JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Intravenous Vitamin C for Patients Hospitalized With COVID-19
Two Harmonized Randomized Clinical Trials

The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators

IMPORTANCE The efficacy of vitamin C for hospitalized patients with COVID-19 is uncertain.

OBJECTIVE To determine whether vitamin C improves outcomes for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Two prospectively harmonized randomized clinical trials enrolled critically ill patients receiving organ support in intensive care units (90 sites) and patients who were not critically ill (40 sites) between July 23, 2020, and July 15, 2022, on 4 continents.

INTERVENTIONS Patients were randomized to receive vitamin C administered intravenously or control (placebo or no vitamin C) every 6 hours for 96 hours (maximum of 16 doses).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of organ support–free days defined as days alive and free of respiratory and cardiovascular organ support in the intensive care unit up to day 21 and survival to hospital discharge. Values ranged from −1 organ support–free days for patients experiencing in-hospital death to 22 organ support–free days for those who survived without needing organ support. The primary analysis used a bayesian cumulative logistic model. An odds ratio (OR) greater than 1 represented efficacy (improved survival, more organ support–free days, or both), an OR less than 1 represented harm, and an OR less than 1.2 represented futility.

RESULTS Enrollment was terminated after statistical triggers for harm and futility were met. The trials had primary outcome data for 1568 critically ill patients (1037 in the vitamin C group and 531 in the control group; median age, 60 years [IQR, 50-70 years]; 35.9% were female) and 1022 patients who were not critically ill (456 in the vitamin C group and 566 in the control group; median age, 62 years [IQR, 51-72 years]; 39.6% were female). Among critically ill patients, the median number of organ support–free days was 7 (IQR, −1 to 17 days) for the vitamin C group vs 10 (IQR, −1 to 17 days) for the control group (adjusted proportional OR, 0.88 [95% credible interval {CrI}, 0.73 to 1.06]) and the posterior probabilities were 8.6% (efficacy), 91.4% (harm), and 99.9% (futility). Among patients who were not critically ill, the median number of organ support–free days was 22 (IQR, 18 to 22 days) for the vitamin C group vs 22 (IQR, 21 to 22 days) for the control group (adjusted proportional OR, 0.80 [95% CrI, 0.60 to 1.01]) and the posterior probabilities were 2.9% (efficacy), 97.1% (harm), and greater than 99.9% (futility). Among critically ill patients, survival to hospital discharge was 61.9% (642/1037) for the vitamin C group vs 64.6% (343/531) for the control group (adjusted OR, 0.92 [95% CrI, 0.73 to 1.17]) and the posterior probability was 24.0% for efficacy. Among patients who were not critically ill, survival to hospital discharge was 85.1% (388/456) for the vitamin C group vs 86.6% (490/566) for the control group (adjusted OR, 0.86 [95% CrI, 0.61 to 1.17]) and the posterior probability was 17.8% for efficacy.

CONCLUSIONS AND RELEVANCE In hospitalized patients with COVID-19, vitamin C had low probability of improving the primary composite outcome of organ support–free days and hospital survival.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT04401150 (LOVIT-COVID) and NCT02735707 (REMAP-CAP)

Editorial page 1739

Supplemental content

CME Quiz at jamacmelookup.com

Group Information: The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators appear at the end of this article and the entire list of the LOVIT-COVID Investigators and the REMAP-CAP Investigators appears in Supplement 3.

Corresponding Authors: Neill K. J. Adhikari, MDCM, MSc, Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada (neill.adhikari@utoronto.ca) and François Lamontagne, MD, MSc, Faculty of Medicine and Health Sciences, Division of Internal Medicine, Université de Sherbrooke, 3001 12th Ave N, Sherbrooke, QC J1H 5N4, Canada (francois.lamontagne@usherbrooke.ca).

Section Editor: Christopher Seymour, MD, Associate Editor, *JAMA* (christopher.seymour@jamanetwork.org).

JAMA. 2023;330(18):1745-1759. doi:10.1001/jama.2023.21407
Published online October 25, 2023. Last corrected on August 20, 2024.

As of October 2023, the World Health Organization reported 771 million cases and 6.96 million deaths due to COVID-19.[1] For hospitalized patients, immunomodulatory and antiviral therapies are effective but imperfect,[2] and global availability remains disparate.[3]

Vitamin C is widely available and its use in patients with septic shock increased before the COVID-19 pandemic[4] until clinical trials failed to demonstrate benefit.[5-7] At the beginning of the COVID-19 pandemic, a World Health Organization report[8] highlighted the use of vitamin C as a potential immunomodulatory agent. Vitamin C attenuates oxidative stress and microvascular thrombosis,[9] which are features of COVID-19, and hospitalized patients with COVID-19 were found to have low serum vitamin C levels.[10] A meta-analysis[11] of trials including patients with COVID-19 reported that vitamin C may reduce hospital mortality.

Two initially separate randomized clinical trials were harmonized to investigate the effect of intravenous vitamin C on need for organ support and hospital survival in hospitalized patients with COVID-19, hypothesizing that vitamin C would increase the number of days alive and free of organ support.

Key Points

Question Does vitamin C administered intravenously to patients hospitalized with COVID-19 improve organ support–free days (composite outcome of in-hospital mortality and days alive and free of intensive care unit–based respiratory and cardiovascular support) up to day 21?

Findings In 2 prospectively harmonized randomized clinical trials, the use of vitamin C vs control (placebo or no vitamin C) yielded posterior probabilities for efficacy of 8.6% among 1568 critically ill patients and 2.9% among 1022 patients who were not critically ill regarding the odds of improvement for organ support–free days.

Meaning Among hospitalized patients with COVID-19, there was a low probability that vitamin C improved organ support–free days.

Methods

Trial Design

Before recruitment commenced, the investigators harmonized and decided to pool data from 2 randomized clinical trials designed to evaluate the same vitamin C regimen. The Lessening Organ Dysfunction with Vitamin C for COVID-19 (LOVIT-COVID) trial was initially designed as a frequentist blinded trial with enrollment occurring in Canada. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial is an international, adaptive unblinded platform trial in patients with severe pneumonia.[12] This report includes patients enrolled in the COVID-19 stratum of the REMAP-CAP trial.

Both trials prospectively adopted the same intervention, outcomes, statistical analysis plan, and reporting, but the control groups were different. The LOVIT-COVID trial used a placebo for the control group and the REMAP-CAP trial used no vitamin C for the control group. Development of the harmonized trial and essential details of the LOVIT-COVID and REMAP-CAP trials appear in Supplement 1 (eMethods and eTable 1). The protocols for each trial and the harmonized statistical analysis plan appear in Supplement 2.

The research ethics committee and regulatory authority in each jurisdiction approved the trial protocols. Informed consent was obtained (either before or after randomization) from all patients or their surrogates in accordance with applicable laws. Each trial had a steering committee (with co-chairs common between the 2 trials). Separate interim analyses were conducted for each trial, which did not incorporate data from the other trial, but the data and safety monitoring boards exchanged information regarding respective trial progress.

Patients

Eligible patients were adults admitted to the hospital with suspected or proven COVID-19. Patients admitted to an intensive care unit and receiving respiratory or cardiovascular organ support at the time of randomization were classified as critically ill and all others as not critically ill. This prospective classification was undertaken because of previous reports suggesting differential treatment effects in these 2 populations.[13-15]

Respiratory support was defined by receipt of invasive ventilation, noninvasive ventilation, or high-flow nasal oxygen and cardiovascular support by a vasopressor or inotrope infusion. In the LOVIT-COVID trial, critically ill patients were enrolled while receiving respiratory support; receipt of cardiovascular support at baseline was an exclusion criterion. Detailed selection criteria appear in the eMethods in Supplement 1.

To account for observed racial and ethnic differences in outcomes during the pandemic, the REMAP-CAP trial collected self-reported race and ethnicity from either participants or their surrogates, according to each region's standards. Data on race and ethnicity were not collected in the LOVIT-COVID trial.

Randomization, Interventions, and Follow-Up

Randomization in both trials was concealed via separate computer-based randomization systems (**Figure 1**). Patients in the LOVIT-COVID trial were assigned in a 1:1 ratio to vitamin C or placebo stratified by site. In the REMAP-CAP trial, randomization was stratified by status (critically ill vs not critically ill), and patients could participate in other domains (eTable 2 in Supplement 1). The initial randomization ratio was 1:1 for vitamin C and no vitamin C, with patients subsequently assigned preferentially to the treatment group that appeared more favorable after each adaptive analysis (additional details appear in the trial protocol in Supplement 2).

In both trials, patients in the intervention group received vitamin C (50 mg/kg of body weight administered intravenously over 30-60 minutes every 6 hours for 96 hours; the maximum was 16 doses). All sites used locally available vitamin C formulations (eMethods in Supplement 1). In the LOVIT-COVID trial, glucose monitoring for patients receiving insulin or oral hypoglycemic agents was protocolized to account for the interference of vitamin C with bedside glucometers

Figure 1. Flow of Patients Through the Harmonized Trial Including the LOVIT-COVID Trial and the Vitamin C Domain of the REMAP-CAP Trial

Additional details appear in eFigures 2-3 in Supplement 1. ICU indicates intensive care unit.

[a]May have been excluded for more than 1 reason.

[b]Of these 7800 adults, 7212 were used for covariate adjustment.

[c]One additional participant had missing primary outcome data.

(eMethods in Supplement 1). In the REMAP-CAP trial, clinician adherence to the glucose monitoring protocol was advised for all patients randomized to vitamin C. All other aspects of care were at the discretion of clinicians. Patients were followed up while in the hospital, and survivors or their relatives were contacted by telephone at 6 months (all patients in the LOVIT-COVID trial and a subset of patients in the REMAP-CAP trial) for additional outcomes.

