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Dapagliflozin for Critically Ill Patients With Acute Organ Dysfunction
The DEFENDER Randomized Clinical Trial

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IMPORTANCE Sodium-glucose cotransporter 2 (SGLT-2) inhibitors improve outcomes in patients with type 2 diabetes, heart failure, and chronic kidney disease, but their effect on outcomes of critically ill patients with organ failure is unknown.

OBJECTIVE To determine whether the addition of dapagliflozin, an SGLT-2 inhibitor, to standard intensive care unit (ICU) care improves outcomes in a critically ill population with acute organ dysfunction.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, open-label, clinical trial conducted at 22 ICUs in Brazil. Participants with unplanned ICU admission and presenting with at least 1 organ dysfunction (respiratory, cardiovascular, or kidney) were enrolled between November 22, 2022, and August 30, 2023, with follow-up through September 27, 2023.

INTERVENTION Participants were randomized to 10 mg of dapagliflozin (intervention, n = 248) plus standard care or to standard care alone (control, n = 259) for up to 14 days or until ICU discharge, whichever occurred first.

MAIN OUTCOMES AND MEASURES The primary outcome was a hierarchical composite of hospital mortality, initiation of kidney replacement therapy, and ICU length of stay through 28 days, analyzed using the win ratio method. Secondary outcomes included the individual components of the hierarchical outcome, duration of organ support–free days, ICU, and hospital stay, assessed using bayesian regression models.

RESULTS Among 507 randomized participants (mean age, 63.9 [SD, 15] years; 46.9%, women), 39.6% had an ICU admission due to suspected infection. The median time from ICU admission to randomization was 1 day (IQR, 0-1). The win ratio for dapagliflozin for the primary outcome was 1.01 (95% CI, 0.90 to 1.13; *P* = .89). Among all secondary outcomes, the highest probability of benefit found was 0.90 for dapagliflozin regarding use of kidney replacement therapy among 27 patients (10.9%) in the dapagliflozin group vs 39 (15.1%) in the control group.

CONCLUSION AND RELEVANCE The addition of dapagliflozin to standard care for critically ill patients and acute organ dysfunction did not improve clinical outcomes; however, confidence intervals were wide and could not exclude relevant benefits or harms for dapagliflozin.

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Visual Abstract

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Supplemental content

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Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are effective at improving clinical outcomes in several randomized clinical trials across the spectrum of cardiovascular, metabolic, and kidney diseases.[1-3] Their use in acute illness, including patients with COVID-19[4,5] or acute heart failure[6,7] and immediately after experiencing myocardial infarction,[8,9] have been recently tested with promising but nondefinitive results. Although the exact mechanism underlying their benefits is debated,[10] various potential beneficial mechanisms are proposed, several of which could be useful for patients with critical illness. These include improvements in endothelial dysfunction, adrenergic tone modulation, oxidative stress, and cardiorenal effects, lending biological plausibility to their use in treating acute organ dysfunction. Experimental models that simulate acute intensive care unit (ICU) conditions reveal that SGLT-2 inhibitors attenuate inflammation and provide protection against organ injury.[11,12] In particular, nephroprotective effects of SGLT-2 inhibitors may be of interest to those treating critically ill populations, given the high incidence of acute kidney injury in this population.[13]

There is no trial that assessed safety and effectiveness of SLGT-2 inhibitors in a broad population of critically ill patients with organ failure. Therefore, we conducted a randomized clinical trial to assess the effects of dapagliflozin when added to standard care of critically ill patients with acute organ dysfunction. We hypothesized that dapagliflozin could reduce the composite outcome of hospital mortality, initiation of kidney replacement therapy (KRT), and the duration of ICU stay.

Key Points

Question Does the addition of dapagliflozin to standard of care improve the hierarchical outcome of hospital mortality, initiation of kidney replacement therapy, and the length of stay in the intensive care unit (ICU) among critically ill patients with acute organ dysfunction?

Findings In this multicenter, open-label, randomized clinical trial that included 507 participants with at least 1 acute organ dysfunction (hypotension, kidney injury, or respiratory), the use of 10 mg of dapagliflozin for up to 14 days did not significantly reduce the combined outcome of hospital mortality, initiation of kidney replacement therapy, and ICU length of stay, assessed by the win ratio method (win ratio, 1.01, not significant) through 28 days after randomization.

Meaning The addition of dapagliflozin to standard care for individuals with critical illness and acute organ dysfunction did not improve clinical outcomes.

Methods

Trial Design and Oversight

The trial protocol (available in Supplement 1) was approved by the institutional review board from each site, and all patients or legal representatives provided written informed consent. The trial design and statistical analysis plan (Supplement 2) were previously published.[14] This was an investigator-initiated, multicenter, open-label, randomized clinical trial conducted across 22 ICUs in Brazil. The trial operations were coordinated by the Academic Research Organization of the Hospital Israelita Albert Einstein. An independent data and safety monitoring board (DSMB) reviewed unblinded study data for safety. The trial was conducted in accordance with the Good Clinical Practice guidelines and is reported following the Consolidated Standards of Reporting Trials (CONSORT) 2010 reporting guideline statement for parallel-group randomized trials.[15]

