

Evaluating the Initiation of Sodium/Glucose Cotransporter 2 Inhibitors within 2 Weeks of an Acute Hospital Admission: A Systematic Review and Meta-Analysis of Nine Clinical Trials

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Highlights of the Study

- There was no increased harm associated with initiation of sodium/glucose cotransporter 2 inhibitor (SGLT2i) within 2 weeks of an acute hospital admission compared to controls.
- The use of SGLT2i in patients with heart failure was associated with a 27% relative risk reduction in rehospitalizations for heart failure.

Keywords

Sodium/glucose cotransporter 2 inhibitors · Acute hospital admission · Efficacy outcomes · Safety outcomes

Abstract

Objective: Recent studies have increasingly shown the benefits of using sodium/glucose cotransporter 2 inhibitor (SGLT2i). However, there are concerns regarding the initiation of SGLT2i during acute hospital admissions due to the potential increased risk of complications. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of SGLT2i initiation within 2 weeks of an acute hospital admission. **Methods:** Four electronic databases

(PubMed, Embase, Cochrane, and Scopus) were searched for articles published from inception up to 27 March 2021 that evaluated the efficacy and/or safety of SGLT2i initiation within 2 weeks of an acute hospital admission. Random-effects pair-wise meta-analysis models were utilized to summarize the studies. The protocol was registered with PROSPERO (CRD42021245492). **Results:** Nine clinical trials were included with a combined cohort of 1,758 patients. Patients receiving SGLT2i had a mean increase in 24-h urine volume of +487.55 mL (95% CI 126.86–848.25; $p = 0.008$) compared to

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those not started on SGLT2i. Patients with heart failure treated with SGLT2i had a 27% relative risk reduction in rehospitalizations for heart failure, compared to controls (risk ratio 0.73; $p = 0.005$). There were no differences in other efficacy and safety outcomes examined. **Conclusion:** There was no increased harm with initiation of SGLT2i within 2 weeks of an acute hospital admission, and its use reduced the relative risk of rehospitalizations for heart failure in patients with heart failure. It was also associated with increased urine output. However, current evidence pool is limited, especially in specific population subtypes.

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Introduction

Sodium/glucose cotransporter 2 inhibitor (SGLT2i) is an emerging class of anti-hyperglycemic drugs. They block glucose reabsorption at the proximal renal tubule, increasing urinary glucose excretion to lower blood glucose in patients with diabetes.

Apart from glycemic control, SGLT2i is increasingly used in conditions like heart failure and chronic kidney disease due to their efficacy as evidenced by landmark studies. The EMPA-REG trial showed that SGLT2i helps reduce mortality from cardiovascular causes and hospitalization rates [1]. The CREDENCE trial demonstrated that SGLT2i reduced development of end-stage kidney disease, need for renal replacement therapy, and death from renal causes [2]. Other beneficial outcomes include lowering weight [3] and blood pressure [4]. The efficacy of SGLT2i is further emphasized as a first-line therapy for patients with type 2 diabetes and established cardiovascular disease in the 2021 European Society of Cardiology guidelines [5].

Current guidelines advise clinicians to withhold SGLT2i in hospitalized patients [6]. This is mainly due to the increased risk of euglycemic diabetic ketoacidosis as compared to patients not on SGLT2i [7]. To date, there have been no meta-analyses determining the safety of SGLT2i use in hospitalized patients. Reviews have advocated for more research and analyses in this aspect [8, 9]. We conducted a systematic review and meta-analysis to evaluate the use of SGLT2i within 2 weeks of an acute hospital admission. We hypothesize that the initiation of SGLT2i within 2 weeks of an acute hospital admission is associated with improved efficacy, and there is no significant difference in safety outcomes compared to those not initiated on SGLT2i.

Methodology

This systematic review and meta-analysis were reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The review protocol was registered with PROSPERO's International Prospective Register of Systematic Reviews (CRD42021245492). Four databases (PubMed, Embase, Cochrane, and Scopus) were searched for articles published from inception up to 27 March 2021. The following search strategy was applied: ("empagliflozin" OR "BI10773" OR "canagliflozin" OR "TA7284" OR "dapagliflozin" OR "BMS512148" OR "ertugliflozin" OR "PF04971729" OR "ipragliflozin" OR "remogliflozin" OR "sotagliflozin" OR "LX4211" OR "luseogliflozin" OR "TS071" or "licogliflozin" OR "LIK066") AND ("trial" OR "cohort" OR "case-control" OR "observational study" OR "longitudinal") AND ("inpatient" OR "in-patient" OR "in-hospital" OR "in-hospital" OR "hospital" OR "hospitals" OR "hospitalization" OR "hospitalization" OR "hospitalizations" OR "hospitalisations" OR "admission" OR "admissions").

