, 52, 104

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; CHF = congestive heart failure; DB = double blind; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; hemoglobin A1C = glycated hemoglobin; Hgb = hemoglobin; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

[a]All trials included sites in Canada.

Source: Heerspink et al. (2020);[9] Pollock et al. (2019);[15] Fioretto et al. (2018);[16] Kohan et al. (2014).[19]

Table 7: Outcomes of Interest Identified in the CADTH Review Protocol

Outcome	DAPA-CKD	DELIGHT	DERIVE	Kohan et al. (2014)
Renal events	• Time to ESKD[b] • Proportion of patients with eGFR > 40 mL/min/1.73 m^2 who enter CKD Stage 4 • Time to potassium values: > 6 mmol/L, > 5.5 mmol/L, < 3.5 mmol/L, and < 3 mmol/L • Time to doubling in serum creatinine	Proportion of patients discontinuing treatment due to sustained serum creatinine increases > 1.5 times baseline	Proportion of patients discontinuing treatment due to worsening renal insufficiency	Proportion of patients with marked abnormalities in serum creatinine
Change in eGFR from baseline	• Time to ≥ 50% sustained decline in eGFR[a] • Time to ≥ 40% sustained decline in eGFR • Time to ≥ 30% sustained decline in eGFR • eGFR change over time	Change in eGFR from baseline	Change in eGFR from baseline	Change in eGFR from baseline

Outcome	DAPA-CKD	DELIGHT	DERIVE	Kohan et al. (2014)
Change in UACR from baseline	Change in UACR from baseline	• Change in UACR from baseline • Proportion of patients achieving a reduction of more than 30% in UACR	Change in UACR from baseline	Change in UACR from baseline
Cardiovascular events	• Time to first fatal or nonfatal MI • Time to first fatal or nonfatal stroke	Not measured	Not measured	Not measured
Mortality	• Time to death of any cause • Time to CV death • Time to renal death	Deaths	Deaths	Deaths
Composite outcomes (renal and/or cardiac events)	• Time to ≥ 50% sustained decline in eGFR[a], ESKD[b], CV death[c], or renal death • Time to ≥ 50% decline in eGFR[a], ESKD[b], or renal death • Time to major CV end point of MI, stroke, or CV death • Time to CV death or hospitalization for HF • Time to chronic dialysis, kidney transplant, or renal death • Time to CV death, MI, stroke, or HF hospitalization[d] • Time to all-cause death, MI, stroke, HF hospitalization, or ESKD[d]	Not measured	Not measured	Not measured
Hospitalization	• Time to hospitalization for HF • Any hospitalization[d] • Any prolonged hospitalization (≥ 7 days) or hospitalization ending in death[d] • Any prolonged hospitalization (≥ 7 days), death, or hospitalization ending in death[d] • First and subsequent hospitalizations[d] • First and subsequent hospitalizations or death[d] • Mean number of hospital days[d]	Not measured	Not measured	Not measured
HRQoL	Change from baseline HRQoL (36-item Kidney Disease Quality of Life and EQ-5D-5L)	Not measured	Not measured	Not measured

Outcome	DAPA-CKD	DELIGHT	DERIVE	Kohan et al. (2014)
Symptom severity	Not measured	Not measured	Not measured	Not measured
Functional status	Not measured	Not measured	Not measured	Not measured

eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; MI = myocardial infarction; UACR = urine albumin to creatine ratio.

[a]Based on 2 consecutive central laboratory values at least 28 days, the start date of the event was noted as the date of the first central laboratory values.

[b]Defined as sustained eGFR < 15 mL/min/1.73 m^2 (based on 2 consecutive central laboratory values at least 28 days apart), chronic dialysis (dialysis ongoing for at least 28 days or when ESKD is deemed irreversible, and dialysis was stopped before day 28), or receiving kidney transplant.

[c]Deaths adjudicated as "cause undetermined" were included under CV deaths.

[d]These outcomes were analyzed post hoc (not prespecified).

Source: Heerspink et al. (2020);[54] Schechter et al. (2023);[13] Pollock et al. (2019);[15] Fioretto et al. (2018);[16] Kohan et al. (2014).[19]

Statistical Analysis

Specifics of the analyses of efficacy end points for each RCT are in Table 8. Analyses in all except Kohan et al. (2014) were based on the full analysis set (FAS). In DAPA-CKD this included all randomized patients, whereas in DELIGHT and DERIVE this included all randomized patients who received at least 1 dose of study drug and who had both baseline and at least 1 postbaseline value. This corresponded to 100% of the randomized patients in DERIVE, and more than 96% of randomized patients in DELIGHT.[15,16,54,57,58] In Kohan et al. (2014), only the difference in the change from baseline eGFR was tested statistically. The analysis included randomized patients with nonmissing baseline and week 52 values.[17]The analysis included randomized patients with nonmissing baseline and week 52 values.[17]

All included RCTs used a priori power calculations based on demonstrating superiority of dapagliflozin over placebo for their primary end point, at a two-sided alpha of 0.05 (DELIGHT used 0.025, as the alpha was split between 2 treatment comparisons). This resulted in a planned sample size of 4,000 patients (681 events) in DAPA-CKD, 426 patients in DELIGHT, 302 patients in DERIVE, and 240 patients in Kohan et al. (2014). All RCTs used a sequential testing procedure to control the risk of type I error among primary and secondary end points. DAPA-CKD was stopped early for efficacy on April 3, 2020 based on the recommendation of the Data Monitoring Committee after observing 408 primary outcome events.[17,57-59]

Relevant prespecified subgroup analyses were by T2DM status, baseline eGFR, and baseline UACR in DAPA-CKD, and by CVD status, baseline eGFR, baseline UACR in DELIGHT. Prespecified subgroup analyses for DERIVE were not reported (redacted in statistical analysis plan). No relevant subgroups were reported for the outcomes of interest in Kohan et al. (2014). Relevant post hoc subgroup analyses in DAPA-CKD were by HF and CVD status.[57-59]

In all RCTs, harms end points were presented descriptively (frequencies, proportions) using the safety analysis set (SAS), which included all randomized patients who had received at least 1 dose of study drug.[57-59]

Table 8: Statistical Analysis of Efficacy End points in the Included RCTs

End point (analysis population)	Statistical model	Stratification and adjustment factors	Sensitivity analyses
DAPA-CKD			
Time-to-event end points (FAS)	• Cox PH regression model • KM estimates of the cumulative incidence • Patients ongoing censored on 3 April 2020 or at date of last assessment (or non-CV or nonrenal death if applicable)	• Stratified by T2DM, UACR • Adjusted for baseline eGFR	Primary end point: • Alternative censoring rules • Tipping point analysis Time to first hospitalization and composites: • Fine-Grey models accounting for competing risk of death
eGFR change over time (FAS)	2-slope mixed effects linear spline model based on REML estimation with day 14 as a knot in the model	• Fixed effect of treatment, stratification factors, baseline eGFR, time, treatment x time; • Random effects of intercept, acute slope (to day 14), chronic slope (day 14 to end)	None
Changes from baseline (FAS)	MMRM	Baseline, treatment group, visit, and group x visit as covariates	None
Post-hoc risk of all hospitalizations and composites (FAS)	• Lin-Wei-Yang-Ying model with robust standard error estimators • Quasi-binomial models comparing mean proportions	None	Alternative models used
DELIGHT			
Continuous end points, change from baseline (FAS)	• MMRM • Values after discontinuation or rescue treatment omitted	Type of glucose-lowering therapy, treatment group, visit, group x visit, baseline, baseline x visit as covariates	None
Proportion with improvement in UACR ≥ 30% (FAS)	Logistic regression model	Type of glucose-lowering therapy, treatment group, and baseline as covariates	None
DERIVE			
Continuous end points, change from baseline (FAS)	• MMRM • Values after discontinuation or rescue treatment omitted	Type of glucose-lowering therapy, treatment group, week, group x week	None
Continuous end points, % change from baseline (FAS)	Analysis of covariance model using last observation carried forward	Type of glucose-lowering therapy, treatment group, and baseline as covariates	None
Kohan et al. (2014)			
Change from baseline eGFR at week 52 (Treated)	Analysis of covariance model, using last observation carried forward	Type of glucose-lowering therapy and treatment group as fixed	NR

End point (analysis population)	Statistical model	Stratification and adjustment factors	Sensitivity analyses
		effects, and baseline value as a covariate	

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; MMRM = mixed model repeated measures; NR = not reported; PH = proportional hazards; RCT = randomized controlled trial; REML = restricted maximum likelihood; T2DM = type 2 diabetes mellitus; UACR = urinary albumin-to-creatinine ratio.

[a]No details of the statistical methods were provided for the outcomes of interest to this review.

Source: Heerspink et al. (2020);[9] Schechter et al. (2023);[13] DAPA-CKD Statistical Analysis Plan;[59] Pollock et al. (2019); DAPA-CKD Statistical Analysis Plan;[59] Pollock et al. (2019);[15] DELIGHT Statistical Analysis Plan;[58] Fioretto et al. (2018); DELIGHT Statistical Analysis Plan;[58] Fioretto et al. (2018);[16] DERIVE Statistical Analysis Plan;[57] Kohan et al. (2014) Redacted Clinical Study Report Summary.[17] DERIVE Statistical Analysis Plan;[57] Kohan et al. (2014) Redacted Clinical Study Report Summary.[17]

Results of the Included Studies

Patient Characteristics

Patients' baseline demographic and disease characteristics across the 3 RCTs are in Table 9. In DAPA-CKD, 57.3% of patients screened were randomized; screening failure was most commonly due to not meeting albuminuria (57.8%) or eGFR (41.4%) criteria. Fewer than 1% of patients in each group discontinued prematurely from the RCT. Thirteen percent of patients in the dapagliflozin group and 14% in the placebo group discontinued prematurely from the treatment, mostly due to AEs or patient decision.[9]

In DELIGHT, 38.8% of 1,187 patients screened were randomized (151 to the dapagliflozin group and 153 to the placebo group). Eight (5.3%) patients in the dapagliflozin group and 5 (3.3%) in the placebo group did not complete follow-up.[15] In DERIVE, 1,123 patients were enrolled, of which 321 (28.6%) were randomized (140 to the dapagliflozin group and 161 to the placebo group). Eleven (7%) patients in the dapagliflozin group and 15 (9%) patients in the placebo group did not complete follow-up.[16]

In Kohan et al. (2014), 631 patients were enrolled, of which 252 (39.9%) were randomized (85 to the dapagliflozin 10 mg group and 84 to the placebo group). Forty-one (24.3%) patients did not complete the 24-week short-term follow-up period, mostly due to AEs (7.1% in the dapagliflozin group and 14.3% in the placebo group). One-hundred and 31 (77.5%) patients entered the long-term double-blind treatment period (24 to 52 weeks; 81.2% in the dapagliflozin group and 73.8% in the placebo group), of whom 9.2% did not complete the period (5.8% in the dapagliflozin group and 12.9% in the placebo group), mainly due to AEs (2.9% in the dapagliflozin group p and 8.1% in the placebo group). One-hundred and 12 (66.3%) patients entered the single-blind long-term follow-up period (52 to 104 weeks; 69.4% in the dapagliflozin group and 63.1% in the placebo group).[17]

Across the RCTs, the mean age ranged from 61.8 to 67.5 years, and most patients were male (56.7% to 70.6%). Most patients in DAPA-CKD (53.2%), DERIVE (87.5%), and Kohan et al. (2014) (86.4%) were white, compared with 40.6% in DELIGHT. There were fewer Asian patients in DERIVE (4.0%) and Kohan et al. (2014) (5.3%) compared to DAPA-CKD (34.1%) and DELIGHT (41.0%). Mean eGFR at baseline was similar across the RCTs, ranging from 43.1 to 51.7 mL/min/1.73 m^2. Mean UACR at baseline was higher in DAPA-CKD (949 g/mg) compared with the other RCTs (median of 257.7 to 270.0 mg/g across groups in DELIGHT; mean of 236.8 mg/g in DERIVE; and mean of 401 mg/g in Kohan et al. (2014)).[9,15,16,19]

Two-thirds (67.5%) of patients in DAPA-CKD had T2DM compared with all patients in the other RCTs. More patients in DELIGHT and Kohan et al. (2014) were taking insulin (72.0% and 65.1%, respectively) compared with DERIVE (49.8%), whereas fewer were taking sulfonylureas (33.1% and 24.9% versus 40.8%). Use of glucose-lowering therapies was not reported for DAPA-CKD. Nearly all patients in DAPA-CKD (98.2%) and DELIGHT (99.0%), and most in DERIVE (83.8%) were taking ACE inhibitors or ARBs. ACE inhibitor and ARB use was not reported in Kohan et al. (2014).[9,15,16,19]

Patient characteristics were generally balanced across groups in all RCTs, although some imbalances were noted in DELIGHT, DERIVE, and Kohan et al. (2014). In DELIGHT, there were more Asian patients in the dapagliflozin group (46%) compared with the placebo group (36%). More patients in the dapagliflozin group (40%) had a history of cardiac disorders compared with the placebo group (28%). More patients in the placebo group were receiving sulfonylureas (39%) and loop diuretics (31%) compared with the dapagliflozin group (27% and 18%, respectively).[15] In DERIVE, more patients in the dapagliflozin group (47.8%) were receiving beta blockers compared with the placebo group (36.9%).[16] In Kohan et al. (2014), there were more white patients in the dapagliflozin group (90.6%) compared with the placebo group (82.1%), and fewer patients in the *other* race category (1.2% versus 9.5%). There were more patients with stage IIIB CKD in the dapagliflozin group (55.3%) compared with the placebo group (40.5%), and fewer with stage IIIA CKD (38.8% versus 48.8%).[19]

Table 9: Patient Characteristics Across Included RCTs

Patient characteristic	DAPA-CKD N = 4,304	DELIGHT N = 461	DERIVE N = 321	Kohan et al. (2014) N = 169
Demographic characteristics				
Age, mean (SD) years	61.8 (12.1)	64.7 (8.5)	65.8 (6.4)	67.5 (8.2)
Male, %	66.9	70.6	56.7	64.5
Race, %				
White	53.2	40.6	87.5	86.4
Asian	34.1	41.0	4.0	5.3
Black	4.4	6.1	7.2	3.0
Other	8.3	12.3	1.3	5.3
Disease characteristics				
eGFR, mean (SD) mL/min/1.73 m^2	43.1 (12.4)	48.9 (13.3)	51.7 (3.9)	44.7 (10.3)
UACR, mean (SD) g/mg	949 (NR)	257.7 to 270.0 (69 to 949)[b]	236.8 (678.8)	401 (1,006)
Type 2 diabetes, %	67.5	100	100	100
A1C, mean %	NR	8.5 (1.1)	8.2 (1.1)	8.3 (1.1)
Blood pressure, mean (SD) mm Hg				
Systolic	137.1 (17.4)	139.1 (17.6)	135.3 (15.1)	NR

Patient characteristic	DAPA-CKD N = 4,304	DELIGHT N = 461	DERIVE N = 321	Kohan et al. (2014) N = 169
Diastolic	77.5 (10.5)	76.3 (10.6)	NR	NR
Concomitant conditions, %				
Dyslipidemia	69.4	NR	NR	NR
Cardiovascular disease	37.4	NR	NR	NR
Cardiac disorders	NR	33.8	NR	NR
Heart failure	10.9	NR	NR	NR
Vascular disorders	NR	14.7	NR	NR
Concomitant therapies				
Antihypertensive therapies, %				
ACE inhibitors and/or ARBs	98.2	99.0	83.8	NR
Statins	64.7	73.7	NR	NR
Beta blockers	NR	NR	42.4	NR
Diuretics	43.7	NR	42.1	NR
Loop diuretics	NR	24.6	NR	NR
Thiazides	NR	23.2	NR	NR
Other antihypertensives	NR	NR	12.8	NR
Glucose-lowering therapies, %				
Insulin	NR	72.0	49.8	65.1
Metformin	NR	56.3	66.7	NR
Sulfonylureas	NR	33.1	40.8	24.9
Thiazolidinedione based	NR	NR	NR	1.8
Other	NR	NR	NR	8.3

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; hemoglobin A1C = glycated hemoglobin; Hg = mercury; NR = not reported; SD = standard deviation; RCT = randomized controlled trial; UACR = urine albumin to creatine ratio.

