Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background COVID-19 can lead to multiorgan failure. Dapagliflozin, a SGLT2 inhibitor, has significant protective benefits for the heart and kidney. We aimed to see whether this agent might provide organ protection in patients with COVID-19 by affecting processes dysregulated during acute illness.

Methods DARE-19 was a randomised, double-blind, placebo-controlled trial of patients hospitalised with COVID-19 and with at least one cardiometabolic risk factor (ie, hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease). Patients critically ill at screening were excluded. Patients were randomly assigned 1:1 to dapagliflozin (10 mg daily orally) or matched placebo for 30 days. Dual primary outcomes were assessed in the intention-to-treat population: the outcome of prevention (time to new or worsened organ dysfunction or death), and the hierarchial composite outcome of recovery (change in clinical status by day 30). Safety outcomes, in patients who received at least one study medication dose, included serious adverse events, adverse events leading to discontinuation, and adverse events of interest. This study is registered with ClinicalTrials.gov, NCT04350593.

Findings Between April 22, 2020 and Jan 1, 2021, 1250 patients were randomly assigned with 625 in each group. The primary composite outcome of prevention showed organ dysfunction or death occurred in 70 patients (11·2%) in the dapagliflozin group, and 86 (13·8%) in the placebo group (hazard ratio [HR] 0·80, 95% CI 0·58–1·10; p=0·17). For the primary outcome of recovery, 547 patients (87·5%) in the dapagliflozin group and 532 (85·1%) in the placebo group showed clinical status improvement, although this was not statistically significant (win ratio 1·09, 95% CI 0·97–1·22; p=0·14). There were 41 deaths (6·6%) in the dapagliflozin group, and 54 (8·6%) in the placebo group (HR 0·77, 95% CI 0·52–1·16). Serious adverse events were reported in 65 (10·6%) of 613 patients treated with dapagliflozin and in 82 (13·3%) of 616 patients given the placebo.

Interpretation In patients with cardiometabolic risk factors who were hospitalised with COVID-19, treatment with dapagliflozin did not result in a statistically significant risk reduction in organ dysfunction or death, or improvement in clinical recovery, but was well tolerated.

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Introduction

Patients who are hospitalised with COVID-19 and have cardiometabolic risk factors, such as type 2 diabetes, cardiovascular disease, and kidney disease, are at high risk for multiorgan failure and death, as well as a slower clinical recovery.[1–7] Given the dearth of efficacious therapies that reduce the risk of disease progression and major clinical events (currently limited only to dexamethasone in critically ill patients),[8] there is a large unmet need for additional treatment options.[9,10]

SGLT2 inhibitors have been shown to reduce cardiovascular and kidney events in large trials of predominantly ambulatory patients with type 2 diabetes, cardiovascular disease, or kidney disease.[11–17] Although the mechanisms underlying these benefits remain a subject of investigation, previous studies (including those of ambulatory patients with diabetes) have shown that SGLT2 inhibitors favourably affect various pathways that are dysregulated in the setting of acute illness (including COVID-19) such as inhibition of glycolysis (a pathway that can be used by respiratory pathogens) and stimulation of lipolysis, reduction in oxidative stress and inflammation, as well as improved endothelial function and oxygen carrying capacity.[18–25] These effects might help to prevent multiorgan damage and improve recovery in patients with COVID-19.

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Research in context

Evidence before this study

Patients with cardiometabolic risk factors who are hospitalised with COVID-19 are at a high risk of organ failure and death. Previous trials of SGLT2 inhibitors in patients with type 2 diabetes, heart failure, and chronic kidney disease showed substantial protective effects on the cardiovascular system and the kidneys, and these agents might provide organ protection in the setting of acute illness, such as COVID-19, by affecting processes that are dysregulated during acute illness. However, the paucity of reliable data has also led to concerns that SGLT2 inhibitors could increase the risk of acute kidney injury and ketoacidosis in patients hospitalised with COVID-19.

We searched PubMed between Jan 1, 2010, and March 1, 2020 for clinical trials of SGLT2 inhibitors in patients with acute illness (including COVID-19) using the search terms: "SGLT2 inhibitor", "dapagliflozin", "canagliflozin", "empagliflozin", "sotagliflozin", and "hospitalised". Except for trials in patients with heart failure, we were unable to identify any trials of SGLT2 inhibitors in an acute setting.

Added value of this study

To our knowledge, DARE-19 is the first, large randomised controlled trial to evaluate efficacy and safety of SGLT2 inhibitors in patients hospitalised with COVID-19 and has implications for clinical practice and future research. Dapagliflozin did not significantly reduce the proportion of patients with organ dysfunction or death or who experienced improved recovery. Although we observed numerically fewer events of organ dysfunction or death in patients who received dapagliflozin as compared with placebo, this difference was not statistically significant, and might not be generalisable to other populations. Importantly, dapagliflozin was well tolerated in one of the highest risk (with respect to organ failure and death) patient populations ever to be treated with SGLT2 inhibitors.

Implications of all the available evidence

Our study shows that dapagliflozin was well tolerated, with no new safety concerns identified in this acutely ill patient population. Therefore, for patients already receiving SGLT2 inhibitors before a COVID-19 diagnosis, our findings support continuation of this treatment, as long as patients are monitored. Because SGLT2 inhibitors do not have a direct anti-viral effect on SARS-CoV2, our findings (although not conclusive) suggest a need for future trials to determine whether dapagliflozin might provide organ protection in non-COVID-19 hospitalised patients at high risk for progressing to critical illness.

In the dapagliflozin in respiratory failure in patients with COVID-19 (DARE-19) trial, we evaluated the efficacy and safety of dapagliflozin in patients who had cardiometabolic risk factors and who were hospitalised with COVID-19.

