UWE Bristol | University of the West of England

Presentation by

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Patient Care Following ROSC: Evidence and Practice

17th Oct 2023

Randomised trial of the clinical and cost effectiveness of a supraglottic airway device versus tracheal intubation during in-hospital cardiac arrest (AIRWAYS-3)

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Sponsor: University Hospitals Bristol and Weston
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NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

WARWICK
CLINICAL TRIALS UNIT

FUNDED BY
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Trial Design

Planned Trial Period	1st January 2022 to 31st December 2026 - **Patient enrolment starts in October 2022**
Trial Design	A multi-centre, open-label, pragmatic, individually randomised, parallel group, superiority trial and economic evaluation to determine the clinical and cost effectiveness of a supraglottic airway (SGA) versus tracheal intubation (TI) during in-hospital cardiac arrest (IHCA). The trial will include an internal pilot to confirm feasibility
Trial Population	Adult IHCA requiring a 2222 call and advanced airway management
Setting	Hospitals in the UK (pilot in England and Wales)
Planned sample size	4190 participants
Treatment Duration	Until return of spontaneous circulation (ROSC) for >20 minutes, or resuscitation efforts cease
Trial Objectives	(1) Conduct an internal pilot study to confirm the feasibility of the large-scale multi-centre trial (2) Determine the clinical effectiveness of SGA management, for adults with in-hospital cardiac arrest, in terms of survival with a favourable functional outcome and health-related quality of life. (3) Estimate, in an integrated economic evaluation, the cost-effectiveness of SGA compared with TI
Outcome Measures	Functional status at hospital discharge as measured by the modified Rankin Scale (mRS) Survival status and Health Related Quality of Life

Physiological Optimisation Following ROSC

Oxygen after ROSC

- Hypoxia is bad
- Hyperoxia is bad for animals
- Results in humans are mixed, and based on observational data
- Prospective randomised trials are needed
- Aim for normoxia immediately after ROSC

ORIGINAL ARTICLE

Oxygen Targets in Comatose Survivors of Cardiac Arrest

H. Schmidt, J. Kjaergaard, C. Hassager, S. Mølstrøm, J. Grand, B. Borregaard, L.E. Roelsgaard Obling, S. Venø, L. Sarkisian, D. Mamaev, L.O. Jensen, B. Nyholm, D.E. Høfsten, J. Josiassen, J.H. Thomsen, J.J. Thune, M.G. Lindholm, M.A. Stengaard Meyer, M. Winther-Jensen, M. Sørensen, M. Frydland, R.P. Beske, R. Frikke-Schmidt, S. Wiberg, S. Boesgaard, V. Lind Jørgensen, and J.E. Møller

ABSTRACT

BACKGROUND

The appropriate oxygenation target for mechanical ventilation in comatose survivors of out-of-hospital cardiac arrest is unknown.

METHODS

In this randomized trial with a 2-by-2 factorial design, we randomly assigned comatose adults with out-of-hospital cardiac arrest in a 1:1 ratio to either a restrictive oxygen target of a partial pressure of arterial oxygen (PaO_2) of 9 to 10 kPa (68 to 75 mm Hg) or a liberal oxygen target of a PaO_2 of 13 to 14 kPa (98 to 105 mm Hg); patients were also assigned to one of two blood-pressure targets (reported separately). The primary outcome was a composite of death from any cause or hospital discharge with severe disability or coma (Cerebral Performance Category [CPC] of 3 or 4; categories range from 1 to 5, with higher values indicating more severe disability), whichever occurred first within 90 days after randomization. Secondary

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Møller can be contacted at jacob.moeller1@rsyd.dk or at the Department of Cardiology, Odense University Hospital, Winsløvvej 4, 5000 Odense C, Denmark.

