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Impact of Dapagliflozin Adjunctive Therapy on Progression of Chronic Kidney Disease in Patients with Type 2 Diabetes and CKD Stage 2–5

A systematic review and meta-analysis

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Abstract

This meta-analysis was conducted by searching PubMed, Scopus, Cochrane, Ovid till November 2022 for randomized controlled trials (RCTs) that utilized dapagliflozin 10 mg as adjunctive therapy in patients with T2DM and CKD stage 2-5 and reported its renal efficacy in terms of mean change in estimated glomerular filtration rate (eGFR) and urinary albumin creatinine ratio (UACR) from baseline. From 1682 identified records, nine studies representing 13,057 patients were selected for this study. Pooled estimate of five studies showed that dapagliflozin did not affect eGFR but caused significantly less chronic eGFR decline than placebo in two studies [Mean difference (MD) +2.74 (95% CI: 1.55, 3.92; p < 0.00001)]. Pooled estimate of four studies showed that dapagliflozin significantly reduced UACR[-23.99 % MD (95% CI - 34.82, -13.15, p-value < 0.0001; = 0%)]. This confirms that long-term dapagliflozin use significantly attenuates eGFR decline and reduces albuminuria in T2DM and CKD stages 2-5 patients.

Keywords: Chronic kidney disease, Dapagliflozin, Estimated GFR, eGFR, SGLT2 inhibitors, Type 2 diabetes mellitus, Urine albumin to creatinine ratio, UACR.

Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by the gradual decline in renal function eventually leading to end-stage renal disease (ESRD) or renal failure. Nearly the 12% of world's population is affected by CKD presently [1] and its prevalence is increasing. Nearly, two-thirds of chronic kidney disease is due to diabetes and hypertension whereas glomerulonephritis, autoimmune diseases & age-related kidney conditions account for the rest of the cases.[2] Diabetic kidney disease (DKD) happens when CKD occurs as a result of diabetic microvascular complications; non-diabetic kidney disease (NDKD) occurs when CKD occurs owing to other reasons.

Patients with diabetes may also have non-diabetic factors contributing to the etiology of their CKD, resulting in NDKD. Only a renal biopsy can provide a definitive diagnosis of CKD etiology, which is not feasible in routine clinical practice. Furthermore, hyperglycemia may hasten the course of CKD in both DKD and NDKD patients and raise the risk of cardiovascular disease (CVD).[2] As a result, the primary therapeutic objective in patients with diabetes and CKD (including DKD and NDKD) is to prevent CKD progression and lower CVD risk.

This objective has been the focus of substantial research into a novel family of anti-diabetic drugs called sodium-glucose co-transporter-2 inhibitors (SGLT2i), especially Dapagliflozin as it had demonstrated considerable reno-protective effects in DAPA-CKD trial. Based on the findings from this trial, they were licensed in 2021 for the management of CKD to lower adverse renal events and CV disease outcomes in patients with and without type 2 diabetes.[1] However, a single summary estimate of its renal efficacy in patients with CKD (stage 2-5) and diabetes has not been reported so far**.**

Estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) are extensively used as surrogate endpoints in clinical settings to measure CKD progression.[3] The combination of a drop in eGFR and an increase in UACR is substantially related to a higher risk of CKD progression than either one alone. Dapagliflozin's reno-protective effects can thus be efficiently documented by evaluating the mean change in eGFR and UACR from baseline.
So, this systematic review and meta-analysis was aimed to estimate the impact of dapagliflozin adjunctive therapy on the progression of chronic kidney disease - measured in terms of mean change in eGFR and UACR from baseline, in individuals with type 2 diabetes and intended to generate enough scientific evidence for its clinical use.

Methods

The Preferred Reporting items for systematic reviews and meta-analysis (PRISMA) [4] criteria were followed for this systematic review and meta-analysis. The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) and it can be accessed in PROSPERO website (CRD42022304631).

Data sources and search

Electronic databases like PubMed, Scopus, Cochrane, and Ovid were searched for publications from the year 2000 to 11th November 2022 for the identification of relevant published studies. Further searches for identifying eligible studies were done in the clinical trials registry of India (CTRI) and clinical trials.gov and manually also.

Medical subject headings (MeSH) terms like “dapagliflozin” AND “CKD”; “dapagliflozin” AND “chronic kidney disease” AND “type 2 diabetes”; “dapagliflozin” AND “albuminuria” AND “eGFR” were used for searching relevant studies. These search results were further refined with filters like full text and English language-only articles.

Before submission, an electronic database search was done once again and a final analysis report was compiled to ensure recent updates were also included. A summary of the electronic database search is given in the supplementary file [Supplementary Table: 1 & 2].

Eligibility criteria

Randomized controlled trials (RCT) and post hoc analysis of RCTs which were conducted in patients with type 2 diabetes and CKD stage 2 - 5 of any etiology (baseline eGFR < 90 ml/min/1.73 m^2); used dapagliflozin 10 mg OD, which is most commonly prescribed dosage in clinical practice for the treatment of CKD, was used as interventional drug adjunct to standard of care (SOC); compared to either placebo or any other OHAs / anti-CKD drugs; conducted for a minimum of ≥ 12 weeks duration, since stabilization period of the dapagliflozin effects on metabolic & renal parameters takes at least 8 – 12 weeks.; assessed renal endpoints like mean change in eGFR and UACR were included.

Study designs other than RCTs (Non-randomized CT, case report, case series, cross-sectional, cohort studies); conducted in type 1 diabetes, CKD stage 1 (KDIGO) (baseline eGFR > 90

ml/min/1.73 m^2) and non-diabetes population. used dapagliflozin 5 mg as intervention or FDC of dapagliflozin or single-arm study were excluded. Studies conducted for < 12 weeks duration and which did not assess desired renal outcomes were also excluded

Study selection

Relevant studies identified from above-said databases were exported to the citation manager (Zotero) for removing duplicates. After removing duplicates, all individual papers were examined by two independent authors for qualification according to eligibility criteria, first by title and abstracts then followed by full texts in cases of uncertainty to eliminate ineligible studies. In case of discrepancies between two authors, the final decision was made by a third independent author.

