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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Diabetic Nephropathy: A Review of Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	September 20, 2019
Report Length:	38 Pages

CADTH

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Cite As: Sodium Glucose Cotransporter 2 Inhibitors for the Treatment of Diabetic Nephropathy: A Review of Clinical Effectiveness. Ottawa: CADTH; 2019 Sep. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

A1C	Glycated hemoglobin
AKI	Acute kidney injury
BMI	Body mass index
CKD	Chronic kidney disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ESKD	End stage kidney disease
FBG	Fasting blood glucose
ITT	Intention-to-treat
MI	Myocardial infarction
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SGLT2	Sodium glucose cotransporter 2
T2D	Type 2 diabetes mellitus
UACR	Urinary albumin creatinine ratio

Context and Policy Issues

Diabetes mellitus or diabetes is a chronic condition and affects 8.2% or 382 million individuals world-wide.[1] According to data from 2013-2014, it was estimated that in Canada the prevalence of diagnosed diabetes was 8.7% in men and 7.6% in women. Type 2 diabetes (T2D) is the most prevalent form of diabetes, and it constitutes 90% of the individuals diagnosed with diabetes.[2] In T2D, the glycemic control is impaired. It occurs when the pancreas is unable to produce enough insulin, or when the body cannot properly use the insulin produced.[3]

Individuals with T2D are at an increased risk of developing diabetic kidney disease and it is the leading cause of end stage renal disease.[4,5] Approximately 40% pf patients with T2D develop chronic kidney disease (CKD) during their lifetime.[6,7] CKD is defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for three months or longer.[6,8] The kidney plays an important role in ensuring glucose homeostasis, gluconeogenesis, and the reabsorption of filtered glucose in the proximal tubules.[4] The sodium glucose cotransporter 2 (SGLT2) present in the proximal tubule is responsible for the glucose reabsorption.[4]

It may be a challenge to adequately manage glycemic control in patients with T2D and CKD, due to both patient and medication issues.[2] Treatment options for managing T2D include injectable medications such as insulin and glucagon-like peptide-1 receptor agonists as well as oral pharmacological agents such as metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sulfonylureas, meglitinides, and α-glucosidase inhibitors.[9] Evidence on the potential benefits of (SGLT2) inhibitors in patients with T2D and CKD is developing.[7] SGLT2 inhibitors available in Canada[10] include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin; other SGLT2 inhibitors include ipragliflozin, sotagliflozin, topogliflozin, bexagliflozin and luseogliflozin. The mechanism of action of SGLT2 inhibitors is different from those of the oral traditional agents. Glycemic control with traditional agents generally involves increasing secretion or sensitivity to insulin whereas SGLT2 inhibitors block reabsorption of glucose in the proximal tubule.[9]

The purpose of this report is to review the clinical effectiveness of SGLT2 inhibitors for treatment of diabetic nephropathy (T2D with CKD).

Research Question

What is the clinical effectiveness of sodium glucose cotransporter 2 inhibitor for the treatment of diabetic nephropathy?

Key Findings

Four systematic reviews and five randomized controlled trials on the clinical effectiveness of sodium glucose cotransporter 2 (SGLT2) inhibitors for treatment of adult patients with type 2 diabetes and chronic kidney disease were identified.

The risks for all-cause death, cardiovascular death, myocardial infarction, and stroke were less with SGLT2 inhibitor compared with placebo, however, the between group differences were not always statistically significant. The risk for heart failure was statistically significantly less with SGLT2 inhibitors compared with placebo.

The risks for renal death, and end stage kidney disease was less with SGLT2 inhibitor compared with placebo, however the between group differences were not always statistically significant. The risks for composite renal outcomes were statistically significantly less with SGLT2 inhibitor compared with placebo. There were inconsistencies in the findings with respect to risk of acute kidney injury.

Albuminuria, doubling serum creatinine, glycated hemoglobin, fasting blood glucose, and body weight were less with SLGT2 inhibitors compared with placebo, however, the between group differences were not always statistically significant. Findings with respect to estimated glomerular filtration rate were inconsistent.

The risks of genital infections and diabetic ketoacidosis were generally higher with SLGT2 inhibitors compared with placebo, though results for diabetic ketoacidosis were not always statistically significant. There were inconsistencies in the findings with respect to adverse events such as hypoglycemia, amputation, and fracture.

Findings however need to be interpreted with caution considering the limitations (such as lack of details regarding patient characteristics in some studies, lack of details regarding background treatments used, variability in study quality, and limited generalizability).

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Sodium-Glucose Cotransporter-2 (SGLT2) and diabetic nephropathy. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 21, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with diabetic nephropathy (T2D and CKD)
Intervention	Standard treatments for T2D (e.g. metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, or insulin) and SGLT2 inhibitor
Comparator	Standard treatment for T2D without SGLT2 inhibitor (or using a placebo)
Outcomes	Clinical effectiveness (e.g., worsening of albuminuria, doubling of serum creatinine, renal replacement therapy/dialysis, time to first occurrence end-stage renal disease, death due to renal failure, sustained change in estimated glomerular filtration rate, blood pressure, weight, heart failure, myocardial infarction, amputations, fractures, A1C levels, glycemia, safety)
Study Designs	Health technology assessments, systematic reviews/meta-analyses, and randomized controlled trials.

A1C = glycated hemoglobin; CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase 4; GLP-1 glucagon-like peptide 1; SGLT2 = sodium glucose cotransporter 2; T2D = type 2 diabetes.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Systematic reviews with all studies included in a selected systematic review were excluded. Primary studies already included in a selected systematic review were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist,[11] and randomized studies were critically appraised using Downs and Black's checklist.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 400 citations were identified in the literature search. Following screening of titles and abstracts, 338 citations were excluded and 62 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 53 publications were excluded for various reasons, and nine publications met the inclusion criteria and were included in this report. These comprised four systematic reviews,[1,6,13,14] and five randomized controlled trials (RCTs)[15-19] Appendix 1 presents the PRISMA[20] flow chart of the study selection.

Summary of Study Characteristics

Characteristics of the selected studies are summarized below, and additional details are provided in Appendix 2, Table 2 and Table 3.

Study Design

The four selected systematic reviews[1,6,13,14] included RCTs ranging in number between six and 27 RCTs. Two systematic reviews[6,14] were published in 2009, and two systematic reviews[1,13] were published in 2008. The literature search dates were up to November 2018 in one systematic review,[14] up to February 2018 in the second systematic review,[6] up to February 2018 in the third systematic review,[1] and up to March 2017 in the fourth systematic review.[13]There was overlap in the RCTs included in the systematic reviews (Appendix 5, Table 8).

The five selected primary studies[15-19] were all RCTs. Three RCTs[15-17] were double-blind studies conducted in multiple centers in multiple countries, one RCT[19] was an open-label study conducted at a single center, and details for the fourth RCT[18] were not presented.

Country of Origin

Countries indicated for the first authors of the systematic reviews were Australia,[1,6] China,[14] and the UK.[13]. Countries indicated for the first authors of the RCTs were Australia,[16,17] China,[18] Japan,[19] and the US[15].

Population

All four systematic reviews[1,6,13,14] included adult patients with T2D and CKD. In one systematic review[1] the total number of patients was 3,453; in the remaining three systematic reviews[6,13,14] the total numbers of patients were not specified. The patient numbers in the included RCTs ranged between 31 and 1819 in one systematic review,[1] between 10 and 2039 in the second systematic review,[6] between 166 and 741 in the third systematic review,[14] and between 81 and 1819 in the fourth systematic review.[13] In the RCTs included in the systematic reviews, the mean ages varied between 33 years and 70; and the proportion of males varied between 48% and 77%. The duration of diabetes was reported for the include RCTs in one systematic review[1] and varied between 11 years to 17 years and was not reported in the remaining three systematic reviews.[6,13,14] Glycated hemoglobin (A1C) was reported for the included RCTs in three systematic reviews[1,6,14] and varied between 7.2% to 11%; AIC was not reported for one systematic review.[13] Of note, the data presented above for age, proportion of males, duration of diabetes, and A1C are the data available as the data were not reported for all the included RCTs in the systematic reviews (details in Appendix 2, Table 2).

All five RCTs[15,17-19,21] included adult patients with T2D and CKD; the patient numbers varied between 42 and 4401, the mean ages varied between 59 years and 70 years, and the proportion of males varied between 44% and 70%. The duration of diabetes varied between 4.5 years and 18 years in four RCTs, [15,17,18,21] and was not reported in one RCT.[19] The mean A1C varied between 7.3 and 8.6 in four RCTs[15,17,19,21] and was not reported in one RCT.[18]

Interventions and Comparators

In the systematic reviews the interventions used comprised canagliflozin,[1,6,13,14] dapagliflozin,[1,6,13,14] empagliflozin,[1,6,13,14] ertugliflozin,[6] ipragliflozin,[1,6] luseogliflozin,[1,6,13] sotagliflozin,[1,6] and topogliflozin.[6] Doses used for canagliflozin were 100 mg or 300mg;[1,13,14]

dapagliflozin were 5 mg or 10 mg;[1,13,14] empagliflozin 10 mg or 25 mg;[1,13,14] ipragliflozin was 50 mg;[1,13] luseogliflozin was 2.5 mg;[1,13] and sotagliflozin 400 mg.[1] In one systematic review[6] doses were not mentioned.

In the RCTs the interventions used were canagliflozin, [16,19] dapagliflozin, [17,18] and bexagliflozin.[15] The dose used for canagliflozin was 100 mg once daily;[16,19] the dose used for dapagliflozin was 10 mg[17] and 50 mg[18] once daily; and the dose used for bexagliflozin was 20 mg.[15]

The comparator in all cases was placebo.

In two systematic reviews,[1,14] for some of the included RCTs it was reported that the patients continued with their existing antidiabetic medications whereas for some RCTs it was not mentioned which other antidiabetic medications may have been used. In the remaining two systematic reviews,[6,13] for the included RCTs it was not mentioned if other antidiabetic medications were used.

In four RCTs, [15,17,19,21] it was reported that the patients continued with their existing antidiabetic medications and in one RCT[18] the patients continued with their routine insulin therapy.