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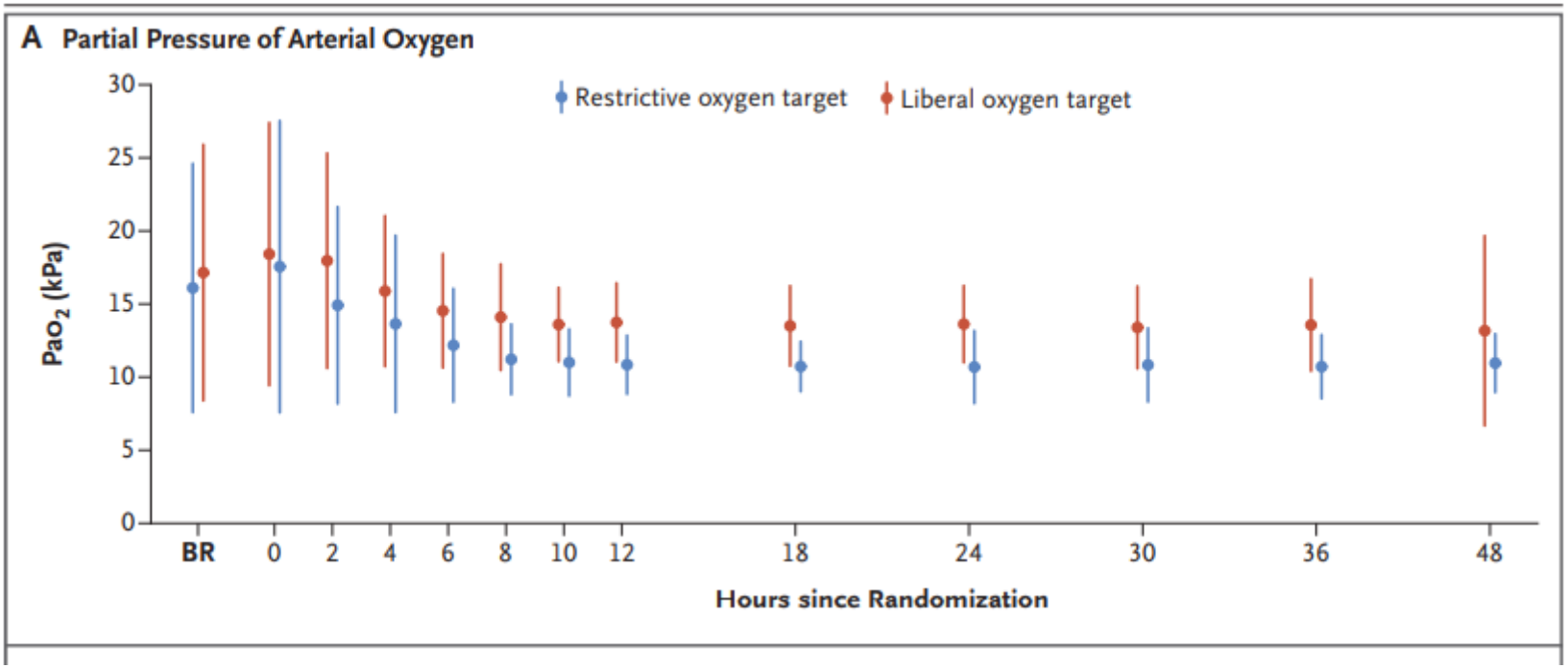
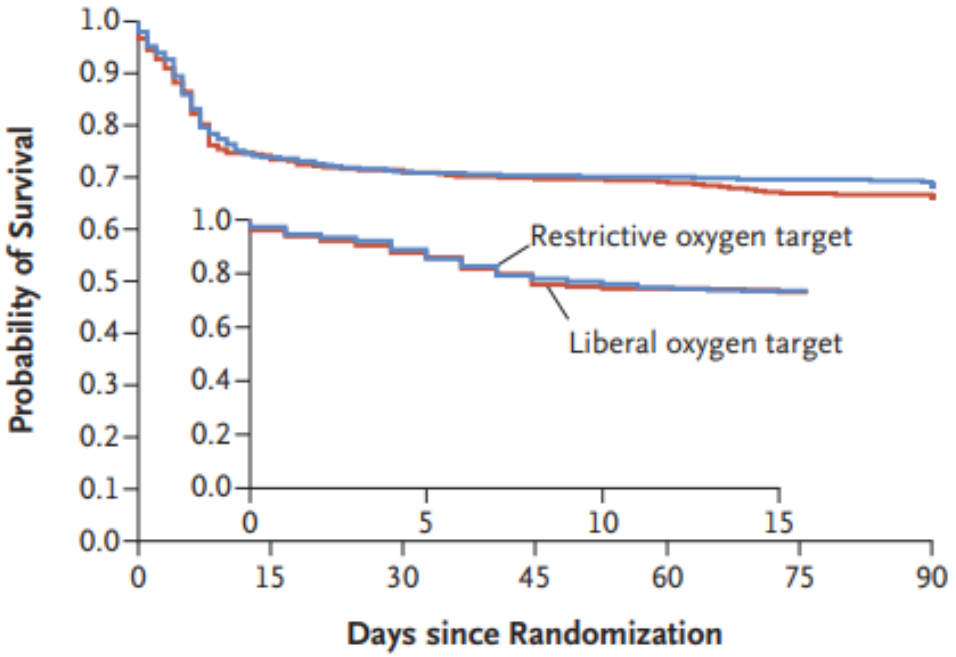
DOI: 10.1056/NEJMoa2208686

