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Optimum Blood Pressure in Patients With Shock After Acute Myocardial Infarction and Cardiac Arrest

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ABSTRACT

BACKGROUND In patients with shock after acute myocardial infarction (AMI), the optimal level of pharmacologic support is unknown. Whereas higher doses may increase myocardial oxygen consumption and induce arrhythmias, diastolic hypotension may reduce coronary perfusion and increase infarct size.

OBJECTIVES This study aimed to determine the optimal mean arterial pressure (MAP) in patients with AMI and shock after cardiac arrest.

METHODS This study used patient-level pooled analysis of post-cardiac arrest patients with shock after AMI randomized in the Neuroprotect (Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients; NCT02541591) and COMACARE (Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation; NCT02698917) trials who were randomized to MAP 65 mm Hg or MAP 80/85 to 100 mm Hg targets during the first 36 h after admission. The primary endpoint was the area under the 72-h high-sensitivity troponin-T curve.

RESULTS Of 235 patients originally randomized, 120 patients had AMI with shock. Patients assigned to the higher MAP target (n = 58) received higher doses of norepinephrine (p = 0.004) and dobutamine (p = 0.01) and reached higher MAPs (86 ± 9 mm Hg vs. 72 ± 10 mm Hg, p < 0.001). Whereas admission hemodynamics and angiographic findings were all well-balanced and revascularization was performed equally effective, the area under the 72-h high-sensitivity troponin-T curve was lower in patients assigned to the higher MAP target (median: 1.14 μg.72 h/l [interquartile range: 0.35 to 2.31 μg.72 h/l] vs. median: 1.56 μg.72 h/l [interquartile range: 0.61 to 4.72 μg. 72 h/l]; p = 0.04). Additional pharmacologic support did not increase the risk of a new cardiac arrest (p = 0.88) or atrial fibrillation (p = 0.94). Survival with good neurologic outcome at 180 days was not different between both groups (64% vs. 53%, odds ratio: 1.55; 95% confidence interval: 0.74 to 3.22).

CONCLUSIONS In post-cardiac arrest patients with shock after AMI, targeting MAP between 80/85 and 100 mm Hg with additional use of inotropes and vasopressors was associated with smaller myocardial injury.
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Mortality in patients with shock after acute myocardial infarction (AMI) is estimated to be approximately 50% and has remained unchanged for the last decades (1–2). Only urgent revascularization of the culprit artery has been shown to impact long-term outcome (3). In the absence of large randomized controlled trials, current American College of Cardiology/American Heart Association guidelines recommend using inotropes and vasopressors to maintain systemic perfusion and preserve end-organ function in patients with AMI presenting with low mean arterial pressures (MAPs) and severe systolic dysfunction (Class IIb) (4). However, guidelines do not issue recommendations on the specific hemodynamic goals that should be targeted in these patients. In clinical practice, many physicians try to minimize the use of inotropes and vasopressors to reduce myocardial oxygen consumption, myocardial infarct size, and the risk for life-threatening ventricular arrhythmias (1,4). However, by underusing inotropes and vasopressors, lower diastolic blood pressure may reduce coronary perfusion and increase infarct size. The optimal level of pharmacologic support that balances coronary perfusion, afterload, myocardial oxygen consumption, and arrhythmogenic risk remains unknown.

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The Neuroprotect (Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients; NCT02541591) and the COMACARE (Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation; NCT02698917) trials previously randomized post-cardiac arrest (CA) patients to conventional (>65 mm Hg) and higher (80/85 to 100 mm Hg) MAP targets to investigate whether increasing cerebral perfusion during the first 36 h of intensive care unit (ICU) stay could reduce anoxic brain damage and improve functional outcome. The primary results of both trials were neutral on neurological outcome (5,6). The aim of this post hoc pooled analysis of both trials was to investigate whether targeting lower versus higher MAP would affect myocardial injury and arrhythmogenic risk within the subgroup of post-CA patients with shock after AMI.

METHODS

TRIAL DESIGN. Both Neuroprotect and COMACARE were prospective, multicenter, randomized, parallel group, open-label, assessor-blinded, monitored, and investigator-driven clinical trials randomizing post-CA patients between lower and higher MAP targets. In addition, COMACARE patients were randomized to either low-normal or high-normal arterial carbon dioxide tensions and to normoxia or moderate hyperoxia according to a 2^3-factorial design. The protocols for the original trials were published previously (7,8). The protocols and the amendment for the present pooled analysis were approved by the local ethics committees. Written informed consent was obtained from a next of kin or, if unavailable, a procedure for inclusion in emergency situations was applied. A definitive post hoc consent was ultimately obtained from patients who recovered sufficiently to make independent decisions.

PATIENTS. In both trials, adult patients (≥18 years) resuscitated from out-of-hospital CA of a presumed cardiac cause and unconscious at hospital admission after a sustained return of spontaneous circulation (ROSC) were eligible for inclusion. Whereas Neuroprotect also included patients with nonshockable rhythms irrespective of the time to ROSC, COMACARE only included patients with shockable rhythms and time from collapse to ROSC between 10 and 45 min. An overview of the inclusion and exclusion criteria of both trials is provided in Supplemental Table 1. In the present pooled post hoc analysis, we only included patients with shock after AMI. We defined AMI as either ST-segment elevation myocardial infarction (STEMI) or a non-STEMI with identification of a clear culprit lesion (a coronary lesion with at least 70% stenosis and the presence of characteristics of plaque disruption) on coronary angiography performed within 2 h after admission. All diagnoses of AMI were established before randomization. We defined shock as the need for vasopressors to maintain assigned MAP targets at any time point during the 36-h intervention period.