Methods

Study design

DARE-19 was a multicentre, randomised, double-blind, placebo-controlled trial to evaluate the effects of treatment with dapagliflozin for 30 days in hospitalised patients with COVID-19. The study methods have been previously published.[26] Patients were recruited across 95 hospitals in Argentina, Brazil, Canada, India, Mexico, the UK, and the USA. DARE-19 was an investigator-initiated collaborative study, with the study design and procedures operationalised through collaboration between Saint Luke's Mid America Heart Institute (sponsor) and AstraZeneca (funding source). An executive committee, consisting of six academic members (MNK, OB, SV, OM, FM, and GGK) and three non-voting members (AML, JO, and RE) from AstraZeneca, was responsible for the design, conduct, and analysis of the trial. The committee members and investigators are listed in the appendix 1 (pp 2–5). The trial was done in accordance with the protocol, which was approved by a central or local ethics committees at each site, and the statistical analysis plan (both available in appendix 2). An independent data and safety monitoring committee oversaw the trial.

Patients

Eligible individuals were at least 18 years of age, hospitalised with laboratory confirmed or clinically suspected SARS-CoV-2 infection no more than 4 days before screening, had oxygen saturation of 94% or greater on supplemental oxygen (no more than 5 L/min), chest radiography findings consistent with COVID-19 pneumonia, and at least one cardiometabolic risk factor: hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease (estimated glomerular filtration rate [eGFR] between 25 mL/min per 1·73 m² and 60 mL/min per 1·73 m²). Key exclusion criteria were evidence of critical illness (eg, need for mechanical ventilation, evidence of acute kidney failure, or need for vasopressor support at the time of screening), eGFR of less than 25 mL/min per 1·73 m², type 1 diabetes, and history of diabetic ketoacidosis. The detailed eligibility criteria are listed in appendix 1 (p 6) and appendix 2. Written informed consent was obtained from all patients. Patients were treated according to local standard of care for COVID-19.

Randomisation and masking

Individuals who met the eligibility criteria were randomly assigned (1:1) to either dapagliflozin 10 mg once daily or to matching placebo with the use of balanced blocks, and randomisation was stratified by country. Investigators used a central interactive response system to determine treatment assignment. Participants and trial personnel were unaware of the treatment assignments.

Procedures

Patients were treated with either dapagliflozin 10 mg once daily orally or matching placebo for 30 days, and if mechanical ventilation became necessary, study medication tablets were crushed and administered via feeding tube. After the last dose of study medication on day 30, patients were followed for an additional observational period of 60 days (appendix 1, p 13). This Article summarises the results of the primary analysis from the 30 day treatment period, as prespecified in statistical analysis plan (appendix 2), with the follow-up data for the additional observational period to be published at later date. During hospitalisation, vital signs, local laboratory assessments, serious adverse events, and organ dysfunction were monitored daily. Monitoring of acid-base balance (in patients with type 2 diabetes) and kidney function was required daily during hospitalisation. If discharged, patients continued treatment up to day 30 and were contacted by telephone on day 15 or day 30, or both, at which time data for serious adverse events, clinical status, concomitant medications, and study medication adherence were collected.

Outcomes

Our trial had dual primary efficacy outcomes. After the original protocol was designed, changes in the standard of care for patients hospitalised with COVID-19 resulted in substantially lower event rates than originally projected.[27,28] Consequently, faster and more complete recovery became an important treatment goal in addition to the prevention of complications and death, prompting the addition of recovery to the primary objectives on Nov 20, 2020. The primary outcome of prevention was a composite of time to new or worsened respiratory, cardiovascular, or kidney organ dysfunction during the index hospitalisation, or death from any cause at any time during the 30 day treatment period (appendix 1, pp 7–8). Respiratory decompensation is defined as requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, continuous positive airway pressure, or bilevel positive airway pressure), or initiation of extracorporeal membrane oxygenation, or both. Cardiovascular dysfunction is defined as new or worsening congestive heart failure during hospitalisation, with heart failure defined as at least one of the following: (1) initiation of new intravenous therapy for heart failure, (2) reinstitution of previous intravenous therapy for heart failure, (3) increase in current intravenous therapy for heart failure. This definition is based on modification of previous definition of in-hospital worsening of heart failure;[29] requirement for vasopressor therapy; or inotropic or mechanical circulatory support, sustained ventricular tachycardia or ventricular fibrillation, or resuscitated cardiac arrest.[30] Kidney organ dysfunction is defined as doubling of serum creatinine or initiation of renal-replacement therapy. The primary outcome of recovery was as a hierarchical composite that ranked patients into categories using the severity and timing of events experienced during the 30 day treatment period: death, organ dysfunction during the index hospitalisation, supplemental oxygen requirement for patients hospitalised at day 30 without organ dysfunction, and hospital discharge before day 30 (appendix 1, pp 7–8; appendix 2).

The secondary outcomes in hierarchical order were: a composite kidney outcome (ie, acute kidney injury defined as doubling of serum creatinine compared with baseline during index hospitalisation or serious adverse event, with the preferred term of acute kidney injury, following discharge, initiation of renal replacement therapy, or death from any cause over 30 days); death from any cause through day 30; total number of days alive and free from mechanical ventilation through day 30; total number of days alive, not in an intensive care unit and free from mechanical ventilation through day 30; and time to hospital discharge.

Safety outcomes included patients who had on-treatment serious adverse events, adverse events leading to study medication discontinuation, or any severity of adverse events of interest, which included acute kidney injury and diabetic ketoacidosis (appendix 1, pp 7–8). These adverse events were reported daily during hospitalisation, at discharge, and at follow-up visits if discharged.

