Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest



AARHUS UNIVERSITY

HLR congress Göteborg, Sweden November 24, 2021



Aarhus University Hospital

Funding and COIs

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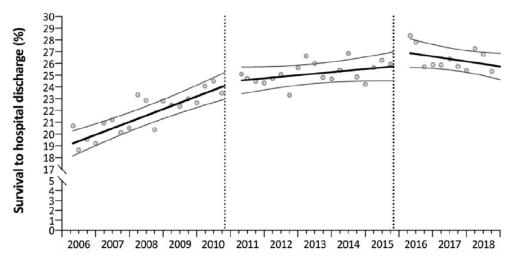
AARHUS UNIVERSITY DEPARTMENT OF CLINICAL MEDICINE





Background

- Incidence:
 - US: 290,000
 - Denmark: 2,000
- ROSC ≈ 55-60%
- Survival ≈ 25-30%



Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States



Clinical paper

Adult in-hospital cardiac arrest in Denmark



Lars W. Andersen^{*a,b,**}, Mathias J. Holmberg^{*a*}, Bo Løfgren^{*a,c,d*}, Hans Kirkegaard^{*a*}, Asger Granfeldt^{*e*}



Clinical paper

Trends in survival and introduction of the 2010 and 2015 guidelines for adult in-hospital cardiac arrest

Mathias J. Holmberg^{a,b,c}, Asger Granfeldt^{d,e}, Saket Girotra^f, Michael W. Donnino^{b,g}, Lars W. Andersen^{a,b,h,i,*}, for the American Heart Association's Get With The Guidelines[®]-Resuscitation Investigators¹

Background

• Lack of evidence for in-hospital cardiac arrest

Circulation: Cardiovascular Quality and Outcomes Volume 9, Issue 6, November 2016; Pages 749-756 https://doi.org/10.1161/CIRCOUTCOMES.116.002916



ORIGINAL ARTICLE

Identifying Important Gaps in Randomized Controlled Trials of Adult Cardiac Arrest Treatments

A Systematic Review of the Published Literature

Shashank S. Sinha, MD, MSc, Devraj Sukul, MD, John J. Lazarus, MD, PhD, Vivek Polavarapu, BS, Paul S. Chan, MD, MSc, Robert W. Neumar, MD, PhD, and Brahmajee K. Nallamothu, MD, MPH



Short paper

Adult post-cardiac arrest interventions: An overview of randomized clinical trials



Lars W. Andersen^{*a,b,**}, Peter Carøe Lind^{*c*}, Lauge Vammen^{*d*}, Maria Høybye^{*a*}, Mathias J. Holmberg^{*a,e*}, Asger Granfeldt^{*b,d*}

ORIGINAL INVESTIGATION

Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest

Spyros D. Mentzelopoulos, MD, PhD; Spyros G. Zakynthinos, MD, PhD; Maria Tzoufi, MD, PhD; Nikos Katsios, MD; Androula Papastylianou, MD; Sotiria Gkisioti, MD; Anastasios Stathopoulos, MD; Androniki Kollintza, PhD; Elissavet Stamataki, MD, PhD; Charis Roussos, MD, PhD

Arch Intern Med. 2009

Single-center

Randomized, double-blind

100 patients with IHCA and \geq 1 adrenaline dose

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest A Randomized Clinical Trial

Spyros D. Mentzelopoulos, MD, PhD; Sotirios Malachias, MD; Christos Chamos, MD; Demetrios Konstantopoulos, MD; Theodora Ntaidou, MD; Androula Papastylianou, MD, PhD; Iosifinia Kolliantzaki, MD; Maria Theodoridi, MD; Helen Ischaki, MD, PhD; Demosthenes Makris, MD, PhD; Epaminondas Zakynthinos, MD, PhD; Elias Zintzaras, MD, PhD; Sotirios Sourlas, MD; Stavros Aloizos, MD; Spyros G. Zakynthinos, MD, PhD

JAMA 2013

3-center

Randomized, double-blind

268 patients with IHCA and \geq 1 adrenaline dose

Intervention:

- Vasopressin (20 IU) + methylprednisolone (40 mg) after the first adrenaline dose
- Vasopressin (20 IU) after each adrenaline dose (max. 100 IU)
- If in shock 4 hours after the cardiac arrest, hydrocortisone (300 mg daily)

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JAMA 2013 3-center Randomized, double-blind **268 patients** with IHCA and ≥ 1 adrenaline dose