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CA = cardiac arrest

CPC = cerebral performance category

hs-cTnT = high-sensitivity cardiac troponin T

IABP = intra-aortic balloon pump

MAP = mean arterial pressure

ROSC = restoration of spontaneous circulation

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

TTM = targeted temperature management

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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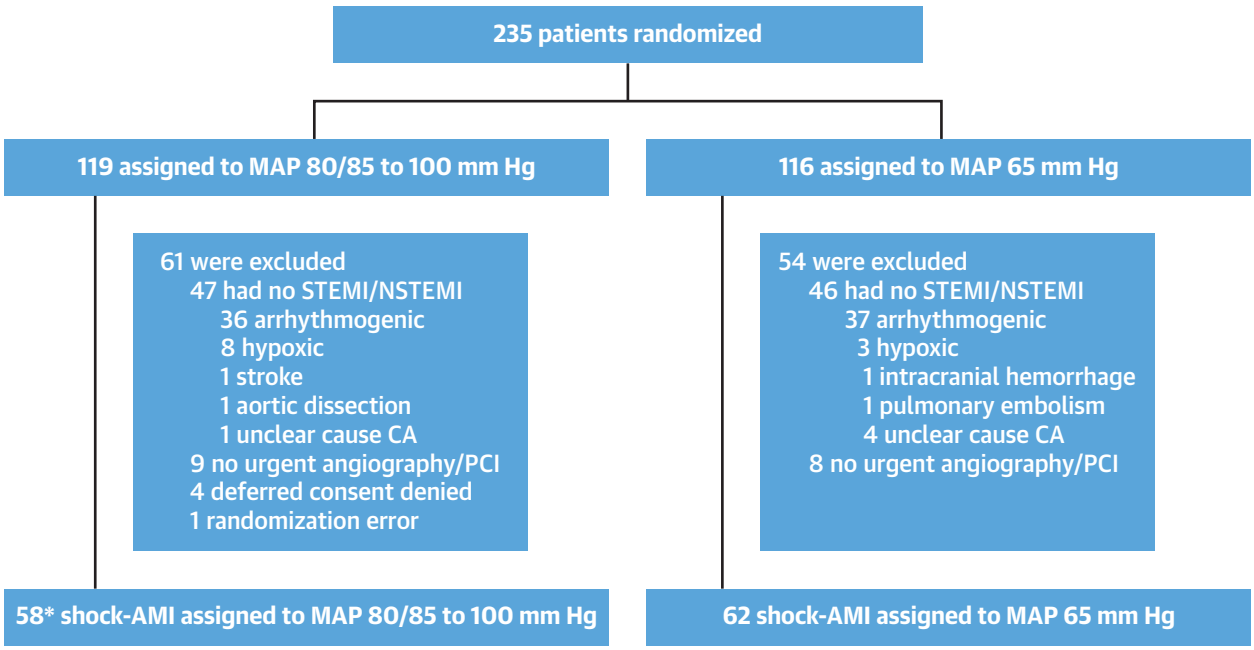
FIGURE 1 CONSORT Diagram



A total of 235 patients were randomized in the 2 trials (123 in COMACARE, 112 in Neuroprotect). After exclusion of patients without acute myocardial infarction (AMI) (n = 93), patients who did not undergo an immediate angiography (n = 17), patients whose next of kin refused informed consent (n = 4), and 1 randomization error, the full analysis set of this study consisted of 120 AMI patients. Of these, 58 patients were randomized to the mean arterial pressure (MAP) 80/85 to 100 mm Hg and 62 patients to the MAP 65 mm Hg arm. *1 patient who died in the catheterization lab immediately after randomization but before starting hemodynamic therapy was excluded from the high-sensitivity cardiac troponin T (hs-cTnT) analysis as he did not receive the assigned therapy. AUC = area under the curve; CA = cardiac arrest; COMACARE = Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation; Neuroprotect = Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction.

GENERAL MANAGEMENT. All patients received standard post-CA treatment based on current guidelines including mechanical ventilation, sedation, targeted temperature management (TTM) at 33°C or 36°C for 24 h and standardized multimodal neuroprognostication (9). Neurologists performing neuroprognostication and outcome assessors were blinded for treatment assignments.

HEMODYNAMIC INTERVENTIONS. The 36-h intervention period started at ICU admission. In patients randomized to the lower MAP target, we did not lower blood pressure by any means other than sedation and pain medication. In COMACARE, the investigators used norepinephrine infusion and fluid boluses as needed to reach the assigned MAP target. In case of confirmed or suspected low cardiac output, the use of inotropes was allowed. In Neuroprotect, cardiac output was monitored for all patients and in the higher MAP group and the investigators targeted mixed venous blood oxygen saturation of 65% to 75% using a combination of fluids, dobutamine, and norepinephrine according to a pre-defined protocol (presented in Supplemental Figure 1).

DATA COLLECTION AND STUDY ENDPOINTS. Individual patient data were anonymously entered into a common database. Hemodynamic data were registered at least hourly. The primary endpoint was myocardial injury as assessed by the area under the 72-h high-sensitive cardiac troponin T (hs-cTnT) curve. Blood samples for hs-cTnT were obtained at hospital admission and 24, 48, and 72 h thereafter in both trials with an additional troponin measurement at 5 h in the Neuroprotect trial. In addition, hs-cTnT was measured at additional timepoints during the first 72 h as per the treating clinician. Determination of hs-cTnT concentration was performed using a COBAS e601 line (Hitachi High Technology Co., Tokyo, Japan) with an electrochemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany). Secondary endpoints included new-onset atrial fibrillation, re-arrest, all-cause mortality, and cerebral performance category (CPC) score at 180 days. The CPC

TABLE 1 Baseline Characteristics

	COMACARE (n = 61)	Neuroprotect (n = 59)	p Value	MAP 80/85 to 100 mm Hg (n = 58)	MAP 65 mm Hg (n = 62)	p Value
Demographics						
Age, yrs	60 ± 10	65 ± 11	0.31	62 ± 10	63 ± 11	0.48
Male	54/61 (88)	50/59 (85)	0.69	51/58 (88)	53/62 (85)	0.69
Medical history						
Previous AMI	8/61 (13)	9/57 (16)	0.68	5/57 (9)	12/61 (20)	0.11
Previous arrhythmia	6/61 (10)	5/58 (9)	0.82	3/57 (5)	8/62 (13)	0.15
Arterial hypertension	32/61 (47)	25/54 (46)	0.89	27/54 (50)	27/61 (44)	0.54
Beta-blocker use	11/60 (18)	11/53 (21)	0.75	10/54 (19)	12/59 (20)	0.81
ACE inhibitor/ARB	17/60(28)	11/53 (21)	0.35	12/54 (22)	16/59 (27)	0.54
Diabetes mellitus	9/61 (15)	4/56 (7)	0.19	8/57 (14)	5/50 (8)	0.33
COPD	5/61 (8)	4/58 (7)	0.79	4/57 (7)	5/62 (8)	0.83
Stroke	4/61 (7)	4/58 (7)	0.94	5/57 (9)	3/62 (5)	0.39
Arrest characteristics						
Public place	34/61 (56)	33/59 (56)	0.98	32/58 (55)	35/62 (56)	0.89
Basic life support	50/61 (82)	40/58 (69)	0.10	45/57 (79)	45/62 (73)	0.42
Presenting rhythm			<0.01			0.87
Shockable	61/61 (100)	46/59 (78)		52/58 (90)	55/62 (89)	
Nonshockable	0/61 (0)	13/59 (22)		6/58 (10)	7/62 (11)	
Time-to-ROSC, min	21 ± 8	21 ± 12	0.86	21 ± 10	21 ± 10	0.70
Admission characteristics						
MAP, mm Hg	86 ± 11	85 ± 25	<0.01	86 ± 19	84 ± 24	0.65
Pupillary reflexes (presence)	30/51 (59)	27/49 (55)	0.70	23/44 (52)	34/56 (61)	0.40
First ER lactate, mmol/l	N/A	6.7 (3.0-9.0)	N/A	6.9 (3.2-10.37)	5.7 (2.9-7.6)	0.89
First ICU lactate, mmol/l	1.9 (1.3-3.4)	2.9 (1.8-4.3)	0.03	2.35 (1.35-3.9)	2.25 (1.4-3.7)	0.70
ICU						
SOFA score	8.43 ± 2.28	9.72 ± 2.86	0.19	9.09 ± 2.37	8.98 ± 2.86	0.13
TTM target			<0.01			0.89
TTM33	45/61 (74)	59/59 (100)		50/58 (86)	54/62 (87)	
TTM36	16/61 (26)	0/59 (0)		8/58 (14)	8/62 (13)	

