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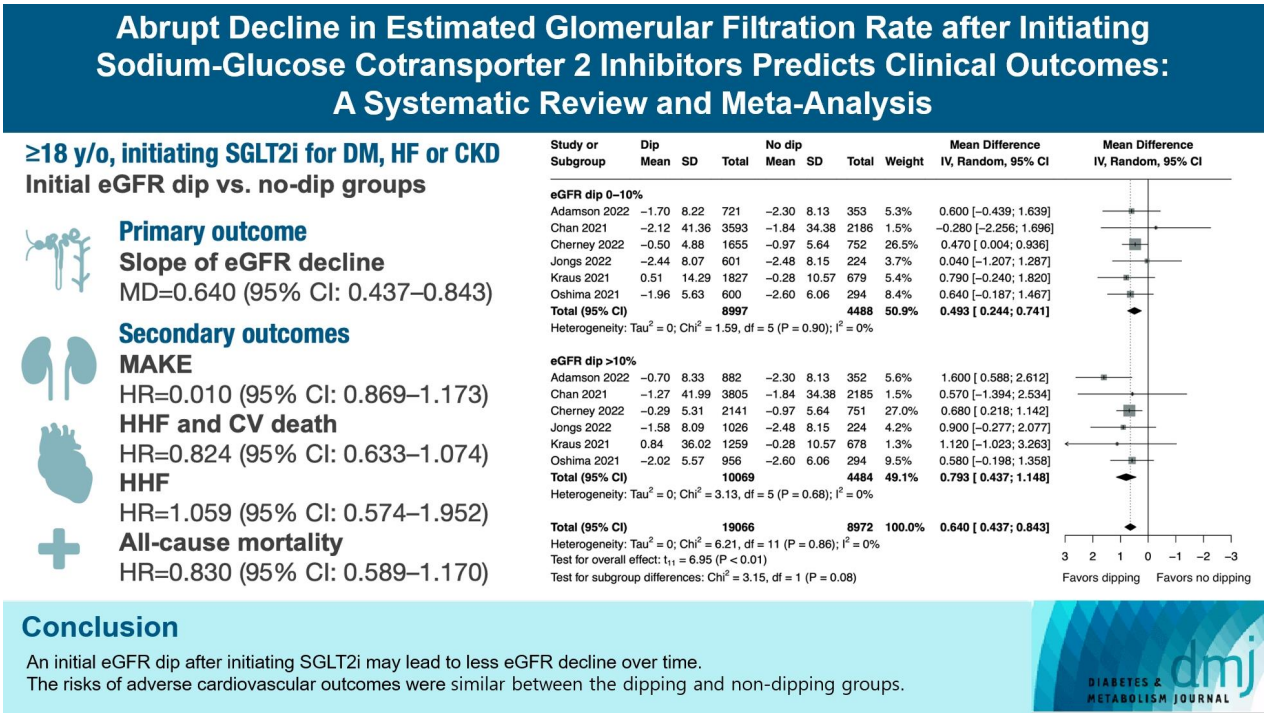

Highlights

- **An initial eGFR dip on SGLT2i might be linked to a slower annual eGFR decline.**
- **Patients with ≤10% eGFR dip had reduced MAKE, unlike those with >10% dip.**
- **No significant differences in mortality and adverse CV outcomes were observed.**

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Abrupt Decline in Estimated Glomerular Filtration Rate after Initiating Sodium-Glucose Cotransporter 2 Inhibitors Predicts Clinical Outcomes: A Systematic Review and Meta-Analysis

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Background: The initiation of sodium-glucose cotransporter-2 inhibitors (SGLT2i) typically leads to a reversible initial dip in estimated glomerular filtration rate (eGFR). The implications of this phenomenon on clinical outcomes are not well-defined.
Methods: We searched MEDLINE, Embase, and Cochrane Library from inception to March 23, 2023 to identify randomized controlled trials and cohort studies comparing kidney and cardiovascular outcomes in patients with and without initial eGFR dip after initiating SGLT2i. Pooled estimates were calculated using random-effect meta-analysis.
Results: We included seven studies in our analysis, which revealed that an initial eGFR dip following the initiation of SGLT2i was associated with less annual eGFR decline (mean difference, 0.64; 95% confidence interval [CI], 0.437 to 0.843) regardless of baseline eGFR. The risk of major adverse kidney events was similar between the non-dipping and dipping groups but reduced in patients with a ≤10% eGFR dip (hazard ratio [HR], 0.915; 95% CI, 0.865 to 0.967). No significant differences were observed in the composite of hospitalized heart failure and cardiovascular death (HR, 0.824; 95% CI, 0.633 to 1.074), hospitalized heart failure (HR, 1.059; 95% CI, 0.574 to 1.952), or all-cause mortality (HR, 0.83; 95% CI, 0.589 to 1.170). The risk of serious adverse events (AEs), discontinuation of SGLT2i due to AEs, kidney-related AEs, and volume depletion were similar between the two groups. Patients with >10% eGFR dip had increased risk of hyperkalemia compared to the non-dipping group.
Conclusion: Initial eGFR dip after initiating SGLT2i might be associated with less annual eGFR decline. There were no significant disparities in the risks of adverse cardiovascular outcomes between the dipping and non-dipping groups.

Keywords: Diabetes mellitus, type 2; Glomerular filtration rate; Kidney; Sodium-glucose transporter 2 inhibitors

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INTRODUCTION

Since the emergence of sodium-glucose cotransporter-2 inhibitors (SGLT2i), numerous randomized controlled trials have demonstrated their efficacy in renoprotection and improving annual estimated glomerular filtration rate (eGFR) decline, beyond their initially intended anti-diabetic effects via inhibition of glucose uptake in the proximal convoluted tubule [1-3]. These agents were shown to reduce the incidence of acute kidney injury by 41% [4] and decrease the composite risk of worsening eGFR, end-stage renal disease, or renal death by 20% to 37% [5-7].

Although SGLT2i are known to have renoprotective effects, their initiation can cause an acute and persistent decline ("dip") in eGFR sometimes exceeding 10% below baseline, which is typically reversible after discontinuation of SGLT2i [8-11]. Glomerular hyperfiltration, observed in 10%–67% and 6%–73% of patients with type 1 and type 2 diabetes mellitus respectively [12], may involve upregulation of SGLTs and an imbalance of vasoactive humoral factors regulating pre- and postglomerular arterioles [13]. By inhibiting SGLT2, SGLT2i may alleviate glomerular hyperfiltration [14-16], and the reversible nature of SGLT2i-induced dip also suggests a hemodynamic regulation of intraglomerular pressure [15,17].

The level of eGFR dip can vary widely among different individuals [8-11] and may reflect the effect of SGLT2i in relieving intraglomerular pressure [18], which has implications for clinical outcomes. However, current understanding of the dip phenomenon is limited and previous studies have yielded inconsistent results. While one study reported a larger initial eGFR dip being associated with a slower chronic decline in eGFR [10], others did not find significant differences among patients with different levels of eGFR dip [9,19]; discrepancies also existed regarding the risk of adverse cardiovascular and mortality outcomes [19,20]. Therefore, we conducted this systematic review and meta-analysis to comprehensively evaluate the kidney, cardiovascular, and survival outcomes among patients with different levels of eGFR dip after initiating SGLT2i.

METHODS

The current study was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table 1) [21]. The protocol for this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42023411012). The current study was exempt from ethics approval because it was conducted through collection of data from primary studies for which ethical approval had been obtained.

Data sources and search strategies

We searched the electronic databases of MEDLINE, the Cochrane Central Register of Controlled Trials, and Embase for eligible studies, with no language restriction, from inception to March 23, 2023. Randomized controlled trials or cohort studies that evaluated differences in kidney or cardiovascular outcomes, risk of death, and adverse events (AEs) among patients with different levels of initial eGFR decline after starting SGLT2i were included. The search terms included various SGLT2i drug names, relevant MeSH or Emtree terms, and related keywords. The syntax of the search strategy was provided in Supplementary Table 2. Manual screening of the references of included articles was also conducted to identify additional potentially eligible studies. Two investigators (M.H.C. and Y.S.T.) searched published reports independently to increase methodological rigor and to prevent ascertainment bias. We then obtained the full text of the selected papers for quality assessment and data synthesis. If necessary, we contacted the authors of the papers to obtain more information.

Inclusion and exclusion criteria

The following criteria were applied to screen for eligible studies: (1) population: adults (age ≥18 years) initiating SGLT2i for type 2 diabetes mellitus, heart failure, or chronic kidney disease; (2) exposure: individuals with initial decline of eGFR after initiating SGLT2i. The time periods defining the initial eGFR decline were based on those of individual studies, ranging from 2 weeks to 3 months; (3) comparison: individuals without initial eGFR decline after initiating SGLT2i; and (4) outcomes: the slope of long-term kidney function decline, mortality risk, adverse kidney outcomes, adverse cardiovascular outcomes, and AEs during treatment.

Criteria for exclusion included: (1) pediatric population (age <18 years); (2) studies without aforementioned exposure and control groups; (2) studies that used SGLT2i for indications other than type 2 diabetes mellitus, heart failure, or chronic kidney disease; (3) those not reporting details for the outcomes of interest; (4) studies on animal models; (5) those published only in abstract format; and (6) those published without peer review.

