Sodium–glucose co-transporter-2 inhibitors for hospitalised patients with COVID-19: a prospective meta-analysis of randomised trials

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Summary

Background Sodium–glucose co-transporter-2 (SGLT2) inhibitors have been proposed as a potential treatment for adults hospitalised with COVID-19, due to their potential anti-inflammatory and endothelial protective effects. Published evidence from randomised control trials (RCTs) does not provide evidence of benefit. We aimed to estimate the effect of oral administration of SGLT2 inhibitors compared with usual care or placebo in adults hospitalised with COVID-19.

Methods Eligible RCTs that estimated the effect of oral administration of SGLT2 inhibitors compared with usual care or placebo on 28-day all-cause mortality (primary outcome) were included in this prospective meta-analysis. The primary safety outcome was ketoacidosis by 28 days. Trials were identified through systematic searches of ClinicalTrials.gov, EudraCT, and the WHO ISRCTN registry between Nov 1, 2022 and Jan 31, 2023. The search terms were "random*" AND "COVID" AND each SGLT2i, not restricted by trial status or language. Individual searches were then combined. Prespecified summary outcome data, overall and within subgroups of interest, were provided by each trial. The primary analyses were inverse variance weighted meta-analysis of odds ratios (ORs). Risk of bias was assessed using the Cochrane Risk of Bias tool. This study was registered with PROSPERO, CRD42023406442.

Findings Three eligible trials randomly assigned 6096 participants (3025 to the SGLT2 inhibitor group and 3071 to the usual care or placebo group). 2381 (39%) patients were women and 1547 (25%) had type 2 diabetes at randomisation. By 28 days, there were 351 deaths in the SGLT2 inhibitor group and 382 deaths in the usual care or placebo group (summary OR 0·93 [95% CI 0·79–1·08]; p=0·33, I^2 for inconsistency across trials 0%). The risk of bias was assessed as being low. Ketoacidosis was observed in seven participants in the SGLT2 inhibitor group and two patients in the usual care or placebo group.

Interpretation Although administration of SGLT2 inhibitor was safe, we found no clear evidence that adding SGLT2 inhibitor therapy improved outcomes in patients hospitalised with COVID-19 compared with usual care or placebo. These data do not support the use of SGLT2 inhibitors as standard treatment in adults hospitalised for COVID-19.

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Introduction

Treatments targeting COVID-19 pathobiology, such as dysregulated immune responses, endothelial damage, microvascular thrombosis, and inflammation, have been shown to improve outcomes of importance.[1,2] Sodium–glucose co-transporter-2 (SGLT2) inhibitors modulate similar pathobiology and provide cardiovascular protection and reduce progression of kidney disease in patients at risk of these events (eg, with type 2 diabetes, heart failure, and kidney disease).[3,4] Before COVID-19, SGLT2 inhibitors have been avoided in acutely ill patients due to concerns around ketoacidosis, and most evidence for SGLT2 inhibitor treatments were in chronic disease management. The DARE-19 trial[5] reported that dapagliflozin was safe, but did not find clear evidence that it improved outcomes in patients with COVID-19 who had cardiometabolic risk factors (ie, those at high risk of progression to severe COVID-19[6–10]). However, even with 1250 randomised patients, the DARE-19 trial alone was not conclusive. Therefore, other randomised clinical trials have evaluated SGLT2 inhibitors, given the uncertainty about their role in acutely ill patients hospitalised with COVID-19.

To address the need for reliable efficacy data to inform clinical practice guidelines,[11] the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group conducted a prospective meta-analysis[12] using aggregate data from RCTs evaluating SGLT2 inhibitors in

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Research in context

Evidence before this study

There is reliable efficacy data on the mortality benefits of sodium–glucose co-transporter-2 (SGLT2) inhibitors in patients with chronic diseases such as type 2 diabetes, heart failure, and kidney disease. Based on these efficacy data, and the potential biological effects, SGLT2 inhibitors have been evaluated as a potential treatment for acute COVID-19. Of relevance, the current clinical practice is to stop SGLT2 inhibitors when patients have an acute illness. We designed a prospective, adaptive meta-analysis of aggregate data to estimate the effect of SGLT2 inhibitors compared with usual care, to provide efficacy estimates that are less prone to bias while trials were still ongoing and yet to report. At the time of designing this study, the efficacy assessment in COVID-19 was limited to one randomised controlled trial reporting no safety concerns (DARE-19 trial), and two other trials (ACTIV-4a and RECOVERY) were recruiting.

Added value of this study

Using prospective meta-analysis methodology, in which aggregate data from all three trials were shared based on standardised definitions of outcomes and subgroups agreed upon in advance of primary trial result analyses, we estimated the benefit of adding SGLT2 inhibitors to usual care in patients hospitalised with COVID-19. Three eligible trials that randomised 6096 participants were identified (DARE-19 trial, ACTIV-4a, and RECOVERY) representing 100% of available randomised trials). Risk of bias was assessed to be low in all three trials for the primary outcome of all-cause mortality by 28-days. By 28 days after randomisation, there were 351 deaths among 3025 patients randomised to SGLT2 inhibitor and 382 deaths among 3071 patients randomised to usual care or placebo (summary odds ratio [OR] 0·93 [95% CI 0·79–1·08]; p=0·33, I^2 for inconsistency across trials 0%). Among 6055 patients not invasively mechanically ventilated at randomisation, the OR for progression to invasively mechanically ventilation or death was 0·90 (95% CI 0·78–1·04). Ketoacidosis was observed in seven and two patients allocated to SGLT2 inhibitor and usual care or placebo, respectively. Although administration of SGLT2 inhibitor was safe, we found no clear evidence that adding SGLT2 inhibitor therapy improved outcomes in patients hospitalised with COVID-19.

Implications of all the available evidence

The current evidence does not support the use of SGLT2 inhibitors as standard care for improving outcomes in patients hospitalised with COVID-19.

patients hospitalised for COVID-19, within the framework previously reported for corticosteroids,[13] and interleukin 6 antagonists.[14] The timeliness of this study is highlighted by the recent stopping of the RECOVERY trial,[15] followed closely by the ACTIV-4a trial.[16]

The primary aim of this prospective meta-analysis was to estimate the class effect of SGLT2 inhibitors compared with usual care or placebo on all-cause mortality up to 28 days after randomisation. The secondary aims were to estimate the effects of SGLT2 inhibitors compared with usual care in preventing progression to more severe COVID-19, to evaluate safety, and to examine effects within prespecified subgroups relating to disease severity and patient characteristics (eg, age, sex, history of type 2 diabetes).

Methods

Search strategy and eligibility criteria

We designed a prospective, adaptive meta-analysis of aggregate data to estimate the effect of SGLT2 inhibitors compared with usual care or placebo, to provide efficacy estimates that are less prone to bias while trials were still ongoing and yet to be reported. Trials were identified through systematic searching of ClinicalTrials.gov, EudraCT, and the WHO ISRCTN registry using the term "random*" AND "COVID" in the title or abstract, along with terms for all SGLT2 inhibitors individually ("dapagliflozin"; "canagliflozin"; "empagliflozin; "ertugliflozin"). Individual searches were then combined. Searches were not restricted by language, trial status (ongoing or completed), publication status, date or language. Additional relevant trials were sought through contact with research and WHO networks, and by full text screening of cited references from relevant published systematic reviews or randomised trials on SGLT2 inhibitors in COVID-19. Searches were initially done on Nov 12, 2022, updated on Jan 10 2023, followed by weekly updates until the first outcome data were received (April 13, 2023) to identify any additional eligible trials. Eligible trials included randomly assigned adult patients (aged ≥18 years) hospitalised with COVID-19 to groups who were administered either SGLT2 inhibitors or placebo or no SGLT2 inhibitors (usual care). We aimed to examine the effects of SGLT2 inhibitors overall and, additionally, for specific SGLT2 inhibitors when sufficient data were available. Trials in which SGLT2 inhibitors were combined with other active agents and trials with active comparators other than current usual care for COVID-19 were excluded. No additional trials were included after outcome data from eligible trials were shared.

