Supplemental Online Content

Vallentin MF, Granfeldt A, Meilandt C, et al. 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. *JAMA*. doi:10.1001/jama.2021.20929

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Discrepancies between the manuscript and the protocol

There are a few discrepancies between the protocol and the manuscript. These are described here.

1) The protocol stated that an article describing the methodology of the trial would be published prior to the end of the trial. As the trial was prematurely stopped, this article was not written.

2) In the protocol, we stated that we would primarily assess pH-corrected ionized calcium values. However, this was a mistake as uncorrected calcium values are more relevant, especially given the severe acidosis in cardiac arrest patients. We have therefore decided to include uncorrected ionized calcium values in the manuscript.

3) The protocol states "Continuous outcomes (e.g. health-related quality-of-life) will be compared using linear regression with station included as a random effect." (section 6.2.4) Upon review of blinded data, it was evident that data on sequential organ failure assessment scores, laboratory values, and health-related quality of life were only approximately normally distributed. To better account for this, we decided to use generalized linear models with robust variance estimation. From version 1.1 to 1.2 of the protocol, we decided to not adjust for the stratification variable in the main analyses. However, this was inadvertently not removed from the analyses of continuous outcomes. To be consistent with the binary outcomes, and in agreement with our intentions, we did not include station as a random effect when analyzing continuous outcomes.

4) Data on vasopressor- and ventilator-free days were extremely skewed and zero-inflated. Before unblinding, we decided not to estimate the mean difference between the groups using generalized linear models as it would be unlikely that we would get valid estimates. These analyses were therefore not performed. We did consider other options (e.g., quantile regression, Hodges–Lehmann median difference), but given the distribution of the data, these approaches were unlikely to give meaningful and valid results.

5) The priors used for the Bayesian analyses were only vaguely defined in the protocol. We used a more systematic approach to the priors as described in the manuscript.

Definitions of past medical history

Coronary artery disease: Myocardial infarction, coronary artery bypass grafting, coronary stenting or angioplasty, or other known occlusive coronary disease including diagnosed angina pectoris.

Chronic heart failure: Chronic heart failure with or without preserved ejection fraction.

Atrial fibrillation: Paroxysmal, persistent, or chronic atrial fibrillation/flutter.

Stroke: Previous ischemic or hemorrhagic stroke or transient ischemic attack.

Venous thromboembolism: Previous deep vein thrombosis, pulmonary embolism, or another venous thromboembolism (e.g., cerebral venous sinus thrombosis).

Arterial hypertension: A diagnosis of hypertension and receiving at least one anti-hypertensive drug (e.g., angiotensin-converting-enzyme [ACE] inhibitor, angiotensin II receptor blockers [ARB], diuretic or beta-blocker).

Diabetes: A diagnosis of diabetes and receiving at least one anti-diabetic drug (i.e., metformin, insulin, biguanides, sulfonylureas, glitazones, dipeptidyl peptidase IV inhibitors, or sodium-glucose co-transporter 2 inhibitor).

Pulmonary disease: Chronic obstructive pulmonary disease or asthma requiring daily inhalation medication or other pulmonary disease e.g., emphysema, interstitial lung disease, cystic fibrosis, or idiopathic pulmonary arterial hypertension.

Renal disease: Chronic kidney disease (CKC) stage 3A or higher i.e., eGFR < 60 mL/min/1.73 m^2.

Liver disease: With or without cirrhosis. This includes chronic hepatitis B or C (not cured), non-alcoholic fatty liver disease/nonalcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, liver disease related to hemochromatosis, etc.

Cancer: Any active solid or hematological cancer. Non-melanoma skin cancers (basal cell or squamous cell carcinoma) are not included. Active is defined as receiving chemotherapy, radiation,

or palliative care, awaiting either of the previous, or awaiting curative or palliative surgery. Previous cancers considered cured should not be included.

Dementia: Alzheimer's disease, vascular dementia, Lewy bodies dementia, frontotemporal dementia, dementia associated with Parkinson's, etc.

eTable 1. Results from the third independent data monitoring committee analysis				
	Calcium	**Placebo**	**Risk ratio (95%CI)**	**Risk difference (95%CI)**
Analyses based on the data set provided to the independent data monitoring committee				
	(n = 186)	(n = 197)		
Return of spontaneous circulation	32 (17)	53 (27)	0.64 (0.43, 0.94)	-9.7 (-18, -1.4)
Survival at 30 days	8 (4.3)	17 (8.6)	0.50 (0.22, 1.10)	-4.3 (-9.6, 0.7)
Favorable neurological outcome at 30 days	5 (2.7)	15 (7.6)	0.35 (0.14, 0.91)	-4.9 (-9.8, -0.5)
Analyses based on the correct data set and treatment assignment at the time of the independent data monitoring committee meeting				
	(n = 186)	(n = 196)		
Return of spontaneous circulation	34 (18)	53 (27)	0.68 (0.46, 0.99)	-8.8 (-17, -0.3)
Survival at 30 days	9 (4.8)	18 (9.2)	0.52 (0.25, 1.12)	-4.3 (-9.8, 0.9)
Favorable neurological outcome at 30 days	6 (3.2)	15 (7.7)	0.42 (0.17, 1.03)	-4.4 (-9.4, 0.2)

Categorical variables are presented as counts and percentages

The data set provided to the independent data monitoring committee consisted of 383 patients. Inadvertently, one patient was included in this data set who should have been excluded (traumatic cardiac arrest), one patient was assigned the wrong treatment ID resulting in a wrong group assignment, and one patient was stated as not having return of spontaneous circulation although the patient did. Analyses based on the data set provided to the independent data monitoring committee is shown on the top. Below are the analyses based on the 382 patients with correct data that should have been analyzed. Results were similar.

eTable 2. Additional baseline characteristics according to treatment assignment		
	Calcium (n = 193)	**Placebo (n = 198)**
Patient Characteristics		
BMI – kg/m^2 *	27 (24, 32)	26 (23, 31)
mRS prior to hospital admission		
mRS 0	59 (31)	62 (31)
mRS 1	68 (35)	65 (33)
mRS 2	34 (18)	29 (15)
mRS 3	15 (8)	28 (14)
mRS 4	14 (7)	5 (3)
mRS 5	2 (1)	2 (1)
Unknown	1 (1)	7 (4)
Frailty prior to hospital admission		
Very fit	0 (0)	2 (1)
Well	40 (21)	41 (21)
Managing well	66 (34)	57 (29)
Vulnerable	34 (18)	40 (20)
Mildly frail	24 (12)	32 (16)
Moderately frail	15 (8)	14 (7)
Severely frail	12 (6)	5 (3)
Terminally ill	1 (1)	0 (0)
Unknown	1 (1)	7 (4)
Cardiac Arrest Characteristics		
Time of day – no. (%)		
Day (07:00 – 14:59)	85 (44)	97 (49)
Evening (15:00 – 22:59)	66 (34)	65 (33)
Night (23:00 – 06:59)	42 (22)	36 (18)
Time of week – no. (%)		
Weekday	135 (70)	144 (73)
Weekend	58 (30)	54 (27)
Presumed cause – no. (%)		
Medical, cardiac	35 (18)	35 (18)
Medical, non-cardiac	13 (7)	11 (6)
Drug overdose	1 (1)	3 (2)
Unknown**	144 (75)	149 (75)
Time to arrival – minutes		
Primary ambulance***	8 (4, 12)	8 (5, 13)
Physician-manned ambulance****	12 (6, 16)	12 (7, 17)