[a]Mean eGFR was not reported; however, 3.6% had eGFR < 30 mL/min/1.73 m^2, 47.9% had eGFR 30 to < 45 mL/min/1.73 m^2, 43.8% had eGFR 45 to < 60 mL/min/1.73 m^2, and 4.7% had eGFR ≥ 60 mL/min/1.73 m^2.

[b]Median and range across groups.

Source: Heerspink et al. (2020);[9] Pollock et al. (2019);[15] Fioretto et al. (2018);[16] Kohan et al. (2014).[19]

Efficacy Results

Renal Events

Time to ESKD and time to doubling of serum creatinine (a marker of an abrupt decline in kidney function) were reported in DAPA-CKD. At the conclusion of the RCT (median follow-up, 2.4 years [range = 2.0 to 2.7]), 109 (5.1%) patients in the dapagliflozin group and 161 (7.5%) patients in the placebo group experienced ESKD, corresponding to 2.5 events and 3.8 events per 100 patient-years, respectively (HR = 0.64, 95% CI, 0.50 to 0.82). Results for outcomes that define ESKD (i.e., eGFR < 15 mL/min/1.73 m^2, long-term dialysis, or

kidney transplant) were aligned with those for ESKD (Appendix 4).[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

At the conclusion of the RCT, 63 (2.9%) patients in the dapagliflozin group and 91 (4.2%) in the placebo group experienced a doubling of serum creatinine, corresponding to 1.4 and 2.0 events per 100 patient-years, respectively (HR = 0.68, 95% CI, 0.49 to 0.94) (P = 0.02). The results were consistent across prespecified subgroups of interest (i.e., T2DM status, eGFR, and UACR at baseline).[7]

The proportion of patients discontinuing treatment due to worsening renal insufficiency was reported in both DELIGHT and DERIVE, and events were infrequent in both groups across the RCTs. In DELIGHT, no patient in the dapagliflozin group and 1 (0.7%) in the placebo group discontinued treatment due to sustained serum creatinine values greater than 1.5 times baseline.[15] In DERIVE, 1 (0.6%) patient in the dapagliflozin group required a treatment interruption due to worsening renal insufficiency (eGFR < 30 mL/min/1.73 m^2); however, eGFR returned to baseline following the interruption. There were no reports of treatment interruptions or discontinuations due to worsening renal insufficiency in the placebo group.[16] In Kohan et al. (2014), the authors reported that the proportion of patients with marked abnormalities in serum creatinine through 104 weeks, defined as an increase of at least 2.5 or at least 1.5 mg/dL from baseline, was similar across groups. Numeric results were not reported.[19]

Change in eGFR

Time to 50% or greater sustained decline in eGFR and change in eGFR over time were reported in DAPA-CKD. Change in eGFR from baseline was also reported in DELIGHT, DERIVE, and Kohan et al. (2014).

At the conclusion of DAPA-CKD (median follow-up, 2.4 years [range = 2.0 to 2.7]), 112 (5.2%) patients in the dapagliflozin group and 201 (9.3%) patients in the placebo group experienced a 50% or greater sustained decline in eGFR, corresponding to 2.6 and 4.8 events per 100 patient-years, respectively (HR = 0.53, 95% CI, 0.42 to 0.67).[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

The LSM eGFR slopes from baseline to 30 months in the dapagliflozin and placebo groups were −2.86 mL/min/1.73 m^2 per year (standard error [SE] = 0.11) and −3.79 (SE = 0.11) mL/min/1.73 m^2 per year, respectively. There was a decline in eGFR in the dapagliflozin group (LSM, −3.96 [SE = 0.15] mL/min/1.73 m^2) during the first 2 weeks of treatment that was not observed in the placebo group (LSM, −0.82 [SE = 0.15] mL/min/1.73 m^2). After this time, patients in the dapagliflozin group experienced a slower decline in eGFR (LSM, −1.67 [SE = 0.11] mL/min/1.73 m^2) compared with those in the placebo group (LSM, −3.59 [SE = 0.11] mL/min/1.73 m^2) (LSM difference, 1.92 mL/min/1.73 m^2; 95% CI, 1.61 to 2.24).[9] The test for subgroup interaction showed that dapagliflozin resulted in a greater attenuation of decline in eGFR relative to placebo among patients with T2DM compared to those without T2DM (interaction P value = 0.040). Dapagliflozin also resulted in a progressively greater attenuation of decline in eGFR relative to placebo in higher relative to lower UACR subgroups (interaction P value < 0.0001).[20] There were no statistically significant subgroup interactions among patients with versus without HF.[12]

Results were similar among patients with CKD and T2DM in DELIGHT and DERIVE (Table 10),[15,16] whereby initial decreases in eGFR were observed in the dapagliflozin groups and the difference between groups reduced over time. Three weeks following the cessation of treatment (week 27), the reduction in eGFR was reversed, with similar values observed in the dapagliflozin and placebo groups. Although the difference between groups was not explicitly reported in DELIGHT, the authors stated that there was no difference between groups at this time point.

In Kohan et al. (2014), the difference in the change from baseline between groups was only reported at 52 weeks (Table 10).[17] Similar to the other RCTs, the authors stated that there was an early mean decrease in eGFR after 1 week of treatment in the dapagliflozin group, followed by long-term stability, compared with a slow decline in the placebo group.[17] Similar to the other RCTs, the authors stated that there was an early mean decrease in eGFR after 1 week of treatment in the dapagliflozin group, followed by long-term stability, compared with a slow decline in the placebo group. Changes from baseline in the dapagliflozin versus placebo groups were −4.80 (SE = 0.82) mL/min/1.73 m^2 versus −0.25 (SE = 0.92) mL/min/1.73 m^2 at 24 weeks (n = 131) and −3.50 (SE = 1.02) mL/min/1.73 m^2 versus −2.38 (SE = 1.01) mL/min/1.73 m^2 at 104 weeks (n = 92); however, adjusted mean differences in change from baseline were reported only at 52 weeks (−3.12 mL/min/1.73 m^2, 95% CI, −6.00 to −0.24).

Table 10: Change From Baseline eGFR in DELIGHT (SAS), DERIVE (SAS), and Kohan et al. (2014) (Patients With Nonmissing Values)

	DELIGHT		DERIVE		Kohan et al. (2014)	
eGFR	Dapagliflozin (n = 145)	Placebo (n = 148)	Dapagliflozin (n = 160)	Placebo (n = 161)	Dapagliflozin (n = 63)	Placebo (n = 49)
Baseline eGFR, mean (SD) mL/min/1.73 m^2	50.2 (13.0)	47.7 (13.5)	53.5 (8.8)	53.7 (10.7)	43.5 (9.0)	47.4 (10.6)
Difference in change from baseline, adjusted mean (95% CI) mL/min/1.73 m^2						
Week 1	−4.8 (−6.3 to −3.3)[a]		NR		NR	
Week 4	NR		−4.90 (−6.73 to −3.07)[c]		NR	
Week 12	NR		−4.75 (−6.98 to −2.52)[c]		NR	
Week 24	−2.4 (−4.2 to −0.5)[b]		−2.49 (−4.96 to −0.02)[c]		NR	
Week 27	NR		0.61 (−1.59 to 2.81)[d]		NR	
Week 52	NA		NA		−3.12 (−6.00 to −0.24)	

CI = confidence interval; eGFR = estimated glomerular filtration rate; NA = not applicable; NR = not reported; SAS = safety analysis set; SD = standard deviation.

[a]P < 0.001; P value not adjusted for multiple comparisons.

[b]P = 0.0075; P value not adjusted for multiple comparisons.

[c]Data analyzed with missing data assumptions specific to the repeated measures model, with missing data considered to be missing at random.

[d]Data analyzed separately using an extension of the analysis model to include week 27, enabling the pattern in missing data to change with the inclusion of post-treatment follow-up.

Source: Pollock 2019;[15] Fioretto 2018;[16] Kohan et al. (2014) Redacted Clinical Study Report Summary.[17] Kohan et al. (2014) Redacted Clinical Study Report Summary.[17]

Change in UACR

Change from baseline UACR was a primary outcome in DELIGHT and an exploratory outcome in DAPA-CKD and DERIVE (Table 11). Change from baseline UACR was a safety outcome in Kohan et al. (2014), but differences between groups were not reported. At 2 weeks follow-up in DAPA-CKD, the difference in geometric mean percent change from baseline was −26.5% (95% CI, −22.1 to −30.9) (P < 0.0001), favouring dapagliflozin. At the conclusion of DAPA-CKD (median follow-up, 2.4 years [range = 2.0 to 2.7]), the difference in geometric mean percent change from baseline was −29.3% (95% CI, −33.1 to −25.2) (P < 0.0001), favouring dapagliflozin. The test for subgroup interaction showed that relative to placebo, dapagliflozin resulted in a greater reduction in mean UACR among patient with T2DM compared to those without (interaction P value < 0.0001). The effects of dapagliflozin on UACR were consistent across categories of baseline eGFR and UACR.[10]

In DELIGHT, the difference in the percent changes from baseline at week 4 and week 24 were −28.3% (95% CI −36.8 to −18.7) (P < 0.0001) and −21.0% (95% CI, −34.1 to −5.2) (P = 0.011), respectively, both favouring dapagliflozin. The results for prespecified subgroups of interest (i.e., baseline eGFR, UACR, CV history) were consistent with the primary analysis.[15] In DERIVE, the difference in the percent change from baseline at week 24 was 8.0% (95% CI, −14.4 to 36.3).[16] In Kohan et al. (2014), the change from baseline was −11.69 (SE = 148.6) mg/g in the dapagliflozin group and 69.7 (SE = 80.1) mg/g in the placebo group at 104 weeks. The difference in the change from baseline was not reported. Values of more than 1,800 mg/g for 104 weeks follow-up was reported in 13.3% of patients in the placebo group compared with 9.5% of patients in the dapagliflozin group.[19] One-third (33.9%) of patients in the dapagliflozin group and 15.8% of those in the placebo group moved to a lower UACR category during follow-up. Fifteen percent of patients in the dapagliflozin group and 27.3% of those in the placebo group progressed to a higher UACR category. Overall, 17.8% and 7.0% of patients in the dapagliflozin and placebo groups, respectively, improved to normoalbuminuric.

The proportion of patients with a 30% reduction in UACR from baseline at 24 weeks was a secondary outcome in DELIGHT. This outcome was not measured in the other RCTs. The proportions of patients with a 30% reduction in UACR from baseline were 45.0% in the dapagliflozin group and 31.3% in the placebo group (OR = 1.9, 95% CI, 1.1 to 3.0; P = 0.013).[15]

Table 11: Change From Baseline UACR in DAPA-CKD, DELIGHT, and DERIVE (FAS)

	DAPA-CKD		DELIGHT		DERIVE	
UACR, g/mg	Dapagliflozin (n = 2.152)	Placebo (n = 2,152)	Dapagliflozin (n = 144)	Placebo (n = 148)	Dapagliflozin (n = 160)	Placebo (n = 161)
Baseline UACR, mean (SD) g/mg	NR	NR	592.0 (766.9)	679.1 (847.0)	225.8 (620.9)	271.7 (861.0)
Baseline UACR, median (IQR) g/mg	965 (472 to 1,903)	934 (482 to 1,868)	NR	NR	NR	NR
Difference in mean change from baseline, (95% CI)						
Week 2	−26.5 (−22.1 to −30.9)[a]		NR		NR	

UACR, g/mg	DAPA-CKD		DELIGHT		DERIVE	
	Dapagliflozin (n = 2.152)	Placebo (n = 2,152)	Dapagliflozin (n = 144)	Placebo (n = 148)	Dapagliflozin (n = 160)	Placebo (n = 161)
Week 4	NR		−28.3 (−36.8 to −18.7)[c]		NR	
Week 24	NR		−21.0 (−34.1 to −5.2)[d]		8.0 (−14.4 to 36.3)	
Median, 2.4 years	−29.3 (−33.1 to −25.2)[b]		NR		NR	

CI = confidence interval; FAS = full analysis set; IQR = interquartile range; UACR = urinary albumin-creatinine ratio; NR = not reported; SD = standard deviation.

[a]Geometric mean change from baseline, P < 0.0001. P value not adjusted for multiple comparisons.

[b]Geometric mean change from baseline at longest follow-up, P < 0.0001. P value not adjusted for multiple comparisons.

[c]P < 0.0001.

[d]P = 0.011.

Source: Jongs 2021;[10] Pollock 2019;[15] Fioretto 2018.[16]

Cardiovascular Events

Time to first fatal or nonfatal MI and time to first fatal or nonfatal stroke were measured but not reported in DAPA-CKD. Cardiovascular events were not measured in the other RCTs.