Primary and Secondary Outcomes

The primary outcome was a composite of an ordinal measure of organ support–free days defined as days alive and free of respiratory and cardiovascular organ support in the intensive care unit up to day 21 and survival to hospital discharge. This hospital-based outcome is associated with 180-day survival.[16] Deaths within the hospital were assigned the worst outcome (-1 organ support–free days). Among hospital survivors, respiratory and cardiovascular organ support–free days were calculated up to day 21; a higher number represents faster recovery. Survival to hospital discharge was censored at 90 days. Patients who were not critically ill and who survived without needing any organ support were assigned the best outcome (22 organ support–free days).

Secondary outcomes were prespecified in the statistical analysis plan (Supplement 2) and included death or persistent organ dysfunction[17] (receipt of invasive ventilation, a vasopressor infusion, or new kidney replacement therapy) at trial day 28, which was the primary outcome in the LOVIT trial[7] of vitamin C in patients with sepsis.

The site investigators reported serious adverse events considered at least possibly related to a trial procedure to the coordinating center and then to the data and safety monitoring board and the national regulatory authorities as required. In the LOVIT-COVID trial, data on hemolysis and hypoglycemia were collected as safety outcomes. Additional in-hospital outcomes collected only in the LOVIT-COVID trial and outcomes after hospital discharge[16] in both trials were not included in the statistical analysis plan.

Statistical Analysis

After harmonization of both trials, scheduled interim analyses of the LOVIT-COVID trial, with an original fixed sample size of 800 participants, continued. In the REMAP-CAP bayesian trial, which had no maximum sample size, adaptive analyses were performed and response-adaptive randomization continued until reaching a predefined statistical trigger, initially specified as efficacy, inferiority, and equivalence (see below for definitions).

The statistical analysis plan for the harmonized trial specified that the trial outcomes would be reported from a merged data set created after both trials had stopped (additional details appear in the eMethods in Supplement 1 and in the statistical analysis plan in Supplement 2). The analysis used bayesian cumulative logistic models, which calculated posterior probability distributions based on accumulated trial evidence and a neutral prior distribution. Distinct treatment effects of vitamin C compared with control were estimated in critically ill patients and patients who were not critically ill using a hierarchical prior that dynamically borrowed information between groups. The hierarchical prior distribution was centered on an overall intervention effect estimated with a prior assuming no treatment effect (a standard normal prior on the log odds ratio [OR]).

The primary statistical model that was used to estimate the effect of vitamin C on organ support–free days, and a similar model that was used for hospital survival and 28-day death or persistent organ dysfunction, adjusted for the trial (the LOVIT-COVID trial vs the REMAP-CAP trial); eligibility and randomization to treatment domains within the REMAP-CAP trial; location (site nested within each country); age (categorized into 6 groups); sex; and period (2-week calendar epochs) to account for changes in clinical care and outcomes during the pandemic. The statistical models were fit using a Markov chain Monte Carlo algorithm that drew iteratively (20 000 draws) from the joint posterior distribution.

There were no interaction terms for vitamin C and other interventions. The model included patients enrolled in all other domains of the REMAP-CAP trial, including those that remained blinded, to provide robust estimation of the covariate effects. Patients enrolled only outside the vitamin C domain in the REMAP-CAP trial did not contribute to estimates for the treatment effect of vitamin C and contributed only to estimates for the covariate effects. The statistical analysis committee conducted the analysis for patients with COVID-19 randomized up to July 15, 2022.

Patients were analyzed according to group assignment and the missing outcomes were not imputed. Posterior ORs with 95% credible intervals (CrIs) were calculated, with an OR greater than 1 corresponding to vitamin C being superior to control. The probabilities of efficacy (OR >1), harm (OR <1), futility (OR <1.2), and equivalence (OR between 1/1.2 and 1.2) were calculated.

For the primary outcome, an ordinal scale with 24 categories (worst category labeled as −1 [death] and best category of alive with 21 days free of organ support labeled as 22), the OR denotes the relative odds of being in the category with a label greater than i vs i or less when i equals -1 to 21. The robustness of the proportional odds assumption was assessed for the primary ordinal regression model. For 90-day survival, and for time to discharge outcomes, an adjusted hazard ratio with a 95% CrI was calculated.

The original predefined statistical triggers for trial conclusions were based on posterior probabilities of efficacy (>99%; an OR for vitamin C >1), inferiority (>99%; an OR <1), and equivalence (>90%; an OR between 1/1.2 and 1.2). After the LOVIT trial[7] found vitamin C increased the risk of 28-day death or persistent organ dysfunction in patients with sepsis, statistical triggers for futility (>95%; an OR <1.2) and harm (>90%; an OR <1) were added.

The sensitivity analyses for the primary outcome and 28-day death or persistent organ dysfunction, and the analyses of all secondary outcomes, used data from patients enrolled in the REMAP-CAP trial domains that had stopped and were unblinded at the time of analysis to inform covariate adjustment. Additional sensitivity analyses with different analysis populations, and prespecified subgroup analyses, appear in the

statistical analysis plan in Supplement 2. One such analysis included 63 patients with COVID-19 enrolled in the LOVIT trial.[7]

Data management and summaries were created using R version 4.1.2 (R Foundation for Statistical Computing). The primary analysis was computed in R version 4.1.3 using the rstan package version 2.21.0.

Results

Patients

The first patient was randomized in the LOVIT-COVID trial on August 23, 2020, and in the vitamin C domain of the REMAP-CAP trial on July 23, 2020. Both trials stopped recruitment on July 15, 2022, as advised by their data and safety monitoring boards because statistical triggers for futility and harm had been met for both strata (critically ill and not critically ill) in the REMAP-CAP trial. The interim analysis reports of both trials appear in the eResults in Supplement 1. The response-adaptive randomization proportions over time in the REMAP-CAP trial appear in eFigure 1 in Supplement 1.

Of 2613 randomized patients, 7 were determined to be ineligible, 15 withdrew consent for follow-up, and 1 critically ill patient in the control group contributed baseline data but data are missing for the primary outcome (Figure 1 and eFigures 2-3 in Supplement 1). The population for the primary statistical model included 2590 randomized and evaluable patients, with 1493 patients assigned to vitamin C and 1097 assigned to control.

There were 1568 critically ill patients from 90 sites and 1022 patients who were not critically ill from 40 sites; 2206 had complete follow-up data for the vitamin C domain of the REMAP-CAP trial and 384 in the LOVIT-COVID trial. Two critically ill patients included in the analysis withdrew consent for follow-up but allowed the collected data to be used for the analyses; their last known status was carried forward for the primary outcome. Accrual rates over time appear in eFigures 4-5 in Supplement 1. Covariate effects for the primary statistical models included 9802 organ support-free days outcomes from any REMAP-CAP trial domain and the LOVIT-COVID trial.

Baseline characteristics are reported in **Table 1** and in eTables 3-8 in Supplement 1. Patients were recruited from Asia (34.7%), North America (28.5%), Europe (27.7%), and Australia (9.2%). Among critically ill patients, respiratory support at enrollment included invasive ventilation (28.0%), noninvasive ventilation (36.2%), and high-flow nasal oxygen (35.1%). Among patients who were not critically ill, most were not receiving respiratory support or only receiving low-flow oxygen (90.7%). Most patients received corticosteroids (95.1%). In the LOVIT-COVID trial, 96.1% of patients received 90% or greater of the scheduled doses (eTable 9 in Supplement 1). In the REMAP-CAP trial, 95.2% of patients did not experience a treatment delivery-related deviation (eTable 10 in Supplement 1).

Primary Outcome

Among critically ill patients, the median number of organ support-free days was 7 (IQR, -1 to 17 days) in the vitamin C group vs 10 (IQR, -1 to 17 days) in the control group and the adjusted proportional OR was 0.88 (95% CrI, 0.73 to 1.06), yielding a posterior probability of 8.6% for efficacy of vitamin C therapy, 91.4% for harm, and 99.9% for futility (**Table 2** and **Figure 2**). Among patients who were not critically ill, the median number of organ support-free days was 22 (IQR, 18 to 22 days) in the vitamin C group vs 22 (IQR, 21 to 22 days) in the control group and the adjusted proportional OR was 0.80 (95% CrI, 0.60 to 1.01), yielding a posterior probability of 2.9% for efficacy of vitamin C therapy, 97.1% for harm, and greater than 99.9% for futility (**Table 3** and **Figure 3**).

Among critically ill patients, survival to hospital discharge was 61.9% (642/1037) in the vitamin C group vs 64.6% (343/531) in the control group and the adjusted OR was 0.92 (95% CrI, 0.73-1.17), yielding a posterior probability of 24.0% for efficacy of vitamin C therapy, 76.0% for harm, and 98.4% for futility. Among patients not critically ill, survival to hospital discharge was 85.1% (388/456) in the vitamin C group vs 86.6% (490/566) in the control group and the adjusted OR was 0.86 (95% CrI, 0.61-1.17), yielding a posterior probability of 17.8% for efficacy of vitamin C therapy, 82.2% for harm, and 98.1% for futility.