Continuous variables are presented as medians with first and third quartiles and categorical variables as counts and percentages

* Data not available on 43 patients in the calcium group and 32 patients in the placebo group

** In the cardiac arrest literature, this is often referred to as “presumed cardiac”

*** Data not available on 1 patient in the calcium group and 3 patients in the placebo group

**** Data not available on 8 patients in the calcium group and 3 patients in the placebo group

eTable 3. Intra-cardiac arrest interventions		
	Calcium (n = 193)	**Placebo (n = 198)**
Number of epinephrine doses*	3 (2, 5)	2 (2, 4)
Other drugs administered		
Calcium outside trial protocol **	4 (2)	2 (1)
Amiodarone	41 (21)	37 (19)
Lidocaine	1 (1)	1 (1)
Atropine	4 (2)	3 (2)
Magnesium	18 (9)	9 (5)
Bicarbonate	9 (5)	9 (5)
Glucose	0 (0)	3 (2)
Any defibrillation	82 (42)	79 (40)
Cardiopulmonary resuscitation during transport	44 (23)	42 (21)
Mechanical chest compression	102 (53)	107 (54)

Continuous variables are presented as medians with first and third quartiles and categorical variables as counts and percentages

* Data not available on 1 patient in the calcium group and 3 patients in the placebo group

** All patients receiving calcium outside the trial protocol received 5 mmol calcium chloride

eTable 4. Post-cardiac arrest characteristics in those surviving at least 24 hours		
	Calcium (n = 34)	**Placebo (n = 42)**
Targeted temperature management	32 (94)	38 (90)
Cardiac interventions		
Coronary angiography	30 (88)	38 (90)
Percutaneous coronary intervention	13 (38)	16 (38)
Coronary artery bypass grafting	0 (0)	2 (5)
Intra-aortic balloon pump	0 (0)	0 (0)
Left ventricular assist device	1 (3)	0 (0)
Veno-arterial extracorporeal membrane oxygenation	4 (12)	3 (7)
Veno-venous extracorporeal membrane oxygenation	0 (0)	0 (0)
Neurological biomarkers/imaging performed/measured		
Computed tomography	27 (79)	38 (90)
Magnetic resonance imaging	8 (24)	10 (24)
Electroencephalogram	21 (62)	21 (50)
Somatosensory evoked potential	21 (62)	18 (43)
Neuron specific enolase	22 (65)	25 (60)
s100b	0 (0)	1 (2)

Categorical variables are presented as counts and percentages

eTable 5. Additional data on return of spontaneous circulation		
	Calcium (n = 193)	**Placebo (n = 198)**
Any return of spontaneous circulation	53 (27)	70 (35)
Return of spontaneous circulation at hospital arrival	31 (16)	44 (22)
Extracorporeal cardiopulmonary resuscitation	6 (3)	4 (2)
Time to return of spontaneous circulation – minutes *	28 (20, 40)	33 (19, 46)
Time to termination of resuscitation - minutes**	32 (23, 45)	30 (25, 45)

* Only including those with return of spontaneous circulation

** Only including those with no return of spontaneous circulation

eTable 6. Organ dysfunction and laboratory values after return of spontaneous circulation			
	Calcium	**Placebo**	**Mean difference (95%CI)**
SOFA score			
2 hours	10.1 (2.6) (n = 36)	10.3 (2.1) (n = 45)	-0.2 (-1.2, 0.8)
24 hours	11.1 (2.5) (n = 32)	11.0 (2.2) (n = 41)	0.1 (-1.0, 1.2)
48 hours	10.8 (3.8) (n = 32)	10.4 (3.4) (n = 39)	0.4 (-1.2, 2.1)
72 hours	10.3 (4.1) (n = 27)	8.6 (4.3) (n = 36)	1.7 (-0.4, 3.8)
Vasopressor-free days	0 (0, 2)	0 (0, 3)	-*
Ventilator-free days	0 (0, 0)	0 (0, 3)	-*
Laboratory values**			
Calcium, ionized – mmol/L***	1.41 (0.15)	1.17 (0.07)	0.23 (0.18, 0.28)
Potassium – mmol/L****	4.2 (0.8)	4.5 (1.1)	-0.3 (-0.7, 0.1)
pH*****	7.13 (0.12)	7.10 (0.16)	0.03 (-0.03, 0.09)
Lactate – mmol/L******	7.8 (4.0)	8.3 (4.6)	-0.5 (-2.3, 1.3)

SOFA: Sequential Organ Failure Assessment

Continuous variables are presented as means with standard deviations or medians with first and third quartiles. SOFA score was only assessed in those alive at the given time point. If a specific SOFA score element was missing, it was assumed to be normal. Vasopressor- and ventilator-free days were defined as the number of days within the first 7 days after the cardiac arrest where the patient did not receive vasopressors or invasive mechanical ventilation, respectively, and were alive. Vasopressor- and ventilator-free days were only assessed in those with return of spontaneous circulation.

* Since the data was extremely skewed and zero-inflated, no effect estimate is provided.

** Based on the first available blood sample after return of spontaneous circulation.

*** Data not available for 2 patients in the calcium group and 4 patients in the placebo group

**** Data not available for 1 patient in the calcium group and 3 patients in the placebo group

***** Data not available for 1 patient in the calcium group and 7 patients in the placebo group

****** Data not available for 1 patient in the calcium group and 6 patients in the placebo group

eTable 7. Hospital disposition and cause of death		
	Calcium	**Placebo**
Disposition in those discharged alive	(n = 10)	(n = 19)
Home	5 (50)	10 (53)
Rehabilitation center	4 (40)	7 (37)
Transferred to non-acute care hospital	1 (10)	2 (11)
Cause of death*	(n = 27)	(n = 34)
Sudden cardiac arrest	3 (11)	7 (21)
Hemodynamic	2 (7)	5 (15)
Respiratory	0 (0)	0 (0)
Withdrawal of life sustaining treatments due to …		
Neurological injury	20 (74)	19 (56)
Severe co-morbidity	0 (0)	3 (9)
Severe acute illness	2 (7)	0 (0)

Categorical variables are presented as counts and percentages

* Cause of death in those with return of spontaneous circulation who died prior to hospital discharge. The following definitions were used:

Sudden cardiac arrest: Sudden cardiac arrest (with CPR) without return of spontaneous circulation not directly caused by any of the other categories. This includes both cardiac and non-cardiac causes of sudden cardiac arrest.

Hemodynamic: Progressive, refractory hemodynamic shock despite aggressive ICU care, or withdrawal of care based on the same. Hemodynamically stable patients (e.g., maintaining their mean arterial blood pressure) on aggressive ICU care (e.g., full vasopressor support) were not included in this category.