Values are mean ± SD, n/N (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; COMACARE = Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation; COPD = chronic obstructive pulmonary disease; ER = emergency room; ICU = intensive care unit; MAP = mean arterial pressure; N/A = not available; Neuroprotect = Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients; ROSC = resume of spontaneous circulation; SOFA = sequential organ failure assessment; TTM = targeted temperature management.

scale ranges from 1 to 5 with 1 representing good cerebral performance or minor disability, 2 moderate disability, 3 severe disability, 4 coma or vegetative state, and 5 brain death. The cause of death was classified as neurologic, cardiac, or other. All Neuroprotect patients underwent transthoracic echocardiography evaluation during the first 24 h.

STATISTICAL ANALYSIS. Data are presented as mean ± SD or median (interquartile range [IQR]). Continuous variables were compared by unpaired Student's *t*-tests, Mann-Whitney U tests, or analysis of variance and categorical variables were compared with Fisher exact or chi-square tests as appropriate. The area under the 72-h hs-cTnT curve was compared between both groups using a Van Elteren test that included study (Neuroprotect/COMACARE) as a stratification factor. Treatment differences were obtained using the Hodges-Lehman estimator. Missing data from patients who died before 72 h were imputed according to the worst case scenario (i.e., the missing value was replaced with the highest hs-cTnT in the corresponding treatment group) (Supplemental Table 2). Missing data from patients surviving beyond 72 h were imputed by regression analysis on the log-transformed cTnT values that were recorded after the Tmax of each patient. In cases where the T0 measurement was missing, we imputed this value with the median value observed in the study at T0. Subgroup analysis was performed according to study (Neuroprotect vs. COMACARE), pre-CA hypertension, pre-CA beta-blocker use, STEMI versus non-STEMI, culprit artery, extent of coronary artery disease, completeness of revascularization, pre-percutaneous coronary intervention (PCI) Thrombolysis In Myocardial Infarction (TIMI) flow and TTM strategy used. Longitudinal data (MAP, diastolic blood pressure, heart rate, and doses of norepinephrine and dobutamine) were analyzed using a generalized estimating equation model for normally

TABLE 2 Angiographic Findings

	MAP 80/85 to 100 mm Hg	MAP 65 mm Hg	p Value
Cause of arrest			0.37
STEMI	46/58 (79)	53/62 (85)	
NSTEMI	12/58 (21)	9/62 (15)	
ROSC-to-catheterization lab time, min	73 ± 50	66 ± 48	0.85
Immediate angiography	58/58 (100)	62/62 (100)	1.00
PCI	58/58 (100)	62/62 (100)	1.00
Culprit artery			0.70
Left main	2/58 (3)	2/62 (3)	
LAD or diagonal	32/58 (55)	39/62 (63)	
LCX or obtuse marginal	8/58 (14)	6/62 (10)	
RCA	14/58 (24)	14/62 (23)	
Other*	2/58 (3)	1/62 (2)	
Extent CAD			0.17
Single-vessel disease	26/50 (52)	36/55 (65)	
2-vessel disease	16/50 (32)	9/55 (16)	
3-vessel disease	8/50 (16)	10/55 (18)	
Chronic total occlusion	14/49 (29)	11/44 (20)	0.30
TIMI flow culprit pre-PCI			0.33
TIMI 0	23/49 (47)	28/52 (54)	
TIMI 1	5/49 (10)	2/52 (4)	
TIMI 2	5/49 (10)	2/52 (4)	
TIMI 3	16/49 (33)	20/52 (38)	
TIMI flow culprit post-PCI			0.14
TIMI 0	4/53 (7)	3/53 (6)	
TIMI 1	0/53 (0)	1/53 (2)	
TIMI 2	0/53 (0)	4/53 (8)	
TIMI 3	49/53 (93)	44/52 (85)	
Complete revascularization	28/49 (57)	34/55 (62)	0.63

Values are n/N (%) or mean ± SD. *Saphenous vein graft or anterolateral branch.

CAD = coronary artery disease; LAD = left anterior descending; LCX = left circumflex coronary artery; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

distributed data that included factors for time (included as a categorical variable), treatment, study, and their interactions. The model included an exchangeable working correlation matrix to account for within-patient correlations. Differences in the profiles over time between the 2 treatment groups were assessed by the interaction. Analyses regarding secondary endpoints were exploratory. SPSS version 24 (IBM, Armonk, New York), SAS version 9.4 (SAS Institute, Cary, North Carolina) and SAS/STAT version 14.2 were used for statistical analysis. All tests were 2-sided and assessed at a significance level of 5%. Because of the exploratory nature of the study, no adjustments were made to the significance level to account for multiple testing.