All events were investigator reported. Rigorous measures were implemented to ensure data quality, including source data verification for reported outcome and safety events, as well as thorough review of events to ensure compliance with the protocol definitions.

See Online for appendix 1
See Online for appendix 2

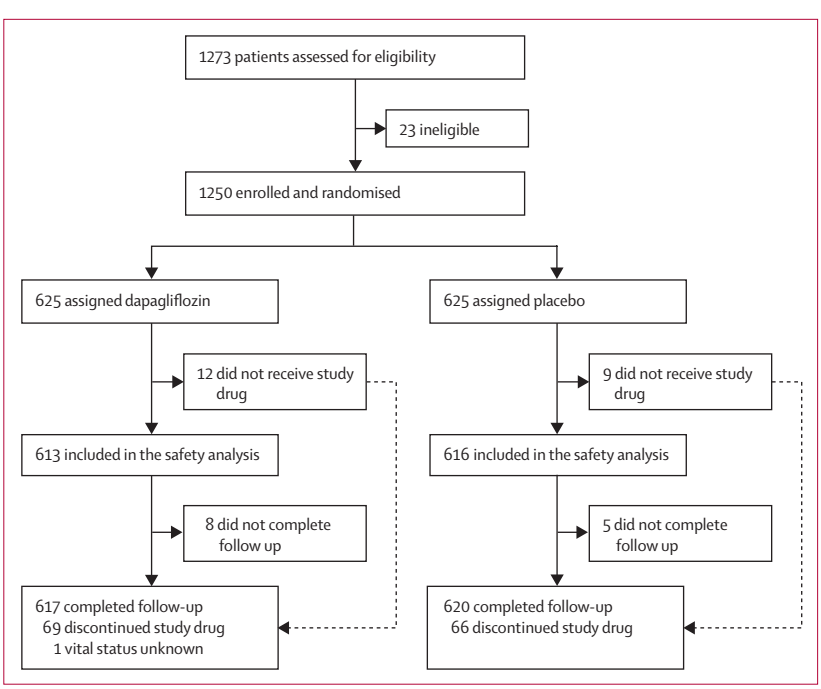

Figure 1: **Trial profile**

	Dapagliflozin (n=625)	Placebo (n=625)	Total (N=1250)
Mean age, years	61·0 (13·4)	61·8 (13·5)	61·4 (13·5)
Sex, female	260 (41·6%)	273 (43·7%)	533 (42·6%)
Mean BMI, kg/m²	30·6 (6·2)	30·9 (6·4)	30·7 (6·3)
Race*			
White	452 (72·6%)	459 (74·3%)	911 (73·4%)
Black	85 (13·6%)	84 (13·6%)	169 (13·6%)
Asian	35 (5·6%)	29 (4·7%)	64 (5·2%)
Native Hawaiian or other Pacific Islander	1 (0·2%)	0	1 (0·1%)
American Indian or Alaska Native	7 (1·1%)	10 (1·6%)	17 (1·4%)
Other	43 (6·9%)	36 (5·8%)	79 (6·4%)
Ethnicity*			
Hispanic or Latino	394 (63·4%)	362 (58·5%)	756 (61·0%)
Not Hispanic or Latino	166 (26·7%)	177 (28·6%)	343 (27·7%)
Not reported or unknown	61 (9·8%)	80 (12·8%)	141 (11·3%)
Inclusion risk factors			
Type 2 diabetes	312 (49·9%)	324 (51·8%)	636 (50·9%)
Heart failure	44 (7·0%)	46 (7·4%)	90 (7·2%)
Hypertension	526 (84·2%)	534 (85·4%)	1060 (84·8%)
Atherosclerotic cardiovascular disease	93 (14·9%)	106 (17·0%)	199 (15·9%)
Chronic kidney disease, eGFR 25–60 mL/min per 1·73 m²	38 (6·1%)	44 (7·0%)	82 (6·6%)
Patients with two or more inclusion risk factors	292 (46·7%)	319 (51·0%)	611 (48·9%)
Other risk factors			
Age ≥60 years	339 (54·2%)	360 (57·6%)	699 (55·9%)
BMI ≥30	296 (47·4%)	305 (48·8%)	601 (48·1%)
Chronic obstructive pulmonary disease	25 (4·0%)	32 (5·1%)	57 (4·6%)
Current smoker	29 (4·6%)	20 (3·2%)	49 (3·9%)
Vitals signs			
Heart rate, beats per min	79·3 (13·7)	79·7 (13·7)	79·5 (13·7)
Blood pressure, mm Hg			
Systolic	126·6 (16·0)	127·0 (16·3)	126·8 (16·1)
Diastolic	76·6 (10·9)	76·2 (10·6)	76·4 (10·7)
Temperature, °C	36·4 (0·6)	36·4 (0·7)	36·4 (0·6)
Oxygen saturation, %†	95·5 (1·7)	95·2 (1·8)	95·3 (1·8)
(Continued from previous column)			
Laboratory values at baseline			
eGFR, mL/min per 1·73 m²	84·1 (25.0)	83·4 (24·6)	83·8 (24·8)
SARS-CoV-2-test result at baseline			
Positive	584 (93·4%)	575 (92·0%)	1159 (92·7%)
Negative	30 (4·8%)	35 (5·6%)	65 (5·2%)
Test results not known	11 (1·8%)	15 (2·4%)	26 (2·1%)
Medication at baseline			
ACE inhibitor or ARB	225 (36·0%)	219 (35·0%)	444 (35·5%)
β-blocker	93 (14·9%)	98 (15·7%)	191 (15·3%)
Calcium blocker	84 (13·4%)	88 (14·1%)	172 (13·8%)
Loop-diuretic	49 (7·8%)	63 (10·1%)	112 (9·0%)
Statin	122 (19·5%)	144 (23·0%)	266 (21·3%)
Anti-coagulant	527 (84·3%)	527 (84·3%)	1054 (84·3%)
Glucose-lowering medication at baseline			
Biguanide	82 (13·1%)	75 (12·0%)	157 (12·6%)
Sulfonylurea	24 (3·8%)	22 (3·5%)	46 (3·7%)
DPP-4 inhibitor	17 (2·7%)	11 (1·8%)	28 (2·2%)
GLP-1 receptor agonist	6 (1·0%)	8 (1·3%)	14 (1·1%)
Insulin	223 (35·7%)	221 (35·4%)	444 (35·5%)
Concomitant COVID-19 medication at baseline			
Remdesivir	114 (18·2%)	111 (17·8%)	225 (18·0%)
Systemic corticosteroids	176 (28·2%)	179 (28·6%)	355 (28·4%)
Dexamethasone	133 (21·3%)	136 (21·8%)	269 (21·5%)
Other systemic glucocorticoid	50 (8·0%)	55 (8·8%)	105 (8·4%)