Respiratory: Respiratory failure or withdrawal of care based on the same. Respiratory failure may be related to hypoxemia, hypercapnia, or the combination thereof. Patients who are oxygenating sufficiently on highest ventilator settings were not included in this category.

Neurological withdrawal of care: Withdrawal of care based on expectations of a poor neurological recovery based on brain imaging, a neurological exam, or a formal opinion of a neurologist stating that the prognosis for neurological recovery is very poor. If an assessment off sedation is not done, there must be other evidence of severe neurological injury (e.g., severe cerebral edema or herniation).

Co-morbidity withdrawal of care: Withdrawal of care or refusal of life-sustaining therapy based on the expectation of a poor quality of life. This may be related to a preexisting or newly discovered terminal illness or other serious medical condition (e.g., dementia or cancer).

Severe acute illness withdrawal of care: Withdrawal of care or refusal of life-sustaining therapy based on an acute illness that is not amenable to treatment. This could be a ruptured aortic aneurism, severe bowel ischemia, multiorgan failure, etc. This category was only used if none of the others applied.

eTable 8. Neurological outcomes				
	30 DAYS		**90 DAYS**	
	Calcium (n = 193)	**Placebo (n = 198)**	**Calcium (n = 193)**	**Placebo (n = 198)**
Modified Rankin Scale (mRS)				
mRS 0	0 (0)	1 (1)	1 (1)	2 (1)
mRS 1	1 (1)	2 (1)	0 (0)	7 (4)
mRS 2	4 (2)	9 (5)	5 (3)	7 (4)
mRS 3	2 (1)	3 (2)	1 (1)	2 (1)
mRS 4	0 (0)	2 (1)	1 (1)	0 (0)
mRS 5	3 (2)	1 (1)	2 (1)	0 (0)
mRS 6	183 (95)	180 (91)	183 (95)	180 (91)
Cerebral Performance Category (CPC)				
CPC 1	5 (3)	12 (6)	6 (3)	14 (7)
CPC 2	2 (1)	5 (3)	1 (1)	4 (2)
CPC 3	2 (1)	1 (1)	3 (2)	0 (0)
CPC 4	1 (1)	0 (0)	0 (0)	0 (0)
CPC 5	183 (95)	180 (91)	183 (95)	180 (91)

Categorical variables are presented as counts and percentages. The cerebral performance category score is a 5-point scale assessing neurological outcome after brain damage with higher scores indicating worse outcomes.

eTable 9. EQ-5D-5L subcategories				
	30 DAYS		**90 DAYS**	
	Calcium (n = 10)	**Placebo (n = 18)**	**Calcium (n = 10)**	**Placebo (n = 18)**
Mobility				
No problems	4 (40)	8 (44)	5 (50)	9 (50)
Slight problems	1 (10)	5 (28)	1 (10)	5 (28)
Moderate problems	2 (20)	2 (11)	1 (10)	3 (17)
Severe problems	1 (10)	2 (11)	1 (10)	1 (6)
Extreme problems	2 (20)	1 (6)	2 (20)	0 (0)
Self-care				
No problems	4 (40)	9 (50)	6 (60)	15 (83)
Slight problems	0 (0)	3 (17)	1 (10)	3 (17)
Moderate problems	4 (40)	3 (17)	0 (0)	0 (0)
Severe problems	0 (0)	2 (11)	1 (10)	0 (0)
Extreme problems	2 (2)	1 (6)	2 (20)	0 (0)
Usual activities				
No problems	0 (0)	1 (6)	1 (10)	5 (28)
Slight problems	1 (10)	2 (11)	2 (20)	2 (11)
Moderate problems	0 (0)	4 (22)	1 (10)	6 (33)
Severe problems	1 (10)	3 (17)	0 (0)	1 (6)
Extreme problems	8 (80)	8 (44)	6 (60)	4 (22)
Pain/discomfort				
No problems	3 (30)	2 (11)	4 (40)	11 (61)
Slight problems	3 (30)	9 (50)	5 (50)	6 (33)
Moderate problems	4 (40)	6 (33)	1 (10)	1 (6)
Severe problems	0 (0)	1 (6)	0 (0)	0 (0)
Extreme problems	0 (0)	0 (0)	0 (0)	0 (0)
Anxiety/depression				
No problems	3 (30)	8 (44)	3 (30)	12 (67)
Slight problems	2 (20)	7 (39)	2 (20)	5 (28)
Moderate problems	4 (40)	1 (6)	4 (40)	1 (6)
Severe problems	1 (10)	1 (6)	1 (10)	0 (0)
Extreme problems	0 (0)	1 (6)	0 (0)	0 (0)

Categorical variables are presented as counts and percentages

eTable 10. Potential adverse events		
	Calcium	**Placebo**
In patients with return of spontaneous circulation	**(n = 37)**	**(n = 53)**
Hypercalcemia*		
None (< 1.33 mmol/L)	9 (26)	48 (98)
Mild (1.33 – 1.46 mmol/L)	12 (34)	1 (2)
Moderate (1.47 – 2.00 mmol/L)	14 (40)	0 (0)
Severe (> 2.00 mmol/L)	0 (0)	0 (0)
Tachyarrhythmia	8 (22)	14 (26)
Acute kidney failure requiring dialysis	7 (19)	3 (6)
Gastrointestinal ulcer	1 (3)	0 (0)
Acute pancreatitis	3 (8)	1 (2)
In those surviving at least 24 hours	**(n = 32)**	**(n = 41)**
Hypercalcemia		
None (< 1.33 mmol/L)	8 (25)	40 (98)
Mild (1.33 – 1.46 mmol/L)	12 (38)	1 (2)
Moderate (1.47 – 2.00 mmol/L)	12 (38)	0 (0)
Severe (> 2.00 mmol/L)	0 (0)	0 (0)
Tachyarrhythmia	7 (22)	12 (29)
Acute kidney failure requiring dialysis	7 (22)	3 (7)
Gastrointestinal ulcer	1 (3)	0 (0)
Acute pancreatitis	3 (9)	1 (2)

Categorical variables are presented as counts and percentages

Definitions for adverse events are provided in the protocol. Hypercalcemia and tachyarrhythmias were assessed within the first 24 hours after return of spontaneous circulation. The remainder of the adverse events were assessed within the first week after return of spontaneous circulation.