- From March 2017 to December 2021, a total of 802 patients were enrolled in the trial.
- 789 patients were included in the intention-to-treat population (394 in the restrictive-target group and 395 in the liberal-target group).
- The characteristics of the patients in the oxygen-target groups were well balanced at baseline.
- The median interval from cardiac arrest to randomization was 146 minutes (interquartile range, 113 to 187).





No. at Risk

Restrictive target	394	290	279	276	275	273	271
Liberal target	395	292	281	275	272	263	262

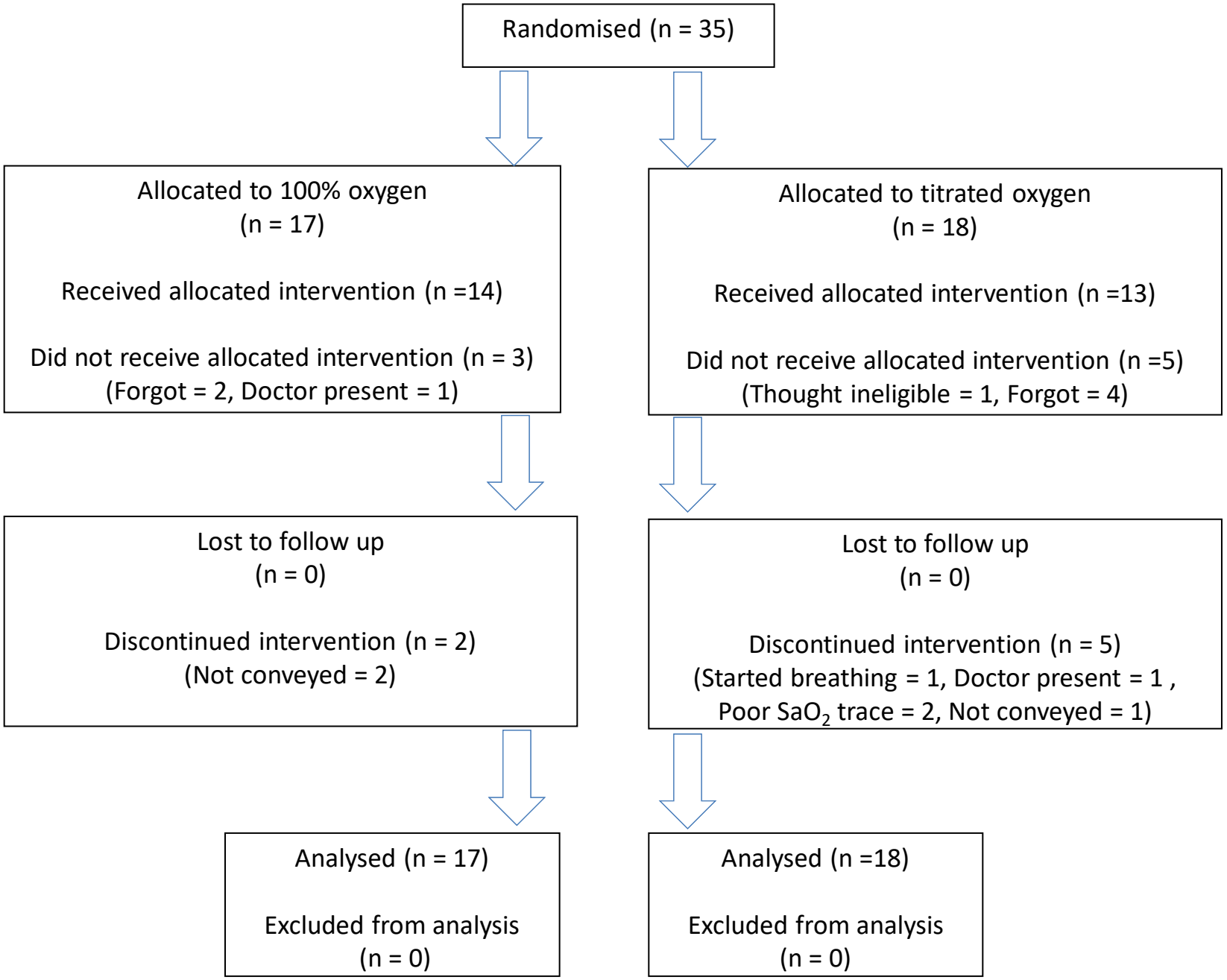
Figure 2. Kaplan–Meier Estimates of Survival.

