

Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial

Jonathan E. Sevransky et al. JAMA 2021; 325:742

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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The VICTAS Randomized Clinical Trial

Jonathan E. Sevransky, MD, MHS; Richard E. Rothman, MD, PhD; David N. Hager, MD, PhD; Gordon R. Bernard, MD; Samuel M. Brown, MD; Timothy G. Buchman, PhD, MD; Laurence W. Busse, MD, MBA; Craig M. Coopersmith, MD; Christine DeWilde, PhD; E. Wesley Ely, MD, PhD; Lindsay M. Fyrargi-Asl, MS; Alpha A. Fowler, MD; David F. Gaieski, MD; Michelle N. Gong, MD; Alex Hall, DHSc, MS; Jeremiah S. Hinson, MD, PhD; Michael H. Hooper, MD; Akram Khan, MD; Mark A. Levine, MD; Roger J. Lewis, MD, PhD; Chris J. Lindell, PhD; Jessica S. Marin, CCPN; Anna McGlothlin, PhD; Brooks L. Moore, MD; Katherine L. Nugent, MD; Samuel Nwosu, MS; Carmen C. Polito, MD, MSC; Todd W. Rice, MD, MSc; Erin P. Ricketts, MSPH; Caroline C. Rudolph, MBA; Fred Sanfilippo, MD, PhD; Kert Viele, PhD; Greg S. Martin, MD, MSC; David W. Wright, MD, for the VICTAS Investigators

IMPORTANCE Sepsis is a common syndrome with substantial morbidity and mortality. A combination of vitamin C, thiamine, and corticosteroids has been proposed as a potential treatment for patients with sepsis.

OBJECTIVE To determine whether a combination of vitamin C, thiamine, and hydrocortisone every 6 hours increases ventilator- and vasopressor-free days compared with placebo in patients with sepsis.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, adaptive-sample-size placebo-controlled trial conducted in adult patients with sepsis-induced respiratory and/or cardiovascular dysfunction. Participants were enrolled in the emergency departments or intensive care units at 43 hospitals in the United States between August 2018 and July 2019. After enrollment of 501 participants, funding was withheld, leading to an administrative termination of the trial. All study-related follow-up was completed by January 2020.

INTERVENTIONS Participants were randomized to receive intravenous vitamin C (1.5 g), thiamine (100 mg), and hydrocortisone (50 mg) every 6 hours ($n = 252$) or matching placebo ($n = 249$) for 96 hours or until discharge from the intensive care unit or death. Participants could be treated with open-label corticosteroids by the clinical team, with study hydrocortisone or matching placebo withheld if the total daily dose was greater or equal to the equivalent of 200 mg of hydrocortisone.

MAIN OUTCOMES AND MEASURES The primary outcome was the number of consecutive ventilator- and vasopressor-free days in the first 30 days following the day of randomization. The key secondary outcome was 30-day mortality.

RESULTS Among 501 participants randomized (median age, 62 [interquartile range (IQR), 50–70] years; 46% female; 30% Black; median Acute Physiology and Chronic Health Evaluation II score, 27 [IQR, 20.8–33.0]; median Sequential Organ Failure Assessment score, 9 [IQR, 7–12]), all completed the trial. Open-label corticosteroids were prescribed to 33% and 32% of the intervention and control groups, respectively. Ventilator- and vasopressor-free days were a median of 25 days (IQR, 0–29 days) in the intervention group and 26 days (IQR, 0–28 days) in the placebo group, with a median difference of -1 day (95% CI, -4 to 2 days; $P = .85$). Thirty-day mortality was 22% in the intervention group and 24% in the placebo group.

CONCLUSIONS AND RELEVANCE Among critically ill patients with sepsis, treatment with vitamin C, thiamine, and hydrocortisone, compared with placebo, did not significantly increase ventilator- and vasopressor-free days within 30 days. However, the trial was terminated early for administrative reasons and may have been underpowered to detect a clinically important difference.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03509350

JAMA. 2021;325(8):742-751. doi:10.1001/jama.2020.24505

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

Hintergrund (I)

Sepsis ist ein sehr häufiges Krankheitsbild mit einer substantiellen Morbidität und Mortalität

Die kombinierte Gabe von Vitamin C, Thiamin und Hydrocortison wird als Behandlungsoption bei Patienten mit Sepsis angesehen

Die vorliegende Studie untersucht die Fragestellung ob die kombinierte Gabe von Vitamin C, Thiamin und Hydrocortison alle 6 Stunden im Vergleich mit Placebo zu einer Zunahme der ventilator- und vasopressorenfreien Tage bei Patienten mit Sepsis führt

Methode (I)