Mortality

Time to death from any cause, time to CV death, and time to renal death were reported in DAPA-CKD (Appendix 4). At the conclusion of DAPA-CKD (median follow-up, 2.4 years [range = 2.0 to 2.7]), 101 (4.7%) patients in the dapagliflozin group and 146 (6.8%) patients in the placebo group had died from any cause, corresponding to 2.2 and 3.1 events per 100 patient-years, respectively (HR = 0.69, 95% CI, 0.53 to 0.88; P = 0.004). In the Kaplan-Meier plot for death from any cause, the 2 curves separated at around 7 months and remained separated throughout follow-up.[9] Results among all prespecified subgroups of relevance (including T2DM status, eGFR, and UACR at baseline) were consistent with the main analysis.[8] There were no statistically significant subgroup interactions among patients with versus without T2DM, CVD, or HF.[11,12,14]

Sixty-five (0.3%) patients in the dapagliflozin group and 80 (3.7%) in the placebo group had died from CV causes (including deaths for which the cause could not be classified), corresponding to 1.4 and 1.7 events per 100 patient-years, respectively (HR = 0.81, 95% CI, 0.58 to 1.12).[9] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

Few deaths occurred in either group due to renal causes. Two (0.1%) patients in the dapagliflozin group and 6 (0.3%) patients in the placebo groups had died from renal causes, corresponding to 0.0 and 0.1 events per 100 patient-years, respectively. The HR and 95% CI were not estimated due to the low number of events.[9]

Mortality was a safety outcome in DELIGHT, DERIVE, and Kohan et al. (2014). After 27 weeks, 1 (0.7%) patient (0.7%) in the dapagliflozin died in DELIGHT.[15] No patient in either group died in DERIVE.[16] After 104 weeks in Kohan et al. (2014), 3 (3.5%) and 5 (6.0%) patients died in the dapagliflozin and placebo groups, respectively.[19]

Composite Outcomes (Renal and/or Cardiovascular Events)

Six relevant composite outcomes were measured in DAPA-CKD (Appendix 4). No composite outcomes were reported in the other RCTs.

In DAPA-CKD, time to ≥ 50% eGFR decline, ESKD, CV death, or renal death was the primary outcome. At the conclusion of the RCT (median follow-up, 2.4 years [range = 2.0 to 2.7]), 197 (9.2%) patients in the dapagliflozin group and 312 (14.5%) patients in the placebo group experienced a component of the composite outcome, corresponding to 4.6 and 7.5 events per 100 patient-years, respectively (HR = 0.61, 95% CI, 0.51 to 0.72; P < 0.001). In the Kaplan-Meier plot of the primary composite outcome the 2 curves separated at around 4 months and remained separated throughout follow-up. Results for each component of the composite outcome were aligned with those for the composite (presented previously),[9]

Results of sensitivity analyses for the primary outcome were consistent with the primary analysis. Results within prespecified subgroups of interest (by T2DM status, eGFR, and UACR at baseline) were consistent with those for the primary analysis.[9] There were no statistically significant subgroup interactions for the composite primary outcome, or any components of the composite, among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to at least 50% eGFR decline, ESKD, or renal death was the secondary outcome. At the conclusion of the RCT, 142 (6.6%) patients in the dapagliflozin group and 243 (11.3%) patients in the placebo group experienced a component of the composite outcome, corresponding to 3.3 and 5.8 events per 100 patient-years, respectively (HR = 0.56, 95% CI, 0.45 to 0.68; P < 0.001). In the Kaplan-Meier plot for this outcome, the 2 curves separated at around 4 months and remained separated throughout follow-up. Results for each component of the composite outcome were aligned with those for the composite (presented previously).[9] There were no statistically significant subgroup interactions for this composite secondary outcome, or any components of the composite, among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to CV death or hospitalization for HF was a secondary outcome. At the conclusion of the RCT, 100 (4.6%) patients in the dapagliflozin group and 138 (6.4%) patients in the placebo group experienced a component of the composite outcome, corresponding to 2.2 and 3.0 events per 100 patient-years, respectively (HR = 0.71, 95% CI, 0.55 to 0.92; P = 0.009). In the Kaplan-Meier plot for this outcome, the 2 curves separated at around 1 month and remained separated throughout follow-up.[9] There was no statistically significant subgroup interaction for this composite secondary outcome among patients with versus without T2DM, CVD, or HF.[11,12,14]

Time to MI, stroke, or CV death was an exploratory outcome. At the conclusion of the RCT, 132 (6.1%) patients in the dapagliflozin group and 143 (6.6%) patients in the placebo group experienced a component of the composite outcome, corresponding to 2.9 and 3.1 events per 100 patient-years, respectively (HR = 0.92, 95% CI, 0.72 to 1.16). There was no statistically significant subgroup interaction among patients with versus without CVD.[11]

Two additional composite exploratory outcomes were analyzed post hoc. At the conclusion of the RCT, 158 (7.3%) patients in the dapagliflozin group and 195 (9.1%) in the placebo group experienced CV death,

MI, stroke, or hospitalization for HF, corresponding to 3.5 and 4.4 events per 100 patient-years, respectively (HR = 0.79, 95% CI, 0.64 to 0.98).[11] Two-hundred and 74 (12.7%) patients in the dapagliflozin group and 376 (17.5%) in the placebo group experienced death (from any cause), MI, stroke, hospitalization for HF, or ESKD, corresponding to 6.5 and 9.1 events per 100 patient-years, respectively (HR = 0.70, 95% CI, 0.60 to 0.82). There were no statistically significant subgroup interactions among patients with versus without CVD.[11]

Hospitalization

Time to hospitalization for HF was an exploratory outcome in DAPA-CKD. At the conclusion of the RCT (median follow-up, 2.4 years [range = 2.0 to 2.7]), 37 (1.7%) patients in the dapagliflozin group and 71 (3.3%) patients in the placebo group required hospitalization for HF, corresponding to 0.8 and 1.6 events per 100 patient-years, respectively (HR = 0.51, 95% CI, 0.34 to 0.76).[11] There were no statistically significant subgroup interactions among patients with versus without CVD or HF.[11,12]

A post hoc analysis of hospitalizations (first and subsequent) was also reported for DAPA-CKD.[13] These outcomes were not prespecified in the protocol. At the conclusion of the RCT (median follow-up, 2.4 years [range = 2.0 to 2.7]), 566 (26.3%) patients in the dapagliflozin group and 658 (30.6%) patients in the placebo group required any hospitalization, corresponding to 143.7 and 171.9 events per 100 patient-years, respectively (HR = 0.84, 95% CI, 0.75 to 0.94). In the Kaplan-Meier plot of the first hospitalization from any cause, the 2 curves separated at around 6 months and remained separated throughout follow-up. Results for the additional hospitalization outcomes, including all (first and subsequent) hospitalizations and composites including prolonged hospitalizations, deaths, and hospitalizations resulting in death all yielded similar results:

- Any hospitalization or death: 591 (27.5%) patients in the dapagliflozin group versus 689 (32.0%) patients in the placebo group (HR = 0.83, 95% CI, 0.75 to 0.93).
- Any prolonged hospitalization (at least 7 days) or hospitalization ending in death: 370 (17.2%) patients in the dapagliflozin group versus 438 (20.4%) patients in the placebo group (HR = 0.83, 95% CI, 0.72 to 0.95).
- Any prolonged hospitalization (7 or more days), death, or hospitalization ending in death: 398 (18.5%) patients in the dapagliflozin group versus 478 (22.2%) patients in the placebo group (HR = 0.82, 95% CI, 0.72 to 0.93).
- First and subsequent hospitalizations: 921 (42.8%) patients in the dapagliflozin group versus 1,151 (53.5%) patients in the placebo group (rate ratio = 0.79, 95% CI, 0.70 to 0.90).
- First and subsequent hospitalizations or death: 973 (45.2%) patients in the dapagliflozin group versus 1,224 (56.9%) patients in the placebo group (rate ratio = 0.79, 95% CI, 0.70 to 0.89).

The mean number of days normalized per patient-year spent in hospital was 2.3 (SD = 7.5) in the dapagliflozin group and 2.8 (SD = 9.6) in the placebo group (P = 0.027).[13]

Hospitalizations were not measured in any of the other RCTs.

Health-Related Quality of Life

Change from baseline HRQoL was measured but not reported in DAPA-CKD. HRQoL was not measured in DELIGHT, DERIVE, or Kohan et al. (2014).

Symptom Severity

Symptom severity was not measured in any of the included RCTs.

Functional Status

Functional status was not measured in any of the included RCTs.

Harms Results

Adverse Events

Any AEs was not reported in DAPA-CDK. In both DELIGHT and DERIVE, approximately half of patients experienced at least 1 AE, and the frequency was relatively consistent across the dapagliflozin and placebo groups (Table 12).[15,16] In Kohan et al. (2014), where the follow-up was longer (104 weeks), most (91.1%) patients experienced at least 1 AE, and the frequency was consistent across the dapagliflozin and placebo groups.[19]

Serious Adverse Events

Across all RCTs, the frequency of patients experiencing at least 1 serious AE was similar across the dapagliflozin and placebo groups.[9,15,16,19] In DAPA-CKD, 633 (29.5%) and 729 (33.9%) patients in the dapagliflozin and placebo groups experienced any serious AE, respectively. In DELIGHT, 12 (8.3%) and 15 (10.8%) patients in the dapagliflozin and placebo groups experience any serious AE, respectively. In DERIVE, 9 (5.6%) and 14 (8.7%) patients in the dapagliflozin and placebo groups experienced any serious AE, respectively. In Kohan et al. (2014), 26 (30.6%) and 26 (31.0%) patients in the dapagliflozin and placebo groups experienced any serious AE, respectively.

Withdrawal Due to Adverse Events

Across all RCTs except for Kohan et al. (2014), few patients withdrew from the assigned interventions, and the frequency was similar across the dapagliflozin and placebo groups.[9,15,16,19] In DAPA-CKD, 118 (5.5%) and 123 (5.7%) patients withdrew from the interventions due to AEs in the dapagliflozin and placebo groups, respectively. In DELIGHT, 4 (2.8%) and 8 (5.4%) patients withdrew from the interventions due to AEs in the dapagliflozin and placebo groups, respectively. In DERIVE, 3 (1.9%) patients withdrew from the interventions due to AEs in both groups. In Kohan et al. (2014), the proportion of patients who withdrew from treatment due to AEs was not reported; however, more patients in the placebo group (26.2%) withdrew from the RCT due to AEs compared with the dapagliflozin group (12.9%).

Deaths Due to Adverse Events

Deaths due to AEs were not reported in any of the RCTs.

Notable Harms

Amputations, DKA, and fractures were generally infrequent and balanced across groups in DAPA-CKD and DELIGHT.[9,15] No patient in DERIVE had an amputation, DKA, or a fracture.[16] Amputations and DKA were not reported in Kohan et al. (2014); however, more patients in the dapagliflozin group (9.4%) compared with the placebo group (0.0%) had a fracture.[19] Major hypoglycemia was infrequent and balanced across groups in DAPA-CKD.[9] No patient had major hypoglycemia in either of DELIGHT or DERIVE.[15,16] Few patients experienced major hypoglycemia in Kohan et al. (2014) (2.4% in the dapagliflozin group and 4.8% in the placebo group).[19] Genital and urinary tract infections, as reported among patients with both CKD and T2DM in DELIGHT and DERIVE, were infrequent.[15,16] Among patients with CKD and T2DM in Kohan et al. (2014),[19] which had longer follow-up, genital infections were more frequent in the dapagliflozin compared with the placebo group (8.2% versus 3.6%), and UTIs were balanced across groups (14.1% versus 14.3%). The incidence of palpitations was not reported in any RCT.

Renal AEs were balanced across groups in all RCTs.[9,15,16,19] In DAPA-CKD, 155 (7.2%) and 188 (8.7%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In DELIGHT, 4 (2.8%) and 6 (4.1%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In DERIVE, 1 (0.6%) and 2 (1.2%) patients in the dapagliflozin and placebo groups had a renal AE, respectively. In Kohan et al. (2014), 8 (9.4%) and 6 (7.1%) patients in the dapagliflozin and placebo groups had a renal AE, respectively.

Volume depletion was balanced across groups in all RCTs except for Kohan et al. (2014).[9,15,16,19] In DAPA-CKD, 127 (5.9%) and 90 (4.2%) patients in the dapagliflozin and placebo groups had volume depletion, respectively, In DELIGHT, 4 (2.8%) and 4 (2.7%) patients in the dapagliflozin and placebo groups had volume depletion, respectively. In DERIVE, 3 (1.9%) patients in the dapagliflozin group and none in the placebo group had volume depletion. In Kohan et al. (2014), more patients in the dapagliflozin group (12.9%) had volume depletion compared with the placebo group (6.0%).

Critical Appraisal of Included Studies

Internal Validity

In all RCTs the randomization appeared successful; some baseline imbalances were observed in DELIGHT, DERIVE, and Kohan et al. (2014) that were likely to have occurred due to chance. Protocol deviations were infrequent in DAPA-CKD, and not reported for the other 3 RCTs. Adherence to the interventions was high (96% to 99%) in both groups in DAPA-CKD (although only 84% of patients had data to assess adherence); 12.7% and 14.4% of placebo and dapagliflozin participants, respectively, discontinued treatment during follow-up. Adherence was not reported in the other RCTs.

In all RCTs, matched placebos were used to maintain blinding of patients and study personnel (the RCTs were described as double blind). Adverse events, including notable harms, appeared generally balanced across groups so it is unlikely that patients or personnel would have become unblinded. In DAPA-CKD, most primary outcome events were adjudicated by an independent blinded committee. Similarly, in the other RCTs most outcomes were measured via a central laboratory. As such, the risk of bias in the measurement of the outcomes is low.

There were some concerns for risk of bias due to missing outcome data in DAPA-CKD. Nearly 20% of patients had missing eGFR assessments. Patients who had incomplete follow-up or were prematurely censored due to withdrawal of consent or loss to follow-up were considered to have missing information for the primary efficacy analysis; however, sensitivity analyses (multiple imputation analyses) supported the primary analyses. There were no notable differences between intervention groups in the proportions of missing outcome data. In both DELIGHT and DERIVE, the risk of bias due to missing outcome data was low, as few (5% or fewer) patients in either group were lost to follow-up. In Kohan et al. (2014), where relevant outcomes were reported at 104 weeks follow-up, there were large amounts (at least 40% for change in eGFR and UACR) of missing data across groups; therefore, the results are at risk of bias due to missing outcome data.

Data were mostly analyzed in accordance with a prespecified analysis plan. Data for some outcomes that were measured were not reported in DAPA-CKD (e.g., HRQoL); whereas other outcomes (composite outcomes, hospitalization outcomes) were analyzed post hoc, so there is a risk of selective results reporting. The statistical analysis methods appear to be acceptable in all RCTs. Appropriate procedures were used to control for type I error (false-positive results). In some studies, the only relevant outcomes were exploratory; these were not adjusted for type I error so there is an increased risk of false-positive results. In Kohan et al. (2014), the between-group differences were sometimes not reported, and differences were not tested statistically, limiting interpretation. Since DAPA-CKD stopped early for efficacy, it is possible that the benefits of dapagliflozin over placebo were overestimated.