Shown is the probability of survival without disability or coma at 90 days after randomization (the primary composite outcome) in the two oxygenation groups. Disability or coma was defined as a Cerebral Performance Category of 3 or 4. Data are for the 789 patients who were included in the intention-to-treat population. The inset shows the same data truncated at 15 days after randomization.


GLOBE

PROXY

To determine the feasibility of a cluster-randomised controlled trial comparing titrated oxygen therapy (target SaO2 94-98%) with 100% oxygen for 1 hour after return of spontaneous circulation (ROSC) following out of hospital cardiac arrest (OHCA)


Randomised (n = 35)
Allocated to 100% oxygen
(n = 17)
Received allocated intervention (n =14)
Did not receive allocated intervention (n = 3)
(Forgot = 2, Doctor present = 1)
Allocated to titrated oxygen
(n = 18)
Received allocated intervention (n =13)
Did not receive allocated intervention (n =5)
(Thought ineligible = 1, Forgot = 4)
Lost to follow up
(n = 0)
Discontinued intervention (n = 2)
(Not conveyed = 2)
Lost to follow up
(n = 0)
Discontinued intervention (n = 5)
(Started breathing = 1, Doctor present = 1 ,
Poor SaO_2 trace = 2, Not conveyed = 1)
Analysed (n = 17)
Excluded from analysis
(n = 0)
Analysed (n =18)
Excluded from analysis
(n = 0)

Patient Outcomes and Follow Up

	100% oxygen (n = 17)	Titrated oxygen (N = 18)
Re-arrest following initial ROSC	8(47)	3(17)
Death recognised on scene n (%)*	2 (12)	1 (6)
Survival to discharge n (%)	3 (18)	10 (55)
Survival to 90 days n (%)	3 (18)	10(55)

*Data missing for two patients; one from each group

JAMA | Original Investigation

Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest
The EXACT Randomized Clinical Trial

Stephen A. Bernard, MD; Janet E. Bray, PhD; Karen Smith, PhD; Michael Stephenson, BHlthSci; Judith Finn, PhD; Hugh Grantham, MBBS; Cindy Hein, PhD; Stacey Masters, PhD; Dion Stub, PhD; Gavin D. Perkins, MD; Natasha Dodge, MPH; Catherine Martin, PhD; Sarah Hopkins, MBBS; Peter Cameron, PhD; for the EXACT Investigators

Figure 1. Flow of Participants in a Study of the Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge After Cardiac Arrest