Secondary Outcomes

Among critically ill patients, 90-day survival was 59.8% (617/1032) in the vitamin C group vs 62.1% (328/528) in the control group and the adjusted hazard ratio was 0.94 (95% CrI, 0.80-1.11), yielding a posterior probability of 22.4% for efficacy of vitamin C therapy (Table 2 and Figure 2). Among patients not critically ill, 90-day survival was 81.5% (370/454) in the vitamin C group vs 82.8% (466/563) in the control group and the adjusted hazard ratio was 0.93 (95% CrI, 0.74-1.19), yielding a posterior probability of 27.2% for efficacy of vitamin C therapy (Table 3 and Figure 3). Survival to 28 days without persistent organ dysfunction was similar in critically ill patients (adjusted OR, 0.90 [95% CrI, 0.72-1.12]; posterior probability of 16.4% for efficacy of vitamin C therapy; Table 2) and in patients not critically ill (adjusted OR, 0.92 [95% CrI, 0.68-1.23]; posterior probability of 26.6% for efficacy of vitamin C therapy; Table 3).

Posterior probabilities of efficacy for vitamin C therapy were less than 33% for all other secondary outcomes (Tables 2 and 3 and eFigures 6-7 in Supplement 1). Serious adverse events were reported in 1.8% of patients (27/1493) in the vitamin C group and 0.8% of patients (9/1098) in the control group (eTable 11 in Supplement 1). There were 4 serious adverse events possibly or probably related to vitamin C, including 1 patient with methemoglobinemia, 2 patients with hypoglycemia, and 1 patient with hemolytic anemia subsequently discovered to have glucose-6-phosphate dehydrogenase deficiency.

Sensitivity, Subgroup, and Exploratory Analyses

The sensitivity analyses of organ support-free days, hospital survival, and 28-day mortality or persistent organ dysfunction using different analysis populations were consistent with the primary analyses (eTables 12-14 in Supplement 1). The 95% CrIs were wider in the LOVIT-COVID trial compared with the

Table 1. Baseline Characteristics of Participants in the LOVIT-COVID Trial and the Vitamin C Domain of the REMAP-CAP Trial[a]

	Critically ill		Not critically ill	
	Vitamin C (n = 1037)	Control (n = 532)[b]	Vitamin C (n = 456)	Control (n = 566)[b]
Age, median (IQR), y	60.0 (49.0-69.0)	61.0 (50.0-72.0)	63.0 (51.0-73.0)	62.0 (51.0-72.0)
Age group, No. (%)				
18-49	268 (25.8)	122 (22.9)	97 (21.3)	132 (23.3)
50-69	512 (49.4)	253 (47.6)	204 (44.7)	258 (45.6)
≥70	257 (24.8)	157 (29.5)	155 (34.0)	176 (31.1)
Sex, No. (%)				
Female	382 (36.8)	182 (34.2)	189 (41.4)	216 (38.2)
Male	655 (63.2)	350 (65.8)	267 (58.6)	350 (61.8)
Body mass index, median (IQR)[c]	29.6 (25.7-35.3) [n = 837]	29.6 (26.0-35.1) [n = 437]	28.4 (25.0-33.8) [n = 358]	28.4 (25.1-32.5) [n = 435]
Continent, No. (%)				
Asia	373 (36.0)	134 (25.2)	156 (34.2)	235 (41.5)
Australia	136 (13.1)	65 (12.2)	15 (3.3)	22 (3.9)
Europe	365 (35.2)	180 (33.8)	74 (16.2)	98 (17.3)
North America	163 (15.7)	153 (28.8)	211 (46.3)	211 (37.3)
Race, No./total (%)[d]				
Asian	32/417 (7.7)	10/219 (4.6)	3/123 (2.4)	4/133 (3.0)
Black	16/417 (3.8)	12/219 (5.5)	14/123 (11.4)	13/133 (9.8)
Multiple	6/417 (1.4)	1/219 (0.5)	0/123	0/133
White	298/417 (71.5)	159/219 (72.6)	97/123 (78.9)	108/133 (81.2)
Other[e]	65/417 (15.6)	37/219 (16.9)	9/123 (7.3)	8/133 (6.0)
APACHE II score, median (IQR)[f]	12.0 (8.0-18.0) [n = 1031]	14.0 (8.0-21.0) [n = 531]	8.0 (5.0-12.0) [n = 278]	8.0 (5.0-11.0) [n = 358]
Clinical Frailty Scale score, median (IQR)[g]	3.0 (2.0-3.0) [n = 979]	3.0 (2.0-3.0) [n = 492]	3.0 (2.0-3.0) [n = 358]	3.0 (2.0-3.0) [n = 463]
Preexisting condition, No./total (%)				
Diabetes	323/1037 (31.1)	159/532 (29.9)	133/456 (29.2)	138/566 (24.4)
Respiratory disease	167/1006 (16.6)	89/505 (17.6)	75/386 (19.4)	86/495 (17.4)
Kidney disease[h]	68/919 (7.4)	46/446 (10.3)	24/371 (6.5)	37/488 (7.6)
Severe cardiovascular disease[i]	42/1037 (4.1)	32/532 (6.0)	25/455 (5.5)	35/565 (6.2)
Any immunosuppressive condition[j]	35/998 (3.5)	33/496 (6.7)	21/367 (5.7)	20/468 (4.3)
Time to enrollment, median (IQR)				
From hospital admission, d[k]	1.1 (0.8-2.7)	1.1 (0.8-2.5)	1.0 (0.7-2.1)	1.0 (0.7-2.1)
From ICU admission, h[l]	15.0 (8.5-19.9) [n = 1034]	15.2 (8.8-20.0) [n = 531]	15.6 (9.6-20.1) [n = 219]	15.0 (7.2-21.0) [n = 283]

(continued)

Table 1. Baseline Characteristics of Participants in the LOVIT-COVID Trial and the Vitamin C Domain of the REMAP-CAP Trial[a] (continued)

	Critically ill		Not critically ill	
	Vitamin C (n = 1037)	Control (n = 532)[b]	Vitamin C (n = 456)	Control (n = 566)[b]
Acute respiratory support, No./total (%)				
Invasive mechanical ventilation	287/1036 (27.7)	151/531 (28.4)	0/456	0/566
Noninvasive ventilation[m]	393/1036 (37.9)	175/531 (33.0)	6/456 (1.3)	8/566 (1.4)
High-flow nasal oxygen[m]	350/1036 (33.8)	200/531 (37.7)	35/456 (7.7)	46/566 (8.1)
No respiratory support or low-flow oxygen	6/1036 (0.6)	5/531 (0.9)	415/456 (91.0)	512/566 (90.5)
Vasopressor support, No./total (%)	152/1036 (14.7)	76/531 (14.3)	0/456	0/566
Concomitant therapies, No./total (%)[n]				
Remdesivir	403/974 (41.4)	174/463 (37.6)	211/355 (59.4)	267/471 (56.7)
Corticosteroids	990/1035 (95.7)	518/531 (97.6)	420/456 (92.1)	531/564 (94.1)
Tocilizumab or sarilumab	296/974 (30.4)	151/463 (32.6)	30/355 (8.5)	52/471 (11.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; LOVIT-COVID, Lessening Organ Dysfunction with Vitamin C for COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia.

[a] Trial-specific baseline characteristics appear in eTables 5-8 in Supplement 1. Percentages may not sum to 100 because of rounding.

[b] Includes all patients randomized to control who were also eligible to be randomized to vitamin C (ie, direct concurrent controls).

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

[d] Collection of data on race and ethnicity was approved only in the UK, Australia, and the US for the REMAP-CAP trial. Data on race and ethnicity were not collected in the LOVIT-COVID trial.

[e] Includes any other reported racial group.

[f] Ranges from 0 to 71; higher scores indicate greater severity of illness and higher risk of death.

[g] Ranges from 1 to 9; higher scores indicate greater frailty.

[h] Determined from the most recent serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130 µmol/L or greater (≥1.5 mg/dL) for males and 100 µmol/L or greater (≥1.1 mg/dL) for females not previously receiving dialysis.

[i] New York Heart Association class IV.

[j] Included receipt of recent chemotherapy or chronic immunosuppressive medications (excluding steroids), neutropenia, solid organ or stem cell transplantation, and HIV-positive status in the LOVIT-COVID trial. Included AIDS; metastatic cancer; specific hematological malignancies or other hematological conditions; and other inherited, primary, and secondary immune deficiencies in the REMAP-CAP trial.

[k] Recorded when the patient left the emergency department or when care in the emergency department was assumed by an inpatient service, depending on the hospital, in the LOVIT-COVID trial. Explicitly includes all time spent in the emergency department in the REMAP-CAP trial.

[l] The patients in the ICU who were not receiving respiratory or cardiovascular organ support were prospectively classified as not critically ill.

[m] When delivered outside the ICU, the patient did not meet the trial definition of having a critical illness.

[n] Given at baseline or within 48 hours of randomization in the REMAP-CAP trial. Given at baseline or on the day of or the day after randomization in the LOVIT-COVID trial. Data on treatment with remdesivir and tocilizumab or sarilumab were specifically collected in the REMAP-CAP trial. These categories could include patients recorded as receiving an "antiviral" or "immunomodulator" in the LOVIT-COVID trial.

