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Dapagliflozin for Chronic Kidney Disease

Rapid Review with Expert Input

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Abbreviations

AE	adverse event
AF	atrial fibrillation
CKD	chronic kidney disease
CI	confidence interval
CV	cardiovascular
eGFR	estimated glomerular filtration rate
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial
ESKD	end-stage kidney disease
FPG	fasting plasma glucose
FSGS	focal segmental glomerulosclerosis
A1C	glycated hemoglobin
HF	heart failure
HR	hazard ratio
IgA	immunoglobulin A
mg	milligram
NRS	non-randomized study
OR	odds ratio
P	probability
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGLT2i	sodium/glucose co-transporter-2 inhibitor
SR	systematic review
T2D	type 2 diabetes
UACR	urine albumin-creatinine ratio

Key Messages

- Recent, large, high-quality trials have demonstrated some benefits of dapagliflozin for the treatment of chronic kidney disease (most often in patients with type 2 diabetes) as compared to placebo.
- Data describing the clinical effectiveness of dapagliflozin have identified both relative benefits and no differences compared to placebo in various measures of renal and cardiovascular health and function, as well as health care utilization, mortality, and adverse events.
- A large proportion of the available data has been generated from the same randomized controlled trial that has recently been reported in multiple publications describing various patient subgroups and outcomes.
- No evidence was identified describing the cost-effectiveness of dapagliflozin for the treatment of patients with chronic kidney disease.

Context and Policy Issues

Chronic kidney disease (CKD) is a common condition, with estimates in the literature that 10% to 12% of the world's population lives with CKD.[1] This finding that is consistent with Canadian data indicating that approximately 10% of adults in Canada are living with the condition.[2] CKD contributes to reduced quality of life,[3] and often progresses to kidney failure and death[4]; it is currently 1 of the most rapidly rising causes of death worldwide, with estimates suggesting that CKD could become the fifth most common global cause of death by the year 2040.[5,6]

There are multiple risk factors for developing CKD, including older age, type 2 diabetes (T2D), obesity, ethnic origin and/or family history.[7] CKD is 1 of several possible comorbid conditions (often co-occurring with cardiovascular [CV] disease), in as many as half of all patients with T2D.[8] And while early intervention has been identified as an important mitigating factor for deleterious outcomes of CKD — including end-stage kidney disease (ESKD) and death — many individuals do not experience symptoms early in the course CKD.[2] This often leads to cases of CKD going undiagnosed, with data from 1 US study showing that as many as 22% of people with later stages 3 to 5 CKD may go undetected in the primary care system.[7] Often, patients are not diagnosed with CKD until they experience CV symptoms, which is associated with later stages of the disease.[9]

The mainstay of current medical treatment for CKD has relied heavily on angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) for several decades.[7,10,11] Nonetheless, CKD persistently progresses to ESKD across time, despite currently available interventions, which emphasizes the need for more effective therapies.[10,12] Indeed, it has been highlighted in the literature that no new medical interventions have come available to mitigate the progression of CKD since the 1990s.[13]

Sodium-glucose co-transporter protein 2 inhibitors (SGLT2is) were developed for patients with T2D and aimed at reducing blood glucose and A1C levels in these patients; 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 CV and kidney diseases.[11] Notably, the protective effects of SGLT2is on kidney function have since been hypothesized to be independent of their effects on reducing glucose,[10,14] and so represent

an important potential advancement in available treatments for CKD. In the literature, enthusiasm around the benefits of SGLT2is on renal and CV health is readily apparent, having been hailed as "a milestone discovery in medicine"(p. 6)[9]; having "revolutionized the treatment of cardiovascular and diabetic kidney disease,"(p. 335)[1] and; ushering in "a new era"[15](p. 144)[5](p. 1090) for patients with these diseases.

Of the available SGLT2is, several have been studied in the context of CKD, including dapagliflozin.[16] The benefits of dapagliflozin in treating the dual epidemic of T2D with CV comorbidities have been recognized, and more recently, dapagliflozin has been approved by the US FDA for treating adults with CKD at high risk for disease progression.[13,17] Approval was also recently granted in the European Union for the use of dapagliflozin in patients with CKD (regardless of their diabetes status).[18]

Given the deleterious impacts of CKD among Canadians and recent advancements in the evidence describing the effects of dapagliflozin, there is a need to consult the available research literature to help inform health care and policy decision-making. Thus, the aim of this review is to identify, assemble and summarize available evidence describing the clinical effectiveness and cost-effectiveness of dapagliflozin for the treatment of CKD.

Research Questions

1. What is the clinical effectiveness of dapagliflozin for adults with chronic kidney disease?
2. What is the cost-effectiveness of dapagliflozin for adults with chronic kidney disease?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International Health Technology Assessment (HTA) Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were dapagliflozin and CKD. No filters were applied to limit the retrieval by study type. Conference abstracts were removed from the search results. The search was also limited to English language documents published between January 1, 2016 and December 11, 2021.

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. Of note, studies were considered eligible regardless of any variation in the definitions used for CKD. All papers describing patients with CKD of any stage were considered eligible and included.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2021. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[19] for systematic reviews and the Downs and Black checklist[20] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 229 citations were identified in the literature search. Following screening of titles and abstracts, 165 citations were excluded and 64 potentially relevant reports from the electronic search were retrieved for full-text review. There were no relevant publications retrieved from the grey literature search for full-text review. Of the potentially relevant articles, 45 publications were excluded for various reasons, and 19 publications met the eligibility criteria for the review and were included in this report. These comprised 2 systematic reviews (SRs), 6 randomized controlled trials (RCTs) — 1 of which was reported across 11 eligible papers included in this review — and 1 non-randomized study. Appendix 1 presents the PRISMA[21] flow chart of the study selection.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with CKD
Intervention	Dapagliflozin (Forxiga) 5 mg and 10 mg oral tablets
Comparator	Q1 and Q2: Placebo, alternative active therapies of CKD management (e.g., ACE inhibitors, angiotensin-II receptor blocker), other SGLT2is (canagliflozin or empagliflozin), GLP-1 agonists
Outcomes	Q1: Clinical effectiveness (e.g., risk of eGFR decline, occurrence of ESKD, CV and renal complications, adverse event including death, hospitalizations, HRQoL) Q2: Cost-effectiveness (e.g., cost per QALY, ICERs, cost per adverse event avoided)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations

ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GLP-1 agonist = glucagon-like peptide-1 agonist; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SGLT2is = sodium glucose co-transporter 2 inhibitors.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

The SRs identified in this review were published in 2021[22] and 2019.[23] Both SRs had broader eligibility criteria than those informing this review i.e., 1 SR sought studies investigating sodium-glucose co-transporter-2 inhibitors (SLGT2is) among patients with type 2 diabetes (T2D) — some of whom also had chronic kidney disease (CKD)[22] — and the other SR sought studies investigating GLP-1 receptor agonists and SGLT2i in patients with both T2D and CKD.[23] Accordingly, both SRs included 1 RCT each that was eligible for inclusion and therefore summarized in this review.[22,23]

The 1 RCT included in the 2021 SR[22] was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, which was also identified and reported in the 11 papers that met eligibility criteria for this review.[24-34] Whereas eligible primary studies that are included within eligible SRs are generally not otherwise included in the review, because the 11 papers contained a much larger amount of data and information than was reported in the SR, all of the papers describing DAPA-CKD were retained for inclusion in this report (including the SR describing the DAPA-CKD trial). The RCT included in the 2019 SR was also described in another eligible publication that conducted a longer-term, post-hoc analysis of the trial data (i.e., a greater amount of data and information) and so, was also included in this review.[35]

The DAPA-CKD study was a randomized, placebo-controlled, double-blind trial with 11 publications identified and included in this review.[24-34] Dapagliflozin was also investigated by some of the same investigators in another randomized, placebo-controlled, double-blind trial — the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study — which produced 1 paper examining the subgroup of patients in that study with CKD and so, was eligible for inclusion in this review.[36] Other RCTs included the dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND) study, which was a placebo-controlled, double-blind crossover RCT[37]; the dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT) RCT, which also used a placebo-controlled and double-blind design[38]; and the Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With type 2 Diabetes (DERIVE) RCT, which similarly used a placebo-controlled, double-blind design.[39] Lastly, 1 non-randomized study (NRS) investigating dapagliflozin compared with empagliflozin was identified in this review, and used a longitudinal, retrospective cohort design.[40]

Country of Origin

The SRs identified in this review were conducted in China[22] and the US.[23] The long-term follow-up study[35] of the same RCT that was included in the 2019 SR[23] was conducted in 111 sites across 13 countries: US, Argentina, Canada, India, Mexico, Peru, Italy, Australia, France, Spain, Denmark, Puerto Rico, and Singapore.[41]

The DAPA-CKD study was conducted in 386 sites across 21 countries, which were not reported individually in the papers included in this review, but were reported in the published protocol: Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Russia, South Korea, Spain, Sweden, Ukraine, UK, US, and Vietnam.[42]

DAPA-HF was conducted in 410 sites across 20 countries[36] which were also not reported individually in the paper included in this review, but were available from the published protocol: Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Germany, Hungary, India, Japan, Netherlands, Poland, Russia, Slovakia, Sweden, Taiwan, UK, US, and Vietnam.[43] The DIAMOND study was conducted in 6 sites across 3 countries: Canada, Malaysia and the Netherlands.[37] The DELIGHT RCT was conducted in 116 sites across 9 countries: Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan, and the US.[38] Similarly, the DERIVE RCT was conducted in multiple sites across multiple countries: 88 sites in Bulgaria, Canada, Czech Republic, Italy, Poland, Spain, Sweden, and the US.[39] And finally, the NRS included in this review was conducted in Taiwan.[40]

Patient Population

The 2021 SR sought data describing patients with T2D, some of whom also had CKD (i.e., patients in the 1 included RCT from the SR, which was the DAPA-CKD study) and so, were eligible for inclusion in this review; 4,304 study participants.[22] The 2019 SR sought studies describing patients with T2D and CKD,[23] which was consistent with the patient eligibility criterion for this review, and the single RCT that was eligible from the SR examined 252 patients. Accordingly, the report of long-term findings from the 1 RCT included in the 2019 SR also described patients with T2D and CKD, but examined the subgroup of 166 patients with stage 3 CKD.[35]

The DAPA-CKD study described adults with CKD — some of whom also had T2D and some of whom did not.[24-34] Several subgroup analyses were conducted and published, describing study patients by estimated glomerular filtration rate (eGFR) status (i.e., less than or greater than, or equal to 45 mL/min per 1.73 m^2[26]); cardiovascular (CV) disease status (i.e., with and without CV disease) and heart failure (HF) status (i.e., with and without HF)[28,29]; glycemic status (i.e., normoglycemic, pre-diabetic and diagnosed T2D),[30] T2D status (i.e., with or without T2D)[32]; stage 4 CKD (i.e., 624 patients)[24]; focal segmental glomerulosclerosis (FSGS) (i.e., 104 patients)[31]; and; immunoglobulin A (IgA) nephropathy (i.e., 270 patients).[33]

The DAPA-HF trial was necessarily focused on patients with HF, but the included paper by Jhund and colleagues reported on the subgroup of 1,926 patients with CKD (defined as an eGFR of < 60 mL/min per 1.73 m^2).[36] The DIAMOND study recruited and assessed 53 non-diabetic patients with CKD.[37] The DELIGHT RCT included 293 patients with moderate to severe CKD and T2D receiving stable doses of an ACE inhibitor or and ARB.[38] The DERIVE trial included 321 patients with stage 3 CKD.[39] The NRS included in this review reported findings on 7,624 adult patients with both CKD and T2D.[40]

Interventions and Comparators

All of the studies in the review examined dapagliflozin at a dosage of 10 mg daily[22-40] and 2 also included data describing dapagliflozin at a dosage of 5 mg daily.[23,35] In addition to investigating the safety and efficacy of dapagliflozin (10 mg) versus placebo, 1 RCT also evaluated a third group of patients who received combination therapy including dapagliflozin (10 mg/day) and saxagliptin[38]; however, data from this arm of the trial were not included or summarized in this review, which excluded combination therapy.

The comparator groups described in all but 1 of the studies[40] included in this review received a placebo.[22-39] The 1 NRS included in this review compared dapagliflozin to empagliflozin (i.e., another SGLT2i) at dosages of 10 mg or 25 mg.[40]

Outcomes

All of the studies included in this review described outcomes of relevance to the efficacy and/or safety of dapagliflozin in CKD, that is, CV and/or renal complications; health care utilization; mortality and/or; adverse events (including serious adverse events).[22-40]

Outcomes describing the efficacy of dapagliflozin included those of renal function; for example, changes in eGFR (measured using mL/min/1.73 m^2)[23,24,26,28-31,34,38-40]; outcomes describing end-stage kidney disease (ESKD)[23,24,28-30,34,35,37-40]; as well as those describing composite and other measures of renal function.[24,25,28-34,36,40] Similarly, multiple studies reported on outcomes of relevance to CV function; that is, risk of atrial fibrillation (AF) and stroke.[23,24,26,28-31,34,38-40]

Additional outcomes of relevance to this review included health care utilization (measured by hospitalizations)[28,29,36]; and mortality (i.e., numbers of patients who died).[24,27-29,32,34-36,38] The comparative safety of dapagliflozin was also reported in many of the papers by describing adverse events (AEs)[24,28,29,31-39] and serious adverse events (SAEs).[24,25,28,29,32-39]

Details regarding the characteristics of included publications are provided in Appendix 2.

Summary of Critical Appraisal

Systematic Reviews

The 2021 SR demonstrated both strengths and limitations. The methods described were generally sound, including clear eligibility criteria and a comprehensive search — the latter of which is a critical component of a well-conducted SR, as it assures the reader that efforts have been made to identify a maximum amount of eligible information. In addition, authors described duplicate screening and data abstraction, which are important features of SRs. Duplicate screening reduces the potential for bias and error, and helps to ensure that all eligible studies are identified and included in the review. Similarly, duplicate data abstraction is important for ensuring that data have been accurately and comprehensively identified. As well, the 2021 SR reported appropriate statistical methods for meta-analyses, and an assessment of both risk of bias and of publication bias.[22] However, the report was limited in its description of a rationale for the selection of study designs. A description of excluded studies (including the rationale behind their exclusion) was missing, and there was an absence of any mention of a protocol or reference to an a priori design of review methods and criteria.[22] These features are important in systematic reviews to ensure transparency of the methods and reproducibility of the findings.[44]

The 2019 SR had many limitations and few strengths.[23] The PICO (population, intervention, comparator and outcomes) criteria were made clear, which is important for framing and establishing the aim and research question(s) of a review. In addition, information about the included studies was sufficiently detailed. However, there was no reference to a protocol, the literature search was limited by lack of a description of a grey literature search, no rationale was provided for the selection of study designs, no description of duplicate screening of citations or data abstraction, and no mention of an assessment of risk of bias of publication bias.[23] For instance, a clear and comprehensive assessment of the risk of bias for included studies is a key component of all SRs,[19] because understanding the quality of a study is an important part of weighing the value and contribution of the evidence it provides in answer to a research question (i.e., a higher quality of evidence provides more confidence in the findings reported, while lower levels of evidence are cause for caution in the interpretation of findings).

The limitations of the 2019 SR included in this review introduce uncertainty as to the extent of the review's utility, as the methods undertaken were not clearly rigorous, drawing into question whether the review may be biased in the studies it summarized and the findings it produced.

Randomized Controlled Trials

Most of the RCTs demonstrated many strengths and few limitations, with generally clear descriptions of robust methods and clear reporting of findings.[24-39] The DAPA-CKD RCT, in particular, demonstrated few limitations, with generally clear reporting and little evidence of threats to internal validity.[24-34] Nonetheless, while there was insufficient information reported in any of the reports to adequately assess the extent to which external validity was robust, because the trial employed a multinational, multi-centre design with thousands of patients across the world, there is a reasonable level of confidence in the external validity of the findings. Further, while a power calculation describing sufficient study power in the full set of study patients was provided,[25,26,34] several of the papers describing subgroup analyses from the trial either did not address power specific to their subgroup analyses,[24,27-30,32] or acknowledged that the analyses had insufficient power to demonstrate a clinically important difference between treatment groups.[31,33] Finally, with 11 papers published in 2 years (as identified by this review), 1 criticism of the DAPA-CKD trial reporting may be that the authors engaged in "salami slicing," that is, the publication of 1 trial across multiple papers.[45] This practice has been described as 1 that can be used as self-serving on the part of study co-authors (e.g., increasing the number of journal publications to support career advancement)[46] and may be problematic if it distorts the findings of the study (e.g., introducing the opportunity for "cherry picking" of data and potentially compromising the power of the analyses to detect a clinically important effect), and/or; diverging from the statistical plan by generating post-hoc analyses that may not have been pre-specified.[45] Importantly, salami slicing may legitimately be used to manage the reporting of large studies and/or datasets that cannot reasonably be described in 1 paper.[46] In the case of the DAPA-CKD trial, the publication of multiple papers describing subgroup analyses is unlikely to have introduced an important risk of bias, because the sufficiently powered findings from the overall trial data demonstrate a significant benefit of the intervention.[34] Nonetheless, the number of papers generated from the DAPA-CKD trial (as identified here) is arguably high, with some of the analyses explicitly described as being post hoc, and representing a potential source of bias in the reporting of results for this RCT.[28,30,31]

Four of the 5 remaining RCT reports included in this review were generally reported clearly, including sufficient detail and demonstrating several strengths and few limitations.[36-39] The papers were clear in their description of the study aims, patients, interventions and outcomes, and demonstrated features of internal and external validity i.e., randomized, double-blind, placebo-controlled designs conducted in multiple sites in multiple countries.[36-39] Although 3 of the reports described a power calculation demonstrating the extent to which the sample size was sufficient to detect a clinically important difference between treatment groups,[37-39] the report describing a sub-analysis of findings from the DAPA-HF trial did not.[36] Nonetheless, the main report of findings for the DAPA-HF trial did describe sufficient power to detect a statistically significant difference between the treatment groups in the primary outcome.[47,36] One of the RCTs used a crossover design (i.e., 6 weeks of dapagliflozin followed by a 6-week washout period and then 6 weeks of placebo, or vice versa),[37] which can introduce the risk of aliasing (i.e., that effects from the first intervention may carry over to the time period during which the next intervention is being assessed, even with a washout period), and contribute to the potential for type II error.[48] The fifth report describing a secondary analysis of trial data demonstrated some important limitations that render it of limited value. There was

insufficient detail provided describing the methods used in the RCT from which the data were taken, with a reference to the main trial paper, leaving the reader without access to the information.[35] In addition, no information on the representativeness of the patients assessed was provided, preventing the reader from considering this as a threat to external validity.[35] While the authors acknowledged that their analyses were post hoc, there were insufficient details provided to assess the potential for bias and confounding; for example, simple outcome data (i.e., numerators and denominators) were not reported; statistical methods were not described in detail, and; no description of the power of the analysis to detect a clinically important difference between treatment groups was provided.[35]

Finally, it was noted that all of the RCTs included in this review were funded by the same for-profit, private industry pharmaceutical manufacturer,[24-39] which manufactures dapagliflozin under the brand name Farxiga. This may or may not introduce risk of bias; for instance, 1 paper in this review reporting subgroup analyses from the DAPA-HF study described oversight by an academic team not employed by the pharmaceutical manufacturer.[36] External (and presumably objective) oversight of an RCT generally represents a strength of the study. Nonetheless, conflict of interest statements for several of these academic co-authors acknowledged the receipt of funds from the same for-profit, private industry pharmaceutical manufacturer in the form of speaking and/or consultation fees, as well as grant monies.[36]

While it is beyond the scope of this Rapid Review to investigate the extent to which the sole-reported source of funding for all RCTs eligible for and included in this review[24-39] may have introduced a risk of bias to the findings summarized herein, it remains an important consideration when assessing the possible impact that a conflict of interest may have on the potential for risk of bias as it concerns these included studies.[49]

Non-Randomized Study

The NRS demonstrated both strengths and limitations. There was a clear report of the aim, study objectives, patient characteristics, interventions, potential confounders, and estimates of random variability.[40] All eligible patients from a large, regional database were included in the analyses, which contributes to the confidence that can be placed in the external validity of the findings.[40] The findings were generated from planned analyses, with data from patients being observed across the same time period and adjustments made to account for potentially confounding factors[40] — all of which contribute to the confidence that can be placed in the study's internal validity. Nonetheless, some limitations were apparent as well; most importantly, the study was necessarily not randomized by virtue of its retrospective, observational design, which introduces a threat to the internal validity of the findings.[40] In addition, some details were either not reported or not clearly reported, including simple outcome data and actual P values for some outcomes, as well as adverse events that were missing from the repot of findings.[40] And while the study reported a large sample size, there was no discussion about the power of the study to detect a clinically important difference between the treatment groups.[40]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical effectiveness of dapagliflozin for adults with chronic kidney disease

Renal Health/Function

Changes in eGFR

Eleven of the 19 papers included in this review reported on changes in eGFR (in mL/min/1.73 m^2)[23,24,26,28-31,34,38-40]; 7 of which reported findings from the DAPA-CKD trial.[24,26,28-31,34] The primary report of findings describing data for all of the 4,304 study patients by treatment group found that statistically significantly fewer patients experienced a decline of at least 50% in eGFR among the dapagliflozin (10 mg) group (i.e., 112/2,152; 5.2%) as compared to those receiving placebo (i.e., 201/2,152; 9.3%), producing a comparative hazard ratio (HR) of 0.53 (95% CI, 0.42 to 0.67) that favoured dapagliflozin (10 mg).[34] This statistically significant improvement favouring patients receiving dapagliflozin (10 mg) as compared to placebo was also observed in several subgroup analyses of DAPA-CKD patients.[26,28,29,31] On the other hand, no significant difference in the number of patients experiencing a decline of at least 50% eGFR was found between dapagliflozin (10 mg) and placebo in several other subgroup analyses.[26,31]

Other RCTs examining changes in eGFR between dapagliflozin (10 mg) and placebo in patients with CKD and T2D produced similar findings favouring dapagliflozin (10 mg). One RCT including data describing 293 patients with moderate to severe CKD and T2D found a statistically significant difference in change of mean eGFR from baseline to 24 weeks favouring dapagliflozin (10 mg) as compared to placebo; that is −2.35 mL/min/1.73 m^2 (95% CI, −4.16 to −0.53, P = 0.011).[38] Similarly, another trial comparing dapagliflozin (10 mg) with placebo in 321 patients with stage 3 CKD reported a statistically significant difference in change of mean eGFR from baseline to 24 weeks favouring dapagliflozin (10 mg) over placebo; that is −2.49 mL/min/1.73 m^2 (95% CI, −1.59 to −0.02).[39] One RCT reported in an SR described changes in mean eGFR across 24 weeks of follow-up for each treatment group only (i.e., no comparative statistics reported), finding a difference of −4.80 mL/min/1.73 m^2 in patients receiving dapagliflozin (10 mg), −2.38 mL/min/1.73 m^2 in patients receiving dapagliflozin (5 mg) and −0.25 mL/min/1.73 m^2 in the placebo group, with authors narratively reporting no statistically significant difference between the groups. Similarly, the 1 NRS included in this review reported no statistically significant difference in mean eGFR between patients receiving dapagliflozin (10 mg) as compared to empagliflozin (10 mg); that is P = 0.145 or empagliflozin (25 mg) i.e., P = 0.217.[40]

ESKD

There were 5 papers that reported on the occurrence of ESKD, all of which used data from the DAPA-CKD trial.[24,28-30,34] The main report describing all 4,304 DAPA-CKD patients found fewer patients with ESKD at the end of follow-up in those receiving dapagliflozin (10 mg); that is 109/2,152 (5.1%) as compared to those receiving placebo; that is 161/2,152 (7.5%).[34] This difference between treatment groups was statistically significant i.e., HR 0.64 (95% CI, 0.50 to 0.82).[34] In an analysis of sub-components of the ESKD outcome, statistically significant benefits were found in the dapagliflozin (10 mg) group with regard to the number of patients experiencing an eGFR of less than 15 mL/min/1.73 m^2 (i.e., HR 0.67 [95% CI, 0.51 to 0.88]) and long-term dialysis (i.e., HR 0.66 [95% CI, 0.48 to 0.90]).[34] The 4 remaining papers reporting on the occurrence of ESKD described subgroup analyses from DAPA-CKD with variable findings reported; some of which were concordant with the statistically significant benefit of dapagliflozin (10 mg) found in the main trial, and some of which were not.[24,28-30] (Table 6)