Data extraction

Data were extracted for assessing the following primary outcomes: mean change in eGFR; mean percentage change in UACR from baseline in both interventional and control groups. Prevention of CKD progression can be defined as an increase in mean eGFR or less decline in eGFR and a decrease in mean percentage UACR from baseline.

From eligible studies, information like study design, study duration, median follow-up duration, interventional drug, comparator drug, sample size, and other information related to outcomes were extracted. For post hoc analysis, primary trials were used as references for some details in addition to the details presented in post hoc papers. "WebPlot digitizer"[5] was used to extract data from the graphs and pictorial representations. Data extraction was primarily carried out by two authors independently (MK, SM) and cross verified by third author (MB).

Quality assessment

Qualitative assessment of included papers was done utilising Cochrane's Risk of Bias assessment tool for RCT (RoB2).[6] The domains used to assess the risk of bias were: the randomisation process, deviation from the intended interventions, missing outcome data, measurement of outcome, and selection of the reported results. Based on the assessments made according to these domains, included papers were categorized into low risk, some concerns, or high risk. Quality assessment was carried out by two independent authors (MK, ST) and cross-verified by third author (MB).

Data synthesis and analysis

Meta-analysis was done for quantitative assessment of outcomes from included studies in Review Manager (RevMan version 5.4) software. Heterogeneity between the studies was estimated using the I^2 test. An I^2 value of above 50% was considered as moderate to high heterogeneity and less than 50% as low to moderate heterogeneity between studies. To pool the data from the included studies random effects model was utilized and mean difference (MD) or standardized mean difference (SMD) with their corresponding 95 % CI for the desired outcomes were calculated between two groups to measure the treatment effect precisely.

After reviewing initial results for one of the primary outcomes - mean change in eGFR from baseline, we further conducted a non-prespecified subgroup analysis to compare the mean change in chronic eGFR slope from two trials between dapagliflozin and placebo. For this analysis, we calculated the mean difference and related 95% confidence interval using the random effects model.

Quality of evidence

The strength of evidence for meta-analysis results was assessed using GRADEpro[7] software using following criteria: risk of bias, inconsistency, imprecision, indirectness, and other considerations like publication bias. Assessing the article according to these criteria, the quality of evidence was graded as any one of the following: high, moderate, low, or very low.

Results

The study selection process is detailed in figure 1 as a PRISMA flow diagram. Total of 1681 records were identified (PubMed: 324, Scopus: 580, Ovid: 491, Cochrane registry: 286) from the initial electronic database search. Around 869 duplicate papers were excluded with the assistance of the citation manager (Zotero) and 488 irrelevant studies were removed using manual filters. From the remaining 219 records, screening based on title & abstract was done by two individual authors and 140 non-RCT records were removed.

Finally, 79 full-text papers were examined for qualification according to our eligibility criteria. From them, nine studies representing 13,057 participants were obtained for inclusion in the systematic review, and seven studies representing 4,713 participants were retained for meta-analysis. Reasons for the exclusion of full-text articles are provided in supplementary table 1.

Baseline characteristics of studies included

The studies considered in this systematic review and meta-analysis were published before 11, November 2022. Baseline demographic details of evaluated studies are summarized in table 1. Among 9 analyzed studies, 6 were RCTs, 1 was post hoc and 2 were secondary exploratory analyses. Included studies had 13,057 subjects as the number of participants with type 2 diabetes and CKD (eGFR < 90 ml/min/1.73 m^2). All studies had dapagliflozin 10 mg OD as their primary intervention along with background standard of care and 8 studies had placebo as their comparator and one study had valsartan 80 mg as its comparator drug. The maximum study duration/ median follow-up among included studies was 4 years and the minimum was 3 months. Dapagliflozin's effect as an adjuvant to SOC on CKD prognostic biomarkers like eGFR and UACR was assessed in these included studies.

Risk of bias in assessed studies

Among 9 included studies, one study (Ying et al.,) [8] had a high overall risk of bias as nothing was mentioned about methods used for randomization, and two studies Paola et al., (2016) [9]; Paola et al., (2018) [10] had a moderate risk of bias due to some concerns in missing outcome data & deviation from intended interventions and six studies had an overall low risk of bias. The summary and graph for the Risk of bias assessment of assessed studies are presented in Figures 3a & 3b.

Systematic Review

Summary of dapagliflozin's effect as an adjunct to SOC on eGFR and UACR in patients with type 2 diabetes and CKD (eGFR < 90 ml/min/1.73 m^2) as predicted in individual studies [8–16] are presented in table 2.

Results from the included studies show that short-term dapagliflozin use [10,14] did not affect eGFR significantly but chronic use prevented the greater decline in eGFR slope.[12,15] Also dapagliflozin use was associated with significant reduction in mean percentage UACR from baseline. Thus, dapagliflozin prevents CKD progression in type 2 diabetes patients with baseline eGFR < 90 ml/min/1.73 m^2.

Meta-Analysis

Meta-analysis was executed for 7 of the 9 qualified studies and the results are displayed as forest plots in the figure: 2. Among 7 studies, 5 studies had results for mean change in eGFR and 4 studies had results for mean percent reduction in UACR from baseline.

Mean change in eGFR from baseline

Five studies, which had 818 individuals in the dapagliflozin group and 815 patients in the placebo group were quantitatively assessed for mean change in eGFR from baseline values. Applying the random effects model, the pooled estimate of 5 studies was determined, which showed a standardized mean difference of +0.13 ml/min/1.73 m^2 [(95% CI -0.25, 0.51) p = 0.50; I^2= 92%, P <0.0001] between two groups. This conveys that when compared to placebo, dapagliflozin as an adjunct to SOC is not linked with a statistically significant rise in eGFR values from baseline.