Table 2. Primary and Secondary Outcomes for Critically Ill Participants in the LOVIT-COVID Trial and the Vitamin C Domain of the REMAP-CAP Trial

	Critically ill		Adjusted absolute risk difference (95% CrI)[a]	Adjusted effect measure (95% CrI)	Posterior probability, %	
	Vitamin C	Control			Efficacy	Harm
Primary outcome						
Organ support–free days to 21 d, median (IQR)[b]	7 (−1 to 17) [n = 1037]	10 (−1 to 17) [n = 531]		0.88 (0.73 to 1.06)[c]	8.6	91.4[d]
Component of primary outcome						
Survival to hospital discharge, No./total (%)	642/1037 (61.9)	343/531 (64.6)	−1.9 (−7.5 to 3.5)	0.92 (0.73 to 1.17)[e]	24.0	76.0[f]
Secondary outcomes						
Survival without persistent organ dysfunction at 28 d, No./total (%)[g]	592/1037 (57.1)	323/532 (60.7)	−2.5 (−8.0 to 2.7)	0.90 (0.72 to 1.12)[e]	16.4	83.6
Treatment through 28 d						
Vasopressor or inotrope–free days, median (IQR)	26 (−1 to 28) [n = 1037]	27 (−1 to 28) [n = 532]		0.84 (0.75 to 0.94)[c]	0.9	99.1
Respiratory support–free days, median (IQR)	13 (−1 to 24) [n = 1037]	16 (−1 to 24) [n = 531]		0.89 (0.73 to 1.01)[c]	3.2	96.8
Endotracheal intubation, No./total (%)	266/750 (35.5)	124/381 (32.5)	−6.2 (−11.3 to −0.2)	0.74 (0.56 to 0.99)[e]	2.1	97.9
Extracorporeal support, No./total (%)[h]	12/1034 (1.2)	7/532 (1.3)				
Survival to 28 d, No./total (%)	671/1032 (65.0)	356/530 (67.2)	−1.4 (−6.6 to 3.7)	0.94 (0.75 to 1.19)[e]	31.2	68.8
Discharged alive[j]						
From the ICU				0.96 (0.84 to 1.10)[i]	28.4	71.6
From the hospital				0.93 (0.82 to 1.05)[i]	12.1	87.9
90-d survival, No./total (%)[k]	617/1032 (59.8)	328/528 (62.1)		0.94 (0.80 to 1.11)[i]	22.4	77.6
WHO Ordinal Scale score at 14 d[l]				0.89 (0.75 to 1.07)[c]	11.0	89.0

Abbreviations: CrI, credible interval; ICU, intensive care unit; LOVIT-COVID, Lessening Organ Dysfunction with Vitamin C for COVID-19; OR, odds ratio; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; WHO, World Health Organization.

[a] The absolute risk differences (vitamin C minus control) are presented for the binary outcomes and are based on the event proportion in the control group and the OR after covariate adjustment from each model.

[b] The model assigns a value of −1 organ support–free days to those who died.

[c] Data are expressed as proportional OR (95% CrI).

[d] The posterior probability of futility was 99.9%.

[e] Data are expressed as OR (95% CrI).

[f] The posterior probability of futility was 98.4%.

[g] The outcome is the complement of 28-day mortality or persistent organ dysfunction to preserve the interpretation of an OR greater than 1, which indicates the superiority of vitamin C.

[h] No model was constructed for this outcome per the statistical analysis plan.

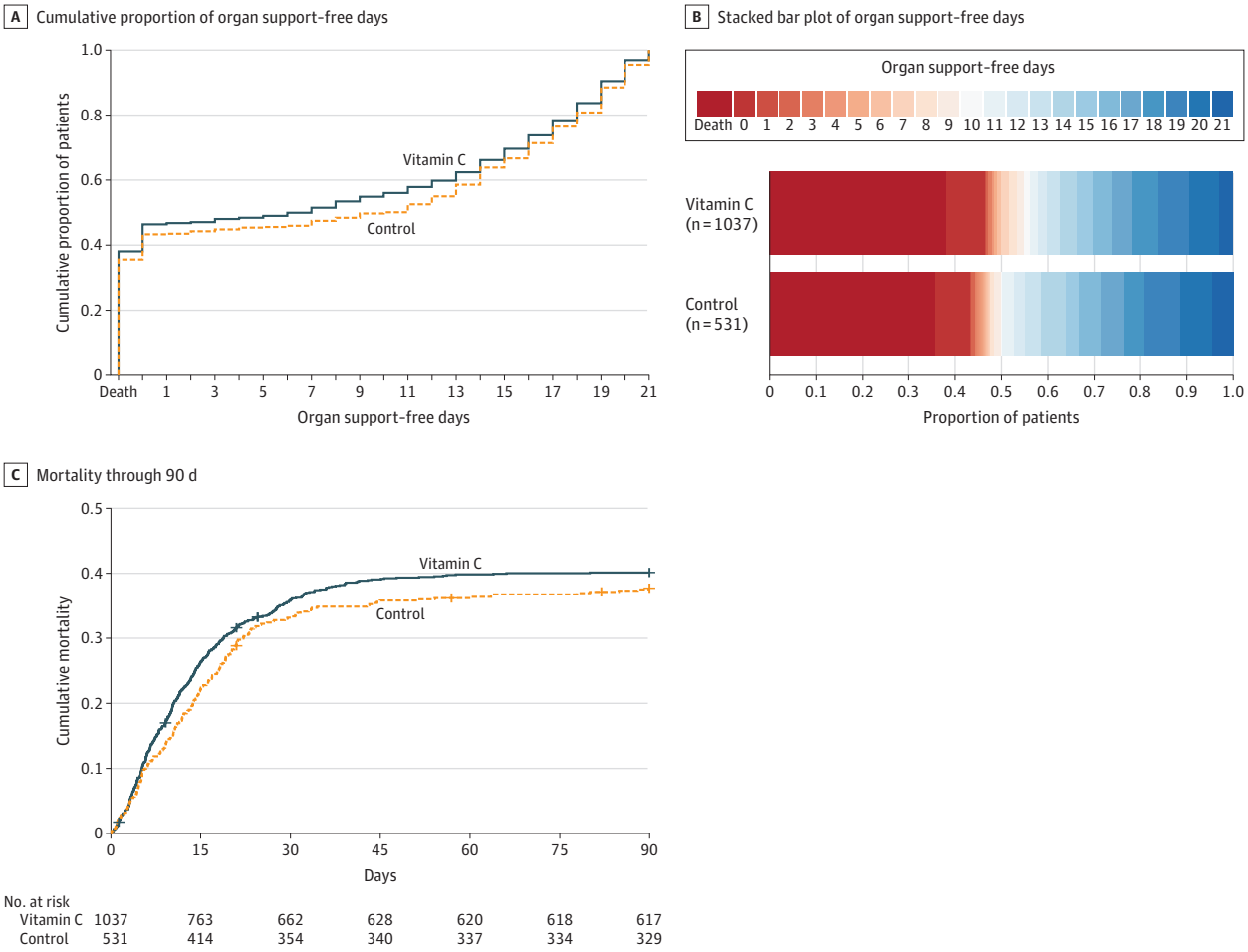
[i] Data are expressed as hazard ratio (95% CrI).

[j] Crude results are not provided because the model assigns a length of stay of 90 days to those who died.

[k] Excludes patients censored alive prior to 90 days (8 critically ill patients were censored).

[l] Measures the patient's overall status at day 14. The score range is 0 (no illness) to 8 (death).[18] Scores between 1 and 7 indicate an increasing need for care. In this analysis, the score categories of 0, 1, and 2 have been condensed into 1 category for all patients discharged from the hospital. In the LOVIT-COVID trial, the categories of 3 and 4 were collapsed into 1 category.

Figure 2. Critically Ill Patients in the Harmonized Trial of Vitamin C vs Control for Those Hospitalized With COVID-19



A, The curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. B, Red represents worse outcomes and blue represents better outcomes. The median adjusted proportional odds ratio from the primary analysis was 0.88 (95% credible interval, 0.73-1.06), yielding a posterior probability of 8.6% for vitamin C being superior to control. C, In the vitamin C group, 415 of 1032 patients died (40.2%) and, in the control group, 200 of 528 patients died (37.9%); the denominators exclude censored patients. Data were not available for 8 patients who were censored prior to 90 days.

REMAP-CAP trial; there was no convincing evidence of divergent effect estimates (eTable 15 in Supplement 1).

There were no differential effects among subgroups (eTable 16 in Supplement 1). The exploratory analyses showed that the in-hospital mortality rates by group in the REMAP-CAP trial shifted over time (eFigures 8a-8b in Supplement 1), with the effect of vitamin C on organ support-free days varying over successive periods defined by randomization ratio (eTable 17 in Supplement 1). The post hoc analyses of treatment effect by continent and by dominant SARS-CoV-2 strain by month in each country of enrollment did not explain this variation (eTables 18-19 in Supplement 1).

Discussion

In this large, harmonized, multinational randomized clinical trial, vitamin C administered to hospitalized patients with COVID-19 did not improve organ support-free days or hospital survival. On the contrary, there were high posterior probabilities (>90% for organ support-free days and >75% for hospital survival) that vitamin C worsened both outcomes in critically ill patients and those not critically ill. These effects were consistent across predefined subgroups and in the sensitivity analyses.