Study selection and data extraction

The titles and abstracts of the retrieved studies were screened by two reviewers (M.H.C. and Y.S.T.) independently for eligibility based on the inclusion and exclusion criteria detailed above. Studies that met the criteria were evaluated in full text by the same two reviewers, and any disagreements were resolved through discussion with a third author. Two reviewers independently extracted data from the included studies, including the first author, year of publication, patient characteristics, study design, sample sizes, therapies administered, initial changes in eGFR after starting SGLT2i, and relevant data on kidney or cardiovascular outcomes, mortality risk, and AEs during SGLT2i treatment. The extracted data were cross-checked for accuracy by the two reviewers.

Outcomes

The primary outcome of the present study was the slope of eGFR decline measured in mL/min/1.73 m^2 per year. Secondary outcomes included major adverse kidney events (MAKE) including sustained ≥50% decrease in eGFR, eGFR <15 mL/min/1.73 m^2, doubling of creatinine level, need for chronic dialysis or renal transplant, or death from renal failure. Other secondary outcomes included hospitalized heart failure, cardiovascular death, all-cause death, and various AE-related outcomes such as discontinuation of SGLT2i due to AEs, serious AEs, volume depletion, hyperkalemia, acute kidney injury, or kidney-related AEs. The outcomes were compared between patients with and without initial eGFR dip, with the non-dipping group set as the reference.

Quality and certainty assessment

Methodological quality of the included studies was assessed independently by two reviewers (M.H.C. and Y.S.T.) using the Newcastle-Ottawa Scale for cohort studies [22]. The scale contained eight items in three categories: selection of cohorts (four items), comparability (one item), and evaluation of outcomes (three items). Studies were scored from 0 to 9 points and those scoring ≥7 points were deemed of high quality. Studies were considered of moderate quality with some risk of bias if they scored 4 to 6, and of low quality if they scored 0 to 3 [23]. Two review authors (Y.S.T. and J.Y.C.) independently assessed and graded the certainty of evidence regarding our primary and secondary outcomes as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24]. Any disagreement between the two reviewers were settled through consultation with a third author (V.C.W.).

Data analysis

Data synthesis was conducted with random-effect meta-analysis. Continuous data was reported as mean difference (MD) with 95% confidence interval (CI) and dichotomous data as odds ratio (OR) with 95% CI using the Mantel-Haenszel method, or hazard ratio (HR) with 95% CI using generic inverse variance analysis. The non-dipping group, i.e., patients whose eGFR remained the same or increased after initiating SGLT2i, was used as the control group. Heterogeneity was assessed using the I^2 statistic and considered substantial if the I^2 exceeded 50% [25]. Publication bias was evaluated through visual inspection of the funnel plot, and we performed sensitivity analysis with the leave-one-out approach to assess the impact of individual trials on the overall outcome estimates. In order to prevent double-counting of the shared group (specifically, the control cohort) in studies with multiple comparative cohorts, the events and total numbers of dichotomous data in the control group were evenly divided if they were included more than once in any particular analysis [26]. Pre-specified subgroup analysis stratified by a cut-off of 10% eGFR dip was conducted to explore differences in primary and secondary outcomes among patients with different levels of initial dip in eGFR. Network meta-analysis was employed for comparison of the annual eGFR decline, MAKE, and cardiovascular outcomes between the subgroups with >10% and ≤10% eGFR. We conducted meta-regression analyses to examine the impact of various study characteristics, such as age, baseline eGFR, proportion of females, and proportion of patients with diabetes mellitus, on kidney outcomes. Trial sequential analysis (TSA) was performed on all-cause mortality and the composite outcome of hospitalized heart failure and cardiovascular death to control type I and type II errors and estimate the required information size since these outcomes had few included studies. The α-spending boundaries were calculated with a two-sided type I error risk of 5%, and the futility boundaries were calculated with a 90% power using the O'Brien-Fleming function. Statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Denmark).

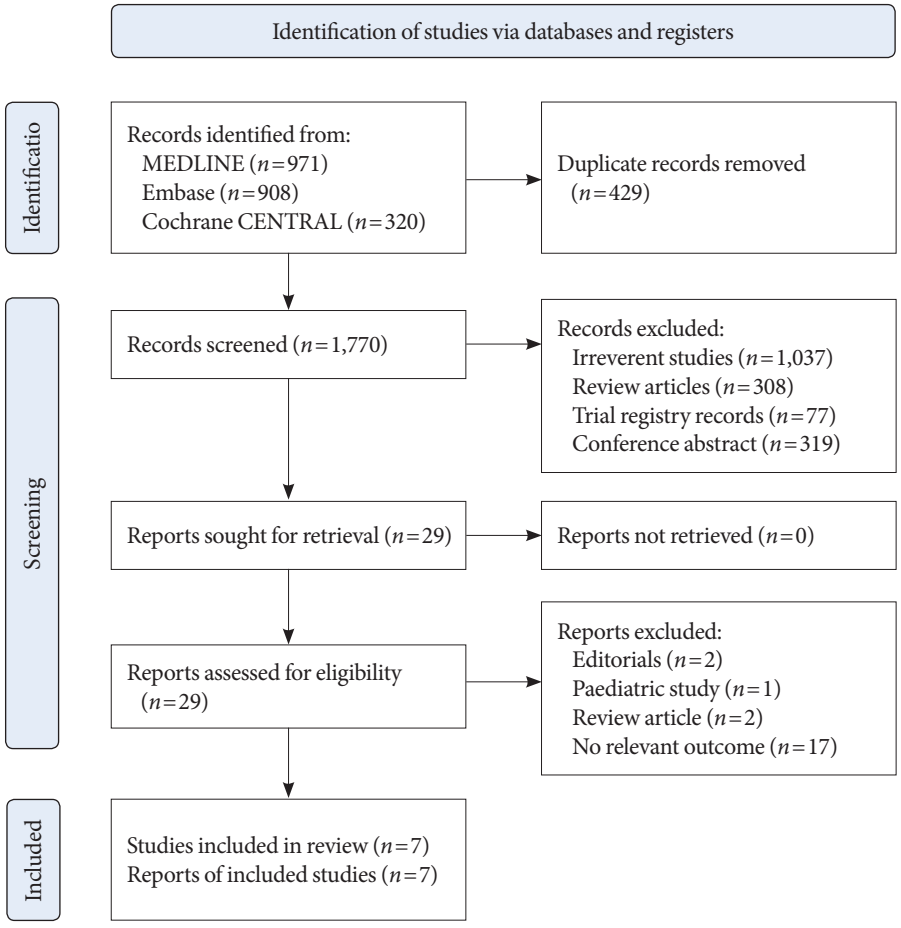

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection for the current systematic review.

RESULTS

Selection and characteristics of studies

A total of 2,199 records were identified through our literature search. After removal of duplicates (n=429), 1,770 records were screened and 29 were evaluated in full text. Finally, seven studies published between 2020 and 2022 were included in the current meta-analysis. A flowchart of the selection process was shown in Fig. 1.

All studies were observational studies. The mean age of participants was between 58.8 and 67.8 years; females comprised 20% to 45% of patients. After initiation of an SGLT2i, 28% to 41% of patients experienced a ≤10% dip in eGFR, while 28% to 49% had a >10% dip. Details regarding characteristics of the included studies were shown in Table 1.

Quality assessment

The included studies scored between 6 and 9 points on the Newcastle-Ottawa Scale. Five studies [9,19,20,27,28] were rated as high quality, while two studies [11,29] were considered to be of moderate quality. Two studies [11,29] raised concern regarding the comparability of cohorts, and five studies [11,20, 27-29] were considered to be at risk of bias in terms of the adequacy of follow-up (Supplementary Table 3).

