JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Sodium Bicarbonate for In-Hospital Cardiac Arrest
A Randomized Clinical Trial

Asger Granfeldt, MD, PhD, DMSc; Bertram Lahn Kirkegaard, MD; Mikael Fink Vallentin, MD, PhD; Mathias J. Holmberg, MD, PhD, MPH, MSc; Nikola Stankovic, MD, MPH, PhD; Peter Carøe Lind, MD, PhD; Anders Gade Kjærgaard, MD, PhD; Nanna Houe, MD; Matias Vested, MD, PhD; Dan Lou Isbye, MD, PhD; Camilla Meno Kristensen, MD; Jesper Kjærgaard, MD, PhD, DMSc; Stine Thorhauge Zwisler, MD, PhD; Søren Nygaard Lundsfryd, MD; Louise Breum Petersen, MD; Fredrik Folke, MD, PhD; Carolina Malta Hansen, MD, PhD; Kasper Karmark Iversen, MD, PhD; Morten Schou, MD, PhD; Sebastian Wiberg, MD, MSc, PhD; Signe Juul Riddersholm, MD, PhD; Bodil Steen Rasmussen, MD, PhD; Kristine Karlsson, RN; Ronni R. Plovsing, MD, PhD; Christian Svendsen Juhl, MD; Mette Krag, MD, PhD; Christian Dalby Sørensen, MD; Peter Kuhne-Qvist, MD; Jakob Oxlund, MD, PhD; Christoffer Grant Sølling, MD, PhD; Jacob Robsahm Hansen, MD; Lars Peter Kloster Andersen, MD, PhD; Jimmi Malmberg Scheel Jensen, MD; Theis Skovsgaard Itenov, MD, PhD; Marlene Lauritzen, MD; Malthe Jessen Pedersen, MD, PhD; Rasmus Philip Nielsen, MD; Hans Fjeldsøe-Nielsen, MD; Naqibullah Mirzada, MD; Niels Secher, MD, PhD; Ulrick Skipper Espelund, MD, PhD; Jennifer Rosenkjær Eskol, MD; Kasper Andersen, MD; Anne Craveiro Brøchner, MD, PhD; Helene Korvenius Nedergaard, MD, PhD; Peter Martin Hansen, MD; Wiebke Henschel, MD; Akil Raad Walli, MD; Michael Sandgaard, MD; Camilla Lundegaard Asferg, MD, PhD; Andrei Ciubotariu, MD; Maria Holm Rosenberg Rasmussen, MD; Victor Le Breton, MD; Lykke Kjærgaard Nielsen, BSc; Frederik Gautier Hansen, MD; Niklas Brændstrup, BSc; Ida Katrine Thomsen, MHSc; Birthe Sindberg, RN; Lars Wiuff Andersen, MD, MPH, PhD, DMSc; for the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) Investigators

IMPORTANCE Patients with in-hospital cardiac arrest have poor outcomes. Sodium bicarbonate is commonly administered during cardiac arrest, but the effects on clinical outcomes are unknown.

OBJECTIVE To determine whether administration of sodium bicarbonate during in-hospital cardiac arrest increases the proportion of patients with return of spontaneous circulation.

DESIGN, SETTING, AND PARTICIPANTS Randomized, parallel-group, double-blind, placebo-controlled clinical trial conducted at 21 hospitals in Denmark. Participants were adults with in-hospital cardiac arrest, who received at least 1 dose of epinephrine. Patients were enrolled from February 6, 2023, to February 11, 2026, with the last 90-day follow-up conducted on May 4, 2026. Final statistical analysis was conducted on May 5, 2026.

INTERVENTION Sodium bicarbonate (up to 100 mmol) or placebo intravenously.

MAIN OUTCOMES AND MEASURES The primary outcome was sustained return of spontaneous circulation. Key secondary outcomes were survival at 30 days and survival at 30 days with a favorable neurologic outcome, defined by a score of 0 to 3 on the modified Rankin Scale (scores range from 0 to 6, with higher scores indicating greater disability).

RESULTS A total of 2913 patients with in-hospital cardiac arrest were screened; 913 patients were randomized, of which 779 were eligible for the primary analyses, with 372 randomized to receive sodium bicarbonate and 407 randomized to receive placebo. The median (IQR) age of patients was 73 (64-79) years and 502 were male (64%). Sustained return of spontaneous circulation occurred in 146 patients (39%) in the sodium bicarbonate group and 150 (37%) in the placebo group (risk ratio, 1.05 [95% CI, 0.88-1.24]; $P = .62$). At 30 days, 45 patients (12%) in the sodium bicarbonate group and 37 (9.1%) in the placebo group were alive (risk ratio, 1.25 [95% CI, 0.84-1.88]); a favorable neurologic outcome at 30 days occurred in 30 patients (8.1%) and 22 patients (5.4%), respectively (risk ratio, 1.39 [95% CI, 0.82-2.34]). Alkalosis and hypernatremia after cardiac arrest were more common in the sodium bicarbonate group.

CONCLUSIONS AND RELEVANCE There was no significant difference in sustained return of spontaneous circulation between sodium bicarbonate and placebo in adults with in-hospital cardiac arrest. These findings do not support routine administration of sodium bicarbonate for patients with in-hospital cardiac arrest.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05564130; ClinicalTrialsRegister.eu Identifier: 2022-501304-10-00

JAMA. doi:10.1001/jama.2026.10628
Published online June 11, 2026.

Visual Abstract
Research Summary
Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) Investigators appear in Supplement 1.

Corresponding Author: Lars Wiuff Andersen, MD, MPH, PhD, DMSc, Department of Anaesthesiology and Intensive Care Medicine, Aarhus University Hospital, Palle Juul-Jensens Blvd 99, 8200 Aarhus N, Denmark (lwandersen@clin.au.dk).