* Data not available for 2 patients in the calcium group and 4 patients in the placebo group

eTable 11. Posterior estimates from Bayesian analyses			
Prior belief[a]	**Posterior mean risk ratio (95% credible interval)**		
	Return of spontaneous circulation	**Survival at 30 days**	**Favorable neurological outcome at 30 days**
Non-informative	0.72 (0.49 to 1.03)	0.56 (0.25 to 1.16)	0.46 (0.18 to 1.09)
Skeptical			
Strong	0.83 (0.64 to 1.09)	0.87 (0.61 to 1.26)	0.87 (0.60 to 1.25)
Moderate	0.77 (0.55 to 1.07)	0.76 (0.46 to 1.26)	0.73 (0.43 to 1.26)
Weak	0.74 (0.51 to 1.05)	0.67 (0.36 to 1.23)	0.63 (0.31 to 1.21)
Optimistic			
Strong	0.94 (0.70 to 1.25)	1.13 (0.92 to 1.38)	1.13 (0.92 to 1.40)
Moderate	0.82 (0.58 to 1.15)	1.04 (0.76 to 1.43)	1.04 (0.75 to 1.45)
Weak	0.75 (0.52 to 1.06)	0.84 (0.51 to 1.38)	0.83 (0.49 to 1.40)
Pessimistic			
Strong	0.70 (0.52 to 0.94)	0.81 (0.66 to 1.00)	0.81 (0.66 to 0.99)
Moderate	0.71 (0.50 to 0.97)	0.78 (0.57 to 1.06)	0.77 (0.55 to 1.06)
Weak	0.71 (0.49 to 1.02)	0.70 (0.42 to 1.15)	0.67 (0.39 to 1.14)

[a] For details about the informative priors, see Figures S7-9

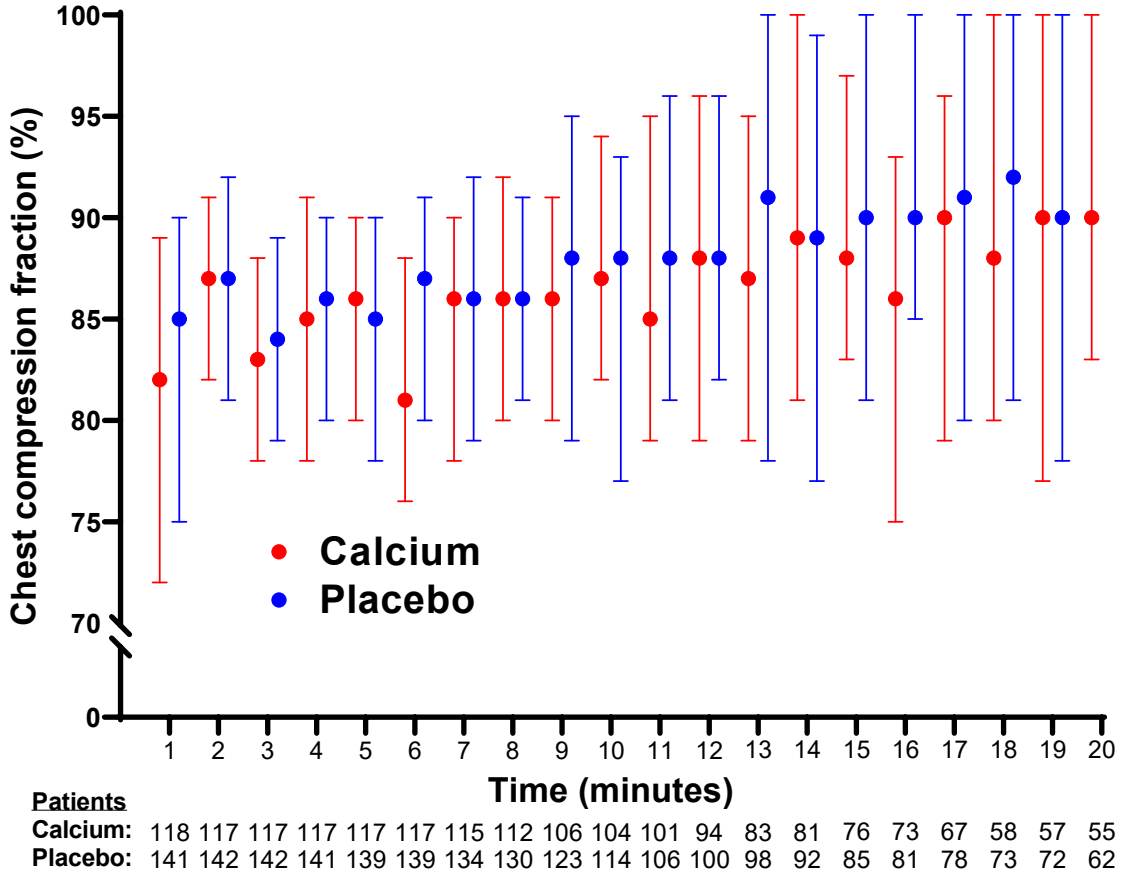
eTable 12. Posterior probabilities of benefit									
	Posterior probability that the intervention effect exceeds the following risk ratios (%)								
Prior belief[a]	**Return of spontaneous circulation**			**Survival at 30 days**			**Favorable neurological outcome at 30 days**		
	> 1.0	**> 1.2**	**> 1.5**	**> 1.0**	**> 1.2**	**> 1.5**	**> 1.0**	**> 1.2**	**> 1.5**
Non-informative	4	0	0	6	2	0	4	1	0
Skeptical									
Strong	9	0	0	23	4	0	23	4	0
Moderate	6	0	0	14	4	0	13	4	1
Weak	5	0	0	10	3	0	8	3	0
Optimistic									
Strong	33	4	0	88	28	0	88	29	0
Moderate	13	1	0	60	18	1	60	20	2
Weak	5	0	0	25	8	1	24	8	1
Pessimistic									
Strong	1	0	0	3	0	0	2	0	0
Moderate	2	0	0	6	0	0	6	0	0
Weak	4	0	0	8	2	0	7	1	0

[a] For details about the informative priors, see Figures S7-9

eTable 13. Posterior probabilities of harm									
	Posterior probability that the intervention effect exceeds the following risk ratios (%)								
Prior belief[a]	**Return of spontaneous circulation**			**Survival at 30 days**			**Favorable neurological outcome at 30 days**		
	< 1.0	**< 0.8**	**< 0.5**	**< 1.0**	**< 0.8**	**< 0.5**	**< 1.0**	**< 0.8**	**< 0.5**
Non-informative	96	72	3	94	83	38	96	89	55
Skeptical									
Strong	91	39	0	77	32	0	77	34	0
Moderate	94	60	1	86	58	5	87	63	8
Weak	95	68	2	90	71	17	92	76	25
Optimistic									
Strong	67	14	0	12	0	0	12	0	0
Moderate	87	44	0	40	5	0	40	6	0
Weak	95	65	2	75	42	2	76	44	3
Pessimistic									
Strong	99	83	2	98	46	0	98	47	0
Moderate	98	76	2	94	57	0	94	59	0
Weak	96	73	3	92	71	10	93	75	14