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. N numbers might differ for some parameters based on data availability, as shown. *Reported by the patient. †Measured on supplemental oxygen.

Table 1: **Demographic, clinical characteristics, and inclusion risk factors of the patients at baseline**

Statistical analysis

The two primary outcomes of prevention and recovery were to be tested in parallel,[31] allocating the two-sided α of 0·05 as follows: 0·015 to the outcome of prevention and 0·035 to the outcome of recovery. If either was significant, the α could be recycled to test the other primary outcome at a two-sided α of 0·04, while a two-sided α of 0·01 could be used to test the composite kidney outcome (a multistage fallback procedure; appendix 1, p 12).[32] If the composite kidney outcome was significant, α could be recycled to test the remaining primary outcome at a two-sided α of 0·05. If after this procedure both primary efficacy outcomes and the composite kidney outcome were significant, the remaining secondary outcomes were to be tested, at a two-sided α of 0·05, in a hierarchical fashion.

The initial study design was event driven. After the addition of the dual primary outcome of recovery, we calculated that 1200 participants would provide at least 80% power for a win ratio[33,34] (WR) of 1·23 (minimal detectable WR of 1·15, which was considered to be clinically meaningful) for the primary outcome of recovery (with an allocated α of 0·035), while the minimal detectable hazard ratio (HR) for the primary outcome of prevention would be 0·72, provided accrual of 150 organ dysfunction or death events, and recycled α of 0·04.

Efficacy analyses were intention to treat, including all randomly assigned patients. A Cox proportional-hazards model, stratified by country and adjusted for age and sex,

was used to calculate the HR and 95% CI for the primary outcome of prevention. The hierarchical primary outcome of recovery was analysed using a WR and 95% CI estimated from a Cox regression model (stratified by country), applied to ranks (with larger ranks for worse outcomes). The p value for this analysis was calculated using a country stratified log-rank test. Time-to-event secondary outcomes were analysed similar to the primary outcome of prevention (except for the composite kidney outcome, which was adjusted for baseline eGFR, while the Cox regression analysis for the hospital discharge resulted in a RR). Outcomes based on the total number of days were compared using a WR, similar to the primary outcome of recovery. Prespecified subgroups were assessed with the use of the same stratified Cox regression models without adjustment for multiple comparisons. We did several prespecified sensitivity analyses for the primary endpoint of prevention: these involved excluding patients that tested negative at baseline for SARS-CoV-2 and evaluating the results within subgroups of patients who did and did not receive remdesivir at baseline. In addition, we did a post-hoc sensitivity analysis evaluating the results for the primary endpoint of prevention within subgroups of patients who did and did not receive systemic corticosteroids at baseline.

Safety analyses were done in the safety population (randomly assigned patients who received at least one dose of study medication). All analyses used SAS software, version 9.4 (SAS Institute). The study was overseen by an Independent Data and Safety Monitoring Committee (appendix 1, p 5).

This study is registered with ClinicalTrials.gov, NCT04350593.

Role of the funding source

The study funder (AstraZeneca) worked in collaboration with the study sponsor (Saint Luke's Hospital, Kansas City, MO, USA) in designing the study, analysing the data, and employees of the funder are authors (RE, JO, JB, AML, PA, SBG) on this Article and contributed to the interpretation of the data, writing the Article, and the decision to submit.

Results

From April 22, 2020 through Jan 1, 2021, 1273 patients were screened, of whom 1250 were randomly assigned to a group with 625 people in each (figure 1; appendix 1, p 14). Baseline characteristics were well balanced between groups (table 1). Mean age was 61·4 (SD 13·5) years, and 533 patients (42·6%) were female. At screening, 636 patients (50·9%) had type 2 diabetes, 1060 (84·8%) had hypertension, 199 (15·9%) had atherosclerotic disease, 90 (7·2%) heart failure, and 82 (6·6%) chronic kidney disease; 611 patients (48·9%) had more than one risk factor, and mean BMI was 30·7 (SD 6·3) kg/m². A positive SARS-CoV-2 test was recorded for 1159 patients (92·7%) with 26 patients (2·1%) who had missing data for this test.

