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Dapagliflozin in patients with chronic kidney disease: a systematic review and meta-analysis on randomized, double-blind, placebo-controlled multicenter trials

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ABSTRACT

Introduction: Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce the mortality rate, hospitalization, and cardiac morbidity in diabetic patients. However, their safety in chronic kidney disease (CKD) individuals is still debatable.

Objectives: The present study aims to evaluate the effect of dapagliflozin on primary composite outcomes and mortality rate in CKD patients using a systematic review and meta-analysis approach.

Materials and Methods: In this meta-analysis, Cochrane, Web of Science, Scopus, and PubMed databases, along with the Google Scholar search engine, were queried until March 2023. Data were analyzed by STATA software version 14 at a significance level of $P < 0.05$.

Results: A total of nine randomized clinical trials (RCTs) articles were reviewed, with a sample size of 16720 in the dapagliflozin group and 13476 in the placebo group. Dapagliflozin use (10 mg/d) compared to placebo improved primary composite outcomes in CKD patients by 39% (OR=0.61, 95% CI: 0.57, 0.65) while reducing the mortality rate by 31% (OR=0.69, 95% CI: 0.63, 0.76). In an analysis by treatment length, no statistically significant change was noted in early composite outcomes (OR=0.70, 95% CI: 0.48, 1.01) and mortality rate (OR=0.75, 95% CI: 0.39, 1.45) between patients who were on dapagliflozin for less than two years and the placebo group. However, patients receiving dapagliflozin for two years and above had significantly improved primary composite outcomes (OR=0.60, 95% CI: 0.55, 0.66) and mortality rate (OR=0.69, 95% CI: 0.61, 0.79) compared to the placebo group.

Conclusion: Dapagliflozin use, compared to placebo, improved the early composite outcomes and mortality rate in CKD patients. Prescribing a daily dose of 10 mg for a treatment duration of over two years seems safe in these patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023422186).

Implication for health policy/practice/research/medical education:
The results of combining nine randomized clinical trials studies showed that dapagliflozin administration (10 mg/d) compared to placebo improved primary composite outcomes in chronic kidney disease patients by 39% while reducing the mortality rate by 31%. In an analysis by treatment length, no statistically significant change was noted in early composite outcomes and mortality rate between patients who were on dapagliflozin for less than two years and the placebo group. However, patients receiving dapagliflozin for two years and above had significantly improved primary composite outcomes and mortality rates compared to the placebo group.

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Introduction

Nearly 700 million people are estimated to suffer from chronic kidney disease (CKD) worldwide (1). Patients with CKD experience a higher mortality rate, hospitalization, and cardiovascular morbidity than those with normal kidney function (2,3). Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower the mortality rate and cardiovascular events in patients with diabetes mellitus type 2 (4-6).

In 2016, U.S. Food and Drug Administration (FDA) warned that diabetic patients treated with SGLT2 inhibitors are subject to acute kidney injury (AKI) risk (7). Contrarily, a meta-analysis of clinical trials concluded that SGLT2 inhibitors confer a protective effect against AKI (8). Thus, the safety of SGLT2 inhibitors is still under debate.

A consensus from the American Diabetes Association and the European Society for the Study of Diabetes in 2018 recommended SGLT2 inhibitors for patients with renal diseases and heart failure (4). Nevertheless, a 2017 study revealed that dapagliflozin and canagliflozin may raise the risk of renal adverse effects, whereas empagliflozin may prove beneficial (9).

The researchers have highlighted that SGLT2 inhibitors preserve renal function and lower the progression risk of renal diseases (6, 10). In some trials, the primary abnormal renal parameters gradually returned to normal in patients receiving SGLT2 inhibitors (11). The present study has evaluated the effect of dapagliflozin administration on primary composite outcomes and mortality rate in patients with CKD using the systematic review and meta-analysis approach.