We included all randomized-controlled trials and observational studies evaluating the efficacy and/or safety of initiating SGLT2i within 2 weeks of an acute hospital admission. Studies reporting SGLT2i being started in the outpatient setting and those that did not specify the time of SGLT2i initiation were excluded. The PICOS inclusion and exclusion criteria are shown in online supplementary Table 1 (see www.karger.com/doi/10.1159/000524435 for all online suppl. material).

The following baseline information of patients was collected, including age, sex, body weight, body mass index, systolic blood pressure, diastolic blood pressure, hemoglobin A1c, low-density lipoprotein cholesterol, smoking status, comorbidities (diabetes mellitus, hypertension, hyperlipidemia, obesity, coronary artery disease, stroke, chronic kidney disease, and heart failure), reason for hospital admission, duration of admission, time of initiation of SGLT2i, and any concomitant drug usage (biguanide, sulfonylurea, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 receptor agonist, and insulin). For the SGLT2i regimes, the drug name, dosage, frequency, control group, length of intervention, and mean length of follow-up were collected. Efficacy outcomes collected included systolic blood pressure, diastolic blood pressure, weight, body mass index, waist circumference, low-density lipoprotein cholesterol, hemoglobin A1c, fasting plasma glucose, postprandial glucose, continuous glucose monitoring, urinary glucose, estimated glomerular filtration rate, urine volume, plasma electrolytes, serum uric acid, plasma osmolality, and urine osmolality. Safety outcomes included overall adverse events, cardiovascular adverse events, acute myocardial infarction, rehospitalizations for heart failure, hypotension, hypovolemia, volume depletion, stroke, respiratory adverse events, gastrointestinal adverse events, hepatic adverse events, pancreatitis, psychiatric adverse events, renal/urinary adverse events, acute kidney injury, renal impairment, urinary tract infection, genital mycotic infection, reproductive adverse events, metabolic adverse events, diabetic ketoacidosis, hypoglycemia, musculoskeletal adverse events, fracture, peripheral arterial disease, amputation, thromboembolic adverse events, venous thrombotic events, infectious adverse events, all-cause mortality, hospitalization, malignancies, and other adverse events not included in the above list.

Four reviewers independently performed the literature search and data extraction using a standard data extraction sheet, and all

