Intensive Care Med
https://doi.org/10.1007/s00134-026-08492-5

ORIGINAL

Early high-dose vitamin C for out-of-hospital cardiac arrest: the VITaCCA randomized clinical trial

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Abstract

Background: Besides temperature management, there is currently no effective therapy to decrease the burden of post-cardiac arrest syndrome. The pleiotropic effects of vitamin C may improve clinical outcome.

Purpose: This trial investigated whether early administration of 3 g or 10 g intravenous vitamin C attenuated organ dysfunction post-cardiac arrest.

Methods: In this double-blind, multi-center, phase 2 trial, comatose adults resuscitated from shockable out-of-hospital cardiac arrest randomly received intravenously placebo, supplementary (3 g) or supraphysiological dose (10 g) vitamin C daily for 96 h. The primary endpoint was the 96 h change in the resuscitation-sequential organ failure assessment (R-SOFA) score. Secondary endpoints included neurological outcome, myocardial injury, vasopressor- and ventilator-free days, renal function, ICU-acquired weakness, delirium, length of ICU and hospital stay, and 28- and 180-day mortality.

Results: 273 patients (93 on placebo, 91 on 3 g and 89 on 10 g) were included in the primary analysis. Mean (SD) change in R-SOFA score at 96 h was −3.2 (5.7) in the placebo group, −2.3 (7.4) in the 3 g group, and −0.8 (7.6) in the 10 g group ($p=0.04$ for overall difference). 10 g vitamin C resulted in 2.5 points less improvement in R-SOFA score compared with placebo (95% CI 0.5–4.5; $p=0.01$), and 1.6 points less improvement compared with 3 g vitamin C (95% CI −0.4 to 3.6; $p=0.12$). Vitamin C 10 g led to higher troponin T release, worse renal function and worse neurological outcomes.

Conclusion: In out-of-hospital cardiac arrest patients, intravenous vitamin C did not reduce organ dysfunction at 96 h, but even worsened organ function outcomes in the 10 g group.

Trial registration: NCT03509662.

Keywords: Cardiac arrest, Ischemia–reperfusion injury, Reactive oxygen species, Oxidative stress, Vitamin C, Ascorbic acid

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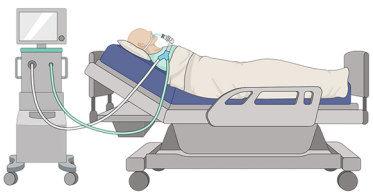
Visual abstract:

EARLY HIGH-DOSE VITAMIN C FOR OUT-OF-HOSPITAL CARDIAC ARREST

The VITaCCA Randomized Clinical Trial



Placebo, n = 93

Vitamin C IV 3 g/day, n = 91
(Supplementation dose)

Vitamin C IV 10 g/day, n = 89
(Pharmacological dose)

Background

Vitamin C may reduce organ dysfunction after cardiac arrest.

Study design

Phase 2 double-blind RCT in 273 comatose out-of-hospital cardiac arrest patients with shockable rhythm.

Key Findings

- Intravenous vitamin C **did not reduce** organ dysfunction.
- The pharmacological dose (10 g/day) led to **less improvement in organ function** at 96 hours, compared with placebo.
- The pharmacological dose was associated with **more harm**: higher Troponin T levels, worse renal and neurological outcomes.
- **Dose-response relationship** with supplementation dose (3 g/day) yielding clinical outcomes between placebo and pharmacological dose.

Clinical implications

- Findings suggests safety concerns in a new population.
  The signal of harm should prompt caution among clinicians and researchers.
- No benefit from supplementation dose, challenging current guideline recommendations that endorse routine supplementation.

Rozemeijer, S., Dubois, E. A., de Grooth, HJ., *et al.* Early High-Dose Vitamin C for Out-of-Hospital 1 Cardiac Arrest: The VITaCCA Randomized Clinical Trial. *Intensive Care Med (2026)*. https://doi.org/**10.1007/s00134-026-08492-5**

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Introduction

Morbidity and mortality among out-of-hospital cardiac arrest patients remain very high due to the post-cardiac arrest syndrome [1], for which treatment is currently only limited to targeted temperature management and supportive care, with no pharmacological interventions having demonstrated benefit in clinical trials [2]. Overwhelming oxidative stress after whole-body ischemia–reperfusion decrease vitamin C plasma concentrations rapidly [3, 4]. Intravenous administration of vitamin C 2–3 g/day normalizes plasma vitamin C concentrations, whereas 10 g/day achieves supraphysiological concentrations [5].

Vitamin C reduces oxidative stress [6], improves endothelial function [7] and may improve myocardial perfusion and function [8, 9]. Several preclinical studies suggest beneficial effects in post-cardiac arrest models [10], although the results are not uniform. Clinical evidence is also limited [11, 12].

Large amounts of reactive oxygen species (ROS) are produced directly after ROSC [13]. Though guidelines recommend against the use of pharmacological doses vitamin C in the heterogenous ICU-population [14], a homogenous post-cardiac arrest patient population with known onset of ischemia–reperfusion and oxidative stress may be more suitable for pharmacologic dosages of vitamin C [15].

The VITaCCA (early VITamin C post-Cardiac Arrest) trial investigates the effect of a supplementary (3 g) and pharmacological (10 g) dose of intravenous vitamin C as compared with placebo on organ dysfunction, initiated early after ROSC in shockable out-of-hospital cardiac arrest patients.