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

In-hospital cardiac arrest is relatively common, with approximately 2000 cases in Denmark and 300 000 cases in the US each year.[1,2] Outcomes remain poor, with 50% to 70% of patients achieving return of spontaneous circulation, but only 25% to 30% surviving to hospital discharge.[1,3,4] For patients who require advanced life support, including administration of epinephrine, only approximately 10% survive.[5,6]

Evidence to support specific treatments during in-hospital cardiac arrest is sparse and largely based on extrapolation from out-of-hospital cardiac arrest research. Routinely recommended drugs are limited to epinephrine (adrenaline) and amiodarone or lidocaine based on trials conducted in the out-of-hospital setting.[7,8] Although international guidelines on advanced life support do not distinguish between in- and out-of-hospital cardiac arrest, important differences between these settings exist.[9,10] This includes earlier administration of advanced life support drugs in the in-hospital setting,[11] which could result in greater therapeutic benefit.

Studies have demonstrated the presence of severe acidosis during and after in-hospital cardiac arrest.[12,13] Severe acidosis has several potential detrimental effects during and after cardiac arrest, including decreased cardiac contractility, attenuated effect of catecholamines (eg, epinephrine), and worsening of ischemic brain damage.[14,15] Administration of sodium bicarbonate increases pH and might mitigate the detrimental effects of severe acidosis, but this has not been tested in a clinical trial for in-hospital cardiac arrest.[16] Although current guidelines suggest against the routine use of sodium bicarbonate based on lack of contemporary trial evidence,[9,10] administration of sodium bicarbonate during in-hospital cardiac arrest is nevertheless common. One study from the US found that sodium bicarbonate was administered in approximately half of in-hospital cardiac arrests, with an increase in use from 2001 to 2016.[17]

The objective of the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) trial was to determine whether administration of sodium bicarbonate during in-hospital cardiac arrest increases return of spontaneous circulation and secondarily improves survival and survival with a favorable neurological outcome.

Key Points

Question Does sodium bicarbonate administered during in-hospital cardiac arrest improve return of spontaneous circulation?

Findings In this randomized clinical trial that included 779 patients with in-hospital cardiac arrest in Denmark, the proportion of patients who achieved return of spontaneous circulation was 39% in the sodium bicarbonate group and 37% in the placebo group, a difference that was not statistically significant.

Meaning These findings do not support routine administration of sodium bicarbonate for patients with in-hospital cardiac arrest.

Methods

Trial Design and Oversight

The BIHCA trial was an investigator-initiated, randomized, parallel-group, double-blind, placebo-controlled superiority trial investigating sodium bicarbonate during adult in-hospital cardiac arrest. The trial was approved by the relevant ethics committee and the Danish Medicines Agency. For incapacitated survivors, written consent was obtained from a close relative and a physician independent of the trial after the cardiac arrest. Patients who regained capacity to provide consent were approached for written consent.

The protocol is available in Supplement 2. Minor discrepancies between the protocol and the current article are described in the eAppendix in Supplement 3. Reporting adheres to the CONSORT reporting guidelines for randomized clinical trials.

An independent data monitoring committee oversaw trial safety and reviewed data after approximately 200 and 400 enrolled patients. The trial had no predefined stopping criteria for harm, futility, or efficacy.

Setting and Patients

The trial was conducted nationwide in Denmark across 21 hospitals. Adult patients (aged ≥18 years) were eligible for the trial if they had an in-hospital cardiac arrest and received at least 1 dose of epinephrine during the cardiac arrest. Exclusion criteria were a clearly documented do-not-resuscitate order prior to the cardiac arrest, prior enrollment in the trial, invasive mechanical circulatory support (extracorporeal circulation or left ventricular assist device) at the time of the cardiac arrest, known or suspected pregnancy at the time of the cardiac arrest, known objection by the patient to participate in the trial, or a clinical indication for sodium bicarbonate administration.

Randomization and Intervention

Patients were randomized based on a computer-generated sequence in a 1:1 ratio to receive either sodium bicarbonate or placebo in blocks of 6 without stratification.

The intervention consisted of 50 mL of 8.4% (1 mmol/mL) sodium bicarbonate (or corresponding placebo) given as soon as possible after the first dose of epinephrine. If the patient remained in cardiac arrest, 1 additional dose of 50 mL was administered after the next dose of epinephrine for a maximum of 2 doses. The placebo consisted of 0.9% (0.15 mmol/mL) sodium chloride from identical vials.

The trial drugs were placed in a blinded kit, which was retrieved by a dedicated member of the clinical cardiac arrest team. The trial was double-blinded, with patients, investigators, clinicians, and outcome assessors unaware of the randomized treatment.

Outcomes

The primary outcome was sustained return of spontaneous circulation, defined as a palpable pulse or other signs of circulation with no further need for chest compressions for at least 20 minutes.

Key secondary outcomes were survival at 30 days and survival at 30 days with a favorable neurologic outcome, defined

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

as a score of 0 to 3 on the modified Rankin Scale (scores range from 0 to 6, with higher scores indicating greater disability).[18]

Additional outcomes included health-related quality of life in survivors at 30 days, assessed with the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire.[19] EQ-5D-5L results are reported both as the patient-assessed numeric value and the index value based on Danish data.[20] Survival, neurologic outcome, and quality of life were also assessed at 90 days, 180 days, and 1 year. The modified Rankin Scale and EQ-5D-5L were assessed based on telephone interviews with the patient or a relative. All telephone interviews were conducted by a trained research nurse. Consistent with the protocol, this article includes 30- and 90-day outcomes, while collection of longer-term outcomes is ongoing.

As a measure of organ dysfunction after sustained return of spontaneous circulation, we collected data on the Sequential Organ Failure Assessment score at 24, 48, and 72 hours after the cardiac arrest. Both the cardiovascular subscore as well as the overall Sequential Organ Failure Assessment score were assessed at these time points. The cardiovascular subscore was also assessed 2 hours after the cardiac arrest. Laboratory values from the first arterial gas, hospital disposition, and cause of death were also collected.