Outcomes

Clinical outcomes reported included all-cause death, [1,6,14,16,17] cardiovascular death,[1,6] myocardial infarction (MI),[1,6] heart failure,[1,6] stroke,[1,6] renal death,[16] end stage kidney disease (ESKD),[1,16] acute kidney injury (AKI)[1,15,16] composite renal outcomes,[13,16] estimated glomerular filtration rate (eGFR),[1,16,18,19] albuminuria,[6,13,14] urinary albumin creatinine ratio (UACR),[1,13,15-17] doubling serum creatinine,[1,16] glycated hemoglobin (A1C),[1,6,15-17] fasting blood glucose (FBG),[1,6,15,16,18] systolic blood pressure (SBP),[1,6,17,19] diastolic blood pressure (DBP),[1,6,19] and body weight or body mass index (BMI).[1,6,15,17,19] Outcomes related to adverse events included serious adverse event (SAE),[15-17] hypoglycemia,[1,6,15,17] diabetic ketoacidosis,[6,16,17] genital infection (not otherwise described),[1,6,14,15,17,19] amputation,[6,16,17,19] and fracture.[1,15-17]

Summary of Critical Appraisal

The critical appraisal of the included studies is presented below and details are available in Appendix 3, Table 4, and Table 5.

The selected systematic reviews[1,6,13,14] were generally well conducted. In all four systematic reviews, [1,6,13,14] the objective was stated; a comprehensive literature search was conducted; article selection was described and a flow chart was presented; list of included studies was presented, article selection and data extraction were done in duplicate; and quality assessment was conducted. In some of the included RCTs in the systematic reviews there was risk of attrition bias and this could have a positive or negative impact on findings. Meta-analysis was conducted in three systematic reviews[1,6,14] using appropriate methods but meta-analysis was not conducted in one systematic review.[13] In three systematic reviews,[1,6,13] some of the authors were associated with industry or the systematic review was funded by industry, hence the potential of bias cannot be ruled out. In one systematic review[14] the authors mentioned that there were no conflicts of interest.

In all the five selected RCTs,[15-19] the objective was mentioned, the inclusion and exclusion criteria were mentioned; and patient characteristics, interventions and outcomes were

described. The randomization method was described in three RCTs,[15-17] and appeared appropriate. The randomization method was not mentioned in two RCTs,[18,19] hence potential for selection bias in these RCTs cannot be ruled out. Three RCTs were double-blind studies. One RCT[19] was an open label study and in one RCT[15] it was unclear if there was any blinding, hence the potential for performance bias and detection bias in these two RCTs cannot be ruled out. Sample size calculations were undertaken in three RCTs[15-17] and the appropriate numbers of patients were recruited. In two RCTs,[18,19] it was not mentioned if sample size calculations had been undertaken, hence it was unclear if there was sufficient power to detect a difference in outcome. The number of withdrawals were different in the intervention and placebo groups in two RCTs,[15,17] however withdrawals were less than 10% and is not anticipated to lead to a meaningful differences between the groups. In one RCT[16] the withdrawals were different in the intervention and placebo groups, and were substantial (up to 25%), and the direction of its impact on the findings is unclear. In three RCTs[15-17] intention-to-treat (ITT) analysis was undertaken. In two RCTs[18,19] it was unclear if ITT analysis had been undertaken, hence the validity of the findings is unclear. In four RCTs[16-19] all or some of the authors were associated with industry and the potential for bias cannot be ruled out. In one RCT[15] the authors mentioned that they had no conflicts of interest.

Summary of Findings

Findings are summarized below, and details are available in Appendix 4, Table 6 and Table 7.

Clinical Effectiveness of sodium glucose cotransporter 2 inhibitors (SGLT2 inhibitors) for treatment of patients with type 2 diabetes (T2D) and chronic kidney disease (CKD)

All cause death

Compared with placebo, risk of all-cause death with SGLT2 inhibitor was reported to be less and statistically significant in one systematic review,[14] and less but statistically not significant in two systematic reviews.[1,6]

In one RCT,[16] compared with placebo, risk of all-cause death with SGLT2 inhibitor (canagliflozin) was reported to be less and statistically not significant. In a second RCT,[17] compared with placebo, risk of all-cause death with SGLT2 inhibitor (dapagliflozin) was reported to be high and statistical significance was not reported.

In summary, findings from three systematic reviews[1,6,14] and one primary study[16] indicated that in most cases the risk of all-cause death was less with SGLT2 inhibitor compared with placebo, however the between group differences were mostly statistically not significant.

Cardiovascular outcomes

Cardiovascular death

Compared with placebo, risk of cardiovascular death with SGLT2 inhibitor was reported to be less and statistically significant in one systematic review,[6] and less but statistically not significant in one systematic review.[1]

Myocardial infarction (MI)

Compared with placebo, risk of MI with SGLT2 inhibitor was reported to be less and statistically significant in one systematic review,[6] and less but statistically not significant in another systematic review.[1]

Heart failure (HF)

Compared with placebo, risk of HF with SGLT2 inhibitor was reported to be less and statistically significant in two systematic reviews.[1,6]

Stroke

Compared with placebo, risk of stroke with SGLT2 inhibitor was reported to be less and statistically significant in one systematic review,[6] and less but statistically not significant in another systematic review.[1]

In summary, findings from two systematic reviews[1,6] indicated that in comparison with placebo, the risk of cardiovascular death, the risk of MI, and the risk of stroke were less with SGLT2 inhibitor and the between group differences were not always statistically significant. Also, the findings from these two systematic reviews[1,6] indicated that in comparison with placebo, the risk of HF was less with SGLT2 inhibitor and the between group differences were statistically significant.

Renal outcomes

Renal death

In one RCT,[16] compared with placebo, the risk of renal death with SGLT2 inhibitor (canagliflozin) was reported to be less but statistical significance was not reported.

End stage kidney disease (ESKD)

In one systematic review,[1] compared with placebo, the risk of ESKD with SGLT2 inhibitor was reported to be less and statistically not significant.

In one RCT,[16] compared with placebo, the risk of ESKD with SGLT2 inhibitor (canagliflozin) was reported to be less and statistically significant.

Acute kidney injury (AKI)

In two systematic reviews,[1,6] compared with placebo, the risk of AKI with SGLT2 inhibitor was reported to be less and statistically not significant.

In one RCT[16] compared with placebo, the risk of AKI with SGLT2 inhibitor (canagliflozin) was reported to be less and statistically not significant. In one RCT,[15] compared with placebo the risk of AKI with SGLT2 inhibitor (bexagliflozin) was reported to be high but statistical significance was not reported.

Composite renal outcomes

In one systematic review,[13] compared with placebo, the risk for composite renal outcome (defined as progression to macroalbuminuria, a doubling of serum creatinine level, accompanied by eGFR 45 ml/min/1.73 m^2, the initiation of renal replacement therapy, or death from renal disease) with SGLT2 inhibitor (empagliflozin) was reported to be less and statistically significant. Also, in this systematic review,[13] compared with placebo, the risk for

another composite renal outcome (defined as a doubling of serum creatinine level, initiation of renal replacement therapy, or death from renal disease) with SGLT2 inhibitor (empagliflozin) was reported to be less and statistically significant. Also, in another systematic review,[6] compared with placebo, the risk for composite renal outcome (defined as doubling of serum creatinine [or 40% decrease in eGFR], ESKD or renal death) with SGLT2 inhibitors was reported to be less and statistically significant.

In one RCT,[16] compared with placebo, the risk for composite renal outcome (defined as ESKD, doubling of serum creatinine level, or renal death) with SGLT2 inhibitor (canagliflozin) was less and statistically significant. Also, in this RCT, compared with placebo the risk for another composite outcome (defined as ESKD, renal death or cardiovascular death) with SGLT2 inhibitor (canagliflozin) was less and statistically significant.

In summary, risk of renal death was less with SGLT2 inhibitor compared with placebo, however the between group difference was not always statistically significant. The risk of ESKD was less with SGLT2 inhibitor compared with placebo, however the between group difference was not always statistically significant. The risk for developing AKI was inconsistent across publications. The risks for composite renal outcomes in patients on an SGLT2 inhibitor were lower and statistically significant, compared to placebo. There were inconsistencies in the findings with respect to risk of AKI.

Biomarkers

Findings with respect to various biomarkers, resulting from the patients being treated with either SGLT2 inhibitor or placebo are reported below.

Estimated glomerular filtration rate (eGFR)

In one systematic review,[1] compared with placebo, eGFR with SGLT2 inhibitor was lower and statistically significant. In another systematic review,[14] compared with placebo, eGFR with SGLT2 inhibitor was lower and statistically significant for up to six weeks, but at later times was higher and statistically significant.

In two RCTs [16,17] compared with placebo, eGFR with SGLT2 inhibitor (canagliflozin or dapagliflozin) was lower and statistically significant. In two other RCTs[18,19] compared with placebo, eGFR with SGLT2 inhibitor (canagliflozin or dapagliflozin) was higher and statistically significant.

Albuminuria

In two systematic reviews,[6,14] compared with placebo, albuminuria measured in patients using SGLT2 inhibitor was lower and statistically significant. In another systematic review,[13] compared with placebo, albuminuria with SGLT2 inhibitor was lower but statistical significance was not reported.

Urinary albumin creatinine ratio (UACR)

In one systematic review,[1] compared with placebo, UACR with SGLT2 inhibitor was lower and statistically significant. In another systematic review,[13] compared with placebo, UACR with SGLT2 inhibitor was lower and statistically not significant.

In three RCTs,[15-17] compared with placebo, UACR with SGLT2 inhibitor (canagliflozin, dapagliflozin, or bexagliflozin) was lower and statistically significant.

Doubling serum creatinine

In one systematic review,[1] compared with placebo, the risk of doubling serum creatinine with SGLT2 inhibitor was lower and statistically not significant.

In one RCT,[16] compared with placebo, the risk of doubling serum creatinine with SGLT2 inhibitor (canagliflozin) was lower and statistically significant.

Glycated hemoglobin (A1C)

In two systematic reviews,[1,6] compared with placebo, A1C with SGLT2 inhibitor was lower and statistically significant.

In one RCT,[15] compared with placebo, A1C with SGLT2 inhibitor (bexagliflozin) was lower and statistically significant. In two RCTs,[16,17] compared with placebo, A1C with SGLT2 inhibitor (canagliflozin or dapagliflozin) was lower and statistically not significant.

Fasting blood glucose (FBG)

In two systematic reviews,[1,6] compared with placebo, FBG with SGLT2 inhibitor was lower and statistically significant.

In one RCT,[15] compared with placebo, FBG with SGLT2 inhibitor (bexagliflozin) was lower and statistically significant. In another RCT,[17] compared with placebo, FBG with SGLT2 inhibitor (dapagliflozin) was lower and statistically not significant. In a third RCT,[18] FBG was similar in both the SGLT2 inhibitor (dapagliflozin) and placebo groups.

Systolic blood pressure (SBP)

In two systematic reviews,[1,6] compared with placebo, SBP with SGLT2 inhibitor was lower and statistically significant.

In one RCT,[19] compared with placebo, SBP with SGLT2 inhibitor (canagliflozin) was lower and statistically significant. In another RCT,[17] compared with placebo, SBP with SGLT2 inhibitor (dapagliflozin) was lower and statistically not significant.

