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

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Higher Blood Pressure Targets in Post-Cardiac Arrest Patients with Shock after Acute Myocardial Infarction

Short title: *Blood Pressure Targets in Patients with Shock After AMI*

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Abstract
Background: In patients with shock after acute myocardial infarction (AMI), the optimal level of pharmacological support is unknown. While higher doses may increase myocardial oxygen consumption and induce arrhythmias, diastolic hypotension may reduce coronary perfusion and increase infarct size.
Objectives: to determine the optimal mean arterial pressure (MAP) in patients with AMI and shock after cardiac arrest.
Methods: patient-level pooled analysis of post-cardiac arrest patients with shock after AMI randomized in the Neuroprotect (NCT02541591) and COMACARE (NCT02698917) trials to MAP 65mmHg or MAP 80/85-100mmHg targets during the first 36 hours after admission. The primary end-point was the area under the 72-hours high sensitivity troponin-T (hs-cTnT) curve.
Results: Out 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 MAP's (86±9 vs 72±10mmHg, p<0.001). While admission hemodynamics and angiographic findings were all well balanced and revascularization was performed equally effective, the area under the 72-hour hs-cTnT curve was lower in patients assigned to the higher MAP target (median [IQR] 1.14 [0.35;2.31] vs 1.56 [0.61;4.72] µg.72hrs/l, p=0.04). Additional pharmacological support did not increase the risk of a new cardiac arrest (p=0.88) or atrial fibrillation (p=0.94). Survival with good neurological outcome at 180 days was not different between both groups (64 vs 53%, OR1.55, 95% CI(0.74;3.22))
Conclusions: In post-cardiac arrest patients with shock after AMI, targeting MAP between 80/85-100mmHg with additional use of inotropes and vasopressors was associated with smaller myocardial injury.

Condensed abstract
This patient-level pooled analysis of 2 randomized controlled trials showed that additional use of inotropes and vasopressors to target a MAP between 80/85-100mmHg during the first 36 hours after admission in post-cardiac arrest patients with shock after acute myocardial infarction was associated with lesser myocardial injury (as evidenced by the area under the 72-hours high sensitivity troponin-T curve) without increasing the risk of recurrent cardiac arrest or arrhythmia's.

Key words
Cardiogenic shock
Acute myocardial infarction
Cardiac arrest

Abbreviations
AMI: acute myocardial infarction
CA: cardiac arrest
CPC: cerebral performance category
IABP: intra-aortic balloon pump
MAP: mean arterial pressure
Hs-cTnT: high sensitivity cardiac troponin T
ROSC: restoration of spontaneous circulation
STEMI: ST elevation myocardial infarction
TIMI: thrombolysis in myocardial infarction
TTM: targeted temperature management

Background

Mortality in patients with shock after acute myocardial infarction (AMI) is estimated to be around 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 ACC/AHA 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 (MAP) 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 arrhythmia's [1,4]. However, by underusing inotropes and vasopressors, lower diastolic blood pressure may reduce coronary perfusion and increase infarct size. The optimal level of pharmacological support that balances coronary perfusion, afterload, myocardial oxygen consumption and arrhythmogenic risk remains unknown.

The Neuroprotect and the COMACARE trials previously randomized post-cardiac arrest (CA) patients to conventional (>65 mmHg) and higher (80/85-100 mmHg) MAP targets to investigate whether increasing cerebral perfusion during the first 36 hours of 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 arrhytmogenic risk within the subgroup of post-CA patients with shock after AMI.

Methods

Trial design

Both Neuroprotect (NCT02541591) and COMACARE (NCT02698917) 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. While Neuroprotect also included patients with non-shockable rhythms irrespective of the time to ROSC, COMACARE only included patients with shockable rhythms and time from collapse to ROSC between 10-45 min. An overview of the inclusion and exclusion criteria of both trials is provided in the supplementary appendix. In the present pooled post-hoc analysis, we only included patients with shock after AMI. We defined AMI as either ST-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 hours after admission. All diagnoses of AMI were

established prior to randomization. We defined shock as the need for vasopressors to maintain assigned MAP targets at any time point during the 36-hour intervention period.

General management

All patients received standard post-CA treatment based on current guidelines including mechanical ventilation, sedation, targeted temperature management (TTM) at 33 or 36 ^{o}C for 24 hours and standardized multimodal neuroprognostication [9]. Neurologists performing neuroprognostication and outcome assessors were blinded for treatment assignments.