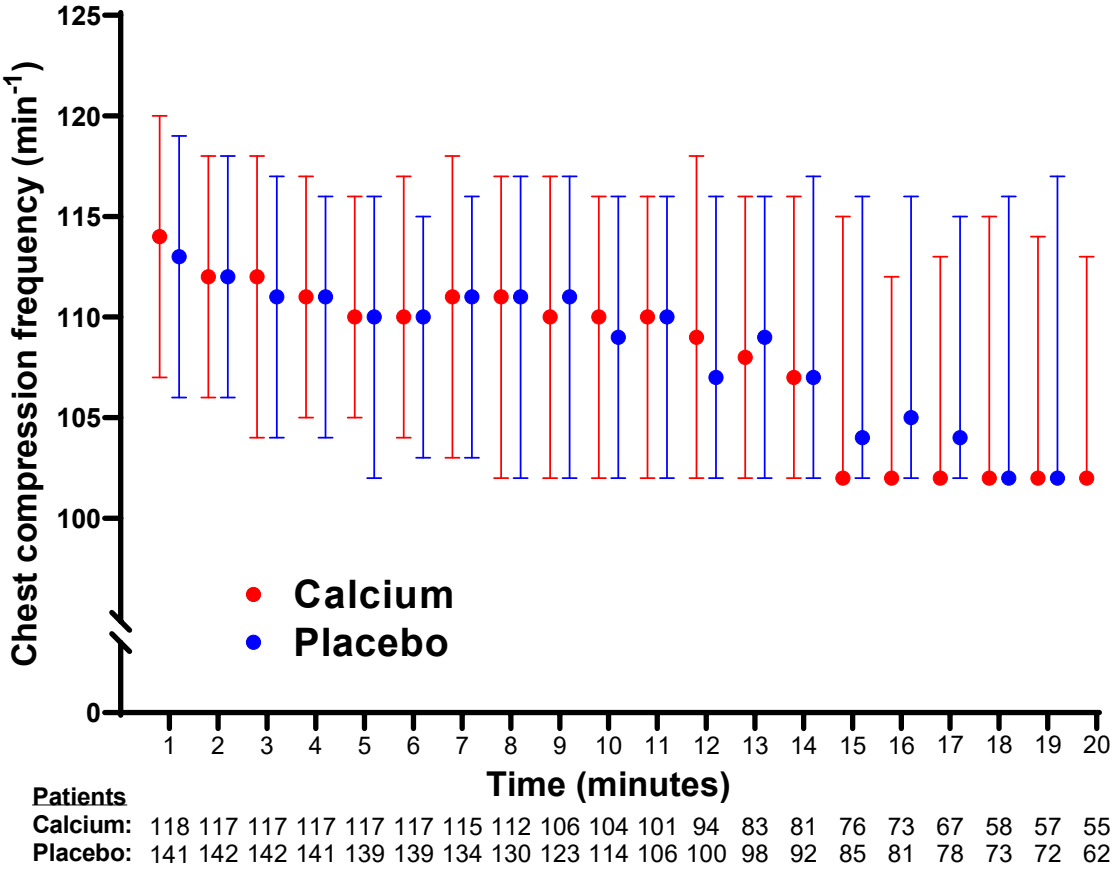
[a] For details about the informative priors, see Figures S7-9

eFigure 1. Chest compression fraction according to treatment assignment

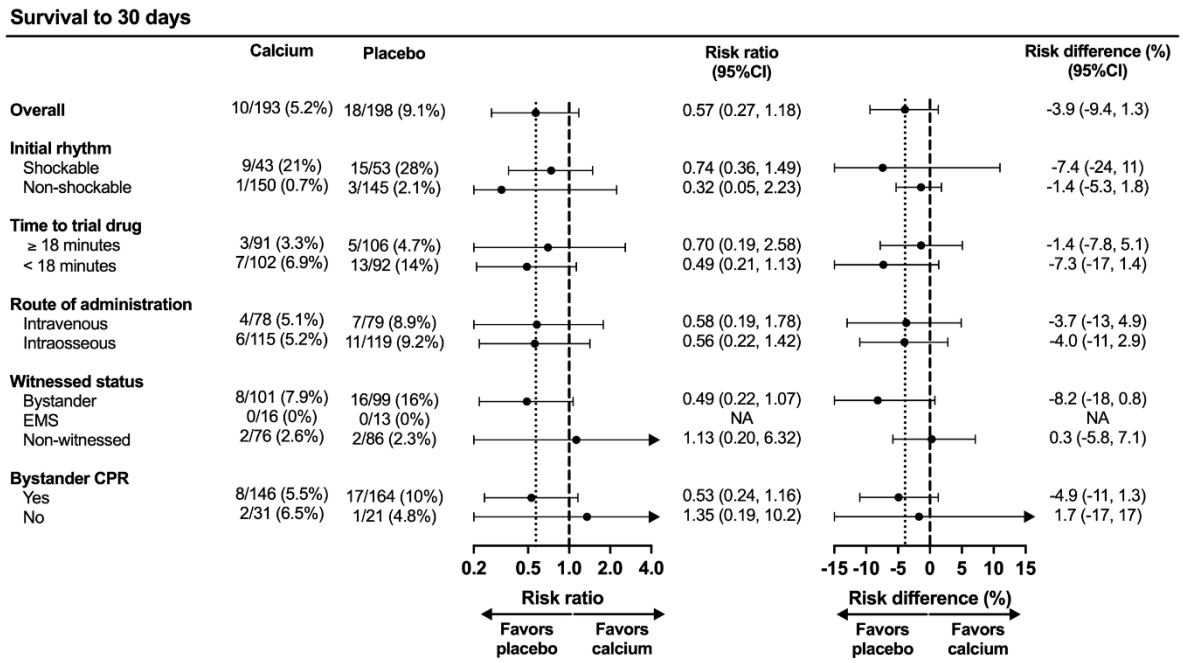


The chest compression fraction is the percentage of time during the cardiac arrest where chest compressions are being performed. This was estimated from impedance data analyzed using CODE-STAT software. Chest compression fraction data was available for 118 patients in the calcium group and 142 patients in the placebo group. The time on the x-axis is the time from the first registration of chest compression data. The dot represents the median and the error bars the 1st and 3rd quartiles. The median time from the cardiac arrest to the first registration of chest compression data was 10 minutes (quartiles: 7, 14) in the calcium group and 10 minutes (quartiles: 7, 15) in the placebo group. The overall median chest compression fraction was 85% (quartiles: 82, 89) in the calcium group and 86% (quartiles: 82, 90) in the placebo group. Below the graph, is the number of patients with data available. Missing data as time progressed was a result of termination of resuscitation, return of spontaneous circulation, arrival at the hospital, or rarely technical issues.