Outcomes

Primary outcome: slope of eGFR decline

Our meta-analysis demonstrated that patients with initial eGFR dip after starting SGLT2i had less annual eGFR decline compared to the non-dipping group (MD, 0.64; 95% CI, 0.437 to 0.843 mL/min/1.73 m^2 per year; P<0.01; I^2=0%; sensitivity analysis, consistent results). Subgroup analysis showed similar

Table 1. Characteristics of included studies ($n=7$)

Study	SGLT2i	Study design	No. of patient[a]	Age, yr	Female, %	Follow-up period	Location	Population	DM, %	HF, %	eGFR, mL/min/1.73 m^2
Oshima et al. (2021) [9]	Canagliflozin	*Post hoc* analyses of RCT	>10%: 956 0%–10%: 600 No dip: 588	63.3±9.3 62.7±8.9 62.1±9.1	33.6 33.7 36.2	Median 2.6 yr	34 Countries	T2DM, CKD with pro-teinuria	100 (inclusion criteria)	13.3 14.3 18.2	57.9±18.1 56.9±18.2 53.6±18.1
Kraus et al. (2021) [11]	Empagliflozin	*Post hoc* analyses of RCT	>10%: 1,259 0%–10%: 1,827 No dip: 1,357	64.6±8.3 62.8±8.4 62.2±8.8	30.5 28.0 27.8	Median 3.1 yr	42 Countries	T2DM, CV disease	100 (inclusion criteria)	10.9 8.2 10.0	68.4±18.1 79.5±22.9 72.9±20.6
Jongs et al. (2022) [19]	Dapagliflozin	*Post hoc* analyses of RCT	>10%: 1,026 0%–10%: 601 No dip: 448	62.9±11.5 61.1±12.1 61.1±12.7	34.0 30.3 34.2	Median 2.3 yr	21 Countries	CKD with pro-teinuria	72.8 62.9 65.2	10.6 9.8 13.4	43.0±12.3 43.4±12.3 43.9±12.5
Zannad et al. (2022) [20]	Empagliflozin	*Post hoc* analyses of RCT	>11.4%: 594 1%–11.4%: 578 No dip: 610	67.7±10.5 67.2±11.0 66.9±10.9	29.0 21.6 20.0	Median 16 mo	20 Countries	HFrEF	NR	100 (inclusion criteria)	60.7±21.7 65.3±21.9 59.3±22.8
Adamson et al. (2022) [27]	Dapagliflozin	*Post hoc* analyses of RCT	>10%: 882 0%–10%: 721 No dip: 706	67.8±10.7 65.3±11.2 65.2±10.8	25.1 20.5 25.4	Median 18.2 mo	20 Countries	HFrEF	46.8 38.8 39.2	100 (inclusion criteria)	62.6±17.9 69.5±20.9 66.6±19.3
Chan et al. (2021) [28]	Empagliflozin, dapagliflozin, canagliflozin	Retrospective cohort study	>10%: 3,805 0%–10%: 3,593 No dip: 4,371	59.5±12.1 58.8±11.6 58.9±11.5	44.5 38.7 40.4	Mean 13.9 mo	Taiwan	T2DM	100 (inclusion criteria)	5.5 4.0 4.7	95.9±32.9 93.0±27.8 87.2±26.1
Cherney et al. (2022) [29]	Ertugliflozin	*Post hoc* anal-yses of RCT	>8%: 2,141 0%–8%: 1,655 No dip: 1,503	64.3±8.1 64.9±8.1 63.7±8.0	30.7 28.5 29.3	Median 3.0 yr	34 Countries	T2DM	100 (inclusion criteria)	NR	81.1±21.5 71.3±20.0 74.2±19.2

Values are presented as mean±standard deviation.
SGLT2i, sodium-glucose cotransporter 2 inhibitor; DM, diabetes mellitus; HF, heart failure; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; NR, not reported.
[a]Participants grouped according to level of eGFR dip after initiation of SGLT2i.

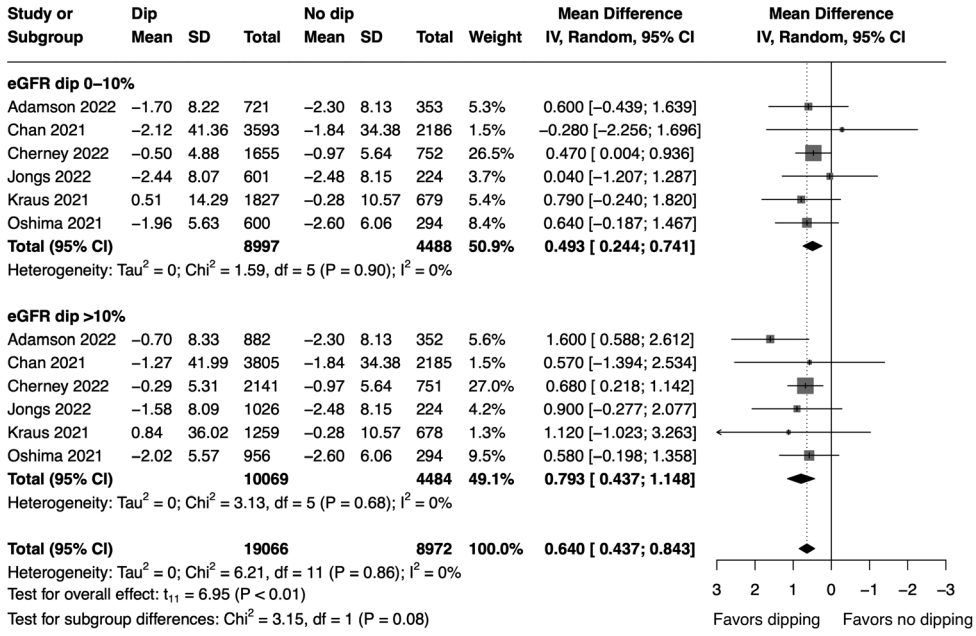

Fig. 2. Forest plot showing difference in slope of annual estimated glomerular filtration rate (eGFR) decline between the dipping and non-dipping groups. SD, standard deviation; IV, inverse variance; CI, confidence interval.

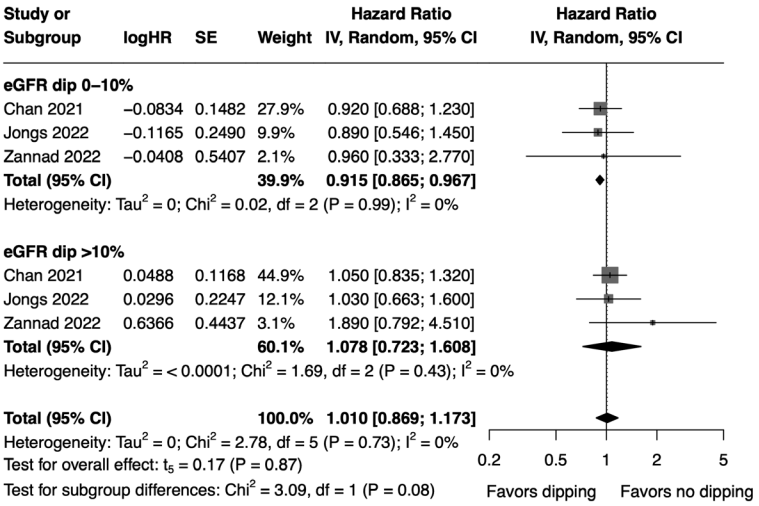

Fig. 3. Forest plot illustrating the comparison of major kidney adverse events between the dipping and non-dipping groups. HR, hazard ratio; SE, standard error; IV, inverse variance; CI, confidence interval; eGFR, estimated glomerular filtration rate.

findings in patients with ≤10% dip in eGFR (MD, 0.493; 95% CI, 0.244 to 0.741 mL/min/1.73 m^2 per year) and those with >10% dip in eGFR (MD, 0.793; 95% CI, 0.437 to 1.148 mL/min/1.73 m^2 per year) (Fig. 2). Comparison between the two subgroups showed that patients with >10% eGFR dip had less annual eGFR decline compared to those with ≤10% dip (MD, 0.299; 95% CI, 0.051 to 0.547 mL/min/1.73 m^2 per year) (Supplementary Table 4). When subgrouped by baseline eGFR, patients with initial eGFR dip had less annual eGFR decline compared to the non-dipping group regardless of their baseline eGFR level (Supplementary Fig. 1).

In comparison, no significant difference in annual eGFR decline was found between the dipping and non-dipping groups in patients given placebo (MD, 0.258; 95% CI, −0.031 to 0.547 mL/min/1.73m^2 per year) (Supplementary Fig. 2). No apparent publication bias was identified through visual inspection of the funnel plot (Supplementary Fig. 3). Results from meta-regression analysis indicated that age, baseline eGFR, proportion of females, and proportion of patients with diabetes were not significant moderators of annual eGFR decline (Supplementary Table 5).

Secondary outcomes: major adverse kidney events

The hazard of MAKE did not significantly differ between the dipping and non-dipping groups (HR, 1.01; 95% CI, 0.869 to 1.173; I^2=0%; sensitivity analysis, consistent results). However, subgroup analysis revealed a marginally lower hazard of MAKE in patients with an initial eGFR dip of ≤10% compared to the non-dipping group (HR, 0.915; 95% CI, 0.865 to 0.967), whereas no significant difference was observed between patients with an initial eGFR dip of >10% and the non-dipping group (HR, 1.078; 95% CI, 0.723 to 1.608) (Fig. 3). The effect sizes were not significantly different between the two subgroups (HR, 1.190; 95% CI, 0.870 to 1.629) (Supplementary Table 4). Meta-regression analysis showed that age, baseline eGFR, proportion of females, and proportion of patients with diabetes mellitus were not significant moderators of MAKE (Supplementary Table 5). Of note, the study by Zannad et al. [20] was not included in our meta-regression analysis for the association between MAKE and proportion of patients with diabetes mellitus due to the unavailability of relevant data in that study.

Secondary outcomes: hospitalized heart failure and cardiovascular death

There was a non-significant reduction in the hazard of the composite outcome of hospitalized heart failure and cardiovascular death in the dipping group, but the difference did not reach statistical significance (HR, 0.824; 95% CI, 0.633 to 1.074; I^2=0%; sensitivity analysis, consistent results) (Fig. 4, Supplementary Fig. 4A). Additionally, no significant difference was observed in the hazard of hospitalized heart failure between the two groups (HR, 1.059; 95% CI, 0.574 to 1.952; I^2=37%; sensitivity analysis, consistent results) (Fig. 4, Supplementary Fig. 4B). No significant differences were observed regarding the cardiovascular outcomes in patients with ≥10% eGFR dip compared to those with <10% eGFR dip (Supplementary Table 4).