Subgroup analyses based on T2DM status, eGFR, and UACR were defined a priori in DAPA-CKD; subgroup data were also reported by CVD and HF status; however, these subgroups were not specified in the protocol. Subgroup analyses by baseline UACR, eGFR, and CV history were prespecified in DELIGHT, but the trials were not powered to detect statistically significant differences. Subgroup analyses were not adjusted for multiple comparisons, so there is an increased risk of type I error for statistically significant subgroup interactions.

External Validity

Per the clinical experts consulted by CADTH, the populations and interventions in the RCTs was generally reflective of clinical practice in Canada. Only patients with stage IIIA CKD were included in DERIVE, which limits the generalizability of the results to patients in other disease stages. The background therapies (e.g., ACE inhibitors and ARBs) were reflective of clinical practice in Canada in most RCTs; however, in Kohan et al. (2014) the use of ACE inhibitors and ARBs was not reported so it is not clear whether background therapy use was reflective of clinical practice in Canada. DAPA-CKD included patients with CKD irrespective of T2DM status, which the clinical experts considered valuable. Since all other RCTs included only patients with T2DM, the results may not be generalizable to patients without T2DM. The length of follow-up in both DELIGHT and DERIVE (24 weeks) was insufficient to inform long-term efficacy and harms. Outcomes that are important to patients, like HRQoL, symptoms, and functional status were not reported in any of the RCTs.

Table 12: Summary of Harms from DAPA-CKD, DELIGHT, DERIVE, and Kohan et al. (2014) (SAS)[a]

Harms	DAPA-CKD		DELIGHT		DERIVE		Kohan et al. (2014)	
	Dapagliflozin N = 2,152	Placebo N = 2,152	Dapagliflozin N = 145	Placebo N = 148	Dapagliflozin N = 160	Placebo N = 161	Dapagliflozin N = 85	Placebo N = 84
Harms, n (%)								
Any AE	NR	NR	79 (54.5)	81 (54.7)	67 (41.9)	77 (47.8)	77 (90.6)	77 (91.7)
Any serious AEs	633 (29.5)	729 (33.9)	12 (8.3)	16 (10.8)	9 (5.6)	14 (8.7)	26 (30.6)	26 (31.0)
WDAE (from study treatment)	118 (5.5)	123 (5.7)	4 (2.8)	8 (5.4)	3 (1.9)	3 (1.9)	NR[b]	NR[b]
Deaths[c]	NR	NR	NR	NR	NR	NR	NR	NR
Notable harms, n (%)								
Amputations	35 (1.6)	39 (1.8)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR
Genital infections	NR	NR	4 (2.8)	0 (0.0)	3 (1.9)	2 (1.2)	7 (8.2)	3 (3.6)
Urinary tract infections	NR	NR	5 (3.4)	4 (2.7)	4 (2.5)	6 (3.7)	12 (14.1)	12 (14.3)
Any definite or probable DKA	0 (0.0)	2 (0.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	NR	NR
Palpitations	NR	NR	NR	NR	NR	NR	NR	NR
Fractures	85 (4.0)	69 (3.2)	1 (0.7)	2 (1.4)	0 (0.0)	0 (0.0)	8 (9.4)	0 (0.0)
Renal-related AEs	155 (7.2)	188 (8.7)	4 (2.8)	6 (4.1)	1 (0.6)	2 (1.2)	8 (9.4)	6 (7.1)
Major hypoglycemia	14 (0.7)	28 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	4 (4.8)
Volume depletion	127 (5.9)	90 (4.2)	4 (2.8)	4 (2.7)	3 (1.9)	0 (0.0)	11 (12.9)	5 (6.0)

AE = adverse event; DKA = diabetic ketoacidosis; SAS = safety analysis set; WDAE = withdrawal due to adverse event.

[a]Median follow-up time was 2.4 years in DAPA-CDK. Follow-up time for DELIGHT and DERIVE was 27 weeks. Follow-up time for Kohan et al. (2014) was 104 weeks.

[b]Withdrawal from treatment due to AEs was not reported. Eleven (12.9%) of patients in the dapagliflozin group and 22 (26.2%) in the placebo group withdrew from the RCT due to AEs.

[c]Mortality was reported in all RCTs as either an efficacy outcome or as an AE; however, deaths due to AEs were not specifically reported.

Source: Heerspink et al. (2020);[9] Pollock et al. (2019);[15] Fioretto et al. (2018);[16] Kohan et al. (2014).[19]

Indirect Evidence

Search and Selection Methods

Indirect evidence was considered given the lack of RCTs directly comparing dapagliflozin with canagliflozin or finerenone. A focused literature search for indirect treatment comparisons dealing with SGLT2 inhibitors and CKD was run in MEDLINE (1946–present) and Embase (1974–present) on August 5, 2022. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. The literature search results were screened by 1 reviewer to identify any indirect comparisons fulfilling the PICO criteria outlined in Table 5 (aside from study design). Updated literature searches were conducted up to May 26, 2023.

Included Indirect Comparisons

A total of 26 records were identified from the initial literature search. After title and abstract screening, 16 full-text articles were reviewed and 2 NMAs were included.[22,25] Of the 14 excluded ITCs, 6 investigated treatment effects in T2DM but not within T2DM comorbidity subgroups (i.e., patients with T2DM and another comorbid condition),[60-65] 5 examined patients with T2DM and CKD but evaluated SGLT2 inhibitors as a class only (i.e., dapagliflozin was not differentiated from other SGLT2 inhibitors),[66-70] 1 planned on assessing different T2DM subgroups but no data were analyzed for patients with T2DM and CKD,[71] 1 included any CV outcome trial evaluating a SGLT2 inhibitor where study populations consisted of a mix of patients with T2DM, HF, or CKD,[72] and 1 did not provided comparative estimates of dapagliflozin versus relevant comparators.[73] Three additional eligible ITCs[21,23,24] were identified from the updated literature searches, resulting in a total of 5 included ITCs.

Methods of Included Network Meta-Analyses

Of the systematic reviews contributing to each NMA, 3 aimed to include RCTs of patients with T2DM and CKD[21-23] treated with dapagliflozin or a wide variety of comparators (other SGLT-2 inhibitors,[21-25] GLP-1 receptor agonists,[23,25] mineralocorticoid receptor antagonists [i.e., finerenone][21,23]). One[24] of the NMAs did not require patients to be affected by T2DM, and in another[25] the group of patients with CKD was a subgroup. In each systematic review, authors searched multiple electronic databases (at minimum PubMed and Embase). One also mentioned scanning reference lists.[24] The date of the last search ranged from May 2020[25] to August 2022.[21] In all systematic reviews, study selection and data extraction were performed independently in duplicate with discrepancies resolved by consensus. The risk of bias of the included RCTs was appraised at the study level using version 1.0[21,22,24,25] or 2.0[23] of the Cochrane Risk of Bias tool. In 2 of the NMAs this was accomplished by 2 independent reviewers with consensus;[23,25] the remaining NMAs did not report specific methods for risk of bias appraisal.[21,22,24]

The analysis method for 3 of the systematic reviews was a frequentist NMA (random effects[21,22] or not reported[23]), while 1 included a Bayesian random effects NMA[24] and another a Bayesian fixed effects NMA with a sensitivity analysis using random effects.[25] Within 4 of the NMAs,[21,23-25] due to a lack of closed loops, assessment of consistency was not relevant. In the NMA by Lin et al. (2022),[22] a node splitting analysis was performed to assess consistency.[22] Assessment of model fit was not mentioned in the included NMAs. No relevant subgroup analyses were performed, however the population of interest in Qiu et al. (2021)[25] was a

subgroup, with CKD being defined as an eGFR < 60 mL/min/1.73 m^2. Funnel plots were used to assess the risk of publication bias in 2 NMAs,[22,25] and an assessment of publication bias was planned for a third NMA but could not be performed due to a small number of included studies.[24]

Results of Included NMAs

Characteristics of Included NMAs

Owing to differences in the populations, comparisons, and outcomes of interest, primary study overlap across the included NMAs was relatively limited (Table 13). Across all included NMAs, the networks were sparse (i.e., there were multiple comparisons but few contributing RCTs). In 4 of the 5 NMAs,[21-24] all eligible RCTs were placebo-controlled; as such, the networks were star-shaped with placebo as the central node and there were no closed loops. In the NMA by Lin et al. (2022),[18] all networks were generally star-shaped, with closed loops comparing various doses of the same SLGT2 inhibitor only.

Table 13: Primary Study Overlap Across the Included NMAs

Trial or author name and Year	Inclusion of trials within NMAs (marked with 'Yes')				
	Chen et al. (2022)	Li et al. (2022)	Lin et al. (2022)	Zhang et al. (2022)	Qui et al. (2021)
Albiglutide vs. placebo					
HARMONY 2018[74]	No	No	No	Yes	Yes
Bexagliflozin vs. placebo					
Allegretti et al. (2019)[75]	No	No	Yes	No	No
Canagliflozin vs. placebo					
CANVAS 2017[76]	No	Yes	No	Yes	Yes
CREDENCE 2019[77]	Yes	Yes	Yes	No	Yes
Takashima et al. (2018)[78]	No	No	Yes	No	No
Yale et al. (2014)[79]	No	No	Yes	No	No
Dapagliflozin vs. placebo					
DAPA-CKD 2020[9]	Yes	No	No	Yes	No
DECLARE-TIMI 58 2019[32]	No	Yes	No	Yes	Yes
DELIGHT 2019[a,15]	No	No	Yes	No	No
DERIVE 2018[16]	No	No	Yes	No	No
Kohan et al. (2017)[19]	No	No	Yes	No	No
Petrykiv et al. (2017)[80]	No	No	Yes	No	No
Dulaglutide vs. Placebo					
REWIND 2019[81]	No	No	No	Yes	Yes
Empagliflozin vs. Placebo					
EMPA-REG 2015[82-84]	No	Yes	Yes	Yes	Yes

Trial or author name and Year	Inclusion of trials within NMAs (marked with 'Yes')				
	Chen et al. (2022)	Li et al. (2022)	Lin et al. (2022)	Zhang et al. (2022)	Qui et al. (2021)
Efpeglenatide vs. Placebo					
AMPLITUDE-O 2021[85]	No	No	No	Yes	No
Ertugliflozin vs. Placebo					
VERTIS-CV 2020[86]	No	Yes	No	Yes	No
VERTIS-RENAL 2017[87]	No	No	Yes	No	No
Exenatide vs. Placebo					
EXSCEL 2017[88]	No	No	No	Yes	Yes
Finerenone vs. Placebo					
ARTS-DN 2015[89]	No	No	No	Yes	No
FIDELIO-DKD 2020[90]	No	Yes	No	Yes	No
FIGARO-DKD 2021[91]	No	Yes	No	Yes	No
Ipragliflozin vs. Placebo					
LANTERN 2014[92]	No	No	Yes	No	No
Liraglutide vs. placebo					
LEADER 2016[93]	No	No	No	Yes	Yes
Lisenglutide vs. placebo					
ELIXA 2015[94]	No	No	No	No	Yes
Luseogliflozin vs. placebo					
Haneda et al. (2016)[95]	No	No	Yes	No	No
Semaglutide vs. placebo					
PIONEER-6 2019[96]	No	No	No	Yes	Yes
SUSTAIN-6 2016[97]	No	No	No	Yes	Yes
Sotagliflozin vs. placebo					
SCORED 2021[98]	Yes	Yes	Yes	Yes	No
SOLOIST-WHF 2021[99]	No	Yes	No	No	No
Cherney et al. (2021)[100]	No	No	No	Yes	No
Zambrowicz et al. (2015)[101]	No	No	Yes	No	No

[a]The trial also includes a saxagliptin group.

Sources: Chen et al. (2022);[24] Li et al. (2022);[21] Lin et al. (2022);[21] Zhang et al. (2022);[23] Qiu et al. (2021).[25]

Characteristics of the NMAs and the RCTs contained within them are in Table 14. Three to 18 RCTs (19,289 to 71,793 patients; not reported in 1 NMA[2]) were included across the individual NMAs. All the NMAs included

comparisons of dapagliflozin to canagliflozin, while those by Li et al. (2022)[21] and Zhang et al. (2022)[23] also included comparisons of dapagliflozin to finerenone.

Four of the 5 NMAs included only patients with both CKD and T2DM,[21-23,25] whereas in the NMA by Chen et al. (2022),[24] 67 to 100% of patients across included RCTs had T2DM. Otherwise, there was some heterogeneity in patient characteristics across the RCTs included in each NMA, namely in terms of the proportion of females (versus males) and baseline disease characteristics (i.e., eGFR and UACR at baseline); however, in many cases little information was reported to judge the degree of heterogeneity in potential treatment effect modifiers across the various RCTs. It was noted in 3 NMAs[24] that the definition of the renal composite or cardiorenal composite differed across the included trials. In the 3 NMAs where it was reported,[22-24] there was large variation in the length of follow-up across the included RCTs.

According to the systematic review authors, across 4 NMAs all included trials were assessed as being at low risk of bias, however it was noted that many RCTs were industry-sponsored.[21,23-25] In the NMA by Lin et al. (2022), 9 (60%) of the included RCTs were considered to be at low risk of bias, 5 (33%) at unclear risk of bias due to missing information about randomization and/or allocation concealment, and 1 (7%) at high risk of bias because it was open-label.[22]

Change in eGFR and UACR were reported in 1 NMA;[21] MI was reported in 1 NMA;[22] CV death was reported in 2 NMAs;[21,23] all-cause death was reported in 1 NMA;[23] a renal composite outcome was reported in 2 NMAs (defined as new onset macroalbuminuria, ESKD, or decline in renal function by Li et al. [2022][22] and as sustained eGFR decline of at least 40% or a doubling of serum creatinine, kidney failure, or renal death by Zhang et al. [2022][23]); a cardiorenal composite was reported in 1 NMA (defined as worsening eGFR, ESKD, renal death, or CV death);[24] MACE was reported in 3 NMAs (defined as death from CV causes, nonfatal MI, or nonfatal stroke);[22,23,25] hospitalization for HF was reported in 2 NMAs;[21,23] and harms were reported in 1 NMA (including AEs, SAEs, UTIs, and discontinuations from treatment).[22]

Efficacy Results of Included NMAs

Renal Events

Renal events were not reported in any of the included NMAs.