Materials and Methods

Study design

The current study investigated the effectiveness of dapagliflozin in CKD patients using a systematic review and meta-analysis method. This article was written based on PRISMA guidelines, and its protocol was registered on the PROSPERO website (CRD42023422186, https://www.crd.york.ac.uk/prospero/#recordDetails).

Search strategy

In this study, the Cochrane, Web of Science, Scopus, and PubMed databases, as well as the Google Scholar search engine, were searched without time restriction until March 2023. The search query used a combination of MeSH terms, including "SGLT2," "chronic kidney disease," "Sodium-glucose cotransporter-2 inhibitors," and "dapagliflozin." A manual search of the reference list in the identified articles was conducted to find relevant articles. The search strategy in PubMed was as follows: "(Chronic Kidney Disease [Title/Abstract]) AND (SGLT2 [Title/Abstract] OR Sodium-glucose cotransporter-2 inhibitors[Title/Abstract] OR Dapagliflozin[Title/Abstract])".

PICO components

Population: studies on patients with CKD, Intervention: Dapagliflozin use, Comparison: Placebo group, Outcomes: Primary composite outcomes and mortality in patients with CKD.

Inclusion criteria

This study involved double-blind, placebo-controlled trials evaluating the effect of dapagliflozin use in CKD patients.

Exclusion criteria

The following studies were excluded: studies lacking necessary information for data analysis; duplicate studies; those published as protocols; those reporting a combination of multiple drugs from the class of SGLT2 inhibitors; low-quality studies based on Cochrane checklist; and those whose full-texts were unavailable.

Quality assessment

Two authors independently assessed the initial articles using the Cochrane Institute checklist for quality assessment of clinical trials (12). This checklist consists of seven items, each evaluating a major dimension or bias in clinical trials. Each item has three choices: "low risk," "high risk," and "unclear risk." Then, all discrepancies between the two evaluating authors regarding the quality of a particular study were resolved by their consensus on a single choice.

Data extraction

Two authors extracted data from studies to minimize data collection errors. They designed a checklist for data extraction, containing the first author's name, the location of the study, the mean age of patients, the publication year of the study, treatment duration, the sample size of the placebo and dapagliflozin groups, the dose of dapagliflozin administration, the odds ratio (OR) for dapagliflozin effect on renal function and mortality in CKD patients.

Statistical analysis

The relationship between dapagliflozin use and renal function in CKD patients was examined using the OR index. The logarithmic OR was applied in each study to pool the results. In addition, the heterogeneity of the studies was evaluated using the I^2 index, and the collected data were analyzed using the random effect model. Data analysis was executed in STATA 14 software at a significance level of $P < 0.05$ for all tests.

Results

Study selection

Initially, 961 articles were retrieved by searching the mentioned databases. After checking the titles, 425 duplicates were eliminated. The abstracts were screened, and 86 out of 536 articles were discarded due to lacking necessary data for meta-analysis. Of the remaining 450 articles, 19 were omitted due to the unavailability of their full texts and another 422 for meeting other exclusion criteria. Eventually, nine high-quality articles entered the systematic review and meta-analysis process (Figure 1).

In total, nine RCTs were reviewed in this meta-analysis, with a sample size of 16720 in the dapagliflozin group (at a daily dose of 10 mg) and 13476 in the placebo group (Table 1).

Dapagliflozin use (10 mg per day) compared to placebo caused a 29% improvement in the primary composite outcomes in CKD patients [OR = 0.61, 95% CI: 0.57, 0.65] (Figure 2).

Figure 3 stratifies the effect of dapagliflozin use (10 mg/d) compared to placebo on primary composite outcomes in CKD patients into two groups based on treatment duration. No statistically significant difference was found between CKD patients who used 10 mg/d of dapagliflozin for less than two years and the placebo group (OR = 0.70, 95% CI: 0.48, 1.01). However, patients receiving dapagliflozin for two years and above had significantly improved primary composite outcomes (OR = 0.60, 95% CI: 0.55, 0.66) compared to the placebo group.