	ROSC	Survival		ROSC	CPC 1-2
Intervention:	39/48 (81%)	9/48 (19%)	Intervention:	109/130 (84%)	18/130 (14%)
Placebo:	27/52 (52%)	2/52 (4%)	Placebo:	91/138 (66%)	7/138 (5%)

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Background

European Resuscitation Council Guidelines for Resuscitation 2015 Section 3. Adult advanced life support

Jasmeet Soar^{a,*}, Jerry P. Nolan^{b,c}, Bernd W. Böttiger^d, Gavin D. Perkins^{e,f}, Carsten Lott^g, Pierre Carli^h, Tommaso Pellisⁱ, Claudio Sandroni^j, Markus B. Skrifvars^k, Gary B. Smith¹, Kjetil Sunde^{m,n}, Charles D. Deakin^o, on behalf of the Adult advanced life support section Collaborators¹

"... these studies are **not generalisable** to all cardiac arrests and **we suggest that steroids are not used routinely for cardiac arrest**."

Part 7: Adult Advanced Cardiovascular Life Support

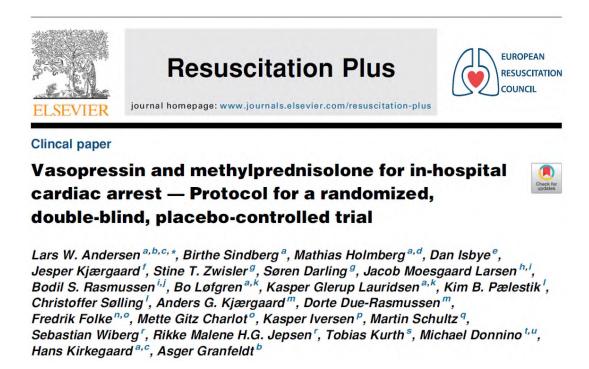
2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Mark S. Link, Chair; Lauren C. Berkow; Peter J. Kudenchuk; Henry R. Halperin; Erik P. Hess; Vivek K. Moitra; Robert W. Neumar; Brian J. O'Neil; James H. Paxton; Scott M. Silvers; Roger D. White; Demetris Yannopoulos; Michael W. Donnino

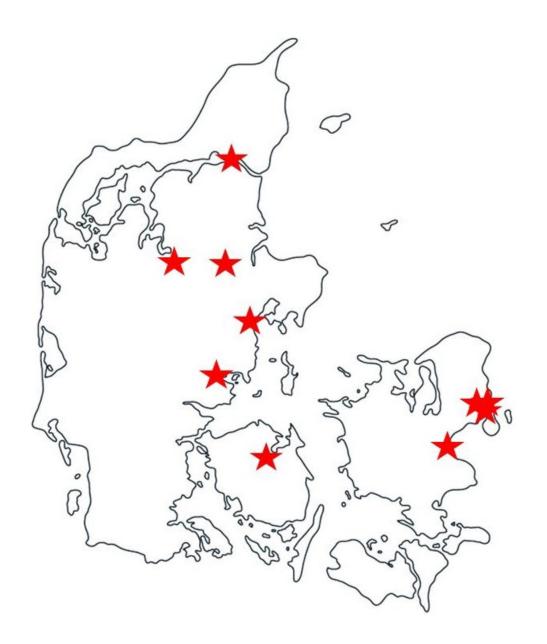
"... the combination of intra-arrest vasopressin, epinephrine, and methylprednisolone and post-arrest hydrocortisone ... **may be considered**; however, **further studies are needed** before recommending the routine use of this therapeutic strategy."



 Investigator-initiated, multicenter, randomized, placebo-controlled, double-blind, trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest



- 10 hospitals in Denmark
 - 4 large university hospitals
 - 6 middle-sized hospitals



• Inclusion criteria

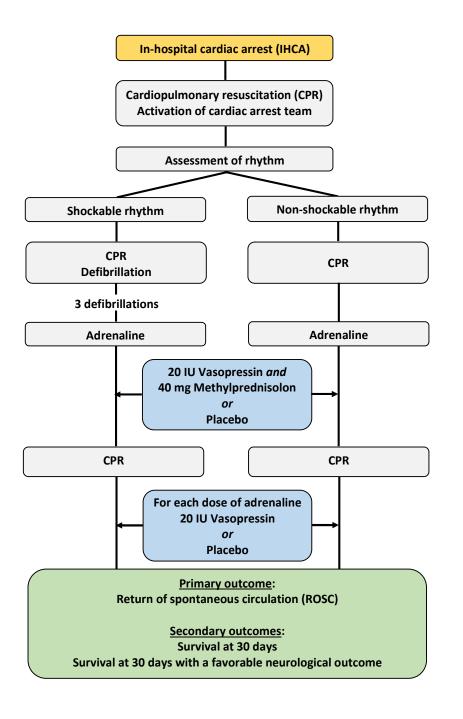
- In-hospital cardiac arrest
- Age \geq 18 years
- Received at least one dose of adrenaline during CPR

