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Effect of Intravenous or Intraosseous Calcium vs Saline on Return of Spontaneous Circulation in Adults With Out-of-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE It is unclear whether administration of calcium has a beneficial effect in patients with cardiac arrest.

OBJECTIVE To determine whether administration of calcium during out-of-hospital cardiac arrest improves return of spontaneous circulation in adults.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, placebo-controlled randomized clinical trial included 397 adult patients with out-of-hospital cardiac arrest and was conducted in the Central Denmark Region between January 20, 2020, and April 15, 2021. The last 90-day follow-up was on July 15, 2021.

INTERVENTIONS The intervention consisted of up to 2 intravenous or intraosseous doses with 5 mmol of calcium chloride (n = 197) or saline (n = 200). The first dose was administered immediately after the first dose of epinephrine.

MAIN OUTCOMES AND MEASURES The primary outcome was sustained return of spontaneous circulation. The secondary outcomes included survival and a favorable neurological outcome (modified Rankin Scale score of 0-3) at 30 days and 90 days.

RESULTS Based on a planned interim analysis of 383 patients, the steering committee stopped the trial early due to concerns about harm in the calcium group. Of 397 adult patients randomized, 391 were included in the analyses (193 in the calcium group and 198 in the saline group; mean age, 68 [SD, 14] years; 114 [29%] were female). There was no loss to follow-up. There were 37 patients (19%) in the calcium group who had sustained return of spontaneous circulation compared with 53 patients (27%) in the saline group (risk ratio, 0.72 [95% CI, 0.49 to 1.03]; risk difference, −7.6% [95% CI, −16% to 0.8%]; $P = .09$). At 30 days, 10 patients (5.2%) in the calcium group and 18 patients (9.1%) in the saline group were alive (risk ratio, 0.57 [95% CI, 0.27 to 1.18]; risk difference, −3.9% [95% CI, −9.4% to 1.3%]; $P = .17$). A favorable neurological outcome at 30 days was observed in 7 patients (3.6%) in the calcium group and in 15 patients (7.6%) in the saline group (risk ratio, 0.48 [95% CI, 0.20 to 1.12]; risk difference, −4.0% [95% CI, −8.9% to 0.7%]; $P = .12$). Among the patients with calcium values measured who had return of spontaneous circulation, 26 (74%) in the calcium group and 1 (2%) in the saline group had hypercalcemia.

CONCLUSIONS AND RELEVANCE Among adults with out-of-hospital cardiac arrest, treatment with intravenous or intraosseous calcium compared with saline did not significantly improve sustained return of spontaneous circulation. These results do not support the administration of calcium during out-of-hospital cardiac arrest in adults.

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Visual Abstract

Multimedia

Supplemental content

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In 2018, more than 5000 out-of-hospital cardiac arrests occurred in Denmark.[1] Survival following out-of-hospital cardiac arrest is poor; only 16% of patients were still alive after 30 days based on data from 2018 for Denmark.[1] Of those with a nonshockable rhythm, which accounts for approximately 80% of all cardiac arrests, less than 10% are alive after 30 days and, compared with those who had a shockable rhythm, survival has not improved substantially over the last decade.[1] Pharmacological interventions for patients with cardiac arrest are limited and there is a need for evidence-based interventions to improve outcomes.[2-4]

Calcium plays an important role in cardiac muscle contraction and is generally acknowledged for its inotropic and vasopressor effects.[5,6] These effects could be beneficial in the setting of cardiac arrest. Two small, randomized trials[7,8] from 1985, including a total of 163 patients, found that administration of calcium did not result in a significant increase in return of spontaneous circulation for patients with out-of-hospital cardiac arrest and asystole or pulseless electrical activity. However, both trials[7,8] had point estimates that favored calcium. Since then, to our knowledge, there have been no randomized clinical trials assessing the effect of administration of calcium during cardiac arrest. Observational studies with high risk of bias[9,10] have found conflicting results.[11-14] Although there are limited data to support the use of calcium during cardiac arrest, calcium is commonly administered during cardiac arrest in some settings.[15,16]

The Calcium for Out-of-Hospital Cardiac Arrest trial was designed to address the hypothesis that administration of calcium during out-of-hospital cardiac arrest would result in improved return of spontaneous circulation.