The regimen of vitamin C was based on a previous trial including patients with sepsis that showed sustained elevation of serum vitamin C levels over the treatment course, in addition to lower mortality, which was a secondary outcome.[19] The results from the current study, which included both a critically ill population with mainly COVID-19 respiratory failure and a population that was not critically ill, are consistent with the LOVIT trial[7] that included patients with sepsis who were treated with vasopressors. Existing analyses do not elucidate the mechanisms of harm, and while future biomarker analyses from the LOVIT-COVID trial may be informative, as shown

Table 3. Primary and Secondary Outcomes for Participants Not Critically Ill in the LOVIT-COVID Trial and the Vitamin C Domain of the REMAP-CAP Trial

	Not critically ill		Adjusted absolute risk difference (95% CrI)[a]	Adjusted effect measure (95% CrI)	Posterior probability, %	
	Vitamin C	Control			Efficacy	Harm
Primary outcome						
Organ support–free days to 21 d, median (IQR)[b]	22 (18 to 22) [n = 456]	22 (21 to 22) [n = 566]		0.80 (0.60 to 1.01)[c]	2.9	97.1[d]
Component of primary outcome						
Survival to hospital discharge, No./total (%)	388/456 (85.1)	490/566 (86.6)	−1.9 (−6.8 to 1.7)	0.86 (0.61 to 1.17)[e]	17.8	82.2[f]
Secondary outcomes						
Survival without persistent organ dysfunction at 28 d, No./total (%)[g]	381/456 (83.6)	477/566 (84.3)	−1.1 (−5.8 to 2.6)	0.92 (0.68 to 1.23)[e]	26.6	73.4
Treatment through 28 d						
Vasopressor or inotrope–free days, median (IQR)	28 (28 to 28) [n = 456]	28 (28 to 28) [n = 566]		0.77 (0.65 to 0.90)[c]	0.5	99.5
Respiratory support–free days, median (IQR)	28 (26 to 28) [n = 456]	28 (27 to 28) [n = 566]		0.83 (0.64 to 0.99)[c]	1.9	98.1
Endotracheal intubation, No./total (%)	63/456 (13.8)	50/566 (8.8)	−3.4 (−5.3 to −1.4)	0.59 (0.38 to 0.83)[e]	0.1	99.9
Extracorporeal support, No./total (%)[h]	2/456 (0.4)	4/566 (0.7)				
Survival to 28 d, No./total (%)	385/454 (84.8)	480/563 (85.3)	−0.8 (−5.5 to 2.7)	0.94 (0.68 to 1.26)[e]	32.9	67.1
Discharged alive from the hospital[j]				0.92 (0.81 to 1.05)[i]	10.6	89.4
90-d survival, No./total (%)[k]	370/454 (81.5)	466/563 (82.8)		0.93 (0.74 to 1.19)[i]	27.2	72.8
WHO Ordinal Scale score at 14 d[l]				0.89 (0.71 to 1.12)[c]	15.6	84.4

Abbreviations: CrI, credible interval; LOVIT-COVID, Lessening Organ Dysfunction with Vitamin C for COVID-19; OR, odds ratio; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; WHO, World Health Organization.

[a] The absolute risk differences (vitamin C minus control) are presented for the binary outcomes and are based on the event proportion in the control group and the OR after covariate adjustment from each model.

[b] The model assigns a value of −1 organ support–free days to those who died.

[c] Data are expressed as proportional OR (95% CrI).

[d] The posterior probability of futility was greater than 99.9%.

[e] Data are expressed as OR (95% CrI).

[f] The posterior probability of futility was 98.1%.

[g] The outcome is the complement of 28-day mortality or persistent organ dysfunction to preserve the interpretation of an OR greater than 1, which indicates the superiority of vitamin C.

[h] No model was constructed for this outcome per the statistical analysis plan.

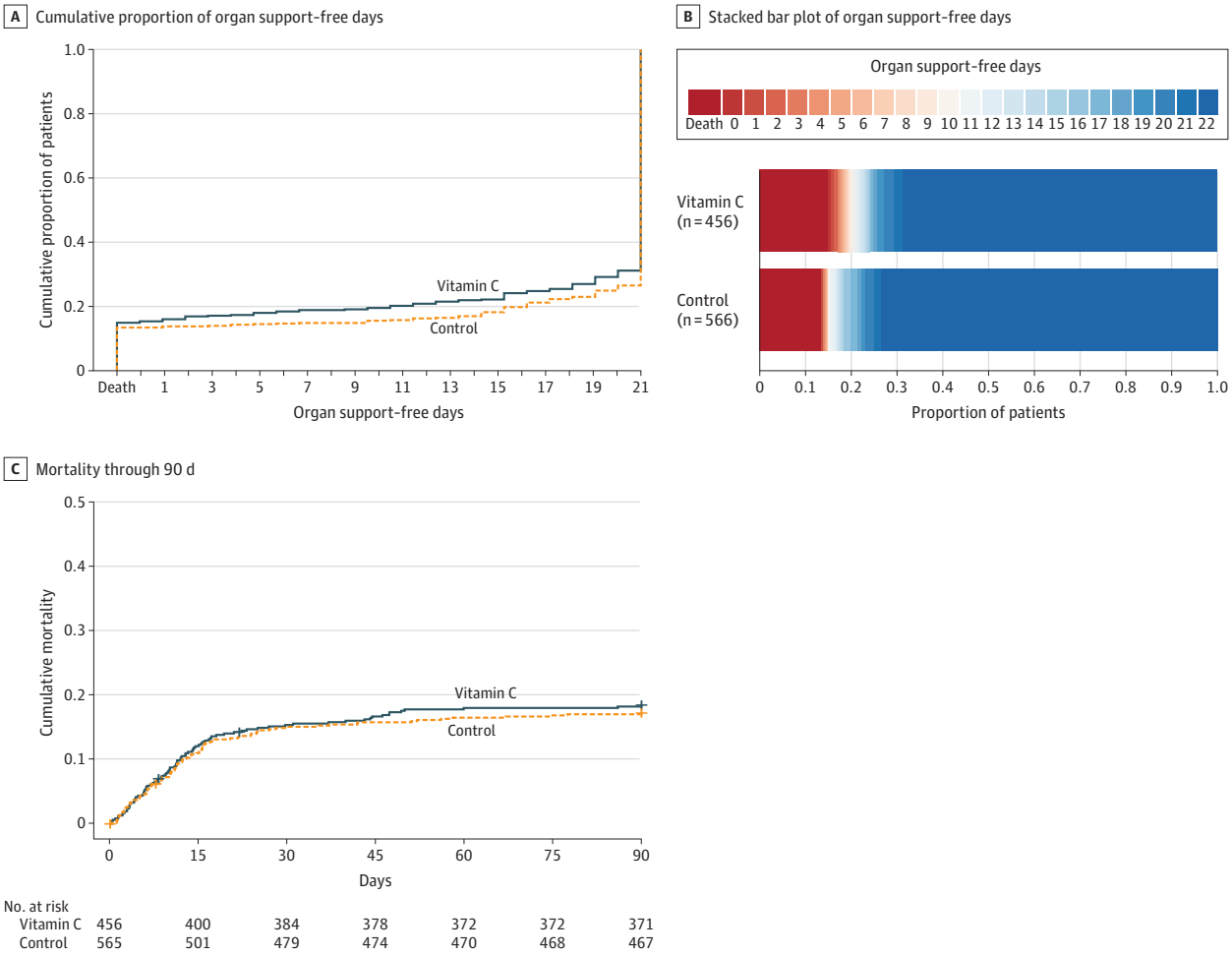
[i] Data are expressed as hazard ratio (95% CrI).

[j] Crude results are not provided because the model assigns a length of stay of 90 days to those who died.

[k] Excludes patients censored alive prior to 90 days (4 patients who were not critically ill were censored).

[l] Measures the patient's overall status at day 14. The score range is 0 (no illness) to 8 (death).[18] Scores between 1 and 7 indicate an increasing need for care. In this analysis, the score categories of 0, 1, and 2 have been condensed into 1 category for all patients discharged from the hospital. In the LOVIT-COVID trial, the categories of 3 and 4 were collapsed into 1 category.

Figure 3. Patients Who Were Not Critically Ill in the Harmonized Trial of Vitamin C vs Control for Those Hospitalized With COVID-19



A, The curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. B, Red represents worse outcomes and blue represents better outcomes. The median adjusted proportional odds ratio from the primary analysis was 0.80 (95% credible interval, 0.60-1.01), yielding a posterior probability of 2.9% for vitamin C being superior to control. C, In the vitamin C group, 84 of 454 patients died (18.5%) and, in the control group, 97 of 563 patients died (17.2%); the denominators exclude censored patients. Data were not available for 4 patients who were censored prior to 90 days.

in a secondary analysis of convalescent plasma in the REMAP-CAP trial,[20] the same biomarkers measured in the LOVIT trial[7] were comparable between the vitamin C and placebo groups. A meta-analysis of 9 trials[11] (the largest included trial randomized 100 patients) found a reduced odds of mortality in patients with COVID-19 receiving vitamin C. These divergent results may be explained by the more extreme effects observed in the small trials.[21]

Several methodological issues are noteworthy. First, the initial decision to limit statistical stopping triggers for efficacy, inferiority, and equivalence facilitated investigation of a small potential treatment benefit. Although the current results do not exclude the possibility of any beneficial effect of vitamin C in COVID-19, it is more likely that vitamin C is ineffective or harmful.

Second, the current study provides separate effects of vitamin C in critically ill patients and those who were not critically ill and is consistent with the study's design. An alternative approach would have included all randomized patients and may have generated a more precise overall treatment effect, with testing for a subgroup effect. Nonetheless, the current model allowed for statistical borrowing between critically ill and noncritically ill strata, thus mitigating the loss of statistical power.

Third, the treatment effect for the primary outcome is presented in relative terms rather than as an absolute difference, which is better suited to shared decision-making. The difference of 1.5 organ support-free days[22] is considered minimally important by the US Food and Drug Administration, but patients' views are unknown.