Diastolic blood pressure (DBP)

In two systematic reviews,[1,6] compared with placebo, DBP with SGLT2 inhibitor was lower and statistically significant.

In one RCT,[19] compared with placebo, DBP with SGLT2 inhibitor (canagliflozin) was lower and statistically significant.

Weight or Body Mass Index (BMI)

In two systematic reviews,[1,6] compared with patients on placebo, weight of patients on SGLT2 inhibitor was lower and statistically significant.

In one RCT,[15] compared with patients using placebo, weight of patients using SGLT2 inhibitor (bexagliflozin) was lower and statistically significant. In another RCT,[17] compared with placebo, weight with SGLT2 inhibitor (dapagliflozin) was lower and statistically not significant. In a third RCT,[19] compared with placebo, BMI with SGLT2 inhibitor (canagliflozin) was lower and statistically significant.

In summary, findings with respect to biomarkers were variable across publications. Findings with respect to eGFR were inconsistent. Albuminuria, UACR, and risk of doubling serum creatinine were lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. A1C and FBG were lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. SBP was lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. DBP was lower with SGLT2 inhibitor compared with placebo, and the between group differences were statistically significant. Weight of patients was lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. BMI of patients on SGLT2 inhibitor (canagliflozin) was lower compared with placebo and the between group difference was statistically significant.

Adverse events

Serious Adverse Event (SAE)

In one RCT,[16] compared with placebo, the risk for SAEs with SGLT2 inhibitor (canagliflozin) was lower and statistically significant. In another RCT,[17] the incidence of SAEs with SGLT2 inhibitor (dapagliflozin) was lower than with placebo but statistical significance was not reported. In one RCT,[15] compared with placebo, the risk for SAE with SGLT2 inhibitor (bexagliflozin) was higher; statistical significance was not reported.

Hypoglycemia

In one systematic review,[1] compared with placebo, the incidence of hypoglycemia with SGLT2 inhibitor was lower but statistically not significant. In another systematic review,[6] compared with placebo, the risk of hypoglycemia with SGLT2 inhibitor was higher but statistically not significant.

In one RCT,[17] compared with placebo, the incidence of hypoglycemia with SGLT2 inhibitor (dapagliflozin) was lower; statistical significance was not reported. In one RCT,[15] the occurrence of hypoglycemia was similar in both the SGLT2 inhibitor (bexagliflozin) and the placebo groups.

Diabetic Ketoacidosis

In one systematic review,[6] compared with placebo, the incidence of diabetic ketoacidosis with SGLT2 inhibitor was higher and statistically not significant.

In one RCT,[16] compared with placebo, the incidence of diabetic ketoacidosis with SGLT2 inhibitor (canagliflozin) was higher and statistically significant. In another RCT,[17] compared with placebo, the incidence of diabetic ketoacidosis with SGLT2 inhibitor (dapagliflozin) was higher; statistical significance was not reported.

Genital Infection

In three systematic reviews,[1,6,14] compared with placebo, incidence of genital infection with SGLT2 inhibitor (canagliflozin) was higher; the difference was statistically significant.

In two RCTs,[15,17] compared with placebo, incidence of genital infection with SGLT2 inhibitor (dapagliflozin, or bexagliflozin) was higher; statistical significance was not reported. In one RCT,[19] it was reported that there were no genital infections in both the SGLT2 inhibitor (canagliflozin) and placebo groups.

Amputation

In one systematic review,[6] compared with placebo, incidence of amputation with SGLT2 inhibitor, was higher and not statistically significant.

In two RCTs,[15,17] compared with placebo, incidence of amputation with SGLT2 inhibitor (dapagliflozin or bexagliflozin), was higher; statistical significance was not reported. In one RCT,[16] compared with placebo, incidence of amputation with SGLT2 inhibitor (canagliflozin) was higher and statistically not significant. In another RCT,[19] it was reported that there were no amputations in both the SGLT2 inhibitor (canagliflozin) and placebo.

Fracture

In one systematic review,[1] compared with placebo, incidence of fracture with SGLT2 inhibitor, was lower and statistically not significant. In another systematic review,[6] compared with placebo, incidence of fracture with SGLT2 inhibitor, was higher and statistically not significant.

In one RCT,[16] compared with placebo, the incidence of fracture with SGLT2 inhibitor (canagliflozin), was lower and was statistically not significant. In another RCT,[15] compared with placebo, the incidence of fracture with SGLT2 inhibitor (bexagliflozin) was higher; statistical significance was not reported. In a third RCT,[17] compared with placebo, the incidence of fracture was the same in both the SGLT2 inhibitor (dapagliflozin) and placebo groups.

In summary, incidence of genital infections and diabetic ketoacidosis was generally higher with SGLT2 inhibitor compared with placebo, though results for diabetic ketoacidosis were not always statistically significant. There were inconsistencies in the findings with respect to incidence of other adverse events such as hypoglycemia, amputation, fracture and serious adverse events.

Limitations

Some patient characteristics were reported for the entire patient population involved in the trial and were not presented separately for the subgroup relevant for this report. The quality of the studies was variable and the impact on the findings was unclear.

All the included studies were RCTs which have strict inclusion and exclusion criteria hence generalizability is limited. Many of the studies excluded patients with advanced CKD, hence the effect of treatment with SGLT2 inhibitor on this patient population is unclear. Also some studies excluded patients with poorly controlled diabetes, or with history of diabetic ketoacidosis, hence the effect of treatment on these patients is unclear. Some of the findings in this report are based on studies (or SRs that included studies) on SGLT2 inhibitors not available in Canada; this may limit the generalizability of the findings to the Canadian setting. In the studies, the patients continued with their background treatments and details of the background treatments were not provided. It is unclear to what extent these background treatments would impact the findings with SGLT2 inhibitors. It is possible that some of the variability observed in the findings from different studies may be due variability in the background treatments.

Primary studies that were included in a selected systematic review were excluded. Many of these primary studies had been published in several reports and it was unclear if the systematic review authors had considered all the reports and selected the relevant ones.

Hence there is a possibility that some details may not have been captured. However, major outcomes were reported in these systematic reviews

Not all outcomes were reported in all RCTs. In many instances, analysis of the CKD subgroup was conducted using data from trials that were not dedicated to renal outcomes or the CKD subgroup had not been defined a priori in the conduct of the trial. Studies were not powered to detect harms and in some instances the number of less common adverse effects were few, hence the safety profiles of these drugs are unclear.

The Perkovic study[16] was stopped early at a planned interim analysis due to benefits associated with use of canagliflozin compared to placebo. This early stopping may result in limited power to detect changes in some secondary outcomes.

Conclusions and Implications for Decision or Policy Making

Four systematic reviews[1,6,13,14] and five RCTs[15-19] reported on the clinical effectiveness of SGLT2 inhibitors for treatment of adult patients with T2D and CKD.

Findings from three systematic reviews[1,6,14] and one primary study indicated that in most cases the risk of all-cause death was lower with SGLT2 inhibitor compared with placebo, however the between group differences were mostly statistically not significant.

Findings from two systematic reviews[1,6] indicated that in comparison with placebo, the risk of cardiovascular death, the risk of MI, and the risk of stroke were lower with SGLT2 inhibitor and the between group differences were not always statistically significant. Also, the findings from these two systematic reviews[1,6] indicated that in comparison with placebo, the risk of HF was reduced with SGLT2 inhibitor and the between group differences were statistically significant.

Risk of renal death was less with SGLT2 inhibitor compared with placebo, however the between group difference was not always statistically significant. The risk of ESKD was less with SGLT2 inhibitor compared with placebo, however the between group difference was not always statistically significant. The risks for composite renal outcomes were lower and were statistically significant. There were inconsistencies in the findings with respect to risk of AKI.

Findings with respect to biomarkers were variable across publications. Findings with respect to eGFR were inconsistent. Albuminuria, UACR, and risk of doubling serum creatinine were lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. A1C and FBG were lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. SBP was lower with SGLT2 inhibitor compared with placebo, but the between group differences were not always statistically significant. DBP was lower with SGLT2 inhibitor compared with placebo, and the between group differences were statistically significant. Weight of patients using an SGLT2 inhibitor was lower compared with placebo, but the between group differences were not always statistically significant. BMI measured in patients using SGLT2 inhibitor (canagliflozin) was lower and statistically significant.

Incidence of genital infections and diabetic ketoacidosis were generally higher with SGLT2 inhibitor compared with placebo, though results for diabetic ketoacidosis were not always statistically significant. There were inconsistencies in the findings with respect to other adverse events such as hypoglycemia, amputation, fracture and serious adverse events.

Overall, current evidence suggests use of SGLT2 inhibitors may provide benefits to patients with T2D and CKD. Findings however need to be interpreted with caution considering the limitations such as lack of details regarding patient characteristics in some studies, lack of details regarding background treatments used, variability in study quality, and limited generalizability. Evidence is still developing in this area, and ongoing studies such as DAPA-CKD[22] may provide further insights. Also, it would be useful to determine which subgroups of patients are likely to achieve the most benefit.