The WHO Chief Scientist's representative invited investigators of potentially eligible trials to participate in this prospective meta-analysis. They participated in regular protocol development calls starting Nov 30, 2022. The study protocol was registered with PROSPERO, CRD42023406442, on March 9, 2023, with a final update on April 14, 2023. Trial eligibility criteria, definitions of outcomes, and subgroups of interest were agreed on before collection of outcome data. All trials secured

institutional review board approval, and participants in all trials provided informed consent. Further approvals were not required for these secondary analyses, as these are in line with the informed consents signed by participants in each trial.

Data collection, outcomes, and subgroups

Data supplied by trial investigators were checked and verified. The investigators provided detailed descriptive information on the trial and on participant characteristics at the time of randomisation. They also supplied summary outcome data (not individual participant data) for each outcome, overall and in prespecified subgroups. The analyses started on July 3, 2023. Finalised outcome datasets for all the trials were received by Aug 4, 2023.

The primary outcome was all-cause mortality 28 days after randomisation. The secondary outcomes were in-hospital mortality and all-cause mortality by 90 days. Other outcomes of interest were progression to acute kidney injury (defined as doubling of creatinine or need for renal replacement therapy) or death by 28 days in those who did not require renal replacement therapy at randomisation; progression to invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) or death by 28 days, in those not receiving IMV at randomisation; duration of IMV up to 28 days in those patients who received IMV at randomisation (accounting for survival status by treating patients who died as having 28 days of IMV); and hospital length of stay up to 28 days (accounting for survival status by treating patients who died as having a hospital stay duration of 28 days from randomisation). The primary safety outcome was ketoacidosis, which was defined in each trial, within strata defined by a history of type 2 diabetes . Additionally, data on serious adverse events or serious adverse reactions (as defined in each trial) were collected and reported by group allocation. The DARE-19 trial[5] defined serious adverse events as any reported on-treatment serious adverse events; on-treatment events leading to study medication discontinuation, or any severity of adverse events of special interest (eg, acute kidney injury and ketoacidosis). The RECOVERY trial[15] defined serious adverse events as any suspected serious adverse reaction. In ACTIV-4a,[16] safety events of interest included ketoacidosis and major bleeding, but other investigator-reported serious adverse events were also captured.

The patient subgroups were prespecified as respiratory support as an indicator of disease severity or treatment (no supplemental oxygen therapy or supplemental oxygen therapy only, patients receiving non-invasive ventilation (including high-flow nasal canula), patients receiving IMV (including ECMO); age (<70 years or ≥70 years); biological sex at birth; race or ethnicity (where available); history of type 2 diabetes (yes or no); history of cardiovascular disease (yes or no); and chronic kidney disease (yes or no), all at the time of randomisation.

For each result from each trial, the risk of bias (low risk, some concerns, or high risk) was assessed using version 2 of the Cochrane tool.[17] Risk of bias assessments were based on trial protocols, CONSORT flow charts, and information supplied by each trial regarding methods used to generate the allocation sequence and to conceal randomised allocation; whether patients and health-care professionals were masked to assigned interventions; methods used to ensure that patients received their allocated intervention; and methods used to measure each outcome. Risk of bias assessments were done independently by two of the investigators (JH, KW) with disagreements resolved through consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence.

Data analysis

Characteristics of trials, and of patients recruited to the trials, were summarised in descriptive tables. The primary analyses were inverse variance weighted (fixed effects) meta-analyses of odd ratios (ORs) (for all binary outcomes). For the duration of IMV therapy and of hospital stay, trial investigators supplied the mean difference and associated 95% CIs or SEs. For 90-day mortality, investigators estimated hazard ratios (HRs) and 95% CIs (or log HRs and SEs) using Cox models. Kaplan–Meier estimates of the cumulative incidence of outcomes by treatment group up to 90 days, were also reported separately for each trial. We quantified inconsistency in effects between trials using I^2 statistics. P values for heterogeneity were derived using the Cochran Q statistic. Precise p values were reported: our protocol prespecified that a threshold for statistical significance would not be used. No meta-analysis was planned for adverse events as low numbers of events were anticipated. Given the small number of trials included, we did not conduct random-effects meta-analyses.

Between-subgroup differences were quantified by ratios of ORs (differences in mean differences for continuous outcomes). Comparisons between subgroups defined by trial characteristics were made using fixed-effects meta-regression (across-trial approach). Comparisons between subgroups defined by patient characteristics followed recommendations by David J Fisher and colleagues[18] by estimating trial-specific ratios of ORs (differences in mean differences for continuous outcomes) comparing intervention effects between subgroups (within-trial approach), then combining these. For characteristics that varied between participants in some but not all trials, we used a within-trial approach restricted to the trials when this was possible and compared this with an approach in which effects in subgroups are estimated in separate meta-analyses, and ratios of ORs derived from the overall effect in each subgroup.[19]

To obtain illustrative absolute risk estimates, approximate risks based on patients receiving usual care or

	Key design features	Experimental group: SGLT2 inhibitor	Duration of intervention	Control group	Population	Recruitment period	Location of trial	Patients analysed for 28-day mortality
Kosiborod et al (DARE-19)[5]	Randomised, parallel assignment; masking: quadruple (participant, care provider, investigator, outcomes assessor)	Dapagliflozin 10 mg once daily	At least 30 days	Placebo	Patients with COVID-19 in respiratory failure	April 22, 2020–Jan 1, 2021	USA, Canada, Brazil, Argentina, Mexico, UK, and India	1250
RECOVERY Collaborative Group (RECOVERY)[15]	Randomised, factorial assignment (participants are randomly allocated between one or more treatment groups; not all treatments are available in all countries); open label	Empagliflozin 10 mg once daily (fixed dose)	28 days (or until discharge if sooner)	Usual care	Hospitalised patients with confirmed COVID-19	July 28, 2021– March 6, 2023	UK, Nepal, Indonesia, Vietnam, South Africa, Ghana, and India	4271
Kosiborod et al (ACTIV-4a)[16]*	Randomised, sequential assignment; adaptive design and open label (independent masked outcome adjudicators)	Dapagliflozin (10 mg) or empagliflozin (10 mg) or canagliflozin (100 mg) daily	At least 30 days	Usual care	Hospitalised adults with COVID-19	Sept 4, 2020– March 31, 2023	USA, Spain, Mexico, Brazil, and Italy	575

SGLT2=sodium–glucose co-transporter-2. *Local standard of care for patients hospitalised with COVID-19 also allowed for intervention and control groups. The ACTIV-4a platform trial also allowed randomisation to other investigational COVID-19 treatments, including P2Y12 inhibitors or crizanlizumab.