	Dapagliflozin (n=625)	Placebo (n=625)	HR, RR, or WR (95% CI)*	p value
Primary outcomes				
Prevention composite outcome	70 (11·2%)	86 (13·8%)	HR 0·80 (0·58–1·10)	0·17
New or worsening organ dysfunction	64 (10·2%)	80 (12·8%)	HR 0·80 (0·57–1·11)	NA
Respiratory decompensation	58 (9·3%)	70 (11·2%)	HR 0·85 (0·60–1·20)	NA
Cardiovascular decompensation	47 (7·5%)	58 (9·3%)	HR 0·81 (0·55–1·19)	NA
Kidney decompensation	24 (3·8%)	35 (5·6%)	HR 0·65 (0·38–1·10)	NA
Death from any cause†	41 (6·6%)	54 (8·6%)	HR 0·77 (0·52–1·16)	NA
Hierarchical composite recovery outcome‡	547 (87·5%)	532 (85·1%)	WR 1·09 (0·97–1·22)	0·14
Secondary outcomes				
Composite of acute kidney injury, initiation of renal-replacement therapy, or death from any cause	48 (7·7%)	65 (10·4%)	HR 0·74 (0·50–1·07)	NA
Total number of days alive and free from mechanical ventilation§	554 (88·6%)	540 (86·4%)	WR 1·03 (0·92–1·15)	NA
Total number of days alive, not in the ICU, and free from mechanical ventilation¶	539 (86·2%)	528 (84·5%)	WR 1·02 (0·92–1·14)	NA
Hospital discharge	567 (90·7%)	556 (89·0%)	RR 1·05 (0·94–1·18)	NA

HR=hazard ratio. RR=rate ratio. WR=win ratio. ICU=intensive care unit. NA=not applicable. *HR >1 favours placebo, RR >1 favours dapagliflozin, WR >1 favours dapagliflozin. †The outcome of death from any cause was also a separate secondary outcome. ‡The number of patients experiencing improvement by day 30 compared with baseline (discharged from hospital without a worsening event and alive, or still in hospital without a worsening event and without oxygen support) in the hierarchical composite endpoint analysis. §The number of patients alive and without any ventilator use during 30 days, in the total number of days analysis. ¶The number of patients alive and without any ventilator and ICU use during 30 days, in the total number of days analysis.

Table 2: **Primary and secondary outcomes**

In total, 1229 patients (98·3%) received at least one dose of study medication (figure 1). Dapagliflozin was discontinued for reasons other than death in 69 (11·3%) of 613 patients, and placebo in 66 (10·7%) of 616 patients (figure 1). The follow-up for the primary outcome of prevention was completed by 1237 patients (99·0%), and vital status was ascertained for all but one patient in the dapagliflozin group.

The primary composite outcome of prevention (organ dysfunction or death from any cause) occurred in 70 (11·2%) of 625 patients in the dapagliflozin group, and 86 (13·8%) of 625 patients in the placebo group (HR 0·80, 95% CI 0·58–1·10; p=0·17; table 2, figure 2A, 2B). New or worsened organ dysfunction occurred in 64 patients (10·2%) in the dapagliflozin group, and 80 (12·8%) in the placebo group (HR 0·80, 95% CI 0·57–1·11). There were 41 (6·6%) deaths in the dapagliflozin group, and 54 (8·6%) in the placebo group (HR 0·77, 95% CI 0·52–1·16; table 2, figures 2A, 3A). For the second primary outcome of recovery (the hierarchical composite), 547 (87·5%) of 625 patients in dapagliflozin group versus 532 (85·1%) of 625 patients in placebo group had improvement in clinical status compared with baseline (alive with no organ dysfunction events, and either discharged from hospital, or still hospitalised at day 30 but without supplemental oxygen; WR 1·09, 95% CI 0·97–1·22; p=0·14; table 2, figure 2C). Given that differences for both primary outcomes did not meet the predefined