Participants

Eligible participants were aged 18 years or older, admitted to the ICU with an expected length of stay of 48 hours or longer, with at least 1 organ dysfunction criterion, (1) hypotension (mean arterial pressure <65 mm Hg, systolic blood pressure <90 mm Hg, or use of vasopressors), (2) signs of acute kidney injury (increase in 0.3 mg/dL [22.88 µmol/L] in serum creatinine or decrease in urine output <0.5 mL/kg/h for ≥6 hours), or (3) need of new use of high-flow nasal catheter, noninvasive, or invasive ventilation (**Table 1**). Key exclusion criteria were the presence of organ dysfunction criteria for more than 24 hours, end-stage kidney disease undergoing maintenance dialysis, prior use of dapagliflozin or other SGLT-2 inhibitor, known type 1 diabetes, a history of diabetic ketoacidosis, and planned ICU admission following elective surgery (**Figure 1**). Further details are found in eTables 1 and 2 in Supplement 3.

Randomization, Allocation Concealment, and Blinding

Eligible patients were randomized in a 1:1 ratio to receive either 10 mg of open-label dapagliflozin in addition to standard care (dapagliflozin intervention group) or standard care alone (control group). Randomization was performed by a central, concealed, web-based automated system (Research Electronic Data Capture [REDCap]), stratified by study site with variable block sizes of 4, 8, and 12. There was no blinding.

Interventions

Dapagliflozin, 10 mg/d, was given orally within 24 hours of randomization, preferably in the morning without fasting, for a duration of 14 days or until ICU discharge, whichever occurred first. For participants who were unable to swallow pills, dapagliflozin was administered enterally after macerating the medication and diluting it in water before administration.[4,5] Study protocol mandated that dapagliflozin administration was discontinued in the following situations: (1) absolute fasting or the inability to access the enteral route for drug administration, (2) occurrence of euglycemic diabetic ketoacidosis (blood glucose ≤250 mg/dL [13.88 mmol/L], metabolic acidosis, and moderate ketonuria [≥2 on urine stick] or ketonemia [blood ketones ≥1.5 mmol/L]), (3) more than 1 episode of severe hypoglycemia (blood glucose ≤50 mg/dL [2.77 mmol/L]), (4) withdrawal of consent, (5) suspected allergic reaction, and (6) initiation of KRT. Adherence was assessed daily for 14 days. Each study site was expected to provide standard of care treatment for critical illness for all trial participants, which was determined solely by the local site health care team and aligned with institutional protocols and international guidelines.

Table 1. Baseline Characteristics of Study Participants

	Dapagliflozin group (n = 248)	Control group (n = 259)
Age, mean (SD), y	63.3 (14.9)	64.5 (15.2)
≥75 y, No. (%)	63 (25.4)	70 (27.0)
Sex at birth, No. (%)		
Female	109 (44.0)	129 (49.8)
Male	139 (56.0)	130 (50.2)
Race, No. (%)	[n = 244]	[n = 256]
Asian	2 (0.8)	1 (0.4)
Black	10 (4.1)	14 (5.5)
Indigenous	0	1 (0.4)
White	177 (72.5)	181 (70.7)
Multiracial	55 (22.5)	59 (23.8)
Admission type, No. (%)		
Medical	205 (82.7)	219 (84.6)
Nonelective surgery	43 (17.3)	40 (15.4)
ICU admission source, No. (%)		
Emergency department	143 (57.7)	156 (60.2)
Operating room	44 (17.7)	40 (15.4)
Transfer from another hospital	35 (14.1)	29 (11.2)
Hospital ward	26 (10.5)	34 (13.1)
Reason for ICU admission, No. (%)[a]		
Infection	100 (40.3)	104 (40.2)
Pneumonia	53 (21.4)	52 (20.1)
Gastrointestinal	16 (6.5)	16 (6.2)
Urinary	14 (5.6)	12 (4.6)
Other	12 (4.8)	13 (5.0)
Cardiovascular	80 (32.3)	82 (31.7)
Neurological	31 (12.5)	39 (15.1)
Respiratory	10 (4.0)	13 (5.0)
Abdominal	7 (2.8)	6 (2.3)
Kidney	4 (1.5)	7 (2.7)
Other[b]	16 (6.4)	8 (3.1)
Body mass index, median (IQR)[c]	25.1 (22.1-28.7) [n = 243]	25.4 (22.1-29.3) [n = 256]
Coexisting conditions, No. (%)		
Hypertension	152 (61.3)	179 (69.1)
Type 2 diabetes	77 (31.0)	91 (35.1)
Dyslipidemia	56 (22.6)	71 (27.4)
Heart failure	47 (19.0)	40 (15.4)
Localized cancer	34 (13.7)	35 (13.5)
Metastatic cancer	13 (5.2)	13 (5.0)
Hematological cancer	4 (1.6)	4 (1.5)
Prior myocardial infarction	38 (15.3)	28 (10.8)
Prior stroke	19 (7.7)	30 (11.6)
Chronic kidney disease	29 (11.7)	24 (9.3)
HIV infection	2 (0.8)	3 (1.2)
Solid organ transplant	2 (0.8)	1 (0.4)
Tobacco use		
Current	46 (18.5)	40 (15.4)
Prior	43 (17.3)	48 (18.5)
Outpatient pharmacology therapy, No. (%)		
RAS inhibitor[d]	110 (44.4)	134 (51.7)
Statin	75 (30.2)	87 (33.6)
Insulin	25 (10.1)	33 (12.7)
Immunosuppressants or glucocorticoids[e]	12 (4.8)	17 (6.6)

