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Review

Blood pressure targets and management during post-cardiac arrest care

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Abstract

Blood pressure is one modifiable physiological target in patients treated in the intensive care unit after cardiac arrest. Current Guidelines recommend targeting a mean arterial pressure (MAP) of higher than 65–70 mmHg using fluid resuscitation and the use of vasopressors. Management strategies will vary based in the setting, i.e. the pre-hospital compared to the in-hospital phase. Epidemiological data suggest that some degree of hypotension requiring vasopressors occur in almost 50% of patients. A higher MAP could theoretically increase coronary blood flow but on the other hand the use of vasopressor may result in an increase in cardiac oxygen demand and arrhythmia. An adequate MAP is paramount for maintaining cerebral blood flow. In some cardiac arrest patients the cerebral autoregulation may be disturbed resulting in the need for higher MAP in order to avoid decreasing cerebral blood flow. Thus far, four studies including little more than 1000 patients have compared a lower and higher MAP target in cardiac arrest patients. The achieved mean difference of MAP between groups has varied from 10–15 mmHg. Based on these studies a Bayesian meta-analysis suggests that the posterior probability that a future study would find treatment effects higher than a 5% difference between groups to be less than 50%. On the other hand, this analysis also suggests, that the likelihood of harm with a higher MAP target is also low. Noteworthy is that all studies to date have focused mainly on patients with a cardiac cause of the arrest with the majority of patients being resuscitated from a shockable initial rhythm. Future studies should aim to include also non-cardiac causes and aim to target a wider separation in MAP between groups.

Keywords: Post cardiac arrest care, Mean arterial blood pressure, Shock, Vasopressors

Introduction

Current guidelines for post-cardiac arrest care recommend targeting a mean arterial pressure (MAP) of at least 65 mmHg to maintain a perfusion pressure sufficient to support urine production and lactate clearance.[1] While the association between hypotension and adverse outcomes is established, the question of potential benefit from targeting a higher MAP than 65 mmHg has so far not received a clear answer. Evidence for a MAP threshold of 65 mmHg stems mainly from large observational studies that do not exclude improved patient outcomes from higher arterial pressure. Recent randomised controlled trials (RCTs) have investigated organ function and patient outcomes in patients treated with a low-normal or a higher MAP target after cardiac arrest (CA).[2–5] No consistent clinical benefit from a higher MAP target has been reported based on a recent systematic review of randomized clinical trials.[6] These studies are arguably limited by primarily enrolling CA patients with generally good outcomes, e.g. resuscitation from a shockable initial rhythm and a cardiac-caused arrest.[7] In addition, there is a limited number of patients with chronic hypertension in whom a higher MAP target could be most convincing, for example, by a shift to the right of cerebrovascular autoregulation.[8,9]

Optimal blood pressure management strategies are likely to depend on the clinical setting, the time since the CA and individual patient factors. In the pre-hospital setting, restoring cerebral perfusion is paramount, and patients may be hypertensive from resuscitation drugs, typically adrenaline, with intermittent and inaccurate blood pressure monitoring (Fig. 1). Sustained arterial hypertension after return of spontaneous circulation (ROSC) can further compromise any ongoing myocardial ischaemia. In the intensive care unit (ICU), myocardial perfusion may have improved following revascularisation procedures, and continuous cardiac and blood pressure monitoring allow precise control of MAP across a wide clinical range (Fig. 2). The differences between these two settings illustrate how treatment strategies are unlikely to be the same throughout all phases of post-CA care, although they are not explicitly addressed in guidelines.

In this narrative review, we discuss the definitions of and treatment options in post-CA care for different MAP targets and their

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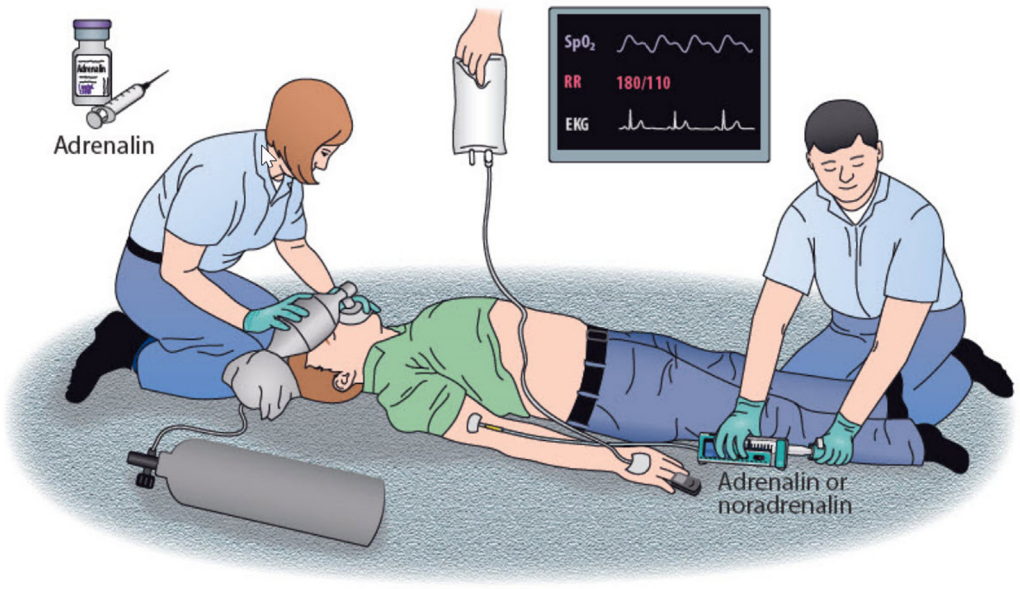

Fig. 1 – Aspects of blood pressure management in the pre-hospital setting.