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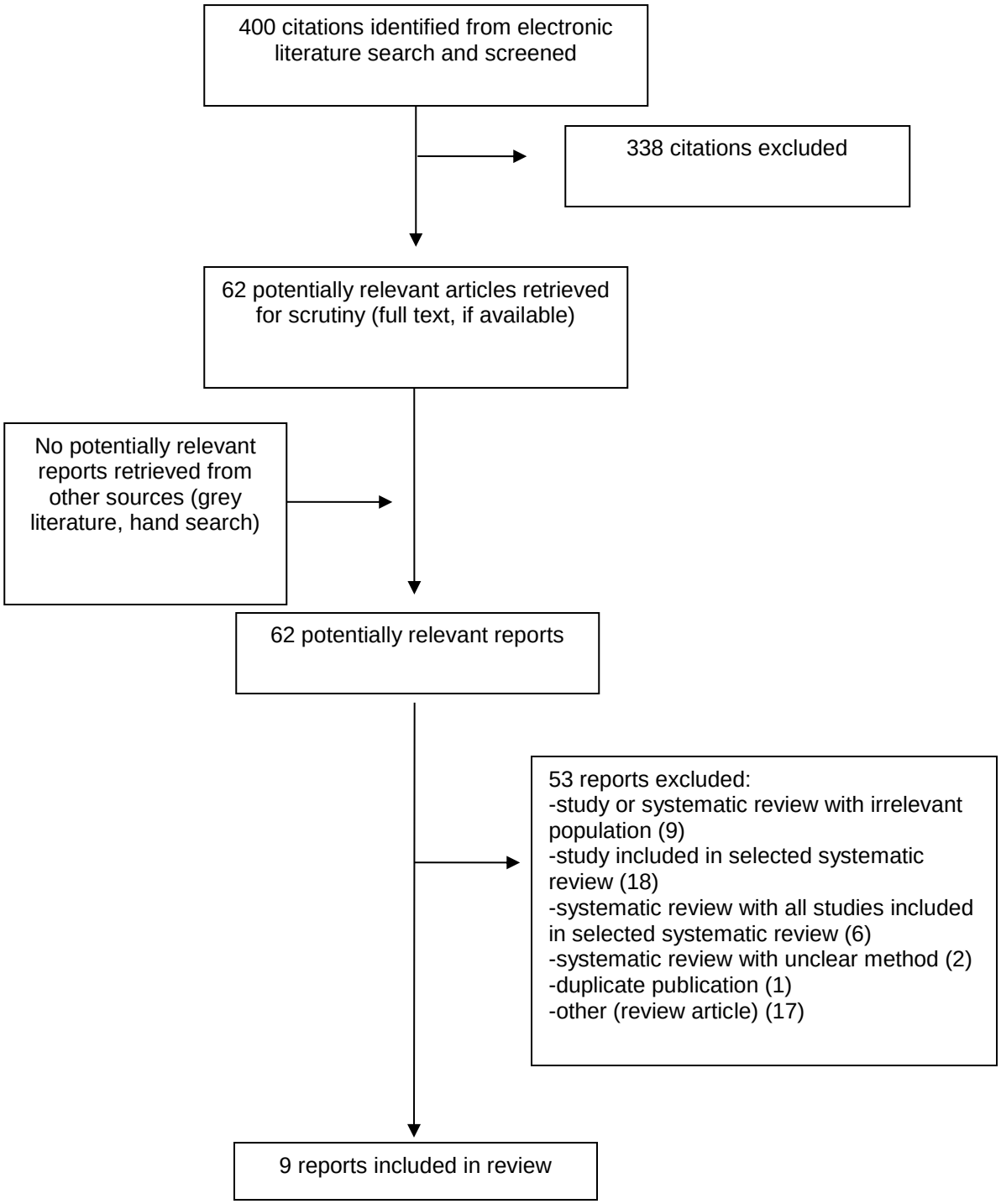
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Toyama,[6] 2019, Australia	Sr-ma included RCTs. 27 studies (18 individual studies, 8 pooled analyses, and one regulatory report) The authors mentioned that they used data from pooled analyses when appropriate and ensured that there was no overlapping of data. Countries where the studies were conducted were not mentioned. Aim: To assess the role of SGLT2 inhibitor for cardio-renal protection in individuals with T2D and CKD	Patients with T2D and CKD (CKD defined as eGFR <60 ml/min/1.73 m^2) Number of patients ranged between 10 and 2039 in the individual studies; Age (years): 63.5 to 68.5 in 12 individual studies (NR in 6 studies) % male: ranged between 48% to 68% in 12 individual studies (NR in 6 studies) Duration of diabetes (mean) (years): 10.9 to 16.9 in 7 studies (NR in 11 studies) A1C (%): 7.2 to 8.4 in 12 studies (NR in 6 studies) eGFR (ml/min/1.73 m^2): 39.4 to 53.5 in 12 studies (NR in 6 studies) Note the values are reported as mean	SGLT2 inhibitor versus placebo SGLT2 inhibitor (number of studies): Canafloglifozin (3), Dapagliflozin (6), Empagliflozin (4), Ertugliflozin (1), Ipragliflozin (1), Luseoglifozin (1), Sotagliflozin (1), Topogliflozin (1). Doses were not reported Other medications used were not mentioned	Biomarkers: A1C, FPG, SBP, DBP, body weight, serum potassium, albuminuria. Cardiovascular outcomes: 3-point MACE, MI, stroke, HF, cardiovascular death, and all-cause mortality. Renal outcomes: eGFR slope, renal composite (doubling of serum creatinine, ESKD, or renal death), renal related AE, acute kidney injury, hyperkalemia. Safety outcomes: hypoglycemia, fracture amputation, UTI, genital infection, hypovolemia, diabetic ketoacidosis. Study duration from 7 days to a median of 4.2 years.
Wang,[14] 2019, China	Sr-ma included 8 RCTs relevant to this report (i.e., those involving patients with T2d and prevalent kidney disease) Countries where the studies were	Adult patients with T2D, and with and without prevalent kidney disease. (Prevalent kidney disease was defined as eGFR <60 mL/min/m^2)	SGLT2 inhibitor versus placebo SGLT2 inhibitor (dose) (number of studies): Empagliflozin (10 mg, 25 mg) (2); Dapagliflozin (5 mg, 10 mg) (4);	eGFR, albuminuria, renal adverse events, all-cause mortality

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	conducted were not mentioned. This sr had a broad focus and only studies relevant for this report are included here. Aim: To assess the efficacy and safety of SGLT2 inhibitor for the treatment of patients with T2D with respect to kidney related outcomes	Number of patients varied between 166 and 17,160 Age (mean) (year) varied between 32.6 to 67.0 in 6 studies; NR in 2 studies % Male ranged between 33% and 70% in 6 studies; NR in 2 studies Duration of diabetes: NR. A1C (mean) (%) ranged between 8% to 8.4% in 6 studies; NR in 2 studies eGFR (mean) (mL/min/m^2) ranged between 39.4 and 53.3 in 5 studies; CKD 2, 3, or 4 in 1 study; NR in 2 studies	Canagliflozin (100 mg, 300 mg) (2) Other medications used were metformin, sulfonylurea, or insulin for one study, and were not mentioned for the remaining 7 studies	
Lo,[1] 2018, Australia	Sr-ma included 9 RCTs relevant to this report 5 RCTs were multi-country studies, 3 RCTs were multi-center studies conducted in Japan, and 1 RCT was a single-center study conducted in US This sr had a broad focus and only studies relevant for this report are included here. Aim: To assess the efficacy and safety of insulin and other pharmacological agents for treating	Patients with T2D and CKD (CKD defined as eGFR <60 ml/min/1.73 m^2) Number of patients:3453 (ranged between 31 and 1819 in the individual studies). Age (mean) (years): 62 to 70 in 5 studies (NR in 4 studies) % male: ranged between 54% to 77% in 4 individual studies (NR in 5 studies)	SGLT2 inhibitor versus placebo SGLT2 inhibitor (dose) (number of studies): Dapagliflozin (5 mg, 10 mg) (2); Canagliflozin (100 mg, 300 mg) (1); Empagliflozin (10 mg, 25 mg) (3); Ipragliflozin(50 mg) (1); Luseogliflozin (2.5 mg) (1); Sotagliflozin or LX4211 (400 mg) (1). In 5 studies patients continued on their usual antidiabetic medications, in 1 study	Biomarkers: A1C, FBG, SBP, DBP, weight, serum potassium, albuminuria. serum creatinine, UACR, serum potassium, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride Cardiovascular and renal outcomes: All-cause death, all cardiovascular death, MI, stroke, HF; eGFR, ESKD, hyperkalemia, AKI, doubling of serum creatinine Adverse events: discontinuation of

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	patients with diabetes and CKD	Duration of diabetes (mean) (years): NR A1C (%) (range for inclusion criteria) ≥7% to 9% (or<10% or 11%), in 6 studies (NR in 3 studies) eGFR (ml/min/1.73/ m^2): < 60 in 8 studies; and CKD 2, 3, 4 in 1 study	patients continued on their usual antidiabetic medications if on medication for ≥12 weeks, and in 3 studies it was not mentioned.	medication due to AE, hypoglycemia, hypovolemia, fracture, diarrhea, diabetic ketoacidosis, upper respiratory tract infection, UTI, genital infection. Follow-up: 7 days; 14 weeks to 192 weeks
Seidu,[13] 2018, UK	Sr included 6 RCTs relevant to this report. Two RCTs were conducted in Japan and 4 RCTs were conducted in multiple countries. This sr had a broad focus and only studies relevant for this report are included here. Aim: To assess the role of SGLT2 inhibitor for the treatment of patients with T2D and with or without renal impairment.	Patients with T2D and renal impairment. (Renal impairment was defined as eGFR ≥30 and <60 ml/min/1.73 m^2 and/or UACR > 300 and ≤5000 mg/g) Number of patients ranged between 81 and 1819 in the individual studies. Age (years): ≥18 in 4 rcts, ≥20 in 1 rct and 20 to 74 in 1 rct. % Male:56.7% to 78.0% Duration of diabetes: NR A1C: NR eGFR ml/min/1.73/ m^2): < 60 in 4 studies, CKD 3 in 2 studies, and prevalent kidney disease in 1 study	SGLT2 inhibitor versus placebo SGLT2 inhibitor (dose) (number of studies): Canaflogliflozin (100 mg, 300mg) (1), Dapagliflozin (5 mg, 10 mg) (1), Empagliflozin (10 mg, 25 mg) (2), ipragliflozin (50 mg) (1), Luseogliflozin (2.5 mg) (1) Other medications used were not mentioned	eGFR, BUN, serum creatinine, urine albumin, UACR, renal composite outcome (doubling in serum creatinine, initiation of renal replacement therapy, or death due to renal disease)