• Exclusion criteria

- Clearly documented "do-not-resuscitate" order prior to the cardiac arrest
- Prior enrollment in the trial
- Extracorporeal circulation at the time of the cardiac arrest
- Known or suspected pregnancy

- Interventions:
 - 20 IU vasopressin after each dose of adrenaline (max 80 IU)
 - **40 mg methylprednisolon** after the first dose of adrenaline

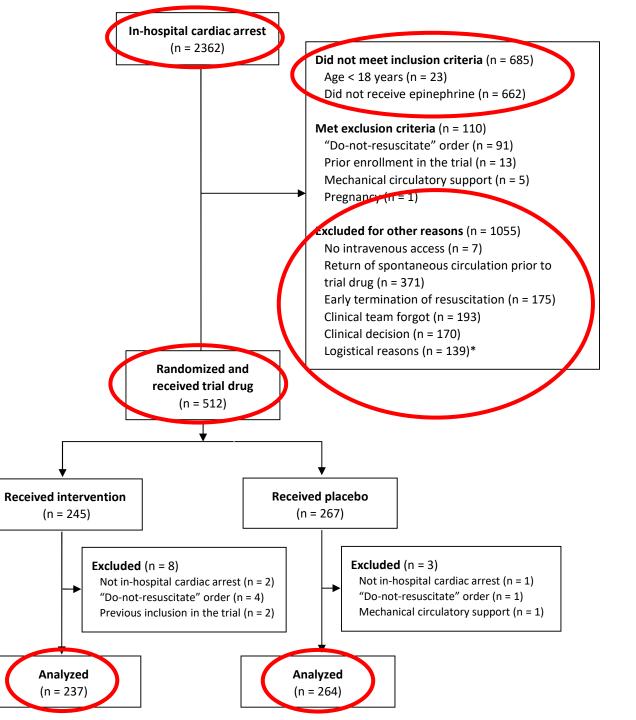




Results

Results

October 15, 2018 to January 21, 2021



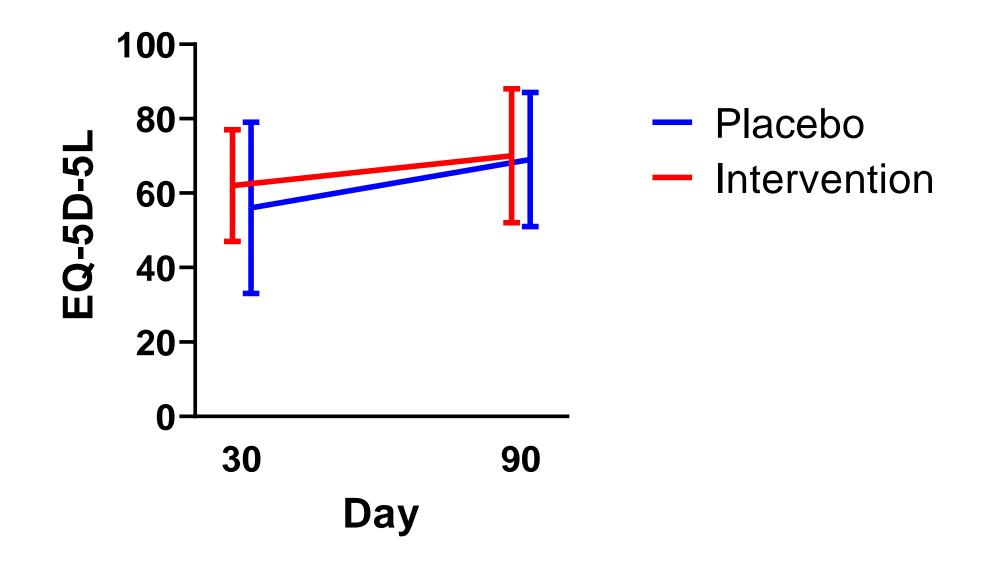
- 501 patients included
- Age: 71 years
- 64% male
- Mostly ward patients (66%)
- Mostly non-shockable (90%)
- Time to epinephrine: 5 min.
- Time to drug: 8 min.
- No loss to follow-up