The OR for the effect of dapagliflozin use compared to placebo on mortality rate in patients with CKD was 0.69 (95% CI: 0.63, 0.76). A daily dapagliflozin dose of 10 mg decreased the mortality rate of patients by 31% compared to placebo (Figure 4).

Figure 5 illustrates the effect of dapagliflozin administration by treatment duration on the mortality rate of CKD patients compared to the placebo. Using 10 mg/d of dapagliflozin for less than two years did not significantly change the mortality rate in these patients compared to the placebo [OR = 0.75, 95% CI: 039, 1.45]. Conversely, patients receiving dapagliflozin (10 mg/d) for
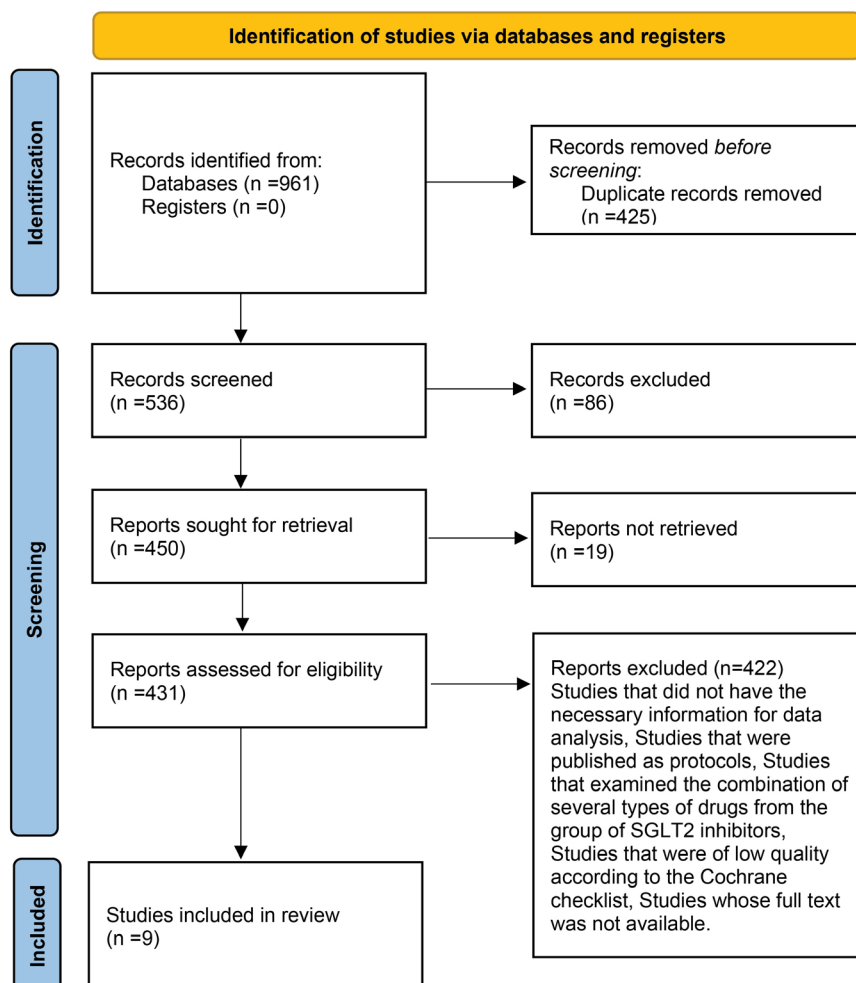