Predefined potential adverse events were alkalosis, hypernatremia, severe hypocalcemia, hypokalemia, and severely elevated lactate (eAppendix in Supplement 3).

Statistical Analyses

Final statistical analysis was conducted on May 5, 2026. The sample size was based on primary outcome event proportions of 33% in the placebo group and 43% in the sodium bicarbonate group, corresponding to a risk ratio (RR) of 1.30. Using a 2-sided α of .05 and a Fisher exact test, a total of 778 patients were required to detect a statistically significant difference between the groups, with 80% power.

Patients were analyzed according to their randomized assignment. The analyses only included patients who received the first dose of the trial drug, met all inclusion criteria, had no exclusion criteria at the time of randomization, and had available data on the relevant outcome. Because the trial was blinded, this modified intention-to-treat approach is unbiased while increasing precision.[21]

Binary data are presented as counts and percentages, with differences between groups expressed as RRs and risk differences accompanied by 95% CIs.[22]

Continuous outcomes are reported as means with SDs or medians with IQRs. Group differences in continuous outcomes are presented as mean differences with 95% CIs derived from a generalized linear model with robust standard errors.

Analyses were adjusted for predefined strong prognostic factors, specifically age, whether the cardiac arrest was witnessed, and the initial rhythm.

Subgroup analyses were conducted according to initial rhythm, whether the cardiac arrest was witnessed, age, time from cardiac arrest to first trial drug, and known metabolic acidosis prior to the cardiac arrest.

Two-sided *P* values are provided for the primary and key secondary outcomes tested in a prespecified hierarchical order. Because of the potential for type I error due to multiple comparisons, findings for analyses of additional outcomes should be interpreted as exploratory. Analyses were performed in R version 4.5.2 (R Foundation).

Results

Patient Characteristics and Adherence

From February 6, 2023, to February 11, 2026, 2913 patients with in-hospital cardiac arrest were screened. A total of 913 patients were randomized, of which 779 were eligible for the primary analyses, with 372 randomized to receive sodium bicarbonate and 407 randomized to receive placebo (**Figure 1**). The last 90-day follow-up was conducted on May 4, 2026. There was limited loss to follow-up.

Baseline characteristics by randomization are provided in **Table 1** and eTable 1 in Supplement 3. The median (IQR) age of patients was 73 (64-79) years and 502 were male (64%). The majority of cardiac arrests (64%) occurred in standard medical or surgical wards and most presented with an initial nonshockable rhythm (88%). The median (IQR) times from the cardiac arrest to epinephrine and trial drug administration were 5 (3-8) minutes and 8 (6-12) minutes, respectively. Representativeness of the trial population in relation to the general US and Danish in-hospital cardiac arrest populations is provided in eTable 2 in Supplement 3.

The second dose of the trial drug was not administered to 29 patients (8%) in the sodium bicarbonate group and 20 patients (5%) in the placebo group, despite the patient still being in cardiac arrest after receiving 2 epinephrine doses. Other protocol deviations were rare. Sodium bicarbonate was administered outside the trial protocol to 23 patients (6%) in the sodium bicarbonate group and 27 patients (7%) in the placebo group. Additional details on intracardiac arrest interventions and protocol deviations are provided in eTable 3 in Supplement 3. Details on post-cardiac arrest interventions are provided in eTable 4 in Supplement 3.