Take-home message

Our trial suggests safety concerns in a new population. The signal of harm observed here, now extending across three distinct patient groups (sepsis, COVID-19, and cardiac arrest), should prompt caution among clinicians and researchers and may have consequences for currently ongoing vitamin C trials. Furthermore, our trial showed no benefit from supplementation dose, challenging current guideline recommendations that endorse routine supplementation.

Methods

Study design

VITaCCA is a multicenter, double-blind, randomized, placebo-controlled, phase 2 trial, conducted at two academic medical centers and four general hospitals in the Netherlands. Funding was provided by the Netherlands Organization for Health Research and Development. Patients' organizations were involved in the design of the trial. The published trial protocol [16] is available in Supplement 1. The statistical analysis plan (SAP) (published prior to unblinding at clinicaltrials.gov/study/NCT03509662) is available in Supplement 2.

The trial was conducted in accordance with the Declaration of Helsinki. The trial protocol was approved by an independent ethics committee of Amsterdam UMC, location VUmc, prior to study initiation (Record METC-2018.120). The independent monitor and the data and safety monitoring board (DSMB), ensured adequate oversight of the trial. The last patient was enrolled on 11 February 2024, and follow-up ended on 29 August 2024. The database was closed on 15 July 2025. On 16 July 2025, the pharmacy first shared the blinded allocation list (intervention A, B or C) to enable us to perform blinded primary analyses. Subsequently, on 24 July 2025, the pharmacy shared the unblinded treatment allocation list.

Trial participants

Adult ($\geq$18 years) patients, who suffered an out-of-hospital cardiac arrest with an initial shockable rhythm and a Glasgow Coma Scale $\leq$8 were eligible for inclusion after ROSC. Exclusion criteria were terminal renal insufficiency, known glucose-6-phosphate dehydrogenase deficiency, urolithiasis, oxalate nephropathy, hemochromatosis, and treatment limitations at randomization (eMethods 1 in Supplement 3). The first dose of study medication had to be administered < 5 h after ROSC.

A deferred proxy consent procedure was used (eMethods 2 in Supplement 3). Written consent had to be obtained < 72 h after ICU-admission, but was waived when patients died < 72 h and consent had not been obtained yet.

Post-cardiac arrest care and prognostication of comatose cardiac arrest survivors, including treatment limitation decisions, was delivered in accordance with current national and international guidelines [17–19] (eMethods 3 in Supplement 3).

Randomization

Randomization occurred as soon as possible after Emergency Department arrival. Participants were allocated 1:1:1 via a computer-generated randomization list, created by the pharmacy of Amsterdam UMC. Randomization used permuted block sizes of 6 and was stratified by site and age ($\leq$66 and > 66 years). Randomization was performed by a pharmacy assistant or a nurse not involved in the direct clinical care of the included patient.

Intervention

Patients received intravenous L-ascorbic acid (ampoules 100 mg/mL Centrafarm, Etten-Leur, the Netherlands in 50 mL 0.9% NaCl) every 12 h: 5 g (10 g group), 1.5 g (3

g group), or 0 g (placebo group). Intervention was continued for 4 days, unless ICU discharge occurred earlier. All patients received intravenous thiamine 200 mg every 12 h for 4 days, unless ICU discharge occurred earlier, to limit endogenous oxalate production [20]. The study medication was prepared by unblinded personnel in a 50 mL amber-colored syringe connected to an orange infusion line, and infused by blinded nurses in 15 min. Higher dosages of thiamine were permitted if clinically indicated. The patients, physicians, nurses, and researchers involved were all blinded to the allocated treatment during the entire study period.

Outcomes

The primary outcome was the change in resuscitation-sequential organ failure assessment (R-SOFA) score measured at baseline and 96 h after randomization (eMethods 4 in Supplement 3). Death at 96 h was counted as the maximum R-SOFA score (24 points). R-SOFA is similar to the classical SOFA score [16], but only taken earlier, before study intervention, to enable