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

First author, year of publication	Place	Number of people in the dapagliflozin group	Mean age in dapagliflozin group	Number of people in the placebo group	Mean Age in placebo group	Time of treatment (y)
Heerspink, 2022 (13)	21 Countries	2152	61.8	2152	61.9	2.4
McMurray, 2021 (14)	NR	1339	63.9	1355	65.5	2.4
Chertow, 2021 (15)	NR	2152	61.8	2152	61.8	NR
McMurray, 2021 (16)	Several countries	3836	61.4	468	65.3	2.4
Heerspink, 2020 (17)	NR	197	61.8	312	61.9	2.4
Wheeler, 2021 (18)	21 Countries	697	56.9	701	56	2.4
Provenzano, 2022 (19)	NR	2043	61.8	2032	61.8	NR
Vart P, 2022 (20)	Asia	692	59	654	59.1	1.9
Vart P, 2022 (20)	Europe	610	61.8	623	62.1	2.3
Vart P, 2022 (20)	Latin America	449	62.6	463	63.1	2.3
Vart P, 2022 (20)	North America	401	65.8	412	64.6	2.1
Waijer, 2022 (21)	NR	2152	61.8	2152	61.8	NR

NR, not reported.

two years or more showed a drastic reduction in mortality rate compared to the placebo group [OR = 0.69, 95% CI: 0.61, 0.79].

As shown in Figure 6, the literature search stage was completed without any bias, and the publication bias plot was statistically non-significant (P = 0.583).

Discussion

This meta-analysis suggested that daily use of 10 mg of dapagliflozin improved the primary composite outcomes by 39% and lowered the mortality rate by 31% in CKD patients compared to the placebo group.

Previous meta-analyses have assessed the impact of SGLT2 inhibitors on cardiac and kidney outcomes and mortality rates in different diseases. McGuire et al

performed a meta-analysis on six RCTs with a sample size of 46 969 patients with type 2 diabetes. Of these, 31 116 had an atherosclerotic cardiovascular illness. The authors found that SGLT2 inhibitors' use reduced the risk of adverse renal outcomes in these patients (hazard ratio [HR]: 0.62; 95% CI: 0.56-0.70) (22). A meta-analysis of observational studies and RCTs by Menne et al examined the effect of SGLT2 inhibitors on renal adverse events. Consistent with the findings of the present meta-analysis that suggest the positive impact of dapagliflozin on outcomes and mortality in CKD patients, their results indicated that SGLT2 inhibitors declined the risk of AKI development up to 36% (OR: 0.64; 95% CI: 0.53–0.78) (23). However, their study differs from ours in that they assessed the effectiveness of all SGLT2 inhibitors, while
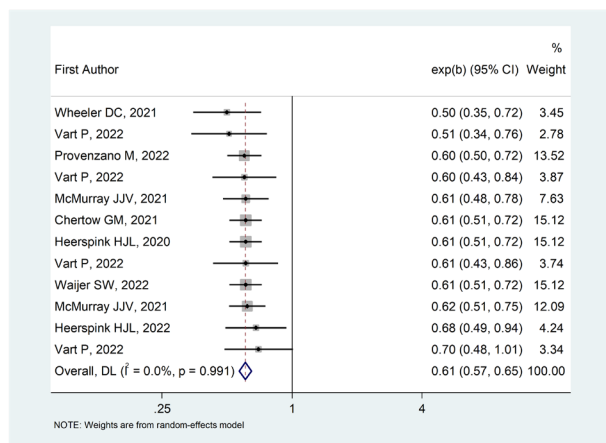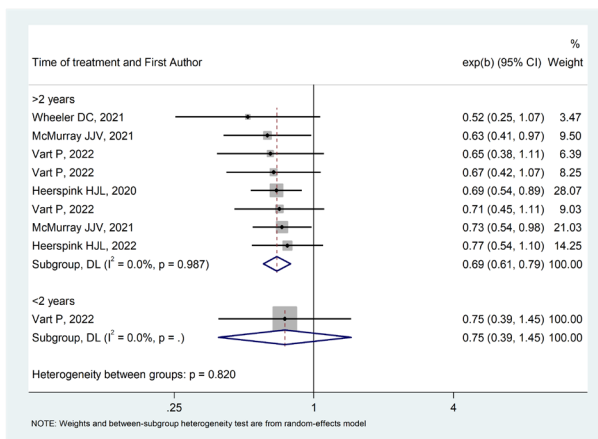

