Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

Higher versus lower blood pressure targets after cardiac arrest: Systematic review with individual patient data meta-analysis

Ville Niemelä[a], *Faiza Siddiqui*[b], *Koen Ameloot*[c,d,e], *Matti Reinikainen*[f], *Johannes Grand*[g], *Johanna Hästbacka*[h], *Christian Hassager*[g], *Jesper Kjaergaard*[g], *Anders Åneman*[i], *Marjaana Tiainen*[j], *Niklas Nielsen*[k,l,m], *Markus Harboe Olsen*[b,o], *Caroline Kamp Jorgensen*[b,r], *Johanne Juul Petersen*[b], *Josef Dankiewicz*[n], *Manoj Saxena*[p,q], *Janus C. Jakobsen*[b,r], *Markus B. Skrifvars*[s,*]

Abstract

Purpose: Guidelines recommend targeting mean arterial pressure (MAP) > 65 mmHg in patients after cardiac arrest (CA). Recent trials have studied the effects of targeting a higher MAP as compared to a lower MAP after CA. We performed a systematic review and individual patient data meta-analysis to investigate the effects of higher versus lower MAP targets on patient outcome.

Method: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, LILACS, BIOSIS, CINAHL, Scopus, the Web of Science Core Collection, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry, Google Scholar and the Turning Research into Practice database to identify trials randomizing patients to higher (≥71 mmHg) or lower (≤70 mmHg) MAP targets after CA and resuscitation. We used the Cochrane Risk of Bias tool, version 2 (RoB 2) to assess for risk of bias. The primary outcomes were 180-day all-cause mortality and poor neurologic recovery defined by a modified Rankin score of 4–6 or a cerebral performance category score of 3–5.

Results: Four eligible clinical trials were identified, randomizing a total of 1,087 patients. All the included trials were assessed as having a low risk for bias. The risk ratio (RR) with 95% confidence interval for 180-day all-cause mortality for a higher versus a lower MAP target was 1.08 (0.92–1.26) and for poor neurologic recovery 1.01 (0.86–1.19). Trial sequential analysis showed that a 25% or higher treatment effect, i.e., RR < 0.75, can be excluded. No difference in serious adverse events was found between the higher and lower MAP groups.

Conclusions: Targeting a higher MAP compared to a lower MAP is unlikely to reduce mortality or improve neurologic recovery after CA. Only a large treatment effect above 25% (RR < 0.75) could be excluded, and future studies are needed to investigate if relevant but lower treatment effect exists. Targeting a higher MAP was not associated with any increase in adverse effects.

Keywords: Cardiac arrest, Target, Blood pressure, Meta-analysis, Systematic review

Introduction

Hypoxic brain injury is the leading cause of death in patients admitted to intensive care unit (ICU) after out-of-hospital cardiac arrest (OHCA) and neurological impairment is common in patients discharged from hospital.[1,2] Current guidelines recommend targeting mean arterial pressure (MAP) > 65 mmHg during post-CA resuscitation in the ICU.[3] This recommendation is based largely on observational data. Higher MAP can potentially alleviate secondary brain injury by increasing cerebral perfusion pressure.[4] Some preliminary evidence suggests that a higher MAP target after OHCA could also reduce myocardial injury.[5] Maintenance of higher MAP after CA in ICU is feasible,[6–8] but higher vasopressor doses may be needed to achieve a higher MAP, which may lead to adverse effects such as arrhythmia, increased myocardial oxygen consumption and impaired microcirculation.[9–11] If fluid resuscitation is used to achieve

* Corresponding author at: Meilahti Hospital (MEM2B), Haartmaninkatu 9, 00290 HUS, Helsinki, Finland.
E-mail address: markus.skrifvars@hus.fi (M.B. Skrifvars).

https://doi.org/10.1016/j.resuscitation.2023.109862
Received 11 April 2023; Received in Revised form 23 May 2023; Accepted 25 May 2023

higher MAP,[12] it can lead to fluid accumulation, resulting in hypoxia and prolonged mechanical ventilation.[13]

The recent BOX trial[8] is the first large trial to investigate mortality and neurological recovery between a higher and a lower blood pressure target after cardiac arrest (CA). It did not demonstrate a benefit by the higher MAP target. This trial's major strength is its blinding of the treating personnel to the MAP difference. The achieved difference in mean MAP between groups was 11 mmHg when the lower target was 63 mmHg, and the higher target was 77 mmHg. Trials are planned to investigate whether a MAP higher than 77 mmHg could convey benefit on patient-centred clinical outcomes.[14]

At least three pilot studies[6,7,15] and one larger study[8] have compared a higher and a lower MAP target after CA. We conducted a systematic review and individual patient data meta-analysis to compare the effects of targeting a higher or a lower MAP in CA patients. This review could inform future clinical guidelines and trials on optimal blood pressure in OHCA patients.

Methods

Our predefined methodology has been described in detail previously.[16] We included trials randomizing adults with CA after return of spontaneous circulation (ROSC) in an ambulance, emergency department and/or ICU. Trials were included irrespective of design, setting, blinding, publication status, publication year and reported outcomes. The experimental intervention was a MAP target $\geq$71 mmHg, and the control intervention was a MAP target of $\leq$70 mmHg.