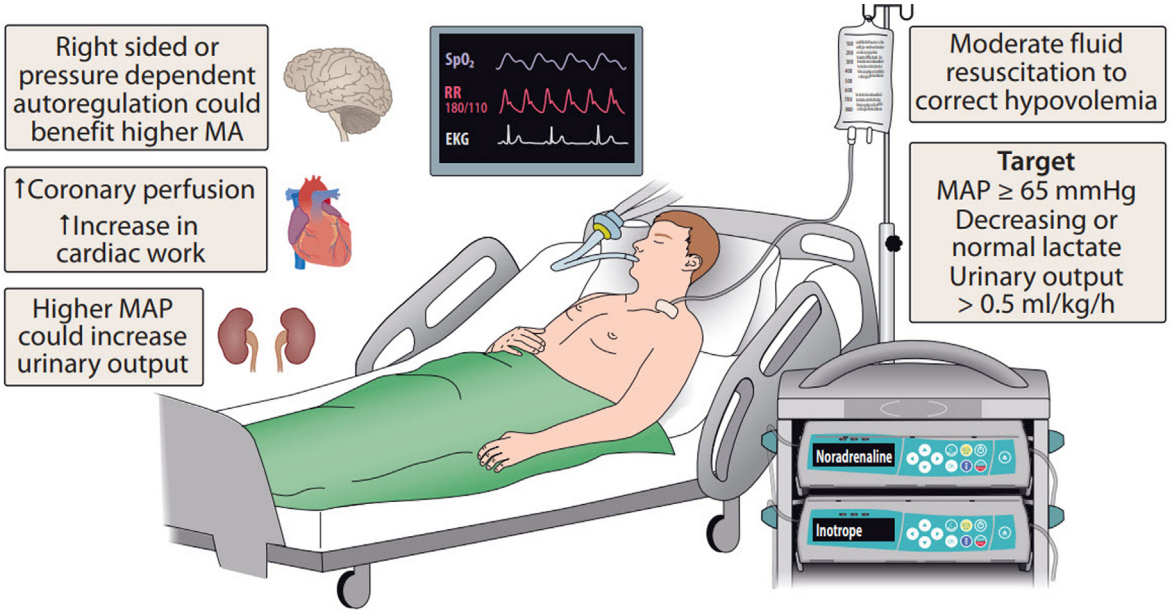

Fig. 2 – Aspects of blood pressure management in the intensive care unit.

physiological rationale, particularly in relation to coronary and cerebral circulation. Finally, we report a brief Bayesian analysis of recent RCTs comparing higher to lower MAP targets to provide a perspective on the probabilities of benefit in future trials.

Prevalence of hypotension after cardiac arrest

The prevalence of significant hypotension is not straightforward to determine given differences in the definition of hypotension (MAP <65 mmHg or systolic blood pressure <90 mmHg) and variable vasopressor use. An Australian observational study of 3620 patients showed that upon hospital arrival (on average 40 minutes from ROSC), 15% of patients had a systolic blood pressure <90 mmHg.[10] This appeared more commonly in female patients with a non-shockable rhythm and prolonged (longer than 15 minutes) cardiopulmonary resuscitation (CPR). Other studies found higher hypotension prevalence rates (25% to almost 90%).[11–13] A recent large ICU registry study showed that 55% of 32,000 CA patients treated in various UK ICUs had a MAP <65 mmHg in the first 24 hours.[14] The highly variable hypotension rates probably reflect patient selection and treatment. A time component is also possible, as soon after ROSC the effect of adrenaline given during CPR is still likely to increase blood pressure, but it wears off after 5 to 10 minutes.[10] In the ICU, patients are likely to receive continuous sedation, which may induce hypotension. In addition, data have shown an associa-

tion between a progressive inflammatory response in the first 24 hours after ROSC and hypotension and the need for vasopressors.[15] Little data is available about patients not sedated for TTM, but evidence suggests that after 24–48 hours arterial blood pressure tends to stabilise.[5] Nonetheless, multiple observational studies show worse outcome in patients with hypotension after cardiac arrest.[16–18] The threshold for systolic blood pressure associated with worse outcome has in studies varied between 90–100 mmHg and appear to be independent of the use of vasopressors.