Hemodynamic interventions

The 36-hour 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 (SvO2) of 65-75% using a combination of fluids, dobutamine and norepinephrine according to a predefined protocol (presented in supplementary appendix).

Data collection and study end-points

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-hour high-sensitive cardiac troponin T (hs-cTnT) curve. Blood samples for Hs-cTnT were obtained at hospital admission and 24, 48 and 72 hours thereafter in both trials with an additional troponin measurement at 5 hours in the Neuroprotect trial. In addition, hs-sTnT was measured at additional time-points during the first 72 hours 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 CPC score at 180 days. The CPC 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 neurological, cardiac or other. All Neuroprotect patients underwent transthoracic echocardiography (TTE) evaluation during the first 24 hours.

Statistical analysis

Data are presented as mean±standard deviation or median [IQR]. Continuous variables were compared by unpaired Student's t-tests, Mann-Whitney U tests or ANOVA and categorical variables were compared with Fisher's exact or chi-square tests as appropriate. The area under the 72-hour 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 of patients who died before 72-hours were imputated according to the worst case scenario (i.e. the missing value was replaced with the highest Hs-cTnT in the corresponding treatment group). Missing data of patients surviving beyond 72hours were imputated 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 betablocker use, STEMI vs non-STEMI, culprit artery, extent of coronary artery disease, completeness of revascularization, pre-percutaneous coronary intervention (PCI) TIMI flow and TTM strategy used. Longitudinal data (MAP, diastolic blood pressure, heart rate, dose norepinephrine and dobutamine) were

analyzed using a generalized estimating equation model for normally 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 two treatment groups were assessed by the interaction. Analysis regarding secondary endpoints were exploratory. SPSS (version 24), SAS (version 9.4) and SAS/STAT (version 14.2) were used for statistical analysis. All tests were two-sided and assessed at a significance level of 5%. Due to 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 two trials (123 in COMACARE and112 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 80/85-100 mmHg and 62 patients to the MAP65 mmHg arm (figure 1). One patient who died in the cathlab immediately after randomization but before starting hemodynamic therapy was excluded from the 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 mmHg and MAP 80/85-100 mmHg arms had comparable pre-randomization characteristics (table 1).

Angiographic data

Most patients presented with an ST segment elevation myocardial infarction upon hospital admission (table 2). All patients underwent immediate angiography with an attempt for

percutaneous intervention (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 80/85-100 mmHg target received significantly higher doses of norepinephrine (p=0.004) (figure 2). The number of patients receiving dobutamine was not different between the groups (14/58 (24%) vs 11/62 (18%), p=0.39), but the dobutamine dose was significantly higher in patients randomized to the MAP 80/85-100mmHg group (4.5±4.2 vs 3.7±2.2 mcg/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 80/85-100 mmHg arm and 1 IABP plus 1 vaECMO in the MAP 65 mmHg arm). While heartrate 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-hour hs-cTnT curve was greater in the lower MAP group (median [IQR] 1.14 [0.35;2.31] vs 1.56 [0.61;4.72] μg.72hrs/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 0-1) in the LAD or left main coronary artery (Figure 4). In the Neuroprotect trial, mean LVEF was higher in patients assigned to the high MAP group (42±12 (n=25/28) vs 35±13 (n=31/31)%, 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 (8/58 (14%) vs 9/61 (15%), OR 0.92 (95% CI 0.33:2.58),

p=0.88) or of new onset atrial fibrillation (4/58 (7%) vs 4/61 (7%), OR 1.05 (95% CI 0.25:4.43), *p*=0.94) during the 36-hours interventional period.

Outcome

We obtained complete follow-up in all patients. At 180 days, the number of patients with good neurological outcome (CPC 1-2) (37/58 (64%) vs 33/62 (53%), OR 1.55 (95% CI 0.74:3.22), p=0.24) and all-cause mortality (21/58 (36%) vs 25/62 (40%), OR 0.84 (95% CI 0.40:1.75), 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 neurological futility (n=32, 70%).