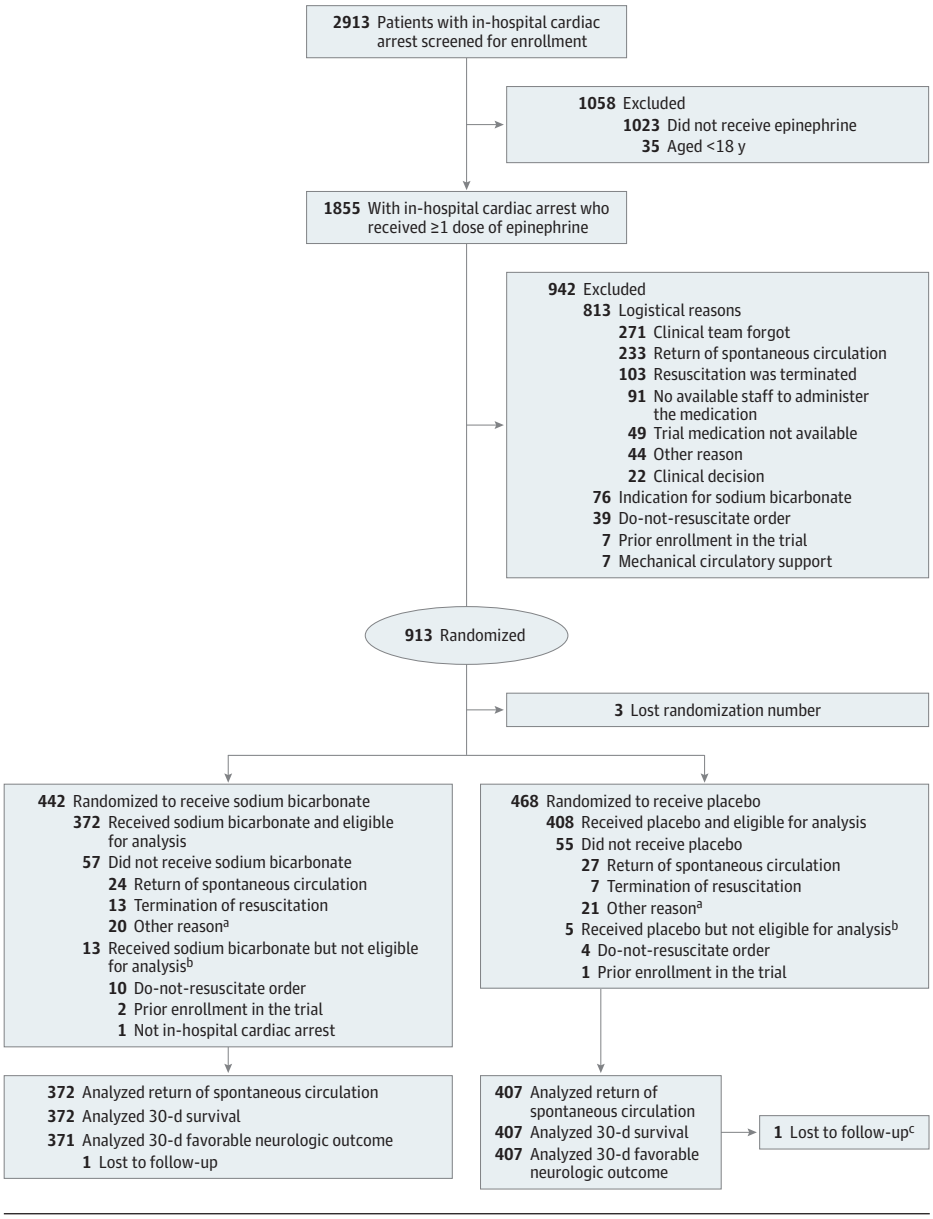
Primary and Key Secondary Outcomes

The primary outcome, sustained return of spontaneous circulation, was achieved in 146 patients (39%) in the sodium bicarbonate group and 150 (37%) in the placebo group, resulting in an RR of 1.05 (95% CI, 0.88-1.24; *P* = .62) (**Table 2**). Consistent results were found across predefined subgroups (**Figure 2**) (eFigure 1 in Supplement 3) and in a post hoc analysis (eAppendix in Supplement 3). The median (IQR) time to return of spontaneous circulation was 16 (10-21) minutes in the sodium bicarbonate group and 15 (11-22) minutes in the placebo group.

At 30 days, survival was observed in 45 patients (12%) in the sodium bicarbonate group and 37 (9.1%) in the placebo group (RR, 1.25 [95% CI, 0.84-1.88]) (Table 2). Survival with a favorable neurologic outcome at 30 days was seen in 30 patients (8.1%) in the sodium bicarbonate group and 22 (5.4%) in the placebo group (RR, 1.39 [95% CI, 0.82-2.34]) (Table 2). Results remained consistent across predefined subgroups (eFigures 2-5 in Supplement 3).

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

Figure 1. Flowchart of Patient Screening and Randomization in the Bicarbonate for In-Hospital Cardiac Arrest Trial



[a]For the sodium bicarbonate group: clinical indication for sodium bicarbonate (n = 7), clinical team forgot (n = 3), do-not-resuscitate order (n = 2), no available staff to administer medication (n = 3), clinical decision (n = 3), miscommunication (n = 1), and use of mechanical circulatory support (n = 1). For the placebo group: clinical indication for sodium bicarbonate (n = 4), do-not-resuscitate order (n = 4), no available staff to administer medication (n = 4), miscommunication (n = 3), clinical decision (n = 2), mechanical circulatory support (n = 1), prior enrollment in the trial (n = 1), no intravenous access (n = 1), and medication vial broke (n = 1).

[b]Patients who were excluded after receiving the trial drug did not meet all inclusion criteria or met any exclusion criteria. These criteria were clearly documented but not known to the clinical team at the time of randomization.

[c]The patient's next of kin denied participation in the trial and requested that all data be deleted.

Additional Outcomes

At 90 days, 39 patients (11%) in the sodium bicarbonate group and 33 (8.1%) in the placebo group were alive (RR, 1.22 [95% CI, 0.79-1.88]) (Table 2). A Kaplan-Meier curve for 90-day survival is presented in eFigure 6 in Supplement 3. Survival with a favorable neurologic outcome at 90 days was observed in 32 patients (8.6%) in the sodium bicarbonate group and 28 (6.9%) in the placebo group (RR, 1.17 [95% CI, 0.73-1.90]) (Table 2).

Details on neurologic outcomes are provided in eTable 5 in Supplement 3. Quality-of-life scores in survivors at 30 and 90 days are provided in Table 2 and eTable 6 in Supplement 3, and showed no clear differences between the 2 groups. Details on hospital disposition and cause of death are provided in eTable 7 in Supplement 3. Of those discharged alive, 30 of 44 (68%) and 26 of 37 (70%) were discharged home in the sodium bicarbonate and placebo groups, respectively. In both groups, most patients who died did so after withdrawal of life-sustaining care. Data on post-cardiac arrest organ dysfunction and laboratory values are provided in eTable 8 in Supplement 3. There were no differences between groups in organ dysfunction at 2, 24, 48, and 72 hours after the cardiac arrest. Post-cardiac arrest values for pH and standard bicarbonate are illustrated in eFigures 7 and 8 in Supplement 3, showing higher values in the sodium bicarbonate group. Prespecified adverse events are reported in eTable 9 in Supplement 3. Alkalosis (35% vs 20%) and hypernatremia (42% vs 29%) after the cardiac

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

arrest were more common in the sodium bicarbonate group compared with the placebo group, respectively (eTable 9 in Supplement 3).

Discussion

This randomized clinical trial showed no significant difference in sustained return of spontaneous circulation between the group randomized to receive sodium bicarbonate and the group randomized to receive placebo during adult in-hospital cardiac arrest. Survival at 30 days and survival at 30 days with a favorable neurologic outcome were also not different between the 2 groups.

Recent European and US guidelines suggest against the routine use of sodium bicarbonate during cardiac arrest.[9,10] These recommendations are based on lack of clinical trial data and US guidelines explicitly acknowledge clinical equipoise.[10] Sodium bicarbonate is commonly used clinically for in-hospital cardiac arrest, with administration in more than half of cardiac arrests in the US,[17,23] suggesting that many clinicians consider sodium bicarbonate beneficial in this setting.[24] Findings from this trial do not support this practice.