The primary outcomes were all-cause mortality and poor functional outcome, defined as a modified Rankin scale (mRS) of 4–6 or cerebral performance category (CPC) scale 3–5.[17] The primary outcomes were assessed at the timepoint closest to 180 days from randomization. The secondary outcomes were ICU mortality, health-related quality of life, new arrhythmia resulting in haemodynamic compromise, hospital-free days within 30 days, and serious adverse events (ICH-GCP).[18]

We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (Ovid, 1946-); Embase (Ovid, 1980-); LILACS (Bireme, 1982-); BIOSIS (Thomson Reuters, 1926-); CINAHL (EBSCO Publishing, 1961-); Scopus (Elsevier, 1788-); Web of Science Core Collection (Clarivate, 1900-); ClinicalTrials.gov (https://clinicaltrials.gov); the World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/); Google Scholar (https://scholar.google.com/); and The Turning Research into Practice (TRIP) database (https://www.tripdatabase.com/). We also searched manually the reference lists of the included randomized clinical trials and relevant reviews. Two independent authors (VN and CKJ) screened the full text of the retrieved articles. Two independent authors working in pairs (FS, JCJ and JJP, CKJ) extracted the data. Any disagreement concerning the extracted data was resolved by discussion with a third author (NN or JCJ). Authors involved in any included trial neither extracted data nor assessed the risk of bias in those trials. Individual patient data were requested from the investigators of the included trials.

The bias assessment was based on the Cochrane Risk of Bias tool, version 2,[19] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence associated with each outcome.[20]

Statistical analysis

Two independent statisticians (MHO and JCJ) performed all the statistical analyses using R version 4.2.1 (R core team, Vienna, Austria) and Stata version 17 (StataCorp LLC, Texas).

Individual patient data meta-analysis

All outcomes were analysed on an intention-to-treat basis. Six primary and secondary outcomes were predefined, but we decided also to conduct one post-hoc analysis based on the individual patient data data received. Therefore given these seven outcomes we defined an adjusted two-sided p value <0.013 as the threshold for statistical significance.[21]

Dichotomous outcomes in the two treatment groups were compared using multivariable logistic regression modelling, adjusting for site as a random intercept. We calculated 95% confidence intervals (CI) for relative risks using the nlcom-command in Stata or G-computation in R. Continuous outcomes were analysed using linear regression, adjusting for the baseline value of the dependent variable (if available) and trial site as a random intercept. Comparisons were made between time to ROSC < 25 minutes or $\geq$25 minutes based on subgroups from large OHCA trial.[22]

Missing data were handled according to the recommendations by Jakobsen et al.[23] Use of multiple imputations or best-worst/worst-best scenarios were not needed. We systematically assessed the underlying statistical assumptions for all the statistical analyses.[24,25]

Meta-analysis of aggregate data

Meta-analyses of aggregate data were performed according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions[20] as supplementary analyses. Both fixed and random effects models were run on all outcomes and more conservative results are reported. Statistical heterogeneity was assessed using forest plots (visual inspection), the chi-square test (threshold $p < 0.10$), and the I^2 statistic. Substantial heterogeneity was explored through sensitivity and subgroup analyses.

Trial sequential analysis

We performed trial sequential analysis (TSA) (Copenhagen Trial Unit; http://www.ctu.dk/tsa/)[26] to account for the risk of random errors. For dichotomous outcomes, we anticipated a relative risk reduction of 25% (RR < 0.75), an alpha of 5%, and a beta of 10%.

Results

We included four randomized trials with a total of 1,087 participants and obtained individual patient data from three trials with total of 276 participants (Fig. 1 and Table 1). The higher MAP group included 546 and the lower MAP group included 541 participants. The main results of the included trials are presented in Table 1. The baseline characteristics of the participants from the individual patient data are summarised in Appendix A, p.3. All trials were assessed as having a low risk of bias.[6–8,15] (Appendix B). The COMACARE trial[6] randomized 123 participants between lower MAP (65–75 mmHg) and higher MAP (80–100 mmHg) target groups, Neuroprotect trial[7] randomized 112 participants between lower MAP (65 mmHg) and higher MAP (85–100 mmHg) target groups, ENDO-RCA trial[15] randomized 50 participants between lower MAP (65 mmHg) and higher MAP (72 mmHg) target groups and BOX trial randomized 802 participants between lower MAP (63 mmHg) and higher MAP (77 mmHg) target