Fourth, response-adaptive randomization in the REMAP-CAP trial, which was designed to favor assignment to the group with superior outcomes at the interim analyses, led to 69% of critically ill patients being assigned to vitamin C despite lack

of efficacy in both strata. This situation arose because early results in critically ill patients favored vitamin C, without reaching a statistical trigger, with the final adaptive analysis conducted 10 months after the penultimate one due to implementation of new processes for international data flow. During this period, more than 50% of enrollment occurred, without changes to domain selection criteria or trial procedures. The final adaptive analysis reported a reversed direction of treatment effect, which was unexplained in the post hoc analyses, underscoring the early instability of treatment effect estimates in trials.[23-25] Because the inferiority trigger was never reached, the REMAP-CAP trial may have continued, even if adaptive analyses had been conducted more frequently, until harm and futility triggers were introduced due to external evidence.[7] Options for avoiding this situation include frequent adaptive analyses and forcing the randomization ratio to remain closer to 1:1.[26,27]

Strengths of this report include selection of a vitamin C regimen based on promising initial evaluations,[19,28] excellent treatment adherence and follow-up, and enhanced generalizability based on enrollment in broad geographic areas.[29]

Limitations

This trial has several limitations, some of which may potentially be addressed in future analyses. First, this report combines data from 2 trials that were designed differently in an attempt to improve efficiency and reduce waste in COVID-19 pandemic research.[30]

Second, fewer patients were enrolled in the placebo-controlled LOVIT-COVID trial and receipt of differential post-randomization care was possible for patients enrolled in the open-label REMAP-CAP trial.

Third, the analyses showing comparable treatment effects in these 2 trials were underpowered. Fourth, the data on individual participant vaccination status, the vitamin C product received, and the baseline vitamin C level were unavailable to inform subgroup analyses; however, a subgroup analysis by baseline vitamin C level in the LOVIT trial[7] was uninformative.

Conclusions

In hospitalized patients with COVID-19, vitamin C had low probability of improving the primary composite outcome of organ support–free days and hospital survival.

ARTICLE INFORMATION

Accepted for Publication: October 2, 2023.

Published Online: October 25, 2023. doi:10.1001/jama.2023.21407

Corrections: This article was corrected December 26, 2023, to fix the spelling of several names in Supplement 3 and on April 30, 2024, to add Christopher Horvat, MD, MHA, to the list of LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators. This article was corrected August 20, 2024, to fix "Matteo Aldo Bonizzoni" in Supplement 3.

The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators: Neill K. J. Adhikari, MDCM, MSc; Madiha Hashmi, MD; Bharath Kumar Tirupakuzhi Vijayaraghavan, MD; Rashan Haniffa, PhD; Abi Beane, PhD; Steve A. Webb, MD, PhD; Derek C. Angus, MD, MPH; Anthony C. Gordon, MBBS, MD; Deborah J. Cook, MD, MSc; Gordon H. Guyatt, MD, MSc; Lindsay R. Berry, PhD; Elizabeth Lorenzi, PhD; Paul R. Mouncey, MSc; Carly Au, BSc; Ruxandra Pinto, PhD; Julie Ménard, PhD; Sheila Sprague, PhD; Marie-Hélène Masse, MSc; David T. Huang, MD, PhD; Daren K. Heyland, MD, MSc; Alistair D. Nichol, MD, PhD; Colin J. McArthur, MD, MSc; Angelique de Man, MD, PhD; Farah Al-Beidh, PhD; Djillali Annane, MD, PhD; Matthew Anstey, MBBS, MPH; Yaseen M. Arabi, MD; Marie-Claude Battista, PhD; Scott Berry, PhD; Zahra Bhimani, MPH; Marc J. M. Bonten, MD, PhD; Charlotte A. Bradbury, MBChB, PhD; Emily B. Brant, MD, MS; Frank M. Brunkhorst, MD, PhD; Aidan Burrell, MBBS, PhD; Meredith Buxton, PhD, MPH; Maurizio Cecconi, MD; Allen C. Cheng, MD, PhD; Dian Cohen, BA (Hons); Matthew E. Cove, MD; Andrew G. Day, MSc; Lennie P. G. Derde, MD, PhD; Michelle A. Detry, PhD; Lise J. Estcourt, MBChB, PhD; Elizabeth O. Fagbodun, MSc; Mark Fitzgerald, PhD; Herman Goossens, MD, PhD; Cameron Green, MSc; Alisa M. Higgins, PhD; Thomas E. Hills, MBBS, PhD; Christopher Horvat, MD, MHA; Nao Ichihara, MD, MPH, PhD; Devachandran Jayakumar, MS, MSc; Salmaan Kanji, PharmD; Muhammad Nasir Khoso, MBBS; Patrick R. Lawler, MD, MPH; Roger J. Lewis, MD, PhD; Edward Litton, MD, PhD; John C. Marshall, MD; Daniel F. McAuley, MD; Anna McGlothlin, PhD; Shay P. McGuinness, MBChB; Zoe K. McQuilten, MBBS, PhD; Bryan J. McVerry, MD; Srinivas Murthy, MD, MHSc; Rachael L. Parke, RN, MHSc, PhD; Jane C. Parker, BN; Luis Felipe Reyes, MD, PhD; Kathryn M. Rowan, PhD; Hiroki Saito, MD, PhD; Nawal Salahuddin, MD; Marlene S. Santos, MD, MSHS; Christina T. Saunders, PhD; Christopher W. Seymour, MD, MSc; Manu Shankar-Hari, MD, PhD; Timo Tolppa, BMBS, BSc; Tony Trapani, RN; Alexis F. Turgeon, MD, MSc; Anne M. Turner, MPH; Andrew A. Udy, MD, MSc; Frank L. van de Veerdonk, MD, PhD; Ryan Zarychanski, MD, MSc; François Lamontagne, MD, MSc.

Affiliations of The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators: Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Adhikari, Pinto); Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada (Adhikari); Department of Critical Care Medicine, Ziauddin University, Karachi, Pakistan (Hashmi); Department of Critical Care Medicine, Apollo Hospitals, Chennai, India (Tirupakuzhi Vijayaraghavan); George Institute for Global Health India, New Delhi (Tirupakuzhi Vijayaraghavan); Centre for Inflammation Research, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, Scotland (Haniffa, Beane); Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand (Haniffa, Beane); Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia (Webb, Nichol, Green, Higgins); St John of God Health Care, Perth, Australia (Webb); University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Angus); University of Pittsburgh, Pittsburgh, Pennsylvania (Angus); Division of Anaesthetics, Pain Medicine, and Intensive Care, Imperial College London, London, England (Gordon); St Mary's Hospital, Imperial College Healthcare NHS Trust, London, England (Gordon); Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Cook); Department of Critical Care, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada (Cook); Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (Cook, Guyatt); Berry Consultants LLC, Austin, Texas (L. R. Berry, Lorenzi, S. Berry, Detry, Fitzgerald, Lewis, McGlothlin, Saunders); Intensive Care National Audit and Research Centre, London, England (Mouncey, Au); Research Centre of the Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada (Ménard, Masse, Battista, Lamontagne); Department of Surgery, McMaster University, Hamilton, Ontario, Canada (Sprague); School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Huang); Department of Critical Care Medicine, Queen's University, Kingston, Ontario, Canada (Heyland); Faculty of Medicine, Nursing, and Health Sciences, Monash University, Clayton, Australia (Nichol, Parker); University College Dublin, Dublin, Ireland (Nichol); Alfred Health, Melbourne, Australia (Nichol, Burrell); Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand (McArthur); Department of Intensive Care Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands (de Man); Imperial College London, London, England (Al-Beidh); UVSQ University Paris Saclay, Institut-Hospitalo Universitaire Prometheus, Paris, France (Annane); Médecine Intensive-Réanimation, Hôpital Raymond-Poincaré, Garches, France (Annane); Sir Charles Gairdner Hospital, Nedlands, Australia (Anstey); University of Western Australia, Perth (Anstey); King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia (Arabi); King Abdullah International Medical Research