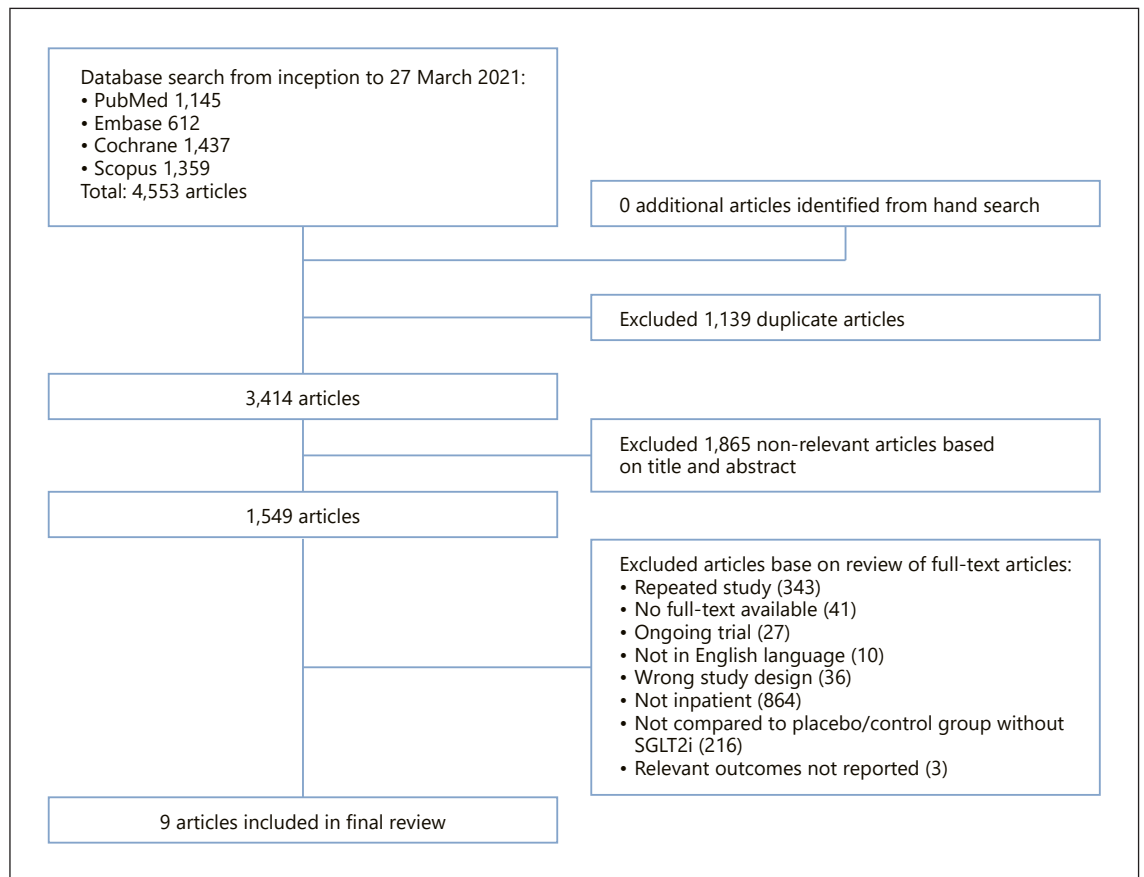


Fig. 1. PRISMA flow diagram of study selection.

disagreements were resolved by mutual consensus. The quality of each included study was evaluated with the Cochrane risk of bias tool [11], as shown in online supplementary Figure 1, and the quality of the pooled evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [12], as shown in online supplementary Table 2. A PRISMA checklist is included in online supplementary Figure 2.

Statistical Analysis

Review Manager (RevMan) Version 5.4 was used to quantitatively pool and analyze the results, as per general approaches stipulated in the Cochrane Handbook. A simple conversion was performed to standardize units reported across studies for the different outcome measures. In studies without standard deviations, p values or confidence intervals were used to generate the standard deviations. Inverse variance was utilized in deriving pooled outcomes. The random-effects model was utilized to account for between-study variance. Between-study heterogeneity was presented using I^2 and τ^2 statistics. An I^2 of <30%, 30–60%, and >60% were used to indicate low, moderate, and substantial heterogeneity, respectively, between studies. Two-sided p values of <0.05 were regarded to indicate nominal statistical significance. Subgroup analysis will be performed if sufficient studies that only enrolled patients initiated on SGLT2i during the acute hospital admission are found. If sufficient data are

found, subgroup analysis will also be performed for the following study-level characteristics: diabetes mellitus, hypertension, chronic kidney disease, heart failure, advanced age, frailty, individual types of SGLT2i, length of intervention, and mean length of follow-up.

Results

Literature search of the databases retrieved 4,553 results. Hand search did not uncover other relevant studies. 1,139 duplicates were removed. Title and abstract screening excluded 1,865 articles as they did not have a control arm or were of an inappropriate study type. Full-text screening excluded further 1,540 articles. Finally, a total of nine articles were included in the meta-analysis. The PRISMA flowchart is presented in Figure 1.

Baseline Characteristics

The nine studies had a combined sample size of 1,758 patients. Heart failure was the commonest reason for hos-