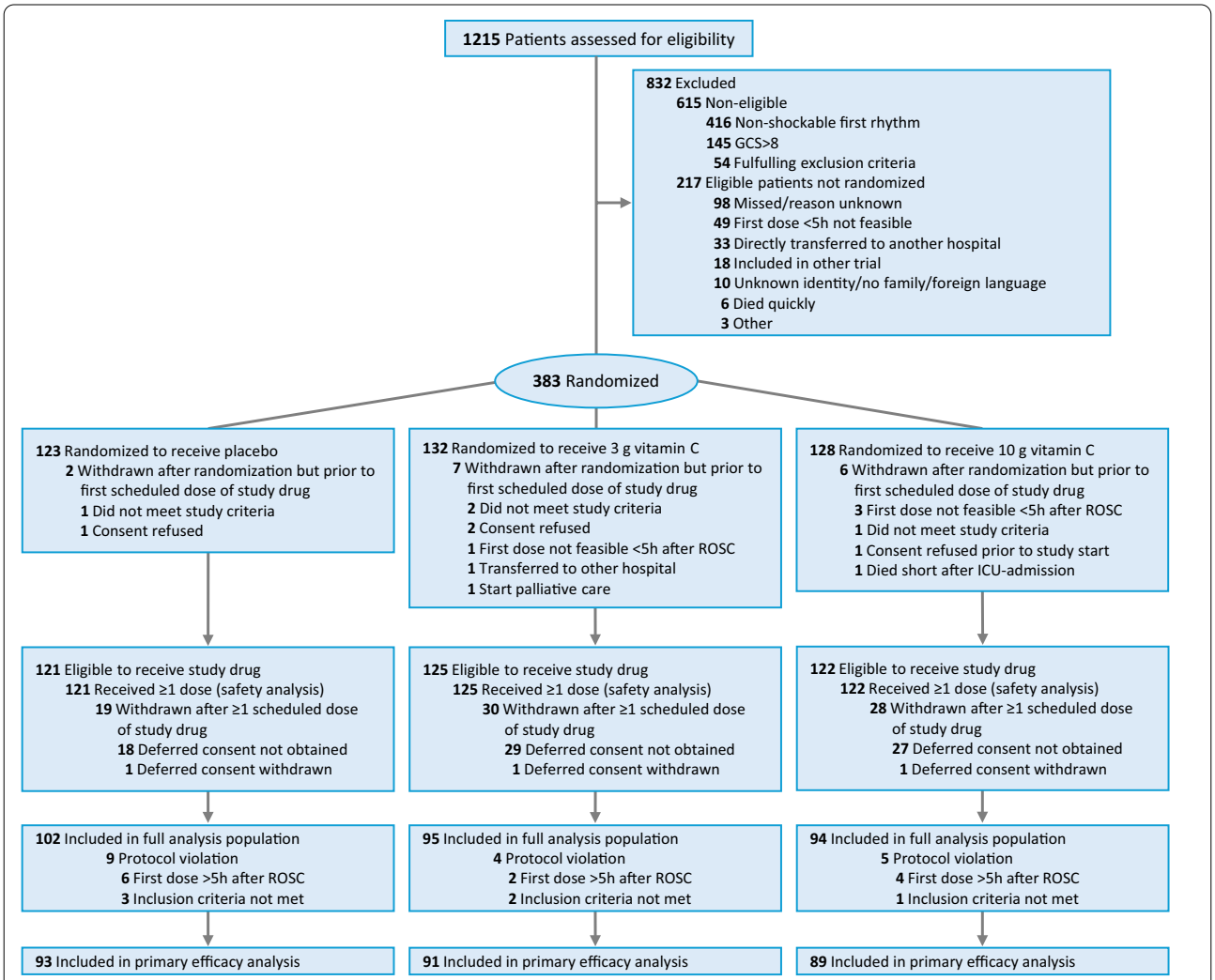

Fig. 1 Flow of participants in the VITaCCA trial. If a post-cardiac arrest patient met the study criteria and if it was feasible to administer the first dose of study medication < 5 h after return of spontaneous circulation, the patient was randomized and assigned to one of the three intervention groups. Some randomized patients did not receive any dose because they were excluded by physicians shortly after randomization (prior to study initiation) in order to prevent the inclusion of non-eligible patients or the administration of a delayed first dose. If deferred consent was not obtained < 72 h or withdrawn later, the patient was excluded. All randomized and treated (at least one dose) patients were included in the safety analysis. In case of obtained deferred consent all patients were included in the full analysis population. Patients who received the first dose more than 5 h after return of spontaneous circulation or who did not fulfill the inclusion criteria after study initiation were subsequently excluded from the modified intention-to-treat population

Table 1 Baseline characteristics of the modified intention-to-treat population

Characteristic	No. (%)		
	Placebo (n = 93)	3 g vit C (n = 91)	10 g vit C (n = 89)
Age, mean (SD), y	62 (13)	64 (11)	63 (12)
Male sex	74 (80)	78 (86)	76 (85)
Body mass index, median (IQR), kg/m^2	26.2 (24.2–30.9)	26.2 (23.2–29.2)	25.9 (24.2–27.9)
Medical history			
Diabetes	15 (16)	9 (10)	17 (19)
Myocardial infarction	22 (24)	28 (31)	21 (24)
Heart failure	4 (4)	10 (11)	7 (8)
Chronic Kidney Disease	0 (0)	2 (2)	5 (6)
COPD	2 (2)	11 (12)	6 (7)
Stroke	13 (14)	7 (8)	4 (4)
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	3 (1–4)
Characteristics of the cardiac arrest			
Bystander-witnessed cardiac arrest	72 (77)	76 (84)	73 (82)
Bystander-performed CPR	79 (85)	74 (81)	78 (88)
Shocks administered, median (IQR)	3 (2–4)	3 (2–6)	3 (2–5)
First rhythm			
Ventricular fibrillation	43 (46)	36 (40)	35 (39)
Ventricular tachycardia without pulse	1 (1)	0 (0)	2 (2)
AED usage, shock administered	49 (53)	55 (60)	52 (58)
Time from cardiac arrest to initiation of CPR, median (IQR), min	0 (0–3)	0.5 (0–4)	2 (0–5)
Time from cardiac arrest to sustained ROSC, median (IQR), min	15 (10–20)	16 (10–25)	15 (10–23)
Time from ROSC to first dose study medication, mean (SD), hours:min	3:35 (0:53)	3:23 (0:51)	3:28 (0:52)
Clinical characteristics on admission			
First measured pH, median (IQR)	7.24 (7.12–7.30)	7.22 (7.14–7.27)	7.20 (7.08–7.28)
Lactate level, first measured, median (IQR), mmol/L	6.3 (4.3–8.3)	5.9 (4.4–7.9)	6.8 (4.1–9.8)
ST-segment elevation myocardial infarction	33 (35)	27 (30)	37 (42)
Non-ST-segment elevation myocardial infarction	39 (42)	40 (44)	33 (37)
Glasgow Coma Scale, median (IQR)	3 (3–5)	3 (3–5)	3 (3–3)