Although the current trial is the first of its kind for patients with in-hospital cardiac arrest, the use of buffering agents has previously been tested in 3 randomized trials during out-of-hospital cardiac arrest.[16,25-27] These trials found no significant benefit or harm of buffer administration.[16] The results of these previous trials are difficult to generalize to contemporary in-hospital cardiac arrest. First, the 2 largest trials were conducted more than 30 years ago,[25,26] when cardiac arrest management and outcomes were substantially different. Second, all 3 trials included patients with out-of-hospital cardiac arrest, in which drugs are often administered late. In the 1 trial that reported time to trial drug delivery, the median time to drug delivery was 31 minutes.[27] Patients who remain in cardiac arrest at this time have a poor prognosis,[28,29] and it is unlikely that any drug will have a meaningful effect on outcomes this late. In contrast, the median time to trial drug delivery was 8 minutes in the current trial. Despite this much earlier drug delivery, no effect of sodium bicarbonate on any outcome was found in this trial.

In the current trial, sodium bicarbonate was administered as a bolus dose of 50 mmol up to 2 times. When sodium bicarbonate is administered during cardiac arrest for special circumstances (eg, hyperkalemia or tricyclic antidepressant overdose), a dose of 1 to 2 mmol/kg or 50 mmol was recommended when the trial was designed.[30,31] As accurate weight-based dosing of sodium bicarbonate during a cardiac arrest was not considered feasible, a fixed dose of 50 mmol, up to 2 times, was chosen. The trial drug resulted in expected changes in post-cardiac arrest laboratory values, including higher pH and higher sodium. Despite this, patients who had return of spontaneous circulation in the sodium bicarbonate group remained severely acidotic after cardiac arrest (median pH, 7.11). Whether higher doses of sodium bicarbonate during cardiac arrest could improve outcomes remains unknown.

Table 1. Demographic and Event Characteristics at Baseline According to Trial Group[a]

Characteristic	No. (%)	
	Sodium bicarbonate (n = 372)	Placebo (n = 407)
Demographic		
Age, median (IQR), y	74 (64-79)	73 (64-79)
Sex		
Male	242 (65)	260 (64)
Female	130 (35)	147 (36)
BMI, median (IQR)[b]	27 (23-31)	25 (23-30)
Comorbidities		
Hypertension	240 (65)	251 (62)
Diabetes	104 (28)	114 (28)
Coronary artery disease	112 (30)	103 (25)
Pulmonary disease	104 (28)	110 (27)
Atrial fibrillation	99 (27)	87 (21)
Chronic heart failure	82 (22)	74 (18)
Kidney disease	72 (19)	80 (20)
Stroke	54 (15)	53 (13)
Cancer	53 (14)	68 (17)
Liver disease	20 (5.4)	25 (6.1)
Venous thromboembolism	18 (4.8)	14 (3.4)
Dementia	6 (1.6)	4 (1.0)
Event		
Known metabolic acidosis prior to cardiac arrest[c]	53 (14)	53 (13)
Location		
Hospital ward	229 (62)	268 (66)
Emergency department	61 (16)	65 (16)
Intensive care unit	33 (8.9)	28 (6.9)
Catheterization laboratory	23 (6.2)	23 (5.7)
Other	19 (5.1)	17 (4.2)
Operating room	7 (1.9)	6 (1.5)
Initial rhythm		
Pulseless electrical activity	196 (53)	209 (51)
Asystole	122 (33)	146 (36)
Ventricular fibrillation	30 (8.1)	34 (8.4)
Pulseless ventricular tachycardia	11 (3.0)	12 (2.9)
Nonshockable, only AED available	9 (2.4)	6 (1.5)
Shockable, only AED available	4 (1.1)	0
Monitored	173 (47)	157 (39)
Witnessed	284 (76)	289 (71)
Time from cardiac arrest to epinephrine administration, median (IQR), min	6 (3-8)	5 (3-8)
Time from cardiac arrest to trial drug administration, median (IQR), min	8 (6-12)	8 (6-12)

Abbreviations: AED, automated external defibrillator; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] See eTable 1 in Supplement 3 for additional demographic and event characteristics.

[b] Data were missing for 40 patients (17 in the sodium bicarbonate group and 23 in the placebo group).

[c] Defined as pH less than 7.35 and base excess less than −2 within 6 hours prior to the cardiac arrest. pH and base excess prior to the cardiac arrest were available for 170 patients in the bicarbonate group and 181 in the placebo group.

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

Table 2. Outcomes According to Trial Group[a]

Outcome	No. (%) Sodium bicarbonate (n = 372)	Placebo (n = 407)	Risk or mean difference (95% CI)[b]	Risk ratio (95% CI)
Primary outcome				
Return of spontaneous circulation[c]	146 (39)	150 (37)	0.0 (−6.4 to 6.5)	1.05 (0.88 to 1.24)
30-d Outcomes				
Survival	45 (12)	37 (9.1)	2.3 (−0.7 to 5.3)	1.25 (0.84 to 1.88)
Survival with a favorable neurologic outcome, No./total No. (%)[d]	30/371 (8.1)	22/407 (5.4)	2.2 (−0.3 to 4.7)	1.39 (0.82 to 2.34)
EQ-5D-5L score, assessed by the patient, mean (SD) [No.][e]	57 (23) [43]	62 (24) [37]	−6 (−17 to 4)	NA
EQ-5D-5L score, index value, mean (SD) [No.][e]	57 (31) [43]	49 (36) [37]	5 (−10 to 21)	NA
90-d Outcomes				
Survival	39 (11)	33 (8.1)	1.8 (−1.1 to 4.6)	1.22 (0.79 to 1.88)
Survival with a favorable neurologic outcome, No./total No. (%)[d]	32/371 (8.6)	28/407 (6.9)	1.2 (−1.4 to 3.9)	1.17 (0.73 to 1.90)
EQ-5D-5L score, assessed by the patient, mean (SD) [No.][e]	69 (19) [38]	70 (20) [33]	−2 (−11 to 7)	NA
EQ-5D-5L score, index value, mean (SD) [No.][e]	77 (22) [38]	64 (34) [33]	13 (0 to 26)	NA

Abbreviations: EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; NA, not applicable.

