ORIGINAL ARTICLE

# Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

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## ABSTRACT

### BACKGROUND

Studies that have evaluated the use of intravenous vitamin C in adults with sepsis who were receiving vasopressor therapy in the intensive care unit (ICU) have shown mixed results with respect to the risk of death and organ dysfunction.

### METHODS

In this randomized, placebo-controlled trial, we assigned adults who had been in the ICU for no longer than 24 hours, who had proven or suspected infection as the main diagnosis, and who were receiving a vasopressor to receive an infusion of either vitamin C (at a dose of 50 mg per kilogram of body weight) or matched placebo administered every 6 hours for up to 96 hours. The primary outcome was a composite of death or persistent organ dysfunction (defined by the use of vasopressors, invasive mechanical ventilation, or new renal-replacement therapy) on day 28.

### RESULTS

A total of 872 patients underwent randomization (435 to the vitamin C group and 437 to the control group). The primary outcome occurred in 191 of 429 patients (44.5%) in the vitamin C group and in 167 of 434 patients (38.5%) in the control group (risk ratio, 1.21; 95% confidence interval [CI], 1.04 to 1.40; P=0.01). At 28 days, death had occurred in 152 of 429 patients (35.4%) in the vitamin C group and in 137 of 434 patients (31.6%) in the placebo group (risk ratio, 1.17; 95% CI, 0.98 to 1.40) and persistent organ dysfunction in 39 of 429 patients (9.1%) and 30 of 434 patients (6.9%), respectively (risk ratio, 1.30; 95% CI, 0.83 to 2.05). Findings were similar in the two groups regarding organ-dysfunction scores, biomarkers, 6-month survival, health-related quality of life, stage 3 acute kidney injury, and hypoglycemic episodes. In the vitamin C group, one patient had a severe hypoglycemic episode and another had a serious anaphylaxis event.

### CONCLUSIONS

In adults with sepsis receiving vasopressor therapy in the ICU, those who received intravenous vitamin C had a higher risk of death or persistent organ dysfunction at 28 days than those who received placebo. (Funded by the Lotte and John Hecht Memorial Foundation; LOVIT ClinicalTrials.gov number, NCT03680274.)

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Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] This disorder causes or contributes to between a third and a half of deaths in hospitals[2] and is responsible for as many as 11 million deaths worldwide each year.[3] Treatment includes antimicrobial therapy, source control, and organ support.

In sepsis, the antioxidant effects of vitamin C therapy[4] may mitigate tissue injury induced by oxidative stress.[5] Vitamin C cannot be synthesized by humans, and levels are low in many critically ill patients, which has increased the plausibility of benefit with supplementation.[6] After a single-center study spurred interest in the use of intravenous vitamin C, administered with hydrocortisone and thiamine,[7] subsequent randomized, controlled trials evaluating this combination treatment did not show benefits.[8,9] In contrast, in a randomized, controlled trial, patients with sepsis and acute lung injury who received a higher dose of vitamin C (50 mg per kilogram of body weight every 6 hours) had a lower 28-day risk of death than those who received placebo.[10] However, recent meta-analyses suggest that the overall evidence supporting the use of vitamin C therapy in patients with sepsis is of low certainty.[8,11]

In the phase 3, multicenter, randomized, controlled Lessening Organ Dysfunction with Vitamin C (LOVIT) trial, we tested the hypothesis that a high dose of vitamin C would reduce the risk of death or persistent organ dysfunction at 28 days in adults with sepsis who were receiving vasopressor therapy in the intensive care unit (ICU).

## Methods

### Trial Design

In this international trial, we enrolled patients in 35 adult medical–surgical ICUs in Canada, France, and New Zealand. The protocol (available with the full text of this article at NEJM.org) has been described previously[12,13] and was approved by the ethics committee at each participating trial site.

The trial was funded by the Lotte and John Hecht Memorial Foundation. Nova Biomedical Canada provided glucometers, testing strips, and control solutions (StatStrip Express) to trial sites that requested them. Without input from the funder, the authors were responsible for the design, planning, and coordination of the trial and for the analysis of the data; all the authors made the decision to submit the manuscript for publication. Site investigators, research personnel, or trained delegates assessed the eligibility of potential patients, and research personnel collected the data. Informed consent was provided by the patients or their legal representatives; after approval by local authorities, consent could be obtained by telephone or patients could be enrolled with deferred consent, followed by informed consent as soon as reasonably possible.