Importance of map for coronary circulation

In patients with a large acute myocardial infarction (AMI), the necrotic infarcted core is surrounded by a large oedematous border zone that on average accounts for half the total area at risk.[19] To salvage the border zone, immediate restoration of the cellular oxygen balance is paramount. Use of inotropes and vasopressors would theoretically increase afterload, contractility, heart rate and stroke work, resulting in an unfavourable increase of myocardial oxygen consumption.[20] Hypothetically, in studies targeting a higher MAP, the observed reduction of myocardial injury could be the net result of increased coronary perfusion resulting from increased diastolic blood pressure that offsets increased oxygen consumption.[21] Under normal physiologic circumstances, myocardial blood flow is kept constant over a wide range of aortic pressures (60–140 mmHg) by myogenic adaptation of the coronary arteriolar vascular tone (i.e. autoregulation).[20] During reperfusion after AMI, microvascular resistance is greatly increased by intraluminal plugging, spasm and external compression by interstitial oedema and intra-myocardial haemorrhage causing a right shift of coronary autoregulation.[22] Increasing diastolic blood pressure may increase the driving pressure for coronary perfusion.

At the microcirculatory level, improving hydrostatic pressure and flow may recruit microcollaterals. Additionally, myocytes and endothelial cells in the border zone are oedematous because of intracellular osmotic overload, and capillaries with higher hydrostatic pressures may better resist external compression by swollen myocytes.[23] Finally, improving microcirculatory flow may promote faster wash-out of microthrombi and facilitate an influx of inflammatory cells that promote the healing response. These macro- and microcirculatory changes together may result in improved infarct core remodelling and better salvage of the border zone.

Current guidelines do not recommend specific haemodynamic goals to target in patients with AMI complicated by cardiogenic shock (CS-AMI).[24] In clinical practice, attempts are often made to minimise the use of inotropes and vasopressors to reduce myocardial oxygen consumption, myocardial infarct size and the risk of life-threatening ventricular arrhythmias.[24] However, in a post hoc pooled analysis of the NEUROPROTECT[2] and COMACARE[4] trials, the use of additional inotropes and vasopressors to target a MAP between 80/85 mmHg and 100 mmHg during the first 36 hours following ICU admission for CA and CS-AMI was associated with a 37% reduction of myocardial injury, as assessed by the area under the cardiac troponin-T curve.[21] This finding was consistent across both trials and mainly driven by results obtained in ST-elevation myocardial infarction patients with a (sub)occlusion of the left anterior descending or left main coronary artery. Targeted temperature management at 33C (TTM33) was used in all the NEUROPROTECT trial patients and in most of the COMACARE trial patients and may have prevented a more unfavourable increase in heart rate and oxygen consumption. Given the TTM33 use and the main vasopressor being noradrenaline, a significant finding was the increase in diastolic blood pressure between the groups, as well as the lack of any increase in heart rate. The larger BOX trial, in which patients were treated with a TTM36 strategy, did not report on myocardial infarct size between both study groups, but the levels of troponin appeared similar, suggesting no clear cardioprotective effect with a higher MAP target.[5]

Importance of map for cerebral circulation

Hypoxic ischaemic brain injury (HIBI) is the main cause of morbidity and mortality in CA patients; hence, the understanding of cerebral tissue oxygenation, blood flow and the influence of MAP on these variables is pivotal in post-CA care. Regional cerebral tissue oxygenation (rsO_2) in the frontoparietal watershed area between the anterior and middle cerebral artery vascular territories can be measured by near infrared spectroscopy, which requires minimal procedural expertise and is applicable at the bedside.[25] An increase in rsO_2 by increasing MAP may serve as a mechanistic proof of concept that the intervention has the potential to ameliorate brain hypoxia. For example, rSO_2 during or immediately following CPR has been correlated with arterial blood pressure but not arterial partial pressure of oxygen (P_aO_2).[26] A linear relationship between MAP and invasively measured oxygen tension in brain tissue was reported by Sekhon et al whereas no correlation was found with rSO2.[27] Furthermore, the same research group also identified that oxygen diffusion is limited in patients with HIBI, thus disrupting the pathway between the vascular delivery of oxygen and its cellular uptake.[27] This phenomenon could limit the usefulness of rSO_2 monitoring that requires further clinical investigation if used to guide MAP interventions. There is no doubt that research have highlighted additional shortcomings with the NIRS technology.[28,29]

The NEUROPROTECT trial investigated whether an increased MAP target during the first 36 hours after ICU admission from standard care of 65 mmHg to 85–100 mmHg with optimisation of cardiac output and mixed venous oxygen saturation could improve cerebral oxygenation.[2] In 112 out-of-hospital cardiac arrest (OHCA) patients, rSO_2 was significantly higher in the intervention group ($n = 56$) for the first 12 hours compared to standard care ($n = 56$), but not over the following 24 hours, with both groups showing a slow increase in rSO_2 over time. The extent of anoxic brain damage shown by magnetic resonance imaging and the number of patients with a favourable neurological outcome did not differ between the groups.

The COMACARE study compared MAP, P_aO_2 and P_aCO_2 levels in a 2^3 factorial design, including 120 OHCA patients in the final analysis.[5] No differences were found in the medians and interquartile ranges for rSO_2 over 36 hours since admission to ICU between the low-normal MAP (65–75 mmHg, $n = 60$) and high-normal MAP (80–100 mmHg, $n = 60$) groups.[19] No differences in neuron-specific enolase or neurological outcomes were observed.