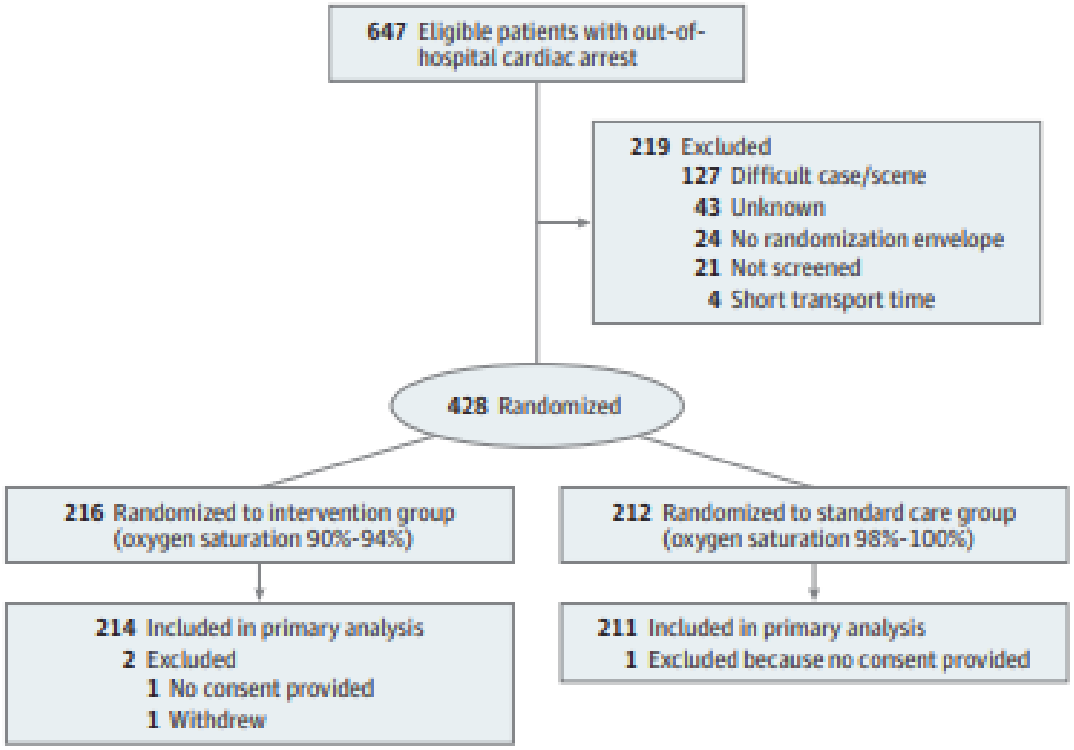


Table 3. Outcomes Collected During Intensive Care Unit and Hospital Stay

Outcome	No. (%)		Difference (95% CI)[a]	Odds ratio (95% CI)	*P* value[b]
	Target Spo_2 90%-94% (n = 214)	Target Spo_2 98%-100% (n = 211)			
Primary					
Survival to hospital discharge	82 (38.3)	101 (47.9)	−9.6 (−18.9 to −0.2)	0.68 (0.46 to 1.00)	.05
Secondary					
Rearrest					
Pre-ICU[c]	27 (12.7) [n = 213]	21 (10.0) [n = 209]	2.6 (−3.4 to 8.7)	1.30 (0.71 to 2.38)	.40
Prehospital	7 (3.3)	3 (1.4)	1.8 (−1.0 to 4.7)		
ED	26 (12.2) [n = 213]	20 (9.5) [n = 210]	2.7 (−3.2 to 8.6)		
Hypoxia (any Spo_2 <90%) prior to ICU	67 (31.3)	34 (16.1)	15.2 (7.2 to 23.1)	2.37 (1.49 to 3.79)	<.001

- Stopped early due to the Covid pandemic
- Targeting low normal oxygen saturations pre-hospital risks causing significant hypoxia
- High survival to hospital discharge (>40%) and % of shockable rhythms (>60% in both groups), limits generalizability

Carbon Dioxide After ROSC

- Hypocapnia is bad
- Hypercapnia is probably bad too
- Likely "U-shaped curve"
- Aim for normal: 4.5–6.0 kPa (35–45 mmHg)
- Lung protective ventilation (6–8 mL/kg ideal body weight)

Blood Pressure After ROSC

- A-line valuable, but rarely urgent
- ED echocardiography to assess pathology and function
- Target MAP to achieve normal or decreasing lactate
- Consider fluids, noradrenaline, dobutamine
- Consider early mechanical circulatory support (intra-aortic balloon pump, LVAD, ECMO) if shocked or unstable

ORIGINAL ARTICLE

Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest

J. Kjaergaard, J.E. Møller, H. Schmidt, J. Grand, S. Mølstrøm, B. Borregaard, S. Venø, L. Sarkisian, D. Mamaev, L.O. Jensen, B. Nyholm, D.E. Høfsten, J. Josiassen, J.H. Thomsen, J.J. Thune, L.E.R. Obling, M.G. Lindholm, M. Frydland, M.A.S. Meyer, M. Winther-Jensen, R.P. Beske, R. Frikke-Schmidt, S. Wiberg, S. Boesgaard, S.A. Madsen, V.L. Jørgensen, and C. Hassager

ABSTRACT

BACKGROUND

Evidence to support the choice of blood-pressure targets for the treatment of comatose survivors of out-of-hospital cardiac arrest who are receiving intensive care is limited.