(continued)

Table 1. Baseline Characteristics of Study Participants (continued)

	Dapagliflozin group (n = 248)	Control group (n = 259)
Hospitalization in the last month, No. (%)	30 (12.1)	31 (12.0)
Illness severity at randomization, No. (%)		
Use of respiratory support		
Invasive mechanical ventilation	115 (46.4)	120 (46.3)
Supplemental oxygen	54 (21.8)	42 (16.2)
Noninvasive mechanical ventilation	17 (6.9)	19 (7.3)
High-flow nasal cannula	8 (3.2)	9 (3.5)
Use of vasopressors		
Norepinephrine	128 (51.6)	125 (48.3)
Vasopressin	30 (12.1)	29 (11.2)
Use of inotrope	40 (16.1)	37 (14.3)
Serum creatinine level, median (IQR), mg/dL	1.35 (0.91-2.09)	1.33 (0.90-2.10)
>2.5 mg/dL, No. (%)	40 (16.1)	53 (20.5)
Platelet count, median (IQR), × 10^9/L	201 (153-273)	210 (160-287)
Platelet count <150 × 10^9/L, No. (%)	59 (23.8)	58 (22.4)
Organ dysfunction eligibility criteria, No. (%)[f]		
Hypotension[g]	118 (47.6)	109 (42.1)
Acute kidney injury[h]	100 (40.3)	112 (43.2)
Respiratory support[i]	123 (49.6)	126 (48.6)
Time from ICU admission to randomization, median (IQR), d[j]	1 (0-1)	1 (0-1)

Abbreviation: ICU, intensive care unit; RAS, renin-angiotensin system.

SI conversion factor: To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

[a] According to the Simplified Acute Physiology Score 3 (SAPS-3) subgroup.

[b] Multiple trauma, oncological, and endocrinological emergencies, suspected intoxication, or surgical complications.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Defined as use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

[e] Defined as dose greater than 20 mg/d of prednisone equivalent.

[f] Defined as new organ dysfunction lasting less than 24 hours. Percentages may not sum to 100 due to participants' fulfilling multiple criteria. A detailed description of the intersection between the organ dysfunction criteria is provided in eFigure 1 in Supplement 3.

[g] Defined as mean arterial pressure of less than 65 mm Hg, systolic blood pressure of less than 90 mm Hg, or vasopressor use.

[h] Defined as an increase in 0.3 mg/dL in serum creatinine or decrease in urine output lower than 0.5 mL/kg/h for at least 6 hours.

[i] Defined as need of new use of high-flow nasal catheter or noninvasive or invasive ventilation.

[j] Counted from the first ICU admission irrespective of hospital transfers.

This included various aspects of care, such as ventilation strategies, management of sepsis, delirium prevention and management, prophylaxis for deep venous thrombosis, sedation practices, pain management, and other relevant components of critical care. A minimum daily carbohydrate intake of 100 g of glucose was suggested for all study participants.

Study Procedures

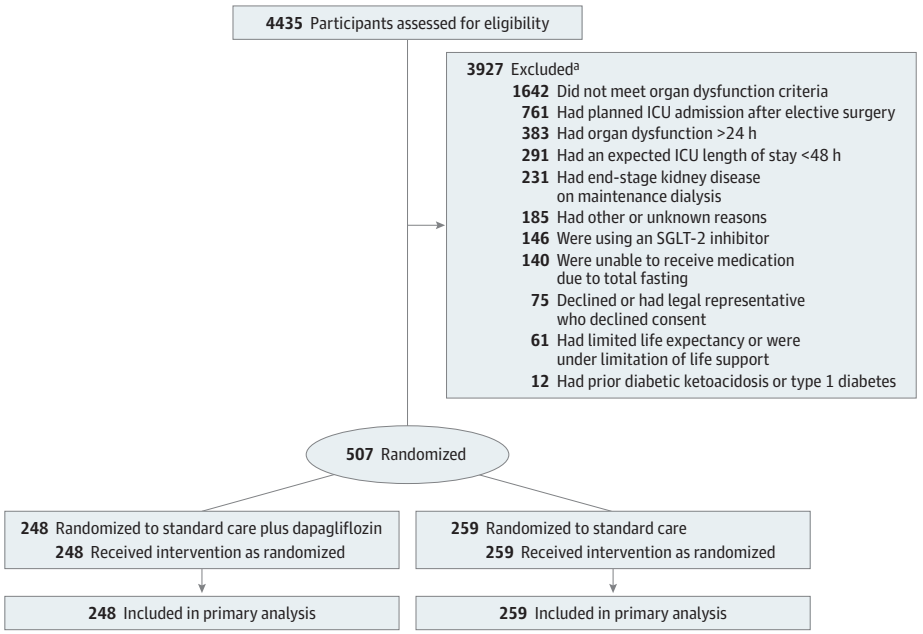
Baseline demographic information, comorbidities, concomitant medications, reasons for ICU admission, and illness severity were collected at enrollment. From days 1 to 5, monitoring included laboratory parameters such as blood gas analysis and serum creatinine levels. Participants were followed up for 28 days or until discharged home from the hospital. Adverse events were observed until trial follow-up was complete. Hospital outcomes were documented either at the time of hospital discharge or after 28 days of follow-up, whichever occurred earlier. All data collection was performed by trained site personnel using a dedicated electronic data capture system, and comprehensive data monitoring was conducted across all sites, either through remote means or on-site evaluations. Records of screening failures were documented in the form of weekly screening logs for each enrolling and active site. To ensure trial representativeness and diversity, self-reported race and ethnicity information was collected by site personnel, using available data from electronic medical records or directly from participants when feasible.