The corresponding authors wrote the first draft of the manuscript. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### Patients

Eligible patients were adults (≥18 years of age) who had been in the ICU for no longer than 24 hours, who had proven or suspected infection as the main diagnosis, and who were receiving a vasopressor. Exclusion criteria included contraindications to vitamin C therapy, receipt of open-label vitamin C, or expected death or withdrawal of life-sustaining therapy within 48 hours. Details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

### Randomization and Treatment

We randomly assigned patients in a 1:1 ratio to receive either vitamin C or placebo, stratified according to site by means of a centralized Web-based system using permuted blocks of variable, undisclosed size. Patients, clinicians, and trial personnel and statisticians were unaware of trial-group assignments.

Patients in the intervention group received intravenous vitamin C in a bolus dose of 50 mg per kilogram mixed in a 50-ml solution of either dextrose 5% in water or normal saline. Doses were administered over 30 to 60 minutes every 6 hours for 96 hours (i.e., 200 mg per kilogram per day, with a maximum of 16 doses) as long as patients remained in the ICU. In the control group, patients received a matching placebo infusion (dextrose 5% in water or normal saline). At each site, pharmacists who were not involved

in the patients' clinical care prepared the respective infusions in an unblinded manner.

All other aspects of care, including the administration of glucocorticoids (including agents with mineralocorticoid effects) and thiamine, were performed at the discretion of the treating teams. Local research staff members collected data on inpatient outcomes, and the central management team conducted telephone interviews with patients or their representatives 6 months after randomization. If patients had been discharged from the hospital before day 28, ascertainment of the primary outcome was completed at the time of the 6-month follow-up interview.

### TRIAL OUTCOMES

The primary outcome was a composite of death or persistent organ dysfunction (defined as receipt of vasopressors, invasive mechanical ventilation, or new renal-replacement therapy)[14] on trial day 28. Secondary outcomes were the number of days without organ dysfunction in the ICU up to day 28; mortality at 28 days and 6 months; quality of life at 6 months; organ failure at days 2, 3, 4, 7, 10, 14, and 28; and biomarkers of global tissue dysoxia (lactate), inflammation (interleukin-1$\beta$ and tumor necrosis factor $\alpha$), and endothelial injury (thrombomodulin and angiopoietin-2) at days 3 and 7. Quality of life was assessed with the use of the European Quality of Life–5 Dimension 5-Level (EQ-5D-5L) questionnaire,[15] which evaluates mobility, personal care, usual activities, pain or discomfort, and anxiety or depression and categorizes each of these dimensions into five levels that range from no problems to extreme problems. Organ failure was measured by means of the score on the Sequential Organ Failure Assessment (SOFA),[16] which grades the function of six organ systems on the basis of blood pressure and vasopressor requirements, oxygenation, platelet count, serum creatinine and bilirubin levels, and the score on the Glasgow Coma Scale. We evaluated the patients' disease severity on the Acute Physiology and Chronic Health Evaluation (APACHE) II, with scores that range from 0 to 71, with higher scores indicating an increased risk of death.

On the basis of potential adverse effects reportedly associated with vitamin C therapy,[17-20] we recorded the incidence of stage 3 acute kidney injury,[17,18] acute hemolysis,[19] and hypoglycemia[20] as safety outcomes. All unexpected serious adverse events (i.e., those neither prespecified nor included as outcomes) that were considered by the investigator to be at least possibly related to a trial procedure were reported to the trial coordinating center within 24 hours and were subsequently investigated and reported to the data and safety monitoring board and to Health Canada, the governmental department responsible for Canadian health policy.

### STATISTICAL ANALYSIS

On the basis of the results of a clinical trial involving a similar population,[21] we anticipated that the risk of death at 28 days or persistent organ dysfunction in the control group would be approximately 50%. Thus, the enrollment of 385 patients per group would provide the trial with 80% power to detect an absolute between-group difference of 10 percentage points in the risk of this outcome with a two-sided type I error rate (alpha) of 0.05. To account for withdrawal of consent and loss to follow-up, we planned to enroll 400 patients per group. On April 23, 2020, the steering committee notified the data and safety monitoring board and Health Canada that patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who fulfilled the eligibility criteria would be offered participation in the trial. We inflated the sample size to ensure that the trial included the originally intended number of patients without SARS-CoV-2 infection.

The primary analysis was performed in the intention-to-treat population to assess the superiority of vitamin C over placebo, according to the assigned trial group. We estimated the risk ratio and 95% confidence interval for the primary outcome in a generalized linear mixed model with binomial distribution and a log-link function, with trial site considered as a random effect.[22] In a secondary analysis of the primary outcome, we adjusted for prespecified baseline characteristics (age, sex, APACHE II score,[23] baseline receipt of glucocorticoids, and time from ICU admission to randomization) using generalized estimating equations.

