ORIGINAL ARTICLE

Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest

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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.

RESULTS

A total of 789 patients were included in the analysis (393 in the high-target group and 396 in the low-target group). A primary-outcome event occurred in 133 patients (34%) in the high-target group and in 127 patients (32%) in the low-target group (hazard ratio, 1.08; 95% confidence interval [CI], 0.84 to 1.37; P=0.56). At 90 days, 122 patients (31%) in the high-target group and 114 patients (29%) in the low-target group had died (hazard ratio, 1.13; 95% CI, 0.88 to 1.46). The median CPC was 1 (interquartile range, 1 to 5) in both the high-target group and the low-target group; the corresponding median modified Rankin scale scores were 1 (interquartile range, 0 to 6) and 1 (interquartile range, 0 to 6), and the corresponding median Montreal Cognitive Assessment scores were 27 (interquartile range, 24 to 29) and 26 (interquartile range, 24 to 29). The median neuron-specific enolase level at 48 hours was also similar in the two groups. The percentages of patients with adverse events did not differ significantly between the groups.

CONCLUSIONS

Targeting a mean arterial blood pressure of 77 mm Hg or 63 mm Hg in patients who had been resuscitated from cardiac arrest did not result in significantly different percentages of patients dying or having severe disability or coma. (Funded by the Novo Nordisk Foundation; BOX ClinicalTrials.gov number, NCT03141099.)

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A central part of goal-directed postresuscitation care is maintaining adequate perfusion pressure, but evidence for specific blood-pressure targets is limited.[1] Blood pressure is actively managed as part of most intensive care protocols to deliver sufficient perfusion pressure to vital organs, such as the brain, heart, and kidneys.[2] However, after a cardiac arrest, patients often have underlying or concomitant heart disease, and lowering the afterload may facilitate cardiac recovery and possibly survival.[3] In addition, vasoactive drugs, including catecholamines, are used to keep the mean arterial blood pressure above 65 mm Hg in the majority of comatose patients who have been resuscitated after an out-of-hospital cardiac arrest,[4] although vasopressor therapy may have adverse effects.[3,5]

Three small randomized trials have compared the efficacy of two different blood-pressure targets with the use of surrogate end points.[6-8] The results of the trials were neutral, and none were powered to evaluate clinical end points and safety.[6,7]

We recently developed a method for performing double-blind prospective trials of blood-pressure targets in patients in intensive care[9] and have used this method in the Blood Pressure and Oxygenation Targets in Post Resuscitation Care (BOX) trial. We tested whether a higher (77 mm Hg) or lower (63 mm Hg) target mean arterial blood pressure would be superior in preventing death or severe anoxic brain injury in comatose survivors of out-of-hospital cardiac arrest.

Methods

Trial Design

In the BOX trial, an investigator-initiated, dual-center, randomized trial with a 2-by-2 factorial design, we assigned comatose patients who had been resuscitated after an out-of-hospital cardiac arrest to be treated to meet one of two blood-pressure targets (a double-blind intervention) and to undergo restrictive oxygenation or liberal oxygenation (an open-label intervention) while the patient remained in the intensive care unit (ICU). Randomization was performed from March 2017 through December 2021 at two tertiary cardiac arrest centers in Denmark with the use of a Web-based system, random permuted blocks of sizes 2, 4, and 6, and stratification according to randomization site. Furthermore, patients underwent a subordinate randomization to undergo device-based fever control after the first 24 hours. The results for the oxygen-target intervention are reported separately,[10] and the results of the assessment of fever control are not included.

Danish legislation permits the immediate inclusion of patients who are unable to provide consent in clinical trials if delayed proxy consent is obtained from a legal representative, most often a relative, and a medical doctor with no relation to the trial. Informed consent from the patient was obtained if the patient regained consciousness, and if the patient died, the need for consent was waived. The protocol (available with the full text of this article at NEJM.org) was approved by the Regional Ethics Committee of the Capital Region of Denmark before initiation of the trial. The trial was designed and overseen by the steering committee (see the Supplementary Appendix, available at NEJM.org), data were collected by the authors and analyzed by the first two authors, and the first author wrote the first draft of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Additional details of the trial design have been published previously.[11]

Patients

Adult patients (≥18 years of age) who had been resuscitated after an out-of-hospital cardiac arrest with a presumed cardiac cause were eligible for inclusion if they had a sustained return of spontaneous circulation (i.e., no chest compressions for >20 minutes) and remained comatose (i.e., were not able to obey verbal commands) on arrival at the hospital. Key exclusion criteria included unwitnessed asystole and suspected acute intracranial bleeding or stroke. A complete list of all inclusion and exclusion criteria is provided in the Supplementary Appendix.