Composite and Other Measures of Kidney Function

Ten publications described composite and other measures of kidney function[24,28-34,36,40]; 8 of these reported data from the DAPA-CKD trial[24,28-34] and 2 reported data from other RCTs.[36,40]

The primary and secondary outcomes from the DAPA-CKD trial were both composed of several component outcomes. The primary outcome was a composite of the number of patients experiencing a first occurrence of decline in eGFR of at least 50%, ESKD, or death from CV or renal causes; the secondary outcome was similar to the primary outcome, but did not include death from CV causes (i.e., the number of patients experiencing a first occurrence of decline in eGFR of at least 50%, ESKD, or death from renal causes). Both outcomes were included in the main report for the trial describing all 4,304 study patients by treatment group only, with investigators finding statistically significantly fewer patients in the dapagliflozin (10 mg) as compared to the placebo group experiencing the primary outcome; that is HR 0.61 (95% CI, 0.51 to 0.72, P < 0.001).[34] Similarly, the secondary composite outcome demonstrated a benefit of dapagliflozin (10 mg) versus placebo with statistically significantly fewer patients experiencing a first occurrence of any of the outcome components; that is HR 0.56 (95% CI, 0.45 to 0.68, P < 0.001).[34] The benefit of dapagliflozin (10 mg) was also reported in several additional papers from the DAPA-CKD trial examining subgroups of patients .Statistically significantly fewer patients receiving dapagliflozin (10 mg) experienced the primary or secondary composite outcomes as compared to those receiving placebo, regardless of the presence or absence of comorbid CV disease[28]; HF[29]; or T2D.[32] Several additional subgroup analyses also indicated a significant benefit of dapagliflozin (10 mg) as compared to placebo in both the primary and secondary composite outcomes (i.e., among DAPA-CKD patients with Stages 2 or 3 CKD[24]; IgA nephropathy[33]; diabetic nephropathy or glomerulonephritis.[32]) Similarly, another paper included analyses from the primary composite outcome only, and likewise found statistically significantly fewer patients among those receiving dapagliflozin (10 mg) versus placebo with pre-diabetes (i.e., HR 0.37 [95% CI, 0.21 to 0.66]) or T2D (i.e., HR 0.64 [95% CI, 0.52 to 0.79]).[30] Nonetheless, several subgroup analyses found no statistically significant difference between the treatment groups in either the primary or secondary composite outcomes, including DAPA-CKD patients with stage 4 CKD[24]; normoglycemia[30]; FSGS[31]; ischemia or hypertension.[32]

The DAPA-HF trial also reported on the same composite outcome as was reported in the DAPA-CKD trial as a secondary outcome; that is patients experiencing a first occurrence of decline in eGFR of ≥ 50%, ESKD, or death from renal causes.[36] However, the group of patients that were eligible for inclusion in this review had HF and reduced ejection fraction (as well as CKD with or without T2D), with authors reporting a non-significant difference between dapagliflozin (10 mg) and placebo i.e., HR 0.95 (95% CI, 0.50 to 1.82).[36]

Other measures of renal health and/or function reported from the DAPA-CKD trial included a detailed analysis of abrupt decline in kidney function, defined as a doubling of serum creatinine between study visits (median interval of 100 days).[25] Investigators found statistically significantly fewer patients receiving dapagliflozin (10 mg) with an abrupt decline in kidney function as compared to patients receiving placebo i.e., HR 0.68 (95% CI, 0.49 to 0.94; P = 0.02).[25] Authors also conducted subgroup analyses, finding a statistically significant benefit of dapagliflozin (10 mg) by number of events observed (per 100 patient-years) in subgroups of patients who were older than 65 years (but not in the subset 65 years of age and younger); female (but not in male patients); diagnosed with T2D or not; found to have an eGFR of lower than 45 mL/min/1.73 m^2 (but not in patients with an eGFR of at least 45 mL/min/1.73 m^2), as well as those not diagnosed with HF (but not patients diagnosed with HF).[25]

The NRS included in this review described the difference in mean serum creatinine (mg/dL) from baseline to at least 28 days among patients with CKD and T2D, reporting a significant benefit of empagliflozin (10 mg) as compared to dapagliflozin (10 mg); that is P = 0.010, but no statistically significant difference between empagliflozin (25 mg) and dapagliflozin (10 mg); that is P = 0.163.[40]

Cardiovascular Health/Function

AF

One RCT described in 1 SR reported on the risk of AF in 4,304 patients with CKD (with or without T2D), reporting an OR of 0.47 (95% CI, 0.2 to 1.09) between dapagliflozin (10 mg) and placebo, indicating no statistically significant difference between the groups.

Composite and Other Measures of Cardiovascular Health/Function

The main report from the DAPA-CKD trial describing all 4,304 study patients reported findings from 1 secondary composite outcome including CV components; that is hospitalization for HF or death from CV causes.[34] Study authors reported a significant difference between groups favouring dapagliflozin (10 mg) compared to matching placebo; that is hazard ratio (HR) 0.71 (95% CI, 0.55 to 0.92, P = 0.009).[34] Related subgroup analyses of this same outcome from the DAPA-CKD RCT were reported in several additional papers, producing variable results across patient characteristics; that is in patients with stage 2 or 3 CKD[24]; CV disease[29]; without HF,[29] or with T2D,[32] a significant benefit of dapagliflozin (10 mg) was found as compared to placebo; whereas no statistically significant difference between dapagliflozin (10 mg) and placebo was observed in this outcome among patients with stage 4 CKD[24]; without CV disease[29]; without T2D, or[32]; with HF.[29] Notably, the DAPA-HF trial reported on a similar composite outcome (i.e., worsening HF/hospitalization for HF or CV death) in 1,926 patients with HF and CKD (defined as an eGFR of < 60 mL/min per 1.73 m2), finding a significant benefit of dapagliflozin (10 mg) relative to placebo; that is HR 0.72 (95% CI, 0.59 to 0.86).[36] This apparent discrepancy in findings concerning the effectiveness of dapagliflozin (10 mg) among patients with CKD and HF may be due to the smaller number of patients included in the subgroup analysis of the DAPA-CKD trial (i.e., N = 468) as compared the number of patients in DAPA-HF, widening the CI in the former study of this subgroup of patients and rendering the finding not statistically significant. Thus, more confidence can be placed in the finding from the DAPA-HF finding due to its assessment of a larger group of patients.

The paper examining data from DAPA-CKD trial patients by CV disease status reported on several additional composite measures of CV outcomes, including a pre-specified exploratory investigation of MI, stroke or death from CV causes, and a post-hoc exploratory analysis of MI, stroke, hospitalization for HF or death from CV causes, as well as MI, stroke, hospitalization for heart failure, ESKD or death from any cause.[29] Whereas no significant differences between dapagliflozin (10 mg) and matching placebo were found in the first 2 of these 3 composite measures for either patients with or without CV disease, a significant benefit in favour of dapagliflozin (10 mg) was reported in the latter outcome in both patients with (HR: 0.72 [95% CI, 0.58 to 0.89]) and without CV disease (HR: 0.68 [95% CI, 0.54 to 0.85]).[29]

One RCT reported on change in hematocrit ratio from baseline to 24 weeks in 293 patients with moderate to severe CKD and T2D, finding a statistically significant benefit in favour of dapagliflozin (10 mg) compared to placebo i.e., difference in mean percentage 0.03 (95% CI, 0.02 to 0.04), P < 0.0001.[38]

Stroke

One RCT described in 1 SR reported on the risk of stroke in 4,304 patients with CKD (with or without T2D), reporting an odds ratio (OR) of 0.86 (95% CI, 0.51 to 1.47) between dapagliflozin (10 mg) and placebo, indicating no statistically significant difference between the groups.

Health Care Utilization

Hospitalization

Three reports from 2 RCTs reported on outcomes including hospitalization for HF in patients with CKD and CV disease (with or without T2D).[28,29,36] The DAPA-CKD trial found statistically significantly fewer patients receiving dapagliflozin (10 mg) were hospitalized, or experienced an urgent visit for HF as compared to those receiving placebo; that is HR 0.66 (95% CI, 0.52 to 0.83).[36] Similarly, subgroup analyses from the DAPA-CKD trial found that statistically significantly fewer patients receiving dapagliflozin (10 mg) experienced a first hospitalization for HF compared with those receiving placebo, whether or not they had CV disease or HF.[28,29] Finally, the DAPA-HF trial likewise found a statistically significant benefit favouring dapagliflozin (10 mg) versus placebo in a composite outcome measuring total hospitalizations for HF or death from CV causes; that is HR 0.79 (95% CI, 0.64 to 0.97).[36]

Mortality

Nine reports of RCT data described mortality among patients with CKD, with or without T2D or HF[24,27-29,32,34-36,38]; 6 of which reported findings from the DAPA-CKD trial,[24,27-29,32,34] and 2 reported data from other RCTs.[35,36,38]

All-Cause Mortality

Both the main report from the DAPA-CKD RCT and a sub-analysis focusing on mortality as the sole outcome of interest found statistically significantly fewer of the 4,304 patients in the study died from any cause in the dapagliflozin (10 mg) group as compared to those receiving placebo; that is HR 0.69 (95% CI, 0.53 to 0.88), P = 0.004).[27,34] The paper describing a detailed sub-analysis of mortality also reported findings on all-cause mortality by various subgroups, observing statistically significantly fewer patients in the dapagliflozin (10 mg) group who died from any cause as compared to placebo among those who were older than 65 years of age; male; either had T2D or not; had an eGFR of less than 45 mL/min/1.73 m^2; had a urine albumin-creatinine ratio (UACR) of greater than 1,000 mg/g or at least 1,000 mg/g; had a systolic blood pressure (SBP) of greater than 130 mm Hg, or; had a serious infection.[27] Conversely, there was no statistically significant difference in all-cause mortality found between the treatment arms in subgroups of patients who were 65 years of age or younger; female; had an eGFR of at least 45 mL/min/1.73 m^2; had a SBP of 130 mm Hg or less, or; had a serious malignancy.[27] Chertow and colleagues also reported on death from any cause in DAPA-CKD patients by stage of disease, finding no statistically significant benefit of dapagliflozin (10 mg) as compared to placebo in patients with stage 4 CKD i.e., HR 0.68 (95% CI, 0.39 to 1.21) but a statistically significant benefit of dapagliflozin (10 mg) in patients with stages 2 and 3 CKD i.e., HR 0.69 (95% CI, 0.52 to 0.92).[24] Two additional subgroup analyses by CV disease and HF status reported by McMurray and colleagues also found statistically significantly fewer patients receiving dapagliflozin (10 mg) died from any cause as compared to placebo, in both patients with and without CV disease or HF.[28,29] Likewise, another subgroup analysis of DAPA-CKD patients by T2D status confirmed the finding summarized above from Heerspink and colleagues[27] observing a statistically significant benefit of dapagliflozin (10 mg) as compared to placebo in all-cause mortality for patients with or without T2D.[32] Similarly, additional subgroup analyses of patients identified statistically significantly fewer

patients with diabetic nephropathy or glomerulonephritis experienced all-cause mortality with dapagliflozin (10 mg) as compared to placebo; however, there was no difference between treatment groups found in patients with ischemia or hypertension, or those with another or unknown cause of CKD.[32]

All-cause mortality was also reported in the DAPA-HF trial, with the authors reporting no significant difference between the treatment groups; that is a HR 0.85 (95% CI, 0.68 to 1.07).[36] And in 2 RCTs, deaths were reported as an adverse event; with 1 death in the dapagliflozin (10 mg) group and no deaths in the placebo group in 1 RCT, and[38]; 3 in the dapagliflozin (10 mg) group, 1 in the dapagliflozin (5 mg) and 4 in the placebo group,[35] with no characterization of the difference between groups was described in either of these latter 2 trials.[35,38]

Death From Renal Causes

Both the main report from the DAPA-CKD RCT and a sub-analysis focusing on mortality as the sole outcome of interest reported no statistically significant difference in death from renal causes (i.e., kidney failure) among patients receiving dapagliflozin (10 mg) as compared to those receiving placebo, that is 2 of 2,152 in the dapagliflozin (10 mg) group and 6 of 2,152 in the placebo group (HR 0.35 [95% CI, 0.07 to 1.73]).[27,34] These data were also reported in subgroup analyses of patients by CV disease and HF status, but the numbers per group were too small to compare statistically and so, no characterization of the differences between groups was reported.[27,34]

Death From CV Causes

The main report of findings from the DAPA-CKD trial found no statistically significant difference between dapagliflozin (10 mg) and placebo in the full set of 4,304 study patients i.e., HR 0.81 (95% CI, 0.58 to 1.12).[34] This lack of difference between dapagliflozin (10 mg) and placebo in CV death was also found in a detailed analysis of mortality (i.e., all CV deaths)[27]; subgroup analyses of patients with or without CV disease or HF,[28,29] and; in DAPA-HF patients i.e., 0.88 (95% CI, 0.69 to 1.13).[36] Similarly, a detailed investigation of CV deaths in DAPA-CKD patients found no difference between treatment groups in patients experiencing sudden cardiac death, acute MI or stroke; but did find statistically significantly fewer patients who died from HF in the dapagliflozin (10 mg) as compared to placebo; that is HR 0.27 (95% CI, 0.08 to 0.98).[27]

Death From Non-CV Causes

The detailed report of mortality in DAPA-CKD patients also reported all deaths caused by reasons other than CV and found significantly fewer non-CV deaths among patients receiving dapagliflozin (10 mg) as compared to placebo i.e., HR 0.54 (95% CI, 0.36 to 0.82).[27] A sub-analysis of components of this outcome identified malignancy as a likely driver of this statistically significant difference; that is HR 0.42 (95% CI, 0.19 to 0.97), while no statistically significant difference was found between treatment groups in deaths from infection or kidney failure.[27] Similarly, no significant difference was found between dapagliflozin (10 mg) and placebo in deaths with no determined cause; that is HR 0.80 (95% CI, 0.47 to 1.38), P = 0.426.[27]

Safety

Adverse Events

Thirteen reports described adverse events (AEs) in patients with CKD[24,28-39]; 8 of which described data from the DAPA-CKD trial[24,28-34] and 5 described data from other RCTs.[35-39] The main report of findings from the full set of study patients in the DAPA-CKD trial found

no statistically significant difference between the numbers of patients in either treatment group experiencing renal events, bone fractures, amputations, diabetic ketoacidosis, or discontinuing study medication; however, there were more patients in the dapagliflozin (10 mg) group (5.9%) who experienced symptoms of volume depletion as compared to those in the placebo group (4.2%), P = 0.01.[34] A subgroup analysis of the DAPA-CKD patients by stage of CKD produced similar findings, with no statistically significant difference identified between treatment groups in either the stage 2 and 3 or stage 4 CKD patients for most of the AEs that were assessed in the main report of findings (i.e., bone fractures, amputations, diabetic ketoacidosis, or discontinuation of study medication).[24] However, volume depletion was experienced by statistically significantly more patients in the dapagliflozin (10 mg) group as compared to placebo in the stage 2 and 3 patients (with no statistically significant difference in stage 4 patients between treatment groups).[24] Likewise, renal AEs were experienced by statistically significantly more stage 2 and 3 patients receiving dapagliflozin (10 mg) as compared to placebo (with no statistically significant difference in stage 4 patients between treatment groups).[24] Similarly, another subgroup analysis of the DAPA-CKD patients by T2D status also produced similar findings, with no statistically significant difference identified between treatment groups in either the patients with or without T2D for most of the AEs that were assessed in the main report of findings (i.e., fractures, amputations, diabetic ketoacidosis, kidney-related AEs or discontinuation of study medication).[32] However, volume depletion was experienced by statistically significantly more patients in the dapagliflozin (10 mg) group as compared to placebo in the patients without T2D (with no statistically significant difference in T2D patients between treatment groups).[32] On the other hand, the total number of any AE were experienced by statistically significantly more T2D patients receiving placebo as compared to dapagliflozin (10 mg) (with no statistically significant difference in patients without T2D between treatment groups).[32] The remaining papers describing subgroup analyses from the DAPA-CKD trial did not characterize the difference between treatment groups, reporting only raw numbers of patients per group and making interpretation of the treatment comparison less clear; data from these papers are detailed in Appendix 4.[28,29,31,33]

The DAPA-HF trial assessed the same AEs as were assessed in the DAPA-CKD trial, with no statistically significant difference found between treatment groups for any of the AEs.[36] The remaining studies did not characterize the difference between treatment groups, reporting only raw numbers of patients per group and making interpretation of the treatment comparison less clear; data from these papers are detailed in Appendix 4.[35,37-39]

Serious Adverse Events

Twelve papers described SAEs in patients with CKD[24,25,28,29,32-39]; 7 of which reported data from the DAPA-CKD trial[24,25,28,29,32-34] and 5 of which reported data from other RCTs.[35-39]

The main report of findings from the full set of study patients in the DAPA-CKD trial found statistically significantly more patients in the placebo group experiencing any SAE (i.e., P = 0.002) or a major episode of hypoglycemia (i.e., P = 0.04) as compared to those in the dapagliflozin (10 mg) group.[34] Similarly, the subgroup analysis of the DAPA-CKD patients by stage of CKD indicated a statistically significant difference between treatment groups in the stage 2 or 3 patients, with fewer patients experiencing any SAE or an episode of major hypoglycemia; however, no statistically significant difference was observed in the stage 4 CKD patients between treatment groups.[24] Similarly, another subgroup analysis of the DAPA-CKD patients by T2D status also produced similar findings, with statistically significantly more patients with T2D receiving placebo experiencing an episode of major hypoglycemia.[32] One

paper focused on abrupt decline in kidney function and acute kidney injury (AKI) in DAPA-CKD patients, reporting no significant difference between treatment groups in AKI-related SAEs; that is HR 0.77 (95% CI, 0.54 to 1.10), P = 0.15.[25] The remaining papers describing subgroup analyses from the DAPA-CKD trial did not characterize the difference between treatment groups, reporting only raw numbers of patients per group and making interpretation of the treatment comparison less clear; data from these papers are detailed in Appendix 4.[28,29,33]

The DAPA-HF found statistically significantly more SAEs in patients receiving placebo as compared to those receiving dapagliflozin (10 mg); P = 0.003.[36] The remaining studies did not characterize the difference between treatment groups, reporting only raw numbers of patients per group and making interpretation of the treatment comparison less clear; data from these papers are detailed in Appendix 4.[35,37-39]

Cost-Effectiveness Of Dapagliflozin for Adults With Chronic Kidney Disease

Because there were no studies identified assessing the cost-effectiveness of dapagliflozin in adult patients with CKD, no summary can be provided.

Appendix 4 presents the main study findings by outcome.

Limitations

This review identified a large number of publications describing the clinical effectiveness of dapagliflozin, but is limited by the lack of available evidence describing the cost-effectiveness of dapagliflozin, as no eligible economic evaluations were identified.

Many of the papers in this review came from the same trial, which indicates that the evidence base describing dapagliflozin for CKD could be smaller than it may appear. This seems to be consistent with the SRs that were included in this review;[22,23] that is, there were few studies included that addressed the use of dapagliflozin in patients with CKD, and there was some overlap between the studies included in the eligible SRs with the primary studies included in this review (though, the data reported in the SRs were very limited compared to those described in the primary study reports).

While this report was not focused on a particular definition or stage of CKD, the studies included focused on patients with stages 3 and 4 CKD, providing informative analyses of the effects of dapagliflozin across a spectrum of disease severity. Nonetheless, research describing a broader range — and more specific subgroups — of patients, dosages of dapagliflozin and/or alternative comparisons, and a wider variety of outcomes may provide additional, useful, and important insights into the clinical effectiveness of dapagliflozin, as well as considerations for implementing its use into clinical practice. For instance, the limitations of the characteristics of the DAPA-CKD study population, which currently represents the largest and most current available dataset describing dapagliflozin in CKD patients, have been highlighted in the literature (i.e., only patients with proteinuria were included[4]; without type 1 diabetes, and; without other forms of CKD; for example those with polycystic kidney disease, lupus nephritis and anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis).[9] Data describing these kinds of patients were also not described in the other studies included in this review and represent opportunities for continued research into the clinical effectiveness of dapagliflozin. And while the DAPA-CKD trial did include patients with non-

diabetic CKD, there have been recent calls in the literature for additional research investigating the effects of SGLT2is in this population, as well.[14]

In addition, while almost all of the studies summarized in the review provided data describing the comparison between dapagliflozin and placebo, there was only 1 study that described dapagliflozin in comparison with another SGLT2i (i.e., empagliflozin),[40] which retrospectively relied on real-world data and necessarily used a non-randomized design, and is therefore methodologically less robust than the RCTs that were summarized in this review. Nonetheless, it is worth highlighting that this sole study of dapagliflozin compared with another SGLT2i in this review found few statistically significant differences between patients receiving either SGLT2i; for example, no statistically significant differences in changes to eGFR.[40] These findings have the potential to be hypothesis generating and emphasize the importance of RCTs comparing various SGLT2is in patients with CKD (and possibly other conditions). Moreover, no information was identified by this review comparing dapagliflozin to ACE inhibitors, ARBs, GLP-1 agonists, or other treatments for managing CKD which represents another potential area for future research.

With regard to outcomes, the DAPA-CKD (from which a large proportion of the data were taken to inform this review) and DAPA-HF trials relied on the use of composites as primary and secondary end points, which have been highlighted in the literature as having the potential to introduce uncertainty or inflated treatment effects.[50-52] In addition, the DAPA-CKD RCT was ended early by an independent committee due to the demonstrated efficacy of dapagliflozin, and this could ostensibly have affected the study's power to establish a clinically relevant difference between treatment groups in the CKD patient population.[11] Finally, there was a broad range of data describing renal and CV function, as well as mortality and safety identified in this review; however, there were no data identified describing quality of life or health-related quality of life, which would provide insight into the patient experience of being treated with dapagliflozin.

Lastly, while most of the RCTs included in this review were found to demonstrate more strengths than limitations, all were funded by the same private industry, for-profit pharmaceutical manufacturer. This represents a possible conflict of interest that could have introduced bias or other threats to the validity of the findings.

Conclusions and Implications for Decision- or Policy-Making

Nineteen reports describing dapagliflozin in patients with CKD were identified and found to be eligible for inclusion in this review: 2 SRs,[22,23] 16 reports of RCT data,[24-39] and 1 NRS.[40] Most studies reported findings describing the clinical effectiveness of dapagliflozin compared with placebo, and no studies describing cost-effectiveness were identified.

The strengths of the studies identified in this review include the identification of data from multiple publications describing trials that used a randomized, double-blind, and placebo-controlled design.[24-39] Two of these studies (1 of which was reported across multiple publications) investigated large groups of patients across multiple sites and centres, which increases confidence in the external validity of the findings.[24-30,32,34,36] All of the RCTs included in this review recruited and observed outcomes in patients from Canadian study sites,[24-39]

which increases confidence in the relevance of the findings from these studies as they pertain to the Canadian context.

Benefits of dapagliflozin (10 mg daily) were found among patients with CKD in measures of kidney function (e.g., composite measures of renal function, including beneficial changes in the components of these composite measures e.g., improved eGFR and reduced ESKD).[23,24,26,28-31,34,38,39] Measures of CV health and/or function produced variable results, with some benefits of dapagliflozin demonstrated in some studies and subgroups for some outcomes,[24,28,29,32,34,36,38,39] but the findings of benefit were not consistent across patient subgroups and outcomes.[22,24,28,29,32,34,36,38,39] Importantly, findings for many of the subgroups and outcomes were not (or likely were not) sufficiently powered to detect a statistically significant difference between treatment groups; these findings are concordant or discordant with sufficiently powered findings, and to an extent they are hypothesis generating, but their capacity to detect an actual difference is limited, and may contribute to variability across the findings summarized in this review. Salient findings from the main report of the DAPA-CKD trial that included all study patients and focused on the primary and secondary outcomes as compared between treatment groups did report statistically significant improvements in the dapagliflozin group in both renal and CV composite outcomes (as well as several of the outcomes' sub-components).[34] This and other findings from the DAPA-CKD RCT and other trials of SGLT2is have been highlighted in much of the editorial literature as demonstrating sufficient cardiorenal protection so as to justify incorporating this class of drugs into standard care for patients with CKD (with or without T2D).[9,10,15] It is worth noting, however, that much of the editorial literature expressing urgency around implementing the use of dapagliflozin and other SGLT2is into clinical care as soon as possible also lists conflicts of interests for the editorials' authors that include the private industry pharmaceutical manufacturer, which has also funded all of the trials in this area of research, constituting a potential source of bias.[5,9,10,15]

With regard to health care utilization, most of the findings summarized in this review indicated a statistically significant protective effect of dapagliflozin as compared to placebo (though, there were only 3 papers that reported on this outcome, which was limited to hospitalizations and did not consider other measures of health care usage).[28,29,36] Nonetheless, reductions in health care utilization, in general, and hospitalization, in particular, are important considerations for patients with CKD, who require significant health care resources to manage their condition.[3] Mortality was significantly reduced in patients receiving dapagliflozin in several of the studies and subgroups summarized in this review; notably, the DAPA-CKD RCT's analysis of all-cause death in the large sample of patients with CKD (and with or without T2D) found statistically significantly fewer patients receiving dapagliflozin who died from any cause as compared to those receiving placebo. However, not all of the studies in this review found a significant benefit in various measures of mortality across various subgroups, so, it may be that some groups could benefit more than others.