Outcomes

The primary outcome was a hierarchical composite of hospital mortality, initiation of KRT, and ICU length of stay through 28 days after randomization. For ICU length of stay, the cumulative number of calendar days (without fractions) spent in the ICU was calculated from randomization until hospital discharge.

The 7 prespecified secondary outcomes included hospital mortality, KRT use, ICU-free days, hospital-free days, vasopressor-free days, mechanical ventilation–free days, and KRT-free days. All secondary outcomes were evaluated within 28 days after randomization. To be considered free of vasopressor and mechanical ventilation, a cutoff of 6 hours or less within a calendar day was used. The ICU-free days, hospital-free days, and KRT-free days were defined as the count of full calendar days (without fractions) in which participants were alive and free from each respective component. These outcomes were measured on an ordinal scale ranging from 0 to

Figure 1. Flow of Participants Through the DEFENDER Randomized Clinical Trial



[a]Information was obtained via screening logs, reporting the single criterion that did not meet eligibility.

ICU indicates intensive care unit; SGLT-2, sodium-glucose cotransporter 2.

29, with higher values signifying more favorable outcomes. Participants who did not survive until hospital discharge were assigned a value of 0. For those discharged to home before day 28, it was assumed that they remained alive and free from the specified outcome beyond their discharge date.

Safety

Adverse events of special interest were collected during the trial: (1) elevation of elevated serum liver transaminases (exceeding 3 times the reference range), (2) skin lesions, (3) hypoglycemia (blood glucose ≤50 mg/dL), (4) urinary tract infections, (5) bloodstream infections, and (6) occurrence of diabetic ketoacidosis (metabolic acidosis and moderate ketonuria [≥2 on urine stick] or ketonemia [blood ketones ≥1.5 mmol/L]). These events were reported without regard to their severity or causality assessment. All serious adverse events occurring during study follow-up were recorded, regardless of presumed causality.

Statistical Analysis

The sample size was calculated under the hypothesis that dapagliflozin would lead to reductions in all the individual components of the hierarchical composite primary outcome, anticipating a 2% absolute reduction in hospital mortality (from 30% to 28%), a 3% absolute reduction in the initiation KRT (from 10% to 7%), and a mean reduction in ICU length of stay by 0.5 days (with an assumed variance of 1.1 days). In simulations, enrolling 500 participants would provide the study with at least 85% statistical power to detect an intervention effect, with a 95% CI for the win ratio exceeding 1.0 and a resulting median simulated value for the win ratio of 1.40. Ten thousand simulations with samples of 500 participants each were conducted, with 95% CIs calculated using bootstrapping. Additional information is shown in Supplements 1 and 2.

The hierarchical composite primary outcome was analyzed using the generalized pairwise comparison method[16] and the treatment effect quantified using the win ratio method. This approach involved comparing each participant in the dapagliflozin group with every participant in the control group, generating all conceivable participant pairs across trial groups. In each pairwise comparison, a win, loss, or tie was defined based on the comparative assessment of participant outcomes in hierarchical fashion. The primary composite outcome hierarchy consisted of 3 hierarchical levels, (1) hospital mortality, (2) initiation of KRT, and (3) ICU length of stay. For the first level of comparison, if both participants in a pair died before discharge, it was classified as an *early tie*. This signifies that the pair is not subjected to further comparison for the second or third hierarchical levels, thus emphasizing the higher importance of hospital mortality.[17] If both participants survived, the pair was subsequently evaluated for the initiation of KRT. In the event of a tie, the participants were then compared with respect to ICU length of stay. The win ratio was calculated by dividing the total number of wins in the dapagliflozin group by the total number of losses. A detailed win ratio hierarchy flowchart is shown in the eMethods section in Supplement 3, and review of the generalized pairwise method is found elsewhere.[18]

The secondary binary outcomes were assessed with a bayesian hierarchical logistic regression (multilevel) model, adjusted for study site (random intercept), participant age, clinical suspicion of sepsis, and the use of vasopressors and mechanical ventilation at randomization using a normally distributed neutral prior, centered at an odds ratio (OR) of 1.0 (corresponding to a 95% credible interval [CrI] ranging between 0.5 and 2.0).[19] Days-free secondary outcomes were analyzed with a hierarchical ordinal bayesian model adjusted for the same covariates. Treatment effects were quantified using