Treatment Protocol

Patients were treated in accordance with guidelines at the discretion of the treating physician. For the duration of the trial, all patients received temperature control to maintain a temperature of 36°C for 24 hours in accordance with guidelines for comatose patients who had had an out-of-hospital cardiac arrest.[12,13] Patients were receiving mechanical ventilation and were sedated, primarily with the use of propofol and fentanyl.

Table 1. Demographic and Clinical Characteristics of the Patients.*

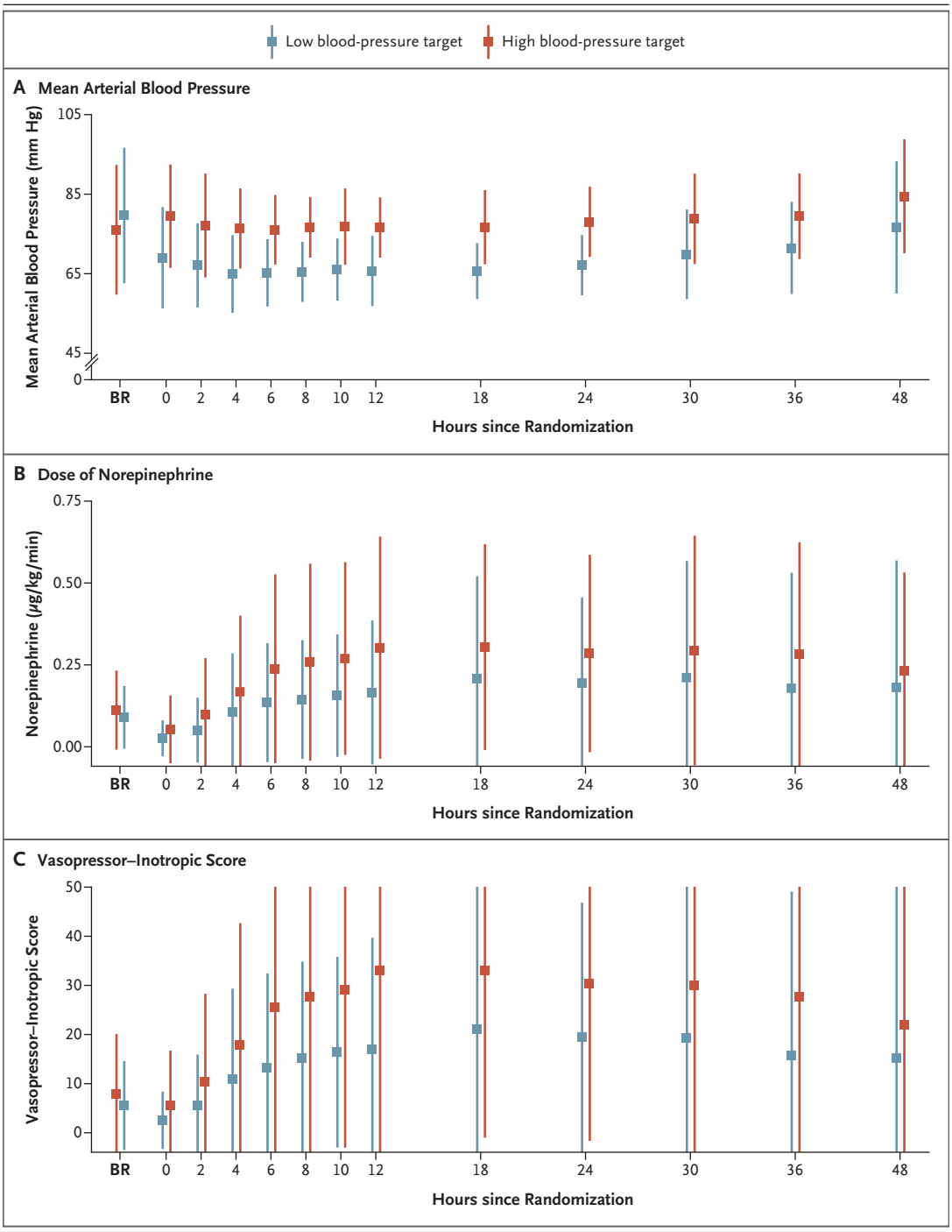
Characteristic	High Blood-Pressure Target (N=393)	Low Blood-Pressure Target (N=396)
Age — yr	63±13	62±14
Range	19–90	18–89
Male sex — no. (%)	316 (80)	320 (81)
Medical history — no./total no. (%)		
Hypertension, medically treated	176/391 (45)	186/396 (47)
Diabetes	48/393 (12)	62/396 (16)
Myocardial infarction	94/393 (24)	78/394 (20)
Atrial fibrillation	67/392 (17)	60/393 (15)
Heart failure	65/392 (17)	72/395 (18)
Chronic obstructive pulmonary disease	30/392 (8)	33/395 (8)
Stroke	23/393 (6)	36/395 (9)
Chronic kidney disease†	22/393 (6)	17/395 (4)
Renal-replacement therapy	2/393 (1)	2/395 (1)
Characteristics of the cardiac arrest		
Shockable rhythm — no./total no. (%)	335/391 (86)	332/396 (84)
Pulseless electrical activity — no./total no. (%)	14/391 (4)	21/396 (5)
Witnessed asystole — no./total no. (%)	14/391 (4)	16/396 (4)
Witnessed arrest — no./total no. (%)	339/392 (86)	333/396 (84)
First defibrillation by automated external defibrillator — no./total no. (%)	98/384 (26)	84/392 (21)
Bystander cardiopulmonary resuscitation — no./total no. (%)	340/387 (88)	339/389 (87)
Time to return of spontaneous circulation — min‡	21±13	21±15
Findings and procedures on arrival at hospital		
ST-segment elevation ECG — no./total no. (%)	172/391 (44)	178/382 (47)
Coronary angiogram obtained — no. (%)	364 (93)	358 (90)
PCI performed — no./total no. (%)	171/363 (47)	165/357 (46)
pH§	7.21±0.13	7.22±0.13
Lactate level — mmol/liter¶	6.1±4.1	5.6±3.6