In a single-centre sub-study of the BOX trial, rSO_2 for up to 96 hours of ICU admission was monitored in OHCA patients randomised to low MAP (63 mmHg, $n = 30$) and high MAP (77 mmHg, $n = 30$).[30] No significant differences in rSO_2 were observed between the groups at any time, with the cardiac index, P_aO_2 and P_aCO_2 also similar between groups. The lack of rSO_2 separation remained irrespective of chronic hypertension. In a pilot study ($n = 10$), Grand et al. did not observe an increase in rsO_2 during stepwise increases in MAP from 65 to 85 mmHg, while increasing cardiac output by per-

missive hypercapnia increased rsO_2, albeit without signs of increased cerebral oxygen uptake.[31] In a similarly small pilot study (n = 10), Bouzat et al. did not observe an increase in rSO_2 when MAP was increased from 72 to 90 mmHg without any parallel monitoring of cardiac output.[32] Taken together, the question whether treating patients with a higher MAP target can increase cerebral oxygenation is currently unanswered. The physiological rationale underpinning an increased MAP, to mitigate the no-reflow phenomenon and delayed hypoperfusion with a resultant increase in brain oxygen delivery, is still supported by the results of studies using invasively measured brain tissue oxygenation.[27,33]

MAP's pivotal importance in maintaining cerebral blood flow, and thus oxygen delivery, and mediation through cerebrovascular autoregulation (CVAR) have been the focus of mainly observational clinical studies.[8,33–36] Using CVAR monitoring to tailor MAP targets specific to individual patients rather than a 'one-size-fits-all' approach is appealing. Monitoring CVAR appears feasible and studies to date indicate a minimum MAP around 85 mmHg to maintain optimal CVAR capacity, which is considerably higher than current recommendations or best evidence from RCTs.[37]

In a review of six studies including 181 patients, no consistent association between targeting the MAP associated with optimal CVAR capacity and neurological outcomes was found.[38] The review emphasised that wide variability in monitoring methods, time, the CVAR parameter reported and its operative definitions made it difficult to analyse the data. Importantly, the optimal MAP for CVAR was reported to be in the 70–114 mmHg range, well above the current recommendation of 65 mmHg. A post hoc study of the COMACARE trial included 108 patients and used an rSO_2-derived measure of CVAR measured up to 48 hours after ICU admission.[9] Impaired CVAR with narrower MAP limits was observed in most patients (70%), more commonly in patients with chronic hypertension. The association with chronic hypertension is in line with previous ischaemic brain injury studies.[38] Furthermore, patients with poor neurological outcomes had a decreased upper limit of CVAR and weakened CVAR capacity for the entire 48-hour period. The MAP associated with the most effective CVAR was most frequently above 75 mmHg. The biomarker neurofilament light was elevated in patients with deranged CVAR compared to patients with intact CVAR. While these associations appear clinically plausible, the nature of rSO2 as a surrogate marker of CBF must be taken into consideration and studies of CVAR using invasive methods have highlighted a poor correlation with rSO2 derived CVAR.[39] Notably, associations with improved brain tissue oxygenation and reduced mortality at higher MAP are also reported using indices of CVAR based on invasive measurements.[33,34]

Vasopressors and potential adverse effects

Theoretically, targeting a higher MAP using additional fluid volume, vasopressors and inotropes may result in pulmonary oedema, limb ischaemia, cardiac arrhythmias and re-arrest in vulnerable patients, such as CA patients with a recent AMI and depressed left ventricular function. Increased noradrenaline doses were necessary in studies investigating high MAP targets, with additional use of fluids and higher doses of dobutamine reported in the NEUROPROTECT trial.[2] Importantly, rigorous monitoring did not reveal any significant increase in the rate of severe adverse events in RCTs enrolling patients in a high MAP strategy. Furthermore, targeting a high MAP did not increase the rates of ventricular arrhythmias or re-arrest (13%–15% in the high MAP groups vs 13%–24% in the low MAP groups) nor increase the rate of new-onset atrial fibrillation (0% in the high MAP groups vs 7% in the low MAP groups).[2] Therefore, earlier restoration of cellular oxygen balance by promoting coronary perfusion seems to offset the potential pro-arrhythmogenic effects of α_1-stimulating inotropic agents.

Other possible side effects include pulmonary oedema (0%–4% of patients) and limb ischaemia (0%–2% patients), but these appear rare during the first 36 hours of an ICU stay. While arteriolar vasoconstriction with vasopressor increases afterload, mechanically ventilated post-CA patients may not, even with severely depressed left ventricular function, develop pulmonary oedema, since the positive intrathoracic pressures also reduce venous return (cardiac preload). Positive intra-alveolar pressure also reduces the pulmonary intravascular-interstitial pressure gradient that could drive fluid towards the alveolus.