A1C = glycated hemoglobin; AE = adverse events; BUN = blood urea nitrogen; CKD = chronic kidney disease; DPB = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; FBG = fasting blood glucose; FPG =fasting plasma glucose; HF = heart failure; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SGLT2 = sodium glucose cotransporter 2; sr = systematic review; sr-ma = systematic review and meta-analysis; T2D = type 2 diabetes; UACR = urinary albumin creatinine ratio.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Allegretti,[15] 2019, US	DB RCT, multicenter, multinational (54 sites in 4 countries: US, Spain, France and Japan). Phase 3 study	Adult patients with T2D and stage 3a/3b CKD. CKD stage and eGFR were calculated using the 4-variable Modification of Diet in Renal Disease Study equation. (Patients were eligible if eGFR was between 30 and 59 mL/min/1.73m^2) CKD 3a (eGFR 45 to <60 mL/min/1.73m^2, CKD 3b (eGFR 30 to <40 mL/min/1.73m^2 N = 312 (157 in bexagliflozin group and 155 in plb) Age (mean ± SD) (year): 69.6 ± 9.2 % Female: 37% Duration of diabetes (mean ± SD) (year): 15.91± 9.08 A1C (mean ± SD) (%): 7.98 ± 0.78 eGFR (mean ± SD) (ml/min/1.73 m^2): 51.52 ± 4.88 for stage 3a CKD, and 37.83 ± 4.59 for stage 3b CKD UACR: 37% with UACR < 30mg/g, 37.8% for UACR 30 to <300 mg/g, and 25% with UACR ≥300 mg/g	Bexagliflozin versus placebo. Bexaglifozin (20 mg) All patients continued on their existing antidiabetic medications	Primary outcome: A1C (change from baseline). Other outcomes: FPG, body weight, BP, and UACR Adverse events Study duration: 26 weeks. (Treatment duration was 24 weeks and final study visit was at 26 week)
Perkovic,[16] 2019, Australia. (CREDANCE)	DB RCT, multicenter (international;690 sites in 34 countries,)	Patients with T2D and CKD (CKD defined as eGFR of 30 to < 90 ml	Canagliflozin (C) versus placebo (plb)	Primary: composite of ESKD or death from renal or cardiovascular disease.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		per minute per 1.73 m2 of body-surface area and UACR > 300 to 5000 with albumin measured in mg and creatinine in g) N = 4401 (2202 in C and 2199 in plb) Age (mean ± SD) (year): 63.0 ± 9.2 % Female: 33.9% Duration of diabetes (mean ± SD) (year): 15.8 ± 8.6 A1C (mean ± SD) (%):8.3 ± 1.3 eGFR (mean ± SD) (ml/min/1.73 m^2): 56.2 ± 18.2 UACR: 927 (median [IQR]): 927 (463 to 1833	C: 100 mg orally once daily. The use of other background treatment for glycemic management and control of cardiovascular risk factors was in accordance with local guidelines.	Secondary: composite of cardiovascular death or hospitalization for HF; composite of cardiovascular death, MI, or stroke; hospitalization for HF; composite of ESKD, doubling of serum creatinine level, or renal death; cardiovascular death; death from any cause; composite of cardiovascular death, MI, stroke or hospitalization for HF or for unstable angina Safety (fracture, pancreatitis, ketoacidosis, and renal-cell carcinoma). Follow-up (median) (year): 2.62
Pollock,[17] 2019, Australia. (DELIGHT)	DB RCT, multicenter (116 centers in Australia, Canada, Japan, Mexico, South Africa, South Korea, Spain, Taiwan, and the US) This study had a broad objective and compared D versus (D+ saxagliptin) versus plb, hence only the relevant comparison D versus plb is considered here	Patients with T2D and CKD (CKD appears to be defined as UACR 30 to 3500mg/g, and eGFR of 25 to 75 mL/min/1.73 m^2) N = 145 in D, and 148 in plb. Age (mean ± SD) (year): 64.7 ± 8.6 in D; 64.7 ± 8.5 in plb. % Female: 30% in D, 29% in plb.	Dapagliflozin (D) versus placebo (plb) Dapagliflozin 10 mg orally, once daily; and matched placebo control Patients continued on their existing antidiabetic medications	Primary outcome: UACR. Secondary outcomes: A1C, body weight, BP, and FPG. Other outcomes: urinary glucose excretion, urinary albumin excretion, LDL cholesterol, HDL cholesterol, uric acid, and hematocrit Adverse events Study duration: 27 weeks (Treatment duration was 24 weeks

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Duration of diabetes mean ± SD) (year): 17.55 ± 7.7 in D, 17.7 ± 9.5 in plb. A1C (mean ± SD) (%): 8.44 ± 1.0 in D, 8.57 ± 1.2 in plb eGFR (mean ± SD) (ml/min/1.73 m^2): 50.2 ± 18.2 in D, 47.7 ± 13.5 in plb UACR (median [IQR]) (mg/g): 270.0 (69 to 751) in D, 257.5 (80 to 949)		followed by a 3-week follow-up)
Jian,[18] 2018, China	RCT (no other details presented)	Adult patients with T2D and CKD (CKD is defined as kidney damage or GFR 90 mL/mi126n) N = 126 (63 in D group and 63 in control group) Age (mean ± SD) (year): 58.7 ± 2.3 % Female: 56% Duration of diabetes (median [range]): 4.5 years (8 months to 7.5 years) A1C: NR eGFR (mean ± SD) (ml/min/1.73 m^2): 45.3 ± 12.1 in D group, 42.3± 10.8 in control group UACR: NR	Dapagliflozin (D) versus control (no D) Dapagliflozin 0.05g per day. Both groups received routine insulin therapy	GFR, FBG Study duration: 1 year (duration of treatment was not stated)

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Takashima,[19] 2018, Japan	RCT, open-label, single-center	Adult patients with T2D and CKD (Patients were eligible if eGFR: 45 to 89 ml/min/1.73 m^2, and UACR: 30 to 2000mg/g, and hypertension had to treated with a fixed dose of RAS inhibitors for at least 12 weeks before start of the study) N = 42 (21 in C group and 21 in plb group) Age (mean ± SD) (year): 64.7 ± 9.8 in C, 65.4 ± 10.4 in plb % Female: 45% in C, 40% in plb Duration of diabetes (year): NR A1C (mean ± SD) (%): 7.5 ± 0.9 in C, 7.3 ± 0.7 in plb eGFR (mean ± SD) (ml/min/1.73 m^2): 57.1 ± 16.2 in C, 55.4 ± 12.3 in plb UACR (median [IQR]) (mg/g): 139 (67 to 1506) C, 159 (58 to 1156) in plb	Canagliflozin (C) versus placebo (plb) Canagliflozin was given orally, 100 mg per day. Patients continued on their existing antidiabetic medications	Primary outcome: albuminuria (UACR) Secondary outcomes: BMI; SB; DBP; eGFR; A1C; urinary L-FABP, NAG, and β_2MG. Treatment duration 52 weeks

A1C = glycated hemoglobin; BP = blood pressure; C = canagliflozin; CKD = chronic kidney disease; D = dapagliflozin; DB = double blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; FBG = fasting blood glucose; FPG = fasting plasma glucose; g = gram; GFR = glomerular filtration rate; HF = heart failure; IQR = interquartile range; mg = milligram; MI = myocardial infarction; plb = placebo; rct = randomized controlled trial; SD = standard deviation; SGLT2 = sodium glucose cotransporter 2; T2D = type 2 diabetes; UACR =urinary albumin to creatinine ratio.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[11]

Strengths	Limitations
Toyama,[6] 2019, Australia	
• The objective was clearly stated • Databases (Medline, EMBASE, and Cochrane Central Register of Controlled trials) searched up to August 2018. Websites of FDA, EMA, and Japanese Pharmaceutical and Medical Devices Agency were searched. Reference list of identified studies, reviews, and reports were hand searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using the Cochrane risk of bias tool. Risk of bias was low with respect to blinding of patient and personnel; and low or unclear with respect to randomization and blinding of assessor. In majority of the studies the risk of bias was high with respect to incomplete outcome data. • Characteristics of the included studies were presented • Meta-analysis was conducted	• A list of excluded studies was not provided • Publication bias was not explored as it was not considered to be feasible as there were few studies reporting on the main composite of cardiovascular and renal outcomes, and also all-cause mortality. • Conflicts of interest were presented and many of the authors had association with industry
Wang,[14] 2019, China	
• The objective was clearly stated • Multiple databases (Medline, EMBASE, Cochrane Library, web of science) up to November 2018 • Study selection was described, and a flow chart was presented • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • A list of excluded studies was provided • Quality assessment was conducted using the Cochrane risk of bias tool. Selection bias was low (in 6 studies) or unclear (in 2 studies); performance bias, detection bias, and reporting bias were low; attrition bias was high in 3 studies, and low or unclear in the remaining 5 studies • Characteristics of the included studies were presented • Meta-analysis was conducted • Publication bias was assessed using the Funnel plot and bias was not evident • The authors mentioned that there were no potential conflicts of interest relevant to the report	• A list of excluded studies was not provided
Lo,[1] 2018, Australia	
• The objective was clearly stated	• Tests for publication bias were not conducted. However authors had mentioned that publication bias would be

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[11]

Strengths	Limitations
• Multiple databases (Medline, EMBASE, Cochrane Central Register of Controlled trials, International Clinical Trials Register, and Clinical trials.gov). Also, hand searching of kidney-related journals and the proceedings of major kidney conferences. • Study selection was described, and a flow chart was presented • A list of included studies was provided • A list of excluded studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using the Cochrane risk of bias tool. Selection bias, performance bias, detection bias, and reporting bias were low or unclear; attrition bias was high in 3 studies, and low or unclear in the remaining 6 studies. Other bias (such as due to conflict if interest) was generally high in all the studies. • Characteristics of the included studies were presented • Meta-analysis was conducted	explored if feasible (i.e., if there were sufficient number of studies) • Conflicts of interest were presented, and four of the 12 authors had association with industry
Seidu,[13] 2018, UK	
• The objective was clearly stated • Multiple databases (Medline, EMBASE, Cochrane Library, web of science) up to March 2017. Also reference lists of selected studies and relevant reviews were hand searched • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted using the Cochrane risk of bias tool. Selection bias and performance bias were low. Authors reported that detection bias was unclear in most studies. • Characteristics of the included studies were presented; patient characteristics lacked detail	• A list of excluded studies was not provided • Publication bias does not appear to have been conducted • Meta-analysis was not conducted • Conflicts of interest of the individual authors were not presented, however it was mentioned that the study was funded by industry.

EMA = European Medicines Agency; FDA = US Food and Drug Administration;

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
Allegrrati,[15] 2019, US	
• The objective was clearly stated • The inclusion and exclusion criteria were stated	• Conflicts of interest were declared. Three authors were associated with industry, and for the remaining 5 authors it

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
• Patient characteristics, intervention and outcomes were described • Randomized study. Randomization was through a central interactive web response system. Allocation codes were maintained by a statistician not involved in the study operations • Double-blinded study. Patients, investigators and the sponsor team were blinded. • Sample size calculation was conducted, and the appropriate number of patients were recruited. • Discontinuation and associated reasons were reported (3.2% in bexagliflozin group, and 7.1 % in the placebo group • ITT analysis was conducted • *P* values were not reported for patient characteristics. *P* values and/or CI were reported for efficacy outcomes but not for safety outcomes.	was reported that there were no conflicts of interest. Also, the study was supported by industry.
Pollock,[17] 2019, Australia. (DELIGHT)	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described • Randomized study. Randomization was done centrally according to a non-center specific randomization scheme. Stratification and randomization were done via the sponsor's interactive voice-web response system. • Double-blind study. There was no difference in appearance between the medications for each group. Patients, treating physicians and all study personnel (except personnel analyzing pharmacokinetic data) were blinded. • Sample size calculation was conducted, and the appropriate number of patients were recruited. • Discontinuation and associated reasons were reported. Discontinuation was 6% in the dapagliflozin group and 3% in the placebo group. • ITT analysis was conducted • *P* values were not reported for patient characteristics. *P* values and/or CI were reported for efficacy outcomes but not for safety outcomes. •	• Conflicts of interest were declared. All the authors were associated with industry; the study was also supported by industry.
Jian,[18] 2018, China	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study but randomization procedure was not described	• Blinding was not mentioned • There was no mention of sample size determination • Unclear if there were any discontinuations • Unclear if ITT analysis was conducted