Finally, there were multiple analyses of the comparative safety of dapagliflozin with placebo,[24,28-39] with a preponderance of data suggesting no significant difference between dapagliflozin and placebo, further indicating the favourability of dapagliflozin. Whereas some data indicated a risk of increased volume depletion or renal AEs in some patients receiving dapagliflozin as compared to placebo, there were also data in the main report of findings from the DAPA-CKD RCT suggesting a statistically significant protective effect of dapagliflozin from the SAEs described therein.[34] This overall finding of the relative safety of dapagliflozin is corroborated in the published literature; for example, that SGLT2is do not appear to increase the risk of hypoglycemia.[53]

As it concerns the benefits of dapagliflozin, subgroup analyses of the DAPA-CKD data indicated that the these may favour some patients more than others; for example, patients with CKD and T2D were demonstrated to experience statistically significant benefits with dapagliflozin as compared to placebo across most outcomes observed in the trial.[32] The focus on treatment with SGLT2i among some subgroups of patients has been the subject of commentary and recommendations; that is in patients with T2D and a high risk of HF or progression of CKD and treatment with SGLT2is has been emphasized as an important intervention.[53] Although much of the published literature has described the effectiveness and safety of SGLT2is in patients with T2D and CKD, there remains less clinical data available describing the effects of SGLT2is, in general (and dapagliflozin, in particular), in non-diabetic CKD[14,54,55]; type 1 diabetes, pediatric populations (e.g., adolescents with diabetic kidney disease), kidney transplant patients[10]; older adults[11]; racial minority and disadvantaged communities (who bear a greater burden of CKD)[13]; as well as CKD patients with various levels of renal function (e.g., moderate or severe).[8] While additional research on the renoprotective effects of the SGLT2i empagliflozin is under way (i.e., the EMPA-KIDNEY RCT investigating a comparison to placebo in patients with or without T2D),[6,13] there remains a need for additional research on the effects of dapagliflozin in various subsets of patients.

Given the preponderance of data and evidence found by this review and discussed in the literature that appears to support the benefit of dapagliflozin in patients with CKD, there remains a need for additional information describing particular patient subgroups, comparisons with other interventions, and additional outcomes (in particular, those which are patient-oriented). This, alongside the unknown cost-effectiveness of dapagliflozin for CKD warrants careful deliberation for decision- and policy-makers when considering the implementation of dapagliflozin into standard care for patients with CKD in Canada.

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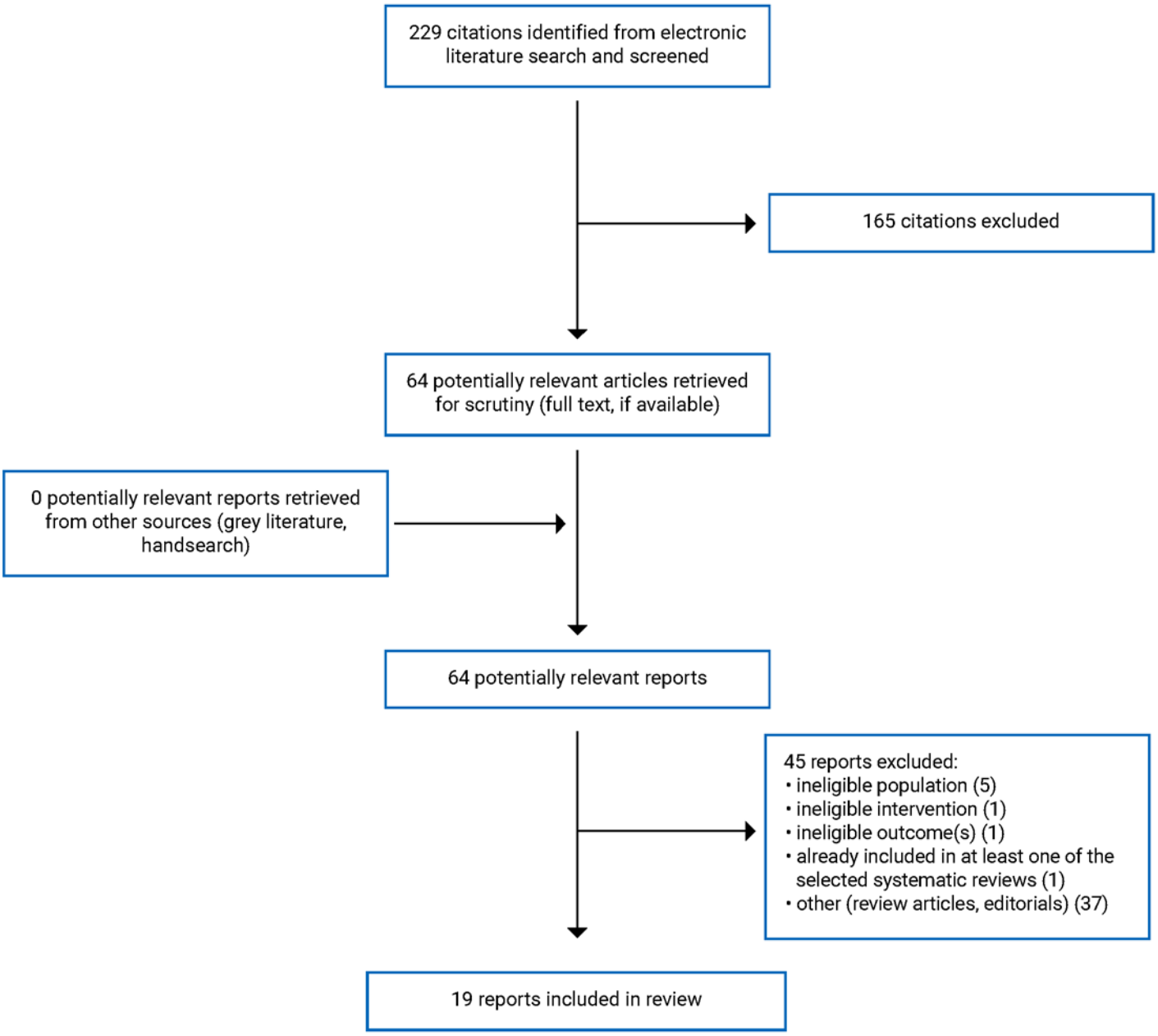
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix was not copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Zheng 2021[22] Country: China Funding: reported as "None"	SR with MA Sought and included: Studies investigating SGLT2i (N = 20) Eligible: 1 RCT (i.e., DAPA-CKD)	Sought: Patients with or without T2D and with or without exposure to SGLT2i Eligible for this review: Patients with CKD, with or without T2DM N = 4,304 Sex, % female: 33.1 Age, mean (SD): 61.8 (12), intervention group 61.9 (1), control group	Intervention: Dapagliflozin, 10 mg once per day Control: Placebo, matching	Outcomes sought: Atrial fibrillation Stroke Outcomes reported in 1 eligible RCT: • Atrial fibrillation, OR • Stroke, RR Follow-up, mean wk: 125
Kelly 2019[23] Country: US Funding: reported as none	SR Sought and included: Studies investigating GLP-1 receptor agonists and SGLT2i (N = 8) Eligible: 1 RCT (Kohan 2014)	Sought and eligible for this review: Patients with CKD and T2D Patients eligible for this review: N = 252 Age, range of mean in yr: 66 to 68 Baseline eGFR < 30 mL/min/1.73 m^2, % pts: 4.0 Baseline eGFR 30 to 59 mL/min/1.73 m^2, % pts: 91.7 Baseline eGFR ≥ 60 mL/min/1.73 m^2, % pts: 4.4 Diagnosed diabetic nephropathy at baseline, % pts: > 66.6	Intervention: Dapagliflozin, 5 mg or 10 mg Control: Placebo	Outcomes sought: Atrial fibrillation Stroke Outcomes reported in 1 eligible RCT: • Mean change in eGFR(mL/min/1.73 m^2) Follow-up, wk: 24 (with some pts completing as many as 104)

A1C = glycated hemoglobin; CKD = chronic kidney disease; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; g = gram(s); GLP-1 receptor agonists = Glucagon-like peptide receptor agonists; m^2 = metre(s) squared; MA = meta-analysis; mg = milligram; min = minute(s); mL = millilitre; N/n = number; OR = odds ratio; pt/pts = patient(s); RCT = randomized controlled trial; RR = relative risk; SGLT2i = sodium/glucose co-transporter-2 inhibitor; SD = standard deviation; SR = systematic review; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; wk = week(s); yr = year(s).

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Chertow 2021[24] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified sub-analysis of DAPA-CKD trial)	Adults with stage 4 CKD, defined as an eGFR of < 30 mL/min/1.73 m^2 (with or without T2D): N = 624 • Intervention group, n: 293 • Comparator group, n: 331 Age, mean (SD) • Intervention: 61.9 (11.8) • Comparator: 62.6 (12.4) Sex, n (%) female • Intervention: 103 (35.2) • Comparator: 122 (36.9) BMI, mean (SD) • Intervention: 29.6 (6.7) • Comparator: 29.0 (6.2) Current smoker, n (%) • Intervention: 43 (14.7) • Comparator: 44 (13.3) T2D, n (%) • Intervention: 190 (64.9) • Comparator: 211 (63.8) CV disease, n (%) • Intervention: 98 (33.5) • Comparator: 133 (40.2) eGFR, mean (SD) mL/ min/1.73kg^2: • Intervention: 26.8 (1.8) • Comparator: 26.8 (1.8)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome, time-to-event analyses of the first occurrence of one of the following: • Composite of: ◦ decline of at least 50% in eGFR ◦ onset of ESKD ◦ death from renal or CV causes Secondary outcomes, time-to-event analyses (in hierarchical order): • Composite of: ◦ sustained decline of at least 50% in eGFR ◦ ESKD ◦ death from renal causes • Composite of: ◦ hospitalization for heart failure ◦ death from CV causes • Death from any cause Other: Adverse events: • AEs leading to discontinuation of study medication • SAEs • Other AEs: ◦ volume depletion symptoms ◦ renal events ◦ major hypoglycemia ◦ bone fractures ◦ amputations ◦ potential diabetic ketoacidosis Follow-up: NR

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Heerspink 2021a[25] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified sub-analysis of DAPA-CKD trial)	Adults with CKD (with or without T2DM): N = 4,304 • Intervention group, n: 2,152 • Comparator group, n: 2,152 Age, mean (SD) • Intervention: 61.8 (12.1) • Comparator: 61.9 (12.1) Sex, n (%) female • Intervention: 709 (32.9) • Comparator: 716 (33.3) T2D, n (%) • Intervention: 1455 (67.6) • Comparator: 1451 (67.4) CV disease, n (%) • Intervention: 813 (37.8) • Comparator: 797 (37.0) HF, n (%) • Intervention: 235 (10.9) • Comparator: 233 (10.8) eGFR, mean (SD) mL/ min/1.73kg^2: • Intervention: 43.2 (12.3) • Comparator: 43.0 (12.4)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Sub-analysis of: (i) abrupt decline in kidney function and (ii) acute kidney injury Follow-up, median yr (IQR): 2.4 (2.0 to 2.7)
Heerspink 2021b[26] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified sub-analysis of DAPA-CKD trial)	Adults with CKD (with or without T2D), examined by subgroups according to eGFR status eGFR < 45 mL/min per 1.73 m^2, n pts: 2,522 • Intervention: 1,272 • Comparator: 1,250 eGFR ≥ 45 mL/min per 1.73 m^2, n pts: 1,782 • Intervention: 880 • Comparator: 902 Age in yrs, mean (SD) eGFR < 45: • Intervention: 62.2 (12.1) • Comparator: 62.1 (12.5) eGFR ≥ 45: • Intervention: 61.2 (12.0) • Comparator: 61.6 (11.6)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Sub-analysis of DAPA-CKD trial examining the chronic rate of eGFR decline, measured from baseline until the end of treatment Follow-up, median yr (IQR): 2.3 (1.8 to 2.6)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Sex, n (%) female eGFR < 45: • Intervention: 434 (34.1) • Comparator: 428 (34.2) eGFR ≥ 45: • Intervention: 275 (31.2) • Comparator: 288 (31.9) T2D, n (%) eGFR < 45: • Intervention: 826 (64.9) • Comparator: 814 (65.1) eGFR ≥ 45: • Intervention: 629 (71.5) • Comparator: 637 (70.6) CV disease, n (%) eGFR < 45: • Intervention: 486 (38.2) • Comparator: 455 (36.4) eGFR ≥ 45: • Intervention: 327 (37.2) • Comparator: 342 (37.9) HF, n (%) eGFR < 45: • Intervention: 145 (11.4) • Comparator: 131 (10.5) eGFR ≥ 45: • Intervention: 90 (10.2) • Comparator: 102 (11.3) Baseline medication, n pts (%) per group eGFR < 45 and ACE inhibitors: • Intervention: 375 (29.5) • Comparator: 357 (28.6) eGFR ≥ 45 and ACE inhibitors: • Intervention: 298 (33.9) • Comparator: 324 (35.9) eGFR < 45 and ARB: • Intervention: 868 (68.2) • Comparator: 852 (68.2)		

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		eGFR ≥ 45 and ARB: • Intervention: 576 (65.5) • Comparator: 574 (63.6) eGFR < 45 and diuretics: • Intervention: 595 (46.8) • Comparator: 615 (49.2) eGFR ≥ 45 and diuretics: • Intervention: 333 (37.8) • Comparator: 339 (37.6) eGFR < 45 and statins: • Intervention: 833 (65.5) • Comparator: 820 (65.6) eGFR ≥ 45 and diuretics: • Intervention: 562 (63.9) • Comparator: 579 (64.2)		
Heerspink 2021c[27] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified sub-analysis of DAPA-CKD trial)	Adults with CKD (with or without T2DM): N = 4,304 • Intervention group, n: 2,152 • Comparator group, n: 2,152 Age, mean (SD) • Intervention: 61.8 (12.1) • Comparator: 61.9 (12.1) Sex, n (%) female • Intervention: 709 (32.9) • Comparator: 716 (33.3) Diabetic nephropathy, n (%) • Intervention: 1,271 (59.1) • Comparator: 1,239 (57.6) Ischemic/hypertensive nephropathy, n (%) • Intervention: 324 (15.1) • Comparator: 363 (16.9) Chronic glomerulonephritis, n (%) • Intervention: 343 (15.9) • Comparator: 352 (16.4) Other/unknown cause of CKD, n (%) • Intervention: 214 (9.9) • Comparator: 198 (9.2) T2D, n (%)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Sub-analysis of DAPA-CKD trial examining mortality Follow-up, median yr (IQR): 2.4 (2.0 to 2.7)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Intervention: 1455 (67.6) • Comparator: 1451 (67.4) CV disease, n (%) • Intervention: 813 (37.8) • Comparator: 797 (37.0) History of HF, n (%) • Intervention: 235 (10.9) • Comparator: 233 (10.8) eGFR, mean (SD) mL/min/1.73 m^2: • Intervention: 43.2 (12.3) • Comparator: 43.0 (12.4)		
Jhund 2021[36] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified sub-analysis of DAPA-HF trial)	Adults with HF and reduced ejection fraction (with or without T2DM), and eGFR of < 60 mL/min per 1.73 m^2 eGFR < 60 mL/min per 1.73 m^2, n pts: 1,926 • Intervention: 964 • Comparator: 962 Age in yrs, mean (SD) • 70.9 (9.0) Sex, n (%) • Male: 1,392 (72.3) • Female: 534 (27.7) T2D at baseline, n (%) • 982 (51.0) History of hospitalization for HF, n (%): 951 (49.4) Baseline medication, n pts (%) • ACE inhibitors: ◦ 1,542 (80.1) • Diuretics: ◦ 1,835 (95.3)	Intervention: Dapagliflozin (10 mg/day) plus standard care Comparator: Placebo (matching) plus standard care	Outcomes: Primary outcome: • Composite of: ◦ Worsening HF or CV death (whichever occurs first) ◦ Hospitalization for HF ◦ CV death Secondary outcomes: • Composite of: ◦ decline of at least 50% in eGFR ◦ ESKD ◦ death from renal cause Safety: • AEs: ◦ SAEs ◦ Causing discontinuation of treatment ◦ Of relevance to CKD Follow-up, median mo: 18.2
McMurray 2021a[28] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (subgroup	Adults with CKD (with or without T2DM), examined by subgroups according to CV disease status CV disease at baseline, n pts (%): 1.610	Intervention: Dapagliflozin (10 mg/day) Comparator:	Outcomes: Primary outcome: • Composite of: ◦ decline of at least 50% in eGFR

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	analysis of DAPA-CKD trial)	• Intervention: 813 (50.5) • Comparator: 797 (49.5) No CV disease at baseline, n pts (%): 2,694 • Intervention: 1,339 (49.7) • Comparator: 1,355 (50.3) Age in yr, mean (SD) CV disease: • Intervention: 66.5 (9.7) • Comparator: 66.2 (9.3) No CV disease: • Intervention: 59.0 (12.5) • Comparator: 59.4 (12.9) Sex, n (%) male CV disease: • Intervention: 587 (72.2) • Comparator: 548 (68.8) No CV disease: • Intervention: 856 (63.9) • Comparator: 888 (65.5)	Placebo (matching)	◦ ESKD ◦ death from renal or CV causes Secondary outcomes: • Composite of: ◦ decline ≥ 50% in eGFR ◦ ESKD ◦ death from renal causes • Composite of: ◦ hospitalization for HF ◦ death from CV causes • Death from any cause Pre-specified exploratory CV outcomes: • CV death, MI or stroke • First HF hospitalization Post-hoc exploratory CV/ cardiorenal outcomes: • CV death, MI, stroke or HF hospitalization • All-cause death, MI, stroke, HF hospitalization or ESKD Other: Adverse events: • AEs leading to discontinuation of study medication • volume depletion symptoms • renal events • major hypoglycemia • bone fractures • amputations Any SAEs Follow-up, median yr (IQR): 2.4 (2.0 to 2.7)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
McMurray 2021b[29] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (subgroup analysis of DAPA-CKD trial)	Adults with CKD (with or without T2D), examined by subgroups according to the presence/ absence of HF at baseline HF at baseline, n pts (%): 468 • Intervention: 235 (50.2) • Comparator: 233 (49.8) No HF at baseline, n pts (%): 3,836 • Intervention: 1,917 (50.0) • Comparator: 1,919 (50.0)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome: • Composite of: ◦ decline of at least 50% in eGFR ◦ ESKD ◦ death from renal causes ◦ death from CV causes Secondary outcomes: • Composite of: ◦ decline ≥ 50% in eGFR ◦ ESKD ◦ death from renal causes • Composite of: ◦ hospitalization for HF ◦ death from CV causes • Death from any cause Pre-specified exploratory CV outcomes: • First HF hospitalization Other: Adverse events: • AEs leading to discontinuation of study medication • volume depletion symptoms • renal events • major hypoglycemia • bone fractures • amputations Any SAEs Follow-up, median yr (IQR): 2.4 (2.0 to 2.7)
Persson 2021[30] Countries: Multiple/ international	Placebo-controlled, double-blind,	Adults with CKD (with or without T2DM), examined by subgroups according to baseline glycemic	Intervention: Dapagliflozin (10 mg/day)	Outcomes: Primary outcome: • Composite of:

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding: AstraZeneca	multi-centre RCT (subgroup analysis of DAPA-CKD trial)	status at baseline Normoglycemia (A1C < 5.7%; 39 mmol/mol) at baseline, n pts (%): 738 • Intervention: 368 (49.9) • Comparator: 370 (50.1) Pre-diabetes (A1C of at least 5.7%; 39 mmol/mol) at baseline, n pts (%): 660 • Intervention: 329 (49.9) • Comparator: 331 (50.1) T2D (history of diabetes or A1C of at least 6.5%; 48 mmol/mol) at baseline, n pts (%): 2,906 • Intervention: 1,455 (50.1) • Comparator: 1,451 (49.9)	Comparator: Placebo (matching)	○ decline of at least 50% in eGFR ○ ESKD ○ death from renal causes ○ death from CV causes Secondary outcome, CKD-specific: • Composite of: ○ decline ≥ 50% in eGFR ○ ESKD Post-hoc analysis of: • Composite of: ○ decline ≥ 40% in eGFR ○ ESKD ○ death from renal causes ○ death from CV causes
Wheeler 2021a[31] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (subgroup analysis of DAPA-CKD trial)	Adults with CKD (with or without T2DM) and FSGS: N pts (%): 104 • Intervention: 45 (43.3) • Comparator: 59 (56.7) Age, mean (SD) • Intervention: 52.2 (14.2) • Comparator: 55.4 (14.3) Sex, n (%) female • Intervention: 13 (28.9) • Comparator: 21 (35.6) T2D, n (%): • Intervention: 5 (11.1) • Comparator: 15 (25.4) History of HF, n (%) • Intervention: 2 (4.4) • Comparator: 0 (0)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome: • Composite of: ○ sustained ≥ 50% ○ decline in eGFR ○ onset of ESKD ○ death from a kidney or CV cause Secondary outcome: • Kidney disease-specific (i.e., similar to the primary outcome but excluding CV death) Safety: • AEs: ○ Any ○ Causing discontinuation of treatment Change in eGFR slope • Acute (baseline to 14 days)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
				• Chronic (wk 2 to end of treatment) Post-hoc analysis • Composite end point of: ◦ sustained decline in eGFR ≥ 40% ◦ onset of ESKD ◦ death from a kidney or CV cause. Follow-up, median yr: 2.4
Wheeler 2021b[32] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (pre-specified of DAPA-CKD trial)	Adults with CKD (with or without T2D), examined by subgroups according to T2D status T2D, n pts (%): 2,906 • Intervention: 1,455 (50.1) • Comparator: 1,451 (49.9) No T2D, n pts (%): 1,398 • Intervention: 697 • Comparator: 701 Age in yr, mean (SD) T2D: • Intervention: 64.1 (9.8) • Comparator: 64.7 (9.5) No T2D: • Intervention: 56.9 (14.6) • Comparator: 56.0 (14.6) Sex, n (%) male per group T2D: • Intervention: 961 (66) • Comparator: 980 (68) No T2D: • Intervention: 482 (69) • Comparator: 456 (65) History of HF, n pts (%) per group T2D: • Intervention: 177 (12) • Comparator: 184 (13) No T2D: • Intervention: 58 (8)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome: • Composite of: ◦ decline of ≥ 50% in eGFR ◦ onset of ESKD ◦ death from renal causes ◦ death from CV causes Secondary outcome: • Kidney disease-specific (i.e., similar to the primary outcome but excluding CV death) • Composite of: ◦ hospitalization for HF ◦ death from CV causes ◦ death from any cause Safety: • AEs: ◦ Any ◦ Causing discontinuation of treatment ◦ Of specific interest in T2D Follow-up, median yr (IQR): 2.4 (2.0 to 2.7)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Comparator: 49 (7) Baseline medication, n pts (%) per group T2D and ACE inhibitors: • Intervention: 451 (31) • Comparator: 443 (31) No T2D and ACE inhibitors: • Intervention: 222 (32) • Comparator: 238 (34) T2D and ARB: • Intervention: 984 (68) • Comparator: 974 (67) No T2D and ARB: • Intervention: 460 (66) • Comparator: 452 (64) T2D and diuretics: • Intervention: 718 (49) • Comparator: 747 (51) No T2D and diuretics: • Intervention: 210 (30) • Comparator: 207 (30) T2D and statins: • Intervention: 1,039 (71) • Comparator: 1,043 (72) No T2D and diuretics: • Intervention: 356 (51) • Comparator: 356 (51)		
Wheeler 2021c[33] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (subgroup analysis of DAPA-CKD trial)	Adults with CKD and IgA nephropathy (with or without T2D) N pts (%): 270 • Intervention: 137 (50.1) • Comparator: 133 (49.9) Age in yr, mean (SD) • Intervention: 52.2 (13.1) • Comparator: 50.1 (13.1) Sex, n (%) female per group • Intervention: 44 (32.1) • Comparator: 44 (33.1) eGFR, mean (SD) mL/	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome: • Composite of: ◦ decline of ≥ 50% in eGFR ◦ onset of ESKD ◦ death from renal causes ◦ death from CV causes Secondary outcome: • Kidney disease-specific (i.e., similar to the primary outcome but