The I^2 value was 92% which means the included studies were statistically highly heterogenous and the effect was inconsistent across the studies. To see the stability of our result, we conducted a sensitivity analysis excluding short-duration studies which showed an SMD + 0.38 ml/min/1.73 m2 [95% CI: -0.04, 0.79, p=0.08; I2 = 87%, P = 0.0005] between two groups. This result also confirmed the statistically insignificant effect of dapagliflozin on the total slope of eGFR in larger duration studies compared to placebo.

Mean change in chronic eGFR slope (Sub-group analysis)

To estimate the chronic treatment effect of dapagliflozin, we further analyzed chronic eGFR slope between 1 to 3 years from two studies [12,15] by applying random effects model which yielded a mean difference of +2.74 ml/min/1.73 m^2 (95% CI: 1.55, 3.92; p < 0.00001; I = 79%, P = 0.03) between two groups and found that dapagliflozin use caused significant attenuation of eGFR decline on chronic use compared to that of placebo. Kohan et al., however, conducted for a longer period (104 weeks), are not included in this analysis due to difficulties in data extraction.

Mean percentage change in UACR from baseline

Four studies that had 380 subjects in the dapagliflozin group and 386 individuals in the placebo group were quantitatively assessed for mean percentage reduction in UACR values from baseline. Applying the random effects model, the pooled estimate of 4 studies revealed a mean

difference of -23.99 % [(95% CI -34.82, -13.15), *p-value* < 0.0001; I^2 = 0%] between the two groups. The I^2 value was 0% which shows that all the analyzed studies were statistically homogenous. This confirms that dapagliflozin adjunct to SOC reduces UACR in a statistically significant manner compared to that of placebo.

Quality of evidence

GRADEPro software was used to grade the quality of evidence for the results obtained in the meta-analysis [Supplementary Figure 1]. Accordingly, results for mean change in UACR from baseline were found to have high quality of evidence – suggesting that future researchers are unlikely to change our effect estimate; mean change in eGFR from baseline had low quality of evidence – implying that future researches are more likely to change our effect estimate and mean change in chronic eGFR slope had the moderate quality of evidence – proposing that future researches might change our effect estimate.[17]

Discussion

Sodium-glucose co-transporter inhibitors are a unique class of oral anti-hyperglycaemic agents approved for the treatment of type 2 diabetes both as monotherapy and as an add-on to standard anti-diabetic care. SGLT2 inhibitors exert their anti-diabetic effect by inhibiting the reabsorption of glucose by SGLT2 channels present in proximal renal tubular cells resulting in urinary loss of glucose. This urinary loss of glucose is associated with significant glucose-induced osmotic diuresis, and natriuresis [18] and this leads to renal hemodynamic changes like activation of tubuloglomerular feedback and afferent arteriolar constriction. These hemodynamic changes appear as acute eGFR reduction clinically [19] and sometimes may result in acute kidney injury (AKI). Since their primary action is on renal PTC, their glycaemic efficacy decreases with worsening renal function [20] but their reno-protective effects will be more prominent as the renal impairment advances.

Dapagliflozin, a highly effective and selective SGLT2 inhibitor has documented promising reno-protective effects in DAPA-CKD trial. [21] At the same time, FDA had issued a warning regarding the greater probability of developing acute kidney injury with its use. [22] Most of the clinical trials that documented the reno-protective effects of dapagliflozin were conducted in both diabetic and non-diabetic populations; across different stages of CKD (KDIGO 1-5) and some even in normal kidney function patients. Renal composite outcome (Sustained decline in eGFR > 40 or > 50%,

progression to ESRD, CV death or Renal death) was the primary endpoint in the majority of the trials and very few trials assessed its direct effect on eGFR slope in T2DM & CKD patients.

So, intending to quantify the effect size, we estimated the impact of dapagliflozin adjunctive therapy on CKD progression in people with type 2 diabetes and CKD stages 2-5 (eGFR 90 ml/min/1.72 m2). To estimate this effect, we have chosen two independent prognostic biomarkers of chronic kidney disease progression – estimated GFR and UACR. [23,24] These two prognostic biomarkers are inexpensive, widely available, and more accurate predictors [25] of renal function in combination than alone. We have selected dapagliflozin 10 mg OD as an intervention as it is the most prescribed dosage in routine clinical practice.

Dapagliflozin, like other SGLT2 inhibitors, might reduce glomerular filtration pressure resulting in UACR reduction. [25] It is clear from all the included trials that dapagliflozin adjuvant to SOC is linked with a significant reduction in UACR, implying that it improves albuminuria and stops CKD from progressing to an advanced state. The meta-analysis results for this outcome also confirmed that dapagliflozin significantly decreased UACR compared to that of placebo.

Regarding the mean change in eGFR, Meta-analysis results were highly inconsistent across the included studies ($I^2 = 92\%$). The probable reason for this inconsistency may be due to the difference in the population studied (Ying et al., [8] - only diabetic nephropathy patients were studied), and shorter study duration (Paola et al., [10] , Pollock et al.,[14]).

Although three studies Kohan et al.,[11]; Hiddo JL et al.,[15] and Ofri et al.,[12] had longer study duration, and almost similar mean baseline eGFR of included participants, their results were not similar. The possible reasons might be due to differences in the proportion of participants in various eGFR subgroups, the differences in mean age (68 years in Kohan et al., and 64.1 years in Hiddo et al.,), mean HbA1c, mean body weight, different formulae used for calculating eGFR (MDRD in Kohan et al., - affected by race; CKD-EPI in Hiddo et al., - preferred in diabetic patients)[26] and difference in the standard of care given to participants.