Key Points

Question Does administration of calcium during out-of-hospital cardiac arrest improve sustained return of spontaneous circulation?

Findings In this randomized clinical trial that included 391 adults with out-of-hospital cardiac arrest, 19% had sustained return of spontaneous circulation after receiving treatment with intravenous or intraosseous calcium compared with 27% after receiving saline. This difference was not statistically significant, but the trial was terminated early due to concerns about harm in the calcium group.

Meaning Treatment with intravenous or intraosseous calcium did not significantly improve sustained return of spontaneous circulation among adults with out-of-hospital cardiac arrest.

Methods

Trial Design and Oversight

This trial was an investigator-initiated, placebo-controlled, parallel group, double-blind, superiority, randomized clinical trial assessing administration of intravenous or intraosseous calcium during out-of-hospital cardiac arrest in adults. The trial protocol (Supplement 1) was written by the steering committee and was approved by the regional ethics committee and the Danish Medicines Agency. Discrepancies between the trial protocol and what is reported in this article appear in the eMethods in Supplement 2. Consent was temporarily obtained from a physician not involved in the trial. Oral and written consent were later obtained for all patients who survived. In accordance with Danish legislation, the patient consents were obtained after the patient regained capacity or when a surrogate became available (additional details appear in Supplement 1). An independent data and safety monitoring committee reviewed the trial data after inclusion of approximately 50, 200, and 400 patients. There were no predefined stopping criteria for harm, futility, or benefit.

Setting and Patients

The trial was conducted in the Central Denmark Region, which has approximately 1.3 million inhabitants. The 2-tiered emergency medical services system responds to all cardiac arrests with an ambulance and a physician-manned mobile emergency care unit.[17] Almost all patients with return of spontaneous circulation or ongoing cardiopulmonary resuscitation during transfer are transported to a single university hospital capable of coronary catheterization and percutaneous coronary intervention, extracorporeal cardiopulmonary resuscitation, and care after cardiac arrest, including targeted temperature management. Treatment both during and after cardiac arrest generally adheres to European guidelines.[18]

Adult patients (aged ≥18 years) were eligible for the trial if they had an out-of-hospital cardiac arrest and received at least 1 dose of epinephrine during the cardiac arrest. The exclusion criteria were traumatic cardiac arrest (including strangulation and foreign body asphyxia), known or strongly suspected pregnancy, prior enrollment in the trial, receipt of epinephrine outside the trial (from a unit not participating in the trial), or a clinical indication (eg, suspected hypocalcemia or hyperkalemia) for calcium administration during the cardiac arrest.

Randomization

Patients were randomized in a 1:1 ratio to either calcium or saline in block sizes of 2, 4, or 6 (**Figure 1**). The randomization was generated using a random-number generator and stratified according to mobile emergency care unit stations.

Intervention

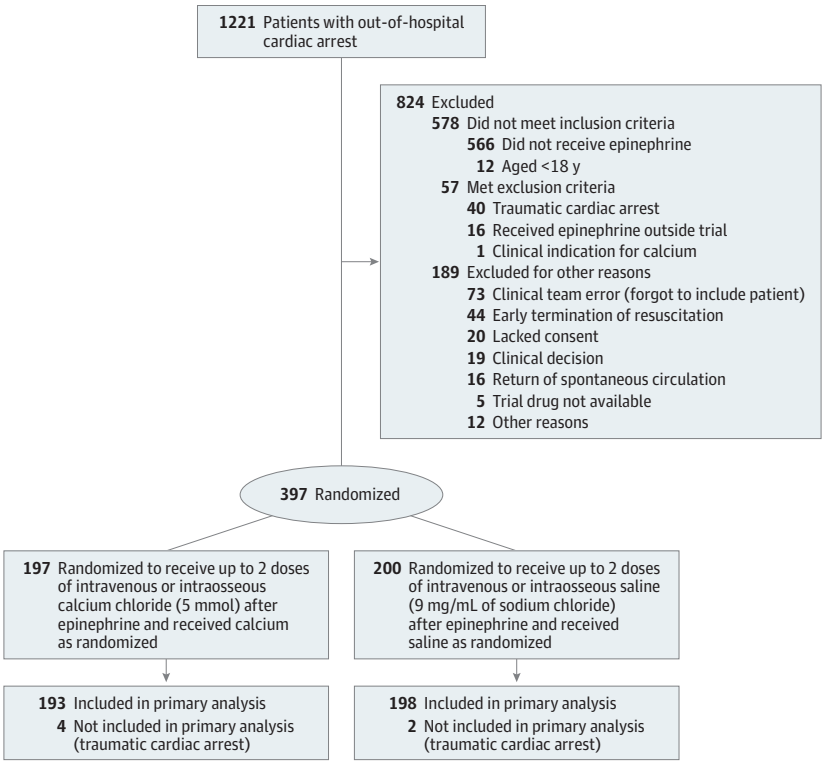
The trial drug consisted of 5 mmol of calcium chloride (corresponding to 200 mg of calcium or 735 mg of calcium chloride dihydrate) or 9 mg/mL of sodium chloride (saline control). The intravenous or intraosseous administration of the trial drug was performed immediately after the first dose of epinephrine. A second dose of the trial drug was administered after the second dose of epinephrine if the patient remained in cardiac arrest. The trial drug was administered as a rapid bolus.