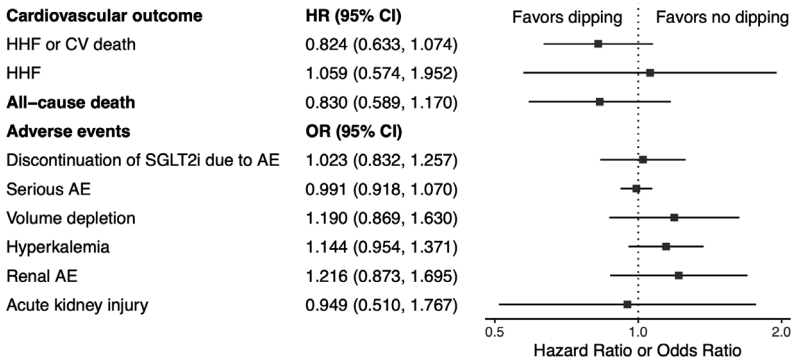

Fig. 4. Comparisons of cardiovascular (CV) outcomes, all-cause death and adverse events (AEs) between the dipping and non-dipping groups. HR, hazard ratio; CI, confidence interval; HHF, hospitalized heart failure; OR, odds ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Secondary outcomes: all-cause mortality

There was no significant difference in the hazard of all-cause mortality between the two groups (HR, 0.83; 95% CI, 0.589 to 1.170; I^2=15%; sensitivity analysis, consistent results) (Fig. 4, Supplementary Fig. 5). The effect sizes were similar in patients with ≥10% and <10% eGFR dip (Supplementary Table 4).

Secondary outcomes: adverse events

There were no significant differences between the dipping and non-dipping groups regarding the risk of SGLT2i discontinuation due to AEs (OR, 1.023; 95% CI, 0.832 to 1.257; I^2=5%) (Fig. 4, Supplementary Fig. 6), serious AEs (OR, 0.991; 95% CI, 0.918 to 1.070; I^2=0%) (Fig. 4, Supplementary Fig. 7), renal AEs (OR, 1.216; 95% CI, 0.873 to 1.695; I^2=56%) (Fig. 4, Supplementary Fig. 8), acute kidney injury (OR, 0.949; 95% CI, 0.510 to 1.767; I^2=56%) (Fig. 4, Supplementary Fig. 9), and volume depletion (OR, 1.190; 95% CI, 0.869 to 1.630; I^2=0%) (Fig. 4, Supplementary Fig. 10). There was no significant difference in the overall risk of hyperkalemia between the two groups (OR, 1.144; 95% CI, 0.954 to 1.371; I^2=0%) (Fig. 4, Supplementary Fig. 11). However, subgroup analysis demonstrated that an initial eGFR dip of >10% was associated with a higher risk of hyperkalemia compared to the non-dipping group (OR, 1.240; 95% CI, 1.148 to 1.338) (Supplementary Fig. 11).

Trial sequential analysis

The required information size for all-cause mortality was estimated to be 16,198 when the incidence in control group was set at 10.5%, and 75,628 for the composite outcome of hospitalized heart failure and cardiovascular death when the incidence in control group was set at 14.4%. The cumulative Z curve of both outcomes did not cross the trial sequential monitoring boundaries, the futility boundaries, or the required information size, suggesting that the current evidence has yet to reach a solid conclusion (Supplementary Figs. 12 and 13).

Certainty of evidence

The certainty of evidence for our primary and secondary outcomes was assessed as low at baseline since the included studies were observational in nature. However, most outcomes were judged to have a low risk of bias, inconsistency, indirectness, and publication bias. Outcomes related to hospitalized heart failure, cardiovascular death, kidney-related AEs, volume depletion, and hyperkalemia were further downgraded due to imprecision of results. More information regarding our certainty of evidence assessment can be found in Supplementary Table 6.

DISCUSSION

Our study demonstrated that the initial eGFR dip induced by SGLT2i was associated with a more favorable annual eGFR decline compared to the non-dipping group. No significant differences were observed in all-cause mortality, the composite outcome of hospitalized heart failure and cardiovascular death, discontinuation of SGLT2i due to AEs, serious AEs, volume depletion, kidney-related AEs, and acute kidney injury between the dipping and non-dipping groups. Notably, patients in the subgroup with a ≤10% dip had a significantly reduced risk of MAKE, while patients with >10% dip exhibited a potential risk of hyperkalemia.

Kidney outcomes

In the current study, it was found that patients who experienced the dip phenomenon had less annual eGFR decline compared to the non-dipping group, supporting the involvement of hemodynamic-related mechanisms given the reversible nature of such dip phenomenon [9-11,15], as well as a potential association between the dip level and intraglomerular pressure before treatment [18]. In addition, the subgroup of patients with dip >10% was found to have greater improved eGFR slope than those with ≤10% dip. These results should encourage clinicians not to abruptly discontinue SGLT2i upon detecting an initial dip in eGFR. The study by Zannad et al. [20] was not included in our analysis for eGFR slope due to lack of relevant data for the calculation of annual eGFR decline, but the trend of eGFR changes observed in that study was generally in line with our findings.

While no significant difference in MAKE was found between the dipping and non-dipping groups, our subgroup analysis revealed a reduced risk of MAKE in patients with ≤10% eGFR dip, but not in those with >10% dip. The discrepancy between annual eGFR decline and the occurrence of MAKE might be due to differences in baseline characteristics among the subgroups. The SGLT2i-induced eGFR dip was reportedly more likely to occur in patients who were older, had a longer history of diabetes, a higher body mass index, or were using diuretics [9,27]. Additional factors found to be associated with an eGFR dip >10% included male sex, increased sodium intake, and lower eGFR at baseline [9,30]. Moreover, the relationship between the risk of MAKE and the dip level might not be linear. An observational study in 2021 suggested that an eGFR dip >30% after initiating SGLT2i was associated with an increased risk of serum creatinine doubling and eGFR <15 mL/min/1.73 m^2 [28], indicating that "extreme dippers" may be at higher risk of MAKE. However, since few studies have evaluated clinical outcomes of such extreme dippers [20,28], a subgroup analysis for this population was not feasible in the current study.

Our meta-regression analysis showed that age, sex, baseline eGFR, and diabetes status were not significantly correlated to renal outcomes. The improved annual eGFR slope in patients with initial eGFR dip compared to the non-dipping group was also consistently observed in all subgroups stratified by baseline eGFR. One potential explanation for the lack of significant moderation by these factors in the overall analysis could be the non-linear relationship between baseline eGFR and renal outcomes that could not be detected by the meta-regression model. Additionally, the included studies displayed relatively low heterogeneity concerning participant characteristics such as mean age, the proportion of females, and the prevalence of diabetes mellitus. This low heterogeneity led to clustered data points, which could potentially limit our ability to demonstrate statistically significant associations.

The exact mechanism of which SGLT2i induce eGFR dip remained an area of active research. Several hypotheses were postulated to explain the renoprotective effect and the dip phenomenon related to SGLT2i. The reversible initial eGFR decline with subsequent improved annual eGFR slope supports the hypotheses that renoprotective effect originate hemodynamically [15,17], which might involve pre-glomerular arteriole constriction and/or post-glomerular arteriole dilatation [31,32].

Inhibition of SGLT-2 has been shown to increase the sodium concentration in the distal convoluted tubule, which in turn leads to pre-glomerular arteriole constriction through tubuloglomerular feedback [33]. This constriction results in a transient decrease in eGFR and can help alleviate intraglomerular pressure [16]. Additionally, there is evidence to suggest that post-glomerular arteriole dilation, similar to the action of renin-angiotensin blockers, may have also contributed to the transient dip in eGFR [31]. A similar phenomenon was observed in the Systolic Blood Pressure Intervention Trial (SPRINT) study, of which the initial eGFR changes in the intensive blood-pressure control group that stabilized during the subsequent study period [34] and subgroup analysis of urine biomarkers of tubule function and repair [35] also suggested that the changes might be caused by hemodynamic factors rather than intrinsic renal damages.

In our study, we found that SGLT2i-induced dip was associated with a reduction in annual eGFR decline and MAKE with ≤10% dipper. The acute change in eGFR after initiating SGLT2i could reflect intraglomerular pressure changes and might be used as a marker for predicting the renoprotective effects of SGLT2i. However, further research is still needed to determine the optimal range of dip, particularly in extreme dippers where limited data were available.

Cardiovascular outcomes

Our study showed a non-significant reduced risk for the composite outcome of hospitalized heart failure and cardiovascular death in patients with initial eGFR dip, but the finding did not reach statistical significance. Moreover, the risk of hospitalized

heart failure was similar between the dipping and non-dipping groups. We included only three studies in our analysis of cardiovascular outcomes (i.e., two [19,20] for evaluation on the composite of hospitalized heart failure and cardiovascular death, and two [20,28] for evaluation of hospitalized heart failure), as the number of eligible studies was limited by high variability in outcome definition and cut-points of dip levels selected to divide the compared groups. Therefore, our findings on cardiovascular outcomes should be interpreted with caution considering their wide CIs and the non-conclusive results from our TSA.