Also, one of the reasons for insignificant pooled estimate results might be due to initial acute eGFR reduction associated with dapagliflozin use that was reported in nearly all included studies. Similar to other SGLT2 inhibitors, dapagliflozin also causes activation of tubuloglomerular feedback leading to hypovolemia and precipitation of acute pre-renal failure. [27]

However, in meta-analysis result we can clearly note a positive effect on eGFR preservation which is still clinically meaningful. [28,29] The estimation of chronic eGFR slope observed in two studies also revealed that dapagliflozin use was associated with significantly lesser eGFR decline over time compared to that of placebo and confirmed that insignificant result was merely due to initial acute eGFR reduction.

Limitations

This study has the following limitations: high heterogeneity between studies for mean change in eGFR from baseline; reliance on the secondary or exploratory or safety endpoints; discrepancies in standard background care given in included studies; exclusion of other language articles. Due to data extraction difficulties, subgroup analysis among distinct eGFR & UACR groups could not be performed.

It is well known that patient factors like age, gender, ethnicity, co-morbid conditions and background medications might affect the net effect estimates [30]. But due to data extraction difficulties, a sensitivity analysis with these factors as co-variates could not be performed for the net effect estimate of both the outcomes.

Conclusion

From this study, it can be concluded that intervention with dapagliflozin as an adjunct to standard of care (SOC) is associated with lesser eGFR decline on chronic therapy and reduction in albuminuria progression significantly in patients with T2DM and CKD stage 2-5. Both eGFR and UACR are independent prognostic predictors of CKD progression and dapagliflozin's favourable effect on both confirm its reno-protective effects. Since, these conclusions were made based only on limited number of included studies, future studies including large number of trials are needed to confirm these findings.

Authors' Contribution

Electronic search was done by authors KM, SM primarily and cross-verified by author MB. Screening of eligible paper was done by authors KM, SM, ST and cross-verified by author MB. Data extraction & analysis was carried out by authors KM & ST primarily and cross-verified by author MB & SH. Manuscript was drafted by authors KM, MSB, MB and reviewed by MB & SH.

Conflicts of Interest

The authors declare no conflict of interests.

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Table 1: Baseline demographic details of included study

S. No	Author / Study year	Study design	Intervention	Comparator	Standard / Background care	Study duration & follow-up	No. of participants	Baseline eGFR (MDRD) & UACR for inclusion	Mean age (SD) in Dapagliflozin group	Mean baseline eGFR (ml/min/1.72 m^2) Mean (SD)	Mean baseline UACR (mg/g) Median (range)	Outcome assessed	Included in SR / MA
1.	Kohan et al. [11] (2014)	Randomized, double-blind, multicentric, placebo-controlled trial	Dapagliflozin 10 mg OD & 5 mg OD	Placebo	Standard pre-enrolment anti-diabetic regimen given	Study duration: 104 weeks	Total: 252 Dapagliflozin 10 mg: 85 Placebo: 84	eGFR: 30 – 60 ml/min/ 1.72 m2 (MDRD)	68(7.7) years	**Dapagliflozin:** 43.9 (10.6) **Placebo:** 45.6 (10.0)	**Placebo:** 67 (20, 367) **Dapagliflozin:** 73 (9, 352)	Change in eGFR from baseline at week 104	SR & MA
2.	Fioretto et al. [9] (2016)	Post-hoc analysis of Kohan DE et al	Dapagliflozin 10 mg OD & 5 mg OD	Placebo	Standard pre-enrolment anti-diabetic regimen given	Study duration: 104 weeks	Total: 166 Dapagliflozin 10 mg: 56 Placebo: 57	eGFR: 30 – 60 ml/min/ 1.72 m2 (MDRD UACR: >= 30 mg/g	68(7.7) years	**Dapagliflozin:** 43.9 (10.6) **Placebo:** 45.6 (10.0)	**Placebo:** 67 (20, 367) **Dapagliflozin:** 73 (9, 352)	Change in UACR from baseline at 104 weeks	SR & MA
3.	Fioretto et al. [10] (2018)	Randomized, double-blind, parallel group, placebo-controlled	Dapagliflozin 10 mg OD	Placebo	Standard pre-enrolment anti-diabetic regimen given	Study duration: 24 weeks	Total: 321 Dapagliflozin 10 mg: 160 Placebo: 161	eGFR: 45 - 59 ml/min/1.72m2 (MDRD) UACR: ≥ 30 mg/g	65.3 years	**Dapagliflozin:** 53.3 (8.7) **Placebo**: 53.6 (10.6)	**Dapagliflozin:** 23.5 (2.7–5852.0) **Placebo:** 29.0 (3.8-8474.0)	Change in UACR & eGFR from baseline at 24 weeks	SR & MA

		study											
4.	Pollock et al. [14] (2019)	Randomized, double-blind, multicentric, placebo-controlled trial	Dapagliflozin 10 mg OD	Placebo & Dapagliflozin + Saxagliptin	Standard pre-enrolment anti-diabetic & antihypertensive (ACEi, ARB) regimen given	Study duration: 24 weeks	Total: 461 Dapagliflozin 10 mg: 145 Placebo: 148	eGFR: 25 -75 ml/min/1.72 m2 (MDRD) UACR: 30 - 3500 mg/g	64.7(8.6) years	**Dapagliflozin:** 50·2 (13·0) **Placebo:** 47·7 (13·5)	Placebo: 257·5 (80–949) Dapagliflozin: 270·0 (69–751)	Change in UACR & eGFR from baseline at 24 weeks	SR & MA
5.	Mosenzon et al. [12] (2019)	Secondary exploratory analysis of randomized, double blind, placebo controlled trial	Dapagliflozin 10 mg OD	Placebo	Adjunct to standard care – pre-enrolment anti-diabetic regimen, ACEi, ARBs	Median follow up years: 4 years	Total: 17,160 < 90 ml/min/1.72 m2: 8997 Dapagliflozin: 4444 Placebo: 4553	Not defined CrCl >60	eGFR 60-90: 66.2 (6.5) & eGFR < 60 ml/min/1.72 m2: 67.3 (6.6)	eGFR 60-90: 77·0 (8·5) eGFR < 60: 51·4 (7·2)	Overall: 13.1 (6.0, 43.6)	Change in eGFR from baseline per year	SR & MA (<60 group alone)
6.	Mosenzon et al. [13] (2021)	Secondary exploratory analysis of randomized, double blind, placebo	Dapagliflozin 10 mg OD	Placebo	Adjunct to standard care – pre-enrolment anti-diabetic regimen,	Median follow up years: 4 years	Total: 17,160 < 90 ml/min/1.72 m2: 8997 Dapagliflozin: 4444	Not defined CrCl >60	eGFR 60-90: 66.2 (6.5) & eGFR < 60 ml/min/1.72 m2:	eGFR 60-90: 77·0 (8·5) eGFR < 60: 51·4 (7·2)	Overall: 13.1 (6.0, 43.6)	Change in UACR from baseline at 48 months	SR