The trial was double-blind with patients, investigators, and the clinical team being unaware of the allocated treatment.

Outcomes

The primary outcome was sustained return of spontaneous circulation, which was defined as spontaneous circulation with no further need for chest compressions for at least 20 minutes. Data

Figure 1. Screening and Randomization of Patients in the Calcium for Out-of-Hospital Cardiac Arrest Trial



also were collected on any return of spontaneous circulation and return of spontaneous circulation at hospital arrival.

The key secondary outcomes included survival at 30 days and survival at 30 days with a favorable neurological outcome, which was defined as a score of 0 to 3 on the modified Rankin Scale. Higher scores indicate worse outcomes on the 7-point modified Rankin Scale.[19] Additional outcomes described below were considered tertiary.

At 30 days, health-related quality of life was assessed using the 5-dimensional, 5-level EuroQol score as a numeric value directly assessed by the patient and as an index value (based on Danish data[20,21]). The numeric value is reported on a scale from 0 to 100 with higher scores indicating a better health-related quality of life. The index value can be negative. Outcomes were assessed in person if the patient was still an inpatient at the hospital or by telephone interview if the patient had been discharged. If the patient was not able to participate, relatives of the patient or clinical personnel provided responses for the assessment. Similar outcomes were assessed at 90 days, 180 days, and 1 year. Results for 30-day and 90-day follow-up are provided in this article.

The Sequential Organ Failure Assessment score was collected at 2, 24, 48, and 72 hours after the cardiac arrest. Data were collected on vasopressor-free and ventilator-free days within the first 7 days. Predefined potential adverse events were collected. A full list of adverse events and definitions appears in the trial protocol (Supplement 1).

Sample Size Calculation

The sample size was based on the primary outcome of sustained return of spontaneous circulation. The original sample size (n = 430) was updated based on blinded review of event data after 270 patients were enrolled in the trial (additional details appear in Supplement 1). Based on this, it was assumed that 27% of patients in the calcium group and 18% in the saline group would achieve return of spontaneous circulation. With these estimates, an α level of .05, and the use of the χ^2 test, a total of 674 patients were required to have 80% power to detect a statistically significant between-group difference.

Statistical Analysis

Patients were analyzed according to their randomized assignment. The analyses only included patients receiving the first dose of the trial drug and meeting all inclusion criteria and no exclusion criteria.[22]

Binary data are presented as counts and percentages and between-group differences are presented as both risk differences and risk ratios with 95% CIs. The 95% CIs were estimated using the method described by Miettinen and Nurmimen.[23] Two-sided *P* values (obtained from the Fisher exact test) are reported for the primary outcome and only for key secondary outcomes. $P<.05$ was considered statistically significant. As a sensitivity analysis, the risk ratio for the primary outcome was estimated while adjusting for the stratification variable and strong prognostic factors (specifically age,

whether the cardiac arrest was witnessed, whether bystander cardiopulmonary resuscitation was initiated, and the initial rhythm) were used as covariates.[24] Log-binomial regression was used for this analysis. Continuous data are presented as means with SDs or medians with IQRs depending on the distribution of the data. Between-group differences for the continuous outcomes are presented as mean differences with 95% CIs obtained from a generalized linear model with robust errors.