[a] Effect estimates were adjusted for initial rhythm, witnessed status, and age. The widths of the 95% CIs have not been adjusted for multiplicity; therefore, the intervals should not be used in place of hypothesis testing.

[b] Risk differences in percentage points are presented for binary outcomes and mean differences are presented for continuous outcomes.

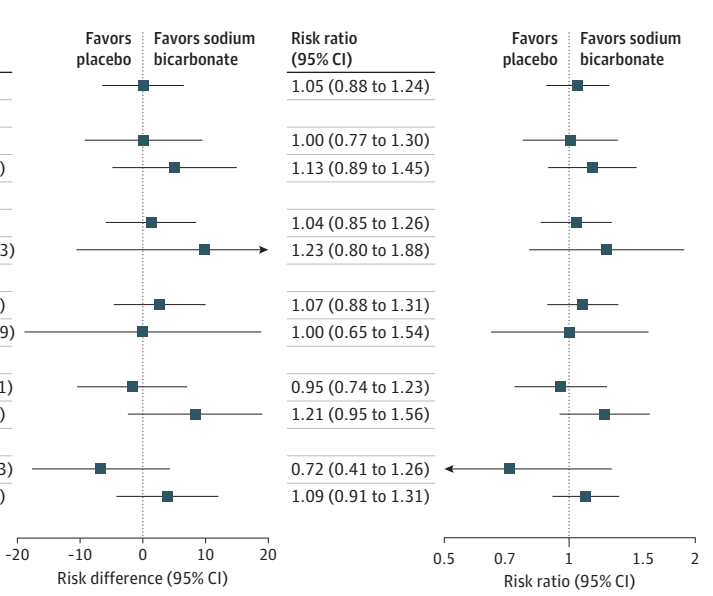
[c] $P = .62$ for the between-group comparison. Because the P value is above .05, no additional P values were calculated for key secondary outcomes (ie, survival at 30 days and survival at 30 days with a favorable neurologic outcome).

[d] Defined as a score of 0 to 3 on the modified Rankin Scale (scores range from 0 to 6, with higher scores indicating greater disability).

[e] The results of the EQ-5D-5L are reported both as the patient-assessed numerical score and as the index value based on Danish data. The numerical score is reported on a scale ranging from 0 to 100, with higher scores indicating better health-related quality of life. The index value can be negative. These analyses included only patients who survived to the specific time point.

Figure 2. Dot and Whisker Plot of Subgroup Analyses of Sustained Return of Spontaneous Circulation

Subgroup	No./total No. (%) Sodium bicarbonate	Placebo	Risk difference (95% CI)	Risk ratio (95% CI)
Overall	146/372 (39)	150/407 (37)	0.0 (-6.4 to 6.5)	1.05 (0.88 to 1.24)
Age, y				
≥73	70/196 (36)	73/205 (36)	0.1 (-9.3 to 9.5)	1.00 (0.77 to 1.30)
<73	76/176 (43)	77/202 (38)	5.1 (-4.9 to 15.0)	1.13 (0.89 to 1.45)
Initial rhythm				
Nonshockable	122/327 (37)	130/361 (36)	1.3 (-5.9 to 8.5)	1.04 (0.85 to 1.26)
Shockable	24/45 (53)	20/46 (43)	9.9 (-10.6 to 30.3)	1.23 (0.80 to 1.88)
Known metabolic acidosis prior to the cardiac arrest				
No	123/319 (39)	127/354 (36)	2.7 (-4.6 to 10.0)	1.07 (0.88 to 1.31)
Yes	23/53 (43)	23/53 (43)	0.0 (-18.9 to 18.9)	1.00 (0.65 to 1.54)
Time from cardiac arrest to trial drug, min				
≥8	73/218 (33)	82/233 (35)	-1.7 (-10.5 to 7.1)	0.95 (0.74 to 1.23)
<8	73/154 (47)	68/174 (39)	8.3 (-2.4 to 19.0)	1.21 (0.95 to 1.56)
Witnessed				
No	15/88 (17)	28/118 (24)	-6.7 (-17.7 to 4.3)	0.72 (0.41 to 1.26)
Yes	131/284 (46)	122/289 (42)	3.9 (-4.2 to 12.0)	1.09 (0.91 to 1.31)



The x-axis for the risk ratios is logarithmic. The risk difference between the groups is shown in percentage points. The effect estimates for the overall effect were adjusted for initial rhythm, witnessed status, and age. The effect estimates within the subgroups were unadjusted. The widths of the 95% CIs have not been adjusted for multiplicity and therefore the intervals should not be used in place of hypothesis testing. Continuous values were dichotomized by the median. Subgroup analyses using continuous values for age and time from cardiac arrest to trial drug are presented in eFigure 1 in Supplement 3.

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

Limitations

This trial has limitations. First, the trial was powered for the outcome of sustained return of spontaneous circulation and not for more patient-centered, long-term outcomes. Such outcomes require large sample sizes to detect between-group differences that are presumed to be relatively small. Achieving such sample sizes for trials including patients with in-hospital cardiac arrest is challenging.[3] Return of spontaneous circulation is more proximately and directly linked to the specific mechanism of drugs used during cardiac arrest. The relatively narrow CI for sustained return of spontaneous circulation suggests that a large difference in this outcome is unlikely. Consequently, a large difference in long-term outcomes also appears unlikely. Second, it was not feasible to measure laboratory values (eg, pH and standard bicarbonate) during the cardiac arrest prior to inclusion in the trial. This is consistent with clinical practice but results in a heterogeneous trial population with various degrees of baseline acidosis. Third, the trial was exclusively conducted in Denmark. Generalizability to other health care systems is unknown.

Conclusions

In this randomized clinical trial, there was no significant difference in sustained return of spontaneous circulation between sodium bicarbonate and placebo in adults with in-hospital cardiac arrest.

ARTICLE INFORMATION

Accepted for Publication: May 23, 2026.