RESULTS

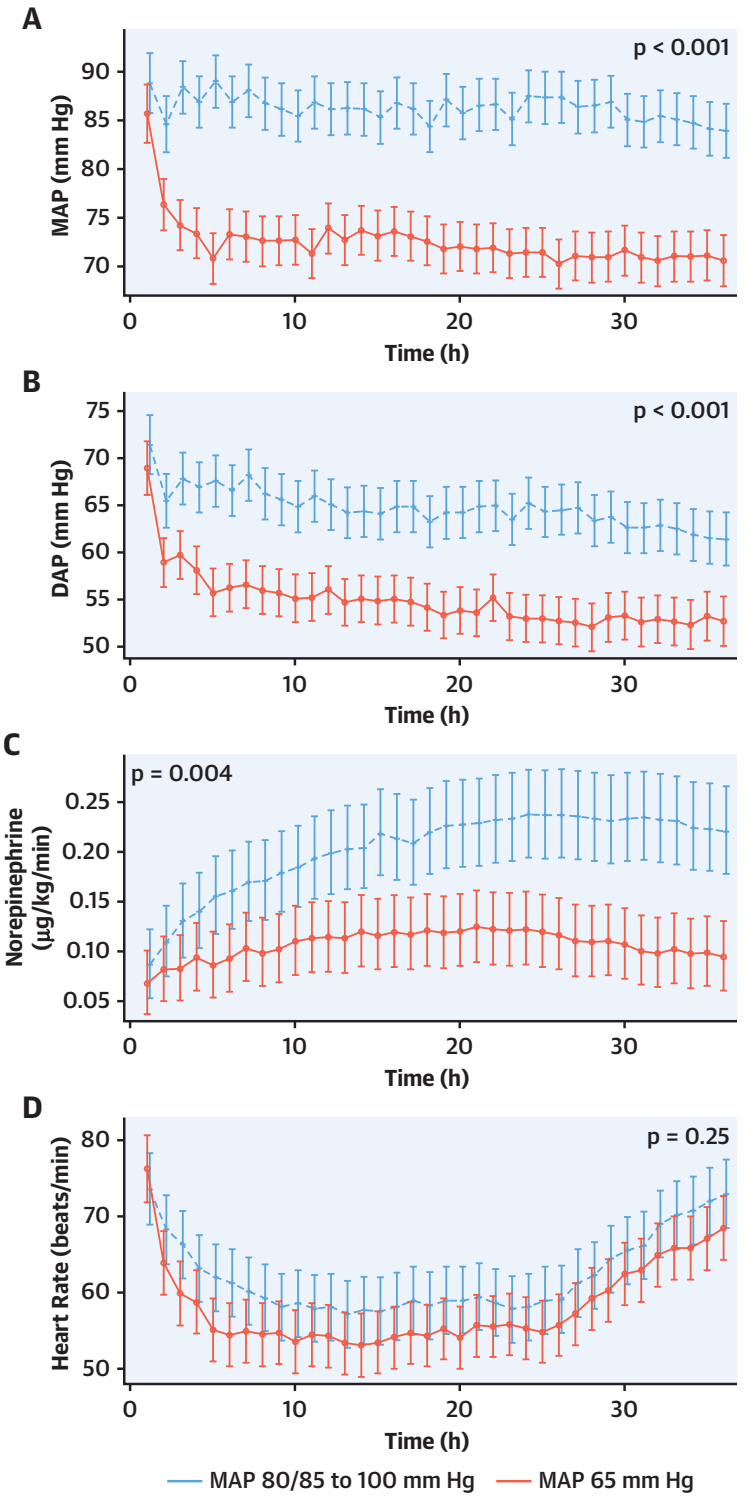
PATIENTS. A total of 235 patients were randomized in the 2 trials (123 in COMACARE and 112 in Neuroprotect). After exclusion of patients without AMI (n = 93), patients who did not undergo an immediate angiography (n = 17), patients whose next of kin refused informed consent (n = 4), and one randomization error, the full analysis set of this study consisted of 120 AMI patients. Of these, 58 patients were randomized to the MAP 80/85 to 100 mm Hg and 62 patients to the MAP 65 mm Hg arm (Figure 1). One patient who died in the catheterization lab immediately after randomization but before starting hemodynamic therapy was excluded from the hs-cTnT analysis as he did not receive the assigned treatment. All 120 patients needed vasopressor support and met for our shock definition for shock. Patients assigned to the MAP 65 mm Hg and MAP 80/85 to 100 mm Hg arms had comparable prerandomization characteristics (Table 1).

ANGIOGRAPHIC DATA. Most patients presented with a STEMI upon hospital admission (Table 2). All patients underwent immediate angiography with an attempt for PCI of the culprit artery. There were no significant differences between the groups with respect to other determinants of infarct size.

HEMODYNAMICS. Patients randomized to the MAP 80/85 to 100 mm Hg target received significantly higher doses of norepinephrine ($p = 0.004$) (Figure 2). The number of patients receiving dobutamine was not different between the groups (14 of 58 [24%] vs. 11 of 62 [18%], $p = 0.39$), but the dobutamine dose was significantly higher in patients randomized to the MAP 80/85 to 100 mm Hg group (4.5 ± 4.2 μg/kg/min vs. 3.7 ± 2.2 μg/kg/min, $p = 0.01$). Six patients were treated with mechanical cardiac support (3 intra-aortic balloon pump [IABP] plus 1 veno-arterial extracorporeal membrane oxygenation [vaECMO] in the MAP 80/85 to 100 mmHg arm and 1 IABP plus 1 vaECMO in the MAP 65 mm Hg arm). Although heart rate was not different ($p = 0.25$), MAP ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) were significantly higher in patients randomized to the higher MAP target.

MYOCARDIAL INJURY. The area under the 72-h hs-cTnT curve was greater in the lower MAP group (median: 1.14 μg.72 h/l [IQR: 0.35 to 2.31 μg.72 h/l] vs. median: 1.56 μg.72 h/l [IQR: 0.61 to 4.72 μg.72 h/l]; $p = 0.04$) (Figure 3, Table 3). This result was highly consistent in both the Neuroprotect and COMACARE trials. According to subgroup analysis, the overall treatment effect was mainly driven by results obtained in STEMI patients presenting with a (sub)occlusion (TIMI flow grade 0 to 1) in the left anterior descending (LAD) or left main coronary artery (Figure 4). In the Neuroprotect trial, mean left

FIGURE 2 Hemodynamics



(A) Mean arterial pressure (MAP) (mm Hg). **(B)** Diastolic blood pressure (mm Hg). **(C)** Dose of norepinephrine (μg/kg/min). **(D)** Heart rate (beats/min). Plots present estimated mean values with corresponding 95% confidence intervals. Predicted values were obtained using a generalized estimating equation model with autoregressive variance-covariance matrix of order 1 to account for within patient correlations. The model includes the following as class variables: time, treatment, their interaction, and study. Raw data are provided in Supplemental Tables 3 to 6 and Supplemental Figure 2.

ventricular ejection fraction (LVEF) was higher in patients assigned to the high-MAP group (42 ± 12% [n = 25 of 28] vs. 35 ± 13% [n = 31 of 31]; p = 0.03).