In other prespecified secondary analyses, we compared mortality at 28 days in unadjusted and adjusted models by applying the same variables that were used in analyzing the primary out-

come. We compared 6-month survival using a Cox model and compared the number of days free of organ dysfunction in the ICU up to day 28 using a cumulative distribution function, with death at 28 days coded as minus one. In addition, we compared SOFA scores during the first 7 days using a linear mixed model that included time, group interaction, and biomarkers according to constrained longitudinal data analysis.[24] For SOFA scores after day 7, we evaluated between-group differences in means and imputed scores for patients who had died or had been discharged before day 7. For safety outcomes, we reported the number of each prespecified safety outcome (after adjudication in the case of hemolysis) and unexpected serious adverse events in each trial group. We report treatment-effect estimates as risk ratios or differences in means or medians as appropriate, with no adjustment for multiple comparisons.

Analyses excluded one patient for whom outcome data were missing after withdrawal of consent for follow-up. We conducted best case–worst case unadjusted sensitivity analyses of death as a component of the primary outcome and as a secondary outcome.

The data and safety monitoring board reviewed the results of two planned interim analyses (after 248 and 525 patients had completed follow-up for the primary outcome) and recommended continuation of the trial. Details regarding all statistical analyses are provided in the protocol[12,13] and the Supplementary Appendix). At the time of this report, all the trial investigators remained unaware of the results of the interim analyses.

We prespecified the subgroup analyses of the primary outcome according to age (<65 years or ≥65 years), sex, frailty (according to a score on the Clinical Frailty Scale[25] of 1 to 4 or ≥5), severity of illness (the quartile of predicted risk of death on the basis of the baseline APACHE II score), presence of septic shock (defined as the use of a vasopressor infusion to maintain a mean arterial pressure of ≥65 mm Hg and the presence of a lactate level of ≥2 mmol per liter[1] vs. the use of vasopressor infusion alone), and the quartile of the baseline vitamin C level (as measured by liquid chromatography–tandem mass spectrometry). We hypothesized that vitamin C would be more beneficial in elderly patients, in those with greater frailty and illness severity at baseline, in those who met strict criteria for septic shock, and in those with a lower baseline vitamin C level. After modifying the protocol to permit the enrollment of patients with SARS-CoV-2, we added a subgroup analysis comparing the effect of vitamin C in patients with and without SARS-CoV-2 that was based on the hypothesis of no difference in treatment effect. In addition, we assessed the credibility of apparent subgroup effects.[26]

**Figure 1 (facing page). Enrollment and Randomization.**
Immediately after randomization but before receiving any dose of either vitamin C or placebo, 8 patients were found to be ineligible and were removed from the trial after blinded adjudication by two steering-committee members. Of these patients, 1 underwent randomization under deferred consent but regained sufficient capacity to decline consent; 5 patients had surrogate decision makers who initially gave and then withdrew consent, 1 patient was found to be allergic to vitamin C, and 1 patient was enrolled in error in a different study using the same randomization system. In addition, 1 patient withdrew consent after receiving the trial infusion. This patient remained part of the trial population according to the intention-to-treat principle. G6PD denotes glucose-6-phosphate dehydrogenase, ICU intensive care unit, and IV intravenous.

## RESULTS

### PATIENTS

From November 14, 2018, to July 19, 2021, we enrolled 872 patients; of these patients, 8 underwent randomization in error and 1 withdrew consent, which left 863 patients in the primary analysis population (429 in the vitamin C group and 434 in the placebo group) (Fig. 1).

The characteristics of the patients at baseline were similar in the two groups (Table 1 and Table S1 in the Supplementary Appendix). Overall, 96.7% of the patients received at least 90% of the scheduled doses of vitamin C or placebo (Table S2). The patients' median stay was 6 days (interquartile range [IQR], 3 to 12) in the ICU and 16 days (IQR, 8 to 32) in the hospital. The use and duration of cointerventions and life-sustaining therapies during the course of the ICU stay were similar in the two groups (Tables S3 and S4). The groups had similar urine output and fluid balance during the first 7 days in the ICU (Table S5).