METHODS

In a double-blind, randomized trial with a 2-by-2 factorial design, we evaluated a mean arterial blood-pressure target of 63 mm Hg as compared with 77 mm Hg in comatose adults who had been resuscitated after an out-of-hospital cardiac arrest of presumed cardiac cause; patients were also assigned to one of two oxygen targets (reported separately). The primary outcome was a composite of death from any cause or hospital discharge with a Cerebral Performance Category (CPC) of 3 or 4 within 90 days (range, 0 to 5, with higher categories indicating more severe disability; a category of 3 or 4 indicates severe disability or coma). Secondary outcomes included neuron-specific enolase levels at 48 hours, death from any cause, scores on the Montreal Cognitive Assessment (range, 0 to 30, with higher scores indicating better cognitive ability) and the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at 3 months, and the CPC at 3 months.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Kjaergaard can be contacted at jesper.kjaergaard.05@regionh.dk or at the Department of Cardiology, the Heart Center, Copenhagen University Hospital Rigshospitalet, 9 Blegdamsvej, DK2100 Copenhagen East, Denmark.

This article was published on August 27, 2022, at NEJM.org.

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- A total of 802 patients were enrolled in the trial from March 2017 to December 2021.
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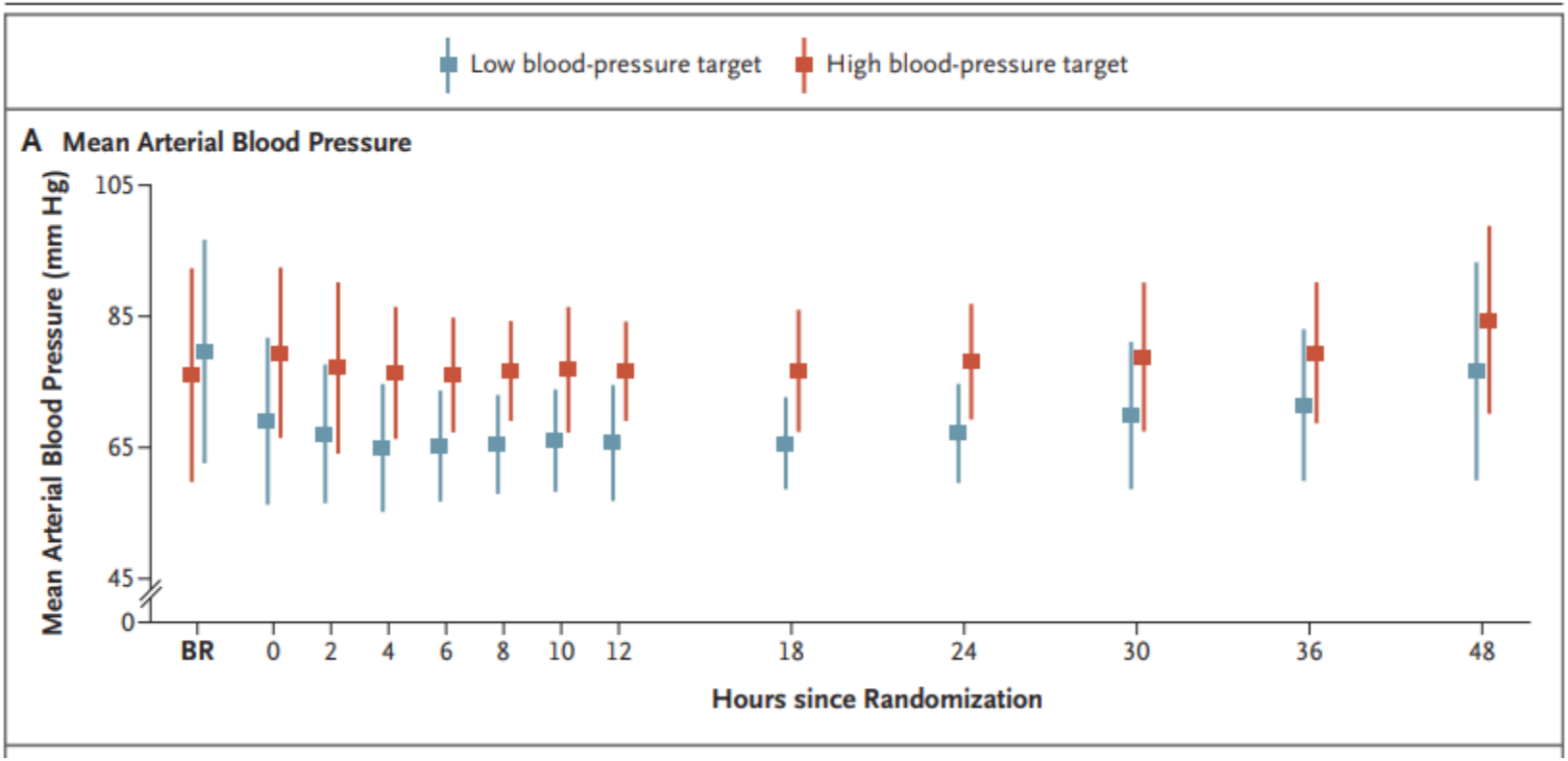
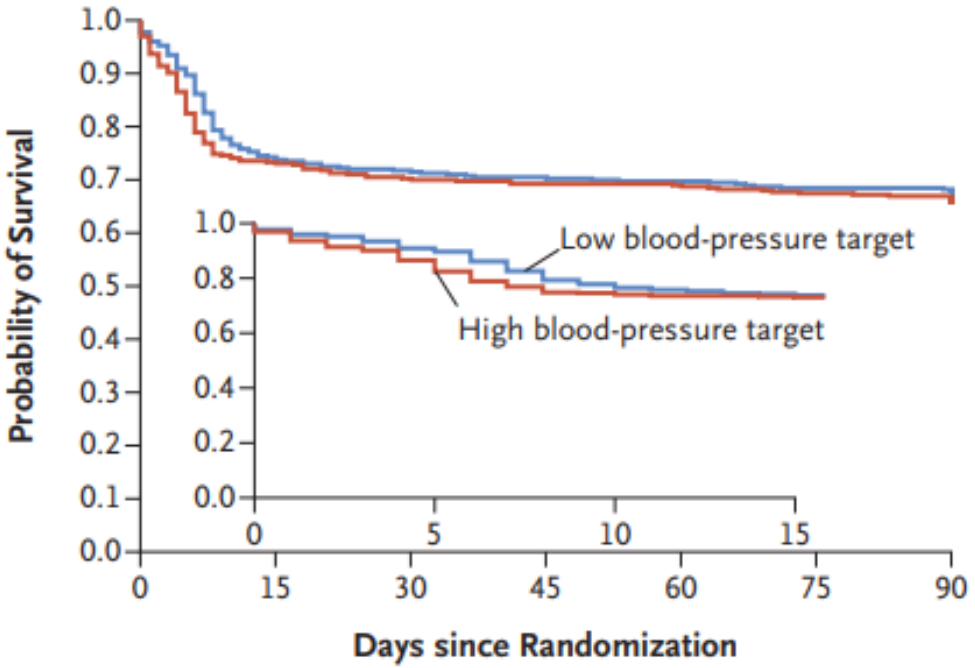