Change in eGFR

In the NMA by Lin et al. (2022),[22] for the comparison of dapagliflozin to canagliflozin 100 mg, the MD in the change from baseline eGFR was −4.20 (95% CI = −6.97 to −1.43) mL/min/1.73 m^2, favouring canagliflozin. For the comparison of dapagliflozin to canagliflozin 300 mg, the MD in the change from baseline eGFR was −1.45 (95% CI = −5.19 to 2.29) mL/min/1.73 m^2. The effect estimate was affected by imprecision, such that the 95% CI included the potential that either drug could be favoured. The extent of statistical heterogeneity was not reported. The authors reported that the analysis of global inconsistency did not detect any differences between the consistency and inconsistency models. The authors noted funnel plot asymmetry, suggesting a risk of publication bias.

Table 14: Characteristics of the NMAs and Their Included Trials

NMA author and Year	RCTs (patients)	Patient characteristics (Range)[a]	Relevant Comparisons (vs dapagliflozin)	Outcomes presented	Median follow-up
Chen et al. (2022)	3 (19,289)	• Age (mean, years): 63 to 69 • Sex (% female): 33 to 46 • Race (% white): 52 to 83 • T2DM (%): 67 to 100 • Duration of T2DM (mean, years): NR • eGFR (mean, mL/min/1.73m^2): 43.0 to 56.3 • UACR (median, mg/g): 74 to 965	Canagliflozin	Cardiorenal composite[b]	16 to 58 months[c]
Li et al. (2022)	9 (71,793)	• Age (mean, years): 63 to 69 • Sex (% female): 28 to 46 • Race (% white): NR • T2DM (%): 100 • Duration of T2DM (mean, years): 10 to 17 (NR in 3 RCTs) • eGFR (mean, mL/min/1.73m^2): NR • UACR (median, mg/g): NR	• Canagliflozin • Finerenone	• MACE[d] • MI • HHF • CV death • Renal composite[e]	NR
Lin et al. (2022)	15 (20,299)	• Age (mean, years): 61 to 70 • Sex (% female): 18 to 51 • Race (% white): NR • T2DM (%): 100 • Duration of T2DM (mean, years): NR • eGFR (mean, mL/min/1.73m^2): NR • UACR (median, mg/g): NR	Canagliflozin	• Change in eGFR • Change in UACR • Any AEs • Any SAEs • UTIs • Discontinuations from treatment	< 1 to 104 weeks
Zhang et al. (2022)	18 (51,496)	• Age (mean, years): 63 to 69 (NR in 6 RCTs) • Sex (% female): NR • Race (% white): • T2DM (%): 100	• Canagliflozin • Finerenone	• MACE[d] • HHF • Renal composite[f]	3 to 65

NMA author and Year	RCTs (patients)	Patient characteristics (Range)[a]	Relevant Comparisons (vs dapagliflozin)	Outcomes presented	Median follow-up
		• Duration of T2DM (mean, years): 14 to 21 (NR in 10 RCTs) • eGFR (mean, mL/min/1.73m^2): 23.9 to 72.2 • UACR (median, mg/g): NR		• CV death • All-cause death	
Qiu et al. (2021)	11 (NR)	• Age (mean, years): 60 to 66 • Sex (% female): 29 to 46 • Race (% white): 67 to 83 • T2DM (%): NR • Duration of T2DM (mean, years): 9 to 16 (NR in 1 RCT) • eGFR (mean, mL/min/1.73m^2): NR • UACR (median, mg/g): NR	Canagliflozin	MACE[d]	NR

AE = adverse event; eGFR = estimated glomerular filtration rate; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular event; MI = myocardial infarction; NR = not reported; SAE = serious adverse event; UACR = urine albumin-to-creatinine ratio; UTIs = urinary tract infections.

[a]Some NMAs presented patient characteristics by treatment group; the data were not combined for presentation in this table.

[b]Defined as: worsening eGFR, ESKD, renal death, or CV death.

[c]Means presented.

[d]Defined as: deaths from CV causes, nonfatal MI, or nonfatal stroke.

[e]Defined as: new onset of macroalbuminuria, ESKD, or decline in renal function.

[f]Defined as: sustained decrease of at least 40% in the eGFR from the baseline or a doubling of the serum creatinine level, kidney failure (a composite of ESKD or sustained decrease in eGFR to < 15 mL/min/1.73 m2), or renal death.

Source: Chen et al. (2022);[24] Li et al. (2022);[21] Lin et al. (2022);[21] Zhang et al. (2022);[23] Qiu et al. (2021).[25]

Change in UACR

In the NMA by Lin et al. (2022),[22] for the comparison of dapagliflozin to canagliflozin 100 mg, the MD in the change from baseline UACR was 99.09 (95% CI, = 11.40 to 186.78) mg/g, favouring canagliflozin. The extent of statistical heterogeneity was not reported. The authors reported that the analysis of global inconsistency did not detect any differences between the consistency and inconsistency models. The authors noted funnel plot asymmetry, suggesting a risk of publication bias.

Cardiovascular Events

In the NMA by Li et al. (2022),[21] for the comparison of dapagliflozin to canagliflozin, the HR for MI was 1.05 (95% CI, 0.53 to 2.05). For comparison of dapagliflozin to finerenone, the HR for MI was 0.99 (95% CI, 0.55 to 1.80). For both comparisons, the effect estimates were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured. The extent of statistical heterogeneity was not reported and the authors did not assess the risk of publication bias.

Mortality

Cardiovascular death was reported in the NMAs by Li et al. (2022)[21] and Zhang et al. (2022)[23] (Table 15). All-cause death was also reported by Zhang et al. (2022).[23] All reported effect estimates across the comparisons were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured. Li et al. (2022) did not report the extent of statistical heterogeneity; Zhang et al. (2022) noted low statistical heterogeneity for the analyses of CV death (I^2 = 4.4%) and all-cause death (I^2 = 0%).[23] The authors of the NMAs did not assess the risk of publication bias.

Table 15: Mortality Results From the NMAs by Li et al. (2022) and Zhang et al. (2022)

Outcome	Effect measure	Effect estimate (dapagliflozin vs. canagliflozin)	Effect estimate (dapagliflozin vs. finerenone)
Cardiovascular death			
Li et al. (2022)	HR (95% CI)	1.18 (0.77 to 1.80)	1.11 (0.73 to 1.70)
Zhang et al. (2022)	RR (95% CI)	0.99 (0.71 to 1.38)	0.97 (0.71 to 1.32)
All-cause death			
Zhang et al. (2022)	RR (95% CI)	0.96 (0.73 to 1.28)	0.90 (0.72 to 1.13)

CI = confidence interval; HR = hazard ratio; NMA = network meta-analysis; RR = risk ratio.
Source: Li et al. (2022);[21] Zhang et al. (2022).[23]

Composite Outcomes (Renal and/or Cardiovascular Events)

A renal composite outcome was reported in the NMAs by Li et al. (2022)[21] and Zhang et al. (2022)[23] (Table 16). Chen et al. (2022)[24] reported a cardiorenal composite outcome, and 3 NMAs[21,23,25] reported on MACE.

For the renal composite outcome reported by Li et al. (2022)[21] (new onset of macroalbuminuria, ESKD, or decline in renal function), the effect estimate for the comparison of dapagliflozin to both canagliflozin and finerenone were affected by imprecision, such that the 95% CI included the possibility that either drug was

favoured. The extent of statistical heterogeneity was not reported. For the renal composite outcome reported by Zhang et al. (2022) (sustained decrease of at least 40% in the eGFR from the baseline or a doubling of the serum creatinine level, kidney failure, or renal death), the effect estimate for the comparison of dapagliflozin to canagliflozin was equally affected by imprecision. In the comparison of dapagliflozin to finerenone, dapagliflozin was favoured. The I^2 for statistical heterogeneity was 37.4%. The risk of publication bias was not assessed in either NMA.

For the cardiorenal composite outcome reported by Chen et al. (2022)[24] (worsening eGFR, ESKD, renal death, or CV death), for the comparison of dapagliflozin to canagliflozin the effect estimate was affected by imprecision, such that the 95% CI included the possibility that either drug was favoured. The authors noted that the results from the inconsistency model were similar. The risk of publication was not assessed due to the small number of trials.

Across the 3 NMAs that investigated MACE (deaths from CV causes, nonfatal MI, or nonfatal stroke), across comparisons (i.e., dapagliflozin versus canagliflozin in 3 NMAs and dapagliflozin versus finerenone in 2 NMAs) the effect estimates were affected by imprecision, such that the 95% CI included the possibility that either drug was favoured. Liu et al. (2022) did not report on the extent of statistical heterogeneity. Qiu et al. (2021) noted that no substantial heterogeneity was observed,[25] while Zhang et al. (2022) reported an I^2 of 34.5%.[23] Publication bias was assessed only by Qiu et al. (2021) and was not detected.

Table 16: Composite Outcomes Results From the NMAs by Li et al. (2022), Zhang et al. (2022), Chen et al. (2022), and Qiu et al. (2021)

Outcome	Effect measure	Effect estimate (dapagliflozin vs. canagliflozin)	Effect estimate (dapagliflozin vs. finerenone)
Renal composite outcome			
Li et al. (2022)[a]	HR (95% CI)	0.80 (0.45 to 1.48)	0.63 (0.35 to 1.10)
Zhang et al. (2022)[b]	RR (95% CI)	0.85 (0.65 to 1.13)	0.70 (0.55 to 0.87)
Cardiorenal composite outcome			
Chen et al. (2022)[c]	OR (95% CrI)	0.88 (0.32 to 2.17)	NR
MACE[d]			
Li et al. (2022)	HR (95% CI)	1.15 (0.85 to 1.59)	1.07 (0.79 to 1.47)
Zhang et al. (2022)	RR (95% CI)	1.19 (0.94 to 1.49)	1.05 (0.85 to 1.29)
Qiu et al. (2021)	HR (95% CrI)	1.26 (0.91 to 1.76)	NR

CI = confidence interval; CrI = credible interval; HR = hazard ratio; NMA = network meta-analysis; NR = not reported; OR = odds ratio; RR = risk ratio.

[a]Defined as: new onset of macroalbuminuria, ESKD, or decline in renal function.

[b]Defined as: sustained decrease of at least 40% in the eGFR from the baseline or a doubling of the serum creatinine level, kidney failure (a composite of ESKD or sustained decrease in eGFR to < 15 mL/min/1.73 m^2), or renal death.

[c]Defined as: worsening eGFR, ESKD, renal death, or CV death.

[d]Defined as: deaths from CV causes, nonfatal MI, or nonfatal stroke.

Source: Chen et al. (2022);[21] Li et al. (2022);[24] Zhang et al. (2022);[23] Qiu et al. (2021).[25]

Hospitalization

Hospitalization for HF was reported in the NMAs by Li et al. (2022)[21] and Zhang et al. (2022)[23] (Table 17). For the comparison of dapagliflozin to canagliflozin, the effect estimates from both NMAs were affected by imprecision, such that the 95% CIs included the potential that either drug could be favoured. For the comparison of dapagliflozin to finerenone, the effect estimate from the NMA by Li et al. (2022)[21] was similarly affected by imprecision. The point estimate (RR) from the NMA by Zhang et al. (2022)[23] favoured dapagliflozin; however, the 95% CI included the possibility of little-to-no difference between the 2 drugs. Li et al. (2022) did not report the extent of statistical heterogeneity; Zhang et al. (2022) reported an I^2 of 44.9%.[23] The risk of publication bias was not assessed for either NMA.

Table 17: HHF Results From the NMAs by Li et al. (2022) and Zhang et al. (2022)

Outcome	Effect measure	Effect estimate (dapagliflozin vs. canagliflozin)	Effect estimate (dapagliflozin vs. finerenone)
Li et al. (2022)	HR (95% CI)	1.14 (0.71 to 1.84)	0.93 (0.58 to 1.50)
Zhang et al. (2022)	RR (95% CI)	0.93 (0.64 to 1.35)	0.71 (0.50 to 1.00)

CI = confidence interval; HR = hazard ratio; NMA = network meta-analysis; RR = risk ratio.

Source: Li et al. (2022);[21] Zhang et al. (2022).[23]

Health-Related Quality of Life

HRQoL was not reported in any of the included NMAs.

Symptom Severity

Symptom severity was not reported in any of the included NMAs.

Functional Status

Functional status was not reported in any of the included NMAs.

Harms

Harms were only reported in the NMA by Lin et al. (2022) (Table 18).[22] Results for AEs, SAEs, UTIs, and discontinuations from treatment were inconclusive due to wide CIs that included the possibility of both benefit and harm for dapagliflozin relative to canagliflozin (100 mg and 300 mg). The extent of statistical heterogeneity was not reported. The authors reported that the analysis of global inconsistency did not detect any differences between the consistency and inconsistency models. The authors noted funnel plot asymmetry, suggesting a risk of publication bias.

Table 18: Harms Results From the NMA by Lin et al. (2022)

Outcome	Effect measure	Effect estimate (vs. canagliflozin 100 mg)	Effect estimate (vs. canagliflozin 300 mg)
AEs	OR (95% CI)	1.18 (0.84 to 1.65)	1.53 (0.73 to 3.22)
SAEs	OR (95% CI)	0.93 (0.60 to 1.45)	0.58 (0.29 to 1.16)
Urinary tract infections	OR (95% CI)	1.85 (0.53 to 6.67)	0.66 (0.22 to 1.96)
Discontinuation from treatment	OR (95% CI)	0.49 (0.14 to 1.75)	0.74 (0.18 to 3.13)

AE = adverse event; CI = confidence interval; OR = odds ratio; SAE = serious adverse event; UACR = urine albumin-creatinine ratio.
Source: Lin et al., (2022).[22]

Critical Appraisal of Included Network Meta-Analyses

Four[21-23,25] of the 5 systematic reviews with NMA were informed by an a priori registered protocol. The search strategies relied heavily on bibliographic databases; only 1 NMA[24] employed an additional strategy (reference list scanning). As a result, there is the potential bias due to missing evidence in the syntheses if eligible studies were missed. In all cases, the methods for study selection and data extraction were adequate to minimize the risk of error, and risk of bias was assessed using appropriate tools. Based on the reported information, analysis methods across the NMAs generally appeared appropriate; however, model parameters (i.e., selection of priors, assessment of model fit, convergence) and assessments of heterogeneity were not always presented.

There was some overlap in the primary studies included across the NMAs, though the impact on the findings across the NMAs is unclear without further investigation. In all but 1 of the systematic reviews, all the included studies were rated to be at low risk of bias, whereas Lin et al. (2022)[22] noted some risk of bias concerns which appeared to be minimal across about one-third of the included studies.