AED automatic external defibrillator, *COPD* chronic obstructive pulmonary disease, *CPR* cardiopulmonary resuscitation, *ROSC* return of spontaneous circulation, *vit* vitamin

baseline assessment of organ failure in post-cardiac arrest patients. If taken during a 24 h period, the SOFA-score could already have been affected by the early administered vitamin C. Secondary endpoints included daily SOFA-scores, highest troponin T and creatine kinase MB level at day 1, vasopressor- and ventilator-free days, renal function, ICU-acquired weakness, delirium, length of ICU and hospital stay, neurological outcome, and 28- and 180-day mortality. The data collection points are summarized in a SPIRIT figure [16]. Safety outcomes included serious adverse events (SAEs) up to day 28 post-randomization (eTable 4 in Supplement 3).

Sample size calculation

Based on Amsterdam UMC data and a recent systematic review [21], change in R-SOFA score has an estimated standard deviation of 3.5 points. We posit that a 2.0-point difference in the change in R-SOFA score between the trial arms would be a clinically meaningful effect. Assuming 10% loss to follow-up, a sample size of 90 per group provided 90% power with a two-sided alpha of 0.01 to detect a 2.0-point difference in the change in R-SOFA score with vitamin C intervention. Results will be presented with effect sizes estimates and 95% confidence intervals (see the SAP in Supplement 2). A prespecified interim analysis for harm (mortality at day 28) was performed at mid-study by the trial statistician.

Statistical analysis

The planned analyses are described in detail in our SAP (Supplement 2). The change in R-SOFA score at 96 h

Table 2 Primary outcome modified intention-to-treat population

Outcome	Mean (SD)			p-value[a]	Est. difference (95% CI) 3 g vs. placebo[b]	p-value	Est. difference (95% CI) 10 g vs. placebo[b]	p-value
	Placebo (n = 93)	3 g vit C (n = 91)	10 g vit C (n = 89)					
Change in R-SOFA score	− 3.2 (5.7)	− 2.3 (7.4)	− 0.8 (7.6)	0.04	0.9 (− 1.1 to 2.9)	0.36	2.5 (0.5–4.5)	0.01

[a] p-value for the overall difference between groups in the linear mixed model, adjusted for age and baseline R-SOFA score

[b] Estimated difference in the linear mixed model, adjusted for age and baseline R-SOFA score

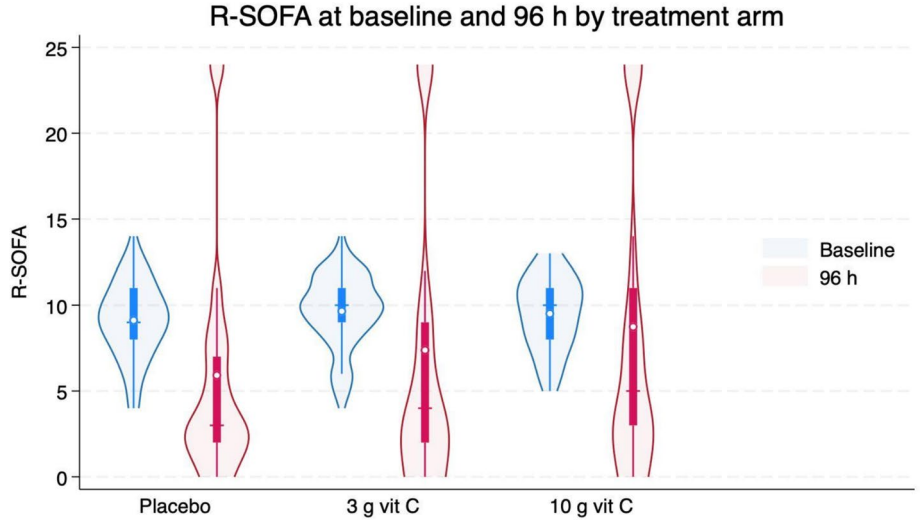

Fig. 2 Resuscitation-SOFA scores at baseline and 96 h. Violin plots display the estimated density of the R-SOFA scores at baseline and 96 h by treatment arm. The shading indicates the estimated probability density function of the R-SOFA score distribution; the horizontal line represents the median; the white dot shows the mean

between randomized groups was analyzed using linear mixed model analyses, with a random intercept for site and fixed effects for baseline R-SOFA score (to prevent regression to the mean) and age (stratification variable). Since the residuals were not normally distributed, the primary outcome was also rank transformed. Prior to full unblinding of the data, an abstract with blinded (treatment A, B or C) primary analysis results and blinded interpretation was sent to the DSMB (eAppendix 3 in Supplement 3).

The prespecified primary analyses were performed in the modified intention-to-treat population, which includes all randomized eligible patients who received the first dose of study medication < 5 h after ROSC (n = 273). The full analysis population (n = 291) also includes non-eligible patients and patients who did not receive the first dose on time. The same linear mixed model analyses were performed in the full analysis population. Analyses for safety events were performed in all randomized patients (exposed to at least one dose, regardless of consent (n = 368)). The trial populations are described in detail in eMethods 5. In the case of ICU-transfer < 96 h after randomization, R-SOFA score at 96 h was collected with patient consent from the hospitals involved. There were no missing data for the main efficacy analyses.