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		min/1.73kg^2: • Intervention: 44.3 (12.4) • Comparator: 43.2 (12.0) History of HF, n pts (%) per group • Intervention: 24 (17.5) • Comparator: 14 (10.5) Baseline medication, n pts (%) per group ACE inhibitors: • Intervention: 44 (32.1) • Comparator: 41 (30.8) ARB: • Intervention: 89 (65.0) • Comparator: 96 (72.2) Diuretics: • Intervention: 29 (21.2) • Comparator: 36 (27.1) Statins: • Intervention: 68 (49.6) • Comparator: 67 (50.4)		excluding CV death) • Composite of: ◦ hospitalization for HF ◦ death from CV causes • All-cause mortality Safety: • SAEs • Causing discontinuation of treatment Follow-up, median yr (range): 2.1 (0.025 to 3.2)
Cherney 2020[37] Countries: Multiple/ international Funding: AstraZeneca	DIAMOND trial: Double-blind, placebo-controlled, crossover RCT	Adults with CKD (without T2D) N pts (%): 53 • Intervention/placebo: 27 (50.9) • Placebo/intervention: 26 (49.1) Age in yrs, mean (SD) • Intervention/placebo: 52 (10) • Placebo/intervention: 51 (16) Sex, n (%) female per group • Intervention/placebo: 9 (33) • Placebo/intervention: 8 (31) mGFR, mean (SD) mL/ min/1.73kg^2: • Intervention/placebo: 58.9 (20.7) • Placebo/intervention: 57.8 (25.5) Baseline medication, n pts (%) per group ACE inhibitors: • Intervention/placebo: 15 (56)	Intervention: Dapagliflozin (10 mg/day), then crossed over to placebo Comparator: Placebo (matching)	Outcomes of relevance to this review: Changes in mGFR Safety: • SAEs ◦ death • AEs ◦ any ◦ of special interest Follow-up: 6 wk of treatment, 6 wk washout, 6 wk placebo (and vice versa)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Placebo/intervention: 16 (62) ARB: • Intervention/placebo: 12 (44) • Placebo/intervention: 10 (38) Diuretics: • Intervention/placebo: 6 (22) • Placebo/intervention: 8 (31)		
Heerspink 2020[34] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (primary analysis of DAPA-CKD trial)	Adults with CKD (with or without T2D): N = 4,304 • Intervention group, n: 2,152 • Comparator group, n: 2,152 Age, mean (SD) • Intervention: 61.8 (12.1) • Comparator: 61.9 (12.1) Sex, n (%) female • Intervention: 709 (32.9) • Comparator: 716 (33.3) Current smoker, n (%) • Intervention: 283 (13.2) • Comparator: 301 (14.0) Cardiovascular disease, n (%) • Intervention: 813 (37.8) • Comparator: 797 (37.0) History of HF, n (%) • Intervention: 235 (10.9) • Comparator: 233 (10.8) eGFR, mean (SD) mL/ min/1.73kg^2: • Intervention: 43.2 (12.3) • Comparator: 43.0 (12.4)	Intervention: Dapagliflozin (10 mg/day) Comparator: Placebo (matching)	Outcomes: Primary outcome, time-to-event analyses of the first occurrence of one of the following: • Composite of: ◦ decline of at least 50% in eGFR ◦ onset of ESKD ◦ death from renal or CV causes Secondary outcomes, time-to-event analyses (in hierarchical order): • Composite of: ◦ sustained decline of at least 50% in eGFR ◦ ESKD ◦ death from renal causes • Composite of: ◦ hospitalization for HF ◦ death from CV causes ◦ Death from any cause Other: Adverse events: • AEs leading to discontinuation of study medication • SAEs • Other AEs: ◦ volume depletion symptoms ◦ renal events ◦ major hypoglycemia

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
				◦ bone fractures ◦ amputations ◦ potential diabetic ketoacidosis Follow-up, median yr: 2.4 (IQR 2.0 to 2.7)
Lin 2019[40] Country: Taiwan Funding: Chang Gung Memorial Hospital (grant numbers: CORPG5F0011, CMRPG3H0401, CMRPG3H0941); Ministry of Science and Technology (grant numbers: NSC-MOST105 to 2628-B-182A-007-MY3 and NSC-MOST 105 to 2628-B-182 to 012-MY3)	Longitudinal, retrospective cohort	Adults with CKD and T2D: N = 7,624 • Intervention (Dapa), n: 3,274 • Comparator (Empa10), n: 1,696 • Comparator (Empa25), n: 2,654 Age, mean yr (SD) • Intervention (Dapa): 61.2 (11.4) • Comparator (Empa10): 63.2 (11.9) • Comparator (Empa25): 62.0 (11.7) Sex, % female: • Intervention (Dapa): 43.5 • Comparator (Empa10): 42.2 • Comparator (Empa25): 39.9	Intervention: Dapagliflozin (10 mg) Comparator: Empagliflozin (10 mg) Empagliflozin (25 mg)	Outcome of relevance to this review: Measure of renal: • eGFR before/after SGLT2i Follow-up: ≥ 28 days
Pollock 2019[38] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (primary analysis of DELIGHT trial)	Adults with moderate to severe CKD and T2D receiving stable doses of an ACE inhibitor or ARB N pt = 293 • Intervention, n pt: 145 • Comparator, n pt: 148 Age, mean (SD) • Intervention: 64.7 (8.6) • Comparator: 64.7 (8.5) Sex, n (%) female • Intervention: 43 (30) • Comparator: 43 (29) History of cardiac disease, n (%) • Intervention: 58 (40) • Comparator: 41 (28) History of vascular disease, n (%) • Intervention: 20 (14) • Comparator: 23 (16) eGFR, mean (SD) mL/ min/1.73kg^2:	Interventions*: Dapagliflozin (10 mg) Comparator: Placebo (matching) *Trial evaluated 3 groups, with another group receiving dapagliflozin plus saxagliptin, which is an ineligible intervention for this review as it uses combination therapy; data are presented for the dapagliflozin and placebo arms only	Outcomes: Safety • Change in eGFR • Proportion of pts who discontinued study medication due to sustained increase in serum creatinine Follow-up, wk: 24

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Intervention: 50.2 (13.0) • Comparator: 47.7 (13.5) Concomitant medication, n pts (%) per group Insulin: • Intervention: 104 (72) • Placebo: 107 (72) Renin-angiotensin inhibitors: • Intervention: 143 (88) • Placebo: 147 (99) Statins: • Intervention: 105 (72) • Placebo: 111 (75)		
Fioretto 2018[39] Countries: Multiple/ international Funding: AstraZeneca	Placebo-controlled, double-blind, multi-centre RCT (primary analysis of DERIVE trial)	Adults with stage 3 CKD (and T2D): N = 321 • Intervention group, n pts: 160 • Comparator group, n pts: 161 Age, mean (median) • Intervention: 65.3 (66.0) • Comparator: 66.2 (68.0) Sex, n (%) female • Intervention: 96 (60.0) • Comparator: 115 (71.4) BMI, mean (SD) • Intervention: 32.6 (4.7) • Comparator: 31.6 (5.0) Duration since T2D dx, yr (SD) • Intervention: 14.3 (8.1) • Comparator: 14.5 (8.3) eGFR, mean (SD) mL/ min/1.73kg^2: • Intervention: 53.3 (8.7) • Comparator: 53.6 (10.6) UACR, median (range) mg/g: • Intervention: 23.5 (2.7 to 5,852.0) • Comparator: 29.0 (3.8 to 8,474.0)	Intervention: Dapagliflozin (10 mg) Comparator: Placebo (matching)	Outcomes of relevance to this review: Safety • AEs • SAEs Follow-up, wk: 24

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Fioretto 2016[35] Country/ies: NR Funding: AstraZeneca	Placebo-controlled RCT	Adults with stage 3 CKD, ≥ 3.4 mg/mmol albuminuria (and T2D): N = 166 • Intervention group (10 mg), n pts: 56 • Intervention group (5 mg), n pts: 53 • Comparator group, n pts: 57 Age, mean (SD) • Intervention group (10 mg): 68 (8.4) • Intervention group (5 mg): 65 (9.8) • Comparator group: 66 (8.3) Sex, n (%) male • Intervention group (10 mg): 44 (78.6) • Intervention group (5 mg): 36 (67.9) • Comparator group: 36 (63.2) eGFR, mL/min/1.73 m2, mean (SD) • Intervention group (10 mg): 44.1 (11.1) • Intervention group (5 mg): 43.9 (9.0) • Comparator group: 45.1 (9.4) Medical history, n pts (%) Diabetic retinopathy • Intervention group (10 mg): 21 (37.5) • Intervention group (5 mg): 26 (49.1) • Comparator group: 21 (36.8) Hypertension • Intervention group (10 mg): 54 (96.4) • Intervention group (5 mg): 50 (94.3) • Comparator group: 51 (89.5) Coronary Artery Disease • Intervention group (10 mg): 18 (32.1)	Interventions: Dapagliflozin (10 mg) Dapagliflozin (5 mg) Comparator: Placebo (no other information reported)	Outcomes of relevance to this review: Safety • AEs • SAEs Follow-up, wk: 104

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Intervention group (5 mg): 18 (34.0) • Comparator group: 20 (35.1)		

AE = adverse event(s); ACE inhibitor(s) = angiotensin-converting enzyme inhibitor(s); ARB = angiotensin receptor blockers; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DAPA = dapagliflozin; dx = diagnosis; eGFR = estimated glomerular filtration rate; Empa10 = empagliflozin 10 mg; Empa25 = empagliflozin 25 mg; ESKD = end-stage kidney disease; FPG = fasting plasma glucose; FSGS = focal segmental glomerulosclerosis; g = gram(s); h = hour(s); A1C = glycated hemoglobin; HF = heart failure; IgA = immunoglobulin A; IQR = interquartile range; kg = kilogram; m2 = metre(s) squared; mg = milligram; mGFR = measured glomerular filtration rate; mg/mmol = milligrams per millimole; MI = myocardial infarction; min = minute(s); mL = millilitre; mmol/mol = millimoles per mol; mo = month(s); N/n = number; pt/pts = patient(s); RCT = randomized controlled trial; SAE = serious adverse event(s); SBP = systolic blood pressure; SD = standard deviation; SGLT2i = sodium/glucose co-transporter-2 inhibitor; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; wk = week(s); yr = year(s).

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix was not copy-edited.

Table 4: Strengths and Limitations of Systematic Reviews Using the AMSTAR Checklist[19]

Strengths	Limitations
Zheng 2021[22]	
• PICOS clearly reported • Comprehensive literature search conducted • Study selection and data abstraction performed in duplicate • Included studies described in sufficient detail • Satisfactory methods used to conduct risk of bias assessment • Appropriate methods used for meta-analysis • Publication bias was adequately investigated	• An explicit description of a review protocol or a priori method was not reported • A rationale for the selection of study designs was not provided • Excluded studies were not listed and the rationales for exclusion were not reported for individual studies • Sources of funding for included studies were not reported • The potential impact of risk of bias or heterogeneity was not discussed in the interpretation of the results of the meta-analyses or the discussion/interpretation of the findings
Kelly 2019[23]	
• PICOS clearly reported • Included studies were described in adequate detail	• An explicit description of a review protocol or a priori method was not reported • A rationale for the selection of study designs was not provided • Literature search was limited and did not describe grey literature • Methods for study selection and data abstraction were not described • Excluded studies were not listed and the rationales for exclusion were not reported for individual studies • There was no mention of risk of bias assessment • Sources of funding for included studies were not reported • There was no mention of publication bias • The potential impact of risk of bias or heterogeneity was not discussed in the interpretation of the results of the meta-analyses or the discussion/interpretation of the findings

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[20]

Strengths	Limitations
Chertow 2021[24]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • The paper did not describe a power calculation demonstrating

Strengths	Limitations
• Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	sufficient power to detect a clinically important difference between treatment groups
Heerspink 2021a[25]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	Reporting • Some numerators and denominators were not reported for some outcome data (but findings are generally reported clearly) External Validity • Number of patients invited to participate in the study (including those who declined) was not reported
Heerspink 2021b[26]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported	Reporting • Some numerators and denominators were not reported for some outcome data (but findings are generally reported clearly)

Strengths	Limitations
• Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • A power calculation specific to the subgroup analyses was not provided
Heerspink 2021c[27]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported

Strengths	Limitations
Jhund 2021[36]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity • Number of patients invited to participate in the study (including those who declined) was described in the report of findings for the overall trial[47] Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • Patient compliance with the interventions was described in the report of findings for the overall trial[47] • No data dredging was apparent	Internal Validity • Patient loss to follow-up was not reported (however, intention-to-treat analyses were specified in the report of findings for the overall trial[47]) Study Power • A power calculation for the subgroup analysis was not provided (but was described in the report of findings for the overall trial with regard to the primary end point[47])
McMurray 2021a[28]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • A power calculation specific to the subgroup analyses was not provided

Strengths	Limitations
time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	
McMurray 2021b[29]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • A power calculation specific to the subgroup analyses was not provided
Persson 2021[30]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • A power calculation specific to the subgroup analyses was not provided

Strengths	Limitations
• Statistical tests appeared appropriate to the data • No data dredging was apparent	
Wheeler 2021a[31]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators and denominators were reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	Reporting • P values were not reported for outcome data External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • Authors concede that their event-driven analyses were underpowered to detect a clinically important effect
Wheeler 2021b[32]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported

Strengths	Limitations
• No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	
Wheeler 2021c[33]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Study Power • Authors explicitly acknowledged that the smaller-than-expected sample size was a particular limitation of the study to detect a clinically important effect
Cherney 2020[37]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period	Reporting • Some information is reported on patient loss to follow-up, however the characteristics of patients lost to follow-up are not described • Some findings are presented graphically only without numbers of patients in the analyses reported External Validity • Number of patients invited to participate in the study (including those who declined) was not reported Internal Validity • Crossover study designs introduce the risk of aliasing, thereby contributing to the potential for Type II error

Strengths	Limitations
• Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	
Heerspink 2020[34]	
Reporting • Aim, objectives, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	Reporting • Some patient characteristics are reported but the paper refers the reader to a protocol document for details External Validity • Number of patients invited to participate in the study (including those who declined) was not reported
Lin 2019[40]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported. External Validity • All eligible patients from a large, regional database were included in the analyses Internal Validity • No data dredging was apparent • Statistical tests appeared appropriate to the data • Patients were observed from the same population and time period	Reporting • Numerators and denominators included for some, but not all, reported outcome data • Actual P values included for some, but not all, reported outcome data • Adverse events not reported Internal Validity • No randomization of patients to treatment was performed • No blinding of patients/clinicians/research staff to treatment • Adjustment for variable length of follow-up was not reported • No sample size calculation was reported

Strengths	Limitations
• Findings were adjusted to account for confounding factors	
Pollock 2019[38]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Numerators, denominators and actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and time period • Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	External Validity • Number of patients invited to participate in the study (including those who declined) was not reported
Fioretto 2018[39]	
Reporting • Aim, objectives, patient characteristics, interventions, potential confounders and estimates of random variability all clearly reported • Actual P values reported for outcome data • Adverse events reported External Validity • Study used a multinational, multi-centre design with a large sample size, contributing to confidence concerning external validity Internal Validity • Patients were randomized to treatment • Patients/clinicians/research staff were blinded to treatment assignment of study patients • Study patients had consistent duration of follow-up and were observed from the same population and	Reporting • Numerators and denominators were not included for all outcome data External Validity • Number of patients invited to participate in the study (including those who declined) was not reported

Strengths	Limitations
time period • Statistical tests appeared appropriate to the data • No data dredging was apparent Study Power • Study described a power calculation demonstrating sufficient power to detect a clinically important difference between treatment groups	
Fioretto 2016[35]	
Reporting • Aim, objectives, patient characteristics, interventions and potential confounders were reported • Adverse events reported Internal Validity • The authors acknowledged that the paper was describing a post hoc (i.e., unplanned) analysis	Reporting • Very little information was reported describing the methods of the RCT from which the data were taken • Numerators and denominators were not included for outcome data • Estimates of random variability not reported • P values not reported for outcome data External Validity • Important details about the representativeness of the study population to the entire population were absent from the report of findings Internal Validity • The study was a post-hoc analyses of data from an RCT with very little information provided on the methods used in the RCT from which the data were taken • Bias and confounding could not adequately be assessed due to the lack of detail provided in the paper Study Power • No sample size calculation was reported

Appendix 4: Main Study Findings

Note that this appendix was not copy-edited.

Table 6: Summary of Findings by Outcome — Renal Outcomes

Study citation and study design	Outcomes
Estimated Glomerular Filtration Rate (eGFR)	
Chertow 2021[24] RCT	Patients with CKD (with or without T2D), change in eGFR mL/min/1.73 m^2 from baseline to end of treatment by stage of CKD, least squares mean difference (SE) • Stage 4 ◦ Dapagliflozin (10 mg) ▪ −2.15 (0.32) ◦ Placebo (matching) ▪ −3.38 (0.31) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ −2.98 (0.12) ◦ Placebo (matching) ▪ −3.87 (0.12)
Heerspink 2021b[26] RCT	Patients with CKD (with or without T2D), change in eGFR (mL/min/1.73 m^2) from baseline to end of treatment by patient characteristics, mean decline in slope (SE) • Overall ◦ Dapagliflozin (10 mg) ▪ −2.88 (0.11) ◦ Placebo (matching) ▪ −3.83 (0.12) ◦ Difference between groups, mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 0.95 (0.63 to 1.27) ◦ Difference between groups, percentage change ▪ 24.8 • Age ≤ 65yrs ◦ Dapagliflozin (10 mg) ▪ −3.03 (0.15) ◦ Placebo (matching) ▪ −4.08 (0.15) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 1.05 (0.63 to 1.46) ◦ Difference between groups, percentage change ▪ 25.7 • Age > 65yrs

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ −2.65 (0.18) ◦ Placebo (matching) ▪ −3.47 (0.18) ◦ Difference between groups mL/min/1.73 m^2 per yr (95% CI), favours dapagliflozin ▪ 0.82 (0.33 to 1.31) ◦ Difference between groups, percentage change ▪ 23.6 ◦ *P*-value for interaction (age) ▪ 0.486 • Male sex ◦ Dapagliflozin (10 mg) ▪ −2.89 (0.14) ◦ Placebo (matching) ▪ −3.85 (0.14) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 0.96 (0.57 to 1.35) ◦ Difference between groups, percentage change ▪ 24.9 • Female sex ◦ Dapagliflozin (10 mg) ▪ −2.85 (0.20) ◦ Placebo (matching) ▪ −3.77 (0.20) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 0.92 (0.37 to 1.47) ◦ Difference between groups, percentage change ▪ 24.4 ◦ *P*-value for interaction (sex) ▪ 0.904 • T2D ◦ Dapagliflozin (10 mg) ▪ −2.84 (0.14) ◦ Placebo (matching) ▪ −4.01 (0.20) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 1.18 (0.79 to 1.56) ◦ Difference between groups, percentage change ▪ 29.2

Study citation and study design	Outcomes
	• No T2D ◦ Dapagliflozin (10 mg) ▪ −2.97 (0.20) ◦ Placebo (matching) ▪ −3.43 (0.20) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), NS ▪ 0.46 (−0.10 to 1.03) ◦ Difference between groups, percentage change ▪ 12.6 ◦ *P*-value for interaction (T2D status) ▪ 0.040 • eGFR < 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ −2.50 (0.15) ◦ Placebo ▪ −3.31 (0.15) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 0.81 (0.39 to 1.23) ◦ Difference between groups, percentage change ▪ 31.4 • eGFR ≥ 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ −3.42 (0.17) ◦ Placebo (matching) ▪ −4.47 (0.17) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), favours dapagliflozin ▪ 1.05 (0.57 to 1.53) ◦ Difference between groups, percentage change ▪ 21.3 ◦ *P*-value for interaction (eGFR status) ▪ 0.462 • Diabetic nephropathy ◦ Dapagliflozin (10 mg) ▪ −2.86 (0.15) ◦ Placebo (matching) ▪ −4.14 (0.15) ◦ Difference between groups mL/min/1.73 m^2 per yr (95% CI), favours dapagliflozin ▪ 1.28 (0.87 to 1.70) ◦ Difference between groups, percentage change

Study citation and study design	Outcomes
	▪ 30.9 • Chronic glomerulonephritis ◦ Dapagliflozin (10 mg) ▪ −3.51 (0.29) ◦ Placebo (matching) ▪ −3.96 (0.29) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), NS ▪ 0.44 (−0.36 to 1.25) ◦ Difference between groups, percentage change ▪ 18.3 • Hypertensive nephropathy ◦ Dapagliflozin (10 mg) ▪ −2.72 (0.30) ◦ Placebo (matching) ▪ −3.33 (0.28) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), NS ▪ 0.61 (−0.19 to 1.40) ◦ Difference between groups, percentage change ▪ 11.1 • Other or unknown etiology of CKD ◦ Dapagliflozin (10 mg) ▪ −2.23 (0.37) ◦ Placebo (matching) ▪ −2.55 (0.38) ◦ Difference between groups mL/min/1.73 m^2 per year (95% CI), NS ▪ 0.31 (−0.73 to 1.35) ◦ Difference between groups, percentage change ▪ 21.3 ◦ *P*-value for interaction ▪ 0.500
McMurray, 2021a[28] RCT	Patients with CKD (with or without T2D), component analysis of the composite primary outcome by CV disease status, n/N pts (%); participants with event per 100 pt-yrs: Decline of ≥ 50% in eGFR • No CV disease ◦ Dapagliflozin (10 mg) ▪ 71/1339 (5.3); 2.7 ◦ Placebo (matching) ▪ 127/1355 (9.4); 4.9 ◦ Difference between groups, % AR (95% CI)

Study citation and study design	Outcomes
	▪ −4.1 (−6.0 to −2.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.57 (0.42 to 0.76) • CV disease ◦ Dapagliflozin (10 mg) ▪ 41/813 (5.0); 2.7 ◦ Placebo (matching) ▪ 74/797 (9.3); 4.7 ◦ Difference between groups, % AR (95% CI) ▪ −4.2 (−6.8 to −1.7) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.50 (0.34 to 0.73) • *P* for interaction (by CV disease status), NS ◦ 0.54
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), component analysis of the composite primary outcome by HF status, n/N pts (%); participants with event per 100 pt-yrs: Decline of ≥ 50% in eGFR • No HF ◦ Dapagliflozin (10 mg) ▪ 99/1,914 (5.2); 2.6 ◦ Placebo (matching) ▪ 176/1,919 (9.2); 4.7 ◦ Difference between groups, % AR (95% CI) ▪ −4.0 (−5.6 to −2.4) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.54 (0.43 to 0.70) • HF ◦ Dapagliflozin (10 mg) ▪ 13/235 (5.5); 2.7 ◦ Placebo (matching) ▪ 25/233 (10.7); 5.4 ◦ Difference between groups, % AR (95% CI) ▪ −5.2 (−10.1 to −0.3) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.49 (0.25 to 0.95) • *P* for interaction (by HF status), NS ◦ 0.59