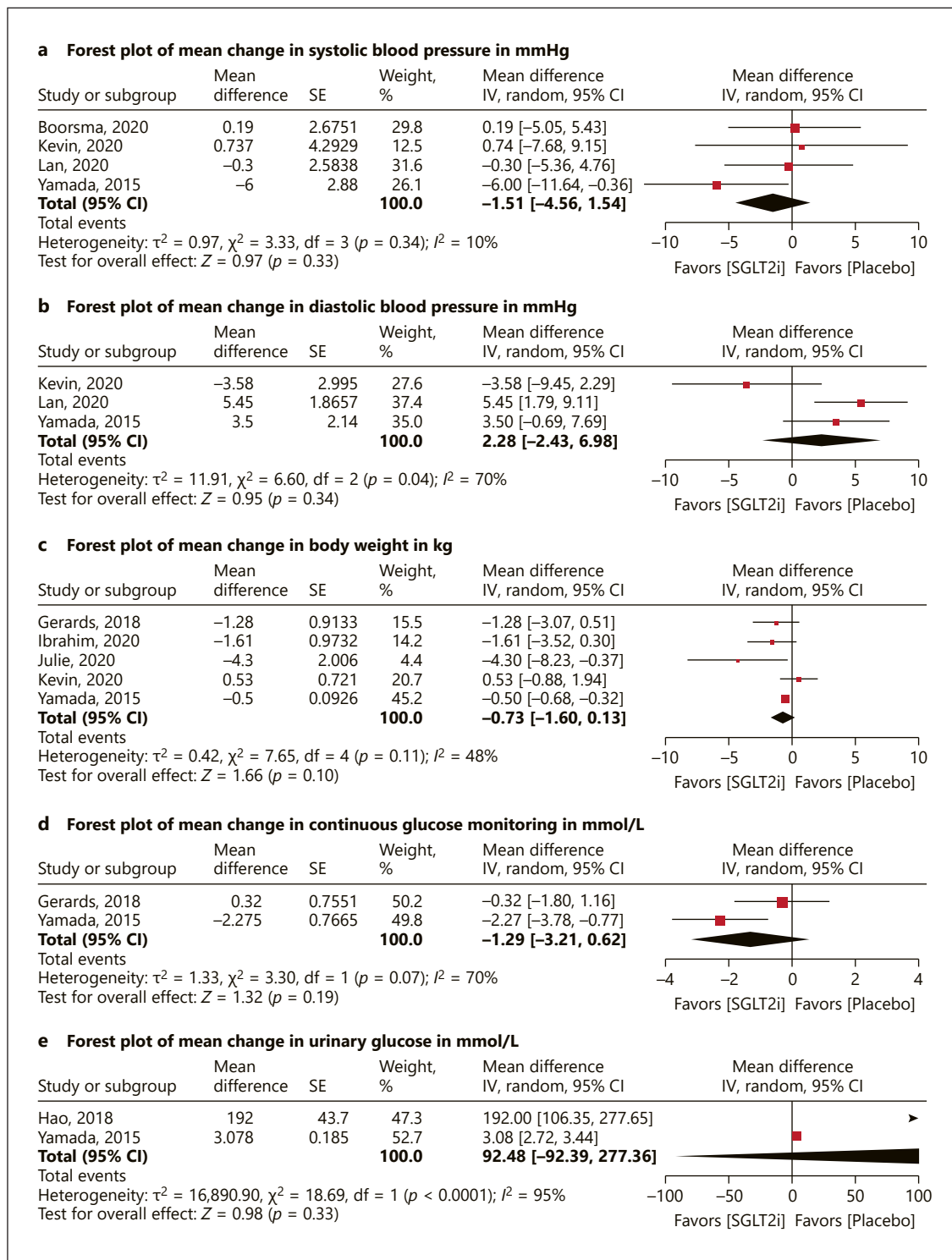
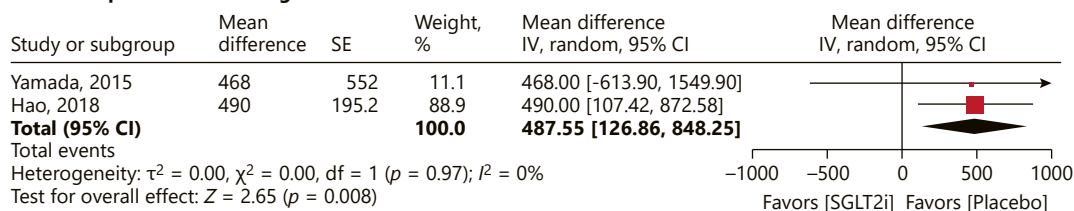


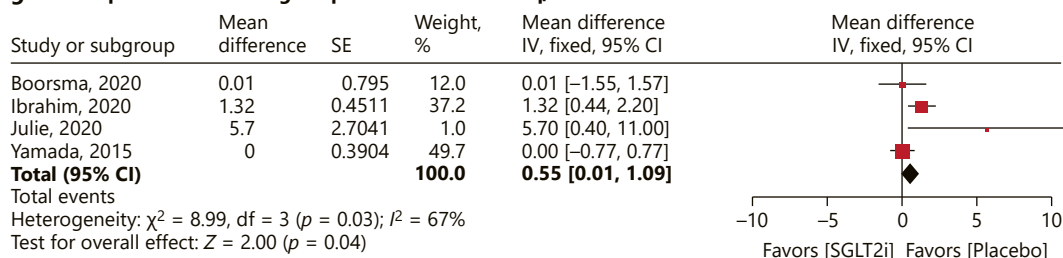
Fig. 2. Forest plot of mean change in (a) systolic blood pressure in mm Hg, (b) diastolic blood pressure in mm Hg, (c) body weight in kg, (d) continuous glucose monitoring in mmol/L, (e) urinary glucose in mmol/L, (f) 24-h urine volume in mL, (g) plasma sodium in mEq/L, (h) plasma potassium in mEq/L, (i) serum uric acid in $\mu\text{mol/L}$, (j) plasma osmolality in mOsm/kg, (k) urine osmolality in mOsm/kg.

(Figure continued on next page.)

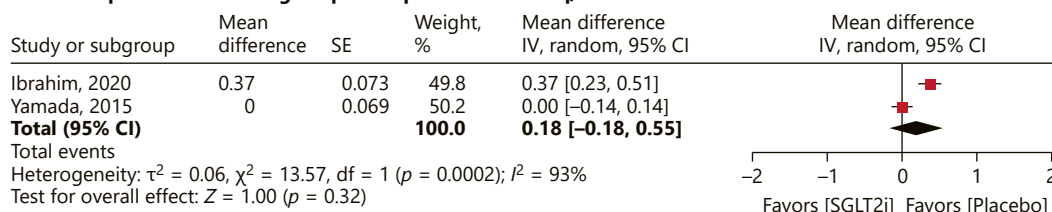
f Forest plot of mean change in 24-hour urine volume in mL