eFigure 2. Chest compression frequency according to treatment assignment



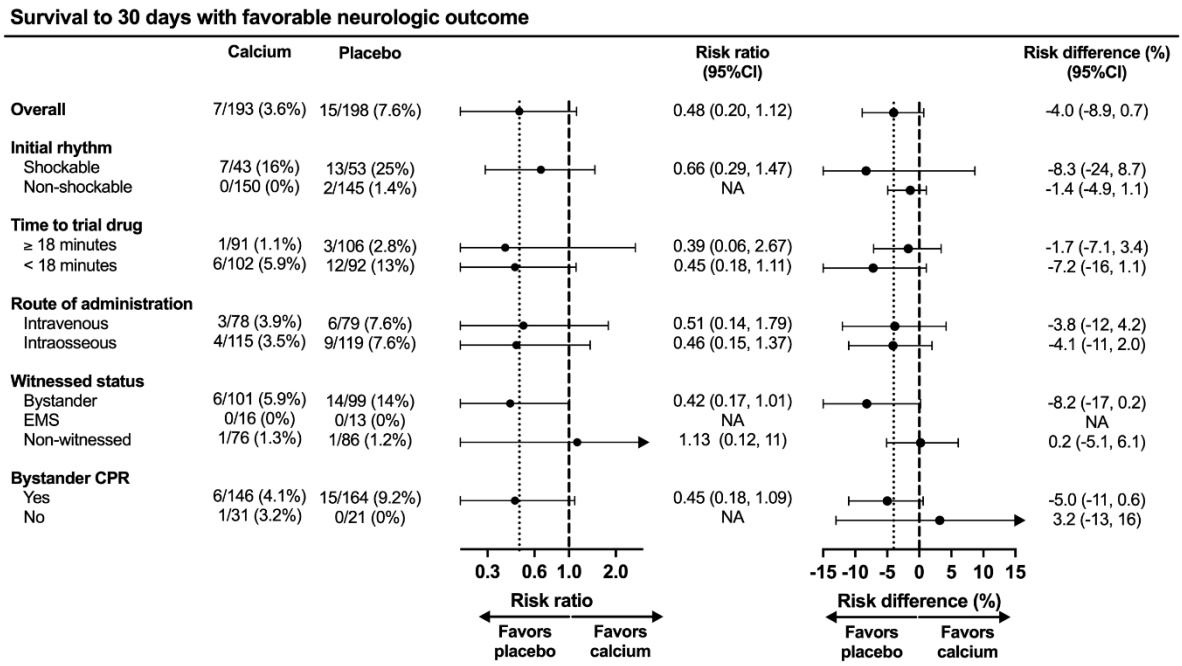
The chest compression frequency (i.e., compressions per minute) was estimated from impedance data analyzed using CODE-STAT software. Chest compression frequency data was available for 118 patients in the calcium group and 142 patients in the placebo group. The time on the x-axis is the time from the first registration of chest compression data. The dot represents the median and the error bars the 1st and 3rd quartiles. When an error is not visible, it reflects that the error bare is similar to the median. The clustering of data at 102 min^{-1} reflects the use of a mechanical chest compression device. The median time from the cardiac arrest to the first registration of chest compression data was 10 minutes (quartiles: 7, 14) in the calcium group and 10 minutes (quartiles: 7, 15) in the placebo group. The overall median chest compression frequency was 109 min^{-1} (quartiles: 104, 114) in the calcium group and 108 min^{-1} (quartiles: 103, 115) in the placebo group. Below the graph, is the number of patients with data available. Missing data as time progressed was a result of termination of resuscitation, return of spontaneous circulation, arrival at the hospital, or rarely technical issues.



eFigure 3. Subgroup results for 30-day survival

Subgroup results are presented for five pre-defined subgroups. Time from cardiac arrest to trial drug administration was dichotomized at the median. Only cardiac arrests not witnessed by Emergency Medical Services were included in the bystander CPR subgroup. It was not possible to calculate a risk ratio when one of the groups had zero events and not possible to calculate either a risk ratio or risk difference when both groups had zero events.

CPR: Cardiopulmonary resuscitation, NA: Not applicable

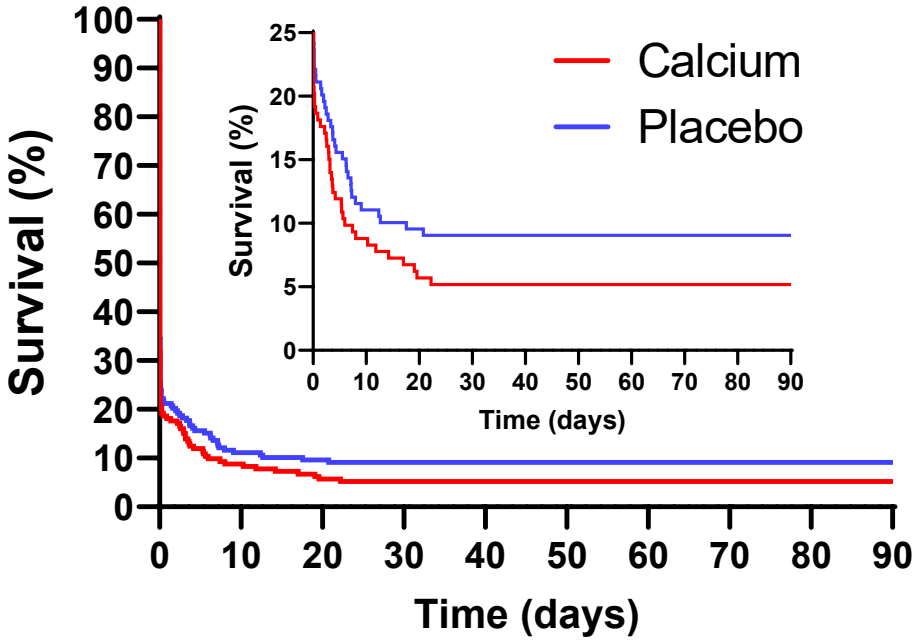


eFigure 4. Subgroup results for 30-day favorable neurological outcome

Subgroup results are presented for five pre-defined subgroups. Time from cardiac arrest to trial drug administration was dichotomized at the median. Only cardiac arrests not witnessed by Emergency Medical Services were included in the bystander CPR subgroup. It was not possible to calculate a risk ratio when one of the groups had zero events and not possible to calculate either a risk ratio or risk difference when both groups had zero events.