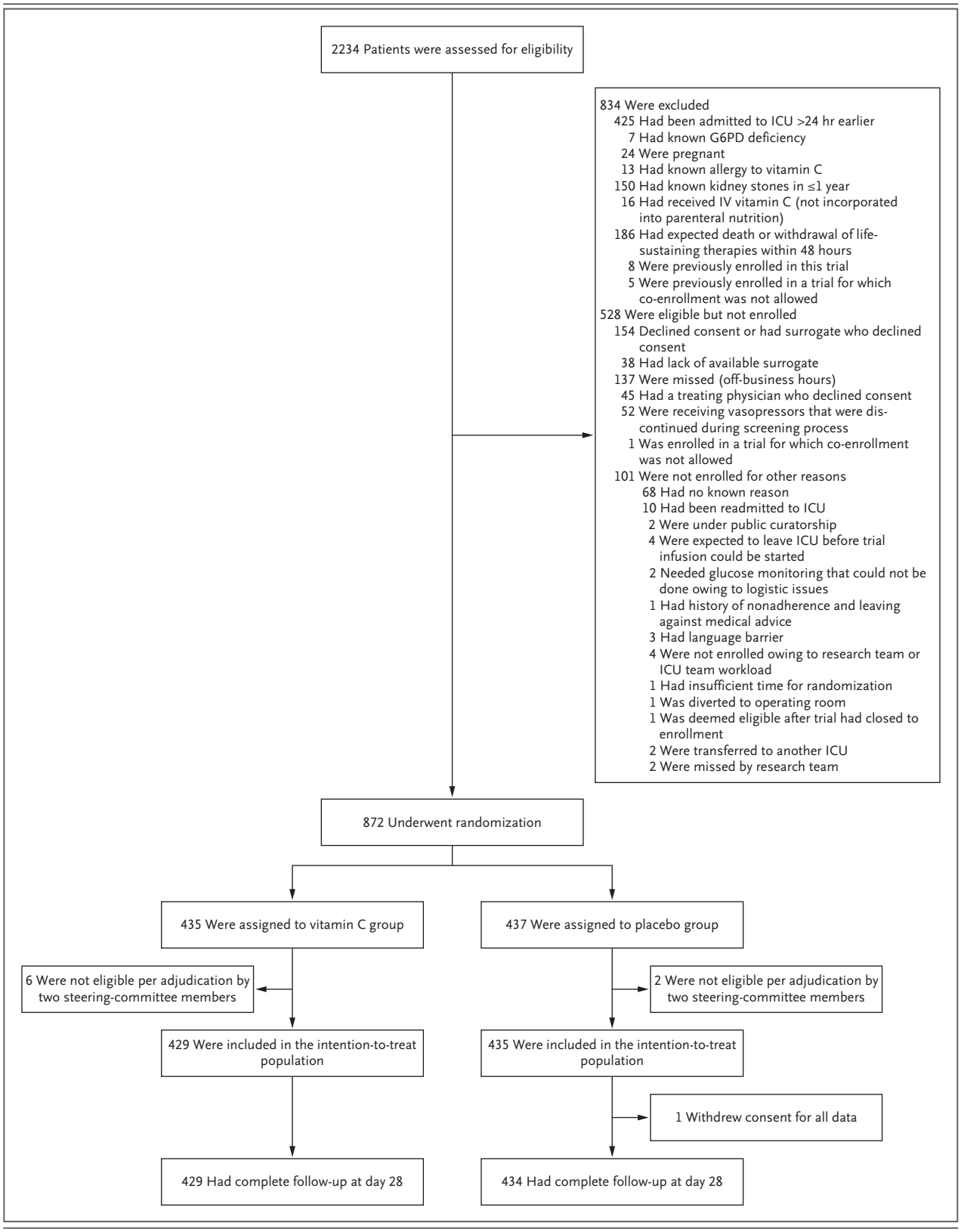

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Vitamin C (N=429) | Placebo (N=433)† |
|---|---|---|
| Age — yr | 65.0±14.0 | 65.2±13.8 |
| Female sex — no. (%) | 151 (35.2) | 173 (40.0) |
| Admission type — no. (%)‡ | | |
| Medical | 350 (81.6) | 369 (85.2) |
| Emergency surgery | 69 (16.1) | 59 (13.6) |
| Elective surgery | 10 (2.3) | 5 (1.2) |
| APACHE II score§ | 24.2±7.4 | 24.1±7.9 |
| SOFA score¶ | 10.2±3.4 | 10.1±3.7 |
| Score on Clinical Frailty Scale‖ | 3.8±1.4 | 3.9±1.4 |
| 1 to 4 — no. (%) | 312 (72.7) | 308 (71.3) |
| ≥5 — no. (%) | 117 (27.3) | 124 (28.7) |
| Primary site of infection — no. (%)** | | |
| Pulmonary | 145 (33.8) | 159 (36.7) |
| Gastrointestinal or intra-abdominal | 133 (31.0) | 112 (25.9) |
| Blood | 55 (12.8) | 59 (13.6) |
| Skin or soft tissue | 55 (12.8) | 62 (14.3) |
| Urinary | 49 (11.4) | 55 (12.7) |
| Central nervous system | 2 (0.5) | 4 (0.9) |
| Other | 30 (7.0) | 27 (6.2) |
| SARS-CoV-2 positive — no. (%)†† | 37 (8.6) | 26 (6.0) |
| Lactate — mmol/liter‡‡ | 3.4±3.2 | 3.0±2.8 |
| Vitamin C — μmol/liter§§ | 20.6±70.6 | 19.1±39.7 |
| Septic shock definition met — no./total no. (%)¶¶ | 195/327 (59.6) | 183/326 (56.1) |
| Time from ICU admission to randomization — hr | 12.9±8.2 | 12.3±6.7 |
| Treatment — no. (%) | | |
| Glucocorticoid‖‖ | 199 (46.4) | 196 (45.4) |
| Mechanical ventilation | 294 (68.5) | 283 (65.4) |
| Renal-replacement therapy | 46 (10.7) | 42 (9.7) |
| Vasopressor infusion*** | 428 (99.8) | 433 (100) |