ARRHYTHMOGENIC RISK. Additional inotropic and vasopressor support in the higher MAP group was not associated with an increased risk of a new CA (8 of 58 [14%] vs. 9 of 61 [15%]; odds ratio [OR]: 0.92; 95% confidence interval [CI]: 0.33 to 2.58; p = 0.88) or of new-onset atrial fibrillation (4 of 58 [7%] vs. 4 of 61 [7%]; OR: 1.05; 95% CI: 0.25 to 4.43; p = 0.94) during the 36-h interventional period.

OUTCOME. We obtained complete follow-up from all patients. At 180 days, the number of patients with good neurologic outcome (CPC 1-2) (37 of 58 [64%] vs. 33 of 62 [53%]; OR: 1.55; 95% CI: 0.74 to 3.22; p = 0.24) and all-cause mortality (21 of 58 [36%] vs. 25 of 62 [40%]; OR: 0.84; 95% CI: 0.40 to 1.75; p = 0.63) were not different between both groups. The major cause of death was post-anoxic encephalopathy with brain death or withdrawal of ICU support because of neurologic futility (n = 32, 70%).

DISCUSSION

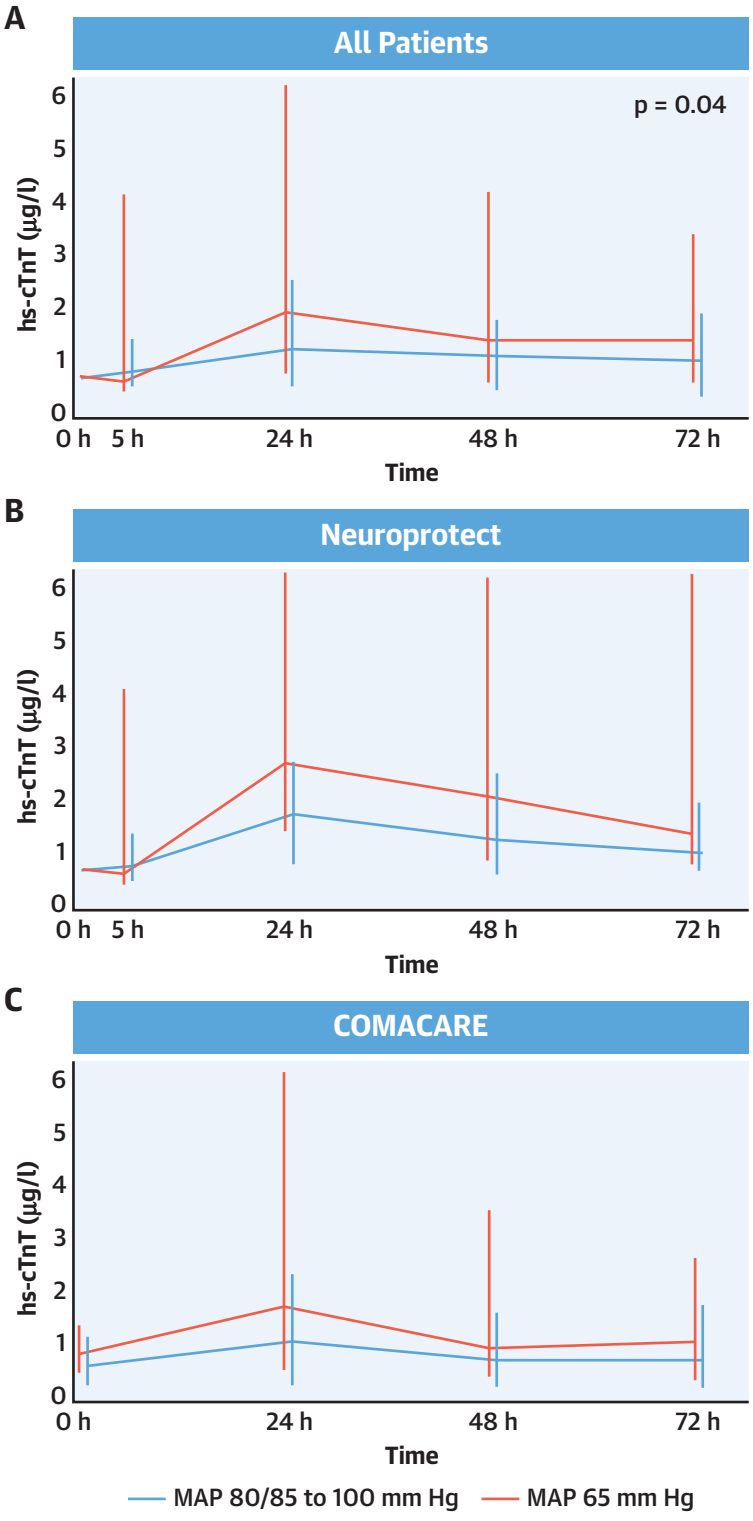
When compared with conventional hemodynamic goals (MAP >65 mm Hg), the use of additional inotropes and vasopressors to target a MAP between 80/85 and 100 mm Hg during the first 36 h of ICU stay in post-CA patients with shock after AMI was associated with a significant reduction of myocardial injury. This finding was consistent across both trials included in this pooled analysis and mainly driven by results obtained in STEMI patients with a (sub)occlusion of the LAD or left main coronary artery.

MYOCARDIAL INJURY. In line with the SHOCK (Early Revascularization in Acute Myocardial Infarction Complicated by Cardiogenic Shock), IABP-SHOCK II (Intra-aortic Balloon Support for Myocardial Infarction with Cardiogenic Shock), and CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trials (2,3,10), our study population was a typical large AMI cohort with the majority of patients having an acute coronary occlusion (pre-PCI TIMI flow grade 0 in 50% of the patients) of the LAD (culprit in 60% of the patients) and another chronic total occlusion present in 27% of the patients. Both groups were well balanced with respect to other known important determinants of myocardial injury including delay to revascularization, distribution of culprit arteries, number of nonculprit vessels, and TIMI flow before and after revascularization. Whereas peak hs-cTnT concentrations at 24 h in patients assigned to the MAP 65-mm Hg arm (median approximately 1.86 μg/l) were in line with the CULPRIT-SHOCK trial (2), the area under the 72-h hs-cTnT curve was 37% smaller in the group of patients randomized to the higher MAP target (**Central Illustration**).