Discussion

When compared with conventional hemodynamic goals (MAP>65mmHg), the use of additional inotropes and vasopressors to target a MAP between 80/85-100 mmHg during the first 36 hours 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, IABP-SHOCK II and CULPRIT-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 0 flow 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 non-culprit vessels, and TIMI flow before and after revascularization. While peak hs-cTnT concentrations at 24 hours in patients assigned to the MAP 65 mmHg arm (median around

1.86 μg/l) were in line with the CULPRIT-SHOCK trial [2], the area under the 72-hour hs-cTnT curve was 37% smaller in the group of patients randomized to the higher MAP target. In patients with a large AMI, the necrotic infarcted core is surrounded by a large edematous border zone that on average accounts for 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 (60-140mmHg) 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 intra-myocardial 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 micro-collaterals. The importance of improving oxygen supply to the border zone was illustrated 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 wash-out of micro-thrombi and facilitate influx of inflammatory cells that promote the healing response. Even the infarcted myocardium, once thought to be "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.

Arrhytmogenic 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 CPR during the 36-hour 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 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 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]. While 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 3 flow 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 prior to 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. Since the cause of death was post-anoxic encephalopathy in 70% of the patients, it's unlikely that an intervention that effectively reduces myocardial injury would have affected mortality in this relatively small sample of patients. Since the odds to die or to develop heart failure increase with 20% per 5% increment of the infarct size, it is anyhow of paramount clinical importance to minimize myocardial infarct size even in patients with undecided neurological 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, LV unloading prior to reperfusion by impella CP 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 prior to reperfusion was reported to be feasible and safe in a human pilot trial with stable anterior AMI patients, human data on coronary perfusion and infarct size with the use of mechanical cardiac support devices such as vaECMO and

Impella are limited [22]. Although the CRISP-AMI study (investigating the benefit of routine IABP in stable anterior AMI) was essentially negative, a sub-study showed mortality benefit in patients with ongoing ischemia and disturbed autoregulation further supporting the concept that increasing coronary perfusion after PCI 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].

Limitations and future perspectives

First, as this is a combined post-hoc analysis of two 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 pre-conditioning, micro-collaterals, 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 day 3-5. 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-hour cTnT curve correlated well with infarct size on MRI and PET and independently predicted long-term left-ventricular ejection fraction (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 ECG abnormalities and rise of the troponins. 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 hours 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 pressors such as dopamine. Finally, the vast majority of our patients (87%) was treated with TTM at 33ºC. 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, less patients had multivessel disease and more patients had pre-PCI TIMI3 flow 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 non-resuscitated 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 non-resuscitated patients with shock after AMI during normothermia. Meanwhile, our data should be considered hypothesis generating.

Conclusion

In post-CA patients with shock after AMI, targeting a MAP between 80/85-100 mmHg with additional inotropes and vasopressors during the first 36 hours 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.

Perspectives

Clinical Competencies: In patients with shock after AMI, many ICU physicians try to minimize the use of inotropes and vasopressors to reduce myocardial oxygen consumption, infarct size and the risk for life threatening ventricular arrhythmia's. However, we showed that the additional use of inotropes and vasopressors in appropriately revascularized patients with shock after AMI to target a MAP between 80/85-100mmHg is associated with a reduction in myocardial injury. We did not observe signals that additional inotropes and vasopressors would increase the risk of recurrent cardiac arrest or arrhythmia's.

Translational Outlook: A future appropriately powered randomized controlled trial should compare lower and higher MAP targets in cardiogenic shock patients and in addition also directly assess differences in coronary perfusion, cardiac metabolites, myocardial injury by cardiac MRI and long-term MACE rate.

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Figure and table legends

Figure: central illustration: Conventional versus higher blood pressure targets in patients with shock after acute myocardial infarction

Out of 235 patients originally randomized in both trials, 120 patients had AMI with shock. Patients assigned to the higher MAP target (n=58) reached higher mean arterial blood pressures (p<0.001). The area under the 72-hour hs-cTnT curve was lower in patients assigned to the higher MAP target (p=0.04)