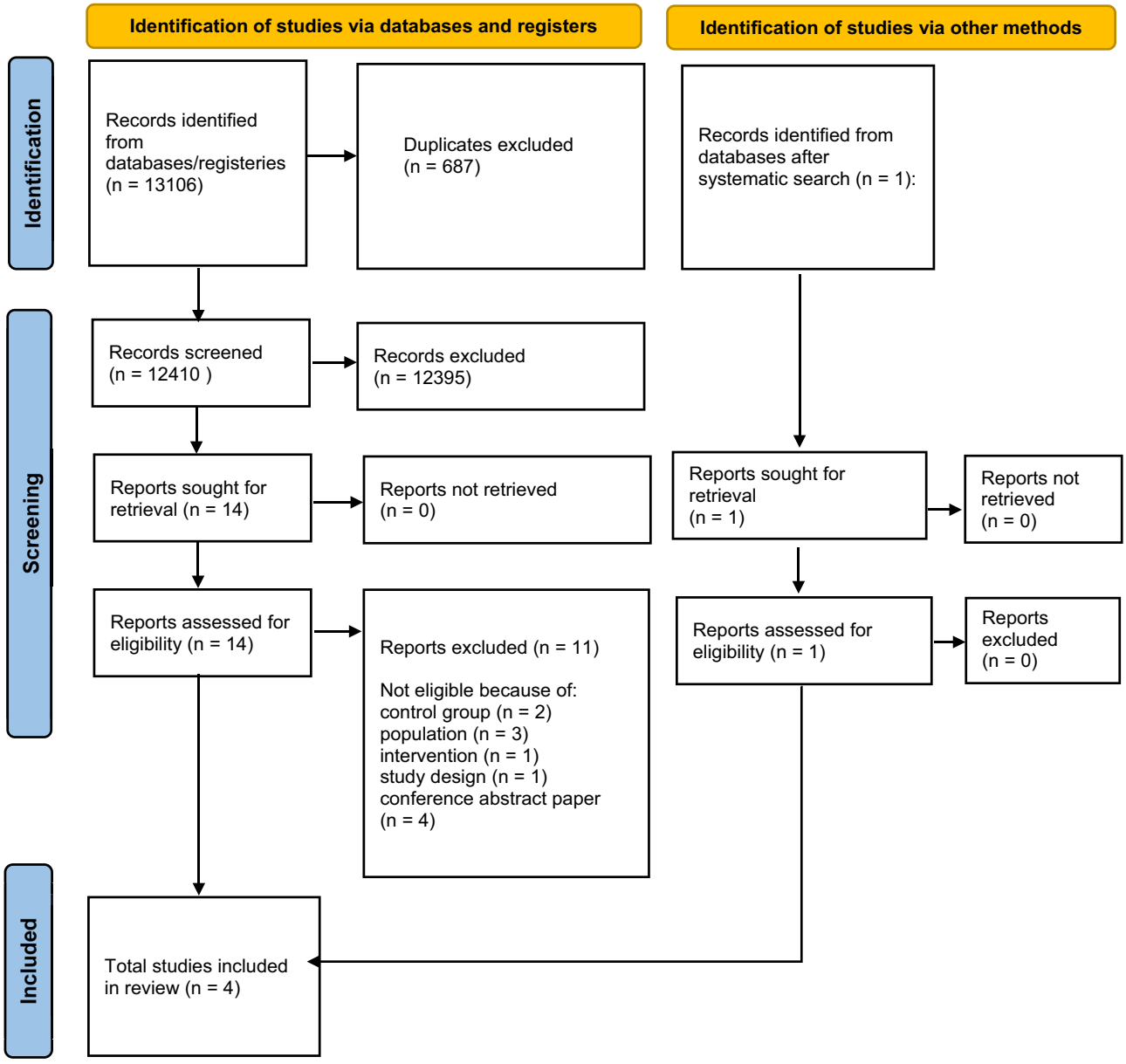

Fig. 1 – PRISMA flow chart.

groups. Amount of missing data was negligible with the exception of 90-day mortality for which missing data was excessive and individual patient data meta-analysis was discarded. We have reported results for aggregate data and individual patient data meta-analyses separately because individual patient data was not available from all trials.

Primary outcome

180-day all-cause mortality

A total of 195 (36.9%) of 528 participants died in the high MAP group compared with 185 (34.4%) of 537 participants in the low MAP group. Mixed-model logistic regression of individual patient data showed no evidence of a difference in 180-day all-cause mortality (risk ratio [RR] = 1.05; 95% CI: 0.81–1.35; $p = 0.71$; 3 trials; Appendix A, p. 5). The aggregate data meta-analysis showed a similar result (RR = 1.08; 95% CI: 0.92–1.26; $p = 0.37$, $I^2 = 0.00\%$: 4 trials; Fig. 2A). Visual inspection of the forest plot and measures to quantify heterogeneity (between-site variance 0.27, 95% CI: 0.05–1.51, likelihood ratio test for site; $p = 1.00$, $I^2 = 0.00\%$) indicated no noteworthy heterogeneity. The TSA showed sufficient information to reject a reduction in the relative risk of death by 25% with a high MAP target Fig. 2B) and insufficient information to reject an effect of 20%. This outcome result was at low risk of bias (Appendix B), and the evidence certainty was moderate (Table 2). The test of interaction comparing the participants with time to ROSC < 25 minutes ($n = 189$) versus time to ROSC ≥ 25 minutes ($n = 76$) showed evidence of a difference (individual patient data test of interaction: $p = 0.02$, Appendix A, p. 25). Mixed-model logistic regression including only the participants with time to ROSC < 25 minutes showed no evidence of a difference in 180-day all-cause mortality (RR 0.86; 95% CI: 0.63–1.15; $p = 0.62$; Appendix A, p. 31). Mixed-model logistic regression including only the participants with time to ROSC ≥ 25 minutes ($n = 76$) showed evidence of increased mortality of a high MAP target on 180-day all-cause mortality (RR 1.74; 95% CI: 1.05–3.32; $p = 0.02$; 3 trials; Appendix A, p. 31). No other tests of interaction

Table 1 – Main results of randomized trials.