Study citation and study design	Outcomes
Persson, 2021[30] RCT	**Patients with CKD (with or without T2D), component analysis of the composite primary outcome by glycemic status, n/N pts (%); participants with event per 100 pt-yrs:** Decline of ≥ 50% in eGFR • Normoglycemia ◦ Dapagliflozin (10 mg) ▪ 20/368 (5.4); 2.9 ◦ Placebo (matching) ▪ 31/370 (8.4); 4.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.58 (0.33 to 1.01) ◦ Difference between groups, % AR (95% CI) ▪ 2.9 (−0.7 to 6.6) • Pre-diabetes ◦ Dapagliflozin (10 mg) ▪ 13/329 (4.0); 2.0 ◦ Placebo (matching) ▪ 30/331 (9.1); 4.6 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.39 (0.20 to 0.74) ◦ Difference between groups, % AR (95% CI) ▪ 5.1 (1.4 to 8.9) • T2D ◦ Dapagliflozin (10 mg) ▪ 79/1455 (5.4); 2.7 ◦ Placebo (matching) ▪ 140/1451 (9.6); 4.9 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.55 (0.42 to 0.72) ◦ Difference between groups, % AR (95% CI) ▪ 4.2 (2.3 to 6.1) • *P* for interaction (by glycemic status), HR, NS ◦ 0.60 • *P* for interaction (by glycemic status), AR, NS ◦ 0.71
Wheeler 2021a[31] RCT	Patients with CKD (with or without T2D), change in eGFR slope, mL/min/1.73 m^2 per year, mean of least squares difference (95% CI) • Overall (baseline to end of treatment) ◦ Dapagliflozin (10 mg) ▪ −3.7 (−4.8 to −2.6) ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ −4.2 (−5.2 to −3.3) ◦ Difference between groups, absolute (95% CI) ▪ 0.54 (−0.91 to 2.00) • Acute (baseline to 14 days) ◦ Dapagliflozin (10 mg) ▪ −4.5 (−5.9 to −3.1) ◦ Placebo (matching) ▪ −0.9 (−2.1 to 0.4) ◦ Difference between groups ▪ NR • Chronic (wk 2 to end of treatment) ◦ Dapagliflozin (10 mg) ▪ −1.9 (−3.0 to −0.9) ◦ Placebo (matching) ▪ −4.0 (−4.9 to −3.0) ◦ Difference between groups, absolute (95% CI) ▪ 2.04 (0.61 to 3.48)
Heerspink 2020[34] RCT	Patients with CKD (with or without T2D), component analysis of the composite primary outcome, n/N pts (%); events per 100 pt-yrs: • Decline of ≥ 50% in eGFR ◦ Dapagliflozin (10 mg) ▪ 112/2152 (5.2); 2.6 ◦ Placebo (matching) ▪ 201/2152 (9.3); 4.8 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.53 (0.42 to 0.67) ▪ P = NR
Lin 2020[40] NRS	Patients with CKD and T2D, difference in eGFR before/after (baseline to ≥ 28 days) SGLT2i, mean mL/min/1.73 m^2: • Dapagliflozin (10 mg) ◦ −0.11 • Empa10 ◦ 0.628 • Empa25 ◦ 0.429 • Difference in change between dapagliflozin (10 mg) and Empa10, NS ◦ P = 0.145 • Difference in change between dapagliflozin (10 mg) and Empa25, NS ◦ P = 0.217

Study citation and study design	Outcomes
Pollock 2019[38] RCT	Patients with CKD and T2D, change in eGFR (secondary outcome) from baseline to 24 wk, mean mL/min/1.73 m^2 (95% CI) • Dapagliflozin (10 mg) vs. placebo ◦ −2.35 (−4.16 to −0.53), favours dapagliflozin ◦ P = 0.011
Kelly 2019[23] SR (1 RCT eligible for this review: Kohan 2014)	Kohan 2014 • Change in mean eGFR (mL/min/1.73 m^2) from baseline to wk 24 ◦ Dapagliflozin (10 mg) ▪ −4.80 ◦ Dapagliflozin (5 mg) ▪ −2.38 ◦ Placebo ▪ −0.25 ◦ Difference between dapagliflozin (10 mg) and placebo, NS ▪ P = NR ◦ Difference between dapagliflozin (5 mg) and placebo ▪ P = NR
Fioretto 2018[39] RCT	Patients with CKD and T2D, change in adjusted mean eGFR from baseline to 24wk (secondary outcome), mL/min/1.73 m^2 (95% CI) • Dapagliflozin (10 mg) vs. placebo ◦ −2.49 (−1.59 to −0.02), favours dapagliflozin
ESKD	
Chertow 2021[24] RCT	Patients with CKD (with or without T2D), ESKD as a component of the composite primary outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by stage of CKD, n/N pts (%); participants with event per 100 pt-yrs: • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 49/293 (16.7); 9.2 ◦ Placebo ▪ 72/331 (21.8); 12.4 ◦ Difference between groups, HR (95% CI), NS ▪ 0.72 (0.50 to 1.04) ◦ Difference between groups, AR (95% CI), NS ▪ 5.0 (−1.1 to 11.2) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 60/1859 (3.2); 1.6 ◦ Placebo ▪ 89/1821 (4.9); 2.4 ◦ Difference between groups, HR (95% CI), favours dapagliflozin

Study citation and study design	Outcomes
	▪ 0.64 (0.46 to 0.89) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ 1.7 (0.4 to 2.9) • *P* for interaction (by stage of CKD), HR, NS ◦ 0.64 • *P* for interaction (by stage of CKD), AR, NS ◦ 0.24
McMurray, 2021a[28] RCT	Patients with CKD (with or without T2D), ESKD as a component of the composite primary outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by history of CV disease status, n/N pts (%); participants with event per 100 pt-yrs: • No CV disease ◦ Dapagliflozin (10 mg) ▪ 72/1339 (5.4); 2.7 ◦ Placebo ▪ 106/1355 (7.8); 4.0 ◦ Difference between groups, % AR (95% CI) ▪ −2.4 (−4.3 to −0.6) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.69 (0.51 to 0.93) • CV disease ◦ Dapagliflozin (10 mg) ▪ 37/813 (4.6); 2.2 ◦ Placebo ▪ 55/797 (6.9); 3.4 ◦ Difference between groups, % AR (95% CI) ▪ −2.3 (−4.6 to −0.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.59 (0.39 to 0.91) • *P* for interaction (by CV disease status), NS ◦ 0.50
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), ESKD as a component of the composite primary outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by history of HF status, n/N pts (%); participants with event per 100 pt-yrs: ESKD • No HF ◦ Dapagliflozin (10 mg) ▪ 100/1,914 (5.2); 2.6 ◦ Placebo (matching) ▪ 145/1,919 (7.6); 3.8 ◦ Difference between groups, % AR (95% CI)

Study citation and study design	Outcomes
	▪ −2.3 (−3.9 to −0.8) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.66 (0.51 to 0.86) • HF ◦ Dapagliflozin (10 mg) ▪ 9/235 (3.8); 3.4 ◦ Placebo (matching) ▪ 16/233 (6.9); 3.4 ◦ Difference between groups, % AR (95% CI) ▪ −3.0 (−7.1 to 1.0) ◦ Difference between groups, HR (95% CI), NS ▪ 0.53 (0.23 to 1.21) • *P* for interaction (by HF status), NS ◦ 0.46
Persson, 2021[30] RCT	Patients with CKD (with or without T2D), ESKD as a component of the composite primary outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by glycemic status, n/N pts (%); participants with event per 100 pt-yrs: • Normoglycemia ◦ Dapagliflozin (10 mg) ▪ 19/368 (5.2); 2.8 ◦ Placebo (matching) ▪ 32/370 (8.6); 4.7 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.54 (0.30 to 0.95) ◦ Difference between groups, % AR (95% CI) ▪ 3.5 (−0.2 to 7.1) • Pre-diabetes ◦ Dapagliflozin (10 mg) ▪ 13/329 (4.0); 2.0 ◦ Placebo (matching) ▪ 20/331 (6.0); 3.1 ◦ Difference between groups, HR (95% CI), NS ▪ 0.57 (0.28 to 1.15) ◦ Difference between groups, % AR (95% CI) ▪ 2.1 (−1.2 to 5.4) • T2D ◦ Dapagliflozin (10 mg) ▪ 77/1455 (5.3); 2.6 ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 109/1451 (7.5); 3.7 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.69 (0.51 to 0.92) ◦ Difference between groups, % AR (95% CI) ▪ 2.2 (0.4 to 4.0) • *P* for interaction (by T2D status), HR, NS ◦ 0.72 • *P* for interaction (by T2D status), AR, NS ◦ 0.81
Heerspink 2020[34] RCT	Patients with CKD (with or without T2D), ESKD as a component of the composite primary outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes), n/N pts (%); events per 100 pt-yrs: • Occurrence of ESKD ◦ Dapagliflozin (10 mg) ▪ 109/2152 (5.1); 2.5 ◦ Placebo (matching) ▪ 161/2152 (7.5); 3.8 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.64 (0.50 to 0.82) ▪ P = NR Patients with CKD (with or without T2D), sub-components of the ESKD component of the primary composite outcome (eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by patient renal characteristics, n/N pts (%); events per 100 pt-yrs: • eGFR of < 15 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ 84/2152 (3.9); 1.9 ◦ Placebo (matching) ▪ 120/2152 (5.6); 2.8 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.67 (0.51 to 0.88) ▪ P = NR • Long-term dialysis ◦ Dapagliflozin (10 mg) ▪ 68/2152 (3.2); 1.5 ◦ Placebo (matching) ▪ 99/2152 (4.6); 2.2 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.66 (0.48 to 0.90) ▪ P = NR • Kidney transplant ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 3/2152 (0.1); 0.1 ◦ Placebo (matching) ▪ 8/2152 (0.4); 0.2 ◦ Difference between groups, HR (95% CI) ▪ NR ▪ P = NR
Composite and Other Measures of Kidney Function	
Chertow 2021[24] RCT	Patients with CKD (with or without T2D), occurrence of the primary composite outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by stage of CKD by stage of CKD, n/N pts (%); events per 100 pt-yrs • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 59/293 (20.1); 11.1 ◦ Placebo (matching) ▪ 87/331 (26.3); 14.9 ◦ Difference between groups, HR (95% CI), NS ▪ 0.73 (0.53 to 1.02) ◦ Difference between groups, AR (95% CI), NS ▪ 6.1 (−0.5 to 12.7) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 138/1859 (7.4); 3.7 ◦ Placebo (matching) ▪ 225/1821 (12.4); 6.2 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.58 (0.47 to 0.71) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ 4.9 (3.0 to 6.9) • *P* for interaction (by stage of CKD), HR, NS ◦ 0.22 • *P* for interaction (by stage of CKD), AR, NS ◦ 0.72 Patients with CKD (with or without T2D), occurrence of the secondary composite outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes) by stage of CKD, n/N pts (%); events per 100 pt-yrs • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 49/293 (16.7); 9.2 ◦ Placebo (matching) ▪ 73/331 (22.1); 12.5 ◦ Difference between groups, HR (95% CI), NS

Study citation and study design	Outcomes
	▪ 0.71 (0.49 to 1.02) ◦ Difference between groups, AR (95% CI), NS ▪ 5.3 (−0.9 to 11.5) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 93/1859 (5.0); 2.5 ◦ Placebo (matching) ▪ 170/1821 (9.3); 4.7 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.51 (0.40 to 0.66) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ 4.3 (2.7 to 6.0) • *P* for interaction (by stage of CKD), HR, NS ◦ 0.13 • *P* for interaction (by stage of CKD), AR, NS ◦ 0.75
Heerspink 2021a[25] RCT	Patients with CKD (with or without T2D), abrupt decline in kidney function (i.e., doubling of serum creatinine), n/N pts (%); events per 100 pt-yrs (95% CI) • Dapagliflozin (10 mg) ◦ 63/2152 (2.9); 1.4 (1.1 to 1.7) • Placebo (matching) ◦ 91/2152 (4.2); 2.0 (1.6 to 2.5) • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.68 (0.49 to 0.94) ◦ P = 0.02 • Difference between groups, incidence rate (95% CI), NS ◦ 0.64 (0.09 to 1.20) ◦ P = NR • Difference between groups, sub-distribution HR (95% CI) (accounts for competing risk of death), favours dapagliflozin ◦ 0.69 (0.50 to 0.95) ◦ P = 0.02 **Patients with CKD (with or without T2D), abrupt decline in kidney function (i.e., doubling of serum creatinine) by patient characteristics, events per 100 pt-yrs** • Age ≤ 65yr ◦ Dapagliflozin (10 mg) ▪ 1.3 ◦ Placebo (matching) ▪ 1.7 ◦ Difference between groups HR (95% CI), NS

Study citation and study design	Outcomes
	▪ 0.77 (0.49 to 1.21) • Age > 65yr ◦ Dapagliflozin (10 mg) ▪ 1.5 ◦ Placebo (matching) ▪ 2.4 ◦ Difference between groups HR (95% CI), favours dapagliflozin ▪ 0.61 (0.39 to 0.98) ◦ *P*-value for interaction (by age) ▪ 0.45 • Male sex ◦ Dapagliflozin (10 mg) ▪ 1.4 ◦ Placebo (matching) ▪ 1.6 ◦ Difference between groups HR (95% CI), NS ▪ 0.89 (0.59 to 1.33) • Female sex ◦ Dapagliflozin (10 mg) ▪ 1.3 ◦ Placebo (matching) ▪ 2.8 ◦ Difference between groups HR (95% CI), favours dapagliflozin ▪ 0.46 (0.27 to 0.79) ◦ *P*-value for interaction (by sex) ▪ 0.05 • T2D ◦ Dapagliflozin (10 mg) ▪ 1.5 ◦ Placebo (matching) ▪ 2.2 ◦ Difference between groups HR (95% CI), favours dapagliflozin ▪ 0.66 (0.46 to 0.96) • No T2D ◦ Dapagliflozin (10 mg) ▪ 1.1 ◦ Placebo (matching) ▪ 1.5 ◦ Difference between groups HR (95% CI), favours dapagliflozin

Study citation and study design	Outcomes
	▪ 0.75 (0.49 to 0.94) ◦ *P*-value for interaction (by T2D status) ▪ 0.77 • eGFR < 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ 1.4 ◦ Placebo (matching) ▪ 2.3 ◦ Difference between groups HR (95% CI), favours dapagliflozin ▪ 0.62 (0.41 to 0.94) • eGFR ≥ 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ 1.3 ◦ Placebo (matching) ▪ 1.7 ◦ Difference between groups HR (95% CI), NS ▪ 0.80 (0.47 to 1.34) ◦ *P*-value for interaction (by eGFR status) ▪ 0.49 • UACR ≤ 1,000 mg/g ◦ Dapagliflozin (10 mg) ▪ 1.2 ◦ Placebo (matching) ▪ 1.8 ◦ Difference between groups HR (95% CI), NS ▪ 0.67 (0.41 to 1.07) • UACR > 1,000 mg/g ◦ Dapagliflozin (10 mg) ▪ 1.6 ◦ Placebo (matching) ▪ 2.2 ◦ Difference between groups HR (95% CI), NS ▪ 0.70 (0.45 to 1.08) ◦ *P*-value for interaction (by UACR status) ▪ 0.86 • Diuretic use ◦ Dapagliflozin (10 mg) ▪ 1.9 ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 2.6 ◦ Difference between groups HR (95% CI), NS ▪ 0.73 (0.48 to 1.11) • No diuretic use ◦ Dapagliflozin (10 mg) ▪ 1.0 ◦ Placebo (matching) ▪ 1.5 ◦ Difference between groups HR (95% CI), NS ▪ 0.63 (0.38 to 1.04) ◦ *P*-value for interaction (by diuretic use status) ▪ 0.66 • HF ◦ Dapagliflozin (10 mg) ▪ 3.3 ◦ Placebo (matching) ▪ 4.3 ◦ Difference between groups HR (95% CI), NS ▪ 0.77 (0.41 to 1.47) • No HF ◦ Dapagliflozin (10 mg) ▪ 1.1 ◦ Placebo (matching) ▪ 1.7 ◦ Difference between groups HR (95% CI), favours dapagliflozin ▪ 0.65 (0.45 to 0.95) ◦ *P*-value for interaction (by HF status) ▪ 0.70 Patients with CKD (with or without T2D), abrupt decline in kidney function by patient characteristics/ outcomes, n/N pts (%) • Underlying disease ◦ Dapagliflozin (10 mg) ▪ 13/63 (20.6) ◦ Placebo (matching) ▪ 25/91 (27.4) ◦ Difference between groups ▪ NR • Dialysis required ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 23/63 (36.5) ◦ Placebo (matching) ▪ 36/91 (39.6) ◦ Difference between groups ▪ NR • Maintenance dialysis required post-event ◦ Dapagliflozin (10 mg) ▪ 13/63 (20.6) ◦ Placebo (matching) ▪ 19/91 (20.9) ◦ Difference between groups ▪ NR • Death post-event ◦ Dapagliflozin (10 mg) ▪ 16/63 (25.9) ◦ Placebo (matching) ▪ 27/91 (29.7) ◦ Difference between groups ▪ NR
Jhund 2021[36] RCT	**Patients with HF and reduced ejection fraction (with or without T2D) and CKD, renal composite outcome (i.e., decline ≥ 50% in eGFR, ESKD, death from renal cause), n/N pts (%); rate* (95% CI)** • Dapagliflozin (10 mg) ◦ 18/962 (1.9); 1.4 (0.9 to 2.2) • Placebo (matching) ◦ 19/964 (2.0); 1.5 (0.9 to 2.3) • Difference between groups, HR (95% CI), NS ◦ 0.95 (0.50 to 1.82) **'rate' is not defined in the document's Table 4[36] (p. 304) where the data are reported*
McMurray, 2021a[28] RCT	Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by CV disease status, n/N pts (%); participants with event per 100 pt-yrs • No CV disease ◦ Dapagliflozin (10 mg) ▪ 106/1339 (7.9); 4.0 ◦ Placebo (matching) ▪ 175/1355 (12.9); 6.7 ◦ Difference between groups, % AR (95% CI) ▪ −5.0 (−7.3 to −2.7) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.61 (0.48 to 0.78)

Study citation and study design	Outcomes
	• CV disease ◦ Dapagliflozin (10 mg) ▪ 91/813 (11.2); 5.5 ◦ Placebo (matching) ▪ 137/797 (17.2); 8.7 ◦ Difference between groups, % AR (95% CI) ▪ −6.0 (−9.4 to −2.6) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.61 (0.47 to 0.79) • *P* for interaction (by CV disease status), NS ◦ 0.90 Patients with CKD (with or without T2D), composite secondary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes) by CV disease status, n/N pts (%); participants with event per 100 pt-yrs • No CV disease ◦ Dapagliflozin (10 mg) ▪ 93/1339 (6.9); 3.6 ◦ Placebo (matching) ▪ 154/1355 (11.4); 5.9 ◦ Difference between groups, % AR (95% CI) ▪ −4.4 (−6.6 to −2.2) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.61 (0.47 to 0.79) • CV disease ◦ Dapagliflozin (10 mg) ▪ 49/813 (6.0); 2.9 ◦ Placebo (matching) ▪ 89/797 (11.2); 5.6 ◦ Difference between groups, % AR (95% CI) ▪ −5.1 (−7.9 to −2.4) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.49 (0.34 to 0.69) • *P* for interaction, NS ◦ 0.29
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by HF history, n/N pts (%); participants with event per 100 pt-yrs • HF ◦ Dapagliflozin (10 mg) ▪ 166/1,914 (8.7); 4.4 ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 261/1,919 (13.6); 7.0 ◦ Difference between groups, % AR (95% CI) ▪ −5.0 (−7.3 to −2.7) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.61 (0.48 to 0.78) • No HF ◦ Dapagliflozin (10 mg) ▪ 31/235 (13.2); 6.5 ◦ Placebo (matching) ▪ 51/233 (21.9); 11.0 ◦ Difference between groups, % AR (95% CI) ▪ −8.7 (−15.5 to −1.8) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.58 (0.37 to 0.91) • *P* for interaction (by HF status), NS ◦ 0.59 Patients with CKD (with or without T2D), composite secondary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes) by HF history, n/N pts (%); participants with event per 100 pt-yrs • HF 1.1. Dapagliflozin (10 mg) ▪ 129/1,914 (6.7); 3.4 1.2. Placebo (matching) ▪ 216/1,916 (11.3); 5.8 1.3. Difference between groups, % AR (95% CI) ▪ −4.5 (−6.3 to −2.7) 1.4. Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.57 (0.46 to 0.71) • No HF ◦ Dapagliflozin (10 mg) ▪ 13/235 (5.5); 2.7 ◦ Placebo (matching) ▪ 27/233 (11.6); 5.8 ◦ Difference between groups, % AR (95% CI) ▪ −6.1 (−11.1 to −1.0) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.45 (0.23 to 0.87) • *P* for interaction (by HF status), NS ◦ 0.36

Study citation and study design	Outcomes
Persson, 2021[30] RCT	Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes) by glycemic status, n/N pts (%); participants with event per 100 pt-yrs • Normoglycemia ◦ Dapagliflozin (10 mg) ▪ 28/368 (7.6); 4.1 ◦ Placebo (matching) ▪ 41/370 (11.1); 6.1 ◦ Difference between groups, HR (95% CI), NS ▪ 0.62 (0.39 to 1.01) ◦ Difference between groups, AR (95% CI), NS ▪ 3.5 (−0.7 to 7.7) • Pre-diabetes ◦ Dapagliflozin (10 mg) ▪ 17/329 (5.2); 2.6 ◦ Placebo (matching) ▪ 42/331 (12.7); 6.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.37 (0.21 to 0.66) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ 7.5 (3.2 to 11.8) • T2D ◦ Dapagliflozin (10 mg) ▪ 152/1455 (10.4); 5.2 ◦ Placebo (matching) ▪ 229/1451 (15.8); 8.0 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.64 (0.52 to 0.79) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ 5.3 (2.9 to 7.8) • *P*-value for interaction (by glycemic status), HR, NS ◦ 0.19 • *P*-value for interaction (by glycemic status), AR, NS ◦ 0.42 Patients with CKD (with or without T2D), primary outcome effectiveness as a function of baseline A1C (presented graphically only) • Difference between groups ◦ Reported only as "no difference between randomized groups"[30] (p. 1895)

Study citation and study design	Outcomes
Wheeler 2021a[31] RCT	Patients with CKD (with or without T2D) and FSGS, composite primary outcome (i.e., eGFR decline ≥ 50%, decline in eGFR, onset of ESKD or death from cardiovascular/renal causes), n/N pts (%);events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 4/45 (8.9); 4.3 • Placebo (matching) ◦ 7/59 (11.9); 5.8 • Difference between groups, HR (95% CI), NS ◦ 0.62 (0.17 to 2.17) Patients with CKD (with or without T2D) and FSGS, composite secondary, kidney disease-specific outcome (excluding death from cardiovascular causes), n/N pts (%); events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 4/45 (8.9); 4.3 • Placebo (matching) ◦ 6/59 (10.2); 5.0 • Difference between groups, HR (95% CI), NS ◦ 0.67 (0.19 to 2.44) Patients with CKD (with or without T2D) and FSGS, composite outcome analyzed post hoc (i.e., eGFR decline ≥ 40%, decline in eGFR, onset of ESKD or death from cardiovascular/renal causes), n/N pts (%); events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 6/45 (13.3); 6.6 • Placebo (matching) ◦ 12/59 (20.3); 10.4 • Difference between groups, HR (95% CI), NS ◦ 0.60 (0.22 to 1.65)
Wheeler 2021b[32] RCT	Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, onset of ESKD or death from cardiovascular/renal causes) by T2D status, n/N pts (%); participants with event per 100 pt-yrs • T2D ◦ Dapagliflozin (10 mg) ▪ 152/1455 (10.4); 5.2 ◦ Placebo (matching) ▪ 229/1451 (15.8); 8.0 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.64 (0.52 to 0.79) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −5.3 (−7.8 to −2.9) • No T2D ◦ Dapagliflozin (10 mg) ▪ 45/697 (6.5); 3.4

Study citation and study design	Outcomes
	◦ Placebo (matching) ▪ 83/701 (11.8); 6.3 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.50 (0.35 to 0.72) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ −5.4 (−8.4 to −2.4) • *P*-value for interaction (by T2D status), HR, NS ◦ 0.24 • *P*-value for interaction (by T2D status), AR, NS ◦ 0.98 Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, onset of ESKD or death from cardiovascular/renal causes) by etiology of CKD, n/N pts (%); participants with event per 100 pt-yrs • Diabetic nephropathy ◦ Dapagliflozin (10 mg) ▪ 139/1271 (10.9); 5.4 ◦ Placebo (matching) ▪ 207/1239 (16.7); 8.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.63 (0.51 to 0.78) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −5.8 (−8.5 to −3.1) • Ischemic or hypertensive ◦ Dapagliflozin (10 mg) ▪ 24/324 (7.4); 3.8 ◦ Placebo (matching) ▪ 35/363 (9.6); 4.9 ◦ Difference between groups, HR (95% CI), NS ▪ 0.75 (0.44 to 1.26) ◦ Difference between groups, AR (95% CI), NS ▪ −2.2 (−6.4 to 1.9) • Glomerulonephritis ◦ Dapagliflozin (10 mg) ▪ 22/343 (6.4); 3.4 ◦ Placebo (matching) ▪ 49/352 (13.9); 7.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.43 (0.26 to 0.71) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −7.5 (−12.0 to −3.1)