Limited data exist on the use of dopamine in CA patients. 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.[40] In contrast, noradrenaline was used as the first-line vasopressor in the NEUROPROTECT[2] and COMACARE[4] trials, and all patients included in the post hoc pooled analysis underwent aggressive revascularisation prior to randomisation. The safety of escalating vasopressor and/or inotropic support, particularly using dopamine, to target higher MAP in patients with less extensive or successful revascularisation prior to the start of the therapy remains unclear.

Is a higher mean arterial pressure likely to provide benefit?

Four RCTs have been published comparing lower (63–75 mmHg) and higher (73–100 mmHg) MAP targets in post-CA patients. This review evaluated their results using a robust Bayesian meta-analysis,[2–5] leveraging data captured in a recent individual patient data meta-analysis, and should be viewed as exploratory.[41] The analysis attempted to illustrate the potential in future studies to find any benefit from higher MAP in post-CA care against a range of beliefs or 'expert opinion' on this treatment.

Bayesian statistics enable the effect estimates of treatments in clinical trials to be explored beyond the frequentist approach of accepting or rejecting the null hypothesis of no difference, based on a threshold p-value of 0.05.[29–31] Briefly, a Bayesian statistical approach combines the results of clinical trials, referred to as the likelihood, with current knowledge or beliefs regarding treatment effects, referred to as the prior, to generate a posterior distribution of probabilities for the effect size.[37] This enables a range of treatment effects, such as risk ratios, to be evaluated from the continuous posterior distribution to assess their probabilities. Furthermore, the relationship between treatment risk and benefit can be evaluated based on a limited number of studies, as the observed treatment effect of one trial is informed by those of the other trials, making the estimated intervention effect less susceptible to trials with small or extreme results.[42,43] The patient-centred outcomes of mortality and poor neurological recovery (cerebral performance category [CPC] 3–5, modified Rankin scale [mRS] 4–6) closest to 180 days after CA were investigated.

A hierarchical robust Bayesian model-averaged meta-analysis combined the results of Bayesian fixed-effect and Bayesian ran-

dom-effect models to generate a model average for effect size (risk ratio [RR]), heterogeneity and publication bias. The details are provided in the Supplementary Material. The mean of the effect size prior positions where the belief in the effect is, while its confidence interval reflects its certainty (greater certainty is reflected in narrower variance). The same priors were applied for mortality and poor neurological outcome.

First, a non-informative prior was used with no assumed effect of the intervention (RR = 1), meaning that all information in the posterior distribution was driven by the results of the clinical trials. Second, an informed pessimistic prior was applied based on a recent systematic review and meta-analysis of MAP targets during vasopressor therapy in six studies comprising 3690 critically ill patients that found no difference in mortality between a higher MAP (75–85 mmHg) compared to a lower MAP (65 mmHg) (RR 1.06, 95% confidence interval [CI] 0.98–1.15).[44] Third, an optimistic prior was chosen to reflect the study protocol of the upcoming STEPCARE trial (NCT05564754), which targets a 5.6% (from 60% to 54.4%) absolute risk reduction of mortality in 3500 participants (corresponding to RR 0.91, 95% CI 0.85–0.96) comparing a MAP > 65 mmHg with a MAP > 85 mmHg. Finally, a more optimistic prior was adopted from the BOX trial protocol, which aimed at an absolute risk reduction of 10% (38% to 28%) in 800 enrolled patients (corresponding to RR 0.74, 95% CI 0.60–0.90).[5] The optimistic priors were set to reflect the 'expert opinion' of clinical researchers launching new studies of higher MAP targets with the hypothesis of benefit from this intervention. The RRs and their 95% confidence intervals from the STEPCARE and BOX protocols were assigned different chances of 80%, 60% and 50% to reflect the true effect size (Table 1). The posterior probability to achieve an RR < 0.95, meaning that the risk of death or an unfavourable neurological outcome would be at least 5% lower in the group of patients treated with a high MAP target compared to the group treated with a low MAP target, is reported for all analyses.

Based on the four clinical trials and an uninformative prior, the posterior probability for an RR < 0.95 was less than 50% for both outcomes (Figs. 3 and 4). Applying an informative pessimistic prior based on the lack of difference between low and high MAP targets in a general, critically ill population reduced the posterior probability to <0.5%, meaning that a benefit for higher MAP is practically excluded and the intervention is futile at best or with potential for harm at worst. Using the optimistic prior based on the STEPCARE protocol (Table 1), accepting that a higher MAP at >30% above the current recommendation of 65 mmHg could provide a 5.6% mortality benefit in a large sample size resulted in a 50% posterior chance of achieving at least an RR < 0.95 for the two most certain beliefs. The very optimistic prior, accepting that a 10% rather than a >30% increase above the recommended MAP could indeed provide the effect size used in the design of the BOX trial and with its sample size, also generated a >50% posterior chance of achieving an RR < 0.95 across all beliefs explored.