Clinical and methodological heterogeneity was noted in patient characteristics (e.g., sex distribution, disease severity), outcome definitions (particularly the composites), and length of follow-up across the included RCTs, which challenged the transitivity assumption underlying the NMAs. In many cases, there was insufficient information reported by the authors of the NMAs to judge the degree of heterogeneity in potential treatment effect modifiers across the various RCTs. The networks were sparse (several comparisons informed by few trials), and all evidence for the comparisons of interest was indirect. Several comparison-outcomes were affected by imprecision which reduced the certainty of the effect estimates; CIs or CrIs often included the potential for no important difference between treatments, or that either treatment could be favoured.

Not all of the NMA authors investigated the potential for publication bias. Because there were few trials per comparison, formal assessments of the risk of publication bias were not possible in the NMA by Chen et al. (2022).[24] Qiu et al. (2021) did not detect publication bias,[25] however Lin et al. (2022) noted funnel plot asymmetry and indicated a potential that the analyses were affected by publication bias.[22] It is also notable that several of the contributing RCTs were industry-sponsored.

Across the NMAs, the included populations were directly relevant and most applicable to patients with both T2DM and CKD. Notably, canagliflozin and finerenone are only indicated in patients with both T2DM and CKD. Clinically relevant outcomes were considered. Several important efficacy outcomes which may be of high relevance to patients (e.g., HRQoL, symptom severity, functional status) were not reported.

Other Relevant Evidence

This section includes a brief overview of studies that were considered to address gaps in the evidence included in the systematic review. Three RCTs are included; 2 provide information specific to patients with HF, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[26,27] trial and the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial.[28,29] One provides information specific to patients with T2DM and a high risk for CV events, the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial.[30-32] These RCTs provide subgroup-level data for patients with CKD.

Methods

DAPA-HF (N = 4,744) and DELIVER (N = 6,263) were multicentre double-blind RCTs that aimed to determine the efficacy and safety of dapagliflozin among adults with HF and either reduced (DAPA-HF) or preserved (DELIVER) ejection fraction. In both RCTs, patients with or without T2DM were eligible. DECLARE-TIMI 58 (n = 17,160) was a multicentre double-blind RCT among adult patients with T2DM and established or risk factors for atherosclerotic CVD. In all RCTs patients were randomized 1:1 to dapagliflozin 10 mg once daily or matching placebo.

In all RCTs efficacy analyses were based on the intention-to-treat population. Time-to-event outcomes were analyzed using Kaplan-Meier estimates and Cox proportional-hazards models. Change from baseline values in DAPA-HF and DELIVER were analyzed using mixed model repeated measures. In DAPA-HF, HF hospitalization or CV death was analyzed using a semiparametric proportional rates model. Patients with eGFR lower than 60 mL/min/1.73m^2 was a prespecified subpopulation of interest in DAPA-HF (n = 1,926)[27] and DECLARE-TIMI 58 (n = 1,265).[32] In DECLARE-TIMI 58 there was an additional subpopulation of patients with UACR 30 up to 300 mg/g and more than 300 mg/g (n = 5,199).[31] Patients with eGFR lower than 45 mL/min/1.73m^2 and 45 to lower than 60 mL/min/1.73m^2 were prespecified subpopulations of interest in DELIVER (n = 1,657).[29] The analyses for outcomes in these subgroups were performed without multiplicity adjustment. Analyses of harms in DAPA-HF and DELIVER included all randomized patients who received at least 1 dose of study drug and were presented as counts and proportions (harms were not reported for relevant subgroups in DECLARE-TIMI 58).

Baseline Characteristics

Baseline characteristics were generally similar across treatment groups in DAPA-HF and DELIVER for the subgroups of interest, with mean age ranging from 71 to 74 years, and half of patients having T2DM.[27,29] There were some differences in the proportion male (72% in DAPA-HF and 51% in DELIVER) and ACE inhibitor or ARB use at baseline (80% in DAPA-HF and 71% in DELIVER) across the trials.[27,29] In DECLARE-TIMI 58, mean age was 64 years, 63% were male, all had T2DM, and 81% were using ACE inhibitors or ARBs at

baseline.[32] The median follow-up was 18.2 (range = 0 to 27.8) months in DAPA-HF, 2.3 (interquartile range = 1.7 to 2.8) years in DELIVER, and 4.2 (interquartile range = 3.9 to 4.4) years in DECLARE-TIMI 58.

Efficacy Results

Renal Events and Composites

The findings for renal events and relevant composites are in Table 19. The composite of worsening renal function was reported in all 3 studies (sustained decrease of 40% or more [DECLARE-TIMI 58] or 50% or more [DAPA-HF and DELIVER], new ESKD, or renal death). Across the reported subgroups, dapagliflozin was favoured among the UACR subgroups in DECLARE-TIMI 58;[32] across the remaining groups few events were reported which generally resulted in wide CIs.[26,28] Time to ESKD and time to reduction of 50% or more in eGFR was reported in DAPA-HF and DELIVER; in both cases few events were recorded which resulted in uncertainty in the potential benefit or harm of dapagliflozin.[26,28] Time to doubling of serum creatinine was reported only in DAPA-HF; the findings favoured dapagliflozin (HR = 0.74, 95% CI, 0.26 to 0.83).[26]

The trend in change in eGFR over time was reported in all trials. In DAPA-HF and DELIVER, among relevant subgroups there was a steep decline in eGFR in the first 2 to 4 weeks in the dapagliflozin group, followed by stabilization in the dapagliflozin group and a decline in the placebo group, such that eGFR was similar across groups at longest follow-up.[26,28] In the DECLARE-TIMI 58 subgroup the findings were similar, but without a steep early decline; at 4 years the decline in the eGFR was lesser in the dapagliflozin group versus placebo.[30]

Change in UACR was reported in DECLARE-TIMI 58 for the subgroups by UACR status. Among these groups, dapagliflozin was favoured for 1-step improvement or worsening of UACR, as well as 2-step improvement among those with UACR 30 mg/g to 300 mg/g or less at baseline.[31] In all relevant subgroups, there was an initial decline in UACR during the first 6 months that was greater in the dapagliflozin group versus placebo; the difference was sustained at all time points over the 4-year follow-up.[31]

Cardiovascular Events, Hospitalizations, and Composites

The findings for CV events, hospitalizations, and relevant composites are in Table 20. All 3 RCTs presented results for the worsening HF composite (hospitalization or urgent visit for HF or CV death) and the composite of hospitalization or urgent visit for heart failure. In the DAPA-HF eGFR less than 60 mL/min/1.73m^2 subgroup and the DELIVER eGFR 45 to less than 60 mL/min/1.73m^2 subgroup, dapagliflozin was favoured; however, in the remaining included groups there was a lack of clarity about the potential benefit of dapagliflozin because CIs included the potential for little-to-no difference or harm.[27,29,32] Time to MACE (CV death, myocardial infarction, or ischemic stroke), MI, and ischemic stroke was reported for the DECLARE-TIMI 58 eGFR lower than 60 mL/min/1.73m^2 subgroup; for each end point the CIs were wide due to a limited number of events being reported.[32]

Mortality

The findings for mortality are in Table 21. Time to renal death was reported in DAPA-HF and DELIVER, but too few events were reported to perform an analysis.[26,28] Time to CV death was reported in all 3 RCTs, however due to low event rates the CIs were wide resulting in a lack of clarity about whether dapagliflozin or placebo was favoured.[26,28,32] This was similarly the case for time to nonCV death[32] and all-cause death.[26,32]

Table 19: Renal Efficacy Results Among Subgroups of Patients With CKD

Study and population	Dapagliflozin n/N (%)	Placebo n/N (%)	Relative effect, HR (95% CI)
Composite of worsening renal function[a]			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	18/962 (1.9)	19/964 (2.0)	0.95 (0.50 to 1.82)
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	15/826 (1.8)	19/831 (2.3)	0.80 (0.41 to 1.57)
DELIVER, eGFR < 45 mL/min/1.73m^2	29/690 (4.2)	21/723 (2.9)	1.46 (0.83 to 2.56)
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	21/606 (3.5)	38/659 (5.8)	0.60 (0.35 to 1.02)
DECLARE-TIMI 58, UACR 30 to ≤ 300 mg/g	39/2017 (1.9)	66/2013 (3.3)	0.59 (0.39 to 0.87)
DECLARE-TIMI 58, UACR > 300 mg/g	31/594 (5.2)	75/575 (13.0)	0.38 (0.25 to 0.58)
End-stage kidney disease			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	NR/962	NR/964	NE[b]
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	0/826 (0)	3/831 (0.4)	NE
DELIVER, eGFR < 45 mL/min/1.73m^2	14/690 (2.0)	13/723 (1.8)	1.11 (0.52 to 2.36)
Doubling of serum creatinine			
DAPA-HF, eGFR < 60 < 60 mL/min/1.73m^2	17/962 (1.8)	36/964 (3.7)	0.74 (0.26 to 0.83)
1-step improvement in UACR[c]			
DECLARE-TIMI 58, UACR 30 to ≤ 300 mg/g	774/2017 (38.4)	576/2013 (28.6)	1.46 (1.31 to 1.62)
DECLARE-TIMI 58, UACR > 300 mg/g	282/594 (47.5)	175/575 (30.4)	1.82 (1.51 to 2.20)
1-step worsening in UACR[d]			
DECLARE-TIMI 58, UACR 30 to ≤ 300 mg/g	156/2017 (7.7)	284/2013 (14.1)	0.52 (0.43 to 0.64)
2-step improvement in UACR[e]			
DECLARE-TIMI 58, UACR ≥ 30 mg/g	422/2611 (16.2)	301/2588 (11.6)	1.43 (1.23 to 1.65)
Reduction of ≥ 50% in eGFR			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	NR/962	NR/964	NE[b]
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	15/826 (1.8)	18/831 (2.2)	0.84 (0.42 to 1.67)
DELIVER, eGFR < 45 mL/min/1.73m^2	24/690 (3.5)	18/723 (2.5)	1.41 (0.76 to 2.60)

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NE = not estimable; NR = not reported; UACR = urine albumin-to-creatinine ratio.

[a]The renal composite in DAPA-HF and DELIVER included the time to first occurrence of sustained decline in the eGFR of at least 50%, end-stage renal disease (sustained eGFR < 15 mL/min/ 1.73 m^2, sustained dialysis, or renal transplant), or renal death. In DECLARE-TIMI 58 the renal composite included sustained decrease in eGFR of at least 40%, end-stage renal disease, or renal death.

[b]There were too few events to analyze. The number of events in each group was not reported.

[c]A 1-step improvement corresponded to moving from the category of 30 to equal or less than 300 mg/g to the category of 15 to less than 30 mg/g or moving from the category of greater than 300 mg/g to 30 to 300 or less mg/g.

[d]A 1-step worsening corresponded to moving from the category of 30 mg/g to equal or less than 300 mg/g to more than 300 mg/g.

[e]A 2-step improvement corresponded to moving from the category of at least 30 mg/g to equal or less than 15 mg/g.

Source: Jhund 2021;[26] McCausland 2022;[28] Wiviott 2018;[32] Monsenzon 2019;[30] Mosenzon 2021.[31]

Table 20: Cardiovascular Efficacy Results Among Subgroups of Patients With CKD

Study and population	Dapagliflozin n/N (%)	Placebo n/N (%)	Relative effect, HR (95% CI)
Composite of worsening HF[a]			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	191/962 (19.9)	254/964 (26.4)	0.72 (0.59 to 0.86)
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	113/826 (13.7)	159/831 (19.1)	0.68 (0.54 to 0.87)
DELIVER, eGFR < 45 mL/min/1.73m^2	176/690 (25.5)	196/723 (27.1)	0.93 (0.76 to 1.14)
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	55/606 (9.1)	81/659 (12.3)	0.78 (0.55 to 1.09)
HHF or urgent visit			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	120/962 (12.5)	173/964 (18.0)	0.66 (0.51 to 0.82)
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	73/826 (8.8)	118/831 (14.2)	0.59 (0.44 to 0.79)
DELIVER, eGFR < 45 mL/min/1.73m^2	142/690 (20.6)	152/723 (21.0)	0.97 (0.77 to 1.22)
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	29/606 (4.8)	48/659 (7.3)	0.70 (0.44 to 1.12)
Major adverse CV event[b]			
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	85/606 (14.0)	104/659 (15.8)	0.92 (0.69 to 1.23)
MI			
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	40/606 (6.6)	52/659 (7.9)	0.88 (0.58 to 1.33)
Ischemic stroke			
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	26/606 (4.3)	24/659 (6.5)	1.23 (0.70 to 2.14)

CI = confidence interval; eGFR = estimated glomerular filtration rate; HHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardian infaction.

[a]The worsening HF composite included the time to first occurrence of unplanned hospitalization or urgent visit requiring IV therapy for heart failure or CV death.

[b]The major adverse CV event composite included the time to first occurrence of CV death, MI, or ischemic stroke.

Source: McMurray 2019;[27] Jhund 2021;[26] Solomon 2022;[29] Wiviott 2018.[32]

Table 21: Mortality Results Among Subgroups of Patients With CKD

Study and population	Dapagliflozin n/N (%)	Placebo n/N (%)	Relative effect, HR (95% CI)
Renal death			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	NR/962	NR/964	NE[a]
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	0/826 (0)	1/831 (0.1)	NE
DELIVER, eGFR < 45 mL/min/1.73m^2	1/690 (0.1)	1/723 (0.1)	NE
Cardiovascular death			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	119/962 (12.4)	134/964 (13.9)	0.88 (0.69 to 1.13)
DELIVER, eGFR 45 to < 60 mL/min/1.73m^2	59/826 (7.1)	68/831 (8.2)	0.87 (0.61 to 1.23)
DELIVER, eGFR < 45 mL/min/1.73m^2	70/690 (10.1)	85/723 (11.8)	0.87 (0.64 to 1.20)
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	32/606 (5.3)	40/659 (6.1)	0.90 (0.57 to 1.44)

Study and population	Dapagliflozin n/N (%)	Placebo n/N (%)	Relative effect, HR (95% CI)
NonCV death			
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	29/606 (4.8)	35/659 (5.3)	0.92 (0.56 to 1.51)
All-cause death			
DAPA-HF, eGFR < 60 mL/min/1.73m^2	143/962 (14.9)	168/964 (17.9)	0.85 (0.68 to 1.06)
DECLARE-TIMI 58, eGFR < 60 mL/min/1.73m^2	71/606 (11.7)	87/559 (15.6)	0.91 (0.67 to 1.25)

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NE = not estimable; NR = not reported.

[a]There were too few events to analyze. The number of events in each group was not reported.