Five predefined subgroup analyses were performed according to the initial rhythm, the timing of the drug administration, intravenous vs intraosseous administration, whether the cardiac arrest was witnessed, and whether bystander cardiopulmonary resuscitation was performed. Because the trial was not powered to detect subgroup differences, these analyses should be considered as exploratory and hypothesis-generating.

Bayesian analyses were conducted to supplement the primary frequentist analyses. Priors were specified to reflect a range of beliefs (the expected treatment effect expressed as a risk ratio) for the included outcomes. The priors included noninformative, skeptical (no effect), optimistic (beneficial effect), and pessimistic (harmful effect) beliefs.[25] The strength of each informative belief (the variance of the expected treatment effect) was characterized as strong, moderate, or weak, allowing for harm or benefit of 5%, 15%, and 30%, respectively. All priors were prespecified using a standardized approach and assumed a normal distribution on a log-risk scale.[25] Posterior probabilities were estimated using Markov chain Monte Carlo methods with 1 chain, 10 000 burn-ins, 1 000 000 iterations, and a thinning rate of 100 to reduce sample autocorrelation. The results are reported graphically and as mean risk ratios with equal-tailed 95% credible intervals and as the posterior probability of significant harm (risk ratio <1.0, <0.8, and <0.5) or benefit (risk ratio >1.0, >1.2, and >1.5).

All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Patient Characteristics

On April 15, 2021, the independent data and safety monitoring committee recommended that the trial be stopped due to a signal of harm in the calcium group (eTable 1 in Supplement 2). This was based on unblinded data from 383 patients included in the trial between January 20, 2020, and April 6, 2021. Based on this recommendation, the steering committee immediately stopped the trial.

From January 20, 2020, to April 15, 2021, a total of 1221 patients had an out-of-hospital cardiac arrest in the Central Denmark Region (Figure 1). Of these, 397 patients received the trial drug. Six patients with a traumatic cardiac arrest (an exclusion criterion) inadvertently received the trial drug and were excluded from the analyses, leaving 193 patients in the calcium group and 198 patients in the saline group. There was no loss to follow-up. The last 90-day follow-up was on July 15, 2021.

Table 1. Baseline Characteristics of Patients

	Calcium (n = 193)	Saline (n = 198)
Age, mean (SD), y	67 (14)	69 (14)
Sex, No. (%)		
Male	131 (68)	146 (74)
Female	62 (32)	52 (26)
Medical history, No. (%)		
Arterial hypertension	76 (39)	90 (45)
Pulmonary disease	49 (25)	56 (28)
Coronary artery disease	46 (24)	46 (23)
Diabetes	38 (20)	43 (22)
Kidney disease	35 (18)	44 (22)
Atrial fibrillation	33 (17)	50 (25)
Chronic heart failure	32 (17)	36 (18)
Stroke	20 (10)	24 (12)
Venous thromboembolism	9 (5)	10 (5)
Dementia	7 (4)	5 (3)
Cancer	5 (3)	9 (5)
Liver disease	3 (2)	5 (3)
Cardiac arrest characteristics		
Location, No. (%)		
Home	160 (83)	159 (80)
Public area	33 (17)	39 (20)
Witnessed status, No. (%)		
Bystander	101 (52)	99 (50)
Emergency medical services	16 (8)	13 (7)
Not witnessed	76 (39)	86 (43)
Bystander response, No./total (%)[a]		
Cardiopulmonary resuscitation	146/177 (82)	164/185 (89)
Automated external defibrillator shock	14/177 (8)	13/185 (7)
Initial manual rhythm analysis by emergency medical services, No. (%)		
Asystole	103 (53)	96 (48)
Pulseless electrical activity	47 (24)	49 (25)
Ventricular fibrillation	39 (20)	49 (25)
Ventricular tachycardia	4 (2)	4 (2)
Administration and drug characteristics		
Intravenous administration, No. (%)	78 (40)	79 (40)
Intraosseous administration, No. (%)	115 (60)	119 (60)
Tibial	103 (90)	103 (87)
Humeral	12 (10)	16 (13)
Time to administration, median (IQR), min		
Epinephrine	17 (12-22)	17 (14-22)
Trial drug	17 (13-23)	18 (15-23)
No. of trial drug doses		
1	53 (27)	53 (27)
2	140 (73)	145 (73)

[a] Not witnessed by emergency medical services (n = 362).