Prespecified additional analyses were adjustment for the time to sustained ROSC and first pH (key prognostic covariates) and effect modification with age and first pH. Two sensitivity analyses were performed: one excluding patients who died < 96 h at the ICU and one excluding randomized patients from whom the study treatment was discontinued prematurely.

For secondary outcomes, dichotomous outcomes were analyzed using logistic mixed model analyses, adjusted for site and age. Continuous outcomes were analyzed using linear mixed models analyses with a random intercept at the site level, adjusted for age. In case of repeated daily measures (SOFA score, creatinine and CRP), a random intercept at the participant level was additionally added to the mixed model, with time as categorial variable and time as interaction with the groups, also adjusted for baseline when applicable.

Table 3 Secondary outcomes of the modified intention-to-treat population

Outcome	Placebo (n = 93)	3 g vit C (n = 91)	10 g vit (n = 89)	Difference/OR (95% CI) 3 g vit C vs. placebo	Difference/OR (95% CI) 10 g vit C vs. placebo
Daily SOFA score, median (IQR)					
Day 1	10 (9–12)	10 (9–12)	10 (9–12)	−0.3 (−0.9 – 0.3)	0.1 (−0.5 – 0.7)
Day 2	8 (6–11)	9 (7–10)	9 (7–12)	−0.4 (−1.2 – 0.3)	0.5 (−0.3 – 1.2)
Day 3	6 (5–10)	7 (4–10)	8 (5–11)	−0.6 (−1.6 – 0.4)	0.9 (−0.04 – 1.9)
Day 4	6 (4–9)	7 (3–10)	8 (5–10)	−0.2 (−1.4 – 1.0)	0.8 (−0.3 – 2.0)
Neuron-specific enolase, median (IQR), ng/mL					
48 h	24.8 (18.9–30.7)	23.2 (16.2–40.2)	28.0 (19.4–41.3)	1.2 (−16.5 – 18.9)	3.3 (−13.6 – 20.2)
72 h	23.2 (18.5–36.8)	26.0 (19.7–58.6)	25.2 (17.3–57.1)	16.6 (−15.7 – 48.8)	13.6 (−16.7 – 43.9)
Maximum Glasgow Coma Scale at ICU-discharge, median (IQR)[a]	15 (14–15)	15 (14–15)	15 (14–15)	0.2 (−0.2 – 0.7)	−0.5 (−1.0 – 0.02)
Hs Troponin T, highest level day 1, median (IQR), ng/L	780 (298–2130)	1193 (462–2377)	1300 (381–5496)	172 (−1447 – 1791)	1926 (302 – 3551)[b]
CK-MB, highest level day 1, median (IQR), mcg/L	72.6 (14.4–300.0)	68.1 (20.2–199.8)	115 (27.6–336.0)	−33 (−110 – 45)	24 (−54 – 102)
Vasopressor duration, median (IQR), hours	38 (26–62)	38 (23–73)	37 (24–70)	1.9 (−9.8 – 13.7)	1.7 (−10.4 – 13.8)
Vasopressor-free days up to day 28, median (IQR)	25 (0–26)	25 (11–26)	25 (0–26)	0.1 (−3.3 – 3.6)	−3.2 (−6.7 – 0.4)
Ventilation duration, median (IQR), days	2.3 (1.3–4.7)	1.8 (1.2–2.9)	2.1 (1.3–4.8)	−0.1 (−1.3 – 1.1)	0.1 (−1.1 – 1.3)
Ventilation-free days up to day 28, median (IQR)	24 (0–26)	25 (6–26)	22 (0–26)	0.5 (−2.8 – 3.9)	−3.0 (−6.4 – 0.5)
Creatinine, median (IQR), µmol/L					
Day 1	87 (74–114)	102 (84–135)	104 (82–138)	4 (−16 – 25)	4 (−16 – 24)
Day 2	83 (70–114)	94 (73–130)	93 (72–148)	4 (−14 – 22)	8 (−10 – 26)
Day 3	83 (72–114)	86 (70–115)	81 (72–126)	−1 (−21 – 20)	12 (−8 – 33)
Day 4	84 (73–114)	83 (66–122)	78 (62–136)	−4 (−30 – 21)	23 (−2 – 47)
Need for renal replacement therapy, no. (%)[c]	1 (1)	2 (2)	8 (10)	2.1 (0.2 – 24.0)[e]	10.4 (1.2 – 87.0)[e]
C-reactive protein, median (IQR), mg/L					
Day 1	16 (7–41)	21 (8–44)	21 (8–47)	−2 (−10 – 7)	−2 (−10 – 7)
Day 2	90 (51–152)	105 (59–161)	126 (83–167)	12 (−7 – 31)	15 (−4 – 34)
Day 3	150 (86–205)	148 (84–194)	147 (97–227)	1 (−26 – 28)	−1 (−28 – 25)
Day 4	100 (67–191)	149 (74–218)	132 (91–180)	17 (−19 – 53)	−3 (−37 – 31)
Day 5	88 (41–217)	129 (87–219)	102 (72–173)	29 (−18 – 76)	−4 (−44 – 36)
ICU-acquired weakness, no. (%)	2 (18)	2 (25)	2 (29)	1.9 (0.2 – 19.8)[e]	2.0 (0.2 – 19.7)[e]
Delirium, no. (%)	32 (59)	24 (47)	25 (53)	0.7 (0.3 – 1.5)[e]	0.8 (0.4 – 1.9)[e]
Length of stay, median (IQR), days					
In ICU	4 (3–6)	3 (2–5)	4 (2–7)	−0.2 (−2.2 – 1.8)	1.0 (−1.1 – 3.1)
In hospital	10 (6–18)	13 (5–22)	11 (4–23)	2.2 (−2.4 – 6.8)	2.2 (−2.6 – 7.0)
Favorable neurological outcome day 28, no. (%)[d]					
Modified Ranking Scale score	28 (33)	33 (40)	27 (33)	1.4 (0.7 – 2.8)[e]	1.0 (0.5 – 2.0)[e]
Cerebral Performance Categories	60 (71)	54 (67)	43 (54)	0.8 (0.4 – 1.5)[e]	0.4 (0.2 – 0.9)[e]
Favorable neurological outcome day 180, no. (%)[d]					
Modified Ranking Scale score	49 (58)	43 (58)	36 (47)	0.9 (0.5 – 1.8)[e]	0.6 (0.3 – 1.1)[e]
Cerebral Performance Categories	58 (69)	47 (64)	42 (55)	0.7 (0.3 – 1.4)[e]	0.5 (0.2 – 0.9)[e]
Health Utilities Index-Mark III at day 180, median [IQR]	0.90 [0 – 0.97]	0.83 [0 – 0.98]	0.63 [0 – 0.97]	−0.04 (−0.20 – 0.11)	−0.14 (−0.29 – 0.02)
Mortality day 28, no. (%)	22 (24)	25 (27)	28 (32)	1.2 (0.6 – 2.4)[e]	1.6 (0.8 – 3.1)[e]
Mortality day 180, no. (%)	26 (28)	26 (29)	32 (36)	1.0 (0.5 – 2.0)[e]	1.6 (0.8 – 3.0)[e]