Table 1: **Description of included trials**

placebo across included trials for each outcome were assumed. Meta-analytic OR estimates were then applied to obtain the corresponding risk estimates with SGLT2 inhibitors. As sensitivity analyses, we obtained estimates, derived from Bayesian inverse-variance weighted meta-analyses, of the following posterior probabilities (OR<1; OR>1; OR<0·9; OR>1·11; OR<0·8; and OR>1·25), for the outcomes of 28-day mortality, progression to IMV or ECMO by 28 days, and progression to acute kidney injury and ketoacidosis. For these analyses, a normal likelihood was used, with a non-informative previous distribution for the mean effect size.[20] Finally, we conducted sensitivity analyses restricted to trial results assessed as at low risk of bias.

Stata statistical software (version 18) was used for all analyses.[21]

Role of the funding source

There was no funding source for this study.

Results

Of four potentially eligible randomised trials identified by our searches, one trial (NCT04393246) was excluded because it compared usual care with a combination therapy of dapagliflozin and ambrisentan (appendix p 2). One of the three included trials (DARE-19) was published,[5] and the remaining two (RECOVERY[15] and ACTIV-4a[16] were unpublished during the protocol development stage. Overall, 6096 patients were recruited, from the UK, the USA, Argentina, Brazil, Canada, Ghana, India, Indonesia, Italy, Mexico, Nepal, South Africa, Spain, and Vietnam from April 22, 2020 to March 31, 2023 (table 1).

See Online for appendix

Of the eligible trials, one (DARE-19;[5] median age 62 years (IQR 52–72) compared placebo (625 patients) with dapagliflozin (625 patients), one (RECOVERY;[15] median age 63 years [IQR 50–75]) compared usual care (2158 patients) with empagliflozin (2113 patients), and one (ACTIV-4a;[16] median age 73 years [IQR 64–80]) compared usual care (288 patients) with a choice of SGLT2 inhibitor (dapagliflozin [232 patients], empagliflozin [41 patients], canagliflozin [five patients], treatment combinations [five patients], and no treatment [four patients]). 2381 (39%) patients were women and 1547 (25%) had type 2 diabetes at the time of randomisation, with the DARE-19[5] trial reporting the highest prevalence of type 2 diabetes (636 [51%] patients). Use of concurrent corticosteroids (4610 [76%] patients) and interleukin-6 antagonists (1009 [17%] patients) at randomisation also varied among the trials, as did the prevalence of cardiovascular disease, which was considerably greater in ACTIV-4a[16] compared with other trials. 4962 (81%) patients received either no supplemental oxygen therapy or supplemental oxygen therapy (≤ 15 L/min) only at randomisation (table 2).

Due to the limited available data (including outcome events), the individual effects of each SGLT2 inhibitor (dapagliflozin, empagliflozin, and canagliflozin) were not estimated. Similarly, given the low number of patients with IMV at baseline, duration of IMV was not reported (appendix p 3). One trial (RECOVERY[15]) did not report in-hospital mortality or 90-day mortality. Because of the diversity of classification of race or ethnicity among different trials, the subgroup analyses according to race or ethnicity were not conducted (appendix p 4).

Risk of bias for 28-day all-cause mortality was low in each trial. For other outcomes, there were some concerns about risk of bias, mainly due to potential subjectivity of outcome definitions, although in no case was this assessed as likely to have been influenced by knowledge of the assigned intervention (appendix pp 5–9).

Data for 28-day mortality were available for all patients from each trial. By 28 days after randomisation, 351 deaths occurred among 3025 patients randomly assigned to

	DARE-19[5]		RECOVERY[15]		ACTIV-4a[16]	
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Usual care	SGLT2 inhibitor	Usual care
Number of patients randomised	625	625	2113	2158	287	288
Age, years	61 (52–71	63 (53–72)	62 (50–74)	63 (50–75)	73 (66–80)	73 (64–80)
Sex						
Male	365 (58%)	352 (56%)	1326 (63%)	1339 (62%)	168 (59%)	165 (57%)
Female	260 (42%)	273 (44%)	787 (37%)	819 (38%)	119 (41%)	123 (43%)
Race*						
White	452 (72%)	459 (73%)	1557 (74%)	1607 (74%)	209 (73%)	200 (69%)
Unknown	2 (<1%)	7 (1%)	195 (9%)	221 (10%)	19 (7%)	25 (9%)
Type 2 diabetes status						
Type 2 diabetes	312 (50%)	324 (52%)	333 (16%)	356 (16%)	112 (39%)	110 (38%)
No diabetes	313 (50%)	301 (48%)	1780 (84%)	1802 (84%)	174 (61%)	176 (61%)
Cardiovascular disease status						
Cardiovascular disease	93 (15%)	106 (17%)	471 (22%)	455 (21%)	237 (83%)	232 (81%)
No cardiovascular disease	532 (85%)	519 (83%)	1642 (78%)	1703 (79%)	50 (17%)	56 (19%)
Chronic kidney disease status						
Chronic kidney disease	38 (6%)	44 (7%)	0	0	45 (16%)	46 (16%)
No chronic kidney disease	587 (94%)	581 (93%)	0	0	241 (84%)	240 (83%)
Unknown	0	0	2113 (100%)	2158 (100%)	1 (<1%)	2 (1%)
Additional treatment†						
Respiratory support						
No supplemental oxygen	0	0	255 (12%)	260 (12%)	70 (24%)	86 (30%)
Supplemental oxygen (≤ 15 L/min)	625 (100%)	625 (100%)	1317 (62%)	1383 (64%)	178 (62%)	163 (57%)
Non-invasive ventilation (>15 L/min)	0	0	512 (24%)	500 (23%)	37 (13%)	32 (11%)
Invasive mechanical ventilation including ECMO	0	0	29 (1%)	15 (1%)	2 (1%)	7 (2%)
Vasoactive medication						
Receiving vasoactive medication	2 (<1%)	6 (1%)	Unknown	Unknown	2 (1%)	7 (2%)
Not receiving vasoactive medication	623 (100%)	619 (99%)	Unknown	Unknown	285 (99%)	281 (98%)
Renal replacement therapy						
Receiving renal replacement therapy	0	0	10 (<1%)	12 (1%)	0	2 (1%)
Not receiving renal replacement therapy	625 (100%)	625 (100%)	2103 (100%)	2146 (99%)	286 (100%)	284 (99%)
Corticosteroids						
Receiving corticosteroids	176 (28%)	180 (29%)	1910 (90%)	1932 (90%)	209 (73%)	203 (70%)
Not receiving corticosteroids	449 (72%)	445 (71%)	203 (10%)	226 (10%)	78 (27%)	85 (30%)
IL-6 inhibitors						
Receiving IL-6 inhibitors	1 (<1%)	2 (<1%)	504 (24%)	491 (23%)	5 (2%)	6 (2%)
Not receiving IL-6 inhibitors	624 (100%)	623 (100%)	1609 (76%)	1667 (77%)	282 (98%)	282 (98%)

Data are median (IQR) or n (%). IL=interleukin. SGLT2=sodium–glucose co-transporter-2. ECMO=extracorporeal membrane oxygenation. *Full details of race and ethnicity of participants for each trial are given in the appendix (p 4). †Local standard of care for hospitalised COVID-19 patients also allowed for intervention and control groups.