Baseline characteristics were similar in the 2 groups (**Table 1** and eTable 2 in Supplement 2). The mean age was 68 years (SD, 14 years) and 114 (29%) were female. Most patients had the cardiac arrest at home (82%) and had an initial nonshockable rhythm (75%). There were data on fraction and frequency of

Table 2. Primary and Secondary Outcomes

	Calcium (n = 193)	Saline (n = 198)	Risk ratio (95% CI)	Difference, % (95% CI)[a]	*P* value[b]
Primary outcome					
Sustained return of spontaneous circulation	37 (19)	53 (27)	0.72 (0.49 to 1.03)	−7.6 (−16 to 0.8)	.09
Secondary outcomes					
Survival at 30 d	10 (5.2)	18 (9.1)	0.57 (0.27 to 1.18)	−3.9 (−9.4 to 1.3)	.17
Survival at 30 d with a favorable neurological outcome[c]	7 (3.6)	15 (7.6)	0.48 (0.20 to 1.12)	−4.0 (−8.9 to 0.7)	.12
5-dimensional, 5-level EuroQol score at 30 d, mean (SD)					
Assessed by the patient[d]	58 (25)	66 (12)		−8 (−24 to 7)	
Index value[e]	52 (23)	62 (30)		−10 (−29 to 9)	
Survival at 90 d	10 (5.2)	18 (9.1)	0.57 (0.27 to 1.18)	−3.9 (−9.4 to 1.3)	
Survival at 90 d with a favorable neurological outcome[c]	7 (3.6)	18 (9.1)	0.40 (0.17 to 0.91)	−5.5 (−11 to −0.7)	
5-dimensional, 5-level EuroQol score at 90 d, mean (SD)					
Assessed by the patient[d]	62 (33)	79 (14)		−17 (−37 to 4)	
Index value[e]	59 (35)	85 (11)		−26 (−47 to −5)	

[a] Risk difference for binary outcomes and mean difference for continuous outcomes.

[b] Obtained from the Fisher exact test and are only provided for the primary and key secondary outcomes per the trial protocol.

[c] Modified Rankin Scale score of 0 to 3 (7-point scale); higher scores indicate worse outcomes.

[d] Reported on a scale from 0 to 100; higher scores indicate better health-related quality of life.

[e] Indexed based on Danish data.[21] Can be a negative value.

chest compression for 65% of the patients and both were comparable between the groups (eFigures 1-2 in Supplement 2).

The median time from the cardiac arrest to administration of the trial drug was 18 minutes (IQR, 14- 23 minutes). The trial drug was most commonly administered through intraosseous access (60%) and 73% of patients received both doses of the trial drug. The only protocol deviations recorded (the second dose of the trial drug was not administered despite the patient still being in cardiac arrest) were in 9 patients (4.7%) in the calcium group and 9 patients (4.5%) in the saline group. Calcium chloride was administered outside the trial protocol to 4 patients (2.1%) in the calcium group and 2 patients (1.0%) in the saline group. Additional details on intracardiac arrest interventions appear in eTable 3 in Supplement 2. Details on interventions used after cardiac arrest appear in eTable 4 in Supplement 2.

Primary Outcome

The primary outcome of sustained return of spontaneous circulation occurred in 37 patients (19%) in the calcium group and 53 patients (27%) in the saline group (risk ratio, 0.72 [95% CI, 0.49-1.03], *P* = .09; **Table 2**). The results for any return of spontaneous circulation and return of spontaneous circulation at hospital arrival were similar (eTable 5 in Supplement 2). The results were attenuated in the adjusted analysis (risk ratio, 0.81 [95% CI, 0.56-1.17]). The results were generally consistent across predefined subgroups (**Figure 2**).

Secondary Outcomes

Survival at 30 days occurred in 10 patients (5.2%) in the calcium group and 18 patients (9.1%) in the saline group (risk ratio, 0.57 [95% CI, 0.27-1.18], *P* = .17; Table 2). Survival at 30 days with a favorable neurological outcome occurred in 7 patients (3.6%) in the calcium group and 15 patients (7.6%) in the saline group (risk ratio, 0.48 [95% CI, 0.20-1.12], *P* = .12; Table 2). The results were generally consistent across predefined subgroups (eFigures 3-4 in Supplement 2).