Figure 2. Forest plot of the effect of dapagliflozin compared to placebo on primary composite outcomes in patients with CKD and its 95% confidence interval
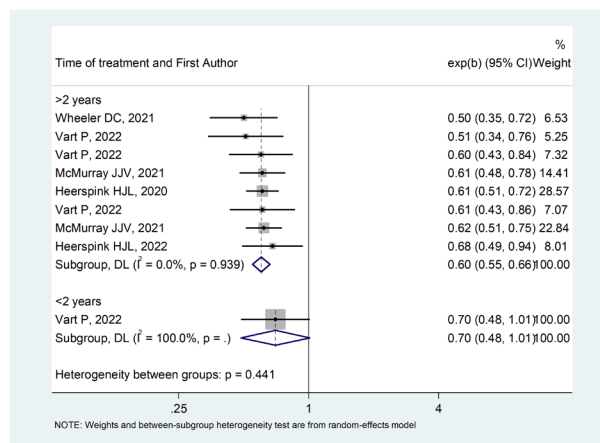
Figure 3. Forest diagram of the effect of dapagliflozin compared to placebo on primary composite outcomes in patients with CKD and its 95% confidence interval according to treatment duration
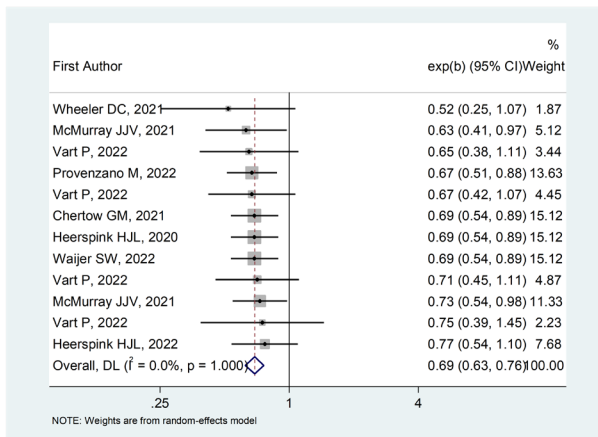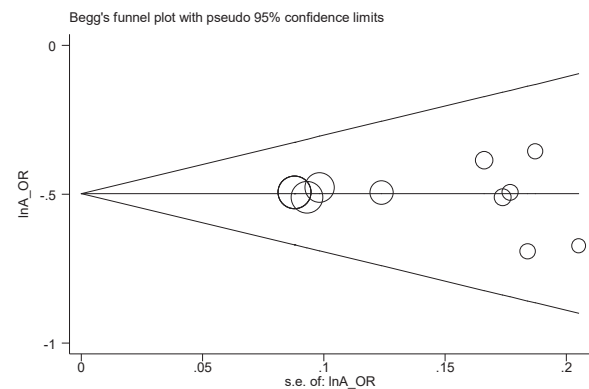
Figure 4. Forest plot of the effect of dapagliflozin compared to placebo on the mortality of patients with CKD and its 95% confidence interval.

Figure 5. Forest plot of the effect of dapagliflozin compared to placebo on the mortality of patients with CKD and its 95% confidence interval according to the duration of treatment.

Figure 6. Publication bias diagram

our meta-analysis focused specifically on evaluating the dapagliflozin effect.