Trial	Neuroprotect	COMACARE	ENDO RCA	BOX
Number randomized to HMAP and LMAP groups	HMAP group 56 LMAP group 56 Total 112	HMAP group 63 LMAP group 60 Total 123	HMAP group 24 LMAP group 26 Total 50	HMAP group 403 LMAP group 399 Total 802
Individual patient data available	Yes	Yes	Yes	No
Overall risk of bias	Low	Low	Low	Low
MAP targets	LMAP target 65 and HMAP target 85–100 mmHg	LMAP target 65–75 and HMAP target 80–100 mmHg	LMAP target 65 and HMAP target 72 mmHg	LMAP target 63 and HMAP target 77 mmHg
180-day all-cause mortality	31/52 (59.6%) in HMAP group vs. 30/55 (54.5%) in LMAP group	18/60 (30%) in HMAP group vs. 20/60 (33.3%) in LMAP group	10/23 (43.5%) in HMAP group vs. 7/26 (27%) in LMAP group	122/393 (31.0%) in HMAP group vs. 114/396 (28.8%) in LMAP group
CPC good outcome	21/52 (40.4%) in HMAP group vs. 21/55 (38.2%) in LMAP group	41/60 (68.3%) in HMAP group vs. 37/60 (61.6%) in LMAP group	10/23 (43.5%) in HMAP group vs. 13/26 (50%) in LMAP group	248/393 (63.1%) in HMAP group vs. 257/396 (64.9%) in LMAP group
Composite outcome: arrhythmia or cardiac arrest	6/52 (11.5%) in HMAP group vs. 16/55 (29.1%) in LMAP group	10/60 (16.7%) in HMAP group vs. 7/59 (11.9%) in LMAP group	N/A	59/393 (15%) in HMAP group vs. 50/396 (12.6%) in LMAP group
New arrhythmia	7/52 (13.5%) in HMAP group vs. 13/55 (23.6%) in LMAP group	4/60 (6.7%) in HMAP group vs. 2/59 (3.4%) in LMAP group	0/23 (0%) in HMAP group vs. 0/26 (0%) in LMAP group	59/393 (15%) in HMAP group vs. 50/396 (12.6%) in LMAP group
Intensive care unit mortality	29/52 (55.8%) in HMAP group vs. 27/55 (49.1%) in LMAP group	17/60 (28.3%) in HMAP group vs. 18/60 (30%) in LMAP group	7/23 (30.4%) in HMAP group vs. 6/26 (23.1%) in LMAP group	N/A
Acute kidney injury	14/52 (27%) in HMAP group vs. 19/55(34.5%) in LMAP group	3/60 (5%) in HMAP group vs. 4/60 (6.6%) in LMAP group	6/23 (26.1%) in HMAP group vs. 8/26 (30.7%) in LMAP group	N/A

HMAP: higher mean arterial pressure, LMAP: lower mean arterial pressure, CPC: cerebral performance category.