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[12]

Strengths	Limitations
• *P* values were reported for patient characteristics and outcomes • The authors mentioned that there were no conflicts of interest	
Perkovic,[16] 2019, Australia (CREDANCE)	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described • Randomized study. Randomization was with the use of randomly permuted blocks with stratification according to 3 eGFR levels at screening. • Double-blind study (further details on blinding were not presented) • Sample size calculation was conducted, and the appropriate number of patients were recruited. • Discontinuation and associated reasons were reported and discontinuation was 27.3% (24.7% in canagliflozin group, and 29.9% in the placebo group) • ITT analysis was conducted • *P* values were not reported for patient characteristics. *P* values and/or confidence intervals were presented for efficacy and safety outcomes	• Conflicts of interest were declared. Majority of the authors were associated with industry; also the study was supported by industry.
Takashima,[19] 2018, Japan	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized study but randomization procedure was not described • Discontinuation and the associated reason were reported (one person in each group was excluded) • *P* values were reported for patient characteristics and for efficacy outcomes but not for safety outcomes.	• Open label study; no blinding • There was no mention of sample size determination • Unclear if ITT analysis was conducted • Conflicts of interest were declared. One author was associated with industry, and for the remaining 7 authors it was reported that there were no conflicts of interest. The authors mentioned that no funding for this research was received from public, commercial, or not-for-profit sectors.

eGFR = estimated glomerular filtration rate; ITT = intention- to-treat;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Toyama,[6] 2019, Australia	

Adult patients with T2D and CKD

Renal outcomes: Comparison of SGLT2 inhibitor with placebo

Outcome	SGLT2 inhibitor	No. of studies	No. of patients	Effect size: HR or RR (95% CI)	Heterogeneity I^2 (%)
Renal composite[a]	C, D, Em	6	5863	0.71 (0.53 to 0.95)	0
Renal related AE	C, D, Em	5	5582	1.04 (0.68 to 1.61)	55
AKI	C, D, Em	4	4767	0.69 (0.45 to 1.06)	0
Hyperkalemia	C, D, Em	5	5294	0.63 (0.48 to 0.83)	0

[a]The renal composite outcome comprised doubling of serum creatinine (or 40% decrease in eGFR), ESKD, or renal death.

eGFR slope (mL/min/1.73 m^2 per year): Effect size (95% CI) was 1.35 (0.78 to 1.93) favoring SGLT2 inhibitor (C, Em), data from 2 studies involving 3524 patients.

Cardiovascular outcomes: Comparison of SGLT2 inhibitor with placebo

Outcome	SGLT2 inhibitor	No. of studies	No. of patients	Effect size: HR or RR (95% CI)	Heterogeneity I^2 (%)
3-point MACE	C, D, Em	7	6150	0.81 (0.70 to 0.94)	0
MI	C, D, Em	7	6150	0.77 (0.60 to 0.99)	38
Stroke	C, D, Em, I, L	9	6376	0.84 (0.61 to 1.16)	51
Cardiovascular death	C, D, Em	7	6150	0.88 (0.71 to 1.09)	0
HF	C, D, Em	6	5881	0.61 (0.48 to 0.76)	0
All-cause mortality	C, D, Em, Er, I, L	11	7363	0.86 (0.73 to 1.01)	0

Biomarkers: Comparison of SGLT2 inhibitor with placebo

Outcome	SGLT2 inhibitor	No. of studies	No. of patients	Effect size: HR or RR (95% CI)	Heterogeneity I^2 (%)
A1C (%)	C, D, Em, Er, I, L, T	14	6589	-0.29 (-0.39 to -0.19)	65
FPG (mmol/L)	C, D, Em, Er, I, L, S	10	2309	-0.65 (-0.94 to -0.36)	52
SBP (mmHg)	C, D, Em, Er, I, L, S	11	6378	-4.03 (-4.79 to -3.26)	0
DBP (mmol/L)	C, D, Em, I, L, S	8	3695	-1.59 (-2.02 to -1.16)	12
Weight (kg)	C, D, Em, Er, I, L	11	6336	-1.42 (-1.57 to -1.26)	0
Serum potassium (mEq/L)	C, D, Em, I,	6	4549	0.00 (-0.02 to 0.02)	0

"In conclusion, currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials." (p.1246)

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion

Albuminuria (%)	C, D	4	>2980	-23.75 (-37.87 to -9.62)	0

Adverse events: Comparison of SGLT2 inhibitor with placebo

Outcome	SGLT2 inhibitor	No. of studies	No. of patients	Effect size: HR or RR (95% CI)	Heterogeneity I^2 (%)
Hypoglycemia	C, D, Em, Er, I, L, S	10	5052	1.05 (0.85 to 1.32)	57
Fracture	C, D, Em, Er	8	6160	1.01 (0.67 to 1.52)	0
Amputation	C, Em	2	4246	1.37 (0.58 to 3.25)	77
UTI	C, D, Em, Er, I, L	9	5021	0.97 (0.81 to 1.16)	30
Genital infection	C, D, Em, Er, I, L	9	5776	2.86 (2.00 to 4.10)	0
Hypovolemia	C, D, Em, Er, I L	9	5192	1.48 (0.94 to 2.32)	70
Diabetic ketoacitosis	C, D, Em	5	4784	2.16 (0.51 to 9.09)	0

Wang,[14] 2019, China

Adult patients with T2D and prevalent kidney disease (i.e.,eGFR < 60 mL/min/1.73 m^2)

Comparison of SGLT2 inhibitor with placebo

Outcome	Number of studies	Effect size, RR (95% CI)	Heterogeneity, I^2 (%)	Treatment favored
Incidence of albuminuria progression	4	0.57 (0.38 to 0.81)	18.6	SGLT2 inhibitor
Incidence of albuminuria regression	4	1.84 (1.36 to 2.48)	0.0	SGLT2 inhibitor
Incidence of renal adverse events	3	0.68 (0.52 to 0.89)	0.0	SGLT2 inhibitor
Incidence of all-cause mortality	6	0.82 (0.67 to 0.99)	0.0	SGLT2 inhibitor
Incidence of genital infection	5	2.44 (1.72 to 3.46)	0.0	placebo
Note: renal adverse events: composite of sustained 40% reduction in eGFR, requirement for renal-replacement therapy, and death from renal causes				

Absolute change in eGFR with time for treatment with SGLT2 inhibitor compared with placebo

Time period (weeks)	Number of studies	Effect size, MD (95% CI)	Heterogeneity, I^2 (%)	Treatment favored
1 to 6	1	-5.02 (-7.60 to -2.44)	NA	
12 to 15	3	-2.21 (-3.42 to -1.00)	0.0	
72 to 104	2	0.07 (-1.56 to 1.69)	0.0	
≥188	1	3.10 (1.88 to 4.32)	72.5	

"In conclusion, SGLT2 inhibitors slowed decline in eGFR, lowered albuminuria progression, improved adverse renal endpoints and reduced all-cause mortality, but increased the risk of genital infection as compared to placebo in patients with T2DM, with or without prevalent kidney disease." (p.1025)

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Lo,[1] 2018, Australia	
Adult patients with T2D and CKD **Biomarkers: Comparison of SGLT2 inhibitor with placebo** A1C: MD (95% CI), -0.29 (-0.38 to -0.19); 7 studies with 1,092 patients. FBP: MD (95% CI, -0.48 (-0.78 to -0.19); 5 studies with 855 patients. SBP: MD (95% CI), -4.68 (-6.69 to -2.68); 7 studies with 1,198 patients DBP: MD (95% CI), -1.72 (-2.77 to -0.66) 6 studies with 1,142 patients Total cholesterol: MD (95% CI), 0.09 (-0.05 to 0.24); 2 studies with 529 patients HDL cholesterol: MD (95% CI), 0.04 (0.01 to 0.07); 4 studies with 918 patients LDL cholesterol: MD (95% CI), 0.04 (-0.06 to 0.14); 4 studies with 917 patients Triglycerides: MD (95% CI), 0.01 (-0.11 to 0.14); 4 studies with 918 patients Weight: MD (95% CI), -1.41 (-1.80 to -1.02); 5 studies with1,029 patients **Cardiovascular and renal outcomes: Comparison of SGLT2 inhibitor with placebo** All-cause death: RR (95% CI), 0.78 (0.60 to 1.02); 5 studies with 2,933 patients All cardiovascular death: RR (95% CI), 0.78 (0.56 to 1.10); 4 studies with 2,788 patients MI: RR (95% CI), 0.63 (0.30 to 1.34); 4 studies with 2,788 patients Stroke: RR (95% CI), 0.96 (0.63 to 1.48); 5 studies with 2,933 patients HF: RR (95% CI), 0.59 (0.41 to 0.87); 3 studies with, 2,519 patients Serum potassium: MD (95% CI), -0.01 (-0.05 to 0.02); studies with 2,443 patients eGFR (mL/min/1.73 m^2): MD (95% CI), -1.85 (-2.76 to -0.94); 4 studies with 848 patients Serum creatinine: MD (95% CI), 3.82 (1.45 to 6.19); 4 studies with 848 patients UACR: MD (95% CI), -8.14 (-14.51 to -1.77), 5 studies with 1,153 patients ESKD: RR (95% CI), 0.71 (0.10 to 4.98); 2 studies with 700 patients Hyperkalaemia: RR (95% CI), 0.58 (0.42 to 0.81); 4 studies with 2,788 patients AKI: RR (95% CI), 0.78 (0.61 to 1.00); 4 studies with 2788 patients Doubling of serum creatinine: RR (95% CI), 0.96 (0.49 to 1.88); 2 studies with 700 patients **Adverse events: Comparison of SGLT2 inhibitor with placebo** Hypoglycemia: RR (95% CI), 0.88 (0.73 to 1.07); 7 studies with 3,086 patients Hypoglycemia requiring third party assistance: RR (95% CI), 0.47 (0.17 to 1.28); 3 studies with 845 patients Discontinuation of medication due to adverse events: RR (95% CI), 0.86 (0.56 to 1.32); 4 studies with 917 patients Hypovolemia: RR (95% CI), 1.07 (0.63 to 1.84); 6 studies with 3,005 patients Fracture: RR (95% CI), 0.81 (0.31 to 2.10); 5 studies with 2860 patients Diabetic ketoacidosis: RR (95% CI), 1.00 (0.09 to 11.02); 2 studies with 1962 patients Upper respiratory tract infection: RR (95% CI), 0.79 (0.43 to 1.44); 2 studies with 593 patients UTI: RR (95% CI), 1.09 (0.82 to 1.43); 7 studies with 3,086 patients Genital infection: RR (95% CI), 2.50 (1.52 to 4.11); 7 studies with 3,086 patients	"Evidence concerning the efficacy and safety of glucose-lowering agents in diabetes and CKD is limited. SGLT2 inhibitors and GLP-1 agonists are probably efficacious for glucose-lowering [….]. Additionally, SGLT2 inhibitors probably reduce BP, heart failure, and hyperkalaemia but increase genital infections, and slightly increase creatinine. […..] More high quality studies are required to help guide therapeutic choice for glucose-lowering in diabetes and CKD." (p.2)
Seidu,[13] 2018, UK	
Adult patients with T2D and impaired renal function	"In conclusion, emerging data suggests that SGLT2 inhibition