* Plus–minus values are means ±SD. The high blood-pressure target was 77 mm Hg, and the low blood-pressure target was 63 mm Hg. ECG denotes electrocardiogram, and PCI percutaneous coronary intervention.
† Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area.
‡ Data were missing for 18 patients (13 in the high-target group and 5 in the low-target group).
§ Data were missing for 43 patients (19 in the high-target group and 24 in the low-target group).
¶ Data were missing for 23 patients (10 in the high-target group and 13 in the low-target group).

Temperature control was achieved with surface cooling (CritiCool and Allon, Belmont Medical Technologies) or with intravenous devices (Thermogard XP and Cool Line Catheter, Zoll). After completion of the 24-hour period of temperature control, the core temperature was gradually increased to normothermia with a rewarming rate of less than 0.5°C per hour, and sedation was tapered. Assessment of neurologic outcomes was performed by the attending physician in accordance with guidelines.[14]

TRIAL INTERVENTION

Clinical staff, investigators, patients, and outcome assessors were unaware of the assigned blood-pressure targets. For all enrolled patients, invasive



blood-pressure monitoring with a patient-specific blood-pressure module (M1006B Invasive Blood Pressure Module, Philips) was used for as long as the patient underwent invasive blood-pressure monitoring in the ICU. These modules had been modified for trial use by adjusting the internal calibration to report a blood pressure that was either 10% higher or 10% lower than the actual blood pressure, depending on the assigned blood-pressure target. Thus, by targeting a mean arterial blood pressure of 70 mm Hg in all patients, half the patients would have an actual target mean arterial blood pressure of 63 mm Hg (low-target group) and the other half would have a target

Figure 1 (facing page). Blood Pressure and Vasopressor Use over the First 48 Hours.