Study citation and study design	Outcomes
	• Other or unknown ◦ Dapagliflozin (10 mg) ▪ 12/214 (5.6); 2.9 ◦ Placebo (matching) ▪ 21/198 (10.6); 5.5 ◦ Difference between groups, HR (95% CI), NS ▪ 0.58 (0.29 to 1.19) ◦ Difference between groups, % AR (95% CI), NS ▪ −5.0 (−10.3 to 0.3) • *P*-value for interaction, HR, NS ◦ 0.53 • *P*-value for interaction, AR, NS ◦ 0.37 Patients with CKD (with or without T2D), composite secondary, kidney disease-specific outcome (i.e., similar to primary but excludes death from cardiovascular/renal causes) by T2D status, n/N pts (%); participants with event per 100 pt-yrs • T2D ◦ Dapagliflozin (10 mg) ▪ 103/1455 (7.1); 3.5 ◦ Placebo (matching) ▪ 173/1451 (11.9); 6.0 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.57 (0.45 to 0.73) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −4.8 (−7.0 to −2.7) • No T2D ◦ Dapagliflozin (10 mg) ▪ 36/697 (4.3); 2.9 ◦ Placebo (matching) ▪ 70/701 (10.0); 5.3 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.51 (0.34 to 0.75) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ −4.4 (−7.2 to −1.6) • *P*-value for interaction (by T2D status), HR, NS ◦ 0.57 • *P*-value for interaction (by T2D status), AR, NS ◦ 0.80 Patients with CKD (with or without T2D), composite secondary, kidney disease-specific outcome (i.e., similar to primary but excludes death from cardiovascular/renal causes) by etiology of CKD, n/N pts (%);

Study citation and study design	Outcomes
	participants with event per 100 pt-yrs • Diabetic nephropathy ◦ Dapagliflozin (10 mg) ▪ 93/1271 (7.3); 3.6 ◦ Placebo (matching) ▪ 157/1239 (12.7); 6.4 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.55 (0.43 to 0.71) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −5.4 (−7.7 to −3.0) • Ischemic or hypertensive ◦ Dapagliflozin (10 mg) ▪ 18/324 (5.6); 2.8 ◦ Placebo (matching) ▪ 26/363 (7.2); 3.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.74 (0.40 to 1.36) ◦ Difference between groups, AR (95% CI), NS ▪ −1.6 (−5.2 to 2.0*) • Glomerulonephritis ◦ Dapagliflozin (10 mg) ▪ 21/343 (6.1); 3.3 ◦ Placebo (matching) ▪ 46/352 (13.1); 7.0 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.43 (0.26 to 0.72) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −6.9 (−11.3 to −2.6) • Other or unknown ◦ Dapagliflozin (10 mg) ▪ 10/214 (4.7); 2.5 ◦ Placebo (matching) ▪ 14/198 (7.1); 3.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.81 (0.35 to 1.83) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −2.4 (−7.0 to −2.2) • *P*-value for interaction, HR, NS ◦ 0.67

Study citation and study design	Outcomes
	• *P*-value for interaction, AR, NS ◦ 0.16 *reported as "-2.0" but forest plot graphic presentation indicates the value as 2.0
Wheeler 2021c[33] RCT	Patients with CKD (with or without T2D) and IgA nephropathy, composite primary outcome (i.e., eGFR decline ≥ 50%, onset of ESKD or death from cardiovascular/renal causes), n/N pts (%); events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 6/137 (4.4); 2.5 • Placebo (matching) ◦ 20/133 (15.0); 8.8 • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.29 (0.12 to 0.73) ◦ P = 0.005 Patients with CKD (with or without T2D) and IgA nephropathy, composite secondary outcome (i.e., similar to the primary outcome but excluding cardiovascular death), n/N pts (%); events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 5/137 (3.6); 2.1 • Placebo (matching) ◦ 20/133 (15.0); 8.8 • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.24 (0.09 to 0.65) ◦ P = 0.002 Patients with CKD (with or without T2D) and IgA nephropathy, component analysis of the composite secondary outcome, n/N pts (%); events per 100 pt-yrs • Composite of ESKD (i.e., sustained eGFR < 15%, chronic dialysis, renal transplant) ◦ Dapagliflozin (10 mg) ▪ 5/137 (3.6); 2.1 ◦ Placebo (matching) ▪ 16/133 (12.0); 6.9 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.30 (0.11 to 0.83) ▪ P = 0.014 • Composite of chronic dialysis, renal transplant and renal death ◦ Dapagliflozin (10 mg) ▪ 2/137 (1.5); 0.8 ◦ Placebo (matching) ▪ 10/133 (7.5); 4.0 ◦ Difference between groups, HR (95% CI), NS ▪ 0.23 (0.05 to 1.04) ▪ P = NC

Study citation and study design	Outcomes
Heerspink 2020[34] RCT	Patients with CKD (with or without T2D), composite primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes), n/N pts (%); events per 100 pt-yrs • Dapagliflozin (10 mg) ◦ 197/2152 (9.2); 4.6 • Placebo (matching) ◦ 312/2152 (14.5); 7.5 • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.61 (0.51 to 0.72) ◦ P < 0.001 **Patients with CKD (with or without T2D), composite secondary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes), n/N pts (%); events per 100 pt-yrs** • Dapagliflozin (10 mg) ◦ 142/2152 (6.6); 3.3 • Placebo (matching) ◦ 243/2152 (11.3); 5.8 • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.56 (0.45 to 0.68) ◦ P < 0.001

AR = absolute risk; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; d = day(s); dL = deciletre; Empa10 = empagliflozin 10 mg; Empa25 = empagliflozin 25 mg; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis; g = gram(s); h = hour(s); A1C = glycated hemoglobin; HF = heart failure; HR = hazard ratio; IgA = immunoglobulin A; m2 = metres squared; mg = milligram; mGFR = measured glomerular filtration rate; min = minute(s); mL = millilitre; N/n = number; NC = not calculable; NR = not reported; NRS = non-randomized study; NS = not significant; OR = odds ratio; P = probability; P-value = P value; pt/pts = patient(s); RCT = randomized controlled trial; SGLT2i = sodium/glucose co-transporter-2 inhibitor; SE = standard error; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; vs. = versus; wk = week(s); yr = year(s).

Table 7: Summary of Findings — Cardiovascular Outcomes

Study citation and study design	Outcomes
AF	
Zheng, 2021[22] SR and MA (1 RCT eligible for this review: DAPA-CKD)	Patients with CKD (with or without T2D), OR (95% CI) • Risk of AF, dapagliflozin (10 mg) vs. matching placebo ◦ 0.47 (0.2 to 1.09) • Difference between groups ◦ NS
Blood Pressure	
Pollock 2019[38] RCT	Patients with CKD and T2D, change in mean SBP from baseline to 24 wk (secondary outcome), mm Hg (95% CI) • Dapagliflozin (10 mg) vs. placebo ◦ −2.8 (−6.4 to 0.80), NS ◦ P = 0.122

Study citation and study design	Outcomes
Fioretto 2018[39] RCT	Patients with CKD and T2D, change in adjusted mean SBP from baseline to 24 wk (secondary outcome), mm Hg (95% CI) • Dapagliflozin (10 mg) vs. placebo ◦ −3.1 (−6.30 to 0.0), favours dapagliflozin ◦ P < 0.05
Fioretto 2016[35] RCT	Patients with CKD and T2D, change in adjusted mean SBP from baseline to 104 wk (secondary outcome), mm Hg (95% CI) • Dapagliflozin (10 mg) ◦ −7.6 (−13.3 to −1.9) • Dapagliflozin (5 mg) ◦ 0.1 (−6.6 to 6.3) • Placebo ◦ 0.6 (−5.6 to 6.9)
Cholesterol	
Pollock 2019[38] RCT	Patients with CKD and T2D, change in cholesterol from baseline to 24 wk (pre-specified exploratory outcome), adjusted mean % mmol/L (95% CI) • LDL ◦ Dapagliflozin (10 mg), n = 118 pts ▪ 4.8 (−4.7 to 15.1) ◦ Placebo, n = 123 pts ▪ −0.40 (−9.3 to 9.5) ◦ Difference in mean change between groups, NS ▪ 5.1 (−3.4 to 14.4) ▪ P = 0.243 • HDL ◦ Dapagliflozin (10 mg), n = 131 pts ▪ 4.0 (−0.5 to 8.6) ◦ Placebo, n = 135 pts ▪ −0.40 (−4.7 to 4.0) ◦ Difference in mean change between groups, favours dapagliflozin ▪ 4.41 (0.5 to 8.5) ▪ P = 0.029
Composite and Other Measures of Cardiovascular Function	
Chertow 2021[24] RCT	Patients with CKD (with or without T2D), composite secondary outcomes by stage of CKD, n/N pts (%); events per 100 pt-yrs • Hospitalization for HF or death from cardiovascular causes ◦ Stage 4 ▪ Dapagliflozin (10 mg): 18/293 (6.14); 2.9 ▪ Placebo (matching): 24/331 (7.25); 3.6

Study citation and study design	Outcomes
	▪ Difference between groups, HR (95% CI), NS: 0.83 (0.45 to 1.53) ▪ Difference between groups, AR (95% CI), NS: 1.1 (−2.8 to 5.0) ◦ Stage 2 or 3 ▪ Dapagliflozin (10 mg): 82/1859 (4.41); 2.0 ▪ Placebo (matching): 114/1821 (6.26); 2.9 ▪ Difference between groups, HR (95% CI), favours dapagliflozin: 0.69 (0.52 to 0.92) ▪ Difference between groups, AR (95% CI), favours dapagliflozin: 1.8 (0.4 to 3.3) ◦ *P* for interaction, HR, NS ▪ 0.63 ◦ *P* for interaction, AR, NS ▪ 0.73
Jhund 2021[36] RCT	Patients with HF and reduced ejection fraction (with or without T2D) and CKD, n/N (%) • Composite of worsening/hospitalization for HF or cardiovascular death, n/N pts (%); rate per 100 pt-yrs (95% CI) ◦ Dapagliflozin (10 mg) ▪ 191/962 (26.4); 14.5 (12.6 to 16.7) ◦ Placebo (matching) ▪ 254/964 (26.4); 20.0 (17.7 to 22.6) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.72 (0.59 to 0.86)
McMurray, 2021a[29] RCT	Patients with CKD (with or without T2D), secondary outcomes by CV disease status, n/N pts (%); participants with event per 100 pt-yrs Composite of hospitalization for HF or death from cardiovascular causes • No CV disease ◦ Dapagliflozin (10 mg) ▪ 24/1339 (1.8); 0.8 ◦ Placebo (matching) ▪ 36/1355 (2.7); 1.3 ◦ Difference between groups, % AR (95% CI) ▪ −0.9 (−2.0 to 0.2) ◦ Difference between groups, HR (95% CI), NS ▪ 0.67 (0.40 to 1.13) • CV disease ◦ Dapagliflozin (10 mg) ▪ 76/813 (9.3); 4.3 ◦ Placebo (matching) ▪ 102/797 (12.8); 6.1 ◦ Difference between groups, % AR (95% CI) ▪ −3.4 (−6.5 to −0.4)

Study citation and study design	Outcomes
	◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.52 to 0.94) • *P* for interaction, NS ◦ 0.88 Patients with CKD (with or without T2D), pre-specified exploratory cardiovascular outcomes by CV disease status, n/N pts (%); participants with event per 100 pt-yrs MI, stroke or death from CV causes • No CV disease ◦ Dapagliflozin (10 mg) ▪ 41/1339 (3.1); 1.4 ◦ Placebo (matching) ▪ 50/1355 (3.7); 1.7 ◦ Difference between groups, % AR (95% CI) ▪ −0.6 (−2.0 to 0.7) ◦ Difference between groups, HR (95% CI), NS ▪ 0.83 (0.55 to 1.25) • CV disease ◦ Dapagliflozin (10 mg) ▪ 91/813 (11.2); 5.2 ◦ Placebo (matching) ▪ 93/797 (11.7); 5.5 ◦ Difference between groups, % AR (95% CI) ▪ −0.5 (−3.6 to 2.6) ◦ Difference between groups, HR (95% CI), NS ▪ 0.94 (0.71 to 1.26) • *P* for interaction, NS ◦ 0.61 **Patients with CKD (with or without T2D), post-hoc exploratory cardiovascular/cardiorenal outcomes by CV disease status, n/N pts (%); participants with event per 100 pt-yrs** MI, stroke, hospitalization for HF or death from CV causes • No CV disease ◦ Dapagliflozin (10 mg) ▪ 44/1339 (3.3); 1.5 ◦ Placebo (matching) ▪ 60/1355 (4.4); 2.1 ◦ Difference between groups, % AR (95% CI) ▪ −1.1 (−2.6 to 0.3) ◦ Difference between groups, HR (95% CI), NS ▪ 0.73 (0.50 to 1.08) • CV disease

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 114/813 (14.0); 6.6 ◦ Placebo (matching) ▪ 135/797 (16.9); 8.3 ◦ Difference between groups, % AR (95% CI) ▪ −2.9 (−6.4 to 0.6) ◦ Difference between groups, HR (95% CI), NS ▪ 0.80 (0.62 to 1.03) • *P* for interaction, NS ◦ 0.72 MI, stroke, hospitalization for HF, ESKD or death from any cause • No CV disease ◦ Dapagliflozin (10 mg) ▪ 118/1339 (8.8); 4.5 ◦ Placebo (matching) ▪ 177/1355 (13.1); 6.8 ◦ Difference between groups, % AR (95% CI) ▪ −4.3 (−6.6 to −1.9) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.68 (0.54 to 0.85) • CV disease ◦ Dapagliflozin (10 mg) ▪ 156/813 (19.2); 9.6 ◦ Placebo (matching) ▪ 199/797 (25.0); 13.1 ◦ Difference between groups, % AR (95% CI) ▪ −5.8 (−9.8 to −1.7) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.72 (0.58 to 0.89) • *P* for interaction, NS ◦ 0.77
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), composite cardiovascular outcomes, n/N pts (%); participants with event per 100 pt-yrs Hospitalization for HF or death • No HF ◦ Dapagliflozin (10 mg) ▪ 64/1,914 (3.3); 1.6 ◦ Placebo (matching) ▪ 90/1,916 (4.7); 2.2

Study citation and study design	Outcomes
	◦ Difference between groups, % AR (95% CI) ▪ −1.4 (−2.6 to −0.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.51 to 0.97) • HF ◦ Dapagliflozin (10 mg) ▪ 36/235 (15.3); 7.1 ◦ Placebo (matching) ▪ 48/233 (20.6); 10.1 ◦ Difference between groups, % AR (95% CI) ▪ −5.3 (−12.2 to 1.7) ◦ Difference between groups, HR (95% CI), NS ▪ 0.68 (0.44 to 1.05) • *P* for interaction, NS ◦ 0.90
Wheeler 2021b[32] RCT	Patients with CKD (with or without T2D) by T2D status, n/N pts (%); participants with event per 100 pt-yrs Composite of CV death or hospitalization for HF (secondary outcome) • T2DM ◦ Dapagliflozin (10 mg) ▪ 85/1455 (5.84); 2.7 ◦ Placebo (matching) ▪ 119/1451 (8.20); 3.8 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.53 to 0.92) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −2.4 (−4.2 to −0.5) • No T2DM ◦ Dapagliflozin (10 mg) ▪ 15/697 (2.15); 1.1 ◦ Placebo (matching) ▪ 19/701 (2.71); 1.3 ◦ Difference between groups, HR (95% CI), NS ▪ 0.79 (0.40 to 1.55) ◦ Difference between groups, AR (95% CI), NS ▪ −0.6 (−2.2 to 1.1) • *P*-value for interaction, HR, NS ◦ 0.78 • *P*-value for interaction, AR, NS ◦ 0.11

Study citation and study design	Outcomes
Heerspink 2020[34] RCT	Patients with CKD (with or without T2D), secondary composite outcomes, n/N pts (%); events per 100 pt-yrs • Composite of hospitalization for HF or death from cardiovascular causes ◦ Dapagliflozin (10 mg) ▪ 100/2152 (4.6); 2.2 ◦ Placebo (matching) ▪ 138/2152 (6.4); 3.0 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.71 (0.55 to 0.92) ▪ P = 0.009
Pollock 2019[38] RCT	Patients with CKD and T2D, change in hematocrit ratio from baseline to 24wk (pre-specified exploratory outcome), adjusted mean % (95% CI) • Dapagliflozin (10 mg), n = 145 pts ◦ 0.03 (0.02 to 0.03) • Placebo, n = 148 pts ◦ −0.00 (−0.01 to 0.00) • Difference in mean change between groups ◦ 0.03 (0.02 to 0.04) ◦ P < 0.0001
Stroke	
Zheng, 2021[22] SR and MA (1 RCT eligible for this review: DAPA-CKD)	Patients with CKD (with or without T2D), risk of stroke, OR (95% CI) • Dapagliflozin (10 mg) vs. matching placebo ◦ 0.86 (0.51 to 1.47) • Difference between groups ◦ NS

AF = atrial fibrillation; AR = absolute risk difference; CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; ESKD = end-stage kidney disease; HF = heart failure; HR = hazard ratio; MA = meta-analysis; mg = milligram; MI = myocardial infarction; mm Hg = millimetres of mercury; mmol/L = millimole per litre; N/n = number; NS = not significant; OR = odds ratio; P = P value; pt/pts = patient(s); RCT = randomized controlled trial; SBP = systolic blood pressure; SR = systematic review; T2D = type 2 diabetes; vs. = versus; wk = week(s); yr/yrs = year(s).

Table 8: Summary of Findings by Outcome — Health Care Utilization

Study citation and study design	Outcomes
Hospitalization	
Jhund 2021[36] RCT	Patients with HF and reduced ejection fraction (with or without T2D) and CKD, n/N (%) • Hospitalization/urgent visit for HF, n/N pts (%); rate per 100 pt-yrs (95% CI) ◦ Dapagliflozin (10 mg) ▪ 120/962 (12.5); 9.1 (7.6 to 10.9) ◦ Placebo (matching) ▪ 173/964 (18.0); 13.7 (11.8 to 15.9) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.66 (0.52 to 0.83) • Total (recurrent) hospitalization for HF/cardiovascular death, n/N pts (%); rate per 100 pt-yrs (95% CI) ◦ Dapagliflozin (10 mg) ▪ 301/962 (31.2); 21.5 (19.2 to 24.1) ◦ Placebo (matching) ▪ 374/964 (38.8); 26.8 (19.2 to 24.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.79 (0.64 to 0.97)
McMurray, 2021a[29] RCT	Patients with CKD (with or without T2D), pre-specified exploratory cardiovascular outcomes by CV disease status, n/N pts (%); participants with event per 100 pt-yrs First HF hospitalization • No CV disease ◦ Dapagliflozin (10 mg) ▪ 4/1339 (0.3); 1.0 ◦ Placebo (matching) ▪ 13/1355 (1.0); 0.5 ◦ Difference between groups, % AR (95% CI) ▪ −0.7 (−1.3 to −0.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.31 (0.10 to 0.94) • CV disease ◦ Dapagliflozin (10 mg) ▪ 33/813 (4.1); 1.9 ◦ Placebo (matching) ▪ 58/797 (7.3); 3.5 ◦ Difference between groups, % AR (95% CI) ▪ −3.2 (−5.5 to −1.0) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.54 (0.35 to 0.82)

Study citation and study design	Outcomes
	• *P* for interaction (by CV disease status), NS ◦ 0.61
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), pre-specified exploratory outcome by HF status, n/N pts (%); participants with event per 100 pt-yrs First heart failure hospitalization • No HF ◦ Dapagliflozin (10 mg) ▪ 17/1,914 (0.9); 0.4 ◦ Placebo (matching) ▪ 42/1,916 (2.2); 1.0 ◦ Difference between groups, % AR (95% CI) ▪ −1.3 (−2.1 to −0.5) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.40 (0.23 to 0.70) • HF ◦ Dapagliflozin (10 mg) ▪ 20/235 (8.5); 3.9 ◦ Placebo (matching) ▪ 29/233 (12.4); 6.1 ◦ Difference between groups, % AR (95% CI) ▪ −3.9 (−9.5 to 1.6) ◦ Difference between groups, HR (95% CI), NS ▪ 0.62 (0.35 to 1.10) • *P* for interaction (by HF status), NS ◦ 0.28

AR = absolute risk; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NS = not significant; P = probability; pt/pts = patient(s); RCT = randomized controlled trial; T2D = type 2 diabetes; yr = year(s).