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
(Renal impairment was defined as eGFR ≥30 and <60 ml/min/1.73 m^2 and/or UACR > 300 and ≤5000 mg/g) eGFR: Four RCTs showed that compared with placebo, SGLT2 inhibitor increased eGFR level over the first few weeks but the eGFR levels decreased thereafter and returned to the baseline values. Blood urea nitrogen (BUN): Pooled results from two RCTs showed that compared with placebo, SGLT2 inhibitor significantly increased BUN (P =0.001). A thirdr study showed that compared with placebo, SGLT2 inhibitor (L) increased BUN levels up to 12 weeks and thereafter remained stable. A fourth study showed that showed that compared with placebo, SGLT2 inhibitor (C) increased BUN at 52 weeks. Serum creatinine: One RCT showed that compared with placebo, SGLT2 inhibitor (I) increased serum creatinine levels in the short term but the levels returned to baseline values at the end of the treatment period. In another RCT, with SGLT2 inhibitor (L) the serum creatinine levels barely changed. In a third RCT, with SGLT2 inhibitor (D) the serum creatinine levels increased the first week and thereafter remained stable. In a fourth study, compared with placebo, SGLT2 inhibitor (C 100mg or 300 mg) increased the serum creatinine levels at the end of the 52-week treatment period. UACR: In one RCT, at 24 weeks UACR decreased greater with SGLT2 inhibitor (C 100mg, or 300mg) than with placebo (-29.9%, -20.9%, and -7.5% for C[100mg], C[300mg], and plb, respectively) and at 52 weeks UACR was still decreased with SGLT2 inhibitor but it had increased with placebo (-16.4%, -28.0%, and +19.7% for C[100mg], C[300mg], and plb, respectively). In another RCT, at 104 weeks, in comparison to placebo, SGLT2 inhibitor (D 5 mg) showed an increase in UACR (8.30), but the difference was not statistically significant (*P* = 0.95) whereas SGLT2 inhibitor (D 10 mg) showed a decrease in UACR -81.39), but the difference was not statistically significant (*P* = 0.63). In a third RCT, at the end of 24 weeks, in comparison to placebo, SGLT2 inhibitor (I 50 mg) showed a decrease in UACR (-55.18), but the difference was not statistically significant (*P* = 0.17). In a fourth RCT, at 52 weeks in comparison to placebo, SGLT2 inhibitor (E25 mg) showed a decrease in UACR (-183.78), and the difference was not statistically significant (*P* = 0.003). Urine albumin: In one RCT, at the end of 52 weeks of treatment, urine albumin decreased with SGLT2 inhibitor (C) but increased with placebo (-34.4%, -49.0%, and +14.3% for C[100mg], C[300mg], and plb, respectively). In another RCT, at 24 weeks, In another RCT, in comparison to placebo, SGLT2 inhibitor (D 5 mg) showed an a decrease in urine albumin (-25.11 mg/g) but the difference was not statistically significant (*P* = 0.68). In a third RCT in comparison to placebo, with SGLT2 inhibitor (C 100 mg or 300 mg) a lower proportion of patients progressed to albuminuria (5.1%, 8.3%, and 11.8% for C[100mg], C[300mg], and plb, respectively). In a fourth RCT, in comparison to placebo, with SGLT2 inhibitor (E 25 mg) a lower proportion of patients progressed from no albuminuria to macroalbuminuria (12.2%, and 22.2% in E and plb, respectively); and from microalbuminuria to macroalbuminuria (2.0%, and 11.4% in E and plb, respectively). In this study, a greater proportion of patients showed improvement in albuminuria with SGLT2 inhibitor (E) compared to placebo: shift from microalbuminuria to microalbuminuria (32.6%, and 8.6% in E and plb, respectively, and shift from microalbuminuria to no albuminuria (27.5%, and 21.4% in E and plb, respectively).	prevents further renal function deterioration in people with type 2 diabetes with or without renal impairment. In patients with renal impairment, though treatment with SGLT2 inhibitors are associated with reductions in eGFR, the reductions are not substantial and are usually seen in the early phases of treatment initiation, with levels returning to baseline values with time. [….] In population with or without renal impairment, SGLT2 inhibition is also associated with reduction in UACR, slows down the progression of albuminuria, improves albuminuria, and is also associated with reduced risk of progression to a doubling of the serum creatinine levels, initiation of kidney transplant, and death from kidney disease." (p.281) "The current findings should stimulate further research on the role of SGLT2 inhibition on renal outcomes in people with diabetes, particularly those with renal impairment." (p.281)

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Composite renal outcomes: One RCT showed that in comparison to placebo, with SGLT2 inhibitor (E 10 mg or 25mg) there was reduced risk of incidence or worsening nephropathy (defined as progression to macroalbuminuria, a doubling of serum creatinine level, accompanied by eGFR 45 ml/min/1.73 m^2, the initiation of renal replacement therapy, or death from renal disease) (HR: 0.58, *P* < 0.001). This RCT also showed that in comparison to placebo, with SGLT2 inhibitor (E 10 mg or 25mg) there was reduced risk of another composite renal outcome (a doubling of serum creatinine level, initiation of renal replacement therapy, or death from renal disease) (HR: 0.51, *P* < 0.01).	

A1C = glycated hemoglobin; AE = adverse event; AKI = acute kidney injury; CI = confidence interval; CKD = chronic kidney disease; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HF = heart failure; HR = hazard ratio; L = liter; MACE =major adverse cardiovascular event; mmHg = milli meter of mercury; mmol = milli mole; plb = placebo; RR = risk ratio; SBP = systolic blood pressure; SGLT2 = sodium glucose cotransporter 2; T2D (or T2DM) = type 2 diabetes; UTI = urinary tract infection

SGLT2 inhibitor: C = canagliflozin, D = dapagliflozin, Em = empagliflozin; Er = ertugliflozin; I = ipragliflozin; L = loseogliflozin; S = sotagliflozin; T = topogliflozin

Table 7: Summary of Findings of Included Primary Clinical Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Allegretti,[15] 2019, US</td></tr>
<tr><td>

Adult patients with T2D and CKD

Outcomes for treatment with bexagliflozin (B) compared with placebo (plb) at 24 weeks (Number of patients: 157 in the B group and 155 in the plb group

Primary outcome (A1C)

Outcome	Effect size (D compared with plb), MD (95% CI)
Reduction in AIC (%) for patients with CKD3a or 3b	0.37 (0.20 to 0.54)
Reduction in AIC (%) for patients with CKD3a	0.31 (0.09 to 0.53)
Reduction in AIC (%) for patients with CKD3b	0.43 (0.16 to 0.69)

Other outcomes

Outcome	Effect size (D compared with plb), MD (95% CI)
FPG reduction (mmol/L)	0.76 (0.26 to 1.26)
Body weight reduction(%)	1.61 (1.00 to 2.22)
SBP reduction (mm Hg)	3.8 (0.6 to 7.1)
UACRreduction (%)	20.1 (2.52 to 34.56)

Adverse events
Adverse events (presented as percentages of patients experiencing the various adverse events)
-Any treatment-related AE: 38.2 % in B group, and 27.1% in plb group
-Any serious AE: 7.0 % in B group, and 5.8% in plb group
-Any serious treatment-related AE: 0.6% in B group, and 0% in plb group

</td><td>"Patients with diabetes and mild to moderate kidney failure have fewer treatment options compared with those with preserved kidney function. Bexagliflozin appears to be beneficial for the intensification of glycemic control for patients in this vulnerable condition. Additional therapeutic advantages of bexagliflozin include reductions in body weight, SBP, and albuminuria. The results of this study support the conduct of additional investigations on the renoprotective potential of bexagliflozin for the management of diabetic kidney disease." (p.336)</td></tr>
</table>

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
-AEs leading to discontinuation: 0.6% in B group, and 2.6% in plb group -AE leading to death: 0 % in B group, and 0% in plb group -Hypoglycemia: 24.8 % in B group, and 24.5% in plb group -UTI: 7.0% in B group, and 3.2% in plb group -AKI: 5.1% in B group, and 3.9% in plb group -Falls and fractures: 4.5% in B group, and 3.9% in plb group -Genital mycotic infection: 3.2% in B group, and 0% in plb group -Amputation: 0.6% in B group, and 0% in plb group -MACE (adjucated): 1.3% in B group, and 0% in plb group -Malignancies: 1.9% in B group, and 2.6% in plb group	
Perkovic,[16] 2019, Australia. (CREDANCE)	
Adult patients with T2D and CKD <u>Outcomes for treatment with canagliflozin compared with placebo (Number of patients: 2202 in the canagliflozin [C] group and 2199 in the placebo [plb] group</u> Outcomes expressed as HR (95% CI), unless indicated otherwise. Primary composite outcome: 0.70 (0.59–0.82); Doubling of serum creatinine level: 0.60 (0.48–0.76) End-stage kidney disease: 0.68 (0.54–0.86) Estimated GFR <15 ml/min/1.73 m^2: 0.60 (0.45–0.80) Dialysis initiated or kidney transplantation 0.74 (0.55–1.00) Renal death: 2/2202 in C, 5/2199 in plb Cardiovascular death: 0.78 (0.61–1.00) *Secondary outcomes:* Cardiovascular death or hospitalization for heart failure 0.69 (0.57–0.83) Cardiovascular death, myocardial infarction, or stroke 0.80 (0.67–0.95) Hospitalization for heart failure 0.61 (0.47–0.80) End-stage kidney disease, doubling of serum creatinine level, or renal death: 0.66 (0.53–0.81) Death from any cause: 0.83 (0.68–1.02) Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina: 0.74 (0.63–0.86) End-stage kidney disease, renal death, or cardiovascular death: 0.73 (0.61–0.87) Dialysis, kidney transplantation, or renal death: 0.72 (0.54–0.97) *Safety:* Any adverse event: 0.87 (0.82–0.93) Any serious adverse event: 0.87 (0.79–0.97) Serious adverse event related to trial drug: 1.45 (0.98–2.14) Amputation: 1.11 (0.79–1.56) Fracture: 0.98 (0.70–1.37) Acute pancreatitis: 5/2200 in C and 2/2197 in plb Hyperkalemia: 0.80 (0.65–1.00) Acute kidney injury: 0.85 (0.64–1.13) Diabetic ketoacidosis: 10.80 (1.39–83.65) Cancer: Renal-cell carcinoma: 1/2200 in C and 5/2197 in plb Breast cancer: 8/761 in C, 3/731 in plb; 2.59 (0.69–9.76) Bladder cancer 10/2200 in C, 9/2197 in plb; 1.10 (0.45–2.72)	"In conclusion, among patients with type 2 diabetes and kidney disease, those in the canagliflozin group had a lower risk of kidney failure and cardiovascular events than those in the placebo group at a median follow-up of 2.62 years." (p.2305)