Panel A shows blood-pressure target assignments and mean blood pressure during the first 48 hours after randomization. Panels B and C show norepinephrine doses (Panel B) and vasopressor–inotropic scores (Panel C) during the first 48 hours after randomization. The before-randomization (BR) time point is the first available blood-pressure value before randomization, and time 0 is the time of randomization (i.e., the first measurement obtained with the trial-specific blood-pressure module). The high blood-pressure target was 77 mm Hg, and the low blood-pressure target was 63 mm Hg. Values shown are means, and error bars indicate the standard deviation. During the period from 2 to 48 hours after randomization, the mean between-group difference in blood pressure was 10.5 mm Hg (95% CI, 9.9 to 11.2), the mean difference in norepinephrine dose was 0.038 μg per kilogram per minute (95% CI, 0.026 to 0.049), and the mean difference in vasopressor–inotropic score was 3.5 points (95% CI, 2.4 to 4.6). A definition of the vasopressor–inotropic score is provided in the Supplementary Appendix; higher scores indicate a higher degree of pharmacologic circulatory support.

mean arterial blood pressure of 77 mm Hg (high-target group).

The offset of the blood-pressure modules was performed at a Core Laboratory at the Technical Department, Rigshospitalet, which had no other part in the trial execution. The patients underwent randomization as soon as possible after arrival at the hospital, usually in the ICU and before invasive monitoring of the systemic arterial pressure was established. After randomization, systemic arterial blood pressure was measured with the trial-specific module only. Other invasive pressure measurements (i.e., central venous pressure or pulmonary artery catheter measurements) were obtained without blinding with modules that had no offset of calibration.

The protocol provided a recommendation for achieving the mean arterial blood pressure of 70 mm Hg in a three-stage approach: volume resuscitation to a central venous pressure of 10 mm Hg, norepinephrine infusion, and the addition of a dopamine infusion for a maximal dose of 10 μg per kilogram of body weight per minute, if needed. Information on the use of vasoactive drugs, including doses, was obtained from electronic ICU databases, and the maximal dose for a given period was captured. The total amount of pharmacologic circulatory support was quantified as the vasopressor–inotropic score (higher scores indicate a higher degree of support)[15,16] (see the Supplementary Appendix).

OUTCOME MEASURES

The primary outcome was a composite of death from any cause or discharge from the hospital with a Cerebral Performance Category (CPC)[17,18] of 3 or 4, indicating severe disability or a coma or vegetative state, within 90 days after randomization (categories range from 1 [no symptoms] to 5 [death]). For patients who were discharged alive with a CPC of 3 or 4, events were recorded at the time of discharge. Secondary outcomes included death from any cause within 90 days, time to renal-replacement therapy, neuron-specific enolase levels at 48 hours after randomization, the Montreal Cognitive Assessment score[19] at 3 months, the modified Rankin scale score at 3 months, and the CPC at 3 months.[20,21] Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The Montreal Cognitive Assessment tests different types of cognitive abilities and assigns a score between 0 and 30, with a score of 26 or higher being normal. Assessment of the CPC, the modified Rankin scale score, and the Montreal Cognitive Assessment score was performed by trained research personnel. Because of coronavirus disease 2019 (Covid-19) pandemic restrictions, these assessments were performed in a telephone interview or through review of hospital charts for some patients, which excluded the use of the Montreal Cognitive Assessment in these patients.

The adverse events included in this report are bleeding, infection, arrhythmia, electrolyte or metabolic abnormalities, acute kidney injury with renal-replacement therapy, and seizures.[11] Plasma levels of neuron-specific enolase in patients who were alive at 48 hours were determined by means of electrochemiluminescence (Roche Diagnostics) and with a Cobas analyzer system (Roche Diagnostics) in accordance with the manufacturer's instructions.

STATISTICAL ANALYSIS

Our previous data indicate that 6-month mortality among hospitalized comatose patients who have been resuscitated after an out-of-hospital