Table 2. Primary and Secondary Outcomes

Outcome	Dapagliflozin group (n = 248)	Control group (n = 259)	Absolute risk difference (95% CrI)	Win ratio (95% CI)	*P* value[a]
Primary outcome through 28 d, total No. of wins (%)					
Hospital mortality	14 240 (22.2)	14 960 (23.3)			
Initiation of KRT	2774 (4.3)	2088 (3.3)			
Shorter ICU length of stay	10 129 (15.8)	9881 (15.4)			
Hierarchical composite of hospital mortality; initiation of KRT; and shorter ICU length of stay	27 143 (42.3)	26 929 (41.9)		1.01 (0.90 to 1.13)	.89
Secondary outcomes through 28 d[b]				**Adjusted OR (95% CrI)**	**Probability of benefit[a]**
Hospital mortality, No. (%)	88 (35.5)	89 (34.4)	1.1 (−5.5 to 7.4)[c]	1.06 (0.76 to 1.52)[d]	.36
Initiation of KRT, No. (%)	27 (10.9)	39 (15.2)	−2.9 (−7.4 to 1.7)[c]	0.76 (0.51 to 1.18)[d]	.90
Days free, median (IQR)[e]					
ICU[f]	18 (0 to 24)	16.5 (0 to 24)		1.03 (0.77 to 1.38)[g]	.48
Hospital[h]	8.5 (0 to 22)	2.5 (0 to 21)		1.14 (0.84 to 1.55)[g]	.63
Mechanical ventilation[i]	25 (0 to 29)	23 (0 to 29)		1.00 (0.74 to 1.39)[g]	.50
KRT	29 (0 to 29)	29 (0 to 29)		0.98 (0.71 to 1.37)[g]	.55
Vasopressor[j]	26 (0 to 29)	25 (0 to 29)		1.07 (0.78 to 1.44)[g]	.39

Abbreviations: CrI, Credible interval; ICU, intensive care unit; KRT, kidney replacement therapy; OR, odds ratio; WR, win ratio.

[a] *P* value for the win ratio primary hierarchical outcome and probability of benefit for all secondary outcomes, obtained from the bayesian models. Probability of benefit (from 0 to 1.0) for the dapagliflozin group, obtained from the percentage of posterior probability distribution favoring dapagliflozin (detailed in Supplement 3).

[b] Data for secondary outcomes of ICU-, hospital-, mechanical ventilation–, KRT- and vasopressor-free days were missing for 3 transferred participants from the control group. All models used for secondary outcomes were adjusted for study site, age, sepsis at randomization, use of vasopressors at randomization, and use of mechanical ventilation.

[c] Adjusted absolute risk difference (dapagliflozin minus control). Average marginal effect calculated from the posterior probability distribution.

[d] Adjusted odds ratio. An OR less than 1.0 indicates a favorable impact of dapagliflozin on hospital mortality and the initiation of KRT.

[e] Days free were defined as the number of calendar days the patient was alive without aid or service.

[f] Not admitted to the ICU.

[g] Adjusted proportional odds ratio. An OR greater than 1.0 is indicative of a favorable effect on the secondary outcomes of ICU-, hospital-, mechanical ventilation-, KRT-, and vasopressor-free days.

[h] Not hospitalized.

[i] Without use of mechanical ventilation (≤6 hours in an entire calendar day).

[j] Without use of vasopressors (≤6 hours in an entire calendar day).

adjusted OR, bayesian 95% CrIs, and probability of benefit for the dapagliflozin group. Further details regarding secondary models' assumptions are provided in Supplement 2 and in the eMethods section in Supplement 3.

To complement the bayesian analysis, additional prespecified frequentist analyses were conducted for the secondary outcomes. For hospital mortality and initiation of KRT, a logistic regression model was used, adjusting for the same covariates used in the bayesian models. For the ordinal secondary outcomes, differences between the groups were computed using the Hodges-Lehmann estimator, with results presented as differences in days between groups along with their corresponding 95% CIs. Comparisons of trends in serum creatinine and pH levels between study groups were conducted from days 1 to 5 using a linear mixed-effects model for repeated measures.

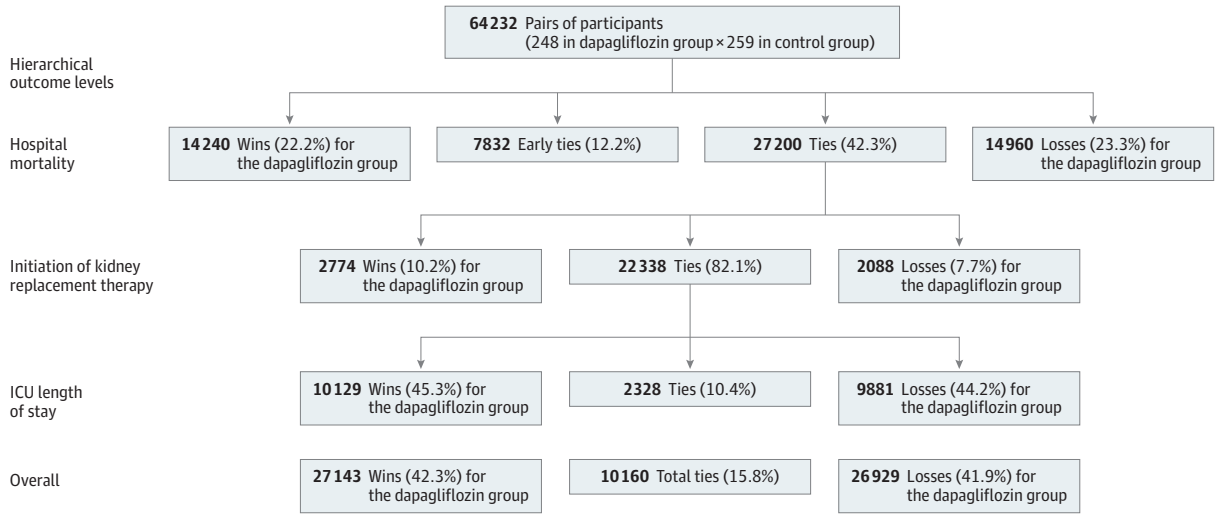
The efficacy and safety analyses included all the participants who underwent randomization (intention-to-treat principle). An additional sensitivity analysis for safety outcomes was conducted in the safety analysis population, comprising participants who received at least 1 dose of dapagliflozin.