Multizentrische randomisiert placebokontrollierte Studie bei erwachsenen Patienten mit sepsisinduzierter respiratorischer und/oder kardiovaskulärer Dysfunktion

Einschluss der Patienten in der Notaufnahme oder auf ITS in 43 US-amerikanischen Krankenhäusern zwischen 8/2018 und 7/2019

Nach Einschluss von 501 Patienten: Stopp Studieneinschluss da die finanzielle Unterstützung beendet wurde

Follow Up bis Januar 2020

Randomisierung

Randomisierung

1:1

S E P S I

Vitamin C 1,5 g, Thiamin 100 mg,
Hydrokortison 50 mg* alle 6 h für 96 h
oder Entlassung von ITS oder Tod

Placebo

*Open Label Hydrokortison möglich, falls ≥ 200 mg/d → Stopp Studien HC/Placebo

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Endpunkte

Primärer
Endpunkt:

- Anzahl konsekutiver Tage ohne Beatmung bzw. Vasopressoren innerhalb von 30 Tagen nach Randomisierung

Sekundärer
Endpunkt:

- 30-Tages Sterblichkeit

Ergebnisse

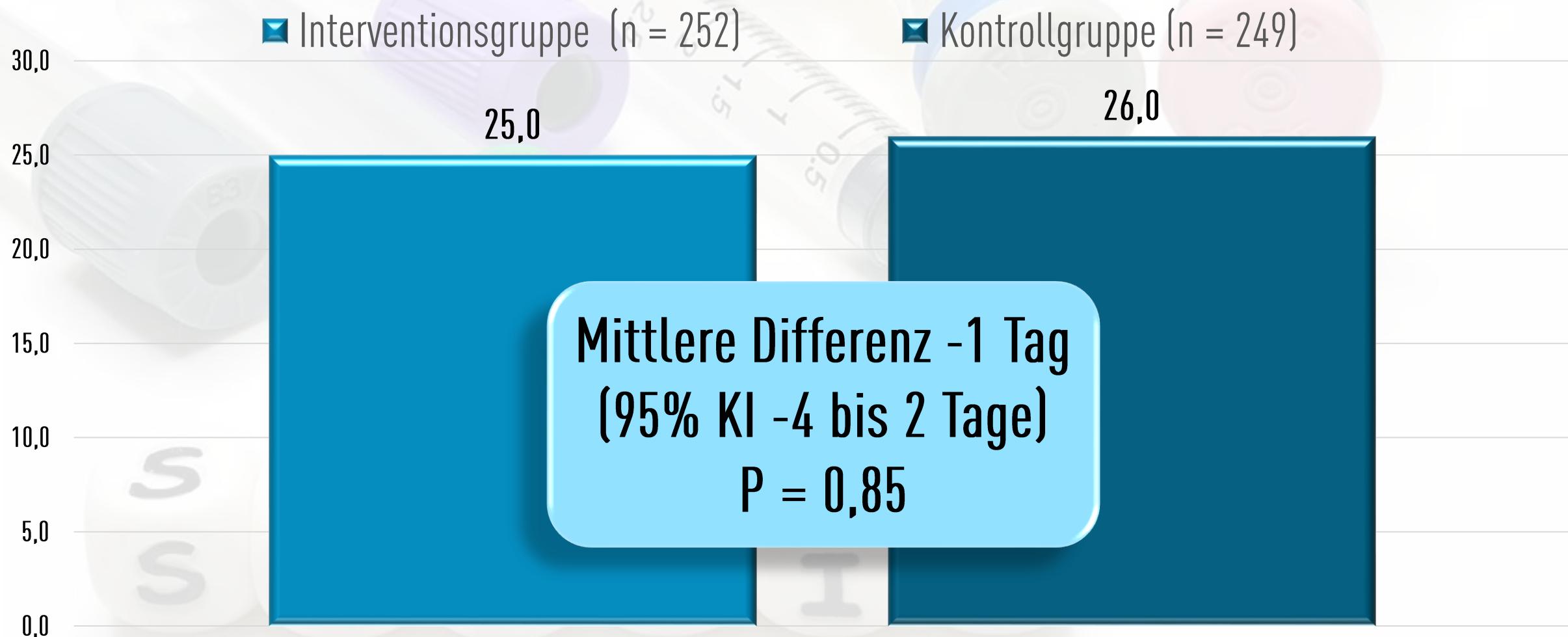
501 Patienten
Medianes Alter 62
(IQB 50-70)