Table 2. Outcomes and Adverse Events.*

Outcome or Event	High Blood-Pressure Target (N = 393)	Low Blood-Pressure Target (N = 396)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Death from any cause or CPC of 3 or 4 at discharge within 90 days — no. (%)†	133 (34)	127 (32)	1.08 (0.84–1.37)	0.56
Secondary outcomes				
Death from any cause within 90 days — no. (%)	122 (31)	114 (29)	1.13 (0.88–1.46)	
Acute kidney injury with renal-replacement therapy — no. (%)	41 (10)	40 (10)	1.03 (0.66–1.59)	
Median CPC at 3 months (IQR)†	1 (1–5)	1 (1–5)		
Median modified Rankin scale score at 3 months (IQR)‡	1 (0–6)	1 (0–6)		
Median Montreal Cognitive Assessment score, per protocol (IQR)§	20 (15–27)	21 (15–27)		
Median Montreal Cognitive Assessment score at 3 months, post hoc (IQR)§	27 (24–29)	26 (24–29)		
Median neuron-specific enolase level at 48 hours (IQR) — μg/liter¶	18 (11–37)	18 (11–34)		
			Relative Risk (95% CI)	
Serious adverse events — no. (%)				
Infection‖	102 (26)	110 (28)	0.96 (0.82–1.11)	0.56
Arrhythmia**	59 (15)	50 (13)	1.10 (0.79–1.38)	0.33
Any bleeding††	82 (21)	92 (23)	0.93 (0.79–1.10)	0.43
Uncontrolled bleeding††	22 (6)	16 (4)	0.85 (0.64–1.13)	0.31
Electrolyte disorder‡‡	23 (6)	34 (9)	0.82 (0.66–1.04)	0.13
Metabolic disorder§§	31 (8)	31 (8)	1.00 (0.77–1.30)	0.98
Seizure¶¶	76 (19)	88 (22)	0.92 (0.78–1.08)	0.32

* Because the statistical analysis plan did not include a provision for correcting for multiplicity when tests for efficacy outcomes other than the primary outcome were conducted, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test.

† The Cerebral Performance Category (CPC) ranges from 1 (no symptoms) to 5 (death); a category of 3 or 4 indicates severe disability or a coma or vegetative state. For the secondary analysis of the score among patients who were alive at 3 months, categories were available for 777 patients (385 in the high-target group and 392 in the low-target group).

‡ Modified Rankin scale scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Scores were available for 774 patients (383 in the high-target group and 391 in the low-target group).

§ Scores on the Montreal Cognitive Assessment range from 0 to 30, with a score of 26 or higher being normal. For the score at 3 months (per protocol), the lowest score found in the trial population was assigned to patients who were not available for follow-up, including deceased patients. In a post hoc analysis, only patients who completed the test were included. Scores were available for 511 patients in the per-protocol analysis (264 in the high-target group and 247 in the low-target group) and for 359 in the post hoc analysis (180 and 179, respectively).

¶ Data were available for 625 patients (297 in the high-target group and 328 in the low-target group). The mean (±SD) levels were 35±46 μg per liter in the low-target group and 36±50 μg per liter in the high-target group.

‖ Infection was defined as severe sepsis, septic shock, pneumonia during or after ventilator therapy, and other.

** Arrhythmia was defined as ventricular fibrillation, ventricular tachycardia, tachycardia (>130 beats per minute), bradycardia (<40 beats per minute), atrial flutter, atrial fibrillation, need for pacing, or circulatory collapse mandating cardiopulmonary resuscitation.

†† Any bleeding included uncontrolled bleeding (>1 unit of blood per 10 kg of body weight per hour), bleeding causing death, or symptomatic bleeding in a critical organ (e.g., intracranial, intraspinal, intraocular, intraarticular, or pericardial bleeding).

‡‡ Electrolyte disorders included hypokalemia (potassium level <3.0 mmol per liter), hypophosphatemia (phosphate level <0.7 mmol per liter), or hypomagnesemia (magnesium level <0.7 mmol per liter).

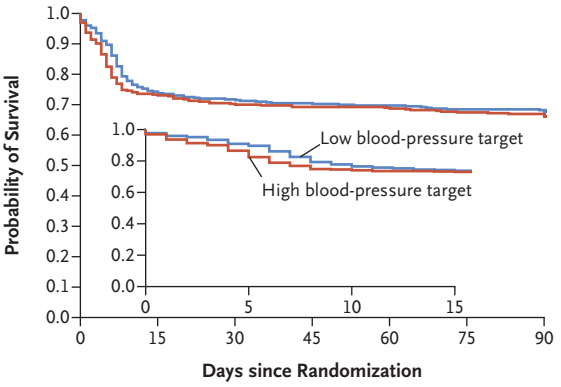
§§ Metabolic disorders included sustained hyperglycemia (blood glucose level >10 mmol per liter for >4 hours) or hypoglycemia (blood glucose level <3.0 mmol per liter for >4 hours).