Tertiary Outcomes

Survival at 90 days was identical to 30-day survival (Table 2). The Kaplan-Meier curve for 90-day survival appears in eFigure 5 in Supplement 2. Survival at 90 days with a favorable neurological outcome occurred in 7 patients (3.6%) in the calcium group and 18 patients (9.1%) in the saline group (risk ratio, 0.40 [95% CI, 0.17-0.91]). Quality-of-life scores in survivors were lower in the calcium group, although the 95% CIs were wide (Table 2).

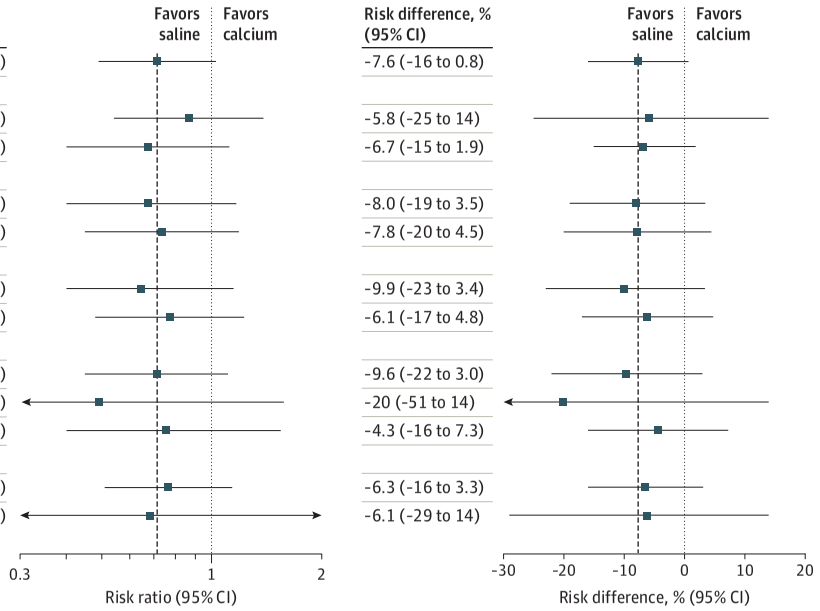
The first ionized calcium level after return of spontaneous circulation was higher in the calcium group (1.41 mmol/L [SD, 0.15 mmol/L]) compared with the saline group (1.17 mmol/L [SD, 0.07 mmol/L]) and the mean between-group difference was 0.23 mmol/L (95% CI, 0.18-0.28 mmol/L), and remained higher for approximately 12 hours (eFigure 6 in Supplement 2). The first collected potassium level, pH level, and lactate level after return of spontaneous circulation appear in eTable 6 in Supplement 2. In addition, data on organ dysfunction after return of spontaneous circulation (assessed by the Sequential Organ Failure Assessment score and vasopressor-free and ventilator-free days) appear in eTable 6 in Supplement 2. Additional details on outcomes appear in eTables 7 through 9 in Supplement 2.

Adverse Events

Among patients with calcium values measured who had return of spontaneous circulation, 26 patients (74%) in the calcium group and 1 patient (2%) in the saline group had hypercalcemia. Additional adverse events appear in eTable 10 in Supplement 2.

Figure 2. Subgroup Results for the Primary Outcome of Sustained Return of Spontaneous Circulation