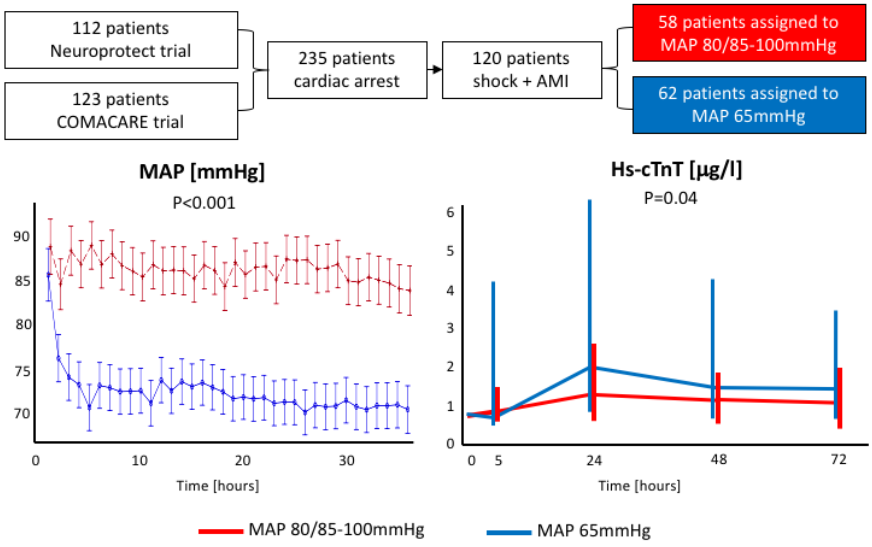


Figure 1: Consort diagram
A total of 235 patients were randomized in the two trials (123 in COMACARE, 112 in Neuroprotect). After exclusion of patients without AMI (n=93), patients who did not undergo an immediate angiography (n=17), patients whose next of kin refused informed consent (n=4) and one randomization error, the full analysis set of this study consisted of 120 AMI patients. Of these, 58 patients were randomized to the MAP 80/85-100 mmHg and 62 patients to the MAP65 mmHg arm. One patient who died in the cathlab immediately after randomization but before starting hemodynamic therapy was excluded from the cTnT analysis as he did not receive the assigned therapy.

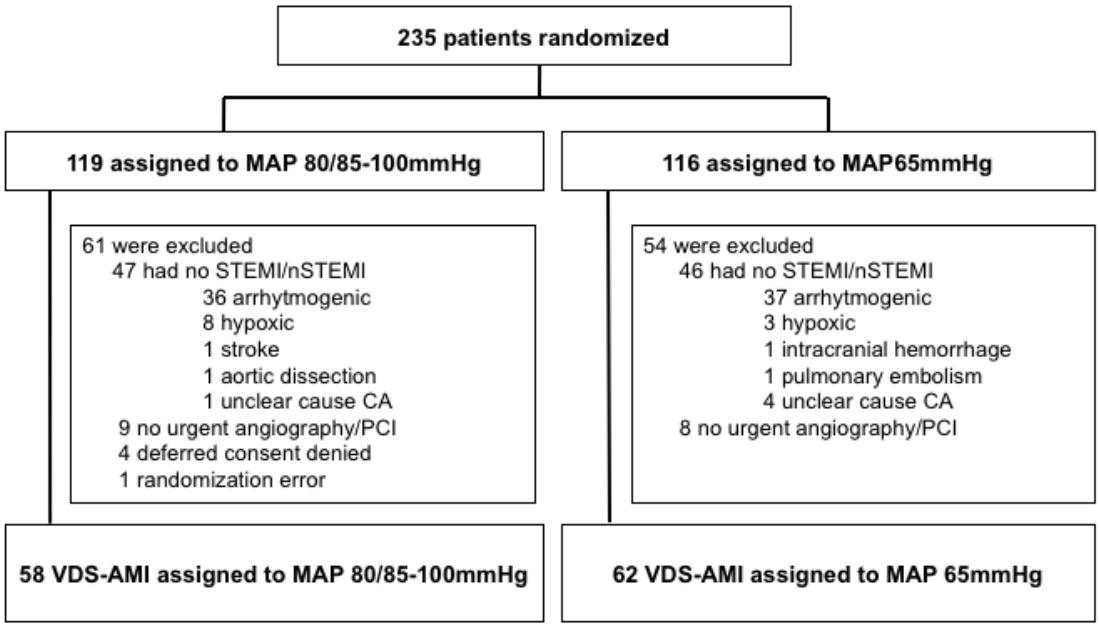


Figure 2: Hemodynamics

Panel (A) mean arterial pressure [mmHg]. Panel (B) diastolic blood pressure [mmHg]. Panel (C) Dose norepinephrine [mcg/kg/min]. Panel (D) heart rate [beats per minute]. Plots present estimated mean values with corresponding 95% confidence intervals. Predicted values were obtained using a GEE 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 the supplementary appendix