Table 9: Summary of Findings by Outcome — Mortality

Study citation and study design	Outcomes
	Mortality
Chertow 2021[24] RCT	Component analysis of the composite primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes), by stage of CKD, n/N pts (%); events per 100 pt-yrs Death from renal or CV causes • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 14/293 (4.8); 2.3 ◦ Placebo (matching) ▪ 18/331 (5.4); 2.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.89 (0.44 to 1.79) ◦ Difference between groups, AR (95% CI), NS ▪ 0.7 (−2.8 to 4.1) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 53/1859 (2.9); 1.3 ◦ Placebo (matching) ▪ 68/1821 (3.7); 1.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.76 (0.53 to 1.09) ◦ Difference between groups, AR (95% CI), NS ▪ 0.9 (−0.3 to 2.0) • *P* for interaction (by stage of CKD), HR, NS ◦ 0.74 • *P* for interaction (by stage of CKD), AR, NS Component analysis of the composite secondary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes) by stage of CKD, n/N pts (%); events per 100 pt-yrs Death from any cause • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 19/293 (6.5); 3.0 ◦ Placebo (matching) ▪ 31/331 (9.4); 4.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.68 (0.39 to 1.21) ◦ Difference between groups, AR (95% CI), NS ▪ 2.9 (−1.3 to 7.1) • Stage 2 or 3

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 82/1859 (4.4); 2.0 ◦ Placebo (matching) ▪ 115/1821 (6.3); 2.9 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.69 (0.52 to 0.92) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ 1.9 (0.4 to 3.4) • *P* for interaction (by stage of CKD), HR, NS ◦ 0.95 • *P* for interaction (by stage of CKD), AR, NS ◦ 0.67
Heerspink 2021c[27] RCT	Patients with CKD (with or without T2D), deaths by cause, n/N pts (%), events per 100 pt-yrs Death from any cause • Dapagliflozin ◦ 101/2152 (4.7), 2.2 • Placebo (matching) ◦ 146/2152 (6.8), 3.1 • Difference between groups, HR (95% CI), favours dapagliflozin ◦ 0.69 (0.53 to 0.88) ◦ P = 0.003 CV deaths by cause of death • All CV deaths ◦ Dapagliflozin (10 mg) ▪ 41/2152 (1.9), 0.9 ◦ Placebo (matching) ▪ 50/2152 (2.3), 1.1 ◦ Difference between groups, HR (95% CI), NS ▪ 0.82 (0.54 to 1.24) ▪ P = 0.338 • Sudden cardiac death ◦ Dapagliflozin (10 mg) ▪ 24/2152 (1.1), 0.5 ◦ Placebo (matching) ▪ 27/2152 (1.2), 0.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.89 (0.52 to 1.55) ▪ P = NR • HF

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 3/2152 (0.1), 0.1 ◦ Placebo (matching) ▪ 11/2152 (0.5), 0.2 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.27 (0.08 to 0.98) ▪ P = NR • Acute MI ◦ Dapagliflozin (10 mg) ▪ 6/2152 (0.3), 0.1 ◦ Placebo (matching) ▪ 5/2152 (0.2), 0.1 ◦ Difference between groups, HR (95% CI), NS ▪ 1.21 (0.37 to 3.96) ▪ P = NR • Stroke ◦ Dapagliflozin (10 mg) ▪ 5/2152 (0.2), 0.1 ◦ Placebo (matching) ▪ 5/2152 (0.2), 0.1 ◦ Difference between groups, HR (95% CI), NS ▪ 1.00 (0.29 to 3.47) ▪ P = NR Non-CV deaths by cause of death • All non-CV deaths ◦ Dapagliflozin (10 mg) ▪ 36/2152 (1.7), 0.8 ◦ Placebo (matching) ▪ 66/2152 (3.1), 1.4 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.54 (0.36 to 0.82) ▪ P = 0.003 • Infection ◦ Dapagliflozin (10 mg) ▪ 18/2152 (0.8), 0.4 ◦ Placebo (matching) ▪ 28/2152 (1.3), 0.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.64 (0.36 to 1.16)

Study citation and study design	Outcomes
	▪ P = NR • Malignancy ◦ Dapagliflozin (10 mg) ▪ 8/2152 (0.4), 0.2 ◦ Placebo (matching) ▪ 19/2152 (0.9), 0.4 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.42 (0.19 to 0.97) ▪ P = NR • Kidney failure ◦ Dapagliflozin (10 mg) ▪ 2/2152 (0.09), < 0.1 ◦ Placebo (matching) ▪ 6/2152 (0.3), 0.1 ◦ Difference between groups, HR (95% CI), NS ▪ 0.35 (0.07 to 1.73) ▪ P = NR Undetermined cause of death, n/N pts (%), events per 100 pt-yrs • All undetermined deaths ◦ Dapagliflozin (10 mg) ▪ 24/2152 (1.1), 0.5 ◦ Placebo (matching) ▪ 30/2152 (1.4), 0.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.80 (0.47 to 1.38) ▪ P = 0.426 **Patients with CKD (with or without T2D), all-cause mortality by patient characteristics, n/N pts (%), events per 100 pt-yrs** Age • ≤ 65yrs ◦ Dapagliflozin (10 mg) ▪ 44/1247 (3.5), 1.6 ◦ Placebo (matching) ▪ 63/1239 (5.1), 2.4 ◦ Difference between groups, HR (95% CI), NS ▪ 0.70 (0.48 to 1.04) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −1.6 (−3.2 to 0.0) • > 65yrs

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 57/905 (6.3), 2.8 ◦ Placebo (matching) ▪ 83/913 (9.1), 4.2 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.66 (0.47 to 0.93) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.8 (−5.2 to −0.3) • *P*-value for interaction (by age) (HR) ◦ 0.833 • *P*-value for interaction (by age) (ARD) ◦ 0.390 Sex • Male ◦ Dapagliflozin (10 mg) ▪ 70/1443 (4.9), 2.3 ◦ Placebo (matching) ▪ 101/1436 (7.0), 3.3 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.52 to 0.96) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.2 (−3.9 to −0.5) • Female ◦ Dapagliflozin (10 mg) ▪ 31/709 (4.4), 2.0 ◦ Placebo (matching) ▪ 45/716 (6.3), 2.9 ◦ Difference between groups, HR (95% CI), NS ▪ 0.66 (0.42 to 1.05) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −1.9 (−4.2 to 0.4) • *P*-value for interaction (by sex) (HR) ◦ 0.821 • *P*-value for interaction (by sex) (AR) ◦ 0.855 T2D status • T2D ◦ Dapagliflozin (10 mg) ▪ 84/1455 (5.8), 2.6

Study citation and study design	Outcomes
	◦ Placebo (matching) ▪ 113/1451 (7.8), 3.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.74 (0.56 to 0.98) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ −2.0 (−3.8 to −0.2) • No T2D ◦ Dapagliflozin (10 mg) ▪ 17/697 (2.4), 1.2 ◦ Placebo (matching) ▪ 33/701 (4.7), 2.3 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.52 (0.29 to 0.93) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.3 (−4.2 to −0.3) • *P*-value for interaction (by T2D status) (HR) ◦ 0.250 • *P*-value for interaction (by T2D status) (AR) ◦ 0.846 Region • Asia ◦ Dapagliflozin (10 mg) ▪ 16/692 (2.3), 1.2 ◦ Placebo (matching) ▪ 20/654 (3.1), 1.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.75 (0.39 to 1.46) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −0.7 (−2.5 to 1.0) • Europe ◦ Dapagliflozin (10 mg) ▪ 32/610 (5.2), 2.3 ◦ Placebo (matching) ▪ 46/623 (7.4), 3.2 ◦ Difference between groups, HR (95% CI), NS ▪ 0.71 (0.45 to 1.11) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −2.1 (−4.8 to 0.6) • North America

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 23/401 (5.7), 2.5 ◦ Placebo (matching) ▪ 35/412 (8.5), 3.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.65 (0.38 to 1.10) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −2.8 (−6.3 to 0.8) • Latin America ◦ Dapagliflozin (10 mg) ▪ 30/449 (6.7), 2.9 ◦ Placebo (matching) ▪ 45/463 (9.7), 4.2 ◦ Difference between groups, HR (95% CI), NS ▪ 0.67 (0.42 to 1.07) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −3.0 (−6.6 to 0.5) • *P*-value for interaction (by region) (HR) ◦ 0.988 • *P*-value for interaction (by region) (AR) ◦ 0.465 eGFR status • < 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ 67/1272 (5.3), 2.5 ◦ Placebo (matching) ▪ 94/1250 (7.5), 3.6 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.68 (0.50 to 0.93) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.3 (−4.2 to −0.3) • ≥ 45 mL/min/1.73 m^2 ◦ Dapagliflozin (10 mg) ▪ 34/880 (3.9), 1.7 ◦ Placebo (matching) ▪ 52/902 (5.8), 2.6 ◦ Difference between groups, HR (95% CI), NS ▪ 0.67 (0.43 to 1.03) ◦ Difference between groups, absolute risk (95% CI), NS

Study citation and study design	Outcomes
	▪ −1.9 (−3.9 to 0.1) • *P*-value for interaction (by eGFR status) (HR) ◦ 0.963 • *P*-value for interaction (by eGFR status) (AR) ◦ 0.801 UACR status • ≤ 1000mg/g ◦ Dapagliflozin (10 mg) ▪ 46/1104 (4.2), 1.9 ◦ Placebo (matching) ▪ 70/1121 (6.2), 2.7 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.68 (0.47 to 0.98) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.1 (−3.9 to −0.2) • > 1,000mg/g ◦ Dapagliflozin (10 mg) ▪ 55/1048 (5.2), 2.4 ◦ Placebo (matching) ▪ 76/1031 (7.4), 3.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.69 (0.49 to 0.98) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.1 (−4.2 to 0.0) • *P*-value for interaction (by UACR status) (HR) ◦ 0.915 • *P*-value for interaction (by UACR status) (AR) ◦ 0.974 Systolic blood pressure • ≤ 130 mm Hg ◦ Dapagliflozin (10 mg) ▪ 29/793 (3.4), 1.7 ◦ Placebo (matching) ▪ 42/749 (5.6), 2.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.65 (0.41 to 1.05) ◦ Difference between groups, absolute risk (95% CI), NS ▪ −2.0 (−4.1 to 0.2) • > 130 mm Hg

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 72/1359 (5.3), 2.4 ◦ Placebo (matching) ▪ 104/1403 (7.4), 3.4 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.52 to 0.95) ◦ Difference between groups, absolute risk (95% CI), favours dapagliflozin ▪ −2.1 (−3.9 to −0.3) • *P*-value for interaction (by SBP status) (HR) ◦ 0.825 • *P*-value for interaction (by SBP status) (AR) ◦ 0.907 **Patients with CKD (with or without T2D), deaths per serious AE, n/N pts (%), events per 100 pt-yrs** • Deaths among patients with serious infections ◦ Dapagliflozin (10 mg) ▪ 15/193 (7.8) ◦ Placebo (matching) ▪ 31/207 (15.0) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.53 (0.29 to 0.99) ▪ P = NR • Deaths among patients with serious malignancies ◦ Dapagliflozin (10 mg) ▪ 9/59 (15.3) ◦ Placebo (matching) ▪ 17/71 (23.9) ◦ Difference between groups, HR (95% CI), NS ▪ 0.69 (0.30 to 1.56) ▪ P = NR
Jhund 2021[36] RCT	**Patients with HF and reduced ejection fraction (with or without T2D) and CKD, n/N pts (%); rate per 100 pt-yrs (95% CI)** • Cardiovascular death ◦ Dapagliflozin (10 mg) ▪ 119/962 (12.4); 8.6 (7.2 to 10.3) ◦ Placebo (matching) ▪ 134/964 (13.9); 9.7 (8.2 to 11.5) ◦ Difference between groups, HR (95% CI), NS ▪ 0.88 (0.69 to 1.13) • All-cause death

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 143/962 (14.9); 10.3 (8.8 to 12.2) ◦ Placebo (matching) ▪ 168/964 (17.4); 12.2 (10.5 to 14.2) ◦ Difference between groups, HR (95% CI), NS ▪ 0.85 (0.68 to 1.07)
McMurray, 2021a[28] RCT	Patients with CKD (with or without T2D), component analysis of the composite primary outcome by CV disease status, n/N pts (%); participants with event per 100 pt-yrs Death from renal causes • No CV disease ◦ Dapagliflozin (10 mg) ▪ 1/1339 (0.1); 0.0 ◦ Placebo (matching) ▪ 2/1355 (0.1); 0.1 ◦ Difference between groups, % AR (95% CI) ▪ NR/NC ◦ Difference between groups, HR (95% CI) ▪ NR/NC • CV disease ◦ Dapagliflozin (10 mg) ▪ 1/813 (0.1); 0.1 ◦ Placebo (matching) ▪ 4/797 (0.5); 0.2 ◦ Difference between groups, % AR (95% CI) ▪ NR/NC ◦ Difference between groups, HR (95% CI) ▪ NR/NC Death from CV causes • No CV disease ◦ Dapagliflozin (10 mg) ▪ 20/1339 (1.5); 0.7 ◦ Placebo (matching) ▪ 24/1355 (1.8); 0.8 ◦ Difference between groups, % AR (95% CI) ▪ −0.3 (−1.2 to 0.6) ◦ Difference between groups, HR (95% CI), NS ▪ 0.85 (0.47 to 1.54) • CV disease ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 45/813 (5.5); 2.5 ◦ Placebo (matching) ▪ 56/797 (7.0); 3.2 ◦ Difference between groups, % AR (95% CI), NS ▪ −1.5 (−3.9 to 0.9) ◦ Difference between groups, HR (95% CI), NS ▪ 0.77 (0.52 to 1.14) • *P* for interaction (by CV disease), NS ◦ 0.80 Patients with CKD (with or without T2D), component analysis of secondary composite outcome by CV disease status, n/N pts (%); participants with event per 100 pt-yrs Death from any cause • No CV disease ◦ Dapagliflozin ▪ 33/1339 (2.5); 1.1 ◦ Placebo ▪ 53/1355 (3.9); 1.8 ◦ Difference between groups, % AR (95% CI) ▪ −1.4 (−2.8 to −0.1) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.63 (0.41 to 0.98) • CV disease ◦ Dapagliflozin ▪ 68/813 (8.4); 3.8 ◦ Placebo ▪ 93/797 (11.7); 5.4 ◦ Difference between groups, % AR (95% CI) ▪ −3.3 (−6.2 to −0.4) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.70 (0.51 to 0.95) ◦ *P* for interaction (by CV disease), NS ▪ 0.71
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D), component analysis of the composite primary outcome by history of HF status, n/N pts (%); participants with event per 100 pt-yrs Death from renal causes • No HF ◦ Dapagliflozin (10 mg) ▪ 2/1,914 (0.1); 0.0 ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 4/1,916 (0.2); 0.1 ◦ Difference between groups, % AR (95% CI) ▪ NR/NC ◦ Difference between groups, HR (95% CI) ▪ NR/NC • HF ◦ Dapagliflozin (10 mg) ▪ 0/235 (0.0); 0.0 ◦ Placebo (matching) ▪ 2/233 (0.9); 0.4 ◦ Difference between groups, % AR (95% CI) ▪ NR/NC ◦ Difference between groups, HR (95% CI) ▪ NR/NC Death from CV causes • No HF ◦ Dapagliflozin (10 mg) ▪ 47/1,914 (2.5); 1.1 ◦ Placebo (matching) ▪ 54/1,916 (2.8); 1.3 ◦ Difference between groups, % AR (95% CI) ▪ −0.4 (−1.4 to 0.7) ◦ Difference between groups, HR (95% CI), NS ▪ 0.87 (0.59 to 1.29) • HF ◦ Dapagliflozin (10 mg) ▪ 18/235 (7.7); 3.4 ◦ Placebo (matching) ▪ 26/233 (11.2); 5.1 ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −3.5 (−8.8 to 1.8) ◦ Difference between groups, HR (95% CI), NS ▪ 0.65 (0.36 to 1.20) • *P* for interaction (by HF status), NS ◦ 0.40 Patients with CKD (with or without T2D), component analysis of the composite secondary outcome by HF status, n/N pts (%); participants with event per 100 pt-yrs Death from any cause • No HF

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 77/1,914 (4.0); 1.9 ◦ Placebo (matching) ▪ 106/1,916 (5.5); 2.6 ◦ Difference between groups, % AR (95% CI) ▪ −1.5 (−2.9 to −0.2) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.73 (0.54 to 0.97) • HF ◦ Dapagliflozin (10 mg) ▪ 24/235 (10.2); 4.6 ◦ Placebo (matching) ▪ 40/233 (17.2); 7.9 ◦ Difference between groups, % AR (95% CI) ▪ −7.0 (−13.2 to −0.8) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.56 (0.34 to 0.93) • *P* for interaction (by HF status), NS ◦ 0.39
Wheeler 2021b[32] RCT	Patients with CKD (with or without T2D) by T2D status, n/N pts (%); participants with event per 100 pt-yrs All-cause mortality • T2D ◦ Dapagliflozin (10 mg) ▪ 84/1455 (5.8); 2.6 ◦ Placebo (matching) ▪ 113/1451 (7.8); 3.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.74 (0.56 to 0.98) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −2.0 (−3.8 to −0.2) • No T2D ◦ Dapagliflozin (10 mg) ▪ 17/697 (2.4); 1.2 ◦ Placebo (matching) ▪ 33/701 (4.7); 2.3 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.52 (0.29 to 0.93) ◦ Difference between groups, AR (95% CI), favours dapagliflozin ▪ −2.3 (−4.2 to −0.3)

Study citation and study design	Outcomes
	• *P*-value for interaction (by T2D status), HR, NS ◦ 0.25 • *P*-value for interaction (by T2D status), AR, NS ◦ 0.85 Patients with CKD (with or without T2D) by CKD diagnosis, n/N pts (%); participants with event per 100 pt-yrs All-cause mortality • Diabetic nephropathy ◦ Dapagliflozin (10 mg) ▪ 78/1271 (6.1); 2.7 ◦ Placebo (matching) ▪ 104/1239 (8.4); 3.8 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.72 (0.54 to 0.97) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −2.3 (−4.3 to −0.2) • Ischemic or hypertensive ◦ Dapagliflozin (10 mg) ▪ 14/324 (4.3); 2.0 ◦ Placebo (matching) ▪ 22/363 (6.1); 2.8 ◦ Difference between groups, HR (95% CI), NS ▪ 0.70 (0.36 to 1.37) ◦ Difference between groups, AR (95% CI), NS ▪ −1.7 (−5.0 to 1.6) • Glomerulonephritis ◦ Dapagliflozin (10 mg) ▪ 3/343 (0.87); 0.4 ◦ Placebo (matching) ▪ 11/352 (3.1); 1.5 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.31 (0.09 to 1.13) ◦ Difference between groups, % AR (95% CI), favours dapagliflozin ▪ −2.3 (−4.3 to −0.2) • Other or unknown ◦ Dapagliflozin (10 mg) ▪ 6/214 (2.8); 1.3 ◦ Placebo (matching) ▪ 9/198 (4.5); 2.2

Study citation and study design	Outcomes
	◦ Difference between groups, HR (95% CI), NS ▪ 0.57 (0.20 to 1.61) ◦ Difference between groups, % AR (95% CI), NS ▪ −1.7 (−5.4 to 1.9) • *P*-value for interaction, HR, NS ◦ 0.55 • *P*-value for interaction, AR, NS ◦ 0.99
Heerspink 2020[34] RCT	Patients with CKD (with or without T2D), component analysis of the primary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from cardiovascular/renal causes), n/N pts (%); events per 100 pt-yrs • Death from renal causes ◦ Dapagliflozin ▪ 2/2152 (< 0.1); 0.0 ◦ Placebo (matching) ▪ 6/2152 (0.3); 0.1 ◦ Difference between groups, HR (95% CI) ▪ NR ▪ P = NR • Death from CV causes ◦ Dapagliflozin ▪ 65/2152 (3.0); 1.4 ◦ Placebo (matching) ▪ 80/2152 (3.7); 1.7 ◦ Difference between groups, HR (95% CI), NS ▪ 0.81 (0.58 to 1.12) ▪ P = NR Patients with CKD (with or without T2D), component analysis of the secondary outcome (i.e., eGFR decline ≥ 50%, ESKD or death from renal causes), n/N pts (%); events per 100 pt-yrs • Death from any cause ◦ Dapagliflozin ▪ 101/2152 (4.7); 2.2 ◦ Placebo ▪ 146/2152 (6.8); 3.1 ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.69 (0.53 to 0.88) ▪ P = 0.004
Pollock 2019[38] RCT	Patients with CKD and T2D, deaths (reported as an AE), n/N (%) pts • Dapagliflozin ◦ 1/145 (1)

Study citation and study design	Outcomes
	• Placebo ◦ 0/148 (0) • Difference between groups ◦ NR Patients with CKD and T2D, deaths (reported as an AE), n/N (%) pts • Dapagliflozin (10 mg) ◦ 3 (5.4) • Dapagliflozin (5 mg) ◦ 1 (1.9) • Placebo ◦ 4 (7.0)
Fioretto 2016[35] RCT	Patients with CKD and T2D, deaths (reported as an AE), n/N (%) pts • Dapagliflozin (10 mg) ◦ 3 (5.4) • Dapagliflozin (5 mg) ◦ 1 (1.9) • Placebo ◦ 4 (7.0)

AE = adverse event; AR = absolute risk; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HR = hazard ratio; mg = milligram; MI = myocardial infarction; mm Hg = millimetres of mercury; N/n = number; NC = not calculable; NR = not reported; NS = not significant; P = probability; P-value = P value; pt/pts = patient(s); RCT = randomized controlled trial; SBP = systolic blood pressure; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; yr = year(s).

Table 10: Summary of Findings by Outcome — Safety

Study citation and study design	Outcomes
	AE
Chertow 2021[24] RCT	Patients with CKD (with or without T2D) by stage of CKD, n/N (%) Discontinuation of study medication • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 28/293 (9.6) ◦ Placebo (matching) ▪ 36/331 (10.9) ◦ Difference between groups, OR (95% CI), NS ▪ 0.87 (0.51 to 1.45) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 90/1856 (4.8) ◦ Placebo (matching) ▪ 87/1818 (4.8) ◦ Difference between groups, HR (95% CI), NS ▪ 1.01 (0.75 to 1.37) • *P* for interaction, OR, NS ◦ 0.61 Other AEs: Volume depletion symptoms • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 14/293 (4.8) ◦ Placebo (matching) ▪ 15/331 (4.5) ◦ Difference between groups, OR (95% CI), NS ▪ 1.06 (0.50 to 2.24) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 113/1856 (6.1) ◦ Placebo (matching) ▪ 75/1818 (4.1) ◦ Difference between groups, HR (95% CI), favours placebo ▪ 1.51 (1.12 to 2.04) ◦ *P* for interaction, OR, NS ▪ 0.39

Study citation and study design	Outcomes
	Renal-related • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 43/293 (14.7) ◦ Placebo (matching) ▪ 44/331 (13.3) ◦ Difference between groups, OR (95% CI), NS ▪ 1.12 (0.71 to 1.77) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 112/1856 (6.0) ◦ Placebo (matching) ▪ 144/1818 (7.9) ◦ Difference between groups, HR (95% CI), favours dapagliflozin ▪ 0.75 (0.58 to 0.96) • *P* for interaction, OR, NS ◦ 0.13 Fracture • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 11/293 (3.8) ◦ Placebo (matching) ▪ 15/331 (4.5) ◦ Difference between groups, OR (95% CI), NS ▪ 0.82 (0.36 to 1.81) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 74/1856 (4.0) ◦ Placebo (matching) ▪ 54/1818 (3.0) ◦ Difference between groups, HR (95% CI), NS ▪ 1.36 (0.95 to 1.95) • *P* for interaction, OR, NS ◦ 0.26 Amputations • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 3/293 (1.0) ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 4/331 (1.2) ◦ Difference between groups, OR (95% CI), NS ▪ 0.85 (0.17 to 3.87) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 32/1856 (1.7) ◦ Placebo (matching) ▪ 35/1818 (1.9) ◦ Difference between groups, HR (95% CI), NS ▪ 0.89 (0.55 to 1.45) • *P* for interaction, OR, NS ◦ 0.95 Diagnosed or probable diabetic ketoacidosis • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 0/293 (0.0) ◦ Placebo (matching) ▪ 1/331 (0.3) ◦ Difference between groups, OR (95% CI) ▪ N/A • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 0/1856 (0.0) ◦ Placebo (matching) ▪ 1/1818 (0.1) ◦ Difference between groups, HR (95% CI) ▪ N/A • *P* for interaction, OR ◦ N/A
Jhund, 2021[36] RCT	Patients with HF and reduced ejection fraction (with or without T2D) and CKD, n/N (%) • AEs causing discontinuation of treatment ◦ Dapagliflozin (10 mg) ▪ 121/960 (12.6) ◦ Placebo (matching) ▪ 130/962 (13.5) ◦ Difference between groups, HR (95% CI), NS ▪ P = 0.59 • Volume depletion ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 97/960 (10.1) ◦ Placebo (matching) ▪ 86/962 (8.9) ◦ Difference between groups, HR (95% CI), NS ▪ P = 0.39 • Renal events ◦ Dapagliflozin (10 mg) ▪ 97/960 (10.1) ◦ Placebo (matching) ▪ 115/962 (12.0) ◦ Difference between groups, HR (95% CI), NS ▪ P = 0.22 • Amputation ◦ Dapagliflozin (10 mg) ▪ 8/960 (0.8) ◦ Placebo (matching) ▪ 9/962 (0.9) ◦ Difference between groups, HR (95% CI), NS ▪ P = 1.00 • Major hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 3/960 (0.3) ◦ Placebo (matching) ▪ 0/962 (0.0) ◦ Difference between groups, HR (95% CI), NS ▪ P = 0.12 • Fracture ◦ Dapagliflozin (10 mg) ▪ 28/960 (2.9) ◦ Placebo (matching) ▪ 25/962 (2.6) ◦ Difference between groups, HR (95% CI), NS ▪ P = 0.68
McMurray, 2021a[28] RCT	Patients with CKD (with or without T2D) by CV disease status, n/N (%) Discontinuation of study medication • No CV disease ◦ Dapagliflozin (10 mg) ▪ 73/1337 (5.5) ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 70/1352 (5.2) • CV disease ◦ Dapagliflozin (10 mg) ▪ 45/812 (5.5) ◦ Placebo (matching) ▪ 53/797 (6.6) • *P* for interaction, NS ◦ 0.36 Volume depletion • No CV disease ◦ Dapagliflozin (10 mg) ▪ 75/1337 (5.6) ◦ Placebo (matching) ▪ 46/1352 (3.4) • CV disease ◦ Dapagliflozin (10 mg) ▪ 52/812 (6.4) ◦ Placebo (matching) ▪ 44/797 (5.5) • *P* for interaction, NS ◦ 0.20 Renal events • No CV disease ◦ Dapagliflozin (10 mg) ▪ 76/1337 (5.7) ◦ Placebo (matching) ▪ 99/1352 (7.3) • CV disease ◦ Dapagliflozin ▪ 79/812 (9.7) ◦ Placebo (matching) ▪ 89/797 (11.2) • *P* for interaction, NS ◦ 0.61 Bone fractures • No CV disease ◦ Dapagliflozin (10 mg) ▪ 44/1337 (3.3) ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 44/1352 (3.3) • CV disease ◦ Dapagliflozin (10 mg) ▪ 41/812 (5.0) ◦ Placebo (matching) ▪ 25/797 (3.1) • *P* for interaction, NS ◦ 0.15 Amputations • No CV disease ◦ Dapagliflozin (10 mg) ▪ 10/1337 (0.7) ◦ Placebo (matching) ▪ 15/1352 (1.1) • CV disease ◦ Dapagliflozin (10 mg) ▪ 25/812 (3.1) ◦ Placebo (matching) ▪ 24/797 (3.0) • *P* for interaction, NS ◦ 0.40
McMurray, 2021b[29] RCT	**Patients with CKD (with or without T2D) by HF status, n/N (%)** AEs causing discontinuation of study medication • No HF ◦ Dapagliflozin (10 mg) ▪ 106/1,914 (5.5) ◦ Placebo (matching) ▪ 113/1,916 (5.9) • HF ◦ Dapagliflozin (10 mg) ▪ 12/235 (5.1) ◦ Placebo (matching) ▪ 10/233 (4.3) • *P* for interaction, NS ◦ 0.588 Volume depletion • No HF ◦ Dapagliflozin (10 mg) ▪ 106/1,914 (5.5)