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion

Outcomes in subgroups

Outcome	Parameter	Subgroup	HR (95% CI)
Primary composite outcome of ESKD, doubling of serum creatinine, renal death or cardiovascular death	Screening eGFR	30 to <45 ml/min/1.73 m^2	0.75 (0.59 to 0.95)
		45 to <60 ml/min/1.73 m^2	0.52 (0.38 to 0.72)
		60 to <90 ml/min/1.73 m^2	0.82 (0.60 to 1.12)
	Baseline UACR	≤1000	0.76 (0.55 to 1.04)
		>1000	0.67 (0.55 t0 0.81)
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death	Screening eGFR	30 to <45 ml/min/1.73 m^2	0.71 (0.53 to 0.94)
		45 to <60 ml/min/1.73 m^2	0.47 (0.31 to 0.72)
		60 to <90 ml/min/1.73 m^2	0.81 (0.52 to 1.26)
	Baseline UACR	≤1000	0.90 (0.54 to 1.50)
		>1000	0.61 (0.49 to 0.76)

Pollock,[17] 2019, Australia. (DELIGHT)

Adult patients with T2D and CKD

Outcomes for treatment with dapagliflozin (D) compared with placebo (plb) (Number of patients: 145 in the D group and 148 in the plb group.

Primary outcome:
The difference in mean change (%) from baseline in UACR was -28.3 (95% CI, -36.8 to -18.7) in the D group compared to the plb group, at week 4. This reduction was sustained through to 24 weeks. Th difference in mean change (%) from baseline in UACR was -21.0 (95% CI, -34.1 to -5.2) in the D group compared to the plb group, at week 24.

Secondary and other outcomes

Outcome at 24 week	Effect size (D compared with plb), MD (95% CI)
A1C (%)	–0·16 (–0·38 to 0·05)
FPG (mmol/L)	–0·11 (–0·76 to 0·54)
Body weight (%)	-0.87 (-2.17 to 0.44)
SBP (mm Hg)	-2.8 (-6.4 to 0.8)
eGFR (mL/min/1.73 m^2)	-2.35 (-4.16 to -0.53)
24-h urinary glucose excretion	44.9 (37.5 to 52.3)
24-h urinary albumin excretion	-19.9 (-35.6 to -0.3)
LDL cholesterol	5.1 (-3.4 to 14.4)
HDL cholesterol	4.4 (0.5 to 8.5)
Uric acid	-5.3 (-22.8 to 12.2)

"In conclusion, the SGLT2 inhibitor dapagliflozin lowers albuminuria when given in combination with angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment, […] in patients with type 2 diabetes and chronic kidney disease." (p.440)

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
<table><tr><td>Hematocrit ratio</td><td>0.03 (0.02 to 0.04)</td></tr><tr><td colspan="2">The mean difference (MD) reported here is ([mean change from baseline with D] - [mean change from baseline with plb])</td></tr></table> Adverse events (presented as percentages of patients experiencing the various adverse events) -Any adverse event: 54% in D group, and 55% in plb group. -Adverse event leading to discontinuation of study drug: 3% in D group, and 5% in plb group. -Any serious adverse event: 8% in D group, and 11% in plb group. -Serious adverse event leading to discontinuation of study drug: 1% in D group, and 4% in plb group. -Any serious adverse event of hypoglycemia: 0% in D group, and 1% in plb group. - Hypoglycaemia leading to study discontinuation: 0% in D group, and 1% in plb group. -Major hypoglycemia: 0% in D group, and 0% in plb group. - Kidney adverse events: 3% in D group, and 4% in plb group. -Urinary tract infection: 3% in D group, and 3% in plb group. -Genital infection: 3% in D group, and 0% in plb group. -Amputation:1% in D group, and 0% in plb group. -Fracture: 1% in D group, and 1% in plb group. -Diabetic ketoacidosis: 1% in D group, and 0% in plb group. -Death: 1% in D group, and 0% in plb group.	
Jian,[18] 2018, China	
Adult patients with T2D and CKD <u>Outcomes for treatment with dapagliflozin (D) compared with control (no D)</u> GFR: Before treatment, GFR (mL/min/1.73 m^2) (expressed as mean ±SD) 45.3 ± 12.1 for D, and 42.3 ± 10.3 for control (*P* = 0.42). After treatment, GFR (mL/min/1.73 m^2) (expressed as mean ±SD) 76.4 ± 21.2 for D, and 43.3 ± 10.9 for control (*P* = 0.001). At 3-month, GFR (mL/min/1.73 m^2) (expressed as mean ±SD) 52.3 ± 12.2 for D, and 51.2 ± 9.8 for control (*P* = 0.77). At 6-month, GFR (mL/min/1.73 m^2) (expressed as mean ±SD) 55.3 ± 18.5 for D, and 45.3 ± 9.4 for control (*P* = 0.52). At 12-month GFR (mL/min/1.73 m^2) (expressed as mean ±SD) 64.4 ± 12.5 for D, and 54.3 ± 10.7 for control (*P* = 0.008). FBG: Before treatment, FBG (mmol/L) (expressed as mean ±SD) 8.81 ± 2.33 for D, and 8.32 ± 1.42 for control (*P* = 0.43). After treatment, FBG (mmol/L) (expressed as mean ±SD) 7.69 ± 0.42 for D, and 7.83 ± 0.82 for control (*P* >0.05). ROS: Before treatment, ROS level (expressed as mean ±SD) 345.3 ± 29.1 for D, and 362.3 ± 21.2 for control (*P* = 0.42).	"The SGLT-2 inhibitor had a good therapeutic effect on renal function in patients with diabetic nephropathy, without having effects on fasting blood glucose. Additionally, it significantly delayed the progression of nephropathy." (p.3994)

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
After treatment, ROS level (expressed as mean ±SD) 76.4 ± 0.42 for D, and 343.3 ± 23.9 for control (*P* = 0.001).	
Takashima,[19] 2018, Japan	
Adult patients with T2D and CKD <u>Outcomes for treatment with canagliflozin (C) compared with placebo (plb)</u> Primary outcome UACR decreased significantly in the C group (from 139mg/g at baseline to 38mg/g at week 52) but change in the plb group was minimal (from 159 mg/g at baseline to 194mg/g at week 52). The between group difference with respect to change in UACR was statistically significant (*P* = 0.004), favoring C. Other outcomes The mean change in A1C (%) was -0.4 for the C group, and -0.2 for the plb group, at week 52. The between group difference with respect to change in A1C (%) was not statistically significant (*P* = 0.38). The mean change in BMI (kg/m^2) was -0.9 for the C group, and 0.1 for the plb group, at week 52. The between group difference with respect to change in BMI (kg/m^2) was statistically significant (*P* < 0.0001). The mean change in SBP (mm Hg) was -3.1 for the C group, and 0.5 for the plb group, at week 52. The between group difference with respect to change in SBP(mm Hg) was statistically significant (*P* < 0.0001). The mean change in DBP (mm Hg) was -1.6 for the C group, and 0.6 for the plb group, at week 52. The between group difference with respect to change in DBP (mm Hg) was statistically significant (*P* < 0.0001). The mean change in eGFR (mL/min/1.73 m^2) was 0.7 for the C group, and -3.4 for the plb group, at week 52. The between group difference with respect to change in eGFR (mL/min/1.73 m^2) was statistically significant (*P* = 0.024). Urinary L-FABP, NAG, and β_2MG levels were reduced in the C group, and were increased in the plb group; the between group differences were statistically significant (*P* <0.0001, *P* <0.0001, *P* <0.001 for L-FABP, NAG, and MG respectively). Adverse events The authors reported that none of the patients experienced significant adverse events such as symptomatic hypoglycemia, UTI, genital infection or limb amputation.	"In conclusion, canagliflozin treatment leads to a reduction in albuminuria, urinary L-FABP, NAG and β2MG levels in diabetes patients with CKD, regardless of simultaneous RAS inhibition. These findings suggest that canagliflozin may be an appropriate treatment option for patients with diabetes and CKD." (p.472)

A1C = glycated hemoglobin; AE = adverse event; AKI = acute kidney injury; CKD = chronic kidney disease; β_2MG = $\beta_2$macroglobulin; CI = confidence interval; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ESKD = end stage renal disease; FPG = fasting plasma glucose; HR = hazard ratio; L-FABP = liver type free acid binding protein; MACE = major adverse cardiac event; MD = mean difference; NAG = N-acetyl-β-D-glucosaminidase; plb = placebo; RAS = renin-angiotensin system; ROS = serum reactive oxygen species; T2D = type 2 diabetes; SBP = systolic blood pressure; SGLT2 = sodium glucose cotransporter 2; UACR =urinary albumin creatinine ratio; UTI = urinary tract infection.

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation			
	Toyama,[6] 2019, Australia	Wang,[14] Wang 2019, China	Lo,[1] 2018, Australia	Seidu,[13] 2018, UK
Barnett 2014 (EMPA-REG RENAL)	x	x		x
Fiorette 2016		x		
Fioretto 2018 (DERIVE)	x	x		
Frias 2016 (DURATION-8)	x			
Grunberger 2018 (VERTIS RENAL)	x			
Haneda 2016	x		x	
Haring 2013	x			
Inagaki 2014	x			
Kaku 2014	x		x	
Kashiwagi 2015 (LANTERN)	x		x	x
Kohan 2014	x	x	x	x
Neal 2017	x	x		
Perkovic 2018 (CANVAS Program)	x			
Petrykiv 2017	x			
Terauchi 2017 (J-STEP/INS)	x			
Tikkanen 2014	x			
Wanner 2016 (EMPA-REG OUTCOME)		x		x
Wiviott 2018		x		
Yale 2014	x	x		x
Yale 2013			x	x
Zambrowicz 2015	x		x	
Zinman 2015	x			
EMPA-REG OUTCOME 2013			x	
EMPA-REG BP 2015			x	
EMPA-REG RENAL 2014			x	