Published Online: June 11, 2026. doi:10.1001/jama.2026.10628

Author Affiliations: Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark (Granfeldt, Kirkegaard, Vallentin, Holmberg, Stankovic, Lind, A. G. Kjærgaard, Houe, Le Breton, L. K. Nielsen, F. G. Hansen, Brændstrup, Thomsen, Sindberg, L. W. Andersen); Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (Granfeldt, Kirkegaard, Vallentin, Holmberg, Espelund, F. G. Hansen, L. W. Andersen); Prehospital Emergency Medical Services, Central Denmark Region, Denmark (Kirkegaard, Vallentin, L. W. Andersen); Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark (Stankovic); Department of Anaesthesia, Centre of Head and Orthopedics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (Vested, Isbye, Kristensen, Krag); Department of Clinical Medicine, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark (Vested, Isbye, J. Kjærgaard, Folke, C. M. Hansen, Iversen, Wiberg, Plovsing, Krag, L. P. K. Andersen); Department of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark (J. Kjærgaard, Wiberg); Department of Anaesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark (Zwisler, Lundsfryd, Petersen, Eskol, K. Andersen); Department of Cardiology, Herlev Gentofte University Hospital, Herlev, Denmark (Folke, C. M. Hansen, Iversen, Schou); Emergency Medical Services, Capital Region, Copenhagen University, Copenhagen, Denmark (Folke, C. M. Hansen); Department of Cardiology, Faculty of Medicine, Aalborg University Hospital, Aalborg, Denmark (Riddersholm, Karlsson); Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark (B. S. Rasmussen); Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (B. S. Rasmussen); Department of Anaesthesia and Intensive Care, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark (Plovsing, Juhl); Department of Anaesthesiology and Intensive Care, Holbæk Hospital, Holbæk, Denmark (Sørensen); Esbjerg and Grindsted Hospital - University Hospital of Southern Denmark, University of Southern Denmark, Odense, Denmark (Kuhne-Qvist, Oxlund); Department of Anaesthesiology and Intensive Care, Viborg Regional Hospital, Viborg, Denmark (Sølling, J. R. Hansen); Department of Anaesthesia and Intensive Care, Zealand University Hospital, Køge, Denmark (L. P. K. Andersen, Jensen); Department of Anaesthesia and Intensive Care, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark (Itenov, Lauritzen); Department of Anaesthesiology and Intensive Care, Gødstrup Hospital, Herning, Denmark (Pedersen, R. P. Nielsen); Department of Anaesthesiology, Zealand University Hospital, Nykøbing Falster, Denmark (Fjeldsøe-Nielsen, Mirzada); Department of Anaesthesiology and Intensive Care, Horsens Hospital, Horsens, Denmark (Secher, Espelund); Department of Anaesthesia and Critical Care Medicine, Hospital Sønderjylland, Aabenraa, Denmark (Eskol, K. Andersen); Department of Anaesthesiology and Intensive Care, University Hospital of Southern Denmark, Kolding, Denmark (Brøchner, Nedergaard); Prehospital Research Unit, Prehospital South – Emergency Medical Services, Region of Southern Denmark, Odense, Denmark (P. M. Hansen); Department of Anaesthesiology and Intensive Care Medicine, Odense University Hospital Svendborg, Svendborg, Denmark (P. M. Hansen, Henschel); Department of Anaesthesiology, Slagelse Hospital, Slagelse, Denmark (Walli, Sandgaard); Department of Cardiology, Zealand University Hospital, Roskilde, Denmark (Asferg); Department of Anaesthesiology and Intensive Care, North Denmark Regional Hospital, Hjørring, Denmark (Ciubotariu, M. H. R. Rasmussen).

Author Contributions: Drs Kirkegaard and L. W. Andersen 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.
Concept and design: Granfeldt, Kirkegaard, Vallentin, Holmberg, Stankovic, L. W. Andersen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Granfeldt, L. W. Andersen.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Kirkegaard, Holmberg, L. W. Andersen.
Obtained funding: Granfeldt, L. W. Andersen.
Administrative, technical, or material support: Isbye, Folke, Schou, Wiberg, Karlsson, Oxlund, L. K. Andersen, Asferg, Sindberg.
Supervision: Folke.

Conflict of Interest Disclosures: Dr Granfeldt reported receiving grants from PAION Pharma GmbH outside the submitted work. Dr J. Kjærgaard reported receiving grants from Novo Nordisk Foundation and Sundhedsdonationer outside the submitted work. Dr Schou reported receiving lecture fees from Boehringer Ingelheim, Novo Nordisk, Novartis, and AstraZeneca and a Bayer Congress Grant to the European Society of Cardiology outside the submitted work. Dr P. Hansen reported receiving grants from Danish Air Ambulance Foundation outside the submitted work. No other disclosures were reported.

Funding/Support: Funding for the trial was provided by the Novo Nordisk Foundation.

Role of the Funder/Sponsor: The Novo Nordisk Foundation 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: Members of the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) Investigators appear in Supplement 1.

Meeting Presentation: This article was presented at the Critical Care Reviews Meeting 2026; June 11, 2026; Belfast, Northern Ireland.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the clinical teams that facilitated inclusion of patients as well as the members of the independent data monitoring committee: Anders Perner, PhD (Copenhagen University Hospital - Rigshospitalet); Gavin Perkins, DSc (University of Warwick); and Giuseppe Ristagno, PhD (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico). The members of the independent data monitoring committee were not compensated for their contributions.