	Vasopressin and Methylprednisolone (n = 237)	Placebo (n = 264)
Patient Characteristics		
Age – years	71 (13)	70 (12)
Male sex – no. (%)	148 (62)	174 (66)
Past medical history – no. (%)*		
Coronary artery disease	76 (32)	92 (35)
Chronic heart failure	47 (20)	56 (21)
Atrial fibrillation	69 (29)	66 (25)
Stroke	46 (19)	40 (15)
Venous thromboembolism	15 (6)	14 (5)
Arterial hypertension	148 (62)	167 (63)
Diabetes	69 (29)	78 (30)
Pulmonary disease	67 (28)	82 (31)
Renal disease	54 (23)	49 (19)
Liver disease	8 (3)	11 (4)
Cancer	55 (23)	49 (19)
Dementia	5 (2)	3 (1)
Cardiac Arrest Characteristics		
Location – no. (%)		
Emergency department	19 (8)	38 (14)
Hospital ward	163 (69)	168 (64)
Intensive care unit	23 (10)	18 (7)
Operating room	4 (2)	3 (1)
Cardiac catherization laboratory	12 (5)	23 (9)
Other	16 (7)	14 (5)
Monitored – no. (%)	87 (37)	121 (46)
Witnessed – no. (%)	168 (71)	202 (77)
Initial rhythm – no. (%)		
Asystole	82 (35)	95 (36)
Pulseless electrical activity	134 (57)	138 (52)
Ventricular fibrillation	17 (7)	22 (8)
Ventricular tachycardia	4 (2)	9 (3)
Time to epinephrine administration - minutes	5 (3, 7)	5 (3, 8)
Time to trial drug administration - minutes	8 (6, 12)	9 (6, 12)

	Vasopressin and Methylprednisolone (n = 237)	Placebo (n = 264)	Risk Difference (95%Cl)	Risk ratio (95%Cl)	P value
Primary Outcome					
Return of spontaneous circulation	100 (42%)	86 (33%)	9.6% (1.1, 18.0)	1.30 (1.03, 1.63)	0.03

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Return of spontaneous circulation	100 (42%)	86 (33%)	9.6% (1.1, 18.0)	1.30 (1.03, 1.63)	0.03
Secondary Outcomes					
30-Day Outcomes					
Survival	23 (9.7%)	31 (12%)	-2.0% (-7.5, 3.5)	0.83 (0.50, 1.37)	0.48
Favorable neurologic outcome (CPC 1-2)	18 (7.6%)	20 (7.6%)	0.0% (-4.7, 4.9)	1.00 (0.55, 1.83)	> 0.99

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circulation			(1.1, 18.0)	(1.03, 1.63)	
Secondary Outcomes					
30-Day Outcomes					
Survival	23 (9.7%)	31 (12%)	-2.0% (-7.5, 3.5)	0.83 (0.50, 1.37)	0.48
Favorable neurologic outcome (CPC 1-2)	18 (7.6%)	20 (7.6%)	0.0% (-4.7, 4.9)	1.00 (0.55, 1.83)	> 0.99
90-Day Outcomes					
Survival	20 (8.4%)	24 (9.1%)	-0.7%	0.93	_
	20 (0.170)	21(3:1/0)	(-5.7, 4.5)	(0.53, 1.62)	
Favorable neurologic outcome (CPC 1-2)	18 (7.6%)	20 (7.6%)	0.0% (-4.7, 4.9)	1.00 (0.55, 1.83)	-