* Plus–minus values are means ±SD.
† One additional patient underwent randomization under deferred consent and died before consent was obtained. The research ethics board allowed the inclusion of this patient only in the primary analysis.
‡ Patients with emergency or elective surgical admission came to the intensive care unit (ICU) from the operating room or postanesthetic care unit.
§ Scores on the Acute Physiologic and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater disease severity and a higher risk of death.
¶ Scores on the Sequential Organ Failure Assessment (SOFA) were calculated from the worst values corresponding to six organ systems on day 1 (day of randomization). As such, the worst values could precede or follow randomization and the first trial infusion. Scores range from 0 to 24, with higher scores indicating more severe organ dysfunction.
‖ Scores on the Clinical Frailty Scale range from 1 to 9, with higher scores indicating greater frailty. One patient in the placebo group had missing data.
** Patients could have more than one site of infection.
†† In these patients, coronavirus disease 2019 was confirmed or suspected at baseline and subsequently confirmed.
‡‡ Data were available for 653 patients (327 in the vitamin C group and 326 in the placebo group).
§§ The normal value for vitamin C in plasma is 22.4 μmol per liter (range, 13.6 to 32.9).[18] Data were available for 646 patients (324 in the vitamin C group and 322 in the placebo group).
¶¶ The definition for septic shock included the requirement for a vasopressor infusion and a lactate level of at least 2 mmol per liter.
‖‖ Data were missing for 1 patient in the placebo group.
*** Vasopressor infusion was discontinued in 1 patient between the time that consent had been obtained and randomization.

**Table 2. Primary and Secondary Outcomes.***

| Outcome | Vitamin C | Placebo | Treatment Effect (95% CI)† |
|---|---|---|---|
| **Primary** | | | |
| Death or persistent organ dysfunction at 28 days — no./total no.(%)‡ | 191/429 (44.5) | 167/434 (38.5) | 1.21 (1.04 to 1.40) |
| Death | 152/429 (35.4) | 137/434 (31.6) | 1.17 (0.98 to 1.40) |
| Persistent organ dysfunction§ | 39/429 (9.1) | 30/434 (6.9) | 1.30 (0.83 to 2.05) |
| Vasopressor use | 8/429 (1.9) | 6/434 (1.4) | 1.36 (0.48 to 3.85) |
| Mechanical ventilation | 25/429 (5.8) | 19/434 (4.4) | 1.31 (0.74 to 2.30) |
| Renal-replacement therapy | 24/429 (5.6) | 18/434 (4.1) | 1.35 (0.73 to 2.5) |
| **Secondary** | | | |
| Median no. of days without organ dysfunction in the ICU by day 28 (IQR)¶ | 17 (–1 to 25) | 19.5 (–1 to 25) | –2.43 (–7.23 to 2.37) |
| Death by 6 mo — no./total no. (%)‖ | 191/417 (45.8) | 185/426 (43.4) | 1.14 (0.93 to 1.39) |
| EQ-5D-5L score at 6 mo¶** | | | |
| Score on visual-analogue scale | 65.8±20.9 | 63.8±22.5 | 2.04 (–1.97 to 6.05) |
| Median dimension score (IQR) | | | |
| Mobility | 2 (1–3) | 2 (1–3) | –0.19 (–0.43 to 0.04) |
| Self-care | 1 (1–2) | 1 (1–2) | –0.07 (–0.29 to 0.15) |
| Usual activities | 2 (2–4) | 2 (2–3) | 0.02 (–0.23 to 0.28) |
| Pain or discomfort | 2 (1–3) | 2 (1–3) | 0.00 (–0.19 to 0.18) |
| Anxiety or depression | 1 (1–2) | 2 (1–2) | –0.08 (–0.24 to 0.09) |
| SOFA score¶†† | | | |
| Day 1 (N=862) | 10.2±3.4 | 10.1±3.7 | 0.05 (–0.42 to 0.53) |
| Day 2 (N=862) | 9.9±5.2 | 9.5±5.1 | 0.39 (–0.30 to 1.07) |
| Day 3 (N=861) | 9.2±6.0 | 9.0±6.0 | 0.23 (–0.57 to 1.03) |
| Day 4 (N=861) | 8.7±6.5 | 8.7±6.6 | –0.03 (–0.90 to 0.85) |
| Day 7 (N=862) | 9.0±7.9 | 8.3±7.3 | 0.66 (–0.35 to 1.67) |
| Day 10 (N=277) | 7.5±4.4 | 7.5±3.9 | 0.05 (–0.94 to 1.05) |
| Day 14 (N=191) | 7.4±4.2 | 7.3±4.2 | 0.07 (–1.12 to 1.26) |
| Day 28 (N=56) | 6.5±3.8 | 7.9±5.7 | –1.42 (–3.98 to 1.14) |
| **Safety outcomes — no./total no. (%)‡‡** | | | |
| Stage 3 acute kidney injury | 162/429 (37.8) | 164/433 (37.9)§§ | 1.00 (0.85 to 1.19) |
| Acute hemolysis¶¶ | 0 | 0 | NA |
| Hypoglycemia | 26/429 (6.1) | 22/433 (5.1)§§ | 1.25 (0.73 to 2.14) |
| Serious adverse events | 1/429 (0.2)‖‖ | 0 | NA |