		controlled trial			ACEi, ARBs		Placebo: 4553		67.3 (6.6)				
7.	Heerspink et al. [15] (2021)	Randomized, double-blind, placebo-controlled, multicentre clinical trial.	Dapagliflozin 10 mg OD	Placebo	Stable maximum doses of ACEi & ARBs are given	Median follow-up years: 2.4 years	Total :4304 Diabetes: 2906 Dapagliflozin & Diabetes: 1455 Placebo & diabetes: 1451	eGFR: 25 - 75 ml/min/1.72m2 (CKD-EPI) UACR: 200 - 5000 mg/g	62(12.1) years	Both groups with diabetes: 43.8 (12.6)	Both groups with diabetes: 1016.5	Change in eGFR from baseline per year	SR & MA
8.	Jongs et al. [16] (2021)	Randomized, double-blind, placebo-controlled, multicentre clinical trial.	Dapagliflozin 10 mg OD	Placebo	Stable maximum doses of ACEi & ARBs are given	Median follow-up years: 2.4 years	Total :4304 Diabetes: 2906 Dapagliflozin & Diabetes: 1455 Placebo & diabetes: 1451	eGFR: 25 - 75 ml/min/1.72m2 (CKD-EPI) UACR: 200 - 5000 mg/g	62(12.1) years	Both groups with diabetes: 43.8 (12.6)	Both groups with diabetes: 1016.5	Change in UACR from baseline at 36 months	SR & MA
9.	Huang et al. [8] (2022)	Randomized, single centre, parallel group trial	Dapagliflozin 10 mg OD	Valsartan 80 mg BD	Standard anti-diabetic regimen followed	Study duration: 3 months	Total: 120 Dapagliflozin 10 mg: 60 Valsartan 80 mg: 60	eGFR: < 60 ml/min/1.72m2 (MDRD) UACR: ≥ 30 mg/g	56.21(11.46) years	Not specified	Not specified	Change in eGFR from baseline at 12 weeks	SR

OD: Once daily; MDRD: Modification of diet in renal disease; CKD-EPI: Chronic kidney disease epidemiology collaboration; eGFR: estimated glomerular filtration rate; UACR: Urinary albumin creatinine ratio; SD: Standard deviation; SR: Systematic review; MA: Meta-analysis

Table 2: Summary of findings for systematic review**:**

Mean change in eGFR from baseline					
S.No	**Study ID**	**Outcome assessed**	**No. of Participants**	**Results**	**Remarks**
1.	Kohan et al. [11] (2014)	Mean change in **eGFR** from baseline at week 104 Reported as secondary objective.	Dapagliflozin: 85 Placebo: 84 **At 104 weeks:** Dapagliflozin: 50 Placebo: 42	**Dapagliflozin:** Mean (SE): -3.50 (1.02) **Placebo:** Mean (SE): -2.38 (1.01)	Decrease from baseline in eGFR were larger with dapagliflozin compared with placebo after 104 weeks **Mean Difference:** -1.12 ml/min/1.72 m2 (95 % CI -3.92, 1.68)
2.	Fioretto et al. [10] (2018)	Mean change in **eGFR** from baseline at 24 weeks. Reported as safety endpoint.	Dapagliflozin: 160 Placebo: 161 **At 24 weeks:** Dapagliflozin: 150 Placebo: 145	**Dapagliflozin:** Mean (SE): -3.3 (1.25) **Placebo:** Mean (SE): -0.8 (1.31)	Decrease from baseline in eGFR were larger with dapagliflozin compared with placebo after 24 weeks **Mean difference:** -2.49mL/ min / 1.72 m2 (95 % CI: -4.96, -0.02)
3.	Pollock et al. [14] (2019)	Mean change in **eGFR** from baseline at 24 weeks Reported as safety endpoint.	Dapagliflozin: 145 Placebo: 148 At 24 weeks: Dapagliflozin: 131 Placebo: 134	**Dapagliflozin**: Mean (SE): -4 (0.80) **Placebo**: Mean (SE): -1.6 (0.80)	Decrease from baseline in eGFR were larger with dapagliflozin compared with placebo after 24 weeks **Mean difference:** -2.4 ml/min/1.73 m2 (95% CI: -4.2, -0.5) (p =0.01)
4.	Mosenzon et al. [12] (2019)	Mean change in **eGFR** from baseline at 4 years. Reported as pre-defined subgroup analysis of secondary composite outcome.	Dapagliflozin: 4444 (60- 90: 3838; at 4 years: 2686 < 60: 606; at 4 years: 382) Placebo: 4553 (60-90: 3894; at 4 years: 2631 <60: 659; at 4 years: 391)	**60-90 eGFR:** **Dapagliflozin:** Mean (SE): -8.18 (0.29) **Placebo:** Mean (SE): -9.81 (0.24) **< 60 eGFR:** **Dapagliflozin:** Mean (SE): -2.45 (0.23) **Placebo:** Mean (SE): -4.27 (0.23)	Decrease in eGFR was less with Dapagliflozin compared to placebo in both 60-90 & < 60 eGFR group **Mean difference:** + 1.63 & +1.82 ml/min/1.72m2 respectively