Return of spontaneous circulation

	Vasopressin and Methylprednisolone	Placebo		Risk ratio (95%Cl)		Risk difference (%) (95%Cl)
Overall	100/237 (42%)	86/264 (33%)	<u>þ-</u> ∳-i	1.30 (1.03, 1.63)	╞ ╴╡ ┥	9.6 (1.1, 18)
Initial rhythm						
Shockable	15/21 (71%)	15/31 (48%)	ı <mark>¦ ∔e</mark> i	1.48 (0.92, 2.38)	ı ¦ ∔ ● ı	23 (-4.7, 47)
Non-shockable	85/216 (39%)	71/233 (30%)	i i i	1.29 (1.00, 1.67)	⊢ ••−1	8.9 (0.0, 18)
Witnessed						
Yes	79/168 (47%)	75/202 (37%)	, ⊢ •−−1	1.27 (1.00, 1.61)	i i i	9.9 (-0.2, 20)
No	21/69 (30%)	11/62 (18%)	⊢	1.72 (0.92, 3.28)	i i i i i i i i i i	13 (-2, 27)
Age						
> 72 years	45/127 (35%)	33/122 (27%)	⊢ ∔ → I	1.31 (0.90, 1.91)	H H	8.4 (-3, 20)
<u><</u> 72 years	55/110 (50%)	53/142 (37%)		1.34 (1.01, 1.78)	⊢ •1	13 (0.3, 25)
Time from arrest						
to trial drug						
> 8 minutes	38/115 (33%)	41/135 (30%)	⊢ ie ÷ I	1.09 (0.75, 1.56)	⊢ ie ÷ i	2.7 (-8.8, 14)
≤ 8 minutes	62/122 (51%)	45/129 (35%)	⊢ ••••	1.46 (1.09, 1.96)		16 (3.7, 28)
Time from epineph	nrine					
to trial drug						
> 2 minutes	42/110 (38%)	35/124 (28%)		1.35 (0.94, 1.96)		10 (-2.1, 22)
≤ 2 minutes	58/127 (46%)	51/140 (36%)		1.25 (0.94, 1.68)		9.2 (-2.6, 21)
			0.7 1.0 1.4 2.0 3.0		-10 0 10 20 30 40 50	
			Risk ratio		Risk difference (%)	
		ب	avors Favors	ح	avors Favors	
			acebo intervention		acebo intervention	

- Improvement in return of spontaneous circulation (42% vs. 33%)
- No difference in survival (10% vs. 12%)
- No difference in neurologic outcome (8% vs. 8%)

Intervention characteristics of included trials						
	2009-trial	2013-trial	2021-trial			
Vasopressin dose	20 IU	20 IU	20 IU			
Max. number of doses	5	5	4			
Methylprednisolone dose	40 mg	40 mg	40 mg			
Post-cardiac arrest steroid	Yes	Yes	No			
Time to trial drug – min.	3 (2, 5)	5 (3, 6)	8 (6, 12)			

Patient characteristics of included trials						
	2009-trial	2013-trial	2021-trial			
Patients	100	268	501			
Centers	1	3	10			
Patient characteristics						
Age – years	73 (58, 79)	68 (54, 76)	72 (64, 79)			
Sex – male	59 (59)	183 (68)	322 (64)			
Cardiac arrest characteristics						
Location						
Intensive care unit	31 (31)	101 (38)	41 (8)			
Not intensive care unit	69 (69)	167 (24)	460 (92)			
Initial rhythm						
Asystole	61 (61)	180 (67)	177 (35)			
PEA	25 (25)	43 (16)	272 (54)			
VF/VT	14 (14)	45 (17)	52 (10)			
Witnessed	81 (81)	247 (92)	370 (74)			
Monitored	35 (35)	111 (41)	208 (42)			

• Strengths

- Relatively large, multicenter trial
- Time to drug delivery = 8 minutes
- Long-term outcomes with no loss to follow-up
- Limitations
 - Many potentially eligible patients not included
 - Time to drug delivery = 8 minutes
 - Low survival (8-9%)?
 - Not powered for 30-day outcomes

- Recommend for/against vasopressin + steroids?
- More trials?
 - Example
 - 8 vs. 12% (RR: 1.50, RD: 4%) = 2362 patients
 - 8 vs. 10% (RR: 1.25, RD: 2%) = 8602 patients

Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest A Randomized Clinical Trial

Visual Abstract

Supplemental content

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Author Amilations: Author

article.

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Research Center for Emergency Medicine, Department of Clinical

Medicine and Emergency

Editorial

CME Quiz at

Lars W. Andersen, MD, MPH, PhD, DMSc: Dan isbve, MD, PhD: Jesper Klænzaard, MD, PhD, DMSc: Camilla M. Kristensen, BS; Søren Darling, MD; Stine T. Zwisler, MD, PhD; Stine Fisker, CRNA; Jens Christian Schmidt, MD; Hans Kirkegaard, MD, PhD, DMSc; Anders M. Grejs, MD, PhD; Jørgen R. G. Rossau, MD; Jacob M. Larsen, MD, PhD; Bodil S. Rasmussen, MD, PhD; Signe Riddersholm, MD, PhD; Kasper Iversen, MD, DMSc; Martin Schultz, MD, PhD; Jakob L. Nielsen, CRNA; Bo Løfgren, MD, PhD; Kasper G. Lauridsen, MD, PhD; Christoffer Sølling, MD, PhD; Kim Pælestik, MD; Anders G. Kjærgaard, MD, PhD; Dorte Due-Rasmussen, MD; Fredrik Folke, MD, PhD; Mette G, Charlot, MD, PhD; Rikke Malene H. G. Jepsen, MD, PhD; Sebastian Wiberg, MD, PhD; Michael Donnino, MD; Tobias Kurth, MD, PhD; Maria Høybye, BS; Birthe Sindberg, RN; Mathias J. Holmberg, MD, MPH, PhD; Asger Granfeldt, MD, PhD, DMSc.