¶¶ Seizures included tonic–clonic, myoclonic, and electrographic status epilepticus.

cardiac arrest is 33%.[22] For the estimation of sample size, we assumed that there was no interaction with the oxygenation intervention. Samples of 732 or 846 patients would provide a power of 0.8 or 0.9, respectively, to detect mortality of 28% in one blood-pressure target group and 38% in the other, under the assumption of a two-sided alpha level of 0.05. Therefore, inclusion of a total of 800 patients was planned, with follow-up for all patients continuing until 3 months after the final patient had been enrolled. Global type I error for the trial was 0.05, and the two-sided alpha level for the analysis of the primary outcome was 0.0471 after correction for the two planned interim analyses. The mean between-group difference in blood pressure, norepinephrine dose, and vasopressor–inotropic score during the period from 2 to 48 hours after randomization was calculated in a repeated-measures variance component model.

The primary outcome and the secondary outcomes relating to death from any cause and receipt of renal-replacement therapy were adjusted for site in a proportional-hazards model. The assumption of proportional hazards was fulfilled. Because the statistical analysis plan did not include a provision for correcting for multiplicity, the results for efficacy outcomes other than the primary outcome are reported as point estimates and 95% confidence intervals, and the intervals should not be used in place of a hypothesis test. Event-free survival was assessed in a Kaplan–Meier analysis.

In prespecified subgroup analyses of the primary outcome, we evaluated subgroups based on sex, median age, site, and status with respect to known chronic obstructive pulmonary disease (COPD), hypertension (receipt of antihypertensive drugs) or renal disease (glomerular filtration rate <30 ml per minute per 1.73 m^2 of body-surface area or current renal-replacement therapy), shockable primary rhythm, and acute ST-segment elevation myocardial infarction. The statistical analysis plan included an analysis of Montreal Cognitive Assessment scores in which missing scores and scores for deceased patients were included as the lowest score measured in the trial population (i.e., 15).[11] A two-sided P value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed with the use of SAS Enterprise statistical software, version 3.8 (SAS Institute).



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).

RESULTS

PATIENTS

A total of 802 patients were enrolled in the trial from March 2017 through December 2021. The screening and inclusion of patients is shown in Figure S1 in the Supplementary Appendix. Consent was withdrawn for 12 patients (use of data was not allowed), and 1 patient underwent randomization twice, leaving 789 patients in the trial population. Four patients died before the intervention was initiated, and in 2 patients the blood-pressure intervention was stopped by the treating physician because of hemodynamic instability; all 6 of these patients remained in the analyses. The median time from cardiac arrest to randomization was 146 minutes (interquartile range, 113 to 187). Two non-Danish patients were transferred and lost to follow-up; data for these patients were censored on the day when the modified Rankin scale score and CPC were recorded (on day 12 for one patient and on day 13 for the

other). The baseline characteristics of the patients were well balanced in the two blood-pressure target groups (Tables 1 and S2).

BLOOD-PRESSURE INTERVENTION

Separation of the blood-pressure values for the high-target and low-target groups was apparent from the first value measured by the offset blood-pressure module, with a mean difference of 10.7 mm Hg (95% confidence interval [CI], 10.0 to 11.4) between the groups. The norepinephrine dose and the vasopressor–inotropic score were higher in the high-target group than in the low-target group (Fig. 1).

OUTCOMES AND ADVERSE EVENTS

At 90 days, 133 patients (34%) in the high-target group and 127 patients (32%) in the low-target group had been discharged from the hospital with a CPC of 3 or 4 or had died (hazard ratio, 1.08; 95% CI, 0.84 to 1.37; P=0.56) (Table 2 and Fig. 2). A total of 24 patients (3%) had been discharged from the hospital with a CPC of 3 or 4: 11 in the high-target group and 13 in the low-target group. No interaction with the oxygen-target intervention was found (P=0.67). The results appeared to be consistent across most of the prespecified subgroups (Fig. 3). A total of 122 of 393 patients (31%) in the high-target group and 114 of 396 patients (29%) in the low-target group died within 90 days (Table 2 and Fig. S2). Renal-replacement therapy was initiated within the first 5 days in 41 patients (10%) in the high-target group and 40 patients (10%) in the low-target group (hazard ratio, 1.03; 95% CI, 0.66 to 1.59).