Considerations in future trials of map targets for post-cardiac arrest care

All trials reported to date investigating low or high MAP targets after CA have focused on patients with a probable cardiac cause of arrest, who have a high likelihood of a good outcome.[45] Future trials will need to include CA patients with a wider range of aetiologies, including those with a lower likelihood of favourable outcomes, such as patients resuscitated from non-shockable rhythms and with other cardiac arrest aetiologies than cardiac. Patients with more severely compromised coronary, cerebral and other organ perfusion may stand to benefit the most from increased MAP. The treatment effect of a higher MAP target is likely to be heterogeneous, similar to most studies of ICU interventions. From a pathophysiological point of view, it is conceivable that haemodynamic support to achieve the same MAP target and any related beneficial effects, differ in patients with cardiogenic hypotension compared to vasodilated hypotension, since inflammatory phenotypes differ in these contexts.[46] It is also possible that a greater separation between low and high MAP targets

Table 1 – The posterior distributions for risk ratio and 95% credible interval for mortality and unfavourable neurological outcome across a range of optimistic prior beliefs and varying certainty using effect estimates from the STEP CARE and BOX trial protocols. The posterior probabilities for achieving a risk ratio of at least <0.95 are listed as percentages.

Optimistic prior belief	**Mortality** risk ratio [95% credible interval]	**Mortality** probability RR < 0.95	**Unfavourable neurology** risk ratio [95% credible interval]	**Unfavourable neurology** probability RR < 0.95
'There is a 9**0%** chance that the RR is 0.91 and lies between 0.85 and 0.96'	0.93 [0.86–0.97]	81%	0.92 [0.87–0.97]	83%
'There is a 7**0%** chance that the RR is 0.91 and lies between 0.85 and 0.96'	0.94 [0.86–1.00]	77%	0.94 [0.86–0.99]	80%
'There is a **50%** chance that the RR is 0.91 and lies between 0.85 and 0.96'	0.96 [0.86–1.00]	44%	0.95 [0.86–1.00]	48%
Very optimistic prior belief				
'There is a 9**0%** chance that the RR is 0.74 and lies between 0.60 and 0.90'	0.82 [0.64–0.94]	95%	0.84 [0.67–0.94]	94%
'There is a 7**0%** chance that the RR is 0.74 and lies between 0.60 and 0.90'	0.90 [0.70–0.96]	60%	0.90 [0.75–0.98]	63%
'There is an **50%** chance that the RR is 0.74 and lies between 0.60 and 0.90'	0.94 [0.79–1.00]	56%	0.94 [0.82–1.00]	58%