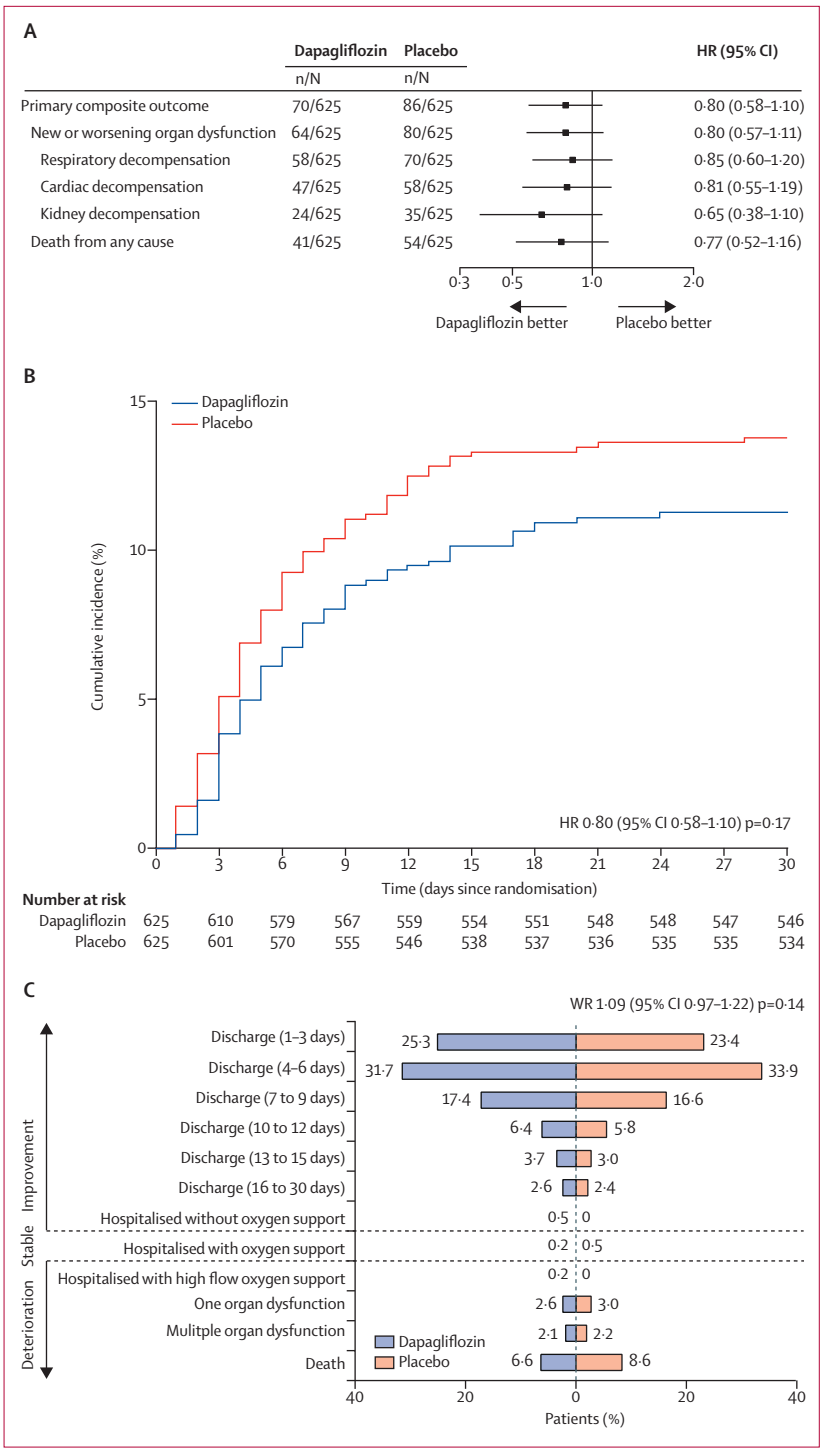

Figure 2: **Primary outcomes**
(A) Forest plot of the primary outcome of prevention (new or worsened respiratory, cardiovascular or kidney organ dysfunction or death from any cause) and its components; (B) Kaplan-Meier of the cumulative estimate of the primary outcome of prevention; (C) the proportion of patients for each of the components of the primary outcome of recovery. HR=hazard ratio. WR=win ratio.

level of statistical significance, analyses of subsequent outcomes were exploratory.

The prespecified subgroup analyses for the primary outcome of prevention and recovery are shown in (appendix 1, p 15), and were generally consistent with the main findings, including in patients with and without diabetes, although there was heterogeneity noted by sex. The results for the primary endpoint of prevention were also consistent in sensitivity analyses: after excluding patients that tested negative at baseline for SARS-CoV-2 (HR 0·81; 95% CI 0·58–1·12); within subgroups of patients that received remdesivir at baseline (0·45, 0·16–1·31) and patients that did not (0·86, 0·61–1·20; $p_{interaction}$=0·25); and within subgroups of patients that received systemic corticosteroids at baseline (0·66, 0·37–1·17) and patients that did not (0·86, 0·59–1·26; $p_{interaction}$=0·48; appendix 1, p 9).

The composite kidney outcome occurred in 48 (7·7%) patients in the dapagliflozin group, and 65 (10·4%) in the placebo group (table 2, figure 3B). Acute kidney injury occurred in 26 (4·2%) patients that received dapagliflozin, and 36 (5·8%) that received placebo (0·70, CI 0·42–1·17). Initiation of renal replacement therapy occurred in 13 (2·1%) patients assigned to dapagliflozin, and 22 (3·5%) patients assigned to placebo (0·56, 0·27–1·13). Results for the total number of days alive, not in an intensive care unit, and free from mechanical ventilation, and time to hospital discharge are in table 2.

12 patients in the dapagliflozin group and nine in the placebo group were excluded from the safety analysis because they did not receive study medication. In total, 65 (10·6%) of 613 patients in the dapagliflozin group, and 82 (13·3%) of 616 patients in the placebo group were reported to have had serious adverse events (table 3; appendix 1, pp 10–11, 16). Adverse events leading to study medication discontinuation were reported in 44 (7·2%) patients in the dapagliflozin group and 55 (8·9%) in the placebo group. Diabetic ketoacidosis was reported in two patients in the dapagliflozin group both of whom had type 2 diabetes at baseline; these events were non-severe and resolved after study medication discontinuation. Safety events of acute kidney injury were reported in 21 (3·4%) patients in the dapagliflozin group, and 34 (5·5%) in the placebo group.

Discussion

DARE-19, a randomised, double-blind, placebo-controlled trial of patients hospitalised with COVID-19 who had cardiometabolic risk factors, showed that dapagliflozin did not significantly reduce the rates of organ dysfunction or death or improve recovery. Although numerically fewer patients treated with dapagliflozin had organ failure or died, these differences were not statistically significant. The results were similar for the key secondary endpoints of worsening kidney function or death from any cause. Dapagliflozin was well tolerated and no new safety signals were identified.

Previous trials of SGLT2 inhibitors in patients with type 2 diabetes, heart failure, and chronic kidney disease showed substantial and consistent protective effects of these treatments for the heart and kidney.[11–17] Furthermore, mechanistic studies indicated that SGLT2 inhibitors have favourable effects on pathways that are dysregulated in a setting of acute illness (such as COVID-19) including inflammation, oxidative stress, glycolysis, lipogenesis, endothelial function, and oxygen carrying capacity.[18–25] Accordingly, the hypothesis tested in our trial was that dapagliflozin might reduce the risk of major clinical events in a population with acute illness that was superimposed on top of pre-existing cardiovascular, metabolic disease, or kidney disease.