Table 2: **Selected patient characteristics at the time of randomisation**

SGLT2 inhibitor and 382 deaths occurred among 3071 patients randomly assigned to usual care or placebo. The summary OR was 0·93 (95% CI 0·79–1·08; p=0·33) for SGLT2 inhibitor, with consistency across trials (I^2=0%; heterogeneity p=0·52; figure 1A). This corresponds to an absolute mortality risk of 11·7% for SGLT2 inhibitor compared with an assumed mortality risk of 12·4% for usual care or placebo. The GRADE assessment of certainty in this result was high.

The summary ORs for 28-day mortality comparing SGLT2 inhibitor with usual care or placebo were 0·82 (95% CI 0·67–1·00) in 4962 patients (445 deaths)

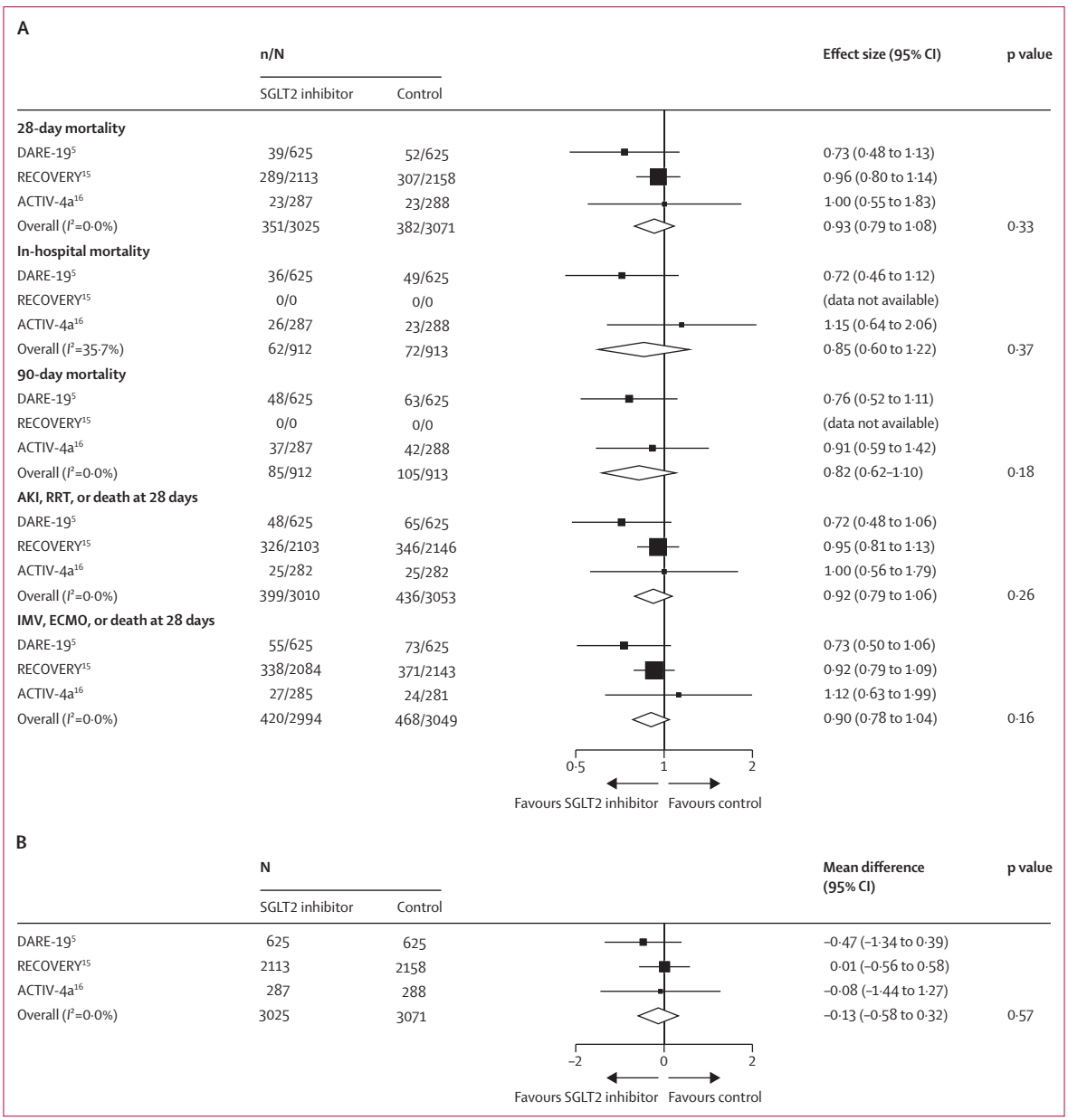

Figure 1: **Effect of SGLT2 inhibitors, compared with usual care or placebo, on prespecified outcomes**
(A) 28-day all-cause mortality; 28-day in-hospital mortality; 90-day mortality; AKI, RRT or death at 28 days; and IMV, ECMO or death at 28 days outcomes. Results presented as odds ratios with 95% confidence intervals with the exception of 90-day mortality, which is presented as hazard ratios with 95% CIs. (B) Hospital length of stay. Results presented as weighted mean difference with 95% CIs. AKI=acute kidney injury. ECMO=extracorporeal membrane oxygenation. IMV=invasive mechanical ventilation. OR=odds ratio. RRT=renal replacement therapy. SGLT2=sodium–glucose co-transporter-2.

receiving either no supplemental oxygen therapy or supplemental oxygen therapy of ≤15 L/min at randomisation; 1·05 (0·80–1·39) in 1081 patients (263 deaths) receiving non-invasive ventilation or high-flow nasal cannula at randomisation; and 1·84 (0·55–6·11) in 53 patients (25 deaths) receiving IMV or ECMO at randomisation. Based on within-trial estimates combined across the three trials, there was little evidence (p=0·25) that the effect of SGLT2 inhibitor on mortality differed between these subgroups; (figure 2; appendix p 10). The effect of SGLT2 inhibitor versus usual care or placebo on 28-day all-cause mortality appeared consistent within subgroups defined by patient characteristics at randomization (all heterogeneity p values ≥0·08; table 3).

Data on in-hospital mortality were available for two trials,[5,16] with 62 in-hospital deaths among 912 patients randomised to SGLT2 inhibitor and 72 among 913 patients randomised to usual care or placebo. The summary OR was 0·85 (95% CI 0·60–1·22; p=0·37),