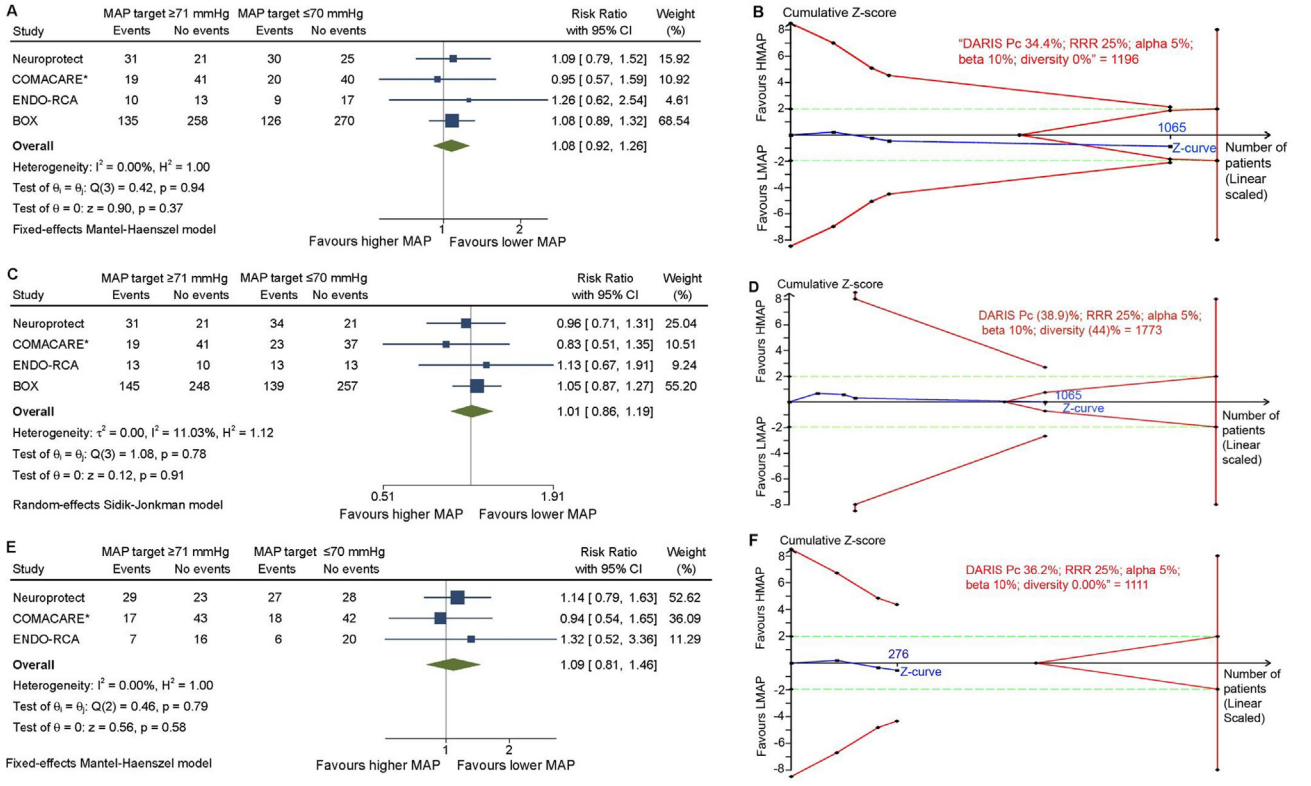

Fig. 2 – Meta-analyses (MA) and trial sequential analyses (TSA) of outcomes. MA and TSA of higher versus lower MAP on 180-day all-cause mortality (A, B), MA and TSA on higher versus lower MAP on functional outcome (C, D), MA and TSA on higher versus lower MAP on ICU mortality (E, F). *Lower MAP target 65–75 mmHg, DARIS: diversity adjusted required information size, RRR: relative risk reduction, HMAP: higher mean arterial pressure, LMAP: lower mean arterial pressure.

showed evidence of a difference (Appendix A, pp. 28, 30 & 31). The interaction between ROSC and shockable rhythm was highly significant ($p = 0.0007$; Appendix A, pp. 32 & 33). In the subgroup analysis for shockable rhythm and ROSC $\geq$ 25 min, the direction of interaction favoured the control group (RR 2.03; 95% CI: 1.20–4.23; $p = 0.02$; Appendix A, p. 33). In the subgroup analysis of shockable rhythm and ROSC < 25 min the interaction was not significant (RR 0.92; 95% CI: 0.64–1.26; $p = 0.73$; Appendix A, p. 33).

Poor functional outcome

A total of 208 (39.4%) of 528 participants had a poor functional outcome in the higher MAP group vs. 209 (38.9%) of 537 participants in the lower MAP group. All trials assessed this outcome at 180 days after randomization using the CPC scale. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in poor functional outcome (RR = 0.94; 95% CI: 0.74–1.18; $p = 0.59$; 3 trials; Appendix A, p. 7). Meta-analysis of the aggregate data showed a similar result (RR 1.01; 95% CI: 0.86–1.19; $p = 0.91$, $I^2 = 11.03\%$: 4 trials; Fig. 2C). Visual inspection of the forest plot and measures to quantify heterogeneity (between-site variance 0.26, 95% CI: 0.05–1.29, likelihood ratio test for site; $p = 1.00$, $I^2 = 11.03\%$) indicated no noteworthy heterogeneity. The TSA showed sufficient information to reject a reduction in the relative risk of poor functional outcome by 25% with a high MAP target (Fig. 2D). This outcome result was at low risk of bias (Appendix B) with moderate evidence certainty (Table 2). None of the subgroup analyses showed evidence of a difference (Appendix A, p. 28).

Secondary outcomes

Serious adverse events

Serious adverse events in the individual patient data included 180-day mortality, new CA in ICU, composite outcome of arrhythmia or CA, allergic reaction, thrombo-embolic event and bleeding, limb ischaemia, acute respiratory distress syndrome, brain oedema and severe hypercapnia. A total of 69 (51.1%) of 135 participants experienced a serious adverse event in the high MAP group vs. 71 (50.4%) of 141 participants in the low MAP group. All serious adverse events, except for 180-day mortality, were assessed during the ICU stay after randomization in all trials. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in serious adverse events (RR = 1.01; 95% CI: 0.81–1.28; $p = 0.89$; 3 trials; Appendix A, p. 12). Measures to quantify heterogeneity (likelihood ratio test for site; $p = 1.00$) indicated no heterogeneity. No subgroup analyses showed evidence of a difference (Appendix A, p. 30).

ICU mortality

A total of 53 (39.2%) of 135 participants died in the ICU in the higher MAP group vs. 51 (36.2%) of 141 participants in the lower MAP group. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in ICU mortality (RR = 1.08; 95% CI: 0.82–1.45; $p = 0.60$; 3 trials; Appendix A, p. 8). Meta-analysis of the aggregate data showed a similar result (RR 1.09; 95% CI: 0.81–1.46; $p = 0.58$, $I^2 = 0.00\%$: 3 trials; Fig. 2E). Visual inspection of the forest plot and measures to quantify heterogeneity (between-site

Table 2 – Summary of findings.