The numerically lower but non-significant rates of organ dysfunction and death among patients treated with dapagliflozin were consistent across the components of this primary outcome. These observations might be of interest for patients hospitalised with COVID-19, and are in line with what was observed in previous trials of dapagliflozin in ambulatory patients with type 2 diabetes, heart failure, or chronic kidney disease, which showed lower risks of cardiovascular and kidney events with dapagliflozin versus placebo.[12,14,17] Furthermore, although statistically non-significant, the numerically lower rates of death with dapagliflozin in our trial (with most deaths being non-cardiovascular) appear to be in line with findings from another trial of dapagliflozin in patients with chronic kidney disease, which also suggested a lower risk of non-cardiovascular deaths (including deaths from infections),[35] and with observational data published in 2021.[36] However, we acknowledge that because the differences were not statistically significant, the lower event rates observed in the dapagliflozin group compared with placebo might also represent a chance finding. The heterogeneity within the subgroup analysis for the primary outcome of prevention by sex should be interpreted with caution, given the small number of events within these subgroups and their exploratory nature. The lower risk of organ failure or death with dapagliflozin versus placebo in men, but not women, could be due to the higher absolute risk of these events in men, a finding that has been well documented during the COVID-19 pandemic, or could be a chance finding. Previous trials of SGLT2 inhibitors in patients with type 2 diabetes, heart failure, and chronic kidney disease have not shown significant heterogeneity of treatment effects based on sex. We did not observe a significant difference between groups in the number of patients that had an improvement in clinical status by day 30; a possible explanation for this (among others) might be the small and non-significant effect of dapagliflozin on time to hospital discharge, which was the main driver for this recovery outcome.

Our findings have implications for clinical practice. To the best of our knowledge, DARE-19 is the first trial that evaluated SGLT2 inhibitors in patients with acute infectious illness, one of the highest risk groups ever tested with this class of agents. Given the paucity of reliable data, there were concerns that SGLT2 inhibitors could increase the risk of volume depletion, acute kidney

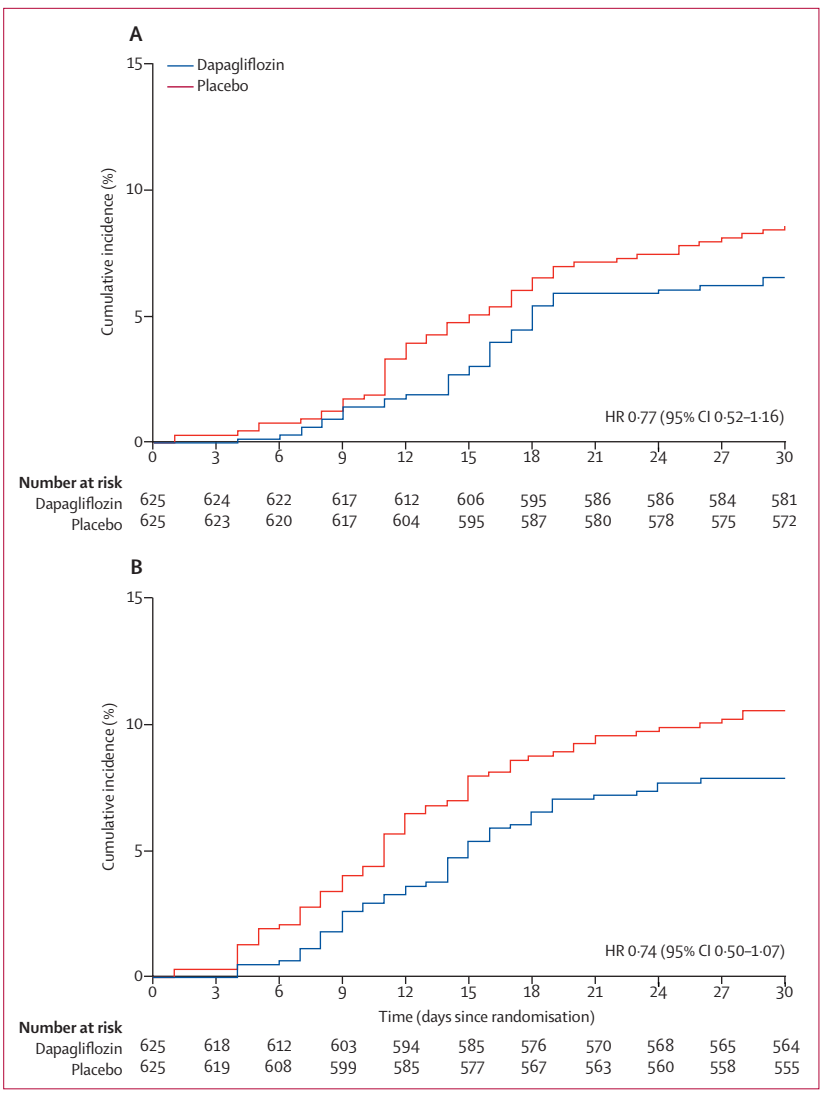

Figure 3: **Key secondary outcomes**
(A) Kaplan-Meier plots of the cumulative estimate of the outcome of death from any cause, (B) and of the composite outcome of acute kidney injury, initiation of renal-replacement therapy or death from any cause. HR=hazard ratio.

	Dapagliflozin (n=613)	Placebo (n=616)
Any serious adverse event, including death	65 (10·6%)	82 (13·3%)
Adverse event with the outcome of death	32 (5·2%)	48 (7·8%)
Discontinuation due to adverse event	44 (7·2%)	55 (8·9%)
Adverse events of interest		
Acute kidney injury	21 (3·4%)	34 (5·5%)
Diabetic ketoacidosis	2 (0·3%)	0

Data are n (%). Data show the number and proportion of patients with the listed outcome with an onset date on or after the date of the first dose and up to and including 2 days after the last dose of the study medication.