	Return of spontaneous circulation, No./total (%)			Risk difference, % (95% CI)
	Calcium	Saline	Risk ratio (95% CI)	
Overall	37/193 (19)	53/198 (27)	0.72 (0.49 to 1.03)	-7.6 (-16 to 0.8)
Initial rhythm				
Shockable	17/43 (40)	24/53 (45)	0.87 (0.54 to 1.39)	-5.8 (-25 to 14)
Nonshockable	20/150 (13)	29/145 (20)	0.67 (0.40 to 1.12)	-6.7 (-15 to 1.9)
Time to trial drug, min				
≥18	15/91 (16)	26/106 (25)	0.67 (0.38 to 1.17)	-8.0 (-19 to 3.5)
<18	22/102 (22)	27/92 (29)	0.73 (0.45 to 1.19)	-7.8 (-20 to 4.5)
Route of administration				
Intravenous	14/78 (18)	22/79 (28)	0.64 (0.36 to 1.15)	-9.9 (-23 to 3.4)
Intraosseous	23/115 (20)	31/119 (26)	0.77 (0.48 to 1.23)	-6.1 (-17 to 4.8)
Witnessed status				
Bystander	24/101 (24)	33/99 (33)	0.71 (0.45 to 1.11)	-9.6 (-22 to 3.0)
EMS	3/16 (19)	5/13 (38)	0.49 (0.15 to 1.58)	-20 (-51 to 14)
Not witnessed	10/76 (13)	15/86 (17)	0.75 (0.36 to 1.55)	-4.3 (-16 to 7.3)
Bystander CPR				
Yes	30/146 (21)	44/164 (27)	0.77 (0.51 to 1.14)	-6.3 (-16 to 3.3)
No	4/31 (13)	4/21 (19)	0.68 (0.20 to 2.30)	-6.1 (-29 to 14)



Results are presented for the 5 predefined subgroups. The time from cardiac arrest to trial drug administration was dichotomized at the median. Only cardiac arrests not witnessed by emergency medical services (EMS) were included in the bystander cardiopulmonary resuscitation (CPR) subgroup. The vertical dashed lines represent the estimated effect in the primary outcome analysis. The vertical dotted lines represent no difference between the calcium and saline groups.

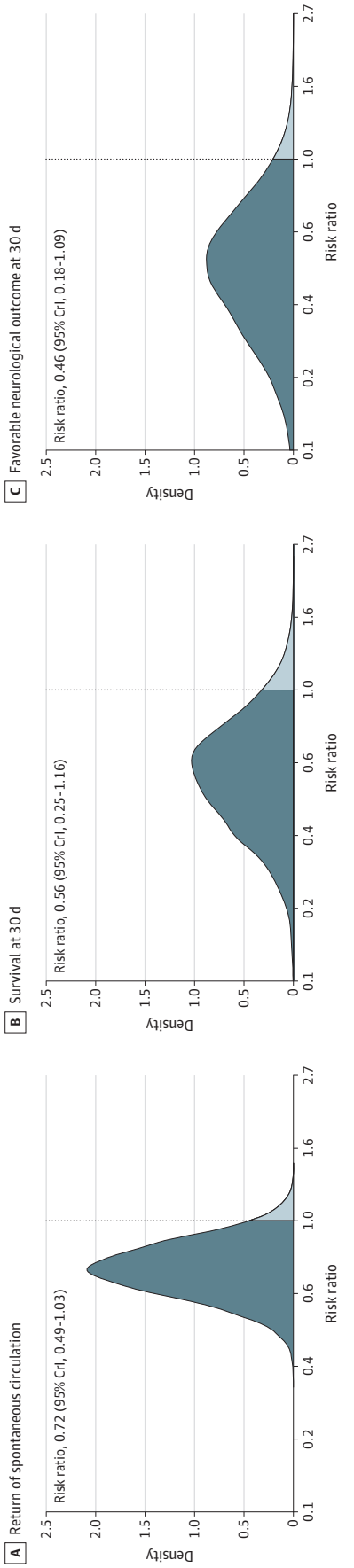


Figure 3. Posterior Probability Distributions Based on Noninformative Priors

The results from the bayesian analyses are presented as posterior probability distributions based on noninformative priors. The x-axis is logarithmic. The vertical dotted lines represent no effect (ie, a risk ratio of 1). The dark blue shaded areas represent values below 1 (ie, a harmful effect of calcium) and the light blue shaded areas represent values above 1 (ie, a beneficial effect of calcium). CrI indicates credible interval. Additional results from the bayesian analysis appear in Supplement 2.

Bayesian Analysis

The posterior probability distribution for return of spontaneous circulation, survival at 30 days, and survival at 30 days with a favorable neurological outcome based on noninformative priors appear in **Figure 3**. The probability that calcium has a beneficial effect (ie, a risk ratio >1.0) based on the data is 4% for return of spontaneous circulation, 6% for survival at 30 days, and 4% for survival with a favorable neurological outcome at 30 days. The corresponding probabilities for a risk ratio greater than 1.2 were 0%, 2%, and 1%. Additional results, including for all the informative priors, appear in eTables 11 through 13 and eFigures 7 through 9 in Supplement 2.