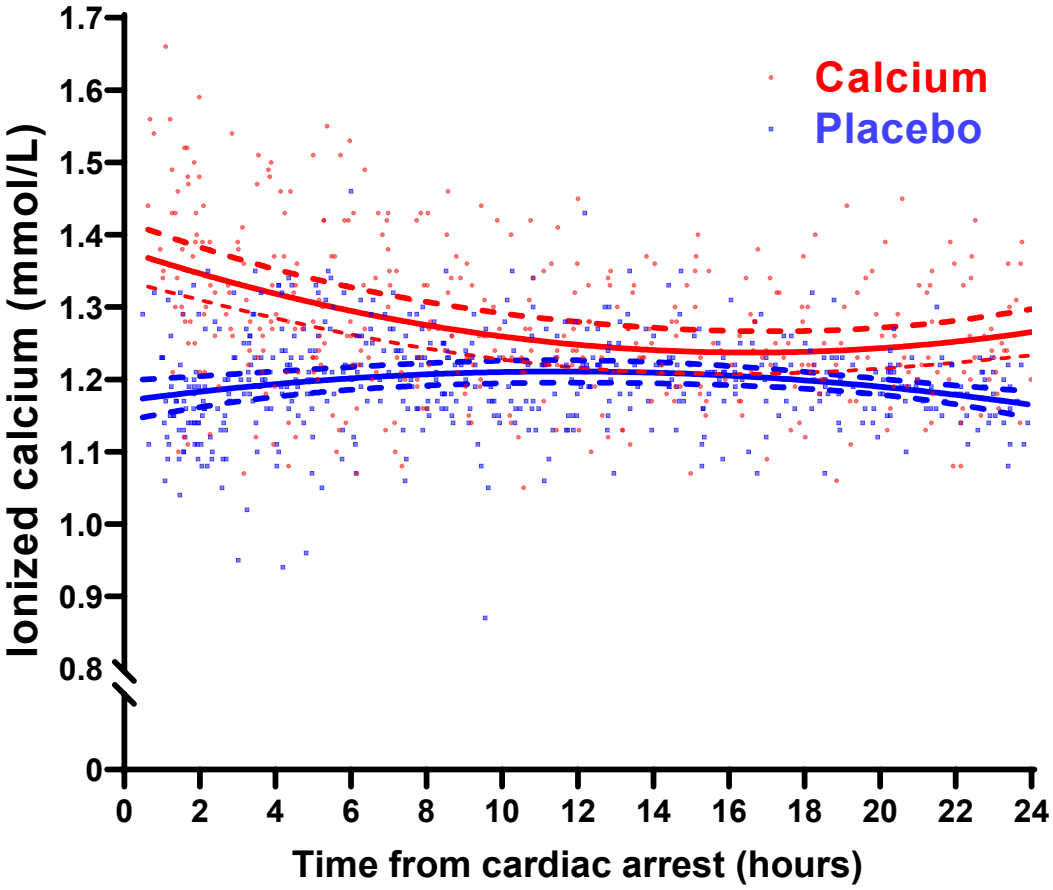
CPR: Cardiopulmonary resuscitation, NA: Not applicable

eFigure 5. Kaplan-Meier curve for 90-day survival according to treatment assignment



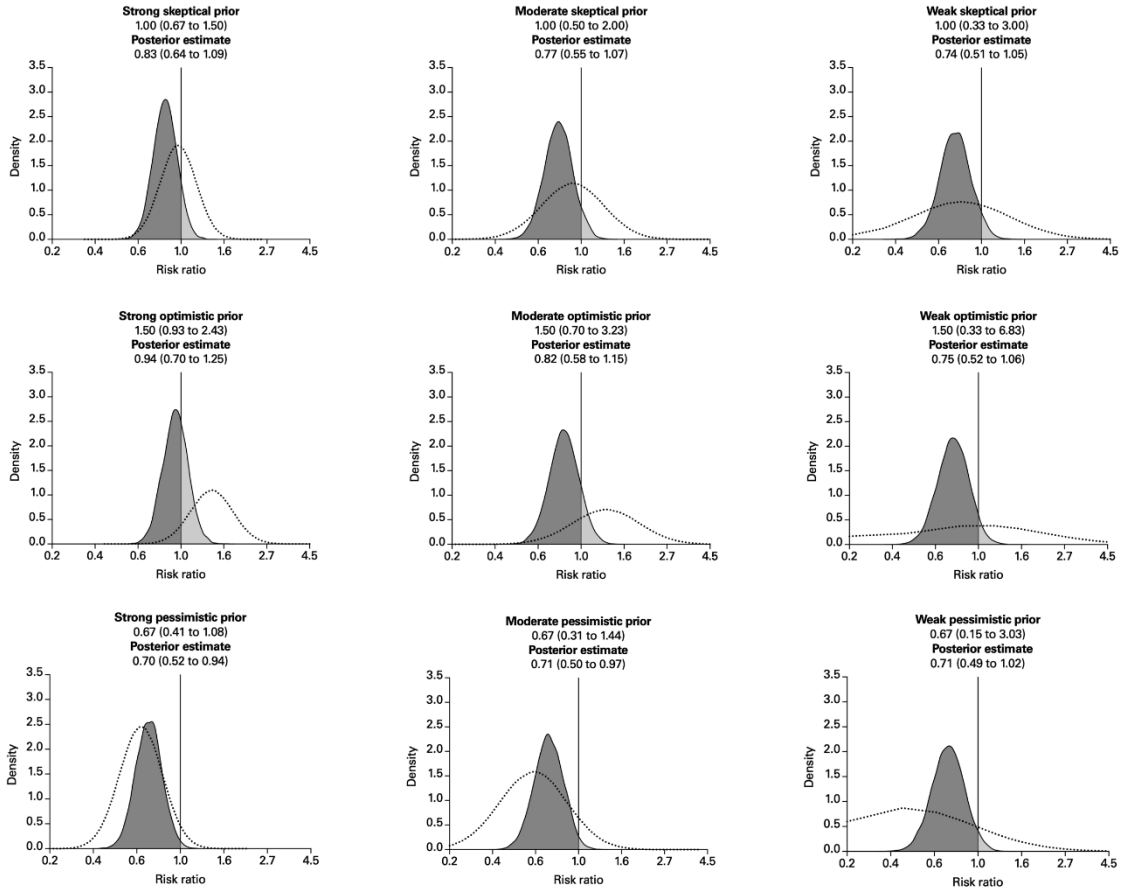
There was no loss to follow-up and therefore no censoring of patients. No patient died between the 30- and 90-day follow-up.

eFigure 6. Ionized calcium values in patients with return of spontaneous circulation