MAP targets ≥71 mmHg compared to MAP target of ≤70 mmHg in cardiac arrest patients

Patient or population: cardiac arrest patients **Setting:** **Intervention:** MAP targets ≥71 mmHg **Comparison:** MAP target of ≤70 mmHg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with MAP target of ≤70 mmHg	Risk with MAP targets ≥71 mmHg			
180-day all-cause mortality	345 per 1.000	**372 per 1.000** (317–434)	**RR 1.08** (0.92–1.26)	1065 (4 RCTs)	⊕⊕⊕○ Moderate[a]
Poor functional outcome (CPC 3-5)	389 per 1.000	**393 per 1.000** (335–463)	**RR 1.01** (0.86–1.19)	1065 (4 RCTs)	⊕⊕⊕○ Moderate[a]
Composite outcome: arrhythmia and cardiac arrest	143 per 1.000	**149 per 1.000** (110–200)	**RR 1.04** (0.77–1.40)	1015 (3 RCTs)	⊕○○○ Very low[a,b]
ICU mortality	362 per 1.000	**394 per 1.000** (293–528)	**RR 1.09** (0.81–1.46)	286 (3 RCTs)	⊕○○○ Very low[a,b]
New arrythmia resulting in hemodynamic compromise	140 per 1.000	**129 per 1.000** (66–251)	**RR 0.92** (0.47–1.80)	896 (2 RCTs)	⊕○○○ Very low[a,b]
Closest to 90-day all-cause mortality	309 per 1.000	**349 per 1.000** (275–445)	**RR 1.13** (0.89–1.44)	1065 (4 RCTs)	⊕○○○ Very low[a,b]

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[a] Downgraded 1 for for indirectness in population.

[b] Downgraded 2 for imprecision for Trial Sequential Analysis showing that there was not enough information to confirm or reject a relative risk reduction (RRR) of 20% and the accrued number of participants is below 50% of the diversity-adjusted required information size (DARIS).

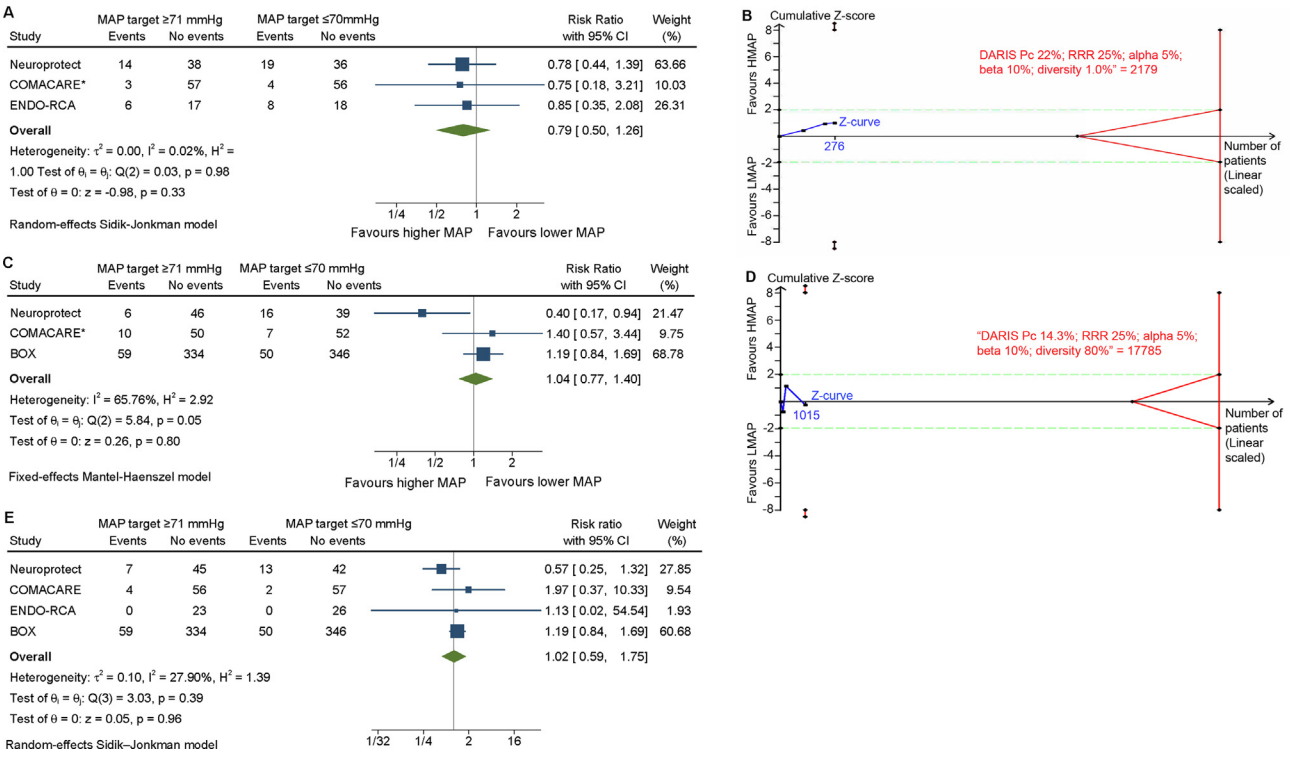

Fig. 3 – Meta-analyses (MA) and trial sequential analyses (TSA) of outcomes. MA and TSA of higher versus lower MAP on acute kidney injury (A, B), MA and TSA of higher versus lower MAP on composite outcome of arrhytmia and cardiac arrest (C, D) and MA and TSA of higher versus lower MAP on new arrhytmia causing haemodynamic compromise (E). *Lower MAP target 65–75 mmHg, DARIS: diversity adjusted required information size, RRR: relative risk reduction, HMAP: higher mean arterial pressure, LMAP: lower mean arterial pressure.