In a *post hoc* analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study [27], patients with initial eGFR dip >10% had lower risks of hospitalized heart failure and cardiovascular death compared to those with dip ≤10% (including the non-dipping individuals). While this finding was generally in line with ours, the difference between the dipping versus non-dipping group was not reported in that study. According to a prior observational study, individuals who experienced an initial eGFR decline of over 30% were at a higher risk of new-onset atrial fibrillation, MAKE, and heart failure [28]. However, it is yet to be determined in future research if the occurrence of these adverse cardiac events ultimately affects cardiovascular survival.

All-cause mortality and adverse events

We found no significant differences in all-cause mortality, hyperkalemia, acute kidney injury, volume depletion, serious AEs, and discontinuation of SGLT2i due to AEs between the dipping and non-dipping groups. However, in the subgroup of patients with an eGFR dip >10%, there was an increased risk of hyperkalemia. It is noteworthy that a substantial eGFR decline exceeding 10%, induced by SGLT2 inhibitors, predominantly manifests in patients with a lower baseline eGFR [9,30]. While we did observe a marked improvement in the chronic eGFR slope and no heightened risk of MAKE in this particular group, impaired urinary potassium excretion can transpire when there is a concurrent reduction in glomerular filtration rate, tubular flow, or sodium delivery to the distal nephron [36]. This consideration underscores the nuanced interplay between eGFR dynamics, the use of SGLT2 inhibitors, and the associated risk of hyperkalemia. As a result, patients with a dip level >10% compared to baseline should have their potassium levels monitored carefully.

Limitation

There were some limitations to consider in the current study. Firstly, variations existed in the included studies regarding their definition of MAKE and the cut-off points for eGFR dip. Although we excluded studies with significantly different cut-off values and outcome definitions to obtain similar patient groups, these variations could still have influenced the results. Secondly, the relationship between clinical outcomes and the dip level might not be strictly linear; furthermore, this study was unable to evaluate outcomes in patients with initial eGFR dip >30% due to limited data. Future studies are required to determine the acceptable dip range. Thirdly, all included studies were observational, and therefore the findings should be interpreted with caution. Though most studies were evaluated to be of high quality and the remaining two of moderate quality, selection bias, information bias, and confounding factors could still have affected our results. Fourth, it is important to note that our findings regarding cardiovascular outcomes should not be deemed conclusive since the number of patients recruited did not exceed the required sample size. Moreover, although our analyses demonstrated low to moderate statistical heterogeneity in all the outcomes, some clinical heterogeneity still existed in the included studies regarding their designs and clinical scenarios. Despite the limitations, our findings contributed to the current understanding of the role of eGFR dip in predicting kidney outcomes in patients treated with SGLT2i.

Conclusion

In summary, our findings suggested that acute eGFR dip induced by SGLT2i was associated with a favorable annual eGFR decline. Patients with a ≤10% dip had a significantly reduced risk of MAKE, while patients with >10% dip had a potential risk of hyperkalemia, emphasizing the importance of monitoring potassium levels in these patients when initiating SGLT2i. However, studies are still needed to determine the optimal threshold for eGFR dip and its impact on clinical outcomes. Our findings should be interpreted with caution given the observational nature of the included studies.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/2023.0201.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: C.Y.C., V.C.W., M.H.
Acquisition, analysis, or interpretation of data: M.H.C., Y.S.T., J.Y.C., H.C.P., V.C.W., M.H.
Drafting the work or revising: all authors.
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Supplementary Table 1. PRISMA 2020 check list

Section and topic	Item no.	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	p.1
Abstract			
Abstract	2	See the PRISMA 2020 for abstracts checklist.	p.3
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pp.5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	pp.5-6
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p.6, Suppl p.4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.7-8
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	pp.9-10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item no. 5]).	pp.9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	pp.9-10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	pp.9-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	pp.9-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	pp.9-10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	pp.9-10

(*Continued to the next page*)

Supplementary Table 1. Continued

Section and topic	Item no.	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	pp.9-10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p.8
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.10, Fig.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p.10, Fig.1
Study characteristics	17	Cite each included study and present its characteristics.	p.10, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.10, Suppl p.5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	pp.10-13, Suppl pp.8-14
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pp.10-13, Suppl pp.8-14
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	pp.10-13, Suppl pp.8-14
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	pp.10-13, Suppl pp.9-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	pp.10-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p.13, Suppl p.7
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pp.13-16
	23b	Discuss any limitations of the evidence included in the review.	p.17
	23c	Discuss any limitations of the review processes used.	p.17
	23d	Discuss implications of the results for practice, policy, and future research.	p.17
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA

(*Continued to the next page*)

Supplementary Table 1. Continued

Section and topic	Item no.	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	p.18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p.18

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NA, not available.

Supplementary Table 2. Search strategies for databases

No.	Search syntax
Embase and MEDLINE via Ovid	
1	("sodium glucose transporter 2 inhibitor*" or "sglt-2*" or "sglt2*" or "canagliflozin" or "dapagliflozin" or "empagliflozin" or "ertugliflozin" or "sotagliflozin" or "bexagliflozin" or "gliflozin*").mp. or "sodium-glucose cotransporter 2 inhibitor".kw.
2	exp "sodium glucose transporter 2 inhibitors"/
3	("eGFR*" or "GFR*" or "glomerular filtration rate").mp.
4	(("kidney" or "renal*") adj function*).mp.
5	exp "glomerular filtration rate"/
6	("fall*" or "dip" or "dipping" or "dips" or "dipped" or "drop*" or "slump*" or "decline*" or "impair*" or "reduc*" or "decrease*" or "change*" or "deteriorat*" or "worsen*" or "diminish*" or "lessen*").mp.
7	"kidney function decline".kw.
8	((randomized controlled trial or controlled clinical trial).pt. or randomi*ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
9	Epidemiologic Studies/ or exp Cohort Studies/ or ((epidemiologic adj (study or studies)) or (cohort adj (study or studies)) or "cohort analy*" or ("follow up" adj (study or studies)) or longitudinal or retrospective* or prospective* or (observ* adj3 (study or studies))).ti,ab.
10	(#1 or #2) and (((#3 or #4 or #5) and #6) or #7) and (#8 or #9)
Cochrane Central Register of Controlled Trials (CENTRAL)	
1	("sodium glucose transporter 2 inhibitor*" or "sglt-2*" or "sglt2*" or "canagliflozin" or "dapagliflozin" or "empagliflozin" or "ertugliflozin" or "sotagliflozin" or "bexagliflozin" or "gliflozin*"):ti,ab,kw
2	[mh "sodium glucose transporter 2 inhibitors"]
3	("eGFR*" or "GFR*" or "glomerular filtration rate"):ti,ab,kw
4	(("kidney" or "renal*") adj function*):ti,ab,kw
5	[mh "glomerular filtration rate"]
6	("fall*" or "dip" or "dipping" or "dips" or "dipped" or "drop*" or "decline*" or "reduc*" or "decrease*" or "change*" or "deteriorat*"):ti,ab,kw
7	(#1 OR #2) AND (#3 OR #4 OR #5) AND #6

Supplementary Table 3. Quality assessment of the included studies

Study	Selection				Comparability[a]	Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Jongs et al. (2022) [19]	*	*	*	*	*	*	*	*	8
Adamson et al. (2022) [27]	*	*	*	*	*	*	*	-[b]	7
Cherney et al. (2022) [29]	*	*	*	*	-	*	*	-[b]	6
Oshima et al. (2021) [9]	*	*	*	*	* *	*	*	*	9
Kraus et al. (2021) [11]	*	*	*	*	-	*	*	-[c]	6
Zannad et al. (2022) [20]	*	*	*	*	*	*	*	-[c]	7
Chan et al. (2021) [28]	*	*	*	*	* *	*	*	-[c]	8

If they adjusted for age, sex, baseline estimated glomerular filtration rate, history of cardiovascular diseases, and status or duration of diabetes mellitus. An additional * was allocated if they also adjusted for covariates that included body mass index and lipid profiles.
[a]Studies were rated, [b]Follow-up rate note stated, [c]Follow-up rate <80% at 1 year.

Supplementary Table 4. Comparison of annual eGFR decline, major kidney adverse events, and cardiovascular outcomes in patients with >10% eGFR dip compared to those with ≤10% eGFR dip

Outcome	MD/HR	95% CI	*P* value
Slope of annual eGFR decline	MD 0.299	0.051–0.547	0.018
Major adverse kidney events	HR 1.190	0.870–1.629	0.277
Hospitalized heart failure and cardiovascular death	HR 1.200	0.851–1.692	0.298
Hospitalized heart failure	HR 1.522	0.440–5.265	0.508
All-cause mortality	HR 1.265	0.851–1.879	0.245

eGFR, estimated glomerular filtration rate; MD, mean difference; HR, hazard ratio; CI, confidence interval.