Gilbert et al presented a meta-analysis of three RCTs to compare patients who received an SGLT2 inhibitor with those treated with a placebo. The authors found a lower likelihood of AKI incidence in those who received SGLT2 inhibitors than in the placebo group, and the observed association was statistically significant (HR: 0.66, 95% CI: 0.54-0.80) (8). A recent meta-analysis of five RCTs by Chen et al concluded that dapagliflozin, compared to placebo, resulted in an 11.2% reduction in the risk of all-cause death (OR = 0.88, 95% CI: 0.81-0.94) while noticeably lowering the AKI risk (OR = 0.71, 95% CI: 0.60-0.83) (24). In another meta-analysis, comprising a total of 38 723 participants, Neuen et al evaluated the effects of SGLT2 inhibitors on major kidney outcomes in cases with type 2 diabetes. The results demonstrated that

SGLT2 inhibitors significantly decreased the dialysis risk, kidney transplantation, or death due to kidney disease (Risk ratio [RR]: 0.67, 95% CI: 0.52-0.86). They also reduced the risk of end-stage kidney disease (RR: 0.65, 95% CI: 0.53-0.81) and AKI (RR: 0.75, 95% CI: 0.66-0.85) (25). As the mentioned studies established, SGLT2 inhibitors caused a drastic reduction in the risk of dialysis, kidney transplantation, AKI, and mortality in patients with type 2 diabetes, which corroborates the results of the present study.

Tang et al conducted a meta-analysis to compare the effect of SGLT2 inhibitors on renal adverse events in patients with type 2 diabetes. According to their findings, dapagliflozin, compared to the placebo, was significantly associated with an increased risk of composite renal events (OR: 1.64, 95% CI: 1.26-2.13). Empagliflozin compared to placebo (OR: 0.63, 95% CI: 0.54-0.72), empagliflozin compared to canagliflozin (OR: 0.48, 95% CI: 0.29-0.82), and empagliflozin compared to dapagliflozin (OR: 0.38, 95% CI: 0.28-0.51) appeared to reduce the risk of composite renal events (9), which contradicts the results of the current meta-analysis. This discrepancy may be justified by the different populations studied, given that Tang et al assessed diabetic patients, whereas this study concentrated on CKD patients. Moreover, different sample sizes can represent another reason for inconsistent results.

Zelniker et al conducted a meta-analysis of three RCTs, including 34 322 diabetic patients, of whom almost 60% suffered from atherosclerotic cardiovascular disorder. The study objective was to determine the effect of SGLT2i inhibitors on cardiovascular and renal outcomes. The obtained results indicated that SGLT2i decreased the progression risk of renal diseases by up to 45% (HR: 0.55, 95% CI: 0.48-0.46) (10). Consistent with our study, Zelniker and colleagues' study suggested the preventive effects of SGLT2 inhibitors on cardiovascular outcomes in diabetic patients. However, it failed to address the safe

dose and duration of SGLT2 inhibitors. In contrast, our study found that daily use of 10 mg of dapagliflozin for two years and above can considerably reduce the mortality risk and primary composite outcomes.

Conclusion
Compared to the placebo, dapagliflozin improved the primary composite outcomes in CKD patients while reducing their mortality rate. Prescribing dapagliflozin at a daily dose of 10 mg and a duration of more than two years seems safe and suitable in patients with CKD. Future studies are suggested to explore various dapagliflozin doses and different age groups of CKD patients to overcome the limitations of the present study.

Limitations of the study
This study faces some limitations. First, a dapagliflozin dose of 10 mg/d was used in all reviewed trials, which hindered further sub-group analysis by drug dose. Second, some studies were performed across several countries. Thus, stratifying the results by study location was not possible. Finally, it failed to conduct a sub-analysis of the results by age group due to the low number of reviewed articles and a nearly similar patient mean age of 61 years reported in most studies.

Authors' contribution
Conceptualization: HKh and LGh.
Methodology: ER and MrF.
Validation: FGh and ER.
Formal analysis: SA and LGh.
Research: NM and FZ.
Resources: HKh, FZ and MrF.
Data curation: ER and SA.
Visualization: ER and LGh.
Supervision: HKh.
Project management: NM.
Writing–original draft: LGh, HKh, MrF, ER and FGh.
Writing–reviewing and editing: NM, SA, FZ, and ER.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author. This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023422186).

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