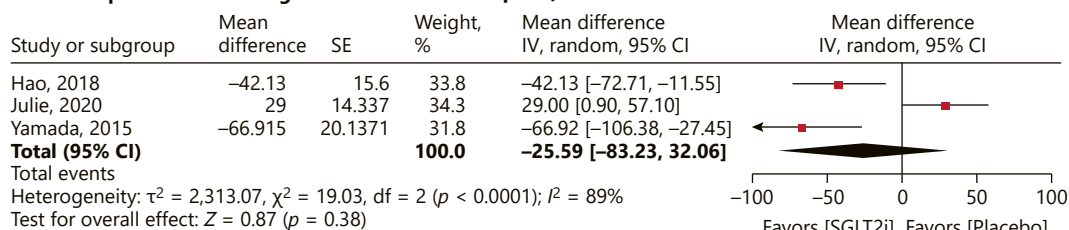
g Forest plot of mean change in plasma sodium in mEq/L



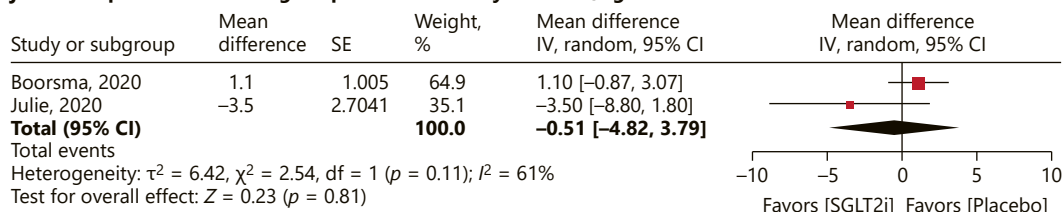
h Forest plot of mean change in plasma potassium in mEq/L



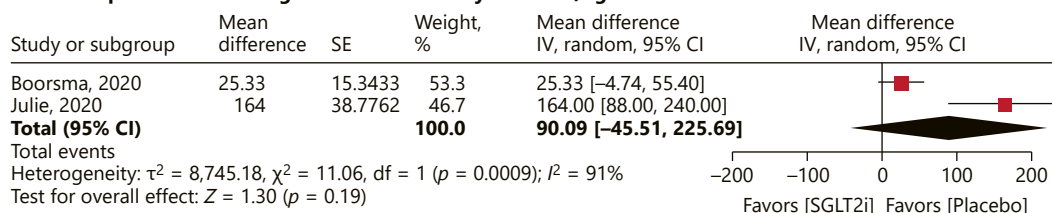
i Forest plot of mean change in serum uric acid in $\mu\text{mol/L}$



j Forest plot of mean change in plasma osmolarity in mOsm/kg



k Forest plot of mean change in urine osmolarity in mOsm/kg



2

pital admission [13–16]. Other reasons for hospital admission include acute chronic obstructive pulmonary disease exacerbation [17], syndrome of inappropriate antidiuretic hormone-induced hyponatremia [18], acute coronary syndrome [19], and poor glycemic control [20]. Hao et al. [21] did not report the reason for hospital admission. The baseline characteristics of the patients in the included studies are shown in online supplementary Table 3.

A summary of the SGLT2i intervention regime in each study is shown in online supplementary Table 4. Empagliflozin and dapagliflozin were used in four and three studies, respectively. Sotagliflozin and ipragliflozin were used in one study each. All regimes were compared to a control group receiving placebo or no drug at all. The length of SGLT2i administration ranged from 2 days to 7.7 months. The length of follow-up ranged from 3 days to 9.0 months.

Pooled Efficacy Outcomes

The pooled efficacy outcomes are presented in Figure 2. The random-effects model demonstrated that the patients receiving SGLT2i had a mean increase in 24-h urine volume of +487.55 mL (95% CI: 126.86–848.25; $p = 0.008$) (as shown in Fig. 2f), compared to those without. There was no statistically significant decrease in systolic blood pressure, diastolic blood pressure, body weight, continuous glucose monitoring, urinary glucose, plasma potassium, serum uric acid, plasma osmolality, and urine osmolality.

Pooled Safety Outcomes

The pooled safety outcomes are presented in online supplementary Figure 3. There were no statistically significant decreases in overall adverse events, adverse cardiovascular events, hypotension, respiratory adverse events, gastrointestinal adverse events, renal/urinary adverse events, renal impairment, urinary tract infection, hypoglycemia, all-cause mortality, duration of hospitalization, rehospitalization, and other adverse events. There were several other safety outcomes that could not be evaluated in our meta-analysis as they were only reported by individual studies. These included psychiatric adverse events (empagliflozin: 0/40, placebo: 1/39), reproductive adverse events (empagliflozin: 0/40, placebo: 0/39), adverse metabolic events (empagliflozin: 9/40, placebo: 9/39), adverse musculoskeletal events (empagliflozin: 5/40, placebo: 5/39), adverse thromboembolic events (empagliflozin: 1/40, placebo: 0/39), venous thrombotic events (sotagliflozin: 0/605, placebo: 7/611), infectious

events (empagliflozin: 1/40, placebo: 0/39), and malignancies (sotagliflozin: 4/605, placebo: 4/611).