Supplementary Table 5. Meta-regression analysis of renal outcomes

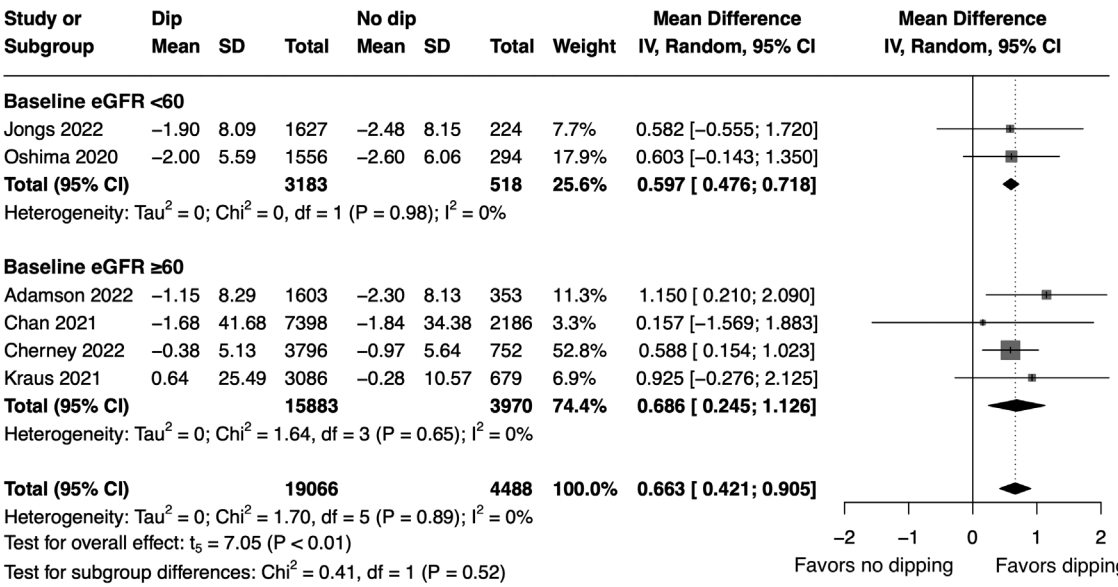
Variable	Coefficient	SE	*P* value	95% CI
Slope of annual eGFR decline				
Mean age	0.147	0.081	0.101	–0.034 to 0.328
Mean baseline eGFR	–0.010	0.013	0.456	–0.038 to 0.018
Proportion of female patients	–0.015	0.038	0.693	–0.099 to 0.069
Proportion of patients with DM	–0.011	0.007	0.159	–0.028 to 0.005
Major adverse kidney events				
Mean age	0.036	0.025	0.230	–0.034 to 0.105
Mean baseline eGFR	–0.0002	0.003	0.962	–0.009 to 0.008
Proportion of female patients	0.0004	0.011	0.972	–0.031 to 0.032
Proportion of patients with DM	0.001	0.003	0.712	–0.013 to 0.016

SE, standard error; CI, confidence interval; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus.

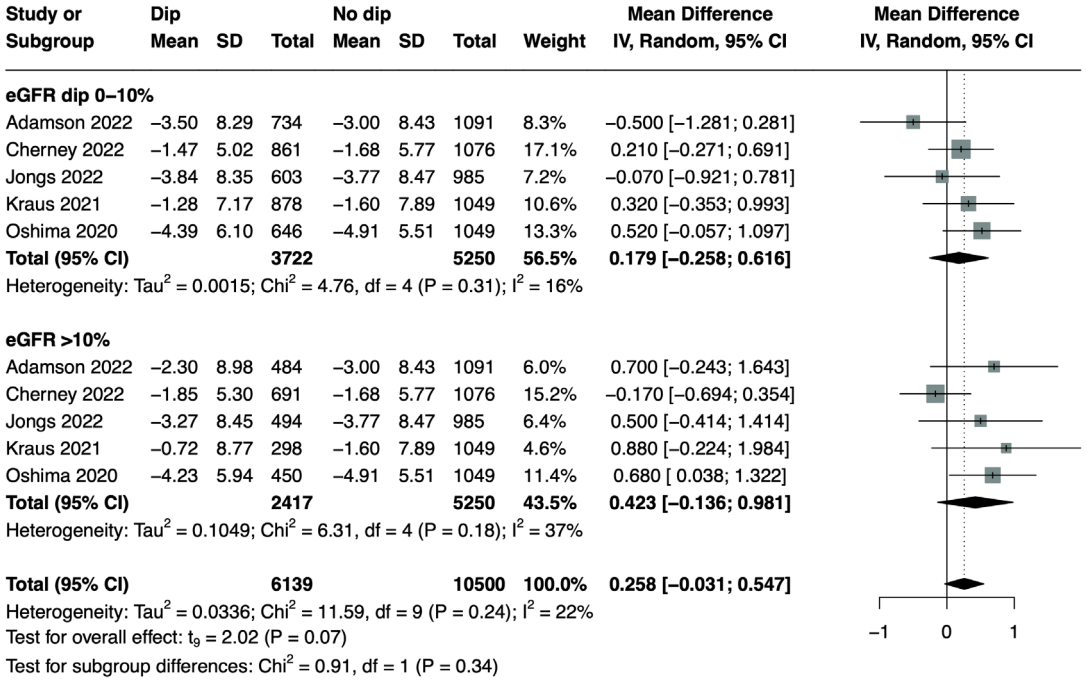
Supplementary Table 6. Certainty of evidence assessment with GRADE approach

Certainty assessment							Summary of findings
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Certainty of evidence	Impact
eGFR slope							
28,038 (6 obs. studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ Low	MD, 0.64; 95% CI: 0.437–0.843; $P<0.01$
Major adverse kidney events							
15,610 (3 obs. studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ Low	HR, 1.01; 95% CI: 0.869–1.173; $P=0.87$
Hospitalized heart failure and cardiovascular death							
3,841 (2 obs. studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕○○○ Very low	HR, 0.824; 95% CI: 0.633–1.074; $P=0.10$
Hospitalized heart failure							
12,030 (2 obs. studies)	Not serious	Not serious	Not serious	Very serious[b]	None	⊕○○○ Very low	HR, 1.059; 95% CI: 0.574–1.952; $P=0.79$
All-cause mortality							
3,857 (2 obs. studies)	Not serious	Not serious	Not serious	Serious[a]	None	⊕○○○ Very low	HR, 0.83; 95% CI: 0.589–1.170; $P=0.18$
Discontinuation of SLGT2i due to adverse events							
11,826 (4 obs. studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ Low	OR, 1.023; 95% CI: 0.832–1.257; $P=0.4$
Serious adverse events							
9,518 (3 obs. studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ Low	OR, 0.991; 95% CI: 0.918–1.070; $P=0.87$
Kidney-related adverse events							
11,826 (4 obs. studies)	Not serious	Not serious	Not serious	Serious[c]	None	⊕○○○ Very low	OR, 1.216; 95% CI: 0.873–1.695; $P=0.21$
Acute kidney injury							
9,222 (3 obs. studies)	Not serious	Not serious	Not serious	Very serious[b]	None	⊕○○○ Very low	OR, 0.949; 95% CI: 0.510–1.767; $P=0.84$
Volume depletion							
4,383 (2 obs. studies)	Not serious	Not serious	Not serious	Serious[c]	None	⊕○○○ Very low	OR, 1.190; 95% CI: 0.869–1.630; $P=0.18$
Hyperkalemia							
7,443 (2 obs. studies)	Not serious	Not serious	Not serious	Serious[c]	None	⊕○○○ Very low	OR, 1.144; 95% CI: 0.954–1.371; $P=0.10$

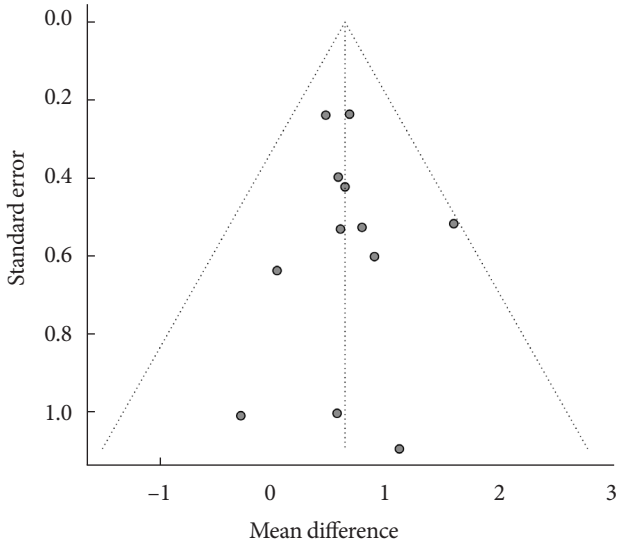
GRADE, Grading of Recommendations Assessment, Development and Evaluation; eGFR, estimated glomerular filtration rate; obs., observational; MD, mean difference; CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor; OR, odds ratio.
[a]The confidence interval includes no difference and potential benefit, [b]The confidence interval includes potential benefit and harm, [c]The confidence interval includes no difference and potential harm.