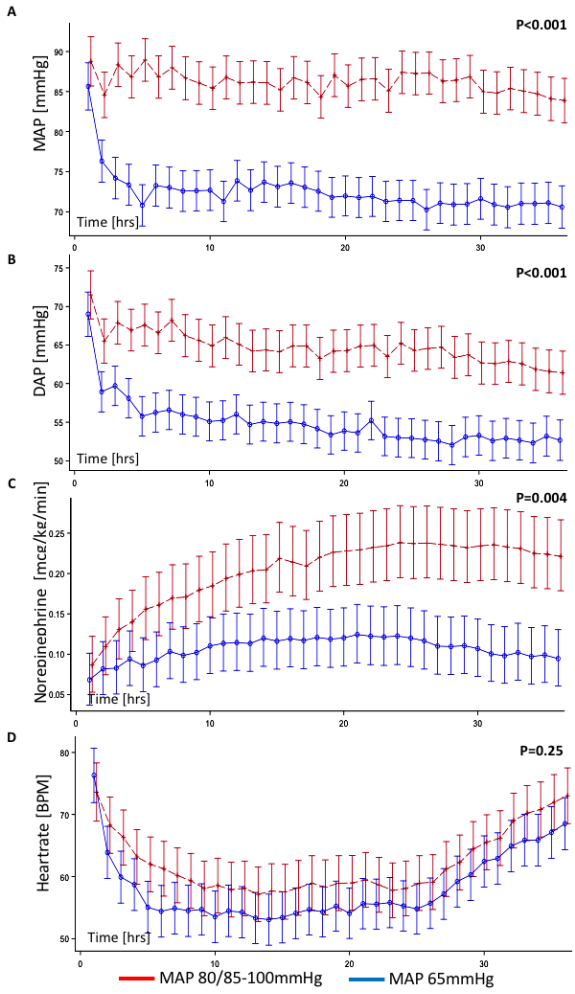


Figure 3: Myocardial injury
Panel (A) Full cohort. Panel (B) Neuroprotect, Panel (C) COMACARE. Plot shows median [Q1, Q3] by randomized group and time. Raw data are provided in the supplementary appendix

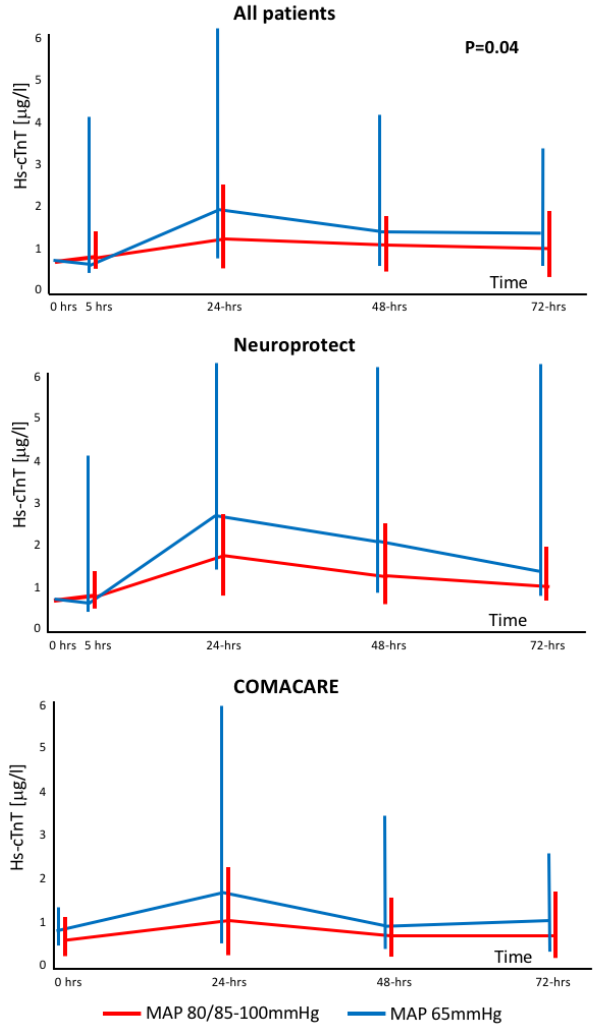
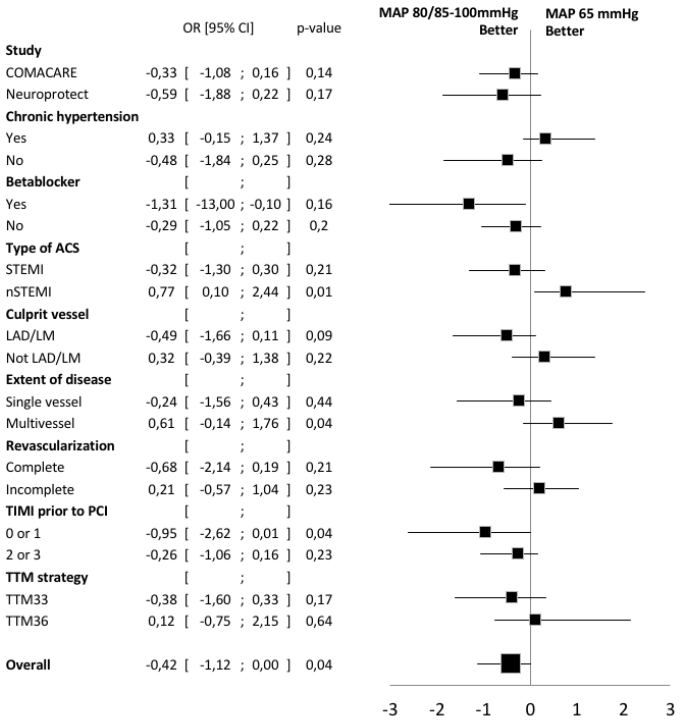