Prespecified subgroup analyses for the primary outcome were conducted using the stratified win ratio method[20] for the following subgroups, (1) presence of clinical suspicion of sepsis at randomization, (2) prior diabetes, (3) serum creatinine levels at enrollment (<1.5 mg/dL, 1.5-3.0 mg/dL, and >3.0 mg/dL [to convert creatinine from mg/dL to µmol/L, multiply by 88.4]), (4) reason for ICU admission due to cardiovascular causes (from the table of reasons for ICU admission of Simplified Acute Physiology Score 3 [SAPS 3]),[21] and (5) age (<65 years and ≥65 years).

The DSMB led all planned safety analyses after the enrollment of 100, 250, and 375 participants. These analyses included the absolute and relative frequencies of all serious adverse events, adverse events of special interest, hospital mortality, and initiation of KRT, according to study groups. An interim analysis was performed when half of the intended trial population (250 participants) was enrolled. At this analysis, the DSMB would recommend halting the trial for safety reasons if the posterior probability of harm associated with dapagliflozin for the composite outcome of hospital mortality or KRT exceeded 80%. No interim analyses were conducted for efficacy or futility (see Supplement 3).

Post hoc exploratory analyses were conducted to assess the effect of dapagliflozin on (1) modified major adverse kidney events (MAKEs), defined as the composite outcome of death, initiation of KRT, or doubling the serum creatinine level during the first 5 days after enrollment, and (2) the use of KRT while accounting for the competing risk of death (see the eMethods section in Supplement 3).

Figure 2. Win Ratio Analysis for the Primary Outcome



Distribution of wins, ties, and losses for the dapagliflozin group among the 64 232 paired comparisons, stratified by each level of the hierarchical primary composite outcome. Every possible pair of participants between groups was compared in a hierarchical fashion with a win, a loss, or a tie determined by the outcome evaluated at each level of the hierarchy. Early ties were determined when both participants in the pair died during hospitalization. Percentages are calculated for each level of the hierarchy. The win ratio equals the total wins for the dapagliflozin group divided by the total losses for the dapagliflozin group: 27 143/26 929 = 1.01 (95% CI, 0.90-1.13; *P* = .89). ICU indicates intensive care unit.

For the primary outcome, a 2-sided *P* value of less than .05 was considered to indicate statistical significance and 95% CIs were calculated using the bootstrap method.[16] *P* values are presented exclusively for the primary outcome and subgroup analyses. The analyses of secondary outcomes were not adjusted for multiple comparisons. All analyses were conducted using R software version 4.2.1 or higher (R Foundation for Statistical Computing).[22]

Results

Patients

From November 22, 2022, to August 30, 2023, 4434 participants were screened, and 507 participants from 22 sites in Brazil were randomized: 248 to receive dapagliflozin plus standard care and 259 to receive standard care (Figure 1; eTable 3 in Supplement 3). All 507 participants (mean age, 63.9 (SD, 15) years; 46.9% women) were included in the analysis, with no loss to follow-up. The database lock was performed on October 20, 2023. Two hundred four (39.6%) had ICU admission due to suspected infection, and the median time from ICU admission to randomization was 1 day (IQR, 0-1 day, Table 1). At randomization, 235 participants (46.4%) required respiratory support with mechanical ventilation and 253 (49.9%) received norepinephrine. Furthermore, and the number of trial participants who met the organ dysfunction eligibility criteria were 249 (49.5%) for respiratory, 227 (44.2%) for hypotension, and 212 (42.2%) for kidney injury. The most common inclusion criterion was kidney injury in isolation (140 patients [27.6%]), followed by respiratory dysfunction in isolation (120 patients [23.6%]), and hypotension in isolation (96 patients [18.9%]); remaining possible combinations and their frequencies are shown in eFigure 1 in Supplement 3.

Adherence to Trial Interventions

All 248 participants randomized to receive dapagliflozin received at least 1 dose of the study medication. None of the control group participants received dapagliflozin or any other SGLT-2 inhibitor during study follow-up (eFigure 2 and eTable 4 in Supplement 3).