Discussion

In this randomized clinical trial, the administration of calcium, compared with saline, did not result in a statistically significant difference in sustained return of spontaneous circulation for patients with out-of-hospital cardiac arrest. In addition, there were no statistically significant differences in 30-day survival or 30-day survival with a favorable neurological outcome. Although not reaching statistical significance, patients receiving calcium had worse outcomes, including worse 30-day survival with a favorable neurological outcome. At 90 days, fewer patients in the calcium group had a favorable neurological outcome and quality of life was lower in survivors.

Given that the trial was stopped early, the results should be interpreted carefully. Trials that are stopped early based on knowledge of the accruing results tend to overestimate the effects.[26] Furthermore, given the widths of the 95% CIs, it is possible that the point estimates suggesting harm are chance findings. In the adjusted analysis for the primary outcome, the effect estimate still suggested harm, but the size of the effect was attenuated. Supporting a true harmful effect of calcium administration during cardiac arrest is the consistent signal across multiple outcomes and time points.

The rationale for the current trial was the well-established inotropic effect of administered calcium, calcium's role in maintaining vascular tone, and a nonsignificant increase in return of spontaneous circulation found in 2 previous small trials.[7,8,27-29] Although contrary to the original hypothesis, there are theoretical mechanisms that could potentially explain a harmful effect of calcium during cardiac arrest. Due to adenosine triphosphate depletion during ischemia, sodium accumulates intracellularly, reducing the transmembrane sodium gradient and causing the sodium-calcium exchanger to operate in reverse mode.[30,31] High levels of calcium immediately after administration of calcium may have caused cytosolic and mitochondrial calcium overload during the cardiac arrest. This may have caused cardiac hypercontraction, a phenomenon termed *stone heart*.[30,32] In addition, because calcium is involved in multiple intracellular signaling pathways, cytosolic and mitochondrial calcium overload could have promoted oxidative stress, release of proapoptotic factors, and activation of calcium-dependent lipases, proteases, and nucleases.[33,34]

European and US cardiac arrest guidelines suggest that calcium should only be administered during cardiac arrest in special circumstances, such as during cardiac arrest caused by hyperkalemia or hypocalcemia or during an overdose of calcium channel blockers.[2,35] Although limited data have been published on the actual use of calcium in the out-of-hospital cardiac arrest setting, calcium is often administered during in-hospital cardiac arrest.[15,16] In a large, multicenter, US registry of in-hospital cardiac arrest, calcium was administered in approximately 25% to 30% of adult patients and 30% to 50% of pediatric patients, corresponding to approximately 90 000 patients receiving calcium during in-hospital cardiac arrest each year in the US alone.[15,16,36] The rationale for administration of calcium in this setting is unclear but could reflect either a perceived etiology of the cardiac arrest in which calcium is currently recommended (eg, hyperkalemia) or based on a hypothesis that calcium would be beneficial in unselected patients with cardiac arrest. The findings from this trial suggest that the administration of calcium to an unselected cardiac arrest population is unlikely to result in improved outcomes and may in fact result in worse outcomes.

This trial has several strengths. Administration of the trial drug was blinded, delivered quickly after the administration of epinephrine, and there were few protocol deviations or use of calcium outside the protocol. The administration of calcium resulted in a clinically relevant increase in ionized calcium values at hospital arrival. The trial included patient-relevant outcomes, including quality of life, and there was no loss to follow-up.

Limitations

The trial also has several limitations. First, the trial was stopped early and did not reach its preplanned sample size. Even though continuing the trial would have resulted in more precise estimates of the treatment effect, it was not considered ethically justified to continue after the results of the interim analysis were evident. This decision was consistent with the recommendations from the independent data and safety monitoring committee.

Second, the trial only tested 1 dosing regime and timing and the trial results cannot necessarily be extrapolated to other doses or a different timing interval.

Third, the current trial was conducted in the out-of-hospital setting with a relatively long time to drug delivery. The generalizability to the in-hospital setting is therefore unclear.

Conclusions

Among adults with out-of-hospital cardiac arrest, treatment with intravenous or intraosseous calcium compared with saline did not significantly improve sustained return of spontaneous circulation. These results do not support the administration of calcium during out-of-hospital cardiac arrest in adults.

ARTICLE INFORMATION

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