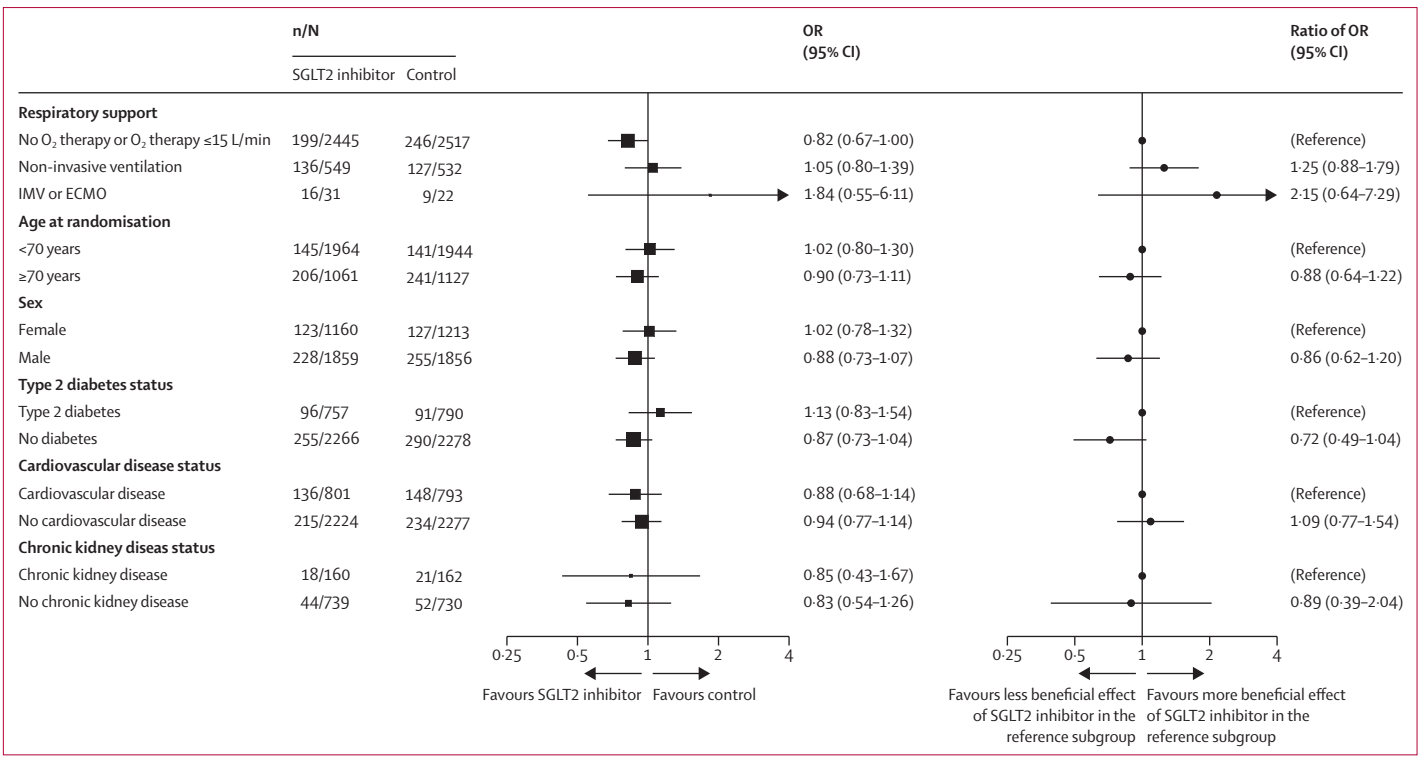

Figure 2: **Subgroup analysis by treatment group for 28-day all-cause mortality**
ECMO=extracorporeal membrane oxygenation. IMV=invasive mechanical ventilation. NIV=non-invasive ventilation. OR=odds ratio. SGLT2=sodium–glucose co-transporter-2.

with some inconsistency between the two trials[5,16] (I^2=36%, heterogeneity p=0·21; figure 1A; appendix p 10). This finding corresponds to an absolute mortality risk of 6·8% for SGLT2 inhibitor compared with an assumed mortality risk of 7·9% for usual care or placebo. The certainty in this result was deemed high in the GRADE assessment. There was little evidence (p=0·78) that the effect of SGLT2 inhibitor on in-hospital mortality differed according to the level of respiratory support at randomisation and for other prespecified subgroups (table 3).

Data on 90-day mortality were available for two trials,[5,16] with 85 deaths by 90 days among 912 patients randomised to SGLT2 inhibitor and 105 deaths by 90 days among 913 patients randomised to usual care or placebo. The summary HR was 0·82 (95% CI 0·62–1·10; p=0·18) (figure 1A; appendix p 10). The certainty in this result was assessed to be high in the GRADE assessment. There was little evidence (p=0·97) that the effect of SGLT2 inhibitor on 90-day mortality differed according to the level of respiratory support at randomization and for other prespecified subgroups (table 3).

Among patients not requiring renal replacement therapy at randomisation (three trials[5,15,16]), 399 (13%) of 3010 participants assigned to SGLT2 inhibitor and 436 (14%) of 3053 participants assigned to usual care or placebo progressed to acute kidney injury, required renal replacement therapy, or died within 28 days. Individual contributing events are reported (appendix p 11). The summary OR was 0·92 (95% CI 0·79–1·06; p=0·26), with consistency across trial results (I^2=0%; figure 1A; appendix p 10). This corresponds to an absolute progression risk of 13·3% for SGLT2 inhibitor compared with an assumed progression risk of 14·3% for usual care or placebo.

Among patients not requiring IMV at randomisation (three trials[5,15,16]), 420 (14%) of 2994 assigned to SGLT2 inhibitor and 468 (15%) of 3049 assigned to usual care or placebo progressed to requiring IMV or ECMO or died within 28 days. Individual contributing events are reported in the appendix (p 12). The summary OR was 0·90 (95% CI 0·78–1·04; p=0·16), with consistency across trial results (I^2=0%; figure 1A; appendix p 10). This finding corresponds to an absolute progression risk of 14·0% for SGLT2 inhibitor compared with an assumed progression risk of 15·3% for usual care or placebo.

Data on the duration of hospital stay were available for all patients from each trial. By 28 days after randomisation, the weighted mean difference was –0·13 (95% CI –0·58 to 0·32; p=0·57) for SGLT2 inhibitor, with consistency across trial results (I^2=0%; heterogeneity p=0·66; figure 1B; appendix p 10).

The effects of SGLT2 inhibitor versus usual care or placebo on these outcomes appeared consistent within subgroups defined by level of respiratory support at randomisation and by patient characteristics at randomisation (table 3).

	Number of events/number of patients		OR (95% CI)	Ratio of ORs*	p value for between-subgroup differences
	SGLT2 inhibitor	Control			
In-hospital mortality†					
Respiratory support at randomisation					0·78
O_2 ≤15 L/min	52/873	60/874	0·86 (0·58 to 1·26)	..	..
Non-invasive ventilation	9/37	8/32	0·96 (0·32 to 2·89)	0·65 (0·17 to 2·50)	..
IMV or ECMO	1/2	4/7	0·75 (0·03 to 17·51)	0·50 (0·02 to 12·93)	..
Age, years					0·53
<70	26/552	27/551	0·99 (0·57 to 1·73)	..	..
≥70	36/360	45/362	0·80 (0·50 to 1·28)	0·79 (0·38 to 1·64)	..
Sex					0·60
Female	22/379	24/396	0·96 (0·53 to 1·74)	..	..
Male	40/533	48/517	0·80 (0·51 to 1·24)	0·82 (0·39 to 1·73)	..
Type 2 diabetes status					0·87
Type 2 diabetes	32/424	37/434	0·87 (0·53 to 1·44)	..	..
No diabetes	30/486	34/476	0·86 (0·52 to 1·43)	0·94 (0·46 to 1·93)	..
Cardiovascular disease status					0·39
Cardiovascular disease	32/330	38/338	0·86 (0·52 to 1·42)	..	..
No cardiovascular disease	30/582	34/574	0·85 (0·51 to 1·41)	1·51 (0·59 to 3·85)	..
Chronic kidney disease status‡					0·98
Chronic kidney disease	16/160	20/162	0·79 (0·39 to 1·58)	..	..
No chronic kidney disease	46/739	50/730	0·90 (0·60 to 1·37)	1·01 (0·43 to 2·37)	..
90-day all-cause mortality†§					
Respiratory support at randomisation					0·97
O_2 ≤15 L/min	73/873	92/874	0·81 (0·59 to 1·10)	..	..
Non-invasive ventilation	11/37	9/32	1·03 (0·43 to 2·50)	1·13 (0·40 to 3·18)	..
IMV or ECMO	1/2	4/7	0·81 (0·09 to 7·41)	0·89 (0·09 to 8·65)	..
Age, years					0·34
<70	31/552	38/551	0·72 (0·44 to 1·17)	..	..
≥70	55/360	67/362	0·98 (0·68 to 1·41)	1·35 (0·73 to 2·48)	..
Sex					0·37
Female	29/379	32/396	0·98 (0·59 to 1·63)	..	..
Male	56/533	73/517	0·76 (0·53 to 1·08)	0·75 (0·40 to 1·40)	..
Type 2 diabetes status					0·53
Type 2 diabetes	43/424	52/434	0·93 (0·62 to 1·40)	..	..
No diabetes	42/486	52/476	0·80 (0·53 to 1·21)	0·83 (0·46 to 1·49)	..
Cardiovascular disease status					0·49
Cardiovascular disease	45/330	61/338	0·79 (0·54 to 1·17)	..	..
No cardiovascular disease	40/582	44/574	0·86 (0·55 to 1·34)	1·32 (0·60 to 2·87)	..
Chronic kidney disease status‡					0·50
Chronic kidney disease	23/160	26/162	0·94 (0·53 to 1·65)	..	..
No chronic kidney disease	61/739	77/730	0·80 (0·57 to 1·12)	0·79 (0·39 to 1·57)	..