Source: Jhund 2021;[26] McCausland 2022;[28] Wiviott 2018.[32]

Harms Results

Only DAPA-HF and DELIVER reported on harms for the relevant subgroups. About half (41% to 53%) of patients in both RCTs experienced at least 1 SAE.[26,28] In DAPA-HF, among patients with eGFR lower than 60 mL/min/1.73m^2, 43% of patients in the dapagliflozin group and 50% in the placebo group had a SAE.[26] In DELIVER, the occurrence of SAEs were balanced between groups and ranged from 41% to 53%.[28]

The incidence of treatment discontinuation due to AEs ranged from 4% to 14%, (highest in DAPA-HF) but was similar across treatment groups.[26,28] The incidence of several AEs of special interest (amputation, fracture, major hypoglycemia, diabetic ketoacidosis [only reported in DELIVER]) was rare (less than 3%) and balanced across treatment groups.[26,28] In DAPA-HF about 10% of patients experienced volume depletion and this was similar across groups.[26] Also in DAPA-HF, renal AEs occurred about 10% in the dapagliflozin group and 12% in the placebo group.[26]

Critical Appraisal

The RCTs were informed by a priori protocols. Though the RCTs were randomized, there was no stratification by baseline eGFR or UACR, therefore prognostic balance across the treatment groups may not be ensured. Across the RCTs, between 11% (DAPA-HF) and 25% (DECLARE-TIMI 58) of patients discontinued treatment; in all cases discontinuations were balanced across the groups. Losses to follow-up from the RCTs were low. The patients and investigators in all RCTs were blinded and efficacy end points were objective and centrally adjudicated. The RCTs were not powered to detect differences between dapagliflozin and placebo in the subgroups, and event rates for some end points were low, resulting in imprecision for several of the estimates. There were no adjustments for multiplicity, resulting in increased risk of type I error for statistically significant findings. The patients, interventions, and outcomes were relevant to clinical practice, and both patients with and without T2DM were included in DAPA-HF and DELIVER. The follow-up time, particularly in DAPA-HF, may have been inadequate for longer term outcomes. Outcomes of importance to patients, like HRQoL, symptom severity, and functional status were not reported.

Economic Evidence

As this review is part of the CADTH nonsponsored reimbursement review program in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for dapagliflozin in this clinical condition. As a result, the economic review consisted of only a cost comparison for dapagliflozin as an add-on to ARBs or ACEs compared to appropriate comparators for the treatment of patients with CKD.[102]

CADTH Analyses

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the product's respective product monographs and validated by clinical experts. If discrepancies in dosing between the product monograph and clinical practice were noted, the dose specified by clinical experts was used. Based on public list prices from the Ontario Drug Benefit Formulary accessed in June 2023, a flat price exists for dapagliflozin 5 mg and 10 mg tablets at $2.73.[2] Pricing for all other treatments were based on publicly available list prices.

In patients with CKD, there are 2 distinct subgroups of interest given that the treatment options would differ between these subgroups: patients with T2DM and those without T2DM. Clinical expert feedback obtained by CADTH suggested that, although ACE inhibitors and/or ARBs monotherapy is a relevant comparator across these 2 subgroups, finerenone and canagliflozin may further be prescribed for CKD in patients with T2DM as an add-on to ACE inhibitors and/or ARBs. Results of the cost comparison demonstrate that, over a year, dapagliflozin is $996 more costly than ACE inhibitors and/or ARBs alone. In the T2DM patient subgroup, dapagliflozin is less costly than both finerenone and canagliflozin (i.e., annual cost savings of $223 and $59, respectively). Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 22.

Table 22: CADTH Cost Comparison Table for Patients with CKD

Treatment	Strength or concentration	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
Dapagliflozin (Forxiga)	**5 mg** **10 mg**	**Tablet**	**2.7300** **2.7300**	**10 mg once daily**	**2.73**	**996**
Nonsteroidal, selective mineralocorticoid receptor antagonist						
Finerenone (Kerendia)[a]	10 mg 20 mg	Tablet	3.3400[b]	Starting: • 20 mg once daily if eGFR ≥ 60 mL/min/1.73m2 • 10 mg once daily if eGFR ≥ 25 to < 60 mL/min/1.73m2 Target: 20 mg once daily	3.34	1,219

Treatment	Strength or concentration	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
SGLT2is						
Canagliflozin (Invokana)[a]	100 mg 300 mg	Tablet	2.8910 2.8910	100 mg to 300 mg daily	2.89	1,055

CKD = chronic kidney disease; T2DM = type 2 diabetes mellitus.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.

[a]Finerenone and canagliflozin are only indicated in T2DM patients.

[b]Costing information obtained from ongoing CADTH reimbursement review. Recommended dosages are from the respective monographs.[47]

Issues for Consideration

- Previous submission history of dapagliflozin: Dapagliflozin has been previously reviewed by CADTH for the treatment of patients with T2DM to improve glycemic control in combination with metformin and sulfonylurea.[6] The recommendation concluded that dapagliflozin should not be listed.[6]
- Anticipated patent expiration of SGLT-2 treatments: The patent of dapagliflozin expired in spring 2023 while the patent of canagliflozin is expected to expire in 2024. With patent expiration, generics have become available for dapagliflozin and are expected for canagliflozin. If generics SGLT-2s are publicly reimbursed, both dapagliflozin and canagliflozin may be less costly and this may impact the cost comparison within this report.
- CDEC issued a positive recommendation for the reimbursement of finerenone.[103] Within that review, clinical expert consulted by CADTH noted that finerenone can be added to SGLT-2 inhibitors in combination with maximal tolerated dose of an ACE inhibitor or ARB 3 months after initiating an SGLT-2 inhibitor for patients who remain with a significant residual proteinuria. In this patient population, dapagliflozin in combination with finerenone and ACE inhibitors and/or ARBs is expected to remain less costly than canagliflozin in combination with finerenone and ACE inhibitors and/or ARBs.
- No cost-effectiveness studies based in Canada were identified based on a literature search conducted on May 26, 2023.

Discussion

Summary of Available Evidence

Two long-term RCTs (DAPA-CKD, median 2.4 years follow-up and Kohan et al. (2014), 104 weeks follow-up) and 2 RCTs with shorter follow-up (27 weeks) met the inclusion criteria for this review (DERIVE and DELIGHT).[9,15,16,19] All RCTs were multicentre (including centres in Canada), placebo-controlled, double-blind trials, and sponsored by AstraZeneca (Kohan et al. (2014) was also sponsored by Bristol-Myers Squibb). RCTs compared dapagliflozin 10 mg to a matched placebo once daily among patients with CKD. DAPA-CKD enrolled patients irrespective of T2DM status, while the other RCTs only enrolled patients with CKD and T2DM. The use of ACE inhibitors and ARBs was required for DAPA-CKD and DELIGHT, but not DERIVE or

Kohan et al. (2014). Most (83.8%) patients were receiving ACE inhibitors or ARBs at baseline in DERIVE, while ACE inhibitor and ARB use was not reported in Kohan et al. (2014). The mean age ranged from 61.8 to 67.5 years across RCTs, and most patients were male (56.7% to 70.6%).

In the absence of direct evidence from RCTs comparing dapagliflozin to canagliflozin or finerenone among patients with CKD and T2DM, 5 NMAs were identified. The relevant outcomes were change in eGFR and UACR were in 1 NMA;[21] MI in 1 NMA;[22] CV death in 2 NMAs;[21,23] all-cause death in 1 NMA;[23] a renal composite in 2 NMAs;[22,23] a cardiorenal composite in 1 NMA;[24] MACE in 3 NMAs;[22,23,25] hospitalization for HF in 2 NMAs;[21,23] and harms in 1 NMA (including AEs, SAEs, UTIs, and discontinuations from treatment).[22] Almost all patients in the NMA analyses had T2DM.

A total of 3 RCTs were included as evidence perceived to address gaps in the systematic review. DAPA-HF[27] and DELIVER[29] were multicentre double-blind RCTs that aimed to determine the efficacy and safety of dapagliflozin among adults with HF and either reduced (DAPA-HF) or preserved (DELIVER) ejection fraction.[27,29] In both RCTs, patients with or without T2DM were eligible. DECLARE-TIMI 58[32] was a multicentre double-blind RCT among patients with T2DM at increased CV risk. All RCTs compared dapagliflozin 10 mg to matched placebo. These RCTs provided subgroup-level data for patients with CKD (based on eGFR or UACR).

Cost

Based on publicly available list prices, dapagliflozin is expected to have an annual cost of $996 per patient. As dapagliflozin would be used as an add-on therapy to ACE inhibitors or ARB, the reimbursement of this treatment would be more costly when compared to ACE inhibitors/ARB monotherapy in all patient subgroups. Specific to patients with T2DM, comparators further include finerenone or canagliflozin as add-on therapy to ACE inhibitors/ARB. Given this, dapagliflozin was found to be a less costly alternative in comparison to finerenone and canagliflozin at current public list price (cost savings of $223 for finerenone and $59 for canagliflozin per patient).

Interpretation of Results

Efficacy

Over a median 2.4 years follow-up in DAPA-CKD, the occurrence of the composite end point (sustained decline in eGFR, ESKD, and renal and CV death) was reduced for patients treated with dapagliflozin compared to placebo. Dapagliflozin was also favoured over placebo for each component of the composite outcome. The total number of hospitalizations for HF, deaths from any cause, and CV deaths were also lower in the dapagliflozin group than the placebo group. Treatment effects were generally consistent across prespecified subgroups, including for T2DM status, eGFR, and UACR at baseline, and CVD and HF at baseline. According to the clinical experts consulted for this review, the between-group differences in the primary composite outcome were clinically important.

The DELIGHT and DERIVE studies, albeit smaller in size and shorter in follow-up, were generally supportive of the efficacy results from DAPA-CKD (for change in eGFR and UACR, and mortality). Findings of Kohan et al. (2014), which was also smaller in size but had longer follow-up, were also generally supportive. The findings

within subgroup populations of DAPA-HF, DELIVER, and DECLARE-TIMI 58 were in general directionally aligned with those of DAPA-CKD, however the number of events was often low, which resulted in imprecision in the effect estimates (i.e., the null and potential harm was often not excluded). Because the findings were from population subgroups, prognostic balance could not be assured and the results may be affected by confounding.

The results of 5 NMAs suggested that canagliflozin 100 mg was favoured over dapagliflozin for change from baseline eGFR and UACR. The results of 2 NMAs suggested that dapagliflozin was favoured over finerenone for the renal composite outcome. However, due to methodological limitations, these results should be considered to be uncertain. The effect estimates were too imprecise to draw a conclusion for other outcomes (e.g., cardiorenal composite outcomes, mortality, MACE), meaning that the CIs or CrIs included the potential that either drug could be favoured.

The clinical experts consulted by CADTH indicated that the patients enrolled in the 4 RCTs included in this review, as well as the interventions and SOC therapies used, are generally reflective of what would be observed in routine clinical practice. Since the use of background therapies was not reported, it is not clear what proportion of patients in Kohan et al. (2014) were taking ACE inhibitors or ARBs, so the generalizability of the results is less certain. Patients stated that improvement in health-related quality of life, functional ability, and reduced CKD symptoms were of primary importance. Although the DAPA-CKD study collected data for these outcomes, the results were not reported. The inclusion of patients both with and without T2DM in DAPA-CKD enhances the generalizability of the findings of this study.

Harms

Data from the 4 RCTs suggest that dapagliflozin is generally a safe option for patients with CKD with or without T2DM. Over a median 2.4 years of follow-up in DAPA-CKD, there were no notable differences in harms outcomes such as SAEs, WDAEs, or notable harms. Most treatment-emergent SAEs were reported in less than 1% of patients and no single SAE was reported in 5% of the patients or more. In addition, the frequency of notable harms such as amputation, DKA, fracture, major hypoglycemia, and volume depletion were low and similar in the dapagliflozin and placebo groups. DELIGHT and DERIVE, albeit smaller in size and shorter in follow-up, were supportive of the harms results from the DAPA-CKD. There appeared to be a greater frequency of genital infections, fractures, and volume depletion in the dapagliflozin group compared with the placebo group during long-term follow-up in Kohan et al. (2014); however, the total sample size and number of events was small, so these findings are uncertain. Subgroup findings from DAPA-HF and DELIVER were also supportive. Results of a NMA that investigated the harms (AEs, SAEs, UTIs, and discontinuations from treatment) of dapagliflozin relative to canagliflozin among patients with CDK and T2DM were inconclusive due to methodological limitations and imprecision in the effect estimates. No NMAs were found that compared harms between dapagliflozin and finerenone.

Conclusions

Evidence from 4 RCTs suggests that dapagliflozin as an add-on to SOC is an effective and safe treatment for adults with CKD (with or without T2DM). Evidence from DAPA-CKD suggests that among patients with CKD (with or without T2DM), dapagliflozin as an add-on to SOC therapy increases the time to CV and renal events relative to placebo. Dapagliflozin also resulted in fewer hospitalizations, reduced all-cause mortality, and reduced CV mortality or hospitalization for HF relative to placebo in DAPA-CKD. Evidence from the 4 RCTs suggests that dapagliflozin results in an initial decline in eGFR. In longer term RCTs (DAPA-CKD and Kohan et al. (2014)), the rate of eGFR decline was slowed relative to placebo thereafter (not formally tested in Kohan et al. (2014)). Abrupt declines in renal function were infrequent in all RCTs and the frequency was similar across groups. At longest follow-up in DAPA-CKD, dapagliflozin resulted in greater reduction in UACR relative to placebo; these results were supported by short-term results in DELIGHT but not DERIVE. Across all RCTs, the number of patients experiencing at least 1 AE or SAE was similar across groups. In all RCTs except for Kohan et al. (2014), most notable harms (i.e., amputations, genital infections, UTIs, DKA, palpitations, fractures, major hypoglycemia) were infrequent. No evidence was identified for HRQoL, symptom severity, or functional status, so the effect of dapagliflozin on these outcomes among patients with CKD is not known. The results of 5 NMAs suggested that canagliflozin 100 mg was favoured over dapagliflozin for change from baseline eGFR and UACR. The results of 2 NMAs suggested that dapagliflozin was favoured over finerenone for the renal composite outcome. However, due to methodological limitations, these results should be considered to be uncertain. The effect estimates were too imprecise to draw a conclusion for other outcomes (e.g., cardiorenal composite outcomes, mortality, MACE, AEs), and no NMAs compared AEs between dapagliflozin and finerenone. The findings of the NMAs are primarily applicable to patients with both CKD and T2DM.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of dapagliflozin plus ACE inhibitors and/or ARBs in adults with CKD could not be determined. Results of the cost comparison of treatment costs demonstrate that, annually, dapagliflozin plus ACE inhibitors and/or ARBs is $996 more costly compared with ACE inhibitors and/or ARBs alone given dapagliflozin is an add-on therapy. However, in the T2DM subgroup where comparators further include finerenone or canagliflozin as add-on therapy to ACE inhibitors and/or ARBs, dapagliflozin plus ACE inhibitors and/or ARBs may be cost savings at current public list prices (annual cost savings of $223 against finerenone plus ACE inhibitors and/or ARBs and $59 against canagliflozin plus ACE inhibitors and/or ARBs). The potential downstream costs savings associated with adding dapagliflozin to ACE inhibitors and/or ARBs given the increased time to occurrence of sustained ≥ 50% increase in eGFR, ESKD, renal or CV death when compared to ACE inhibitors and/or ARBs monotherapy were not considered as part of the cost comparison. To adequately consider the health care resource implications associated with the comparative clinical benefits reported within the clinical trials, a cost-effectiveness analysis of dapagliflozin plus ACE inhibitors and/or ARBs would be required. Given the uncertainties in the comparative clinical benefits between dapagliflozin, finerenone and canagliflozin as an add-on therapy to ACE inhibitors and/or ARBs monotherapy, it remains unclear whether and which therapy would represent the most cost-effective option in patients with CKD and T2DM.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: August 5, 2022

Alerts: Biweekly search updates until May 26, 2023

Search filters applied: No filters were applied to limit retrieval by study type.