69% Frauen
30% Schwarze

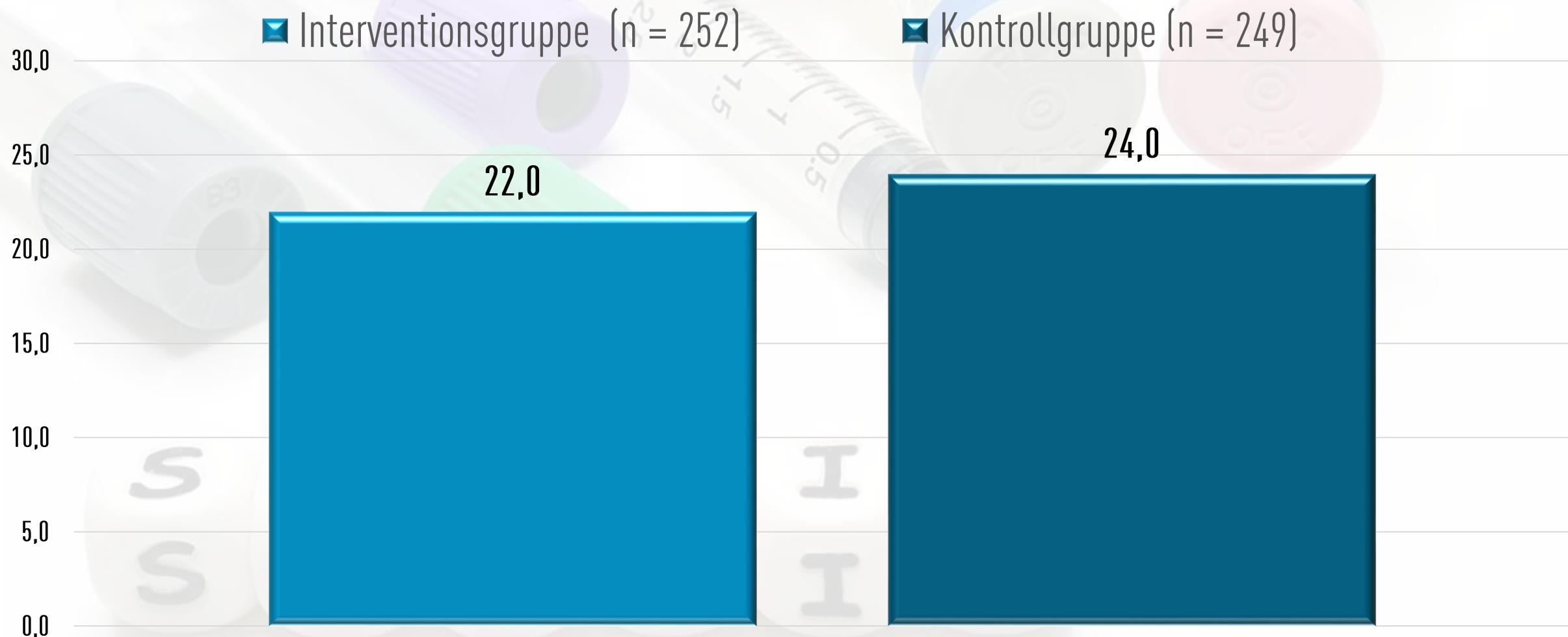
APACHE II im Median 27
(IQB 20,8-33)
SOFA Score median 9
(IQB 7-12)