Subgroup Analysis of Patients Initiated on SGLT2i during Acute Hospital Admission

For studies that only enrolled patients initiated on SGLT2i during acute hospital admission, the pooled efficacy outcomes are presented in online supplementary Figure 4. There was a statistically insignificant decrease in systolic blood pressure, diastolic blood pressure, body weight, plasma sodium, serum uric acid, plasma osmolality, and urine osmolality. The pooled safety outcomes of patients initiated on SGLT2i during acute hospital admission are shown in online supplementary Figure 5. There were no significant decreases in overall adverse events, cardiovascular adverse events, hypotension, respiratory adverse events, gastrointestinal adverse events, renal/urinary adverse events, urinary tract infection, all-cause mortality, duration of hospitalization, rehospitalization, and other adverse events.

Subgroup Analysis of Patients with Heart Failure

For studies that enrolled only patients with heart failure, the pooled efficacy outcomes are presented in online supplementary Figure 6. The random-effects model demonstrated that patients receiving SGLT2i had a mean increase in plasma sodium of +1.00 mEq/L (95% CI: 0.23–1.77; $p = 0.01$) (as shown in online suppl. Fig. 6c) compared to those without. There was no statistically significant decrease in systolic blood pressure and body weight. The pooled safety outcomes of patients with heart failure are shown in online supplementary Figure 7. Comparing patients receiving SGLT2i to patients without, the random-effects model demonstrated that risk ratio for rehospitalizations for heart failure was 0.73 (95% CI: 0.59–0.91; $p = 0.005$) (as shown in online suppl. Fig. 7a). Two studies were included in this analysis; Bhatt et al. [13] had a median follow-up duration of 9.0 months, while Damman et al. [16] assessed for adverse events at 60 days. There were no statistically significant decreases in hypotension, acute kidney injury, renal/urinary adverse events, urinary tract infection, diabetic ketoacidosis, and all-cause mortality.

Discussion

In our meta-analysis of nine clinical trials, we demonstrated that patients started on SGLT2i within 2 weeks of an acute hospital admission had an increase in 24-h urine,

compared to those not started on SGLT2i. In addition, we found that in the subgroup of patients with heart failure, patients started on SGLT2i within 2 weeks of an acute hospitalization had a 27% reduction in relative risk in re-hospitalizations for heart failure compared to the control group. There were no detectable differences in the other efficacy and safety outcomes examined.

The protective effect of SGLT2i against the risk of heart failure has been demonstrated in many studies [22, 23]. However, the beneficial effects of SGLT2i have not been well established during an acute hospital admission due to limited data on its efficacy and safety in hospitalized patients [8]. Our meta-analysis has shown that in patients with heart failure, initiation of SGLT2i within 2 weeks of an acute hospital admission brings about a reduction in relative risk in rehospitalizations for heart failure. A mechanism for the heart failure effect has been proposed to be via the SGLT2i-mediated blockade of glucose reabsorption that prevents excess sodium reabsorption and its downstream effect of volume expansion [24].

In this subgroup of patients with heart failure, we also demonstrated that there were no significant differences between the risks of diabetic ketoacidosis in patients initiated on SGLT2i within 2 weeks of an acute hospital admission compared to the control group. Two studies were included in our analysis. Bhatt et al. [13] evaluated patients from the SOLOIST-WHF trial (NCT03521934) where patients were initiated on SGLT2i either before or within 3 days after hospital discharge. Damman et al. [16] evaluated patients from the EMPA-RESPONSE-AHF trial (NCT03200860) where SGLT2i was initiated on the day of admission. One of the main concerns of SGLT2i use in the patients admitted to the hospital is the high risk of diabetic ketoacidosis given the patient profile of hospitalized patients [8]. In a cross-sectional survey of physicians, diabetic ketoacidosis was the most commonly reported SGLT2i-related adverse event that physicians witnessed in the inpatient setting, and it had a high level of severity [25]. Our meta-analysis showed that despite the additional factors in hospitalized patients that could predispose to diabetic ketoacidosis, the risk of diabetic ketoacidosis is similar in those initiated on SGLT2i within 2 weeks of an acute hospital admission versus controls. Thus, clinicians can consider initiation of SGLT2i within 2 weeks of acute hospital admission in suitable patients.