* Plus–minus values are means ±SD. IQR denotes interquartile range, and NA not applicable.
† The treatment effect is a risk ratio unless otherwise indicated. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.
‡ P=0.01 for this comparison.
§ The analysis of the individual components of persistent organ dysfunction was added post hoc. Patients could have more than one component.
¶ The treatment effect in this category is the between-group difference.
‖ The treatment effect in this category is a hazard ratio.
** Scores on the EQ-5D-5L instrument range from 1 to 5, with higher scores indicating greater impairment or worse function. Scores on the visual-analogue scale in that instrument range from 0 to 100, with higher scores indicating better health status. Data were available for 222 patients in the vitamin C group and for 233 in the placebo group.
†† Missing SOFA scores for days 1 to 7 were imputed according to the statistical analysis plan, with the exception of one patient on days 3 and 4 because of withdrawal of consent.
‡‡ Additional data regarding safety outcomes are provided in Table S8 in the Supplementary Appendix.
§§ One patient who had undergone randomization under deferred consent died before consent was obtained. The research ethics board allowed the inclusion of this patient only in the primary analysis.
¶¶ Included in this category are the results of adjudicated events.
‖‖ An anaphylactic reaction in this patient was considered by the investigator to be possibly related to the vitamin C infusion.

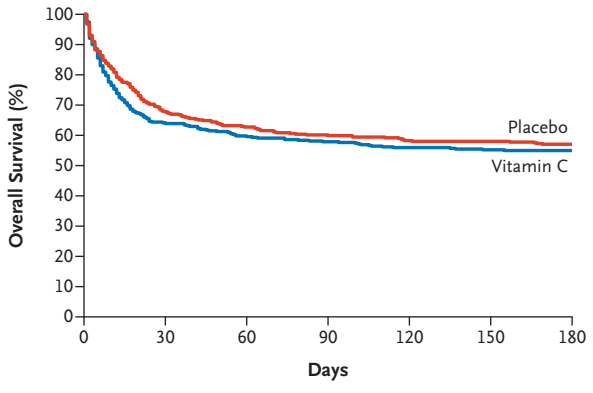


**Figure 2. Kaplan–Meier Analysis of Survival at 6 Months.**

Shown is the percentage of patients who were alive at the 6-month follow-up (226 patients [54.2%] in the vitamin C group and 241 [56.6%] in the placebo group), which was a secondary outcome in the trial.

### PRIMARY OUTCOME

At day 28, 191 of 429 patients (44.5%) in the vitamin C group had died or had persistent organ dysfunction, as compared with 167 of 434 patients (38.5%) in the placebo group (risk ratio, 1.21; 95% confidence interval [CI], 1.04 to 1.40; P=0.01) (Table 2). In the analysis performed after adjustment for prespecified baseline characteristics, the risk ratio for the primary comparison was 1.15 (95% CI, 0.90 to 1.47) (Table S6). In the best case–worst case sensitivity analyses that accounted for the single patient with unknown status regarding the primary outcome, the results were similar to those in the primary analysis.