The number of patients analyzed for each outcome are presented in eTable 2 in Supplement 3

[a] Only survivors

[b] Findings remained essentially unchanged when performing a log transformation on the data

[c] Only one patient had chronic kidney disease at baseline

[d] A favorable neurologic outcome was defined as a Cerebral Performance Category score of 1 or 2 on a scale of 1 to 5, and a Modified Rankin Score-9Q of 0 to 2 on a scale of 0 to 6, with higher scores indicating more severe disability. See supplements for more data

[e] Odds ratio

If applicable, secondary outcomes were transformed in case of not normally distributed residuals. The frequencies of SAEs were summarized by treatment assignment.

SPSS version 28 (IBM Corp) was used for most of the analyses. The rank-transformation was performed with R version 4.3.1 (R Foundation for Statistical Computing) and the logistic mixed model analyses with Stata version 17 (StataCorp LLC). Figures were computed with Stata version 19 (StataCorp LLC).

Results

From October 7 2019, to February 11 2024, a total of 1215 patients were assessed for eligibility, of whom 383 patients were randomized (Fig. 1). The study treatment was initiated in 368 patients (received ≥ 1 dose). After excluding patients without consent, 291 patients were included in the full analysis population and 273 patients in the modified intention-to-treat population (93 on placebo, 91 on 3 g, and 89 on 10 g). The baseline characteristics of the modified intention-to-treat population are shown in Table 1. The mean (SD) age was 63 (12) years, and 84% of the patients were male. Overall, 57% of the patients were ≤ 66 years old (eTable 1 in Supplement 3 for numbers per group). The first dose of study medication was administered a mean (SD) 3 h 29 min (52 min) after ROSC.

In all three intervention groups, patients received a mean (SD) of 6 (2) infusions. Study treatment was discontinued prematurely in 10 patients in the placebo group (due to ICU-ICU transfer), seven patients in the 3 g vitamin C group (six due to ICU-ICU transfer and one due to a safety exclusion criterion), and in four patients in the 10 g vitamin C group (due to ICU-ICU transfer).

The primary outcome was obtained in all patients. Mean (SD) change in R-SOFA scores at 96 h was −3.2 (5.7) in the placebo group, −2.3 (7.4) in the 3 g vitamin C group, and −0.8 (7.6) in the 10 g vitamin C group, respectively (p = 0.04 for overall difference, Table 2 and Fig. 2). 10 g vitamin C dose led to 2.5 points less improvement in R-SOFA score compared with placebo (95% CI 0.5–4.5; p = 0.01) and 1.6 points less improvement compared with 3 g vitamin C (95% CI −0.4 to 3.6; p = 0.12) (Table 2). These findings remained essentially unchanged when the primary endpoint was rank-transformed due to bimodally distributed model residuals (p = 0.04 for overall difference) (eAppendix 2 in Supplement 3).

When including the 18 patients excluded from the modified intention-to-treat analysis (full analysis population, n = 291), the results were similar for the primary analysis (p = 0.04 for overall difference; eAppendix 2 in Supplement 3). Results were also similar in the additional analyses (adjusted for time to sustained ROSC and first pH) and sensitivity analysis on treatment discontinuation. When excluding patients who died < 96 h the differences between groups were less pronounced (eAppendix 2 in Supplement 3). Subgroup analyses suggested a heterogeneous treatment effect according to age (p = 0.03 for interaction), with increasing age resulting in less improvement in organ function in both the 3 g and 10 g vitamin C groups as compared with placebo (eAppendix 2 in Supplement 3).