In patients with a large AMI, the necrotic infarcted core is surrounded by a large edematous border zone that on average accounts for one-half of the total area at risk (11). Although it is incompletely understood how the border zone may be salvaged, immediate restoration of the cellular oxygen balance is paramount. Additional use of inotropes and vasopressors would theoretically increase afterload, contractility, heart rate, and stroke work resulting in an unfavorable increase of myocardial oxygen consumption (4). Although we did not measure coronary perfusion and cardiac metabolites, one may assume that the reduction of myocardial injury is the net result of an increased oxygen delivery that offsets increased oxygen consumption. Under normal physiologic circumstances, myocardial blood flow is kept constant over a wide range of aortic pressures (60 to 140 mm Hg) by adapting the tonus of the coronary arterioles which is known as autoregulation (12). During reperfusion after AMI, microvascular resistance is highly increased by intraluminal plugging, spasm, and external compression by interstitial edema and intramyocardial hemorrhage causing right shifting of coronary autoregulation (13). Thus, increasing diastolic blood pressure plausibly provides more driving pressure for coronary perfusion and may potentially also recruit microcollaterals. The importance of improving oxygen supply to the border zone has been demonstrated in a recent cardiac magnetic resonance imaging (MRI) study showing that acute myocardial blood flow during the first 3 days post-AMI in the culprit artery was an independent predictor of final infarct size at 6 months (14). Furthermore, patients with restoration of normal flow in the culprit artery had lower mortality in the SHOCK trial (15).

At the microcirculatory level, improving hydrostatic pressure and flow may have additional beneficial effects. Myocytes and endothelial cells in the border zone are edematous due to intracellular osmotic overload and capillaries with higher hydrostatic pressures may better resist external compression by swollen myocytes (16). Finally, improving microcirculatory flow may promote faster washout of microthrombi and facilitate influx of inflammatory cells that promote the healing response. Even the infarcted myocardium, once thought to be

FIGURE 3 Myocardial Injury



(A) Full cohort. **(B)** Neuroprotect. **(C)** COMACARE. Plot shows median [Q1, Q3] by randomized group and time. Raw data are provided in Supplemental Table 7. Abbreviations as in **Figure 1**.

TABLE 3 Study Endpoints

	MAP 80/85 to 100 mm Hg	MAP 65 mm Hg	Treatment Effect	p Value*
Primary endpoint				
Imputed 72 h AUC cTnT, µg.72 h/l	1.14 (0.35 to 2.31)	1.56 (0.61 to 4.72)	-0.42 (-1.12 to 0.00)	0.04
Secondary endpoints				
New onset atrial fibrillation	4/58 (7)	4/61 (7)	1.05 (0.25 to 4.43)	0.94
Recurrent cardiac arrest within 36 h	8/58 (14)	9/61 (15)	0.92 (0.33 to 2.58)	0.88
CPC 1 to 2 180 days	37/58 (64)	33/62 (53)	1.55 (0.74 to 3.22)	0.24
All-cause mortality 180 days	21/58 (36)	25/62 (40)	0.84 (0.40 to 1.75)	0.63

Values are mean (interquartile range) or n/N (%). *p values for all secondary endpoints are exploratory.
AUC = area under curve; cTnT = Cardiac troponin T; CPC = cerebral performance category; IQR = interquartile range.

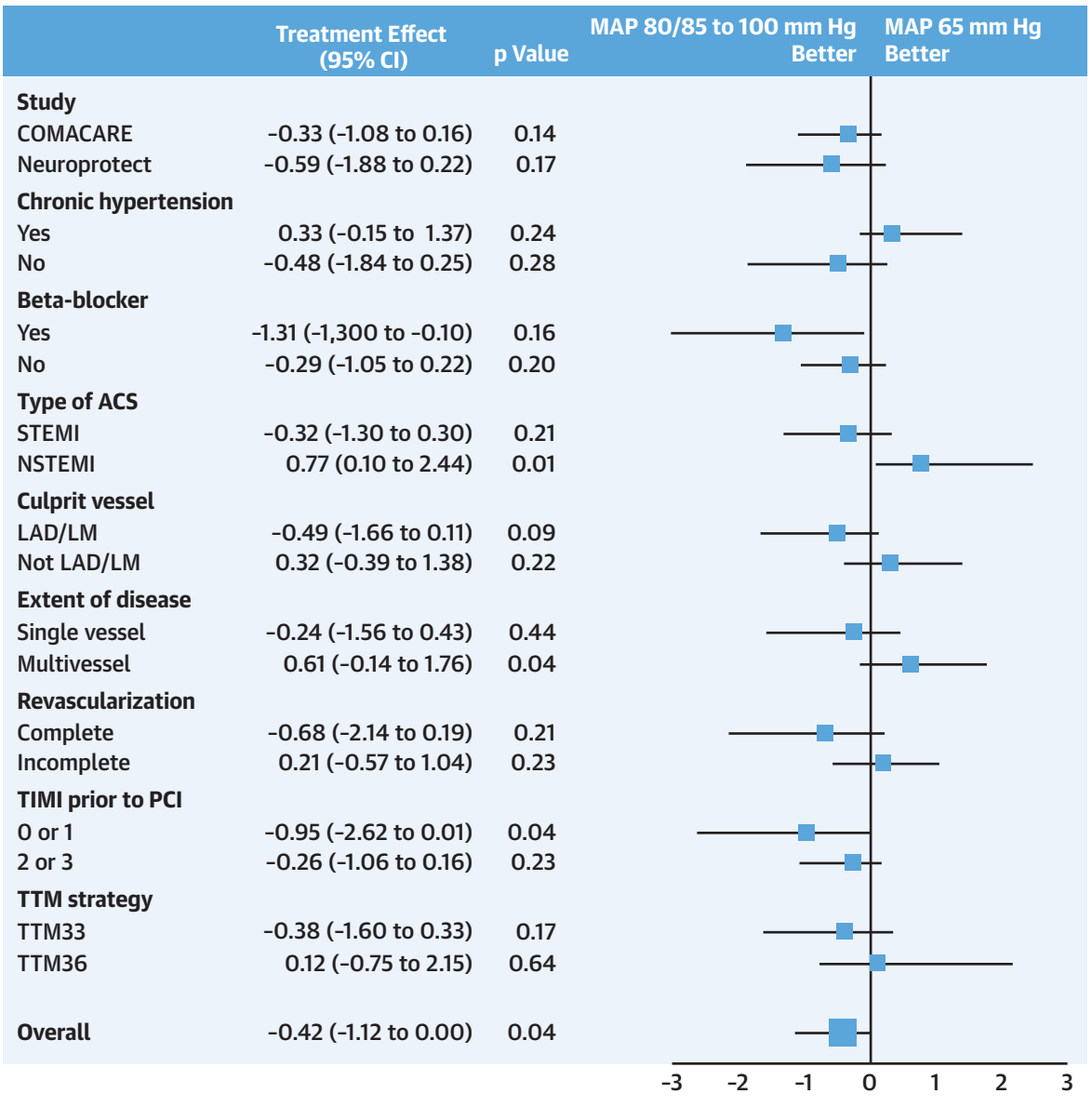
"dead," is a dynamic tissue undergoing an extensive process of remodeling, ultimately forming a core of scar, surrounded by neo-angiogenesis in the infarct border zone (14,17). Taken together, these microcirculatory changes may result in improved infarct core remodeling and better protection of the infarct border zone through enhanced neo-angiogenesis.