Interventionsgruppe
 $n = 252$
Kontrollgruppe
 $n = 249$

Primärer Endpunkt: Ventilator-/ Vasopressorenfreie Tage



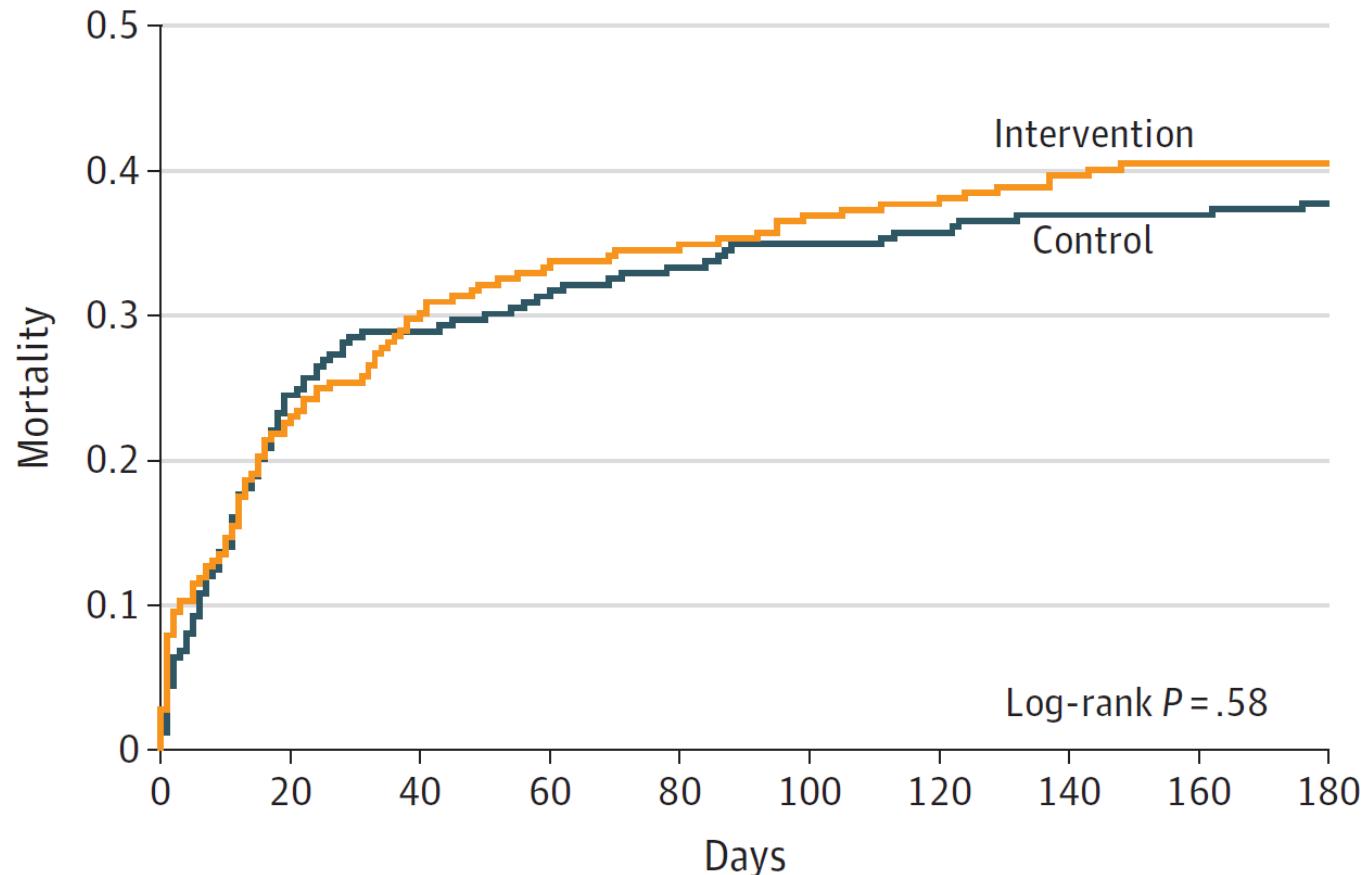
Sekundärer Endpunkt: 30-Tages-Sterblichkeit



Endpunkte

Outcomes	Intervention group	Control group	Difference (95% CI)	P value
Main analysis				
Total No.	252	249		
Mortality before ICU discharge, No. (%)	52 (20.6)	49 (19.7)	0.9 (-8.0 to 6.1)	.79
Mortality at 180 d, No. (%)	102 (40.5)	94 (37.8)	2.7 (-11.3 to 5.8)	.53
Change in SOFA score, median (IQR) ^a	5 (3-7)	5 (2-7)	0.0 (-1.0 to 0.0)	.10
Length of ICU stay, median (IQR), d	4 (2-8) [n = 250]	4 (2-8) [n = 245]	0.0 (-2.0 to 1.0)	.82
Length of hospital stay, median (IQR), d	10 (6-17) [n = 250]	9 (5-17) [n = 246]	1.0 (-3.0 to 2.0)	.66
Coma-/delirium-free days, median (IQR) ^b	4 (2-5) [n = 237]	4 (2-5) [n = 241]	0.0 (0.0 to 1.0)	.45
Kidney replacement therapy-free days, median (IQR)	30 (0-30)	30 (0-30) [n = 247]	0.0 (0.0 to 0.0)	.58

Kaplan-Meier Kurve Überleben bis Tag 180



No. at risk

Intervention	252	195	177	168	165	159	157	152	150	150
Control	249	188	177	171	166	162	160	157	157	155

Zusammenfassung

Bei kritisch kranken Patienten mit Sepsis führt eine Behandlung mit Vitamin C, Thiamin und Hydrokortison im Vergleich mit Placebo nicht zu einer Zunahme der ventilator- und vasopressorfreien Tage innerhalb der ersten 30 Tage

Aus administrativen Gründen wurde die Studie vorzeitig beendet, daher möglicherweise unzureichende statistische Power um einen klinisch relevanten Unterschied nachzuweisen

Weitere Informationen und Ergebnisse

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