The secondary outcomes are shown in Table 3. The number of patients analyzed for each secondary endpoint are summarized in eTable 2 and eTable 3 in Supplement 3. Patients who received 10 g vitamin C had higher troponin T levels at day 1 (difference, 1926 ng/L [95% CI 302–3551 ng/L]; p = 0.02), needed more renal replacement therapy (OR, 10.4 [95% CI 1.2–87.0]; p = 0.03) and had a lower rate of favorable neurological outcome (CPC) at days 28 and 180 (OR, 0.4 [95% CI 0.2–0.9]; p = 0.02, and OR, 0.5 [95% CI 0.2–0.9]; p = 0.03, respectively; eTable 3 and eFigure 1 in Supplement 3) compared with placebo. Mortality at 96 h (post-hoc endpoint) was 19% in the 10 g vitamin C group, 15% in the 3 g vitamin C group and 9% in the placebo group (OR 10 g vitamin C vs. placebo, 2.7 [95% CI 1.1–6.8]; p = 0.03), whereas on day 28 mortality was 32% in the 10 g vitamin C group, 28% in the 3 g vitamin C group and 24% in the placebo group (OR 10 g vitamin C vs. placebo, 1.6 [95% CI 0.8–3.1]; p = 0.19) (see also Table 3, eTable 6 and eFigure 2 in Supplement 3). No clear differences were found between the 3 g vitamin C and placebo group.

The number of reported SAEs can be found in eTable 4 of Supplement 3. The occurrence of SAEs increased dose-dependently: 43 in the placebo group, 46 in the 3 g group and 61 in the 10 g group (total n = 368). Renal replacement therapy and deaths were more often reported in the 10 g vitamin C group. No clear differences in other SAEs were found.

Discussion

In this randomized clinical trial involving comatose post-cardiac arrest patients with shockable rhythm, early intravenous vitamin C did not reduce organ dysfunction compared with placebo. The 10 g dose resulted in less improvement in organ function at 96 h compared with placebo. Subsequent adjusted and sensitivity analyses confirmed these findings, with subgroup analyses highlighting an even more pronounced effect in older patients. Secondary analyses revealed higher troponin T concentrations, worse renal function, and worse neurological outcomes in the 10 g vitamin C group. Further, there appeared to be a dose–response relationship with 3 g vitamin C yielding clinical outcomes between placebo and 10 g vitamin C.

Two prior studies in post-cardiac arrest patients with vitamin C have been published [11, 12]. An observational before-and-after study (n = 234) showed that treatment with intravenous thiamine (200 mg) and vitamin C (3 g) at 12 h intervals for 3 days was not associated with neurologic outcomes [12]. A small pilot trial (n = 30) investigating daily 3 g intravenous vitamin C for 4 days reported inconclusive results regarding neuron-specific enolase levels [11].

We performed the first phase 2 trial investigating vitamin C post-cardiac arrest. An important finding was the higher number of early deaths at 96 h (post-hoc endpoint) observed in the vitamin C groups. On the one hand, this may reflect baseline differences in disease severity despite randomization and well-balanced baseline characteristics. On the other hand, a potentially harmful effect of the intervention cannot be excluded. Notably, when excluding patients who died within 96 h, the differences in the primary outcome were attenuated.

Our results are consistent with the clinical outcome in two different patient populations in the LOVIT [22] and LOVIT-COVID/REMAP-CAP trials [23]. In septic shock and hospitalized COVID-19 patients intravenous vitamin C (200 mg/kg/day for 4 days) had a higher risk of death and organ dysfunction [22, 23]. Evidence of harm from high-dose vitamin C in three different patient populations raises concerns about administering high-dose vitamin C in clinical practice or in any future trials.

We studied differences in clinical outcome between a supplementation and a pharmacological dose. We chose 3 g vitamin C as a supplementary regimen as 2–3 g/day normalizes plasma vitamin C concentrations [5]. We chose 10 g vitamin C as a pharmacological regimen since this leads to supraphysiological plasma concentrations [5], and since it is between the 6 g and 16 g doses used in previous studies [20, 24–28]. The dose–effect relation of our trial is remarkable. Whereas a 10 g dose resulted in a worse clinical outcome, the supplementary dose of 3 g did not yield beneficial effects either, which is a crucial finding for clinical practice.

There are several potential explanations for the negative results of our trial. First, administering a uniform dose of vitamin C for a fixed duration to a specific patient population without determining their functional vitamin C status may be disadvantageous. Because ROS contribute to physiological signalling and tissue repair, potent radical scavenging may not be beneficial during every phase of the underlying condition. Second, the biochemical composition of vitamin C used in our trial may have contributed to the signal for harm. As in LOVIT [22] and LOVIT-COVID/REMAP-CAP [23], we administered L-ascorbic acid, with a pH range 5.4–5.6. Administering sodium ascorbate (pH 6.5–7.2) to cardiac arrest patients with metabolic acidosis and diminished buffering capacity might have yielded different results [29].

Our trial has several major strengths. It is the first large vitamin C trial in a relatively homogeneous population (comatose post-cardiac arrest with first shockable rhythm). It has been executed in a difficult research population with numerous logistical challenges. We chose SOFA score as it is a robust and clinically meaningful endpoint, sensitive to changes in organ function, and a validated predictor for morbidity and mortality. We used the R-SOFA score to enable baseline assessment of organ failure in post-cardiac arrest patients. Additionally, our trial explored a dose–effect relationship.