5.	Heerspink et al. [15] (2021)	Mean change in **eGFR** from baseline per year. Reported as primary pre-specified outcome.	Dapagliflozin: 1455 Placebo: 1451 **At 36 months:** Dapagliflozin: 113 Placebo: 108	**Dapagliflozin:** Mean (SE): -2.84 (0.14) **Placebo**: Mean (SE): -4.01 (0.14)	Dapagliflozin attenuated loss of kidney function compared to placebo. **Mean difference**: + 1·18 mL/min per 1·73 m² per year (95% CI: 0·79 to 1·56)
6.	Huang et al. [8] (2022)	Mean change in **eGFR** from baseline at 12 weeks. Reported as secondary outcome.	Dapagliflozin: 60 Valsartan: 60	**Dapagliflozin:** Baseline:111.17 ± 29.22 At 12 weeks: 113.01 ± 26.66 **Valsartan:** Baseline: 110.08 ± 27.64 At 12 weeks: 111.79 ± 24.72	eGFR increased by + 1.84 ml/min/1.72 m2 in dapagliflozin group and by + 1.71 ml/min/1.72 m2 in valsartan group. **Mean difference**: 0.13 ml/min/1.72 m2 (p > 0.05)
Mean change in UACR from baseline					
1.	Fioretto et al. [9] (2016)	Mean % change in **UACR** from baseline at 104 weeks. Reported as exploratory endpoint.	Dapagliflozin: 56 Placebo: 57 **At week 104:** Dapagliflozin: 29 Placebo: 25	**Dapagliflozin:** Mean (SE): -43.9 (15.6) **Placebo:** Mean (SE): 31 (39.1)	Placebo-corrected UACR reductions (95% CI) of -57.2% (-77.1, -20.1) occurred in dapagliflozin group.
2.	Fioretto et al. [10] (2018)	Mean % change in **UACR** from baseline at 24 weeks. Reported as exploratory endpoint.	Dapagliflozin: 160 Placebo: 161 **At 24 weeks:** Dapagliflozin: 60 Placebo: 69	**Dapagliflozin:** Mean (SE): -43.7 (14.8) **Placebo:** Mean (SE): -34.6 (16.2)	Dapagliflozin reduced mean percent changes from baseline in UACR at Week 24 Mean difference: -9.0% (95% CI: −52.19, 33.99; P = 0.4)
3.	Pollock et al. [14] (2019)	Mean % change in **UACR** from baseline at 24 weeks Reported as primary efficacy endpoint.	Dapagliflozin: 145 Placebo: 148 **At 24 weeks:** Dapagliflozin: 132 Placebo: 132	**Dapagliflozin:** Mean (SE): -22.92 (7.24) **Placebo:** Mean (SE): -1.7 (9.09)	Dapagliflozin significantly reduced UACR. Difference in mean change from baseline in UACR: -21·0% [-34·1 to -5·2; p=0·011]

4.	Mosenzon et al. [13] (2021)	Mean change in **UACR** from baseline at 48 months. Reported as pre-defined subgroup analysis of secondary composite outcome.	Dapagliflozin: 4444 (60- 90: 3838; at 4 years: 2612 < 60: 606; at 4 years: 367) Placebo: 4553 (60-90: 3894; at 4 years: 2552 <60: 659; at 4 years: 376)	**60-90 eGFR:** **Dapagliflozin:** Mean UACR mg/g Baseline: 19.89; at 48 months: 23.23 **Placebo:** Mean UACR mg/g: Baseline: 20.32; at 48 months: 27.20 **< 60 eGFR:** **Dapagliflozin:** Mean UACR mg/g Baseline: 32.6; At 48 months: 40.82 **Placebo:** Mean UACR mg/g: Baseline: 36.16; at 48 months: 60.27	Dapagliflozin treatment caused significant reduction in UACR (p <0.001) compared to placebo in both eGFR groups at 6 months and it is sustained throughout 4 years of study period.
5.	Jongs et al. [16] (2021)	Mean % change in **UACR** from baseline at 36 months Reported as pre-specified exploratory outcome.	Dapagliflozin: 1455 Placebo: 1451 **At 36 months:** Dapagliflozin: 159 Placebo: 158	**Dapagliflozin:** Mean (SE): -42 (3.72) **Placebo:** Mean (SE): -17 (5.54)	Relative to placebo, treatment with dapagliflozin resulted in a mean percentage change of −25% (95% CI −38·03 to −11.97; p<0·0001) at 36 months end.

OD: Once daily; MDRD: Modification of diet in renal disease; CKD-EPI: Chronic kidney disease epidemiology collaboration; eGFR: estimated glomerular filtration rate; UACR: Urinary albumin creatinine ratio; SD: Standard deviation; SE: Standard error; 95% CI: Confidence interval; SR: Systematic review; MA: Meta-analysis