The Montreal Cognitive Assessment score was

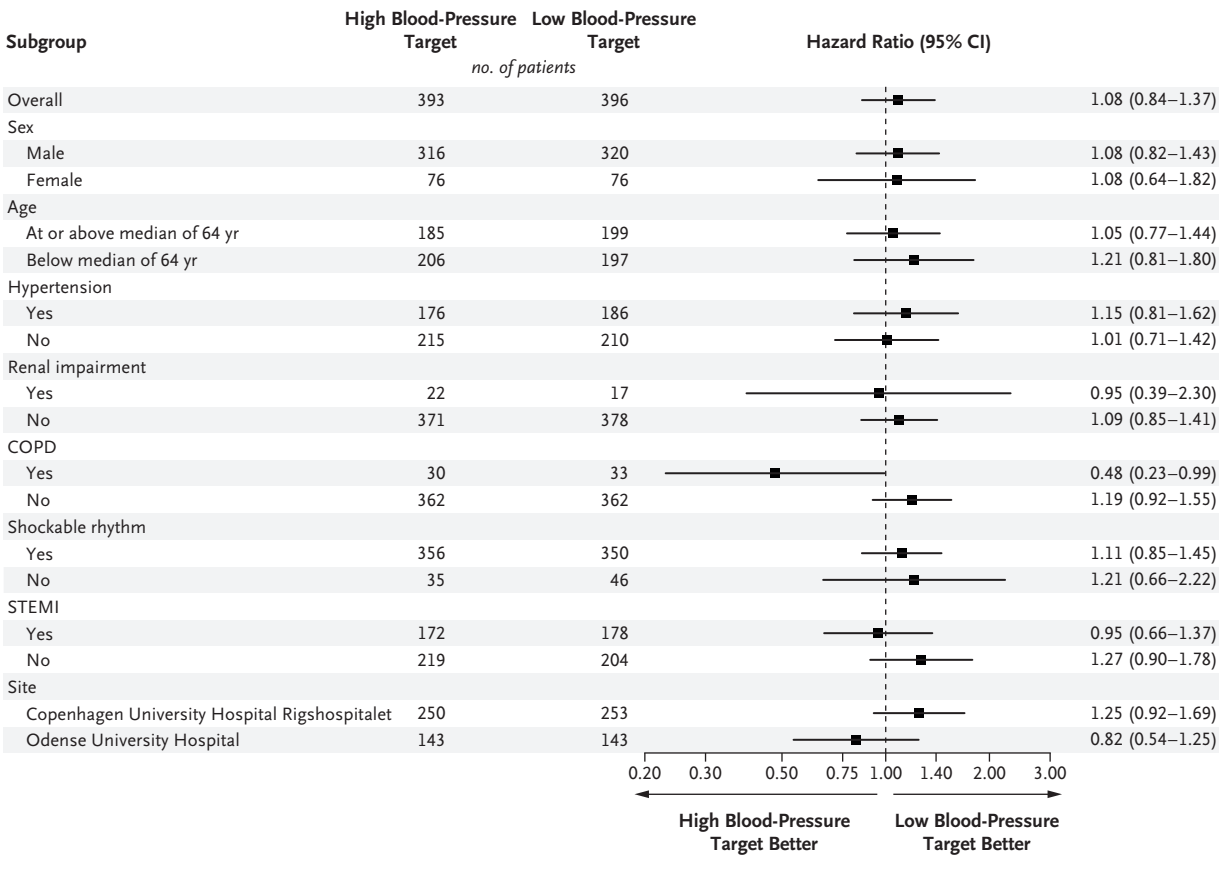


Figure 3. Subgroup Analysis of the Primary Outcome.

Data are for prespecified subgroup analyses of the primary outcome (death from any cause or discharge from the hospital with a Cerebral Performance Category score of 3 or 4). COPD denotes chronic obstructive pulmonary disease, and STEMI ST-segment elevation myocardial infarction.

available for 359 of the 552 patients (65%) who were alive at 3 months. Data on the CPC, modified Rankin scale score, and Montreal Cognitive Assessment score at 3 months and on plasma levels of neuron-specific enolase at 48 hours are summarized in Table 2. The distributions of results on the CPC and modified Rankin scale are shown in Figure S4. Data on median neuron-specific enolase levels were available for 79% of the patients; the median level was 18 μg per liter (interquartile range, 11 to 37) in the high-target group and 18 μg per liter (interquartile range, 11 to 34) in the low-target group. No significant differences were found in the percentages of patients with adverse events, including infection, arrhythmia, bleeding, and seizures (Table 2).