Primary Outcome

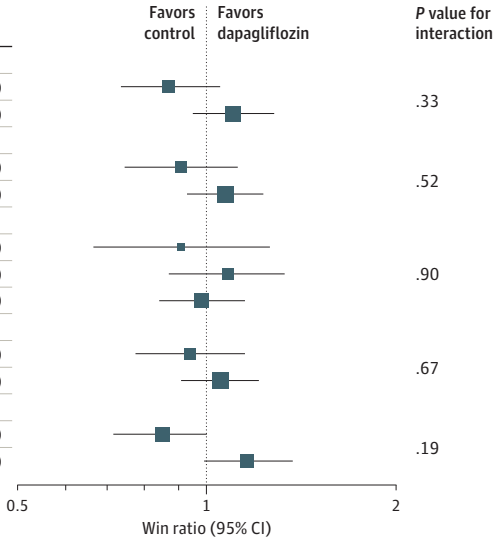
Dapagliflozin treatment did not result in a higher number of wins than the standard care alone group for the primary hierarchical composite outcome. The total number of wins was 27 143 (42.3%) in the dapagliflozin group and 26 929 (41.9%) in the standard care alone group, a win ratio of 1.01 (95% CI, 0.90 to 1.13; *P* = .89; **Table 2**). Among all pairwise comparisons, there were 10 160 ties (15.8%), with 7832 (12.2%) occurring in the hospital mortality comparison and classified as early ties (**Figure 2**).

Secondary Outcomes

Within 28 days, hospital mortality occurred in 88 of 248 participants (35.5%) in the dapagliflozin group compared with 89 of 259 participants (34.4%) in the standard care alone group. The adjusted OR for the bayesian model, accounting for study site, age, sepsis at randomization, use of vasopressors at randomization, and use of mechanical ventilation, was 1.06 (95% CrI, 0.76-1.52; Table 2). Initiation of KRT occurred in 27 participants (10.9%) in the dapagliflozin group compared with 39 participants (15.1%) in the standard care alone group (adjusted OR, 0.76; 95% CrI, 0.50-1.18). The posterior probabilities

Figure 3. Primary Outcome in the Prespecified Subgroup Analyses

Subgroup	No. of participants	No. of wins		Win ratio (95% CI)	*P* value for interaction
		Dapagliflozin (n = 248)	Control (n = 259)		
Suspected sepsis[a]					
Yes	204	4024	4600	0.87 (0.73-1.05)	.33
No	303	10241	9278	1.10 (0.95-1.28)	
Diabetes					
Yes	168	2722	2996	0.91 (0.74-1.12)	.52
No	339	12667	11839	1.07 (0.93-1.23)	
Serum creatinine, mg/dL[b]					
>3	65	409	449	0.91 (0.66-1.26)	.90
1.5-3	161	2773	2571	1.08 (0.87-1.33)	
<1.5	281	8319	8463	0.98 (0.84-1.15)	
Cardiovascular reason for ICU admission[c]					
Yes	162	2744	2924	0.94 (0.77-1.15)	.67
No	345	12604	12050	1.05 (0.91-1.21)	
Age, y					
<65	230	5279	6236	0.85 (0.71-1.00)	.19
≥65	277	8420	7247	1.16 (0.99-1.37)	



[a]Determined by physician's assessment.

[b]Baseline serum creatinine levels. To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

[c]According to the Simplified Acute Physiology Score 3 subgroup.

Shown is the win ratio for the composite hierarchical primary outcome of hospital mortality, initiation of kidney replacement therapy, and intensive care unit (ICU) length of stay stratified for prespecified subgroups. A win ratio greater than 1.0 indicates a favorable effect for the dapagliflozin group. The width of point estimates are scaled according to the number of participants in each subgroup. The 95% CIs were not adjusted for multiple comparisons and should not be used to infer treatment effects.

indicating that the use of dapagliflozin reduced the risk of hospital mortality and initiation of KRT compared with standard of care alone, were .36 and .90, respectively (Table 2 and eFigures 3 and 4 in Supplement 3).

For the secondary ordinal outcomes of ICU-free days, hospital-free days, mechanical ventilation-free days, KRT-free days, and vasopressor-free days, the results from the bayesian hierarchical logistic regression models were inconclusive about treatment effect on these outcomes, yielding posterior probabilities of benefit for dapagliflozin between 0.39 to 0.63 (Table 2 and eFigures 5-10 in Supplement 3). The complementary frequentist analyses of the secondary outcomes yielded results that were consistent with bayesian analysis, with an adjusted OR of 1.08 (95% CI, 0.73-1.60) for hospital mortality and 0.67 (95%CI, 0.39-1.13) for use of KRT (eTable 5 in Supplement 3). No significant differences between study groups were observed for serum creatinine and pH levels during the initial 5 days of trial follow-up (eFigure 11 in Supplement 3).

Subgroup and Post Hoc Exploratory Analyses

No evidence of heterogeneity of treatment effect was detected in predefined subgroups (**Figure 3**), as assessed in a one-at-a-time subgroup analysis. Among patients receiving dapagliflozin compared with standard care, there was a posterior probability of benefit of .60 for modified MAKEs (eTable 6 and eFigure 12 in Supplement 3). When considering the competing risk of death, the cause-specific adjusted hazard ratio for the dapagliflozin group for the use of KRT was 0.72 (95% CI, 0.44-1.18), a similar result was obtained from the Fine and Gray model (adjusted HR, 0.71; 95% CI, 0.45-1.13; eTable 7 and eFigure 13 in Supplement 3).