variance 0.27, 95% CI: 0.05–1.40, likelihood ratio test for site; p = 1.00, I^2 = 0.00%) indicated no noteworthy heterogeneity. The TSA showed insufficient information to confirm or reject the meta-analysis results (Fig. 2F). This outcome result was at low risk of bias (Appendix B) with very low evidence certainty (Table 2). The test of interaction comparing participants with time to ROSC < 25 minutes vs. time to ROSC ≥ 25 minutes showed evidence of a difference (individual patient data test of interaction: p = 0.004, Appendix A, p. 25). Mixed-model logistic regression including only participants with time to ROSC < 25 minutes (n = 189) showed no evidence of a difference in ICU mortality (RR 0.83; 95% CI: 0.59–1.13; p = 0.36; Appendix A, p. 31). Mixed-model logistic regression including only participants with time to ROSC ≥ 25 minutes (n = 76) showed evidence of a harmful effect of a high MAP target on 180-day all-cause mortality (RR 1.99; 95% CI: 1.23–3.71; p = 0.006; 3 trials; Appendix A, p. 31). None of the remaining tests of interaction showed evidence of a difference (Appendix A, pp. 29, 30 & 31).

New arrhythmia resulting in haemodynamic compromise

A total of 70 (13.2%) of 528 participants experienced a new arrhythmia resulting in haemodynamic compromise in the higher MAP group vs. 65 (12.1%) of 536 participants in the lower MAP group. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in new arrhythmia resulting in haemodynamic compromise (RR = 0.80; 95% CI: 0.33–1.73; p = 0.55; 3 trials; Appendix A, p. 10). Meta-analysis of the aggregate data showed a similar result (RR 1.02; 95% CI: 0.59–1.75; p = 0.96, I^2 = 27.90%: 4 trials; Fig. 3E). Visual inspection of the forest plot and measures to quantify heterogeneity (likelihood ratio test for site; p = 0.95, I^2 = 27.90%) indicated moderate heterogeneity that could not be resolved. The TSA showed insufficient information to confirm or reject the meta-analysis results (alpha-spending boundaries ignored). This outcome result was at low risk of bias (Appendix B) with very low evidence certainty (Table 2). None of the remaining tests of interaction showed evidence of a difference (Appendix A, pp. 29, 30 & 31).

Exploratory outcomes

Acute kidney injury

A total of 23 (17.0%) of 135 participants experienced acute kidney injury (KDIGO score 2–3) in the ICU in the higher MAP group vs. 31 (22%) of 141 participants in the lower MAP group. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in acute kidney injury (RR = 0.76; 95% CI: 0.43–1.31; p = 0.24; 3 trials; Appendix A, p. 13). Meta-analysis of the aggregate data showed a similar result (RR 0.79; 95% CI: 0.50–1.26; p = 0.33, I^2 = 0.02%: 3 trials; Fig. 3A). Visual inspection of the forest plot and measures to quantify heterogeneity (likelihood ratio test for site; p = 0.99, I^2 = 0.02%) indicated no noteworthy heterogeneity. The TSA showed we had insufficient information to confirm or reject the meta-analysis results (Fig. 3B). Mixed-model logistic regression of the individual patient data showed no evidence of a difference in neurofilament light (NFL) at 48 h, level of high sensitivity troponin (h-sTNT) at 12, 24, 48 and 72 h during ICU care, hospital mortality or time to extubation.

Post-hoc analysis

Composite outcome of arrhythmia or cardiac arrest

A total of 75 (14.8%) of 505 participants experienced the composite outcome of arrhythmia or CA during their ICU stay in the higher MAP group vs. 73 (14.3%) of 510 participants in the lower MAP group. Mixed-model logistic regression of the individual patient data showed no evidence of a difference in composite outcome (RR = 0.74; 95% CI: 0.42–1.27; $p = 0.31$; 2 trials; Appendix A, p. 32). Meta-analysis of the aggregate data showed a similar result (RR 1.04; 95% CI: 0.77–1.40; $p = 0.80$, $I^2 = 65.76\%$: 3 trials; Fig. 3C). Visual inspection of the forest plot and measures to quantify heterogeneity (between-site variance 0.38, 95% CI: 0.07–1.97, likelihood ratio test for site; $p = 0.34$, $I^2 = 65.76\%$) indicated substantial heterogeneity that could not be resolved. The TSA showed we had insufficient information to confirm or reject the meta-analysis results (Fig. 3D). This outcome result was at low risk of bias (Appendix B) with very low evidence certainty (Table 2).

Discussion

Here, we identified four randomized controlled trials (RCTs) comparing higher and lower MAP targets after CA. We found no differences between targeting higher or lower blood pressure in 180-day mortality (moderate certainty), neurological recovery (moderate certainty), composite outcome of arrhythmia or CA (very low certainty), ICU mortality (very low certainty) or new arrhythmia resulting in haemodynamic compromise (very low certainty). In the subgroup analysis, patients with ROSC $\geq$ 25 minutes had a tendency towards worse survival and neurologic recovery in the higher blood pressure group, but this finding should be interpreted cautiously. This review's findings do not suggest any need to deviate from the current recommendation of targeting MAP > 65 mmHg in OHCA patients. Notably, this review can only rule out a relative benefit larger than 25%. Future studies comparing higher and lower MAP targets in OHCA patients are needed.