Table 3: **Safety outcomes in the safety population**

injury, and ketoacidosis in this patient group. These concerns fuelled recommendations from expert groups to discontinue SGLT2 inhibitors in patients hospitalised with COVID-19, even if they had conditions in which this class has been proven to produce substantial benefits.[29,37] In our trial, dapagliflozin was well tolerated, with rates of serious adverse events (including acute kidney injury) being numerically lower in patients that received dapagliflozin versus placebo; and despite active protocol-required surveillance, only two non-severe events of diabetic ketoacidosis were reported. Therefore, our results do not support routine discontinuation of dapagliflozin in a setting of COVID-19 as long as patients are monitored.

Additionally, our results also have implications for future research. Because SGLT2 inhibitors do not have a direct antiviral effect on SARS-CoV2, our findings (although not conclusive) suggest a need for future trials to determine whether dapagliflozin might provide organ protection in hospitalised patients at high risk for progressing to critical illness (eg, sepsis). This might be especially relevant for prevention of major kidney outcomes in hospitalised patients, common and morbid complications for which few efficacious treatments currently exist. Considering our findings, any such future trials of SGLT2 inhibitors in patients hospitalized with COVID-19 (or other types of acute illness) might need to focus on prevention of organ failure or death, and recruit patient populations that would allow accruing a sufficient number of these events to detect a similar HR to that suggested by DARE-19.

Our trial had limitations. The rates of organ dysfunction and death were lower than initially anticipated due to improvement in standard of care for treatment of COVID-19.[27,28,38] Consequently, the accrued number of events would not allow detection of statistically significant treatment effects with a HR exceeding 0·72 (which is a possible explanation for the observed lack of statistical significance for the primary endpoint of prevention, given the observed HR of 0·80). Accordingly, we amended the protocol to elevate recovery from a secondary endpoint to be included as a dual primary outcome, as faster and more complete recovery had become an important treatment goal and a frequently used trial endpoint in patients hospitalised with COVID-19. Confirmation of COVID-19 positive test at baseline was not available in a small number (fewer than 8%) of patients due to the widespread unavailability of testing supplies at the start of the trial; however, this issue did not affect the overall findings. The proportion of patients receiving remdesivir and systemic corticosteroids was relatively modest; however, neither of these therapies were established as standard of care for COVID-19 at the time our trial was initiated, and patients that derive the greatest benefit from systemic corticosteroids (ie, patients who are critically ill and on mechanical ventilation at baseline) were not included. Furthermore, our results were consistent between patients who did and did not receive remdesivir or systemic corticosteroids at baseline. Finally, we used specific eligibility criteria that might limit generalisability.

In patients with cardiometabolic risk factors hospitalised with COVID-19, treatment with dapagliflozin did not result in a statistically significant risk reduction in organ dysfunction or death, or improvement in clinical recovery, but was well tolerated.

Contributors

The study was designed by the DARE-19 executive committee (MNK, OB, SV, OM, FM, GGK, AML, JO, RE); MNK, RHMF, FM, OM, SV, VC, FT, KG, SLW, EEA, RVPS, DDFM, MA, CRHF, ADMF, AF, VG, RAG, AJ, CPJ, PEL, MN, MP, FSS, WKSB, JRLS, LNM and OB were involved in data collection; statistical analyses were done by the sponsor (FT, KG) and replicated by AstraZeneca (SBG, JB). All authors contributed to the interpretation of the results. The first draft of the manuscript was prepared by MNK and OB who had unrestricted access to the data. The Article was reviewed and approved by all authors. All authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors accessed all the data reported in the study. MNK, OB, FT, KG, SBG, JB, RE, JO, AML, SW also verified the data.

Declaration of interests

MA, EA, WKSB, ADMF, CRHF, AF, KG, RAG, CPJ, LNM, DDFM, JRLS, FT, SLW, OM, VC, RVPS, VG, PEL, FSS, and MP declare no competing interests. MNK has received a research grant for the conduct of this study from AstraZeneca. He has also received grant and research support from AstraZeneca. He has received a grant and honoraria from Boehringer-Ingelheim, and honoraria from Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Janssen, Bayer, Novartis, Eli Lilly, and Vifor Pharma. OB reports grants from AstraZeneca, Novartis, Bayer, Amgen, Boehringer-Ingelheim, and Pfizer. GGK is the Principal Investigator of a biostatistics grant from AstraZeneca. He is also the Principal Investigator for biostatistics grants from other biopharmaceutical sponsors that have no relationship to the submitted work. SV reports receiving grants, speaker honoraria and consulting fees from Boehringer-Ingelheim, AstraZeneca, and Janssen. He has received speaker honoraria and consulting fees from Eli Lilly, and speaker honoraria from EOCI Pharmacomm Ltd, Sun Pharmaceuticals, and Toronto Knowledge Translation Working Group. He has also received grants and consulting fees from Amgen; grants, speaker honoraria and consulting fees from Bayer, and from Merck; grants from Bristol-Myers Squibb; speaker honoraria and consulting fees from HLS Therapeutics, Novo Nordisk, and Sanofi; and speaker honoraria from Novartis. AJ received research support for this study from AstraZeneca. He has stock options in DexCom, and has a pending patent for fusion protein nanodiscs for the treatment of heart failure. RF reports research grants and personal fees from AstraZeneca, Bayer and Servier; and research grants from Pfizer, EMS, Aché, Brazilian Ministry of Health, University Health Network, and Lemann Foundation Reseach Fellowship. MN is a consultant for Roche, Vifor, and Amgen, and has received speaking honoraria from Abbott. RE, JO, SBG, JB, AML, and PA are employees and stockholders of AstraZeneca.

Data sharing

Data for this article are not available.

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