ARRHYTHMOGENIC RISK. Clinicians often try to minimize the use of potentially arrhythmogenic β_1-stimulating agents in patients with AMI immediately after revascularization. However, in this study, the additional use of inotropes and vasopressors in patients assigned to the higher-MAP arm did not increase the overall risk of recurrent CA mandating cardiopulmonary resuscitation during the 36-h interventional period. Our results (14% risk of re-arrest) are in line with the TTM trial (10% risk of re-arrest) considering that less than one-half of the TTM patients had a STEMI and therefore by nature a smaller arrhythmogenic risk (18). Earlier restoration of cellular oxygen balance by promoting coronary perfusion seems to offset the potential pro-arrhythmogenic effects of β_1-stimulating inotropic agents. In the SOAP (Sepsis Occurrence in Acutely Ill Patients) trial, increased mortality associated with dopamine use in the subgroup of patients with cardiogenic shock was largely caused by fatal arrhythmias in patients receiving the highest dopamine doses (19). Although our study population was a homogenous cohort including exclusively revascularized patients with shock after AMI, only 57% of the patients with cardiogenic shock in the SOAP trial were related to AMI and not all of them were appropriately revascularized. Post-PCI TIMI flow grade 3 was achieved in 90% of our trial patients. The safety of additional vasopressor and/or inotropic support in patients with less extensive or less successful revascularization before the start of the therapy remains to be investigated.

MORTALITY. In line with the results of both COMACARE and Neuroprotect main trials (5,6), the 180-day mortality was not different between patients randomized to high or low MAP targets in this subgroup with shock after AMI. Because the cause of death was post-anoxic encephalopathy in 70% of the patients, it is unlikely that an intervention that effectively reduces myocardial injury would have affected mortality in this relatively small sample of patients. Because the odds to die or to develop heart failure increase with 20% per 5% increment of the infarct size, it is in any event of paramount clinical importance to minimize myocardial infarct size even in patients with undecided neurologic prognosis (20). Aggressive goal-directed hemodynamic resuscitation immediately after successful revascularization may prevent entering the deathly spiral of cardiogenic shock where diastolic hypotension leads to insufficient coronary perfusion and results in further reductions of cardiac output and blood pressure, ultimately leading to vital organ hypoperfusion and multiple organ failure. Unfortunately, the current study was underpowered to assess this hypothesis.

MECHANICAL CARDIAC SUPPORT. Only 6 patients (5%) needed bail-out mechanical support by either IABP or vaECMO. Based on animal models, left ventricular unloading before reperfusion by Impella CP (Abiomed, Danvers, Massachusetts) support may be a more powerful and safer way than inotropes to increase coronary perfusion while simultaneously reducing myocardial oxygen consumption and therefore myocardial infarct size (21). Although this concept of unloading before reperfusion was reported to be feasible and safe in a human pilot trial with stable anterior AMI patients, human data on coronary

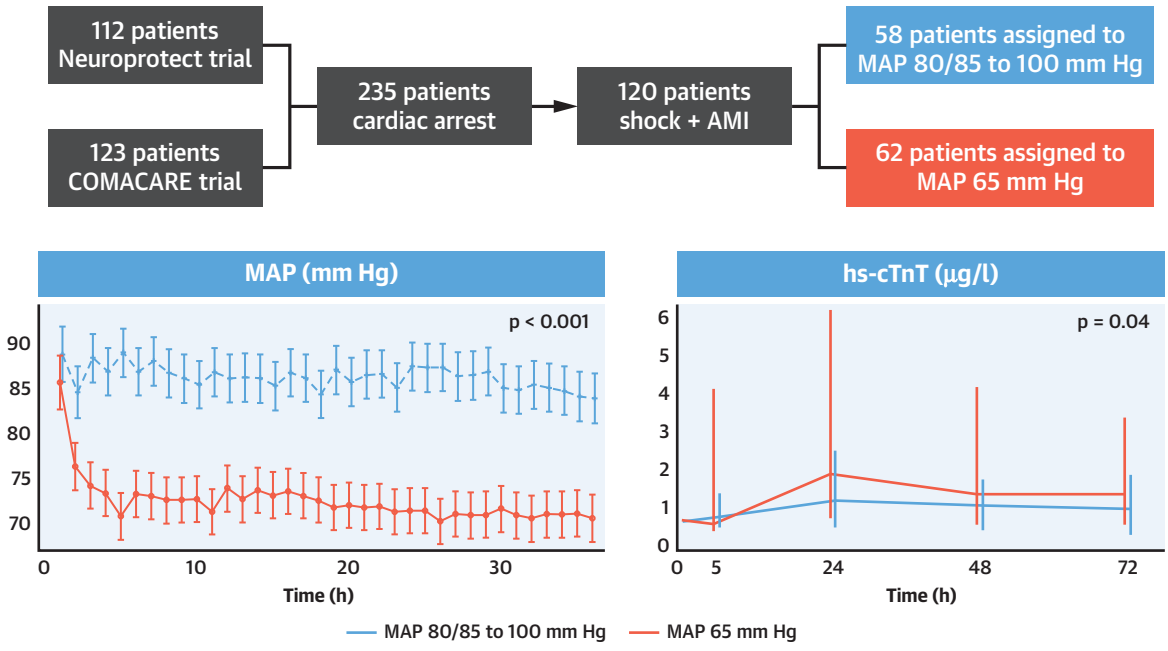
FIGURE 4 Forest Plot



Subgroup analysis comparing the 72-h AUC hs-cTnT curve per MAP strategy (MAP 65 mm Hg versus 80/85 to 100 mm Hg) according to trial (Neuroprotect vs. COMACARE), baseline use of anti-hypertensive drugs, baseline use of beta-blockers, type of ACS (STEMI vs. NSTEMI), culprit vessel (LAD and left main versus other), single versus multivessel disease, complete versus incomplete revascularization, and pre-PCI TIMI flow and targeted temperature management at 33°C or 36°C. In COMACARE, hs-cTnT levels were not different between patients randomized to either low-normal versus high-normal arterial carbon dioxide tensions and patients randomized to normoxia or moderate hyperoxia (34). Results were analyzed using a Van Elteren test with study as stratification factor. Treatment differences were obtained using the Hodges-Lehman estimator. Values represent treatment effect (95% CI). ACS = acute coronary syndrome; LAD = left anterior descending; LM = left main; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.