(Table 3 continues on next page)

Data on ketoacidosis at 28 days after randomisation were available in each trial (6096 patients, nine events). Ketoacidosis was observed in seven patients allocated to SGLT2 inhibitor, and two patients allocated to usual care or placebo (appendix p 13). No meta-analysis was conducted for this outcome due to the small number of events. We noted considerable variation in rates and definitions of adverse events between the included trials. There were 73 serious adverse events in 3025 patients receiving SGLT2 inhibitor, and 93 events in 3071 patients receiving placebo or usual care. Due to differences in approach to collecting serious adverse events between trials, no meta-analyses were performed for this outcome (appendix p 13).

The estimates derived from Bayesian inverse-variance weighted meta-analyses, were consistent with main results with a mean OR of 0·93 (95% credible interval

	Number of events/number of patients		OR (95% CI)	Ratio of ORs*	p value for between-subgroup differences
	SGLT2 inhibitor	Control			
(Continued from previous page)					
Progression to acute kidney injury, renal replacement therapy, or death by 28 days¶					
Respiratory support at randomization					0·13
O_2 ≤15 L/min	225/2433	286/2504	0·79 (0·66 to 0·95)	..	..
Non-invasive ventilation	156/547	139/527	1·11 (0·85 to 1·46)	1·37 (0·98 to 1·93)	..
IMV or ECMO	18/30	11/22	1·57 (0·48 to 5·08)	1·90 (0·58 to 6·27)	..
Age, years					0·97
<70	175/1957	182/1934	0·95 (0·76 to 1·18)	..	..
≥70	224/1053	254/1119	0·94 (0·76 to 1·15)	0·99 (0·73 to 1·34)	..
Sex					0·63
Female	137/1157	148/1205	0·96 (0·75 to 1·23)	..	..
Male	262/1853	288/1848	0·90 (0·75 to 1·08)	0·93 (0·68 to 1·26)	..
Type 2 diabetes status					0·09
Type 2 diabetes	112/754	109/781	1·09 (0·81 to 1·45)	..	..
No diabetes	287/2254	326/2269	0·87 (0·73 to 1·03)	0·73 (0·52 to 1·05)	..
Cardiovascular disease status					0·85
Cardiovascular disease	148/796	157/783	0·90 (0·70 to 1·17)	..	..
No cardiovascular disease	251/2214	279/2269	0·91 (0·76 to 1·10)	1·03 (0·74 to 1·44)	..
Chronic kidney disease status					0·60
Chronic kidney disease	21/160	24/160	0·86 (0·45 to 1·63)	..	..
No chronic kidney disease	51/734	64/726	0·77 (0·53 to 1·14)	0·81 (0·37 to 1·76)	..
Progression to IMV, ECMO or death by 28 days‖					
Respiratory support at randomization					0·69
O_2 ≤15 L/min	243/2445	290/2517	0·85 (0·71 to 1·02)	..	..
Non-invasive ventilation	117/549	178/532	0·95 (0·74 to 1·22)	1·07 (0·77 to 1·48)	..
Age					0·37
<70	206/1939	209/1925	0·98 (0·80 to 1·20)	..	..
≥70	214/1055	259/1124	0·86 (0·70 to 1·06)	0·88 (0·65 to 1·17)	..
Sex					0·42
Female	146/1149	157/1202	0·97 (0·76 to 1·24)	..	..
Male	274/1839	311/1845	0·87 (0·73 to 1·04)	0·88 (0·65 to 1·19)	..
Type 2 diabetes status					0·16
Type 2 diabetes	111/754	112/783	1·04 (0·78 to 1·39)	..	..
No diabetes	309/2238	355/2263	0·86 (0·73 to 1·02)	0·78 (0·55 to 1·10)	..
Cardiovascular disease status					0·73
Cardiovascular disease	149/798	161/784	0·88 (0·68 to 1·13)	..	..
No cardiovascular disease	271/2196	307/2264	0·90 (0·75 to 1·07)	1·06 (0·77 to 1·47)	..
Chronic kidney disease status‡					0·83
Chronic kidney disease	20/160	24/162	0·82 (0·43 to 1·57)	..	..
No chronic kidney disease	61/737	71/723	0·83 (0·58 to 1·19)	0·92 (0·43 to 1·96)	..

(Table 3 continues on next page)

0·791–1·078) for the outcome of 28-day mortality and posterior probabilities of 84% for OR less than 1, and 36% for OR less than 0·9 (appendix p 14).

Discussion

In this prospective meta-analysis with a prespecified analysis plan, based on 6096 patients hospitalised with COVID-19 from three randomised trials,[5,15,16] there was no clear evidence that administration of SGLT2 inhibitor reduced all-cause mortality 28 days after randomisation, compared with usual care or placebo. Similarly, there was no clear evidence that administration of SGLT2 inhibitor reduced progression to acute kidney injury or death, or IMV or death, in patients not receiving corresponding organ support at randomisation. Estimated effects of SGLT2 inhibitor, compared with usual care or placebo, were consistent across predefined subgroups. Data on all-cause in-hospital mortality and mortality at