No. at Risk

Low blood-pressure target	396	294	284	279	276	271	270
High blood-pressure target	393	288	276	272	271	265	263

Figure 2. Kaplan–Meier Analysis of the Primary Outcome.

Shown is a plot of the probability of survival free from death from any cause or discharge from hospital with a Cerebral Performance Category score of 3 or 4 up to 90 days after randomization. Data are for the 789 patients in the intention-to-treat population. The inset shows the same data on an enlarged x axis (truncated at 15 days after randomization).

Temperature after ROSC

TTM2:

- International, multicentre, randomised superiority trial
- Randomised in the ED to hypothermia (target 33^{o}) or normothermia (<37.8^{o})
- 1900 randomised
- 1861 analysed ITT: 930 in Hypothermia arm, 931 in Normothermia arm
- 1850 analysed for survival (11 lost to follow-up)
- Baseline characteristics very similar

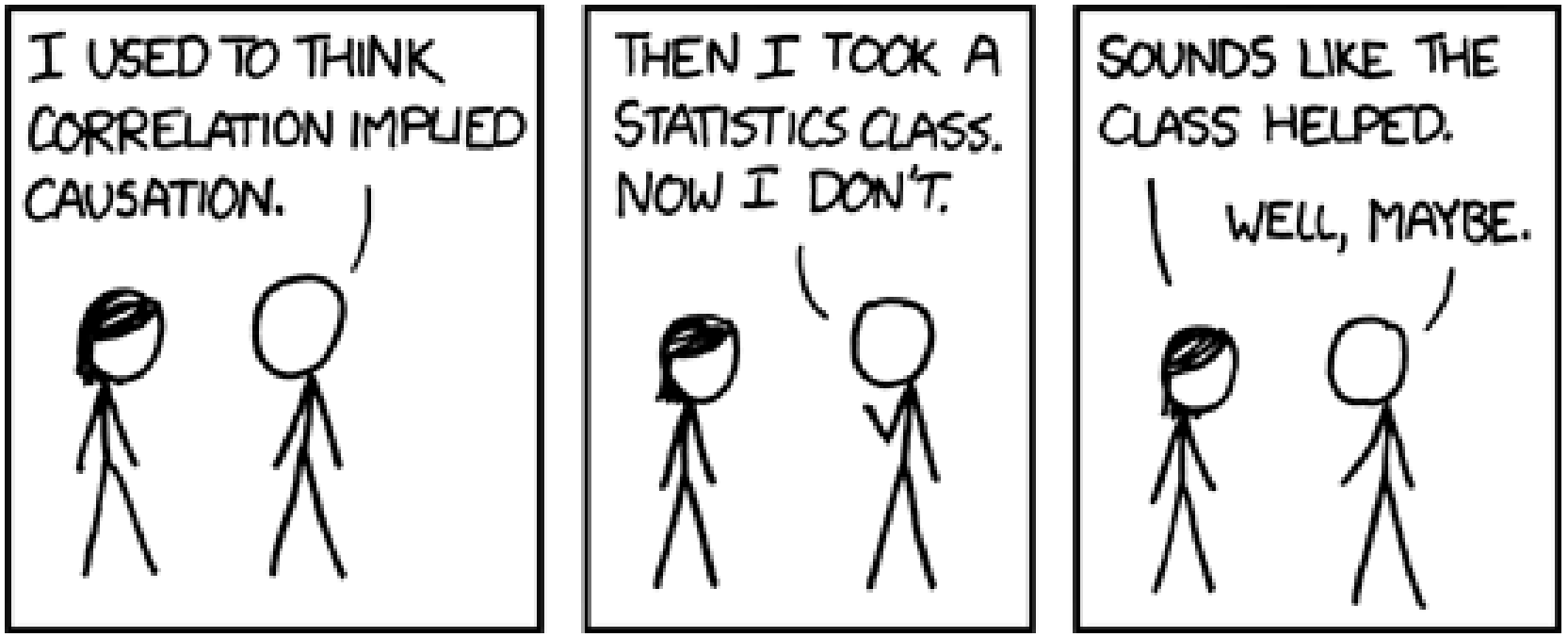
Primary Outcome		
	Hypothermia	Normothermia
6-month all-cause mortality	465/925 (50%)	446/925 (48%)
RR 1.04 (95% CI 0.94 - 1.14), p = 0.37		
Main Secondary Outcomes		
Score of 4 - 6 on mRS at 6 months	488/881 (55%)	479/866 (55%)
When mRS broken down into individual scores from 0 - 6 there is no difference between groups		
Mean EQ-VAS score at 6 months (Health - related quality of life) - participants alive	74 (SD 20)	75 (SD 20)
EQ-VAS is a visual analogue scale where 0 is worst health and 100 best health imaginable		
Serious Adverse Events		
Arrythmia resulting in haemodynamic instability	222/927 (24%)	152/921 (16%)
RR 1.45 (95% CI 1.21 - 1.75), p < 0.001. ARR 7.44% (95% CI 3.80 - 11.09%)		
Bleeding	44/927 (5%)	46/922 (5%)
Skin complications	10/927 (1%)	5/922 (<1%)
Pneumonia	330/927 (36%)	322/921 (35%)
Sepsis	99/926 (11%)	83/922 (9%)

Questions remain regarding the effect of very early cooling

Physiological Optimisation Following ROSC

Other Things…

- Blood glucose
- Seizure control
- Aspiration pneumonia
- Stress ulcer prophylaxis
- Deep venous thrombosis prophylaxis


I USED TO THINK CORRELATION IMPLIED CAUSATION.
THEN I TOOK A STATISTICS CLASS. NOW I DON'T.
SOUNDS LIKE THE CLASS HELPED.
WELL, MAYBE.

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