IMPORTANCE Previous trials have suggested that vasopressin and methylprednisolone administered during in-hospital cardiac arrest might improve outcomes.

OBJECTIVE To determine whether the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improves return of spontaneous circulation.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled trial conducted at 10 hospitals in Denmark. A total of 512 adult patients with in-hospital cardiac arrest were included between October 15, 2018, and January 21, 2021. The last 90-day follow-up was on April 21, 2021.

INTERVENTION Patients were randomized to receive a combination of vasopressin and methylprednisolone (n = 245) or placebo (n = 267). The first dose of vasopressin (20 IU) and methylprednisolone (40 mg), or corresponding placebo, was administered after the first dose of epinephrine. Additional doses of vasopressin or corresponding placebo were administered after each additional dose of epinephrine for a maximum of 4 doses.

MAIN OUTCOMES AND MEASURES The primary outcome was return of spontaneous circulation. Secondary outcomes included survival and favorable neurologic outcome at 30 days (Cerebral Performance Category score of 1 or 2).

RESULTS Among 512 patients who were randomized, 501 met all inclusion and no exclusion criteria and were included in the analysis (mean [5D] age, 71 [13] years; 322 men [64%]). One hundred of 237 patients (42%) in the vasopressin and methylprednisolone group and 86 of 264 patients (33%) in the placebo group achieved return of spontaneous circulation (risk ratio, 1.30 [95% Cl, 1.03-1.63]; risk difference, 9.6% [95% Cl, 1.1%-18.0%]; P = .03). At 30 days, 23 patients (9.7%) in the intervention group and 31 patients (12%) in the placebo group were alive (risk ratio, 0.83 [95% CI, 0.50-1.37]; risk difference: -2.0% [95% CI, -7.5% to 3.5%]; P = .48). A favorable neurologic outcome was observed in 18 patients (7.6%) in the intervention group and 20 patients (7.6%) in the placebo group at 30 days (risk ratio, 1.00 [95% CI, 0.55-1.83]; risk difference, 0.0% [95% CI, -4.7% to 4.9%]; P > .99). In patients with return of spontaneous circulation, hyperglycemia occurred in 77 (77%) in the intervention group and 63 (73%) in the placebo group. Hypernatremia occurred in 28 (28%) and 27 (31%), in the intervention and placebo groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the likelihood of return of spontaneous circulation. However, there is uncertainty whether this treatment results in benefit or harm for long-term survival.

TRIAL REGISTRATION Clinical Trials, gov Identifier: NCT03640949

JAMA

Kjærgaard, MD, PhD, DMSc; Camilla M. Kristensen, BS; Søren Darling, MD; Stine T. Zwisler, MD, PhD; Stine Fisker, CRNA; Jens Christian Schmidt, MD; Hans Kirkegaard, MD, PhD, DMSc; Anders M. Grejs, MD, PhD; Jørgen R. G. Rossau, MD; Jacob M. Larsen, MD, PhD; Bodil S. Rasmussen, MD, PhD; Signe Riddersholm, MD, PhD; Kasper Iversen, MD, DMSc; Martin Schultz, MD, PhD; Jakob L. Nielsen, CRNA; Bo Løfgren, MD, PhD; Kasper G. Lauridsen, MD, PhD; Christoffer Sølling, MD, PhD; Kim Pælestik, MD; Anders G. Kjærgaard, MD, PhD; Dorte Due-Rasmussen, MD; Fredrik Folke, MD, PhD; Mette G. Charlot, MD, PhD; Rikke Malene H. G. Jepsen, MD, PhD; Sebastian Wiberg, MD, PhD; Michael Donnino, MD; Tobias Kurth, MD, PhD; Maria Høybye, BS; Birthe Sindberg, RN; Mathias J. Holmberg, MD, MPH, PhD; Asger Granfeldt, MD, PhD, DMSc

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Published September 29, 2021

Available at jama.com





November 30th