### SECONDARY OUTCOMES

At 28 days, death had occurred in 152 patients (35.4%) in the vitamin C group and in 137 patients (31.6%) in the placebo group (risk ratio, 1.17; 95% CI, 0.98 to 1.40). The median number of days without organ dysfunction at day 28 was 17 in the vitamin C group and 19.5 in the placebo group (median difference, –2.43 days; 95% CI, –7.23 to 2.37) (Table 2 and Fig. S1). We observed no material differences between groups in SOFA scores (Fig. S2), biomarkers (Table S7), 6-month survival (Fig. 2), or health-related quality of life (Table 2).

### SAFETY OUTCOMES AND SUBGROUP ANALYSES

We observed no material between-group differences in the prespecified safety outcomes (Table 2). There were 4 adverse events in the vitamin C group and 1 in the placebo group (Table S8). In the vitamin C group, 1 patient had a serious adverse event of anaphylaxis and another had a severe hypoglycemic episode[27] that triggered a protocol amendment requiring modifications in blood-glucose monitoring in many centers. There was no evidence of credible subgroup effects (Fig. 3 and Table S9).

## DISCUSSION

In this international, randomized, placebo-controlled clinical trial involving adults with sepsis who were receiving vasopressor infusions in the ICU, the composite primary outcome (death or persistent organ dysfunction at trial day 28) occurred more frequently in patients who had received intravenous vitamin C than in those who had received placebo. This was an unexpected finding, and the secondary analyses — which included the evaluation of five biomarkers of tissue dysoxia, inflammation, and endothelial injury measured up to day 7 — did not determine a putative mechanism for harm.

Our findings differ from those of recent meta-analyses of vitamin C monotherapy,[8,11] which included two smaller randomized trials evaluating the same vitamin C regimen as was used in our trial.[10,28] The first of these was a dose-finding trial[28] involving 24 patients with severe sepsis who were randomly assigned to receive vitamin C at a dose of either 12.5 mg or 50 mg per kilogram or placebo every 6 hours for 4 days.[28] The higher-dose vitamin C regimen was associated with a reduction in SOFA scores during a 96-hour period. In the second trial (Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury [CITRIS-ALI]),[10] 167 patients with sepsis and acute respiratory distress syndrome were randomly assigned to receive vitamin C (50 mg per kilogram) or placebo every 6 hours for 4 days. SOFA scores during a 96-hour period were similar in the two groups without accounting for the competing risk of death, but 28-day mortality was significantly lower in the vitamin C group. As in our trial, in the CITRIS-ALI trial, patients had undergone randomization within 24 hours