Figure 4: Forest plot

Subgroup analysis comparing the 72-hours AUC cTnT curve per MAP strategy (MAP 65mmHg versus 80/85-100mmHg) according to trial (Neuroprotect vs COMACARE), baseline use of anti-hypertensive drugs, baseline use of betablockers, type of ACS (STEMI vs nSTEMI), culprit vessel (LAD and Left main versus other), single vs multivessel disease, complete vs incomplete revascularization, pre-PCI TIMI flow and targeted temperature management at 33ºC or 36ºC. In COMACARE, Hs-cTnT levels were not different between patients randomized to either low-normal vs 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].



	Comacare	Neuroprotect	p	MAP80-100mmHg	MAP65mmHg	p
Number	61	59		58	62	
Demographics						
Age [years]	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 arrhytmia	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
Betablocker use	11/60 (18%)	11/53 (21%)	0.75	10/54 (19%)	12/59 (20%)	0.81
ACE-I/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%)	
Non-shockable	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 [mmHg]	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] (median [IQR])	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] (median [IQR])	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%)	

Table 1: Baseline characteristics

AMI: acute myocardial infarction

COPD: chronic obstructive pulmonary disease

ER: emergency room

ICU: intensive care unit

MAP: mean arterial pressure

ROSC: resume of spontaneous circulation

TTM: targeted temperature management

	MAP80-100mmHg	MAP65mmHg	p
Cause of arrest			0.37
STEMI	46/58 (79%)	53/62 (85%)	
nSTEMI	12/58 (21%)	9/62 (15%)	
ROSC-to-cathlab 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

Table 2: Angiographic findings

CAD: coronary artery disease

PCI: percutaneous coronary intervention

ROSC: resume of spontaneous circulation

STEMI: ST elevation myocardial infarction

TIMI: thrombolysis in myocardial infarction

	MAP80-100mmHg	MAP65mmHg	treatment effect	p-value
Primary end-point				
Imputed 72-hrs AUC cTnT [mcg.72hrs/l]	1.14 [0.35;2.31]	1.56 [0.61;4.72]	-0.42 [-1.12;0.00]	0.04
Secundary end-points				
New onset atrial fibrillation	4/58 (7%)	4/61 (7%)	1.05 [0.25:4.43)	0.94
Recurrent cardiac arrest within 36-hours	8/58 (14%)	9/61 (15%)	0.92 [0.33:2.58]	0.88
CPC 1-2 180 days	37/58 (64%)	33/62 (53%)	1.55 [0.74:3.22]	0.24
All-cause mortality 180 days	21/58 (36%)	25/62 (40%)	0.84 [0.40:1.75]	0.63

Table 3: Study end-points

AUC: area under curve

cTnT: Cardiac troponin T

CPC: cerebral performance category

P-values for all secondary end-points are exploratory