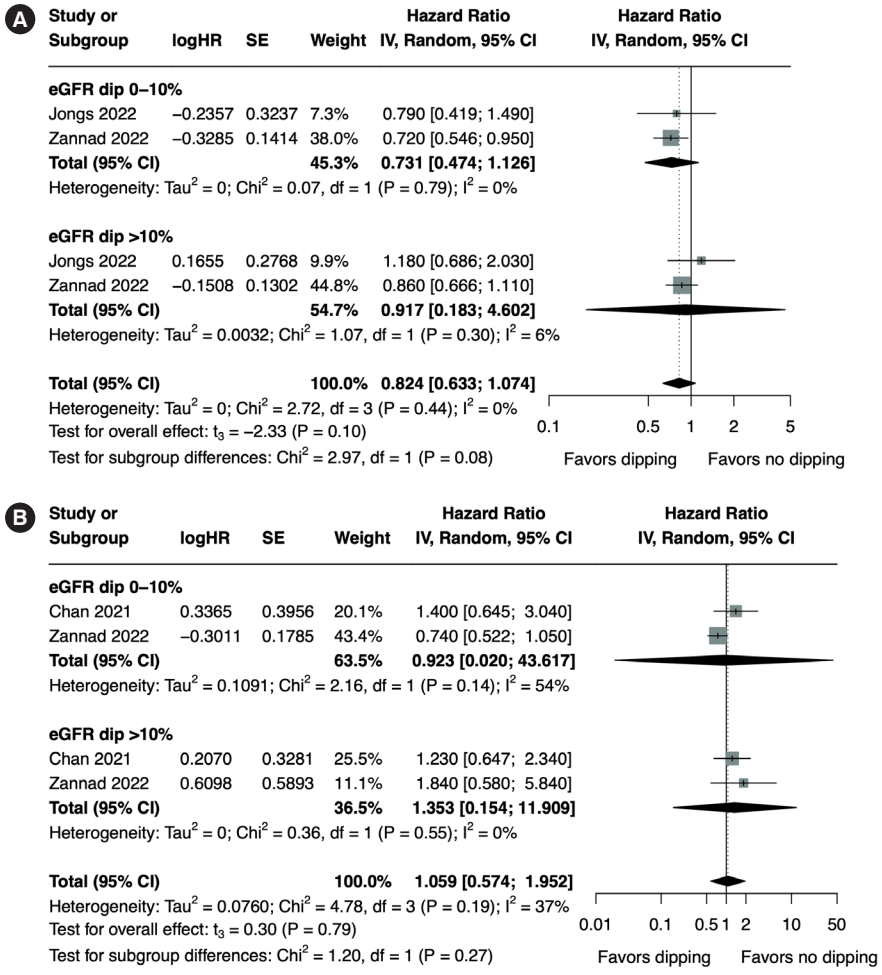
Supplementary Fig. 1. Forest plot showing difference in slope of annual estimated glomerular filtration rate (eGFR) decline between the dipping and non-dipping groups stratified by baseline eGFR level. SD, standard deviation; IV, inverse variance; CI, confidence interval.



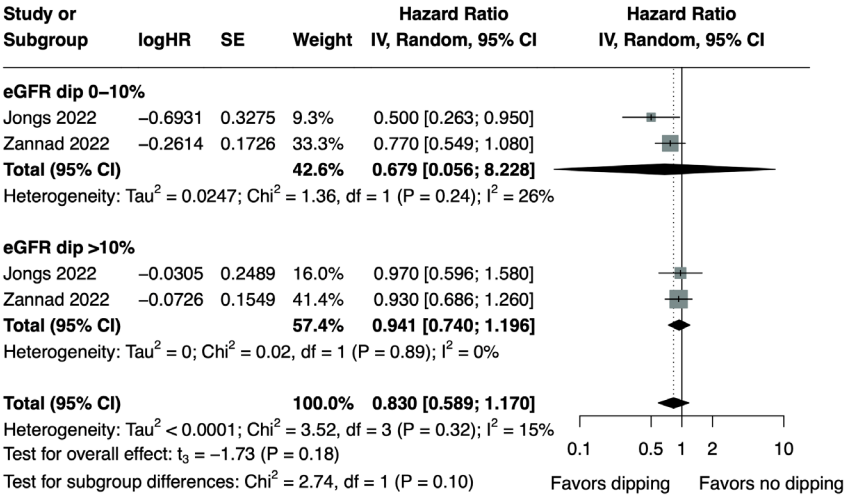
Supplementary Fig. 2. Forest plot showing difference in slope of annual estimated glomerular filtration rate (eGFR) decline between the dipping and non-dipping groups in patients given placebo. SD, standard deviation; IV, inverse variance; CI, confidence interval.



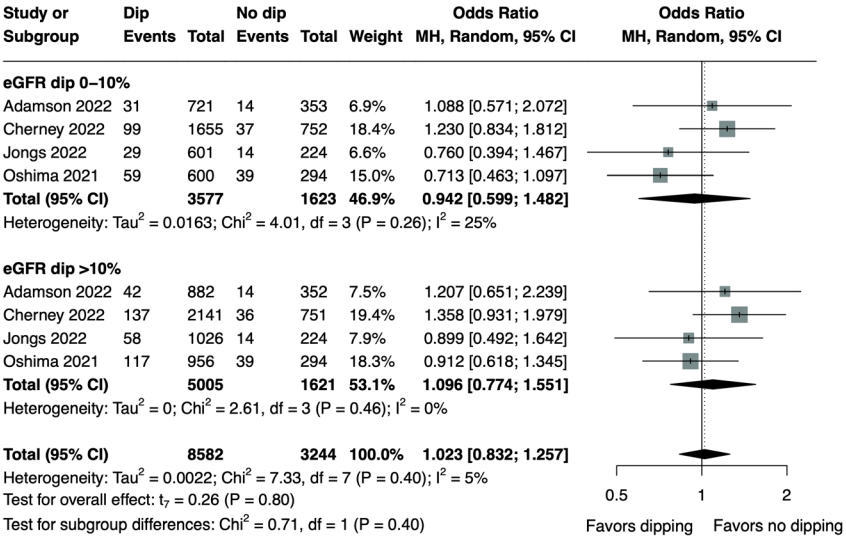
Supplementary Fig. 3. Funnel plot showing a low risk of publication bias on slope of estimated glomerular filtration rate decline.



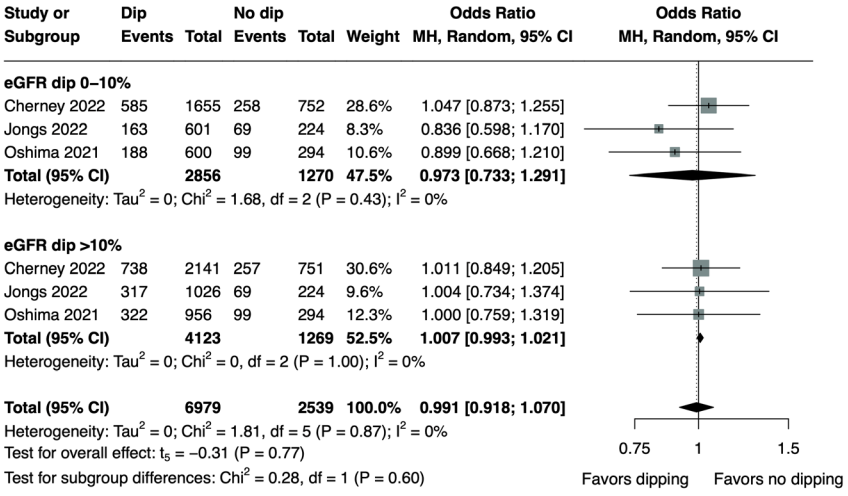
Supplementary Fig. 4. Forest plot displaying the comparison of cardiovascular outcomes between the dipping and non-dipping groups, including the (A) composite of hospitalized heart failure and cardiovascular death, and (B) hospitalized heart failure. HR, hazard ratio; SE, standard error; IV, inverse variance; CI, confidence interval; eGFR, estimated glomerular filtration rate.



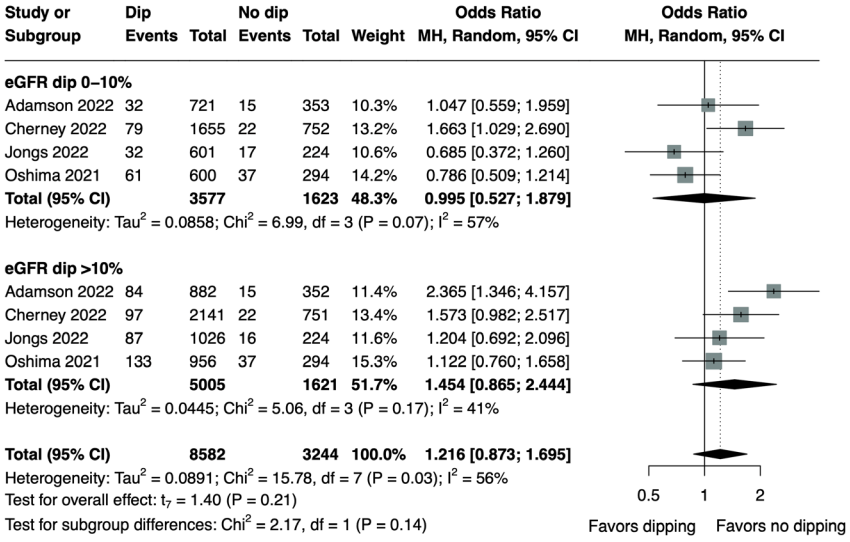
Supplementary Fig. 5. Forest plot showing the comparison in all-cause mortality between the dipping and non-dipping groups. HR, hazard ratio; SE, standard error; IV, inverse variance; CI, confidence interval; eGFR, estimated glomerular filtration rate.