Another risk of SGLT2i mentioned in the literature is that of acute kidney injury, which is often associated with an acute illness [26]. Subgroup analysis on heart failure patients also showed that the risk of acute kidney injury was similar in the patients initiated on SGLT2i within 2

weeks of acute hospital admission versus controls. Notably, the two studies included in this analysis, Bhatt et al. [13] and Damman et al. [16], enrolled patients with heart failure on treatment with intravenous diuretic therapy. Due to its effect on the kidneys, the use of diuretics necessitates careful monitoring of renal function [27] even prior to SGLT2i initiation.

Notably, there are several ongoing clinical trials such as the DICTATE-AHF trial (NCT04298229) and EMPULSE trial (NCT04157751) which are also evaluating effect of SGLT2i in patients hospitalized for heart failure. The results of our meta-analysis should be updated upon completion of these trials. Future studies are required to determine if patients initiated on SGLT2i within 2 weeks of an acute hospital admission have a higher risk of heart failure, diabetic ketoacidosis, and/or acute kidney injury compared to those on controls in other population subtypes, such as in patients who were admitted for acute myocardial infarction, sepsis, or post-surgical patients.

Other main adverse effects of SGLT2i that restrict the use of SGLT2i during an acute hospital admission include the increased risk of urinary tract infections and volume depletion [8]. It has been proposed that the risk of urinary tract infections is particularly relevant in hospitalized patients given that many of these patients have indwelling urinary catheters [9]. However, the results of our meta-analysis show that in the overall combined population, there was no significant difference between the risk of urinary tract infections and hypotension between patients started on SGLT2i within 2 weeks of an acute admission versus control.

Strengths and Limitations

To the best of our knowledge, this is the first meta-analysis evaluating the initiation of SGLT2i within 2 weeks of an acute hospital admission. Given the numerous benefits of SGLT2i reported in outpatient settings, it is of interest to investigate if these effects can be reproduced in patients with a recent hospitalization without compromising patient safety. Our meta-analysis helps address these concerns by analyzing a wide spectrum of efficacy and safety outcomes in patients initiated on SGLT2i within 2 weeks of an acute admission.

Our study should be interpreted keeping in mind the following limitations. First, the number of studies that were included for analysis of each outcome was few, ranging from two to four studies per outcome, and is notably dependent on the study by Bhatt et al. [13], the largest study among the 9 studies we have included in our meta-analysis; this study had an overall sample size of 1,222

patients compared to the average sample size of 67 patients (range 42–100) in the other studies. Thus, overall effect measures obtained from our analysis are limited in robustness and should be interpreted with caution. Future clinical trials are required to expand the existing evidence pool. Second, the included studies had notable differences in their population (e.g., reason for hospital admission), intervention (e.g., type of SGLT2i, length of administration of the drug), and duration of follow-up. These factors can contribute to differences in outcomes of each study. While subgroup analysis for heart failure patients was performed in our meta-analysis, the same analysis for other population subtypes, such as patients who are frail or of advanced age, could not be done due to the scarcity of similar studies. This must be taken into consideration as patients who are frail or of advanced age are typically more susceptible to the adverse effects of medications, and hence, the promising results on the safety of SGLT2i initiation shown in our analysis may not be applicable to these unique populations. Future studies with subgroup analyses of other population subtypes are needed when more such studies become available.

Conclusion

Despite the various adverse effects of SGLT2i reported in the literature, available evidence from clinical trials shows that there was no increased harm with SGLT2i initiation within 2 weeks of an acute hospital admission compared to controls, and SGLT2i can reduce the relative risk of rehospitalizations for heart failure in the subgroup of patients with heart failure. SGLT2i use was also associated with an increase in urine output. However, current

evidence pool is limited, and future clinical trials are required to expand the evidence pool, especially in specific population subtypes.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Jenny Hui Ling Chieng, Yao Hao Teo, and Ching-Hui Sia developed the study protocol. Jenny Hui Ling Chieng, Tze Kai Sia, Joseph Zi An Wong, and Tricia Jing Ying Ng were responsible for data collection. Yao Hao Teo, Yao Neng Teo, and Nicholas L.X. Syn analyzed the data. All authors contributed to manuscript writing and approved the final manuscript.

Data Availability Statement

Data used for this study can be accessed upon request from the principal investigator (Dr. Ching-Hui Sia) at: ching_hui_sia@nuhs.edu.sg.