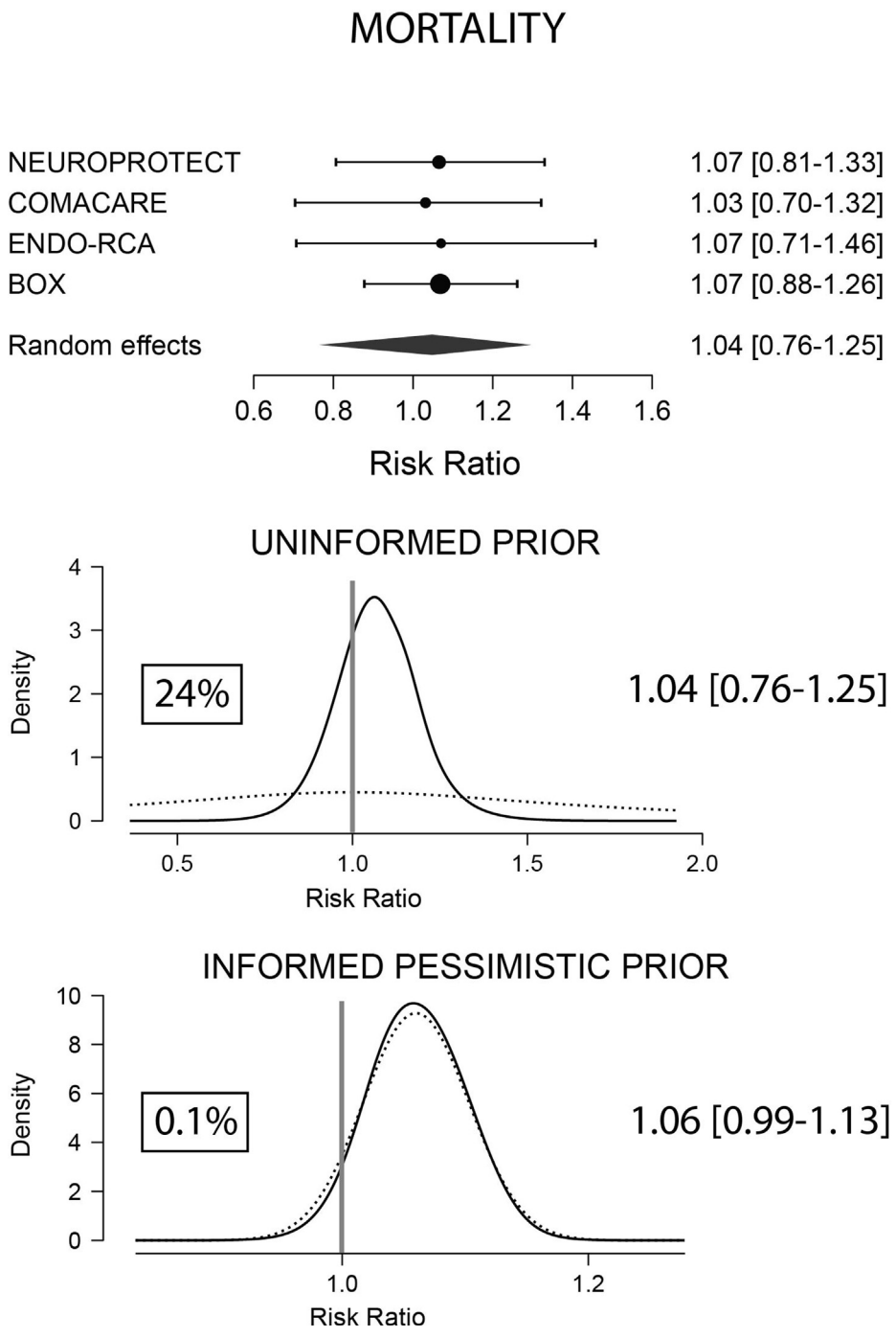

Fig. 3 – Results from the hierarchical robust Bayesian meta-analyses of mortality (Fig. 3) and unfavourable neurological outcome (Fig. 3) closest to 180 days after CA in the four studies included in the individual patient data meta-analysis. The estimated risk ratios (RRs) and their 95% confidence intervals are shown for the individual studies with the model average (top). The posterior probability distribution using an uninformed prior is shown in the middle, reflecting that all information comes from the four studies. The informed pessimistic prior, using the RR from a recent systematic review and meta-analysis effect demonstrating no benefit from targeting a higher MAP in a general, critically ill population,[35] is shown at the bottom. The posterior risk ratios and credible intervals are given to the right of the graphs, with the posterior chances as percentages of achieving at least an RR < 0.95 given to the left of the graphs in boxes.

than in studies so far is needed to achieve discernible clinical effects. The BOX trial results did not indicate any adverse effects from a MAP of 77 mmHg, with almost half the study cohort comprised of patients with ST-elevation myocardial infarction.[2] Previous feasibility studies support targets of up to 90 mmHg as safe, with favourable effects on neurological and cardiac biomarkers.[21] The upcoming