REFERENCES

1. Andersen LW, Holmberg MJ, Løfgren B, Kirkegaard H, Granfeldt A. Adult in-hospital cardiac arrest in Denmark. *Resuscitation*. 2019;140:31-36. doi:10.1016/j.resuscitation.2019.04.046

2. Holmberg MJ, Ross CE, Fitzmaurice GM, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12(7):e005580. doi:10.1161/CIRCOUTCOMES.119.005580

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026

3. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA*. 2019;321(12):1200-1210. doi:10.1001/jama.2019.1696

4. Holmberg MJ, Granfeldt A, Girotra S, Donnino MW, Andersen LW; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Trends in survival and introduction of the 2010 and 2015 guidelines for adult in-hospital cardiac arrest. *Resuscitation*. 2020;157:112-120. doi:10.1016/j.resuscitation.2020.10.022

5. Donnino MW, Salciccioli JD, Howell MD, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ*. 2014;348:g3028. doi:10.1136/bmj.g3028

6. Andersen LW, Isbye D, Kjærgaard J, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2021;326(16):1586-1594. doi:10.1001/jama.2021.16628

7. Kudenchuk PJ, Brown SP, Daya M, et al; Resuscitation Outcomes Consortium Investigators. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374(18):1711-1722. doi:10.1056/NEJMoa1514204

8. Perkins GD, Ji C, Deakin CD, et al; PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379(8):711-721. doi:10.1056/NEJMoa1806842

9. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council guidelines 2025 adult advanced life support. *Resuscitation*. 2025;215(suppl 1):110769. doi:10.1016/j.resuscitation.2025.110769

10. Wigginton JG, Agarwal S, Bartos JA, et al. 2025 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2025;152(suppl 2):S538-S577. doi:10.1161/CIR.0000000000001376

11. Høybye M, Stankovic N, Holmberg M, Christensen HC, Granfeldt A, Andersen LW. In-hospital vs out-of-hospital cardiac arrest: patient characteristics and survival. *Resuscitation*. 2021;158:157-165. doi:10.1016/j.resuscitation.2020.11.016

12. Wang CH, Chang WT, Huang CH, et al. Associations between early intra-arrest blood acidaemia and outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. *J Formos Med Assoc*. 2020;119(2):644-651. doi:10.1016/j.jfma.2019.08.020

13. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2013;310(3):270-279. doi:10.1001/jama.2013.7832

14. Vukmir RB, Bircher N, Safar P. Sodium bicarbonate in cardiac arrest: a reappraisal. *Am J Emerg Med*. 1996;14(2):192-206. doi:10.1016/S0735-6757(96)90133-3

15. Bar-Joseph G, Kette F, von Planta M, Wiklund L. Acid–base considerations and buffer therapy. In: Chamberlain DA, Halperin HR, Kern KB, Paradis NA, Wenzel V, eds. *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*. 2nd ed. Cambridge University Press; 2007:674-697. doi:10.1017/CBO9780511544828.039

16. Lind PC, Hansen FG, Holmberg MJ, Jessen MK, Granfeldt A, Andersen LW. Bicarbonate and other buffer therapies in acute metabolic acidosis: a systematic review and meta-analysis. *Acta Anaesthesiol Scand*. 2026;70(4):e70212. doi:10.1111/aas.70212

17. Moskowitz A, Ross CE, Andersen LW, Grossestreuer AV, Berg KM, Donnino MW. Trends over time in drug administration during adult in-hospital cardiac arrest. *Crit Care Med*. 2019;47(2):194-200. doi:10.1097/CCM.0000000000003506

18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607. doi:10.1161/01.STR.19.5.604

19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736. doi:10.1007/s11136-011-9903-x

20. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. *Appl Health Econ Health Policy*. 2021;19(4):579-591. doi:10.1007/s40258-021-00639-3

21. Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ*. 2002;325(7365):652-654. doi:10.1136/bmj.325.7365.652

22. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985;4(2):213-226. doi:10.1002/sim.4780040211

23. Holmberg MJ, Granfeldt A, Andersen LW. Bicarbonate, calcium, and magnesium for in-hospital cardiac arrest—an instrumental variable analysis. *Resuscitation*. 2023;191:109958. doi:10.1016/j.resuscitation.2023.109958

24. Ross CE, Sorcher JL, Gardner R, et al. Why physicians use sodium bicarbonate during cardiac arrest: a cross-sectional survey study of adult and pediatric clinicians. *Resusc Plus*. 2024;20:100830. doi:10.1016/j.resplu.2024.100830

25. Dybvik T, Strand T, Steen PA. Buffer therapy during out-of-hospital cardiopulmonary resuscitation. *Resuscitation*. 1995;29(2):89-95. doi:10.1016/0300-9572(95)00850-S

26. Vukmir RB, Katz L; Sodium Bicarbonate Study Group. Sodium bicarbonate improves outcome in prolonged prehospital cardiac arrest. *Am J Emerg Med*. 2006;24(2):156-161. doi:10.1016/j.ajem.2005.08.016

27. Ahn S, Kim YJ, Sohn CH, et al. Sodium bicarbonate on severe metabolic acidosis during prolonged cardiopulmonary resuscitation: a double-blind, randomized, placebo-controlled pilot study. *J Thorac Dis*. 2018;10(4):2295-2302. doi:10.21037/jtd.2018.03.124

28. Okubo M, Komukai S, Andersen LW, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Duration of cardiopulmonary resuscitation and outcomes for adults with in-hospital cardiac arrest: retrospective cohort study. *BMJ*. 2024;384:e076019. doi:10.1136/bmj-2023-076019

29. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association between duration of resuscitation and favorable outcome after out-of-hospital cardiac arrest: implications for prolonging or terminating resuscitation. *Circulation*. 2016;134(25):2084-2094. doi:10.1161/CIRCULATIONAHA.116.023309

30. Panchal AR, Bartos JA, Cabañas JG, et al; Adult Basic and Advanced Life Support Writing Group. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(suppl 2):S366-S468. doi:10.1161/CIR.0000000000000916

31. Lott C, Truhlář A, Alfonzo A, et al; ERC Special Circumstances Writing Group Collaborators. European Resuscitation Council Guidelines 2021: cardiac arrest in special circumstances. *Resuscitation*. 2021;161:152-219. doi:10.1016/j.resuscitation.2021.02.011

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Ben Gurion Univ of the Negev user on 06/24/2026