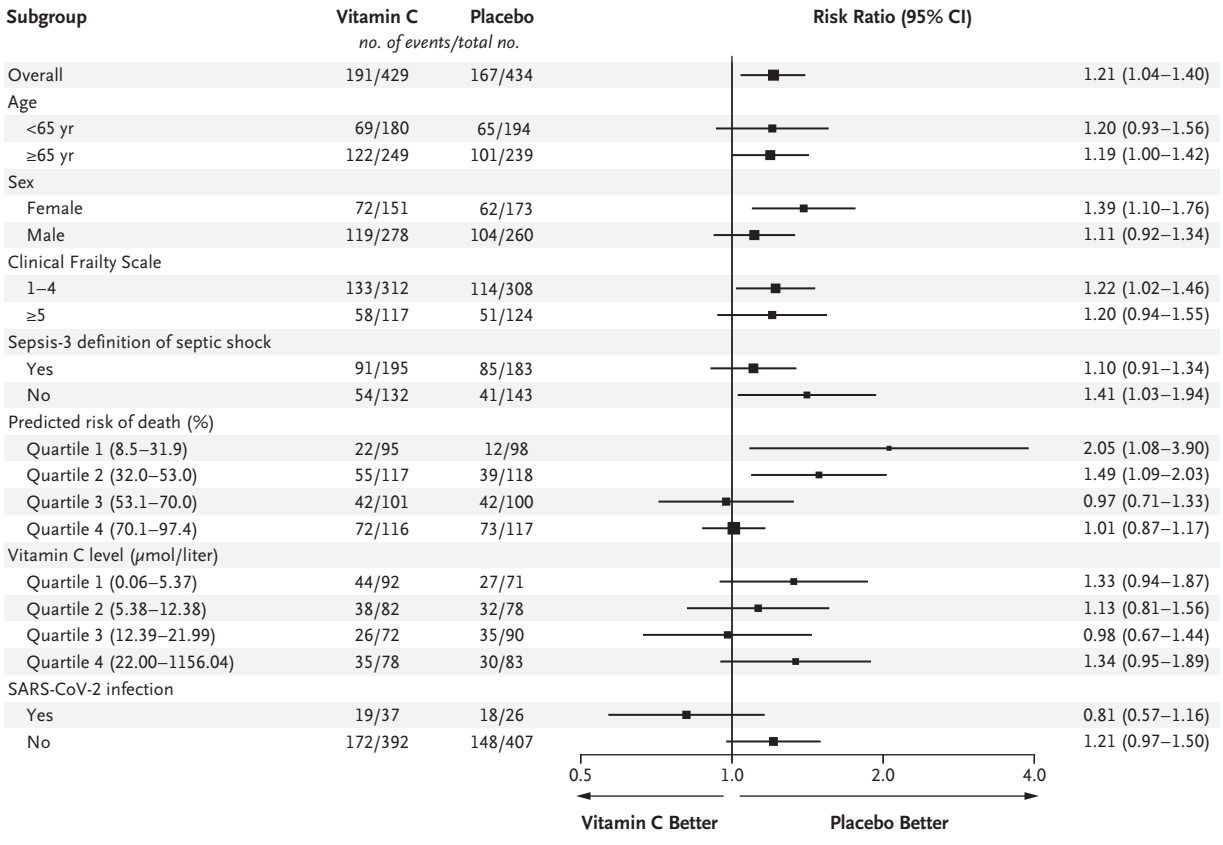


**Figure 3. Subgroup Analyses.**

Shown is a forest plot of the primary outcome in prespecified subgroups. Risk ratios are based on generalized linear mixed models after adjustment for trial site, assigned group, subgroup, and the interaction between subgroup and assigned group. For the subgroup with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a generalized estimating equation was used because the generalized linear mixed model did not converge. The score on the Clinical Frailty Scale was missing for one patient in the placebo group. Statistical tests for interaction appear in Table S9. Confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible. The predicted risk of death was estimated on the basis of the patient's score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, on which higher scores indicate an increased risk of death. Higher scores on the Clinical Frailty Scale indicate more severe frailty. Sepsis-3 denotes the Third International Consensus Definitions for Sepsis and Septic Shock.

after eligibility had been confirmed. However, in our trial, patients did not need to have severe respiratory failure and may have been recruited earlier relative to the onset of sepsis and peak oxidative stress than were the patients in the CITRIS-ALI trial. In our trial, vitamin C was administered within 4 hours after randomization, as compared with 6 hours in the CITRIS-ALI trial.

One plausible explanation for the divergent findings regarding mortality is that large effect estimates from smaller trials may occur by chance.[29] Differences in baseline characteristics, such as the presence of respiratory failure or receipt of vasopressors, may also explain such differences. Such knowledge gaps may be addressed in ongoing trials of vitamin C in patients with SARS-CoV-2 infection (ClinicalTrials.gov numbers NCT02735707 and NCT04401150) and in those with acute respiratory distress syndrome (EudraCT number, 2020-003923-40).

The primary outcome in our trial, a composite of death or persistent organ dysfunction, included death to address the competing-risk issue.[14] Vitamin C had a consistent effect across all elements of the composite outcome and on 6-month

mortality. These factors, in addition to increased statistical efficiency, mitigate the disadvantages of using a composite outcome.[30,31] Other strengths of our analyses include blinding to limit ascertainment bias, a median enrollment time of approximately 12 hours after ICU admission, high protocol adherence, ascertainment of the renal-replacement therapy component of the primary outcome in patients who were discharged from the hospital before day 28, and assessment of biomarkers and baseline vitamin C levels.

However, the trial also has several limitations. Nine patients who had undergone randomization did not contribute data to the primary analysis; of these patients, eight had not received either vitamin C or placebo and had met the prespecified criteria for exclusion after randomization.[32] Only one patient who withdrew consent could not be included in the intention-to-treat analysis. Given the high number of events that were recorded in each group, the effect of these exclusions is probably small. Information regarding specific pathogens and the appropriateness of antimicrobial therapy was not collected; however, systematic differences in postrandomization care are less likely in blinded trials. Information to ascertain the presence of acute respiratory distress syndrome at baseline was not collected, so it remains unclear whether this subgroup had a different response to vitamin C. Although the patients were representative of those with sepsis being treated in the ICU in many high-income countries, the trial population differs substantially from patients in many low- and middle-income countries, where the incidence of sepsis and the associated case fatality rate are highest (Table S10).[3]

In adults with sepsis who were receiving vasopressor therapy in the ICU, the receipt of intravenous vitamin C resulted in a higher risk of death or persistent organ dysfunction at 28 days than the receipt of placebo.

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## APPENDIX

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