Our difficult research population led to challenging logistics and statistics and therefore to several important limitations. First, although the time to administration of vitamin C was relatively short compared to the sepsis trials, it still missed the highest peak of ROS release, which occurs within minutes after reperfusion [13]. Second, in 20 modified intention-to-treat patients, the study treatment had to be discontinued due to ICU transfer within 96 h. However, primary analysis results were similar in the sensitivity analysis excluding these patients. When the 10 ICU-transferred patients in the placebo group were not excluded from the model, 10 g vitamin C was even more harmful (eAppendix 2 in Supplement 3). Third, the total number of patients transferred to another ICU was the largest in the 10 g vitamin C group (eTable 5 in Supplement 3), resulting in relatively more missing secondary outcome data in this group. Fourth, 21% of the patients were excluded after randomisation due to not obtaining deferred consent, which could raise concerns about potential attrition bias. However, groups were comparable at baseline. Post-randomization exclusion is inherent to a deferred consent procedure during a 72 h period, where an early study intervention has already been started. Failure to obtain consent within the specified timeframe will result in the participants' exclusion from the study and the removal of all previously collected data, as required by regulatory and ethical obligations. Our exclusion rate of 21% is in line with other ICU-trials using a deferred consent procedure [30, 31]. Fifth, the SD of 3.5 used for the power calculation underestimated the observed delta R-SOFA (5.7–7.6). Nevertheless, our sample size was adequate for its purpose: to open or close the door for a subsequent phase 3 trial. Sixth, our primary endpoint had a bimodal distribution due to the maximum R-SOFA score in case of death and implies that the primary endpoint is strongly influenced by early mortality. Nevertheless, the observed signal of harm remained consistent after rank-transformation of the data, and across all additional analyses.

In conclusion, in comatose out-of-hospital cardiac arrest patients with shockable rhythm, early intravenous vitamin C did not reduce organ dysfunction during the first 96 h of ICU stay. A 10 g vitamin C dosing regimen resulted in more organ failure compared with placebo. These findings raise serious concerns about administering high-dose vitamin C in daily clinical practice or in any future trials.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-026-08492-5.

Abbreviations
AED: Automatic external defibrillator; CPC: Cerebral performance categories; COPD: Chronic obstructive pulmonary disease; CPR: Cardiopulmonary resuscitation; DSMB: Data safety monitoring board; GCS: Glasgow come scale; HUI: Health utilities index; ICU: Intensive care unit; IV: Intravenous; MRs: Modified ranking scale; OHCA: Out-of-hospital cardiac arrest; ROS: Reactive oxygen species; R-SOFA: Resuscitation-sequential organ failure assessment; ROSC: Return of spontaneous circulation; SAE: Serious adverse event; SUSAR: Suspected unexpected severe adverse reaction; TTM: Targeted temperature management; VF: Ventricular fibrillation; Vit: Vitamin; VT: Ventricular tachycardia; VITaCCA: VITamin C in post-Cardiac Arrest syndrome.

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Acknowledgements
We would like to thank all the research nurses for their assistance during the study: Erna Alberts, Ingrid van den Hul, Ditty van Duijn, Patricia Ormskerk, Melanie Glasbergen – van Beijeren, Saar Mahfoud, Jan Willem Wijnhoven, Matty Koopmans, Eryk Toscano and Marianne Bouw-Ruiter.

Author contributions
SR, HOvS, HJdG, AG, and AdM designed the study. SR is the coordinating investigator, and AdM is the principal investigator in the coordinating center. CdU, ED, TR, AvZ, and BvdB are the principal investigators of the participating hospitals. SR, JT, HJdG, and AdM performed the statistical analysis. SR and PS designed the figures. All authors contributed to the writing of the final manuscript. Authorship eligibility follows accepted academic standards.

Funding
Funding for the VITaCCA-trial was provided by contract to Amsterdam UMC, location VUmc, the study sponsor, by the Netherlands Organization of Health Research and Development (ZonMW) (No 848081001). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and materials
The datasets will be made available upon reasonable request to the corresponding author.

Declarations

Conflicts of interest
SR, HJdG, TR, AvZ, PE, AG, HOvS and AdM received funding for this trial from the Netherlands Organization of Health Research and Development. AdM received an honorarium for a lecture for Pascoe and travel expenses for the Critical Care Reviews Down Under in Melbourne. AdM and AvZ received recently a grant from the EU (MSCA-DN) for the BIO-MICRO project. AvZ received honoraria for advisory board meetings, lectures, research, and travel expenses from AOP Pharma, Abbott, Baxter, Cardinal Health, Danone-Nutricia, Dutch Medical Food, Fresenius Kabi, GE Healthcare, GSK, InBody, and Rousselot. The other authors declare that they have no potential conflicts of interest, any relevant financial activities outside the submitted work, or any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written in the submitted work.

Ethical approval
The study was approved by the ethics committee at Amsterdam UMC, location VUmc (VU University Medical Centre Protocol Record METC-2018.120). The ethics committee approved starting study interventions before obtaining informed consent to avoid treatment delays. All substantial protocol amendments were submitted to the Central Committee on Research Involving Human Subjects and the Medical Ethics Committee of Amsterdam UMC, location VUmc. Approved amendments were communicated to the principal investigators of the participating hospitals.

Publisher's Note

Received: 20 March 2026 Accepted: 14 May 2026
Published online: 16 June 2026

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