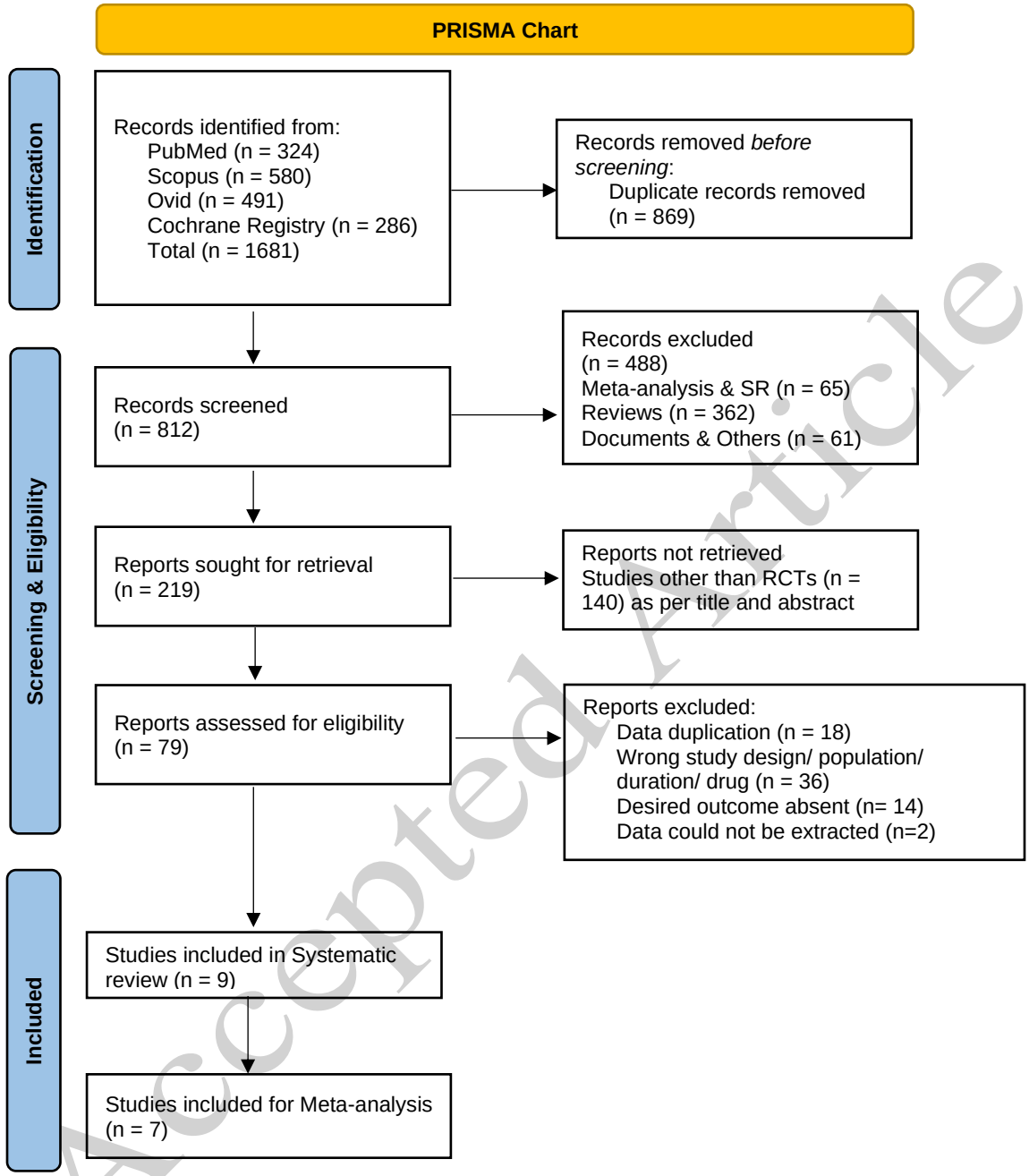


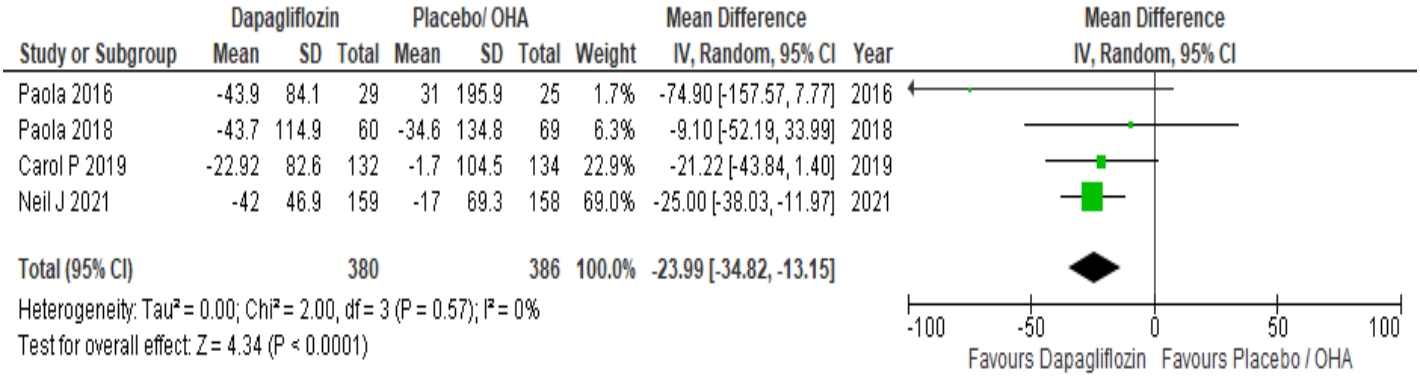
Figure 1: PRISMA chart

Abbreviations: RCT – Randomized Controlled Trial

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

A)



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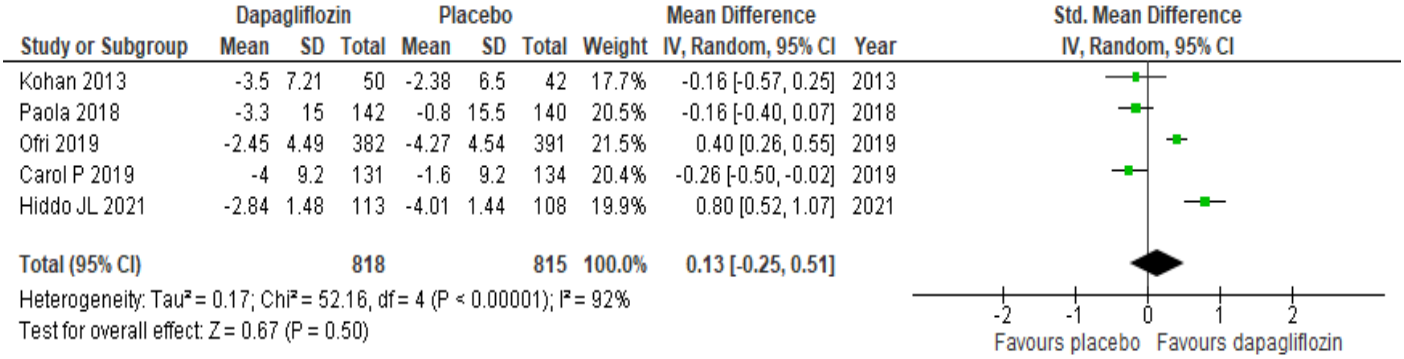