	Number of events/number of patients		OR (95% CI)	Ratio of ORs*	p value for between-subgroup differences
	SGLT2 inhibitor	Control			
(Continued from previous page)					
Duration of hospital stay (days)**					
Respiratory support at randomization					0·50
O2 ≤15 L/min	2445	2517	−0·24 (−0·71 to 0·23)	..	..
Non-invasive ventilation	549	532	−0·13 (−1·28 to 1·01)	0·03 (−1·26 to 1·31)	..
IMV or ECMO	31	22	1·90 (−1·47 to 5·27)	2·05 (−1·36 to 5·47)	..
Age, years					0·77
<70	1964	1944	0·01 (−0·50 to 0·51)	..	..
≥70	1061	1127	−0·10 (−0·91 to 0·71)	−0·15 (−1·15 to 0·85)	..
Sex					0·03
Female	1160	1213	0·45 (−0·25 to 1·14)	..	..
Male	1859	1856	−0·54 (−1·13 to 0·05)	−1·02 (−1·93 to −0·11)	..
Type 2 diabetes status					0·64
Type 2 diabetes	757	790	−0·05 (−0·91 to 0·81)		..
No diabetes	2266	2278	−0·22 (−0·93 to 0·49)	−0·27 (−1·41 to 0·87)	..
Cardiovascular disease status					0·31
Cardiovascular disease	801	793	−0·44 (−1·38 to 0·49)	..	..
No cardiovascular disease	2224	2277	−0·02 (−0·53 to 0·48)	0·62 (−0·57 to 1·80)	..
Chronic Kidney disease status‡					0·94
Chronic kidney disease	160	162	−0·28 (−2·23 to 1·68)	..	..
No chronic kidney disease	739	730	−0·39 (−1·17 to 0·39)	−0·08 (−2·19 to 2·02)	..

ECMO=extracorporeal membrane oxygenation. IMV=invasive mechanical ventilation. OR=odds ratio. SGLT2=SGLT2=sodium–glucose co-transporter-2. WMD=weighted mean difference. *Ratio of ORs presented compare the interaction OR with the first (reference) group (eg, ratio of the OR for patients with older age group compared with the younger age group). †Data for this outcome is not available for the RECOVERY trial. ‡Data on chronic kidney disease not available from the RECOVERY trial. §Results are presented as hazard ratios with 95% CIs, and as a ratio of hazard ratios with 95% CIs. ¶Excluding patients who had pre-existing chronic kidney disease at the time of randomisation. ||Excluding patients who were receiving IMV or ECMO at the time of randomisation. **Results presented as mean difference (in days) between treatment and control with associated SEs, and a difference in mean differences with 95% CIs.

Table 3: **Effect of SGLT2 inhibitors *vs* usual care or placebo by pre-defined patient subgroups defined at the time of randomisation (secondary and other outcomes)**

90 days were limited to two trials.[5,16] Administration of SGLT2 inhibitor was safe, with rare cases of ketoacidosis, which represents a clinically acceptable risk, compared with usual care or placebo.

We designed the prospective meta-analysis when two of the trials[5,16] were still recruiting patients, and the outcomes were unknown. The protocol, outcomes, specification of subgroups, and analysis plans were made publicly available on the PROSPERO database before data analysis or receipt of outcome data. Our study data collection forms were prespecified, provided by investigators, cross-checked, and include additional data (not published by trialists) on outcomes and subgroups that informed the risk of bias assessments, and will inform clinical practice and policy in the form of WHO clinical practice guidelines. Provision of pooled data in prespecified subgroups meant that participants were compared only with other participants randomised in the same trial, and this facilitated rapid analysis.

Our study had limitations. Although the trial populations were broadly similar based on clinical descriptions, there were differences in eligibility criteria, and the trials were conducted at different stages of the COVID-19 pandemic with evolving standards of usual care and incidence (and risk) of clinical outcomes. Unlike the DARE-19 trial,[5] the ACTIV-4a trial[16] and the RECOVERY trial[15] were adaptive designs, which could theoretically bias results based upon marginal raw count totals, with the direction of bias being unpredictable. Furthermore, there is a potential for bias in the estimated treatment effect when an adaptive trial is stopped early. However, the magnitude of such bias is highest when an adaptive design is used to stop early for benefit: the potential for bias is far lower when trials stop early for futility,[22] as was the case for the ACTIV-4a[16] and RECOVERY trials.[15] Bias due to stopping early for futility is likely to be in the direction of underestimation of the treatment effect. We were unable to conduct meta-analysis by race or ethnicity due to inconsistent categorisation between trials. Although the trials tested different SGLT2 inhibitor, there was little evidence for inconsistency between trials. Some outcomes were not available in all trials. As the adverse event (adverse event and serious adverse event) definitions, and reporting of these events, differed between trials, we decided a priori

that no meta-analyses for adverse events and serious adverse events would be conducted. We also note the limited data on ketoacidosis driven by the low event rates, differences in prevalence of type 2 diabetes between trials and the absence of information on type 2 diabetes management in the trial participants.

Evidence for clinically substantial cardiovascular and renal protective effects of SGLT2 inhibitor use comes from management of patients with chronic diseases such as type 2 diabetes, heart failure, and chronic kidney disease.[23,24] Although mechanisms for these benefits are still being elucidated, the rationale for testing SGLT2 inhibitor in acutely ill patients with COVID-19 was based on their favourable effects on inflammation, oxidative stress, glycolysis, lipogenesis, endothelial function, and oxygen carrying capacity.[25–33]

For the primary outcome of 28-day mortality, 95% CI for the estimated effect of SGLT2 inhibitor in patients hospitalised with COVID-19 (OR between 0·80 and 1·09) includes both no effect (OR equal to 1) and affect comparable with the effects of SGLT2 inhibitor on all-cause mortality in patients with type 2 diabetes (OR 0·88 [95% CI 0·83–0·94]; 257 trials with 342 237 participants; high certainty[34]), heart failure (OR 0·86 [95% CI 0·79–0·94]; nine trials with 15 724 participants[35]), and kidney disease (OR 0·89 [95% CI 0·85–0·94]; nine trials with 90 000 participants[24]). However, further large trials would be required to confirm or refute an effect of SGLT2 inhibitor in patients hospitalised with COVID-19, and it seems unlikely that such trials will be done.

Although there was no clear evidence of between-study heterogeneity, the strongest efficacy signal was from the DARE-19 trial,[5] in which the eligibility criteria perhaps involved a trial population with greater likelihood of benefit, and higher likelihood of COVID-19 illness progression, with features such as 56% prevalence of type 2 diabetes and cardiometabolic risk factors,[5] compared with the other two trials. However, no statistically significant difference in SGLT2 inhibitor treatment effect was observed by type 2 diabetes status subgroup. Further, there was no discernible trend in treatment effect between respiratory support subgroups that are indicators of COVID-19 severity (ie, no supplemental oxygen therapy or supplemental oxygen therapy only *vs* patients receiving non-invasive ventilation *vs* patients receiving IMV or ECMO). Thus, given the availability of other more efficacious options for this population,[11] the use of SGLT2 inhibitor as usual care for all patients hospitalised with COVID-19 is not recommended.

An important finding of our meta-analysis is the low incidence of ketoacidosis when SGLT2 inhibitor was administered in acutely unwell patients hospitalised with COVID-19. SGLT2 inhibitor treatment is often stopped due to risk of ketoacidosis when patients with chronic diseases (eg, type 2 diabetes, heart failure) have an acute illness that requires hospitalisation.[36] At the start of the COVID-19 pandemic, there were concerns that SGLT2 inhibitors could increase the risk of volume depletion, acute kidney injury, and ketoacidosis,[37,38] with guidance to routinely discontinue SGLT2 inhibitors in patients hospitalised with COVID-19. Thus, the safety data from our meta-analysis is of clinical relevance given that patients who are likely to be on chronic SGLT2 inhibitor therapy are also at risk of adverse outcomes from COVID-19, and the prevalence of chronic SGLT2 inhibitor therapy is likely to increase in the coming years. Our data also provides indirect evidence for revisiting the notion that chronic SGLT2 inhibitor therapy must be discontinued when patients with chronic diseases (eg, heart failure, kidney disease or type 2 diabetes) are hospitalised for acute illness.