Center, Riyadh, Saudi Arabia (Arabi); St Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada (Bhimani); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands (Bonten); European Clinical Research Alliance on Infectious Diseases, Utrecht, the Netherlands (Bonten, Derde); University of Bristol, Bristol, England (Bradbury); Department of Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Brant, Horvat, Seymour); Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany (Brunkhorst); Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (Burrell); Global Coalition for Adaptive Research, Larkspur, California (Buxton); Department of Biomedical Sciences, Humanitas University, Milan, Italy (Cecconi); IRCCS Humanitas Research Hospital, Milan, Italy (Cecconi); Monash Infectious Disease, Monash Health and School of Clinical Sciences, Monash University, Clayton, Australia (Cheng); School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia (Cheng); Bishop's University, Sherbrooke, Quebec, Canada (Cohen); Massawippi Valley Foundation, Ayer's Cliff, Quebec, Canada (Cohen); Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Cove); Kingston Health Sciences Centre and Queen's University, Kingston, Ontario, Canada (Day); Intensive Care Centre, University Medical Centre Utrecht, Utrecht, the Netherlands (Derde); Department of Haematology, NHS Blood and Transplant, Bristol, England (Estcourt); Radcliffe Department of Medicine, University of Oxford, Oxford, England (Estcourt); Imperial Clinical Trials Unit, Imperial College London, London, England (Fagbodun); Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium (Goossens); Medical Research Institute of New Zealand, Wellington (Hills, McGuinness, Parke, Turner); Department of Cardiovascular Surgery, School of Medicine, Jikei University, Tokyo, Japan (Ichihara); Dr Kamakshi Memorial Hospital Apollo, Chennai, India (Jayakumar); Ottawa Hospital, Ottawa, Ontario, Canada (Kanji); Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Kanji); South City Hospital, Karachi, Pakistan (Khoso); University Health Network, Toronto, Ontario, Canada (Lawler); University of Toronto, Toronto, Ontario, Canada (Lawler); McGill University Health Centre, Montreal, Quebec, Canada (Lawler); Fiona Stanley Hospital, Department of Intensive Care Unit, University of Western Australia, Perth (Litton); Department of Surgery, University of Toronto, Toronto, Ontario, Canada (Marshall); Queen's University of Belfast, Belfast, Northern Ireland (McAuley); Centre for Infection and Immunity, Royal Victoria Hospital, Belfast, Northern Ireland (McAuley); Auckland City Hospital, Cardiothoracic and Vascular Intensive Care Unit, Auckland, New Zealand (McGuinness, Parke); Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia (McGuinness, Trapani, Udy); Monash University, Monash Health, Clayton, Australia (McQuilten); Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (McVerry); Department of Pediatrics, University of British Columbia, Vancouver, Canada (Murthy); School of Nursing, University of Auckland, Auckland, New Zealand (Parke); Department of Infectious Diseases, Universidad de La Sabana, Chia, Colombia (Reyes); Department of Critical Care Medicine, Clinica Universidad de La Sabana, Chia, Colombia (Reyes); Intensive Care National Audit and Research Centre, London, England (Rowan); Department of Emergency and Critical Care Medicine, St Marianna University Yokohama Seibu Hospital, Yokohama, Japan (Saito); National Institute of Cardiovascular Diseases, Karachi, Pakistan (Salahuddin); Department of Critical Care, St Michael's Hospital, Toronto, Ontario, Canada (Santos); Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, Scotland (Shankar-Hari); Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, Scotland (Shankar-Hari); National Intensive Care Surveillance, Colombo, Sri Lanka (Tolppa); Department of Anesthesiology and Critical Care, Université Laval, Quebec City, Quebec, Canada (Turgeon); Population Health and Optimal Health Practices Research Unit, Departments of Traumatology, Emergency Medicine, and Critical Care Medicine, Université Laval Research Center, CHU de Québec-Université Laval, Quebec City, Quebec, Canada (Turgeon); Department of Intensive Care and Hyperbaric Medicine, Alfred Hospital, Melbourne, Australia (Udy); Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands (van de Veerdonk); Department of Internal Medicine, University of Manitoba, Winnipeg, Canada (Zarychanski); Department of Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada (Lamontagne).

Author Contributions: Drs Adhikari and Lamontagne had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Adhikari and Lamontagne are joint first and senior authors.
Concept and design: Adhikari, Webb, Angus, Gordon, Cook, Guyatt, L. Berry, Lorenzi, Sprague, Huang, Heyland, McArthur, de Man, Anstey, S. Berry, Bhimani, Bonten, Brunkhorst, Cecconi, Cheng, Cohen, Derde, Estcourt, Goossens, Hills, Kanji, Khoso, Lewis, Litton, McAuley, McQuilten, Murthy, Parke, Rowan, Seymour, Shankar-Hari, Trapani, Turgeon, Udy, Lamontagne.
Acquisition, analysis, or interpretation of data: Adhikari, Hashmi, Tirupakuzhi Vijayaraghavan, Haniffa, Beane, Webb, Angus, Gordon, Cook, Guyatt, L. Berry, Lorenzi, Mouncey, Au, Pinto, Ménard, Sprague, Masse, Huang, Nichol, McArthur, Al-Beidh, Annane, Arabi, Battista, S. Berry, Bradbury, Brant, Brunkhorst, Burrell, Buxton, Cecconi, Cheng, Cove, Day, Derde, Detry, Fagbodun, Fitzgerald, Green, Higgins, Hills, Horvat, Ichihara, Jayakumar, Kanji, Khoso, Lawler, Lewis, Litton, Marshall, McAuley, McGlothlin, McGuinness, McVerry, Parker, Reyes, Rowan, Saito, Salahuddin, Santos, Saunders, Seymour, Shankar-Hari, Tolppa, Turgeon, Turner, van de Veerdonk, Zarychanski, Lamontagne.
Drafting of the manuscript: Adhikari, Tirupakuzhi Vijayaraghavan, Gordon, Sprague, Huang, Heyland, Bhimani, Cecconi, McAuley, Murthy, Shankar-Hari, Lamontagne.
Critical review of the manuscript for important intellectual content: Adhikari, Hashmi, Tirupakuzhi Vijayaraghavan, Haniffa, Beane, Webb, Angus, Gordon, Cook, Guyatt, L. Berry, Lorenzi, Mouncey, Au, Pinto, Ménard, Sprague, Masse, Huang, Heyland, Nichol, McArthur, de Man, Al-Beidh, Annane, Anstey, Arabi, Battista, S. Berry, Bonten, Bradbury, Brant, Brunkhorst, Burrell, Buxton, Cecconi, Cheng, Cohen, Cove, Day, Derde, Detry, Estcourt, Fagbodun, Fitzgerald, Goossens, Green, Higgins, Hills, Horvat, Ichihara, Jayakumar, Kanji, Khoso, Lawler, Lewis, Litton, Marshall, McAuley, McGlothlin, McGuinness, McQuilten, McVerry, Parke, Parker, Reyes, Rowan, Saito, Salahuddin, Santos, Saunders, Seymour, Shankar-Hari, Tolppa, Trapani, Turgeon, Turner, Udy, van de Veerdonk, Zarychanski, Lamontagne.
Statistical analysis: L. Berry, Lorenzi, Pinto, S. Berry, Day, Detry, Fitzgerald, Khoso, Lewis, McGlothlin, Saunders, Lamontagne.
Obtained funding: Adhikari, Webb, Gordon, Masse, Heyland, Nichol, McArthur, Annane, Bonten, Burrell, Buxton, Cheng, Cove, Derde, Goossens, Higgins, Hills, Ichihara, Litton, Marshall, McAuley, McGuinness, Murthy, Rowan, Saito, Shankar-Hari, Turgeon, Lamontagne.
Administrative, technical, or material support: Adhikari, Hashmi, Tirupakuzhi Vijayaraghavan, Beane, Webb, Angus, Gordon, Cook, Mouncey, Au, Pinto, Ménard, Sprague, Masse, Nichol, McArthur, de Man, Al-Beidh, Battista, Bhimani, Brant, Brunkhorst, Buxton, Cheng, Derde, Green, Higgins, Horvat, Ichihara, Jayakumar, Kanji, Khoso, McAuley, McGuinness, McQuilten, Parker, Rowan, Saito, Santos, Shankar-Hari, Tolppa, Trapani, Turner, Zarychanski, Lamontagne.
Supervision: Adhikari, Angus, Gordon, Guyatt, Ménard, Nichol, Arabi, S. Berry, Burrell, Cecconi, Derde, Hills, Kanji, Khoso, Lewis, McAuley, Murthy, Reyes, Rowan, Seymour, Lamontagne.

Conflict of Interest Disclosures: Dr Haniffa reported receiving grants from Wellcome Trust, Medical Research Council Africa, and International COVID-19 Data Alliance. Dr Webb reported receiving grants from the National Health and Medical Research Council, the Minderoo Foundation, and the Medical Research Future Fund. Dr Gordon reported receiving personal fees from AstraZeneca, Janssen, Novartis, and 30 Respiratory (all fees paid to institution). Dr L. Berry reported receiving grants and being an employee of Berry Consultants. Dr Lorenzi reported being an employee of Berry Consultants. Dr Nichol reported receiving grants from the European Commission. Dr de Man reported receiving grants from the Netherlands Organisation of Health Research. Dr S. Berry reported being part owner of Berry Consultants. Dr Bradbury reported receiving personal fees from Bristol Myers Squibb, Pfizer, Bayer, Amgen, Lilly, Sobi, Sanofi, Novartis, and Janssen. Dr Cecconi reported receiving personal fees from Edwards Lifesciences, Directed Systems, and GE Healthcare. Dr Cove reported receiving grants from National University Health System; receiving personal fees from Baxter, Medtronic, B Braun, and Jafron; and holding a patent for the removal of carbon dioxide via dialysis. Dr Derde reported receiving grants from the European Commission and serving as a member of the international advisory board for Sepsis Canada. Dr Detry reported receiving grants from the European Commission and the Global Coalition for Adaptive Research and being a director and senior statistical scientist at Berry Consultants. Dr Fitzgerald reported receiving grants from the European Commission and the Global Coalition for Adaptive Research. Dr Higgins reported receiving grants from the National Health and Medical Research Council, the Minderoo Foundation, and the Medical Research Future Fund. Dr Horvat reported receiving

grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr Lawler reported receiving personal fees from the American College of Cardiology and McGraw Hill. Dr Lewis reported being a senior medical scientist at Berry Consultants. Dr Marshall reported receiving personal fees from AM Pharma and Matisse. Dr McAuley reported receiving grants from Innovate UK, Northern Ireland Health and Social Care, the Medical Research Council, and Wellcome Trust; receiving personal fees from Bayer, GSK, Boehringer Ingelheim, Novartis, Eli Lilly, Vir Biotechnology, Aptarion, Aviceda, and Direct Biologics; holding a patent for an anti-inflammatory treatment (issued to Queen's University Belfast) for a novel treatment for inflammatory disease; and being the co-director of research for the Intensive Care Society and the program director for the National Institute for Health and Care Research/ Medical Research Council Efficacy and Mechanism Evaluation. Dr McGlothlin reported receiving grants from the European Commission and the Global Coalition for Adaptive Research. Dr McVerry reported receiving grants from the Pittsburgh Foundation and the National Institutes of Health and receiving personal fees from Boehringer Ingelheim, Synairgen, and BioAegis. Dr Parke reported receiving grants from Fisher and Paykel Healthcare Ltd. Dr Reyes reported receiving grants from Merck Sharp & Dohme and Pfizer and receiving personal fees from GSK. Dr Rowan reported receiving grants from the European Commission. Dr Saunders reported receiving grants from the European Commission and the Global Coalition for Adaptive Research. Dr Seymour reported receiving grants from the National Institutes of Health and personal fees from Beckman Coulter and Inotrem, Inc. Dr Shankar-Hari reported receiving grants from the Chief Scientist Office Scotland, the National Institute for Health and Care Research (Efficacy and Mechanism Evaluation and Health Technology Assessment programs), the Medical Research Council, and the Huo Foundation. Dr Udy reported nonfinancial support from Integra Lifesciences. No other disclosures were reported.