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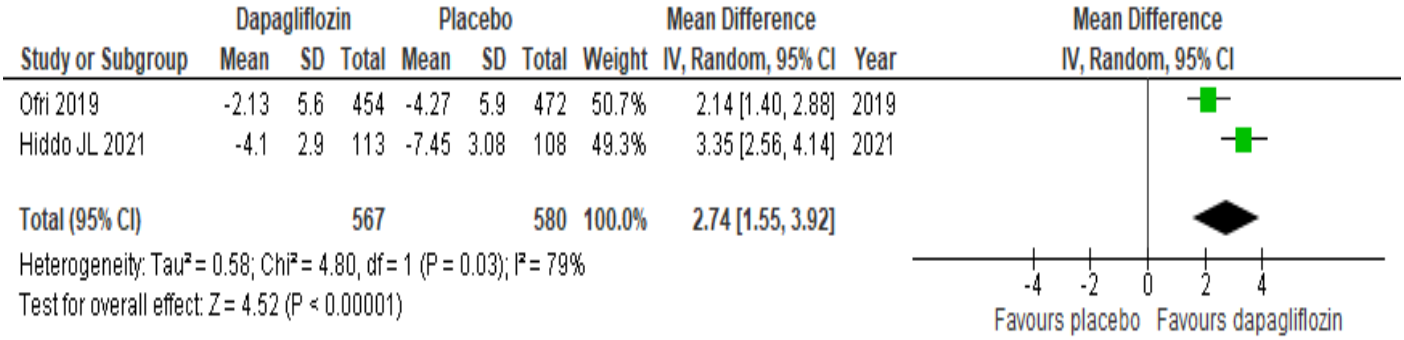

C) Mean change in chronic eGFR slope (ml/min/1.73 m^2)

Abbreviations: UACR - Urinary albumin creatinine ratio; eGFR - estimated glomerular filtration rate

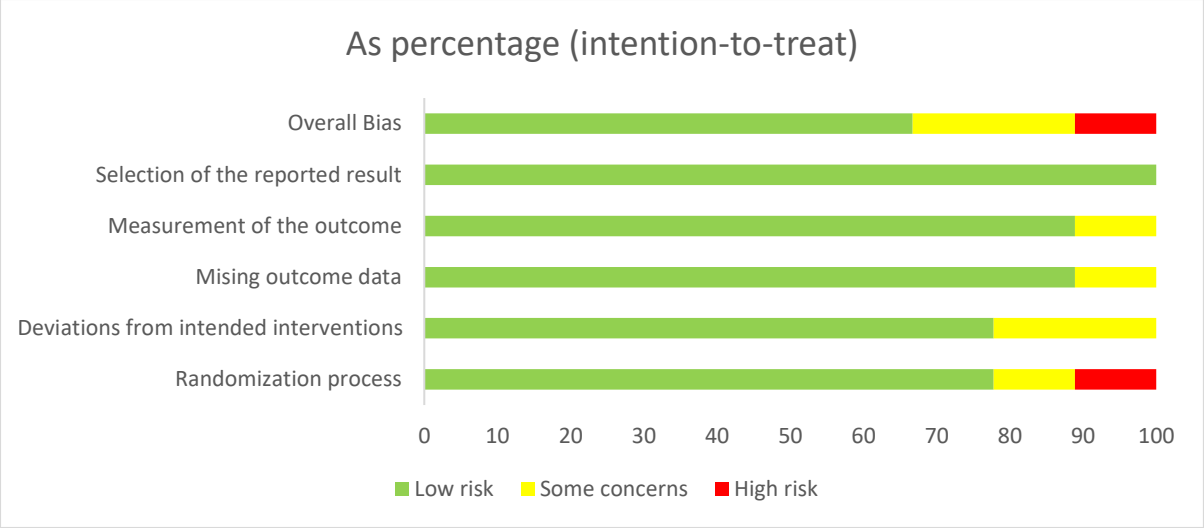

Figure 3a: Risk of Bias assessment graph

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Kohan DE, 2013	Dapagliflozin	Placebo	Mean change in eGFR fi	1	+	+	+	+	+	+
Paola 2016	Dapagliflozin	Placebo	Mean % change in UAC	1	!	+	!	+	+	!
Paola, 2018	Dapagliflozin	Placebo	Mean change in eGFR a	1	+	!	+	+	+	!
Pollock, 2019	Dapagliflozin	Placebo	Change in UACR from b	1	+	+	+	+	+	+
Mosenzon, 2019	Dapagliflozin	Placebo	Change in eGFR from b	1	+	+	+	+	+	+
Mosenzon, 2021	Dapagliflozin	Placebo	Change in UACR from b	1	+	+	+	+	+	+
Hiddo, 2021	Dapagliflozin	Placebo	Change in eGFR from b	1	+	+	+	+	+	+
Neils, 2021	Dapagliflozin	Placebo	Change in UACR from b	1	+	+	+	+	+	+
Ying, 2022	Dapagliflozin	Valsartan	Change in eGFR from b	1	-	!	+	!	+	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 3b: Overall risk of bias assessment

Abbreviations: UACR - Urinary albumin creatinine ratio; eGFR - estimated glomerular filtration rate