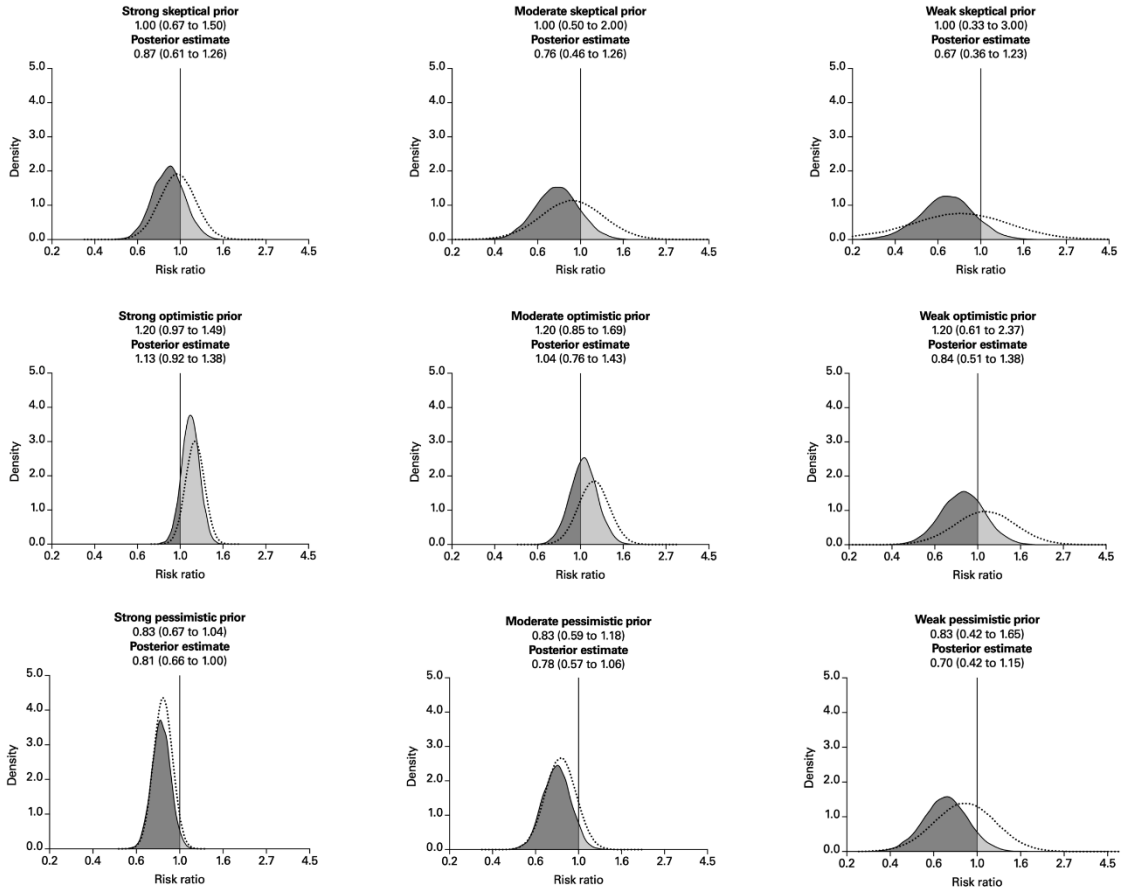
In patients with return of spontaneous circulation, 35 patients in the calcium group and 49 patients in the placebo group had any ionized calcium value available after return of spontaneous circulation. Measurement of ionized calcium was not protocolized. Each dot represents one ionized calcium value. The median (first and third quartile) number of ionized calcium values within the first 24 hours per patient was 12 (quartiles: 10, 15) in the calcium group and 11 (quartiles: 9, 14) in the placebo group. The solid lines and corresponding 95% confidence intervals (dotted line), were estimated from a generalized linear model with time included as a linear and squared variable. The correlation of calcium values within patients was accounted for by specifying an independent covariance structure. Data was modelled separately for calcium and placebo.

eFigure 7. Posterior probability distributions for return of spontaneous circulation



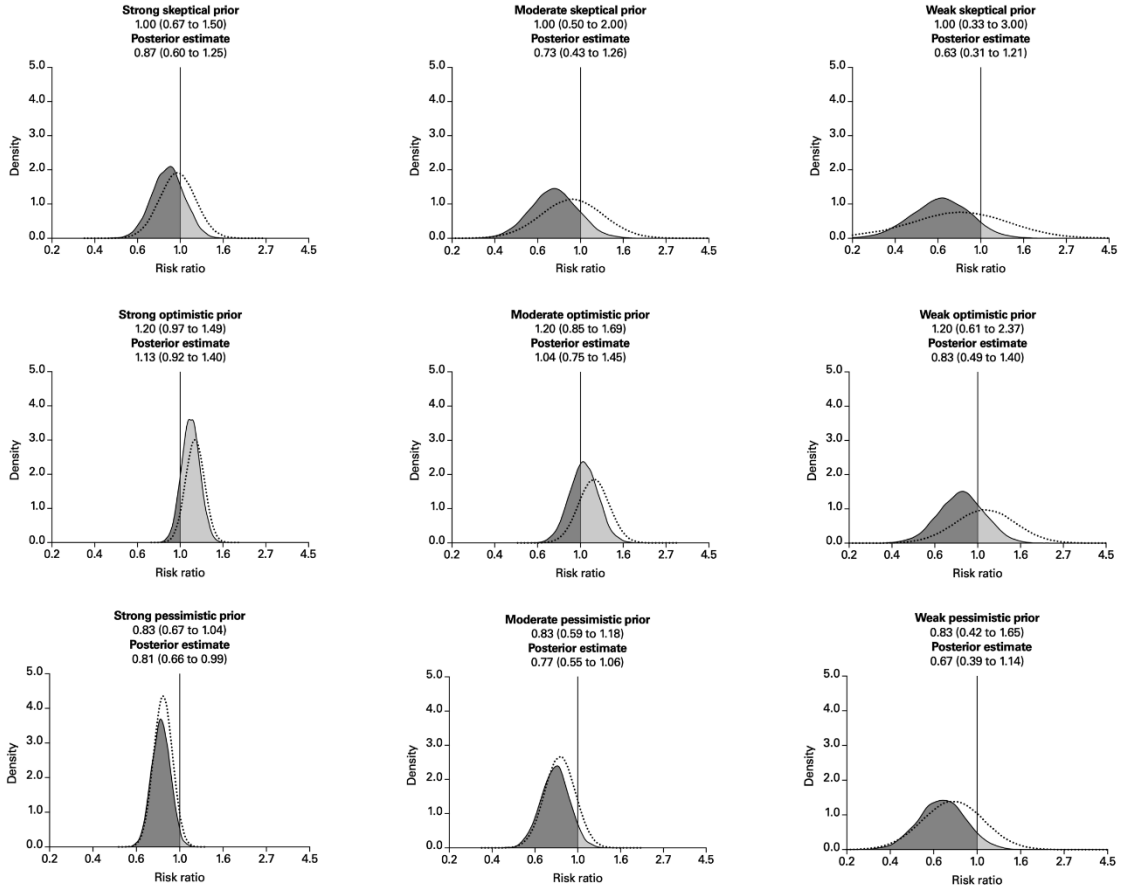
Results from Bayesian analysis presented as posterior probability distributions based on informative priors for return of spontaneous circulation. The x-axis is logarithmic. The values listed represents the prior and posterior mean risk ratio and the 95% credibility interval. The vertical line represents no effect (i.e., a risk ratio of 1). The dotted line represents the prior and the solid line the posterior. The dark shaded area for the posterior are values below 1 (i.e., a harmful effect of calcium) and the light shaded area are values above 1 (i.e., a beneficial effect of calcium).

eFigure 8. Posterior probability distributions for survival at 30 days



Results from Bayesian analysis presented as posterior probability distributions based on informative priors for survival at 30 days. The x-axis is logarithmic. The values listed represents the prior and posterior mean risk ratio and the 95% credibility interval. The vertical line represents no effect (i.e., a risk ratio of 1). The dotted line represents the prior and the solid line the posterior. The dark shaded area for the posterior are values below 1 (i.e., a harmful effect of calcium) and the light shaded area are values above 1 (i.e., a beneficial effect of calcium).

eFigure 9. Posterior probability distributions for favorable neurological outcome at 30 days



Results from Bayesian analysis presented as posterior probability distributions based on informative priors for favorable neurological outcome at 30 days. The x-axis is logarithmic. The values listed represents the prior and posterior mean risk ratio and the 95% credibility interval. The vertical line represents no effect (i.e., a risk ratio of 1). The dotted line represents the prior and the solid line the posterior. The dark shaded area for the posterior are values below 1 (i.e., a harmful effect of calcium) and the light shaded area are values above 1 (i.e., a beneficial effect of calcium).