DISCUSSION

In this double-blind, randomized trial comparing two clinically relevant mean arterial blood-pressure targets, we found no significant difference in the percentage of patients who died or were discharged from the hospital with a poor neurologic outcome (CPC of 3 or 4) within 90 days. The results were consistent in the prespecified subgroups.

Our results add to those of two smaller, open-label trials of blood-pressure targets in postresuscitation care in which findings on magnetic resonance imaging of the head[6] and levels of neuron-specific enolase were used as markers of the extent of neurologic brain injury.[7] In these two trials, mean pressures of approximately 70 to 74 mm Hg in the lower target range and 84 to 87 mm Hg in the higher target range were attained, and the neuron-specific enolase levels were 20 to 22 μg per liter in one trial[7] and 42 to 59 μg per liter in the other,[6] as compared with 35 to 36 μg per liter in the present trial. At 6 months, 70%[7] and 45%[6] of the patients in the two trials were alive, as compared with 67% of the patients in the current trial.

Perfusion of the brain depends on the mean arterial pressure and is controlled through cerebrovascular autoregulation to ensure adequate perfusion at varying blood pressures. After an out-of-hospital cardiac arrest, this delicate balance between flow and pressure may be disrupted, with lower perfusion at a given pressure during the first 12 to 24 hours after the cardiac arrest.[23,24] Observational data suggest that the mean arterial blood pressure that should be used to secure flow to the postanoxic brain is at least 75 mm Hg,[25] whereas guidelines suggest that mean arterial pressure should be maintained above 65 mm Hg.[1,14] Maintenance of a higher mean arterial pressure in the postresuscitation period may be warranted in patients with preexisting hypertension.[23] In patients with sepsis, targeting a higher blood pressure has been associated with lower rates of dialysis among those with preexisting hypertension.[26] Our results do not suggest a benefit of a higher blood-pressure target in the subgroup of patients with known hypertension.

The interaction of preexisting COPD favoring a high blood-pressure target is likely to be spurious and should be interpreted with great caution. In addition, as compared with the lower target, the higher blood-pressure target in our trial was not associated with an increased risk of adverse events. In contrast, a higher blood pressure in patients with sepsis has previously been associated with increased risk of arrhythmia.[26]

Our trial has limitations. The mean difference in blood pressure between the groups was 10.7 mm Hg and therefore was lower than the expected value (14 mm Hg). However, since a clinically significant separation in blood pressure was observed between the groups, and the doses of norepinephrine and vasopressor were substantially higher in the high-target group than in the low-target group, we believe that the trial provides strong evidence for an absence of clinically important differences in the assessed outcomes, although our findings cannot be extrapolated to blood-pressure targets that are higher or lower than those used in this trial. Although the hypothesized treatment effect may be seen as overly optimistic, given the consistency of the results in the two groups, the risk of type 2 error seems low.

Follow-up in our trial was challenging as a result of Covid-19 restrictions, including a temporary pause in research-related follow-up visits and a subsequent reluctance among patients to visit a hospital. As a result, the number of patients available for follow-up visits and assessment of cognitive testing was lower than expected. The number of blood samples in the biobank was also lower than expected, mainly because of delayed initiation of sampling for the biobank at one site.

A strength of our trial is that the results were consistent across the objective outcomes we examined (death, neurologic outcomes, and labo-

ratory findings). Furthermore, our sample size, which was seven times as large as those in previous trials,[6,7] and the small number of patients who did not meet screening requirements, the consistency of the eligibility criteria with those used in previous trials, and the double-blinded intervention increase the generalizability of our results and reduce the risk of bias. However, the trial was conducted in only two high-volume cardiac arrest centers and included a population of patients with a high prevalence of acute coronary syndrome and a relatively good prognosis based on risk factors on arrival at the hospital. These aspects of the trial may affect the generalizability of our results.

In this trial, targeting a mean arterial blood pressure of 77 mm Hg as compared with 63 mm Hg in patients who had been resuscitated after an out-of-hospital cardiac arrest did not result in a significant difference in the percentage of patients who died or had severe disability or coma.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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