Limits:

- Conference abstracts: excluded.

Table 23: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)

Syntax	Description
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq = #	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multidatabase Strategy

1. (Dapagliflozin or forxiga* or farxiga* or BMS 512148 or BMS512148 or lyn045 or “lyn 045” or edistride* or ckd380 or ckd 380 or oxra*).ti,ab,kf,rn,nm,ot,hw.
2. 1ULL0QJ8UC.rn,nm.
3. or/1-2
4. exp renal insufficiency, chronic/
5. (chronic adj3 (kidney or renal)).ti,ab,kf.
6. ((nephropath* or nephrit* or glomerulo* or glomerular disease*) adj3 (recur* or chronic)).ti,ab,kf.
7. (CKF or CKD or CRF or CRD).ti,ab,kf.
8. (((stage 5 or stage 4 or end-stage or terminal or late or advanced) adj4 (ckd or kidney or renal)) or ckd4 or ckd5).ti,ab,kf.
9. (ESRF or ESKF or ESRD or ESKD).ti,ab,kf.
10. or/4-9
11. and/3,10
12. 11 use medall
13. *dapagliflozin/
14. (Dapagliflozin or forxiga* or farxiga* or BMS 512148 or BMS512148 or lyn045 or “lyn 045” or edistride* or ckd380 or ckd 380 or oxra*).ti,ab,kf,dq.
15. or/13-14
16. exp Chronic kidney failure/
17. End stage renal disease/
18. (chronic adj3 (kidney or renal)).ti,ab,kf,dq.

19. ((nephropath* or nephrit* or glomerulo* or glomerular disease*) adj3 (recur* or chronic)).ti,ab,kf,dq.
20. (CKF or CKD or CRF or CRD).ti,ab,kf,dq.
21. (((stage 5 or stage 4 or end-stage or terminal or late or advanced) adj4 (ckd or kidney or renal)) or ckd4 or ckd5).ti,ab,kf,dq.
22. (ESRF or ESKF or ESRD or ESKD).ti,ab,kf,dq.
23. or/16-22
24. and/15,23
25. 24 use oemezd
26. (conference abstract or conference review).pt.
27. 25 not 26
28. or/12,27
29. remove duplicates from 28

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | dapagliflozin or chronic kidney disease or CKD]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- dapagliflozin or chronic kidney disease or CKD]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- dapagliflozin or chronic kidney disease or CKD]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- dapagliflozin or chronic kidney disease or CKD]

Grey Literature

Search dates: July 27, 2022 – August 2, 2022

Keywords: dapagliflozin or chronic kidney disease or CKD

Limits: None

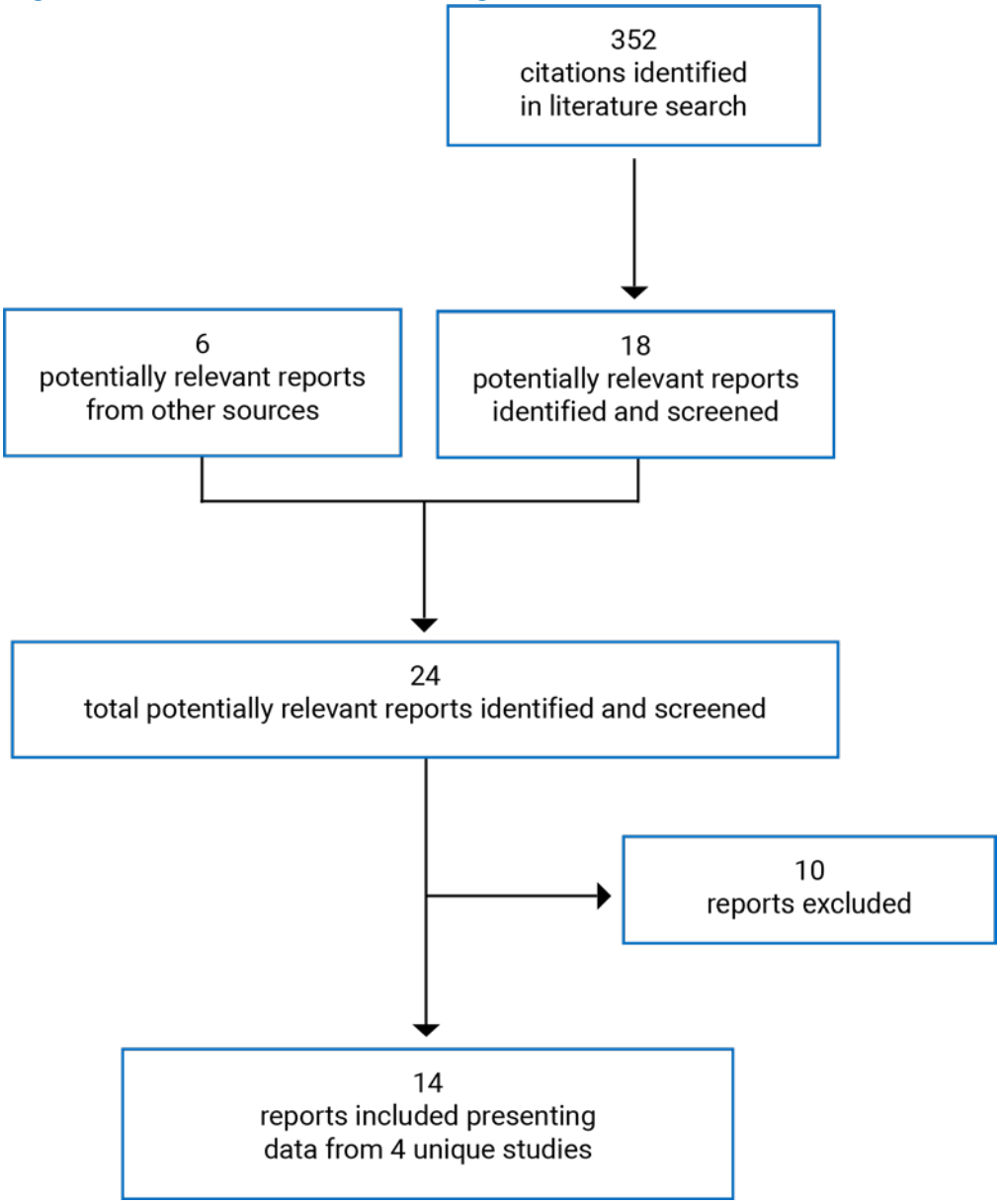
Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search.

Appendix 2: Study Selection

Figure 1: Flow of Studies Through the Selection Process



Appendix 3: Excluded Studies List

Note that this appendix has not been copy-edited.

Table 24: Excluded Studies

Author	Reference	Reason for exclusion
CHERNEY, D. Z. I., et al.	Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomized, double-blind, crossover trial. Lancet Diabetes and Endocrinology 2020;8(7):582 to 593.	phase II
CHERTOW, G. M., et al.	Quetelet (body mass) index and effects of dapagliflozin in chronic kidney disease. Diabetes, Obesity and Metabolism 2022; 24(5):827 to 837.	Ineligible subgroup
PETRYKIV, S.I., et al.	The albuminuria-lowering response to dapagliflozin is variable and reproducible among individual patients. Diabetes Obesity and Metabolism 2017;19(10):1363 to 1370.	Unclear phase with < 50 patients (likely phase II)
PROVENZANO, M., et al.	The Kidney Protective Effects of the Sodium-Glucose Cotransporter-2 Inhibitor, Dapagliflozin, Are Present in Patients With CKD Treated With Mineralocorticoid Receptor Antagonists. KI Reports 2022;7(3):436 to 443.	Ineligible subgroup
PROVENZANO, M., et al.	Albuminuria-Lowering Effect of Dapagliflozin, Eplerenone, and Their Combination in Patients with Chronic Kidney Disease: A Randomized Crossover Clinical Trial. Journal of the American Society of Nephrology 2022;33(8):1569 to 1580.	Ineligible subgroup
SEN, T., et al.	Effects of dapagliflozin on volume status and systemic hemodynamics in patients with chronic kidney disease without diabetes: Results from DAPASALT and DIAMOND. Diabetes, Obesity and Metabolism 2022;24(8):1578 to 1587.	Ineligible outcome
VART, P., et al.	Efficacy and Safety of Dapagliflozin in Patients With CKD Across Major Geographic Regions. KI Reports 2022 7(4):699 to 707.	Ineligible subgroup
WIVIOTT, S.D., et al.	Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine 2019;380:347 to 357.	Ineligible subgroup
WHEELER, D. C., et al.	Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: A prespecified analysis of the DAPA-CKD trial. Nephrology Dialysis Transplantation 2022;37(8):1647 to 1656.	Ineligible subgroup
WHEELER, D. C., et al.	A prespecified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. Kidney International 2021;100(1):215 to 224.	Ineligible subgroup

Appendix 4: Results from DAPA-CKD[9]

Note that this appendix has not been copy-edited.

Figure 2: Primary and Secondary Outcomes and Adverse Events of Special Interest

Table 2. Primary and Secondary Outcomes and Adverse Events of Special Interest.*

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004
Safety outcomes‡						
Discontinuation of regimen due to adverse event	118/2149 (5.5)	—	123/2149 (5.7)	—	—	0.79
Any serious adverse event	633/2149 (29.5)	—	729/2149 (33.9)	—	—	0.002
Adverse events of interest						
Amputation§	35/2149 (1.6)	—	39/2149 (1.8)	—	—	0.73
Any definite or probable diabetic ketoacidosis	0/2149	—	2/2149 (<0.1)	—	—	0.50
Fracture¶	85/2149 (4.0)	—	69/2149 (3.2)	—	—	0.22
Renal-related adverse event¶	155/2149 (7.2)	—	188/2149 (8.7)	—	—	0.07
Major hypoglycemia‖	14/2149 (0.7)	—	28/2149 (1.3)	—	—	0.04
Volume depletion¶	127/2149 (5.9)	—	90/2149 (4.2)	—	—	0.01

* NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy.
† For the composite of long-term dialysis or kidney transplantation, there were 69 outcome events in the dapagliflozin group and 100 outcome events in the placebo group (hazard ratio, 0.66; 95% CI, 0.49 to 0.90).
‡ Safety analyses included all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo.
§ Shown are cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma.
¶ These outcomes are based on a predefined list of preferred terms.
‖ The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

Table 25: CADTH Cost Comparison Table for ACE Inhibitors and ARBs

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Annual cost
Angiotensin-converting enzyme inhibitor (ACEi)						
Benazepril (generics)	5 mg 10 mg 20 mg	Tablet	0.8333 0.9870 1.1311	5 mg daily If creatine clearance < 30mL/min: max 10 mg daily;	0.83 t to 1.13	304 to 413

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Annual cost
				If creatine clearance > 30mL/min: 10 mg to 20mg daily		
Enalapril (generics)	2.5 mg 5 mg 10 mg 20 mg	Tablet	0.1863 0.2203 0.2647 0.3195	5 mg to 20 mg daily, 1 or 2 doses	0.22 to 0.32	80 to 117
Fosinopril (generics)	10 mg 20 mg	Tablet	0.2178 0.2619	20 mg to 40 mg daily	0.26 to 0.52	96 to 191
Lisinopril (generics)	5 mg 10 mg 20 mg	Tablet	0.1347 0.1619 0.1945	5 mg to 35 mg daily	0.13 to 0.49	49 to 179
Perindopril (Coversyl)	2 mg 4 mg 8 mg	Tablet	0.1632 0.2042 0.2831	2 mg to 4 mg daily	0.16 to 0.20	60 to 75
Quinapril (Accupril)	5 mg 10 mg 20 mg 40 mg	Tablet	0.4642 0.4642 0.4642 0.4642	5 mg to 20 mg, twice daily	0.46	168
Ramipril (generics)	1.25 mg 2.5 mg 5 mg 10 mg 15 mg	Cap	0.0708 0.0817 0.0817 0.1034 0.8132	1.25 mg to 5 mg daily (if creatinine clearance < 10 mL/min/1.73m2: max of 2.5 mg daily)	0.07 to 0.08	26 to 30
Trandolapril (Mavik)	0.5 mg 1 mg 2 mg 4 mg	Cap	0.2372 0.1762 0.2025 0.2498	0.5 mg daily. Max of 1 mg daily.	0.24 to 0.18	87 to 64
Angiotensin II receptor blocker						
Candesartan (generics)	4 mg 8 mg 16 mg 32 mg	Tablet	0.1700 0.2281 0.2281 0.2281	32 mg daily	0.23	83
Irbesartan (generics)	75 mg 150 mg 300 mg	Tablet	0.2281 0.2281 0.2281	150 mg to 300 mg daily	0.23	83
Losartan (generics)	25 mg 50 mg 100 mg	Tablet	0.3147 0.3147 0.3147	50 mg to 100 mg daily	0.31	115

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Annual cost
Olmesartan (Olmetec)	20 mg 40 mg	Tablet	0.3019 0.3019	20 mg daily	0.30	110
Telmisartan (generics)	40 mg 80 mg	Tablet	0.2161 0.2161	80 mg daily	0.22	79
Valsartan (generics)	40 mg 80 mg 160 mg 320 mg	Tablet	0.5823 0.2159 0.2159 0.2098	80 mg to 160 mg, twice daily	0.21 to 0.22	76 to 79

CKD = chronic kidney disease; Cap = capsule.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.

[a]Sponsor submitted price for reimbursement review. Recommended dosages are from the respective monographs.[7 to 20]

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