Safety

Investigator-reported serious adverse events were documented in 115 participants (46.4%) in the dapagliflozin group and in 123 participants (47.5%) in the control group (**Table 3** and eTable 8 in Supplement 3). Adverse events of special interest, including urinary tract infections (4 [1.6%] vs 3 [1.2%]), hypoglycemia (2 [0.8%] vs 0), and bloodstream infections (1 [0.4%] vs 4 [1.5%]) were reported in the dapagliflozin group vs the control group, respectively. There were no reported cases of ketoacidosis.

Discussion

In this randomized, open-label, controlled clinical trial involving 507 participants, the addition of dapagliflozin to standard care was not associated with an increase in the win ratio for a hierarchical end point of hospital mortality, use of KRT, and ICU length of stay. Of the 7 secondary end points, a suggestion of benefit was found for only 1 (the use of KRT, 0.90 probability of benefit). As expected in critically ill patients, a substantial number of serious adverse events were reported in both trial groups. However, dapagliflozin use was well tolerated, with numerically fewer serious adverse events reported in this group than the standard care alone group.

Table 3. Investigator-Reported Adverse Events

Investigator-reported adverse events[a]	No. (%) of participants	
	Dapagliflozin group (n = 248)	Control group (n = 259)
Serious adverse events	115 (46.4)	123 (47.5)
Infections and infestations	50 (20.2)	57 (22.0)
Kidney and urinary disorders	22 (8.9)	34 (13.1)
Cardiac disorders	26 (10.5)	29 (11.2)
Nervous system disorders	15 (0.6)	8 (3.1)
Metabolism and nutrition disorders	10 (4.0)	6 (2.3)
Respiratory, thoracic, and mediastinal disorders	9 (3.6)	15 (5.8)
Vascular disorders	9 (3.6)	12 (4.6)
Gastrointestinal disorders	3 (1.2)	3 (1.2)
General disorders and administration site disorders	2 (0.8)	1 (0.4)
Hepatobiliary disorders	2 (0.8)	1 (0.4)
Neoplasms benign, malign, and unspecified	1 (0.4)	1 (0.4)
Injury, poisoning, and procedural complications	0	2 (0.8)
Blood and lymphatic system	0	1 (0.4)
Immune system disorders	0	1 (0.4)
Reproductive system and breast disorders	0	1 (0.4)
Adverse events of special interest[b]		
Urinary tract infection	4 (1.6)	3 (1.2)
Blood stream infection	1 (0.4)	4 (1.5)
Hypoglycemia	2 (0.8)	0
Elevation of serum liver transaminases	0	2 (0.8)

[a] Events are classified by system organ class and preferred terms according to the latest version of the *Medical Dictionary for Regulatory Activities* (*MedDRA*). Versions 26.0 and 26.1 were used during the course of the study.

[b] Adverse events of special interest were collected irrespective of seriousness criteria.

There is increasing interest in SGLT-2 inhibitors for treating acutely ill patients. There is high-quality evidence to support their use in outpatients with diabetes,[1] heart failure,[2] and chronic kidney disease,[3] and there is some potential benefit for patients with myocardial infarction.[8,9] The benefits of SGLT-2 inhibitors may derive from their nephroprotective effects.[3,23] Experimental evidence suggests that this may be evident in models of sepsis,[12] and the biological rational may also involve different pathways (including inflammation, energy metabolism, and endothelial function),[24-26] which are mediators for organ dysfunction among acutely illness patients.[27-29] This trial was designed to extend the prior evidence and assess the effects of dapagliflozin in an unselected population of critically ill patients in a randomized trial.

These results have several implications. First, despite a neutral result for the primary end point, dapagliflozin use appeared safe in a population of critically ill patients with a hospital mortality rate of 35%. More specifically, adverse events of interest that have been suggested to occur with dapagliflozin use, including bloodstream or urinary infections, were uncommon and occurred at similar rates in both groups, and no ketoacidosis event was reported during the trial. Second, although the results were also inconclusive for all secondary end points, they do not exclude the potential benefits or harms from this therapy. Third, the probability of benefit for the prespecified secondary outcome of reducing KRT use was 0.90. This was not confirmed in a post hoc analysis that considered composite kidney end points or competing risks. Although the finding may be due to chance, it is aligned with several trials in the outpatient setting that suggested a nephroprotective effect of SGLT-2 inhibitors. For example, the DARE-19 trial[4] found that kidney events were numerically lower in patients with COVID-19 who were treated with dapagliflozin. Taken together, these trial results suggest that further study of SGLT-2 inhibitors on critically ill patients should continue and that renal outcomes could be favored as a potential target.

Limitations

This trial has several limitations. First, the unblinded nature of the trial may introduce bias. Second, the trial enrolled an unselected and heterogeneous population of critically ill patients across various stages of acute illness. It is conceivable, for example, that participants with specific features (diabetes, chronic kidney disease, etc) may have differential treatment effects, but these were not observed. As a first trial of its kind, broad inclusion criteria were used to assess safety and the drug effects on clinical outcomes.[30] Third, no data were available on the biological response to dapagliflozin, and it is possible that inadequate absorption of the oral drug may have influenced the findings. Fourth, the analysis of secondary outcomes used models adjusted for clinical suspicion of sepsis based on physicians' assessment rather than confirmed through objective criteria.

Conclusions

The addition of dapagliflozin to standard care for critically ill patients and acute organ dysfunction did not improve clinical outcomes; however, confidence intervals were wide and could not exclude relevant benefits or harms for dapagliflozin.

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