References

- 1 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–28.
- 2 Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; 380(24):2295–306.
- 3 Yoshida A, Matsubayashi Y, Nojima T, Suganami H, Abe T, Ishizawa M, et al. Attenuation of weight loss through improved antilipolytic effect in adipose tissue via the SGLT2 inhibitor tofogliflozin. *J Clin Endocrinol Metab*. 2019;104(9):3647–60.
- 4 Briasoulis A, Al Dhaybi O, Bakris GL. SGLT2 inhibitors and mechanisms of hypertension. *Curr Cardiol Rep*. 2018;20(1):1.
- 5 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021; 42(36):3599–726.
- 6 Mazer CD, Arnaout A, Connelly KA, Gilbert JD, Glazer SA, Verma S, et al. Sodium-glucose cotransporter 2 inhibitors and type 2 diabetes: clinical pearls for in-hospital initiation, in-hospital management, and postdischarge. *Curr Opin Cardiol*. 2020;35(2):178–86.
- 7 Hamblin PS, Wong R, Ekinici EI, Fourlanos S, Shah S, Jones AR, et al. SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission. *J Clin Endocrinol Metab*. 2019; 104(8):3077–87.

- 8 Koufakis T, Mustafa OG, Ajjan RA, Garcia-Moll X, Zebekakis P, Dimitriadis G, et al. The use of sodium-glucose co-transporter 2 inhibitors in the inpatient setting: is the risk worth taking? *J Clin Pharm Ther.* 2020;45(5):883–91.
- 9 Levine JA, Karam SL, Aleppo G. SGLT2-I in the hospital setting: diabetic ketoacidosis and other benefits and concerns. *Curr Diab Rep.* 2017;17(7):54.
- 10 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.
- 11 Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.
- 12 Schünemann H, Brożek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013.
- 13 Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2021;384(2):117–28.
- 14 Boorsma EM, Beusekamp JC, Ter Maaten JM, Figarska SM, Danser AHJ, van Veldhuisen DJ, et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail.* 2021;23(1):68–78.
- 15 Ibrahim A, Ghaleb R, Mansour H, Hanafy A, Mahmoud NM, Abdelfatah Elsharaf M, et al. Safety and efficacy of adding dapagliflozin to furosemide in type 2 diabetic patients with decompensated heart failure and reduced ejection fraction. *Front Cardiovasc Med.* 2020;7:602251.
- 16 Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail.* 2020;22(4):713–22.
- 17 Gerards MC, Venema GE, Patberg KW, Kross M, Potter van Loon BJ, Hageman IMG, et al. Dapagliflozin for prednisone-induced hyperglycaemia in acute exacerbation of chronic obstructive pulmonary disease. *Diabetes Obes Metab.* 2018;20(5):1306–10.
- 18 Refardt J, Imber C, Sailer CO, Jeanloz N, Pottasso L, Kutz A, et al. A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol.* 2020;31(3):615–24.
- 19 Lan NSR, Yeap BB, Fegan PG, Green G, Rankin JM, Dwivedi G. Empagliflozin and left ventricular diastolic function following an acute coronary syndrome in patients with type 2 diabetes. *Int J Cardiovasc Imaging.* 2021;37(2):517–27.
- 20 Yamada K, Nakayama H, Yoshinobu S, Kawano S, Tsuruta M, Nohara M, et al. Effects of a sodium glucose co-transporter 2 selective inhibitor, ipragliflozin, on the diurnal profile of plasma glucose in patients with type 2 diabetes: a study using continuous glucose monitoring. *J Diabetes Investig.* 2015;6(6):699–707.
- 21 Hao Z, Huang X, Shao H, Tian F. Effects of dapagliflozin on serum uric acid levels in hospitalized type 2 diabetic patients with inadequate glycemic control: a randomized controlled trial. *Ther Clin Risk Manag.* 2018;14:2407–13.
- 22 Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2016;4(5):411–9.
- 23 Teo YH, Yoong CSY, Syn NL, Teo YN, Cheong JYA, Lim YC, et al. Comparing the clinical outcomes across different sodium/glucose cotransporter 2 (SGLT2) inhibitors in heart failure patients: a systematic review and network meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol.* 2021 Oct;77(10):1453–64.
- 24 Ortola FV, Ballermann BJ, Anderson S, Mendez RE, Brenner BM. Elevated plasma atrial natriuretic peptide levels in diabetic rats. Potential mediator of hyperfiltration. *J Clin Invest.* 1987;80(3):670–4.
- 25 Patakfalvi L, Brazeau AS, Dasgupta K. Physician experiences with sodium-glucose cotransporter (SGLT2) inhibitors, a new class of medications in type 2 diabetes, and adverse effects. *Prim Health Care Res Dev.* 2018;20:1–6.
- 26 Szalat A, Perlman A, Muszkat M, Khamaisi M, Abassi Z, Heyman SN. Can SGLT2 inhibitors cause acute renal failure? Plausible role for altered glomerular hemodynamics and medullary hypoxia. *Drug Saf.* 2018;41(3):239–52.
- 27 Al-Naher A, Wright D, Devonald MAJ, Pirmohamed M. Renal function monitoring in heart failure – what is the optimal frequency? A narrative review. *Br J Clin Pharmacol.* 2018;84(1):5–17.