Study citation and study design	Outcomes
	◦ Placebo (matching) ▪ 78/1,916 (4.1) • HF ◦ Dapagliflozin (10 mg) ▪ 21/235 (8.9) ◦ Placebo (matching) ▪ 12/233 (5.2) • *P* for interaction, NS ◦ 0.503 Renal events • No HF ◦ Dapagliflozin (10 mg) ▪ 133/1,914 (6.9) ◦ Placebo (matching) ▪ 157/1,916 (8.2) • HF ◦ Dapagliflozin (10 mg) ▪ 22/235 (9.4) ◦ Placebo (matching) ▪ 31/233 (13.3) ◦ *P* for interaction, NS ▪ 0.495 Bone fractures • No HF ◦ Dapagliflozin (10 mg) ▪ 75/1,914 (3.9) ◦ Placebo (matching) ▪ 64/1,916 (3.3) • HF ◦ Dapagliflozin (10 mg) ▪ 10/235 (4.3) ◦ Placebo (matching) ▪ 5/233 (2.1) • *P* for interaction, NS ◦ 0.343 Amputations • No HF ◦ Dapagliflozin (10 mg) ▪ 30/1,914 (1.6)

Study citation and study design	Outcomes
	◦ Placebo (matching) ▪ 34/1,916 (1.8) • HF ◦ Dapagliflozin (10 mg) ▪ 5/235 (2.1) ◦ Placebo (matching) ▪ 5/233 (2.1) • *P* for interaction, NS ◦ 0.864
Wheeler 2021a[31] RCT	Patients with FSGS (with or without T2D) and CKD, n/N (%) • Any AE ◦ Dapagliflozin (10 mg) ▪ 9/45 (20.0) ◦ Placebo (matching) ▪ 16/58 (27.6) • AE causing discontinuation of treatment ◦ Dapagliflozin (10 mg) ▪ 3/45 (6.7) ◦ Placebo (matching) ▪ 3/58 (5.2)
Wheeler 2021b[32] RCT	Patients with CKD (with or without T2D) by T2D status, n (%) Any AE • T2D ◦ Dapagliflozin (10 mg) ▪ 483 (33) ◦ Placebo (matching) ▪ 562 (39) ◦ Difference between groups, OR (95% CI), favours dapagliflozin ▪ 0.79 (0.68 to 0.92) • No T2D ◦ Dapagliflozin (10 mg) ▪ 150 (22) ◦ Placebo (matching) ▪ 167 (24) ◦ Difference between groups, OR (95% CI), NS ▪ 0.88 (0.68 to 1.12) • *P*-value for interaction, NS ◦ 0.48 AEs causing discontinuation of treatment

Study citation and study design	Outcomes
	• T2D ◦ Dapagliflozin (10 mg) ▪ 82 (6) ◦ Placebo (matching) ▪ 94 (6) ◦ Difference between groups, OR (95% CI), NS ▪ 0.86 (0.63 to 1.17) • No T2D ◦ Dapagliflozin (10 mg) ▪ 36 (5) ◦ Placebo (matching) ▪ 29 (4) ◦ Difference between groups, OR (95% CI), NS ▪ (0.77 to 2.09) • *P*-value for interaction, NS ◦ 0.20 AEs of special interest to T2D Amputation • T2D ◦ Dapagliflozin (10 mg) ▪ 35 (2) ◦ Placebo (matching) ▪ 38 (3) ◦ Difference between groups, OR (95% CI), NS ▪ 0.92 (0.57 to 1.46) • No T2D ◦ Dapagliflozin (10 mg) ▪ 0 (0) ◦ Placebo (matching) ▪ 1 (< 1) ◦ Difference between groups, OR (95% CI) ▪ NA • *P*-value for interaction, NS ◦ 0.26 Confirmed or probable diabetic ketoacidosis • T2D ◦ Dapagliflozin (10 mg) ▪ 0 (0) ◦ Placebo (matching)

Study citation and study design	Outcomes
	▪ 2 (< 1) ◦ Difference between groups, OR (95% CI), NS ▪ 0.92 (0.57 to 1.46) • No T2D — NA Fractures • T2D ◦ Dapagliflozin (10 mg) ▪ 65 (4) ◦ Placebo (matching) ▪ 51 (4) ◦ Difference between groups, OR (95% CI), NS ▪ (0.89 to 1.87) • No T2D ◦ Dapagliflozin (10 mg) ▪ 20 (3) ◦ Placebo (matching) ▪ 18 (3) ◦ Difference between groups, OR (95% CI), NS ▪ 1.12 (0.59 to 2.15) • *P*-value for interaction, NS ◦ 0.72 Kidney-related AEs • T2D ◦ Dapagliflozin (10 mg) ▪ 121 (8) ◦ Placebo (matching) ▪ 148 (10) ◦ Difference between groups, OR (95% CI), NS ▪ 0.80 (0.62 to 1.03) • No T2D ◦ Dapagliflozin (10 mg) ▪ 34 (5) ◦ Placebo (matching) ▪ 40 (6) ◦ Difference between groups, OR (95% CI), NS ▪ 0.85 (0.53 to 1.35) • *P*-value for interaction, NS ◦ 0.83 Volume depletion

Study citation and study design	Outcomes
	• T2D ◦ Dapagliflozin (10 mg) ▪ 92 (6) ◦ Placebo (matching) ▪ 71 (5) ◦ Difference between groups, OR (95% CI), NS ▪ 1.31 (0.96 to 1.81) • No T2D ◦ Dapagliflozin (10 mg) ▪ 35 (5) ◦ Placebo (matching) ▪ 19 (3) ◦ Difference between groups, OR (95% CI), favours placebo ▪ 1.90 (1.09 to 3.41) • *P*-value for interaction, NS ◦ 0.27
Wheeler 2021c[33] RCT	Patients with CKD (with or without T2D) and IgA nephropathy, n/N pts (%) • AEs causing discontinuation of study medication ◦ Dapagliflozin (10 mg) ▪ 6/137 (4.4) ◦ Placebo (matching) ▪ 7/133 (5.3)
Cherney 2020[37] RCT	Non-diabetic patients with CKD, n/N (%) Any AE • Dapagliflozin (10 mg) ◦ 17/53 (32) • Placebo (matching) ◦ 13/52 (25) Causing discontinuation of treatment • Dapagliflozin (10 mg) ◦ 1/53 (2) • Placebo (matching) ◦ 1/52 (2) Other AEs of special interest • Volume depletion ◦ Dapagliflozin (10 mg) ▪ 0/53 (0) ◦ Placebo (matching) ▪ 2/52 (4)

Study citation and study design	Outcomes
	• Kidney-related events ◦ Dapagliflozin (10 mg) ▪ 1/53 (2) ◦ Placebo (matching) ▪ 0/52 (0) • Amputation ◦ Dapagliflozin (10 mg) ▪ 0/53 (0) ◦ Placebo (matching) ▪ 0/52 (0) • Fracture ◦ Dapagliflozin (10 mg) ▪ 1/53 (2) ◦ Placebo (matching) ▪ 0/52 (0) • Urinary tract/genital infection ◦ Dapagliflozin (10 mg) ▪ 2/53 (4) ◦ Placebo (matching) ▪ 0/52 (0) • Diabetic ketoacidosis ◦ Dapagliflozin (10 mg) ▪ 0/53 (0) ◦ Placebo (matching) ▪ 0/52 (0) • Hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 0/53 (0) ◦ Placebo (matching) ▪ 0/52 (0)
Heerspink 2020[34] RCT	Patients with CKD and T2D, n/N pts (%) AEs resulting in discontinuation of study medication • Dapagliflozin (10 mg) ◦ 118/2152 (5.5) • Placebo (matching) ◦ 123/2152 (5.7) • Difference between groups, NS ◦ P = 0.79 Other AEs:

Study citation and study design	Outcomes
	• Volume depletion symptoms ◦ Dapagliflozin (10 mg) ▪ 127/2152 (5.9) ◦ Placebo (matching) ▪ 90/2152 (4.2) ◦ Difference between groups, favours placebo ▪ P = 0.01 • Renal events ◦ Dapagliflozin (10 mg) ▪ 155/2152 (7.2) ◦ Placebo (matching) ▪ 188/2152 (8.7) ◦ Difference between groups, NS ▪ P = 0.07 • Bone fractures ◦ Dapagliflozin (10 mg) ▪ 85/2152 (4.0) ◦ Placebo (matching) ▪ 69/2152 (3.2) ◦ Difference between groups, NS ▪ P = 0.22 • Amputations ◦ Dapagliflozin (10 mg) ▪ 35/2152 (1.6) ◦ Placebo (matching) ▪ 39/2152 (1.8) ◦ Difference between groups, NS ▪ P = 0.73 • Diagnosed or probable diabetic ketoacidosis ◦ Dapagliflozin (10 mg) ▪ 0/2152 (0.0) ◦ Placebo (matching) ▪ 2/2152 (< 0.1) ◦ Difference between groups, NS ▪ P = 0.50
Pollock 2019[38] RCT	Patients with CKD and T2D, n/N (%) Any AE • Dapagliflozin (10 mg) ◦ 79/145 (54)

Study citation and study design	Outcomes
	• Placebo (matching) ◦ 81/148 (55) AE causing discontinuation of study medication • Dapagliflozin (10 mg) ◦ 4/145 (3) • Placebo (matching) ◦ 8/148 (5) Hypoglycemia • Minor hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 35/145 (24) ◦ Placebo (matching) ▪ 29/148 (20) • Other hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 19/145 (13) ◦ Placebo (matching) ▪ 16/148 (11) Other AEs of special interest • Kidney-related events ◦ Dapagliflozin (10 mg) ▪ 4/145 (3) ◦ Placebo (matching) ▪ 6/148 (4) • Sustained increase in creatinine ◦ Dapagliflozin (10 mg) ▪ 0/145 (0) ◦ Placebo (matching) ▪ 1/148 (1) • Urinary tract infection ◦ Dapagliflozin (10 mg) ▪ 5/145 (3) ◦ Placebo (matching) ▪ 4/148 (3) • Genital infection ◦ Dapagliflozin (10 mg) ▪ 4/145 (3) ◦ Placebo (matching) ▪ 0/148 (0)

Study citation and study design	Outcomes
	• Volume depletion ◦ Dapagliflozin (10 mg) ▪ 4/145 (3) ◦ Placebo (matching) ▪ 4/148 (3) • Amputation ◦ Dapagliflozin (10 mg) ▪ 1/145 (1) ◦ Placebo (matching) ▪ 0/148 (0) • Fracture ◦ Dapagliflozin (10 mg) ▪ 1/145 (1) ◦ Placebo (matching) ▪ 2/148 (1) • Diabetic ketoacidosis ◦ Dapagliflozin (10 mg) ▪ 1/145 (1) ◦ Placebo (matching) ▪ 0/148 (0)
Fioretto 2018[39] RCT	Patients with stage 3 CKD and T2D, % Any AEs, n/N (%) pts • Dapagliflozin (10 mg) ◦ 67/160 (41.9) • Placebo (matching) ◦ 77/161 (47.8) AEs leading to discontinuation of study medication, n/N (%) pts • Dapagliflozin (10 mg) ◦ 3/160 (1.9) • Placebo (matching) ◦ 3/161 (1.9) Patients receiving rescue medication during the 24wk treatment period, n (%) pts • Dapagliflozin (10 mg) ◦ 8 (5.0) • Placebo (matching) ◦ 10 (6.2) • Difference between groups, % (95% CI), NS ◦ −1.2 (−6.2 to 3.9) ◦ P = 0.809

Study citation and study design	Outcomes
	Hypoglycemia, n/N (%) pts, n events • Dapagliflozin (10 mg) ◦ 20/160 (12.5), 44 • Placebo (matching) ◦ 22/161 (13.7), 62 Other AEs of special interest, n/N (%) pts • Genital infection ◦ Dapagliflozin (10 mg) ▪ 3/160 (1.9) ◦ Placebo (matching) ▪ 2/161 (1.2) • Urinary tract infection ◦ Dapagliflozin (10 mg) ▪ 4/160 (2.5) ◦ Placebo (matching) ▪ 6/161 (3.7) • Hypotension/dehydration/hypovolemia ◦ Dapagliflozin (10 mg) ▪ 3/160 (1.9) ◦ Placebo (matching) ▪ 0/161 (0) • Renal impairment/failure ◦ Dapagliflozin (10 mg) ▪ 1/160 (0.6) ◦ Placebo (matching) ▪ 2/161 (1.2) • Bone fracture ◦ Dapagliflozin (10 mg) ▪ 0/160 (0) ◦ Placebo ▪ 0/161 (0) • Diabetic ketoacidosis ◦ Dapagliflozin (10 mg) ▪ 0/160 (0) ◦ Placebo (matching) ▪ 0/161 (0)
Fioretto 2016[35] RCT	Patients with stage 3 CKD and T2D, % AEs, n (%) pts • At least 1 AE

Study citation and study design	Outcomes
	◦ Dapagliflozin (10 mg) ▪ 50 (89.3) ◦ Dapagliflozin (5 mg) ▪ 50 (94.3) ◦ Placebo ▪ 53 (93.0) • AE leading to discontinuation ◦ Dapagliflozin (10 mg) ▪ 8 (14.3) ◦ Dapagliflozin (5 mg) ▪ 12 (22.6) ◦ Placebo ▪ 19 (33.3) • Renal ◦ Dapagliflozin (10 mg) ▪ 6 (10.7) ◦ Dapagliflozin (5 mg) ▪ 1 (1.9) ◦ Placebo ▪ 2 (3.5) • Volume reduction ◦ Dapagliflozin (10 mg) ▪ 5 (8.9) ◦ Dapagliflozin (5 mg) ▪ 5 (9.4) ◦ Placebo ▪ 4 (7.0)
SAE	
Chertow 2021[24] RCT	Patients with CKD (with or without T2D) by stage of CKD, n/N (%) Any SAE • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 101/293 (34.5) ◦ Placebo (matching) ▪ 138/331 (41.7) ◦ Difference between groups, OR (95% CI), NS ▪ 0.74 (0.53 to 1.02) • Stage 2 or 3 ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 532/1856 (28.7) ◦ Placebo (matching) ▪ 591/1818 (32.5) ◦ Difference between groups, OR (95% CI), favours dapagliflozin ▪ 0.83 (0.72 to 0.96) • *P* for interaction, OR, NS ◦ 0.49 Major hypoglycemia • Stage 4 ◦ Dapagliflozin (10 mg) ▪ 2/293 (0.7) ◦ Placebo (matching) ▪ 8/331 (2.4) ◦ Difference between groups, OR (95% CI), NS ▪ 0.28 (0.04 to 1.12) • Stage 2 or 3 ◦ Dapagliflozin (10 mg) ▪ 12/1856 (0.6) ◦ Placebo (matching) ▪ 20/1818 (1.1) ◦ Difference between groups, OR (95% CI), favours placebo ▪ 0.59 (0.28 to 1.18) • *P* for interaction, OR, NS ◦ 0.37
Heerspink 2021a[25] RCT	Patients with CKD (with or without T2D), n/N pts (%); events per 100 pt-yrs • AKI-related SAEs ◦ Dapagliflozin (10 mg) ▪ 54/2149 (2.5); 1.2 ◦ Placebo (matching) ▪ 69/2149 (3.2); 1.5 ◦ Difference between groups, HR (95% CI), NS ▪ 0.77 (0.54 to 1.10) ▪ P = 0.15 ◦ Difference between groups, incidence rate (95% CI), NS ▪ 0.35 (−0.14 to 0.86) ▪ P = NR ◦ Difference between groups, subdistribution HR accounting for competing risk of death (95% CI), NS ▪ 0.77 (0.54 to 1.10) ▪ P = 0.16

Study citation and study design	Outcomes
Jhund, 2021[36] RCT	Patients with HF, reduced ejection fraction and CKD (with or without T2D), n/N (%) SAEs • Dapagliflozin (10 mg) ◦ 417/960 (43.4) • Placebo (matching) ◦ 482/962 (50.1) • Difference between groups, favours dapagliflozin ◦ P = 0.003
McMurray, 2021a[28] RCT	**Patients with CKD (with or without T2D) by CV disease status, n/N (%)** Any SAE • No CV disease ◦ Dapagliflozin (10 mg) ▪ 287/1337 (21.5) ◦ Placebo (matching) ▪ 371/1352 (27.4) • CV disease ◦ Dapagliflozin (10 mg) ▪ 346/812 (42.6) ◦ Placebo (matching) ▪ 358/797 (44.9) • *P* for interaction, NS ◦ 0.09 Major hypoglycemia • No CV disease ◦ Dapagliflozin (10 mg) ▪ 3/1337 (0.2) ◦ Placebo (matching) ▪ 13/1352 (1.0) • CV disease ◦ Dapagliflozin (10 mg) ▪ 11/812 (1.4) ◦ Placebo (matching) ▪ 15/797 (1.9) • *P* for interaction, NS ◦ 0.12
McMurray, 2021b[29] RCT	Patients with CKD (with or without T2D) and HF, n/N (%) Any SAE • No HF ◦ Dapagliflozin (10 mg)

Study citation and study design	Outcomes
	▪ 503/1,914 (26.3) ◦ Placebo (matching) ▪ 607/1,916 (31.7) • HF ◦ Dapagliflozin (10 mg) ▪ 130/235 (55.3) ◦ Placebo (matching) ▪ 122/233 (52.4) • *P* for interaction, NS ◦ 0.055 Major hypoglycemia • No HF ◦ Dapagliflozin (10 mg) ▪ 12/1,914 (0.6) ◦ Placebo (matching) ▪ 22/1,916 (1.1) • HF ◦ Dapagliflozin (10 mg) ▪ 2/235 (0.9) ◦ Placebo (matching) ▪ 6/233 (2.6) • *P* for interaction, NS ◦ 0.556
Wheeler 2021b[32] RCT	Patients with CKD (with or without T2D) by T2D status, n/N (%) Major hypoglycemia • T2D ◦ Dapagliflozin (10 mg) ▪ 14 (1) ◦ Placebo (matching) ▪ 28 (2) ◦ Difference between groups, OR (95% CI), favours dapagliflozin ▪ 0.49 (0.25 to 0.93) • No T2D – N/A
Wheeler 2021c[33] RCT	Patients with CKD (with or without T2D) and IgA Nephropathy, n/N pts (%) • SAEs, n/N pts (%) per subgroup ◦ Dapagliflozin (10 mg) ▪ 22/137 (16.1) ◦ Placebo (matching) ▪ 34/133 (25.6)

Study citation and study design	Outcomes
Cherney 2020[37] RCT	Non-diabetic patients with CKD, n/N (%) • Any SAE ◦ Dapagliflozin (10 mg) ▪ 1/53 (2) ◦ Placebo (matching) ▪ 1/52 (2)
Heerspink 2020[34] RCT	Patients with CKD and T2D, n/N pts (%) • Any SAE ◦ Dapagliflozin (10 mg) ▪ 633/2152 (29.5) ◦ Placebo (matching) ▪ 729/2152 (33.9) ◦ Difference between groups, favours dapagliflozin ▪ P = 0.002 • Major hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 14/2152 (0.7) ◦ Placebo (matching) ▪ 28/2152 (1.3) ◦ Difference between groups, favours dapagliflozin ▪ P = 0.04
Pollock 2019[38] RCT	Patients with CKD and T2D, n/N (%) Any SAE • Dapagliflozin (10 mg) ◦ 12/145 (8) • Placebo (matching) ◦ 16/148 (11) SAE causing discontinuation of study medication • Dapagliflozin (10 mg) ◦ 1/145 (1) • Placebo (matching) ◦ 6/148 (4) Hypoglycemia • Any SAE of hypoglycemia ◦ Dapagliflozin (10 mg) ▪ 0/145 (0) ◦ Placebo (matching) ▪ 1/148 (1)

Study citation and study design	Outcomes
Fioretto 2018[39] RCT	Patients with stage 3 CKD and T2D, n (%) • Any SAE, n (%) pts ◦ Dapagliflozin (10 mg) ▪ 9 (5.6) ◦ Placebo (matching) ▪ 14 (8.7) • SAEs leading to discontinuation of study medication, n/N (%) pts ◦ Dapagliflozin (10 mg) ▪ 2/160 (1.3) ◦ Placebo (matching) ▪ 2/161 (1.2)
Fioretto 2016[35] RCT	Patients with stage 3 CKD and T2D, n (%) SAEs • At least 1 SAE ◦ Dapagliflozin (10 mg) ▪ 20 (35.7) ◦ Dapagliflozin (5 mg) ▪ 14 (26.4) ◦ Placebo ▪ 18 (31.6) • Leading to discontinuation of study medication ◦ Dapagliflozin (10 mg) ▪ 2 (3.6) ◦ Dapagliflozin (5 mg) ▪ 5 (9.4) ◦ Placebo ▪ 5 (8.8) • Renal ◦ Dapagliflozin (10 mg) ▪ 1 (1.8) ◦ Dapagliflozin (5 mg) ▪ 1 (1.9) ◦ Placebo ▪ 1 (1.8) • Volume reduction ◦ Dapagliflozin (10 mg) ▪ 1 (1.8) ◦ Dapagliflozin (5 mg) ▪ 0 (0.0)

Study citation and study design	Outcomes
	◦ Placebo ▪ 0 (0.0)

AE = adverse event(s); AKI = acute kidney injury; AR = absolute risk; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis; HF = heart failure; HR = hazard ratio; IgA = immunoglobulin A; mg = milligram; MI = myocardial infarction; mm Hg = millimetres of mercury; N/n = number; NA = not applicable; NC = not calculable; NR = not reported; NS = not significant; OR = odds ratio; P = probability; P-value = P value; pt/pts = patient(s); RCT = randomized controlled trial; SAE = serious adverse event(s); SBP = systolic blood pressure; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; wk = week(s); yr = year(s).

Appendix 5: References of Potential Interest

Note that this appendix was not copy-edited.

Reports of Combined Data Describing at least 2 SGLT2is (including dapagliflozin) and/or at least 2 Indications or Conditions

Barratt, J. and J. Floege (2021). "SGLT-2 inhibition in IgA nephropathy: the new standard of care?" *Kidney International* 100(1): 24-26. PubMed

Kobayashi, K., et al. (2021). "The evaluation of noninferiority for renal composite outcomes between sodium-glucose cotransporter inhibitors in Japan." *Primary care diabetes* 15(6): 1058-1062. PubMed

Patoulias, D., et al. (2021). "Meta-analysis of Dedicated Renal Outcome Trials Assessing the Cardio-renal Efficacy of Sodium-Glucose Co-transporter-2 Inhibitors in Patients With Chronic Kidney Disease and Albuminuria." *American Journal of Cardiology* 138: 116-118. PubMed

Qiu, M., et al. (2021). "Safety of four SGLT2 inhibitors in three chronic diseases: A meta-analysis of large randomized trials of SGLT2 inhibitors." *Diabetes & Vascular Disease Research* 18(2): 14791641211011016. PubMed

Abridged Summary of Findings From DAPA-CKD

Molony, D. A. and F. I. LeMaistre (2021). "In CKD, dapagliflozin reduced a composite of eGFR decline, end-stage kidney disease, or CV or renal mortality." *Annals of Internal Medicine* 174(2): JC20. PubMed

Letter to the Editor of the New England Journal of Medicine About DAPA-CKD

Vogt, L. (2021). "Dapagliflozin in Patients with Chronic Kidney Disease." *New England Journal of Medicine* 384(4): 388-389. PubMed

Meta-Analysis Without Systematic Review

Dekkers, C. C. J., et al. (2018). "Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease." *Nephrology Dialysis Transplantation* 33(11): 2005-2011. PubMed