In this prospective meta-analysis of randomised clinical trials evaluating patients hospitalised for COVID-19 there was no clear evidence that administration of SGLT2 inhibitor, compared with usual care or placebo, reduced 28-day all-cause mortality, or other prespecified efficacy outcomes. Although safe, these findings do not support the use of SGLT2 inhibitor as standard care in acutely ill patients hospitalised with COVID-19.

Contributors

CV, PJG, DF, and JACS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PWH (RECOVERY), ML (RECOVERY), MNK (DARE-19 and ACTIV-4a), and JSH (ACTIV-4a) are the principal investigators of the trials included in this prospective meta-analysis. JACS, CV, PJG, and DF designed the statistical analyses. PJG and DF did the statistical analyses. MSH led the study, with guidance and input on development of the protocol and interpretation of the data from members of the WHO REACT team (JACS, CV, PJG, DF, JD, JM, and SM), to which all authors contributed. Trial investigators for the three included trials (PWH, MNK, JSH, ADA, OB, RHMF, SBG, RH, GGK, ML, EL, MDN, and NS) had access to raw data; summary results were supplied for inclusion in this meta-analysis and verified by RH (RECOVERY), ADA (ACTIV-4a), and MNK (DARE-19). JPTH and KW completed the risk of bias and GRADE assessments. MSH, CV, and JACS wrote the first draft of the manuscript. All authors contributed to the revision of manuscript for important intellectual content. All authors were involved in the decision to submit for publication. MSH had final responsibility for the decision to submit the manuscript.

Declaration of interests

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Data sharing

For the RECOVERY trial, the protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online at www.recoverytrial.net. As described in the protocol, the Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. Deidentified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication. Data will be made available in line with the policy and procedures described at https://www.ndph.ox.ac.uk/data-access. Those wishing to request access should complete the form at https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx and e-mailed to: data.access@ndph.ox.ac.uk

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References

1 Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26:** 1017–32.
2 van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P, et al. A guide to immunotherapy for COVID-19. *Nat Med* 2022; **28:** 39–50.
3 Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023; **388:** 117–27.
4 McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021; **6:** 148–58.
5 Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2021; **9:** 586–94.
6 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.
7 Sharifi Y, Payab M, Mohammadi-Vajari E, et al. Association between cardiometabolic risk factors and COVID-19 susceptibility, severity and mortality: a review. *J Diabetes Metab Disord* 2021; **20:** 1743–65.
8 Chen Q, Wang L, Li C, et al. Chronic cardio-metabolic disease increases the risk of worse outcomes among hospitalized patients with COVID-19: a multicenter, retrospective, and real-world study. *J Am Heart Assoc* 2021; **10:** e018451.
9 Leong A, Cole JB, Brenner LN, Meigs JB, Florez JC, Mercader JM. Cardiometabolic risk factors for COVID-19 susceptibility and severity: a Mendelian randomization analysis. *PLoS Med* 2021; **18:** e1003553.
10 Denson JL, Gillet AS, Zu Y, et al. Metabolic syndrome and acute respiratory distress syndrome in hospitalized patients with COVID-19. *JAMA Netw Open* 2021; **4:** e2140568.
11 Agarwal A, Hunt B, Stegemann M, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020; **370:** m3379.
12 Tierney JF, Fisher DJ, Vale CL, et al. A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials. *PLoS Med* 2021; **18:** e1003629.
13 Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; **324:** 1330–41.
14 Shankar-Hari M, Vale CL, Godolphin PJ, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a Meta-analysis. *JAMA* 2021; **326:** 499–518.
15 RECOVERY Collaborative Group. Empagliflozin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Diabetes Endocrinol* 2023; **11:** 905–14.
16 Kosiborod MN, Windsor SL, Vardeny O, et al. Effect of sodium–glucose co-transporter-2 inhibitors on survival free of organ support in patients hospitalised for COVID-19 (ACTIV-4a): a pragmatic, multicentre, open-label, randomised, controlled, platform trial. *Lancet Diabetes Endocrinol* 2024; published online Sept 6. https://doi.org/10.1016/S2213-8587(24)00218-3.
17 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.
18 Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017; **356:** j573.
19 Godolphin PJ, White IR, Tierney JF, Fisher DJ. Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: a within-trial framework. *Res Synth Methods* 2023; **14:** 68–78.

20 Carlin JB. Meta-analysis for 2 x 2 tables: a Bayesian approach. *Stat Med* 1992; **11:** 141–58.

21 StataCorp. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC, 2023.

22 Walter SD, Han H, Guyatt GH, et al. A systematic survey of randomised trials that stopped early for reasons of futility. *BMC Med Res Methodol* 2020; **20:** 10.

23 Usman MS, Siddiqi TJ, Anker SD, et al. Effect of SGLT2 inhibitors on cardiovascular outcomes across various patient populations. *J Am Coll Cardiol* 2023; **81:** 2377–87.

24 Baigent C, Emberson JR, Haynes R, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; **400:** 1788–801.

25 Kosiborod M, Berwanger O, Koch GG, et al. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: Design and rationale for the DARE-19 study. *Diabetes Obes Metab* 2021; **23:** 886–96.

26 Daniele G, Xiong J, Solis-Herrera C, et al. Dapagliflozin enhances fat oxidation and ketone production in patients with type 2 diabetes. *Diabetes Care* 2016; **39:** 2036–41.

27 Solini A, Giannini L, Seghieri M, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. *Cardiovasc Diabetol* 2017; **16:** 138.

28 Ohara K, Masuda T, Morinari M, et al. The extracellular volume status predicts body fluid response to SGLT2 inhibitor dapagliflozin in diabetic kidney disease. *Diabetol Metab Syndr* 2020; **12:** 37.

29 Maayah ZH, Ferdaoussi M, Takahara S, Soni S, Dyck JRB. Empagliflozin suppresses inflammation and protects against acute septic renal injury. *Inflammopharmacology* 2021; **29:** 269–79.

30 Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; **15:** 853–62.

31 Kim SR, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat Commun* 2020; **11:** 2127.

32 Ghanim H, Abuaysheh S, Hejna J, et al. Dapagliflozin suppresses hepcidin and increases erythropoiesis. *J Clin Endocrinol Metab* 2020; **105:** dgaa057.

33 Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diabetes Metab* 2018; **44:** 457–64.

34 Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2023; **381:** e074068.

35 Cardoso R, Graffunder FP, Ternes CMP, et al. SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: a systematic review and meta-analysis. *EClinicalMedicine* 2021; **36:** 100933.

36 Khunti K, Aroda VR, Bhatt DL, et al. Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: A perspective based on the updated evidence. *Diabetes Obes Metab* 2022; **24:** 2071–80.

37 Milder TY, Stocker SL, Day RO, Greenfield JR. Potential safety issues with use of sodium-glucose cotransporter 2 inhibitors, particularly in people with type 2 diabetes and chronic kidney disease. *Drug Saf* 2020; **43:** 1211–21.

38 Scheen AJ. SGLT2 inhibition during the COVID-19 epidemic: Friend or foe? *Diabetes Metab* 2020; **46:** 343–44.