perfusion and infarct size with the use of mechanical cardiac support devices such as vaECMO and Impella are limited (22). Although the CRISP-AMI (Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction) study (investigating the benefit of routine IABP in stable anterior AMI) was essentially negative, a substudy showed mortality benefit in patients with ongoing ischemia and disturbed autoregulation further supporting the concept that increasing coronary perfusion after PCI

CENTRAL ILLUSTRATION **Conventional Versus Higher Blood Pressure Targets in Patients With Shock After Acute Myocardial Infarction**



Ameloot, K. et al. J Am Coll Cardiol. 2020;76(7):812-24.

Of 235 patients originally randomized in both trials, 120 patients had acute myocardial infarction (AMI) with shock. Patients assigned to the higher mean arterial pressure (MAP) target (n = 58) reached higher MAPs ($p < 0.001$). The area under the 72-h high-sensitivity cardiac troponin T (hs-cTnT) curve was lower in patients assigned to the higher MAP target ($p = 0.04$). COMACARE = Carbon Dioxide, Oxygen and Mean Arterial Pressure After Cardiac Arrest and Resuscitation; Neuroprotect = Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients.

may limit infarct size (23,24). Neither the IABP-SHOCK II study (comparing IABP with inotropes/vasopressors in shock after AMI) nor the IMPRESS study (comparing Impella CP with IABP for cardiogenic shock) showed any mortality benefit and neither trial reported any data on myocardial infarct size (10,25).

STUDY LIMITATIONS. First, as this is a combined post hoc analysis of 2 randomized trials, patients were not strictly randomized. Although baseline characteristics were well balanced between both groups and the results of both trials separately are highly concordant, the possibility of bias by unknown confounders such as potential differences with respect to ischemic preconditioning, microcollaterals, wall stress, and blush grade cannot be fully excluded. Second, we used hs-cTnT to assess myocardial injury although MRI is the current gold standard. Cardiac MRI was not included in the protocols of the COMACARE or Neuroprotect trials as it would not have been feasible or safe in many patients with shock after AMI at days 3 through 5. Also, the patients with the largest infarct sizes would have already died by refractory shock before the MRI. In previous studies the area under the 72-h cTnT curve correlated well with infarct size on MRI and positron-emission tomography and independently predicted long-term LVEF and major adverse cardiac events during the first 30-days after AMI (26-28). While being an accurate measure of absolute infarct size, biomarkers do not allow estimation of myocardial salvage relative to the area at risk. Third, we had to adapt the universal definitions for AMI since patients had to be unconscious for inclusion (precluding the AMI chest pain criterion) and virtually all post-CA patients have post-ROSC electrocardiogram abnormalities and an increase of the troponin level. Likewise, previous shock definitions included criteria for end-organ hypoperfusion such as altered mental status, cold skin, increased lactate level, and decreased urine output that are not applicable in sedated post-CA patients with hypothermia-induced cold diuresis and consistently elevated lactate levels upon admission (1,2). Our definitions for shock (need for vasopressors to achieve assigned MAP targets) and AMI were in line with previous studies in post-CA patients and provided the most robust data

possible in this setting (29). Fourth, we did not perform long-term echocardiographic or MRI follow-up. It is unclear whether the acute improvement of LVEF as assessed with echocardiography within the first 24 h is indicative of a treatment effect with more rapid and efficient salvage of the border zone or just the transient result of inotropic stimulation. Fifth, both trials used mainly norepinephrine to boost MAP in the interventional arm and our results cannot be extrapolated to other types of vasopressors such as dopamine. Finally, the vast majority of our patients (87%) was treated with TTM at 33°C. There is controversy regarding the potential benefit of systemic or intracoronary hypothermia on myocardial infarct size (30,31). Although treatment effects in our study were not influenced by the applied TTM strategy, hypothermia may have prevented a more pronounced and potentially unfavorable increase of the heart rate by inotropic stimulation (32,33). Additionally, when compared with other cardiogenic shock trials, fewer patients had multivessel disease and more patients had pre-PCI TIMI flow grade 3 reflecting survival selection in our resuscitated cohort (10). Therefore, the hemodynamic profile, angiographic findings, and prognosis of our post-CA cohort may be different from nonresuscitated patients with shock after AMI who do not receive TTM, and one should be cautious to generalize our results to these patients. Future interventional trials are warranted to establish the optimal vasoactive drug regimen and the possible effect on clinical outcomes in resuscitated and nonresuscitated patients with shock after AMI during normothermia. Meanwhile, our data should be considered hypothesis-generating.

CONCLUSIONS

In post-CA patients with shock after AMI, targeting a MAP between 80/85 and 100 mm Hg with additional inotropes and vasopressors during the first 36 h of ICU stay was associated with lower hs-cTnT values, suggesting smaller myocardial injury. These findings justify a larger trial focusing on MAP targets in patients with shock after AMI with or without preceding CA.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with cardiogenic shock after acute myocardial infarction and revascularization, administration of inotropic and vasopressor medications to maintain mean arterial blood pressure between 80 or 85 and 100 mm Hg is associated with reduction in myocardial injury without raising the risk of arrhythmia or recurrent cardiac arrest.

TRANSLATIONAL OUTLOOK:

Adequately powered randomized trials are needed to compare the outcomes associated with various blood pressure targets in patients with cardiogenic shock and to correlate these with measurements of coronary perfusion, myocardial metabolites, and myocardial injury.

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KEY WORDS acute myocardial infarction, cardiac arrest, cardiogenic shock

APPENDIX For supplemental tables and figures, please see the online version of this paper.