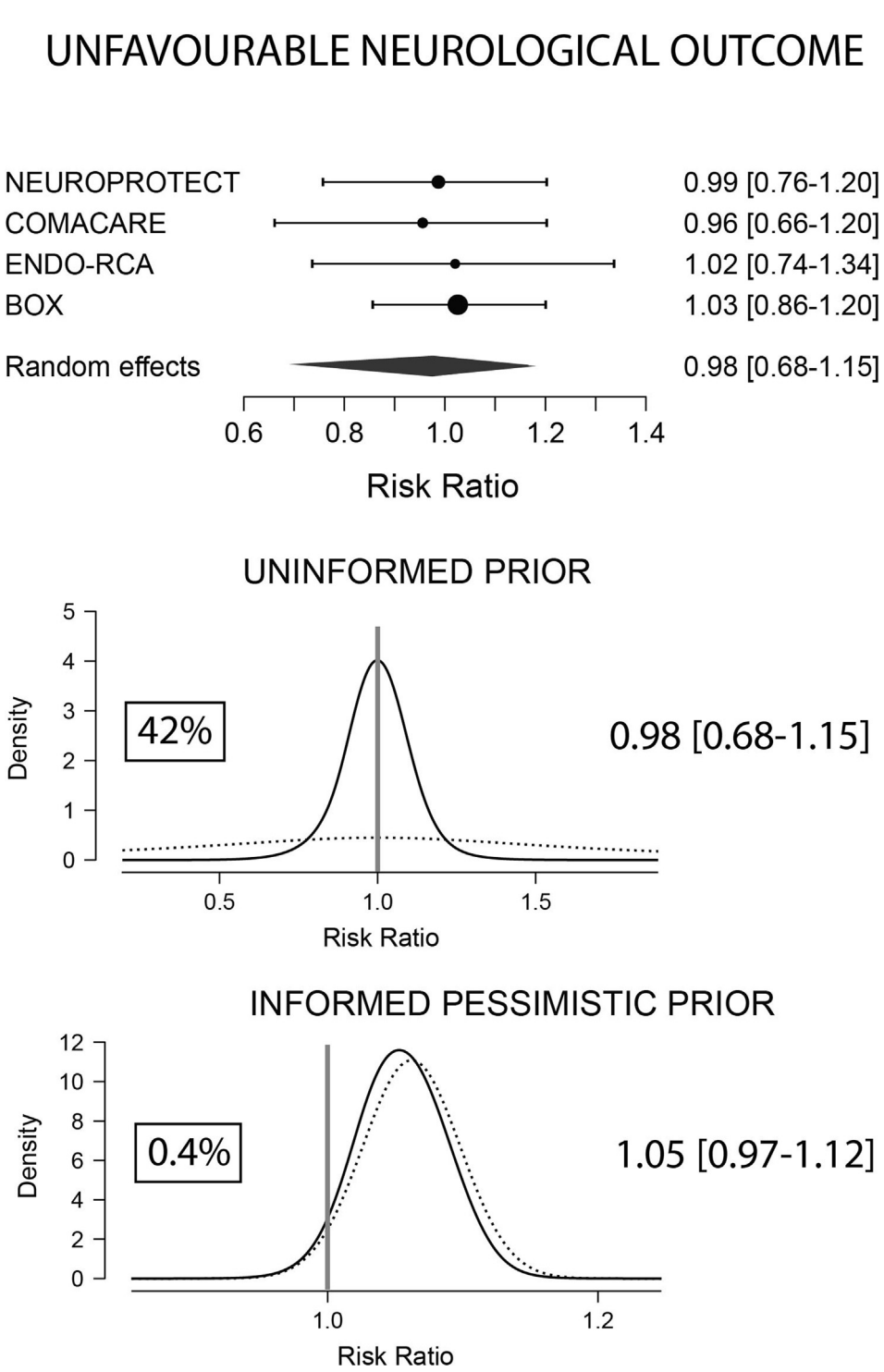

Fig. 4 – Results from the hierarchical robust Bayesian meta-analyses of mortality (Fig. 3) and unfavourable neurological outcome (Fig. 3) closest to 180 days after CA in the four studies included in the individual patient data meta-analysis. The estimated risk ratios (RRs) and their 95% confidence intervals are shown for the individual studies with the model average (top). The posterior probability distribution using an uninformed prior is shown in the middle, reflecting that all information comes from the four studies. The informed pessimistic prior, using the RR from a recent systematic review and meta-analysis effect demonstrating no benefit from targeting a higher MAP in a general, critically ill population,[35] is shown at the bottom. The posterior risk ratios and credible intervals are given to the right of the graphs, with the posterior chances as percentages of achieving at least an RR < 0.95 given to the left of the graphs in boxes.

STEPCARE trial (NCT05564754) will investigate the effects of an increased MAP target to >85 mmHg compared to >65 mmHg using all-cause mortality at six months as the primary outcome. This trial's sample size will also allow for hypothesis-generating subgroup analyses including studies of CVAR in relation to MAP targets. These results should help clarify how CVAR differs during the reperfusion and dysregulation phases of post-CA brain injury. The optimal MAP regarding cerebral perfusion is likely to depend on pre-morbid and morbid patient characteristics and the temporal course following CA. A multicentre observational study of 269 patients reported an average MAP > 90 mmHg over the first six hours following ROSC to be independently associated with good neurological function (mRS $\leq$ 3) at hospital discharge.[13] A similar time-dependent course of rSO_2 was observed in a recent multicentre, prospective observational study of in-hospital CA patients where an increased rSO_2 (73% vs 66% rSO_2) in the first two hours of ICU admission was associated with favourable neurological outcome (CPC 1–2) at hospital discharge.[47] It therefore appears reasonable that clinical trials need to encompass dynamic MAP targets rather than a set minimum MAP level that remains the same throughout all post-CA care.

As a corollary from increased MAP, diastolic pressure is likely to increase with augmented coronary perfusion pressure. In a prospective observational study of 1371 comatose CA patients admitted to the ICU with retrospective collection of haemodynamic data, the strength of the association between diastolic pressure and poor neurological outcome (CPC 3–5) surpassed that of systolic pressure and MAP.[48] The addition of heart rate to identify patients with a longer diastolic time further enhanced the predictive power of diastolic pressure. Targeted diastolic pressure as part of a higher MAP approach warrants further clinical investigation.

The Bayesian meta-analysis we have briefly reported included 1065 patients from three feasibility studies and one RCT. The probability based on these study results of achieving a greater than 5% reduction of the RR by using a higher compared to a lower MAP had a posterior probability of <50%. Importantly, these results also indicate a non-negligible risk of an increased risk of adverse outcomes that equally needs to be considered. Extrapolating the lack of benefit from targeting a higher MAP in critically ill patients in general, which was included in the informed prior, would strongly argue against this strategy in post-CA care with an inappreciable chance of benefit. While caution must be exercised before deviating from the current guideline recommendation of MAP > 65 mmHg, it is important to recognise future trials' particular design features. Differences in study cohorts, eligibility criteria, interventions and estimates of treatment effects are all conducive to contributing new and valuable evidence. The optimistic priors reflecting the design of recent and upcoming RCTs support further investigation, even when applying a measured prospect of success. This argument is advanced further if a treatment effect of 2% is accepted, which has been reported as a minimal clinically important difference in post-CA care.[49]

Conclusion

Currently, little evidence supports use of a higher MAP target than the 65 mmHg guideline recommendation. Pathophysiological reasoning and feasibility data argue that a higher MAP target has potential clinical value, although the largest RCT to date did not demonstrate benefit with this approach. Current clinical trials will add important evidence to this area.

CRediT authorship contribution statement

Markus B. Skrifvars: Conceptualization, Writing – original draft, Methodology, Writing – review & editing. **Koen Ameloot:** Writing – review & editing, Writing – original draft, Conceptualization. **Anders Åneman:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Markus Skrifvars reports having received speaker's fees from BARD Medical (Ireland). Markus Skrifvars a member of the editorial board of the journal Resuscitation. Anders Åneman and Koen Ameloot declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109886.

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