Funding/Support: The LOVIT-COVID trial was funded by the Lotte and John Hecht Memorial Foundation, which also supported the REMAP-CAP trial via a subcontract. Nova Biomedical Canada, Ltd provided glucometers, testing strips, and control solutions (StatStrip Express) to trial sites that requested them in the LOVIT-COVID trial. The vitamin C that was used by the LOVIT-COVID sites (all in Canada) was purchased from Mylan. The REMAP-CAP trial was funded by FP7-health-2013-innovation-1 grant 602525 from the Platform for European Preparedness Against Re-Emerging Epidemics Consortium of the European Union, grant 101003589 from the Rapid European COVID-19 Emergency Research Response Consortium of the European Union's Horizon 2020 Research and Innovation Programme, grant APP1101719 from the Australian National Health and Medical Research Council, grant 16/631 from the Health Research Council of New Zealand, grant 158584 from the Canadian Institutes of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program, funding from the National Institute for Health and Care Research (NIHR) and the NIHR Imperial Biomedical Research Centre, grant CTN 2014-012 from the Health Research Board of Ireland, funding from the University of Pittsburgh Medical Center Learning While Doing Program, funding from the Translational Breast Cancer Research Consortium, grant PHRC-20-0147 from the French Ministry of Health, funding from the Office of Health and Medical Research NSW Health, funding from the Minderoo Foundation, grant 215522 from the Wellcome Trust Innovations Project, grants 20fk0108526h0001, 21fk0108591h0001, and 22fk0108528h0001 from the Japan Agency for Medical Research and Development, and funding from the National University Health System research office, Singapore. The sponsor for the LOVIT-COVID trial was the Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke. The REMAP-CAP trial has 4 regional nonprofit sponsors: Monash University (Melbourne, Australia), Utrecht Medical Center (Utrecht, the Netherlands), Unity Health Toronto (Toronto, Ontario, Canada), and the Global Coalition for Adaptive Research (San Francisco, California).

Role of the Funder/Sponsor: The funders/ sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The entire list of the LOVIT-COVID Investigators and the REMAP-CAP Investigators appears in Supplement 3.

Disclaimer: Dr Angus is a Senior Editor, Dr Lewis is a Statistical Editor, and Dr Seymour is an Associate Editor of *JAMA* but were not involved in any of the decisions regarding review of the manuscript or its acceptance.

Meeting Presentation: Presented in part at the European Society of Intensive Care Medicine; October 25, 2023; Milan, Italy.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the trial patients and their caregivers; the clinicians; the research, pharmacy, and laboratory staff members; and the trial and data coordinators; the National Institute for Health and Care Research Clinical Research Network, the University of Pittsburgh Medical Center Health System Health Services Division, and the Direction de la Recherche Clinique et de l'Innovation de l'AP-HP for their support of participant recruitment; the Unité de Recherche Clinique et Épidémiologique of the Centre de Recherche du CHU de Sherbrooke for providing support in the conduct of the LOVIT-COVID trial; the Canadian Critical Care Trials Group, including Bram Rochwerg, MD, MSc, for his uncompensated review of the manuscript; and the uncompensated members of the data and safety monitoring boards (LOVIT-COVID: Andreas Laupacis, MD, MSc, Lauren Griffith, PhD, and Scott Halpern, MD, PhD; REMAP-CAP: Victoria Manax, MD, Jason Connor, PhD, Alexandre Cavalcanti, MD, PhD, Simon Finfer, MBBS, DrMed, Simon Gates, PhD, Adrienne Randolph, MD, MSc, John Reynolds, PhD, and Tom van der Poll, MD, PhD).

Additional Information: This article was written with gratitude to and in memory of our friend and colleague, Wilma van Bentum-Puijk, MSc.

REFERENCES

1. World Health Organization. COVID-19 dashboard. Accessed March 30, 2023. https://covid19.who.int/

2. Lamontagne F, Agarwal A, Rochwerg B, et al. A living WHO guideline on drugs for COVID-19. *BMJ*. 2020;370:m3379. doi:10.1136/bmj.m3379

3. Usher AD. The global COVID-19 treatment divide. *Lancet*. 2022;399(10327):779-782. doi:10.1016/S0140-6736(22)00372-5

4. Vail EA, Wunsch H, Pinto R, et al. Use of hydrocortisone, ascorbic acid, and thiamine in adults with septic shock. *Am J Respir Crit Care Med*. 2020;202(11):1531-1539. doi:10.1164/rccm.202005-1829OC

5. Fujii T, Luethi N, Young PJ, et al; VITAMINS Trial Investigators. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020;323(5):423-431. doi:10.1001/jama.2019.22176

6. Sevransky JE, Rothman RE, Hager DN, et al; VICTAS Investigators. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS randomized clinical trial. *JAMA*. 2021;325 (8):742-750. doi:10.1001/jama.2020.24505

7. Lamontagne F, Masse MH, Menard J, et al; LOVIT Investigators and the Canadian Critical Care Trials Group. Intravenous vitamin C in adults with sepsis in the intensive care unit. *N Engl J Med*. 2022;386 (25):2387-2398. doi:10.1056/NEJMoa2200644

8. World Health Organization. A coordinated global research roadmap: 2019 novel coronavirus. Published March 12, 2020. Accessed October 6, 2023. https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap

9. Carr AC, Rowe S. The emerging role of vitamin C in the prevention and treatment of COVID-19. *Nutrients*. 2020;12(11):3286. doi:10.3390/nu12113286

10. Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care*. 2020;24 (1):522. doi:10.1186/s13054-020-03249-y

11. Olczak-Pruc M, Swieczkowski D, Ladny JR, et al. Vitamin C supplementation for the treatment of COVID-19: a systematic review and meta-analysis. *Nutrients*. 2022;14(19):4217. doi:10.3390/nu14194217

12. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study: rationale and design. *Ann Am Thorac Soc*. 2020;17(7):879-891. doi:10.1513/AnnalsATS.202003-192SD

13. Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436

14. ATTACC, ACTIV-4a Investigators, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med*. 2021;385(9): 790-802. doi:10.1056/NEJMoa2105911

15. REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789. doi:10.1056/NEJMoa2103417

16. Higgins AM, Berry LR, Lorenzi E, et al; Writing Committee for the REMAP-CAP Investigators. Long-term (180-day) outcomes in critically ill

patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA*. 2023;329(1):39-51. doi:10.1001/jama.2022.23257

17. Heyland DK, Muscedere J, Drover J, Jiang X, Day AG; Canadian Critical Care Trials Group. Persistent organ dysfunction plus death: a novel, composite outcome measure for critical care trials. *Crit Care*. 2011;15(2):R98. doi:10.1186/cc10110

18. WHO Working Group on the Clinical Characterisation and Management of COVID-19 Infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7

19. Fowler AA III, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA*. 2019;322(13):1261-1270. doi:10.1001/jama.2019.11825

20. Fish M, Rynne J, Jennings A, et al; REMAP-CAP Immunoglobulin Domain UK Investigators. Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized clinical trial. *Intensive Care Med*. 2022;48(11):1525-1538. doi:10.1007/s00134-022-06869-w

21. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ*. 2013;346:f2304. doi:10.1136/bmj.f2304

22. Laterre PF, Berry SM, Blemings A, et al; SEPSIS-ACT Investigators. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT randomized clinical trial. *JAMA*. 2019;322(15):1476-1485. doi:10.1001/jama.2019.14607

23. Canner PL. The Coronary Drug Project: monitoring of the data for evidence of adverse or beneficial treatment effects. *Control Clin Trials*. 1983;4(4):467-483. doi:10.1016/0197-2456(83)90029-6

24. Abraham E, Reinhart K, Opal S, et al; OPTIMIST Trial Study Group. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA*. 2003;290(2):238-247. doi:10.1001/jama.290.2.238

25. Wheatley K, Clayton D. Be skeptical about unexpected large apparent treatment effects: the case of an MRC AML12 randomization. *Control Clin Trials*. 2003;24(1):66-70. doi:10.1016/S0197-2456(02)00273-8

26. Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med*. 2016;375(1):65-74. doi:10.1056/NEJMra1510061

27. Granholm A, Kaas-Hansen BS, Lange T, et al. An overview of methodological considerations regarding adaptive stopping, arm dropping, and randomization in clinical trials. *J Clin Epidemiol*. 2023;153:45-54. doi:10.1016/j.jclinepi.2022.11.002

28. Fowler AA III, Syed AA, Knowlson S, et al; Medical Respiratory Intensive Care Unit Nursing. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32. doi:10.1186/1479-5876-12-32

29. Ramanan M, Tong SYC, Kumar A, Venkatesh B. Geographical representation of low- and middle-income countries in randomized clinical trials for COVID-19. *JAMA Netw Open*. 2022;5(2):e220444. doi:10.1001/jamanetworkopen.2022.0444

30. Glasziou PP, Sanders S, Hoffmann T. Waste in COVID-19 research. *BMJ*. 2020;369:m1847. doi:10.1136/bmj.m1847