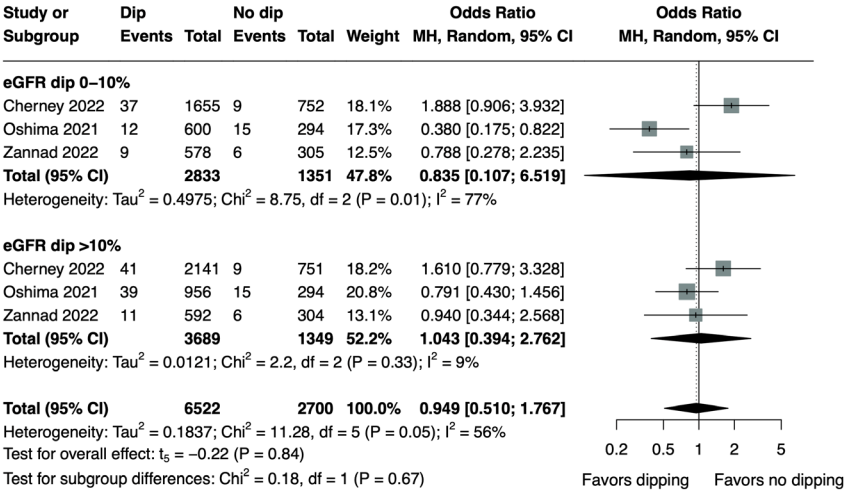
Supplementary Fig. 6. Forest plot comparing discontinuation rates of sodium-glucose cotransporter 2 inhibitors due to adverse events between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



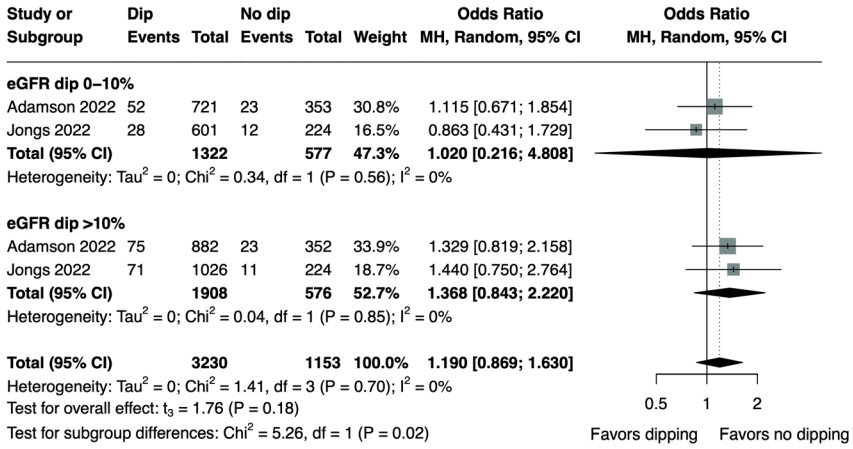
Supplementary Fig. 7. Forest plot depicting the comparison of serious adverse events between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



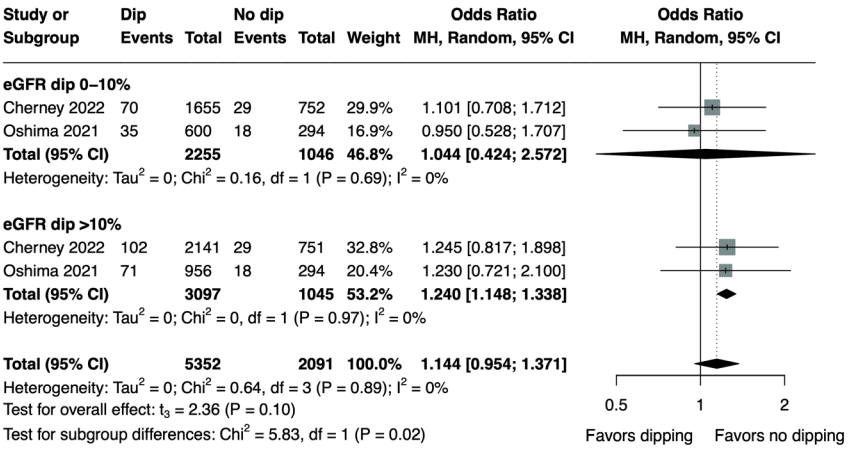
Supplementary Fig. 8. Forest plot showing the comparison in kidney-related adverse events between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



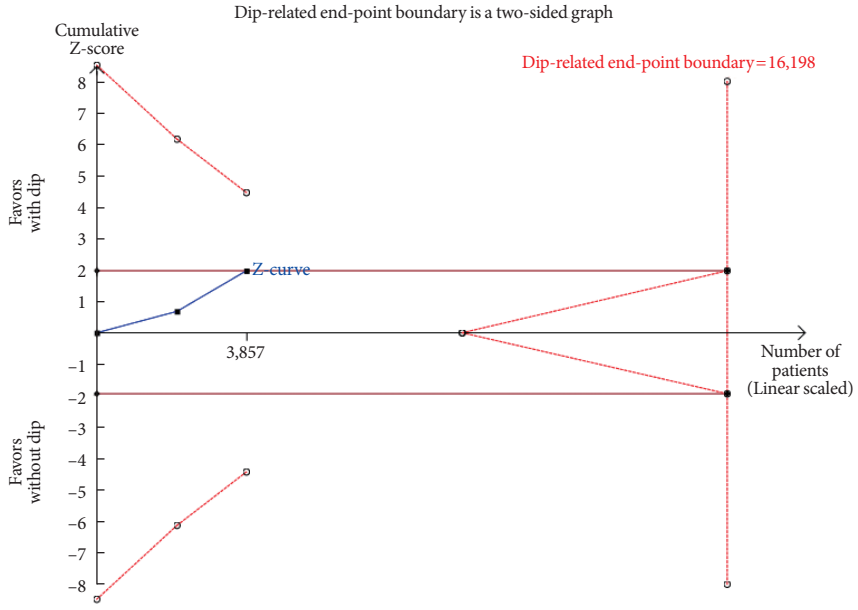
Supplementary Fig. 9. Forest plot showing the comparison in acute kidney injury between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



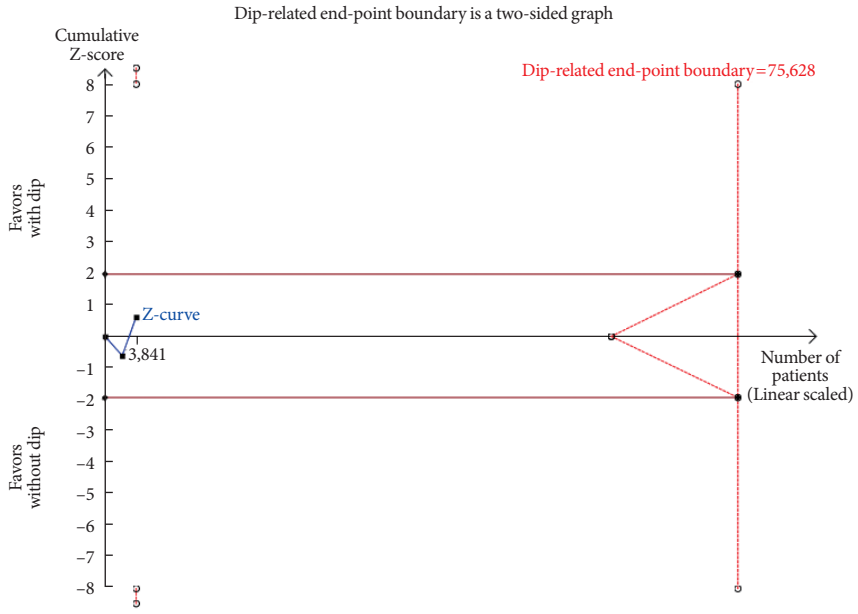
Supplementary Fig. 10. Forest plot showing the comparison in volume depletion between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



Supplementary Fig. 11. Forest plot showing the comparison in hyperkalemia between the dipping and non-dipping groups. MH, Mantel-Haenszel; CI, confidence interval; eGFR, estimated glomerular filtration rate.



Supplementary Fig. 12. Trial sequential analysis comparing all-cause mortality between the dipping and non-dipping groups.



Supplementary Fig. 13. Trial sequential analysis comparing the composite outcome of hospitalized heart failure and cardiovascular death between the dipping and non-dipping groups.