Several observational studies that investigated associations between blood pressure and outcome after CA had mixed results.[27–31] Two US studies showed a higher likelihood of good neurological outcome in patients with a MAP > 80 mmHg during the first 24 h post-CA.[27,31] These findings appeared independent of vasopressor need. Other observational studies failed to show such an association.[28,30] Based on this review, the treatment effects suggested by these observational studies appear implausible. A realistic treatment effect of any intervention to improve outcome after CA is likely much smaller.

Findings from this meta-analysis are in line with a meta-analysis of the effects of higher and lower MAP in other critically ill populations.[32] A meta-analysis of 3,690 ICU patients with shock showed that a higher MAP target did not affect the risk of mortality, acute kidney injury (AKI) or need for renal replacement therapy (RRT). The meta-analysis did, however, find a decrease in RRT need in patients with a history of chronic hypertension who were treated with a higher MAP target.[32] We found no such association, possibly due to lack of power. Severe AKI appears uncommon in ICU-treated OHCA patients and is more common in in-hospital-cardiac arrest patients.[33,34] Another meta-analysis investigating the effects of MAP targets in vasodilatory shock likewise showed no mortality difference.[35] Conversely, neither that review nor our review found signal for harm from targeting a higher MAP with regards to adverse effects such as digital or mesenteric ischaemia or any difference in cardiac arrhythmias resulting in hemodynamic compromise. However, higher incidence of supraventricular tachycardias with a higher MAP target was demonstrated in vasodilatory shock.[35] We analysed only the prevalence of arrhythmias causing haemodynamic compromise (i.e., VF/VT) and found no difference. Only one study in our meta-analysis reported an incidence of new onset atrial fibrillation, which was 0% in the higher and 7 % in the lower MAP group.[7]

A higher MAP target has been considered beneficial for CA and critically ill patients with a history of hypertension.[36] This could be due to a right shift in cerebral autoregulation, meaning that a higher MAP is needed to maintain sufficient blood flow. Conversely, a large RCT demonstrated a signal of lower mortality in elderly patients with distributive shock in a lower MAP group vs. a higher one.[37] This is surprising, as chronic hypertension tends to be more common in the elderly.[38]

The main cause of death in CA patients is brain injury, and therefore these patients are different from most other types of critically ill patients.[2] Whether a higher MAP could alleviate brain injury is currently unclear. In the COMACARE pilot trial, a higher MAP for 36 h did not decrease the level of neuron specific enolase at 48 h.[6] Similar findings came from the Neuroprotect and BOX trials.[7,8] Post-hoc analyses of the COMACARE and Neuroprotect trials did, however, show lower levels of the axonal injury marker, neurofilament light chain, and troponin, but these findings should be interpreted cautiously.[5,39] Importantly, most patients included in these RCTs had CA with a likely cardiac cause. This group has generally good outcomes, and more studies on targeting a higher MAP but with other CA causes are needed.

Strengths and limitations

To our knowledge, this is the first systematic review and individual patient data meta-analysis on blood pressure targets in CA patients. We conducted this study according to a previously published protocol, searched all the significant databases, included individual patient data if available, conducted TSA and included only randomized controlled trials.

We acknowledge the following weaknesses and limitations in this study. Although we predefined control and intervention group MAP target ranges, they varied between studies, and in two included studies[6,15] the higher and lower MAP target ranges were overlapping. In one included trial[6] the limit for lower MAP target range (75 mmHg) was higher than our prespecified MAP limit ($\leq$70 mmHg)[16] for lower MAP group. We decided to include this trial[6] as it compares higher and lower MAP targets. These issues may have influenced the results. Second, we had insufficient data to rule out less than a 25% relative risk reduction, which would still be clinically significant. Third, although we assessed all trials to be at low risk of bias, three of four trials were unblinded which could be of some concern.

Conclusion

Targeting a higher MAP than the currently recommended >65 mmHg does not decrease mortality or increase the proportion of patients with good neurological outcome. Current evidence can only rule out relative treatment effects of more than 25%. A higher and lower MAP target did not seem to result in any difference in adverse events.

CRediT authorship contribution statement

Ville Niemelä: Investigation, Visualization, Writing – original draft. **Faiza Siddiqui:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Koen Ameloot:** Writing – review & editing, Methodology. **Matti Reinikainen:** Methodology, Writing – review & editing. **Johannes Grand:** Methodology, Writing – review & editing. **Johanna Hästbacka:** Methodology, Writing – review & editing. **Christian Hassager:** Methodology, Writing – review & editing. **Jesper Kjaergaard:** Methodology, Writing – review & editing. **Anders Åneman:** Methodology, Writing – review & editing. **Marjaana Tiainen:** Methodology, Writing – review & editing. **Niklas Nielsen:** Methodology, Writing – review & editing. **Markus Harboe Olsen:** Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Caroline Kamp Jorgensen:** . **Johanne Juul Petersen:** Methodology, Writing – review & editing. **Josef Dankiewicz:** Methodology, Writing – review & editing. **Manoj Saxena:** Methodology, Writing – review & editing. **Janus C. Jakobsen:** Data curation, Formal analysis, Methodology, Resources, Writing – review & editing. **Markus B. Skrifvars:** Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: '**Christian Hassager:** Research grants from Lundbeck Foundation (R186-2015-2132) and Novo Nordisk Foundation (NNF20OC0064043). **Johanna Hästbacka:** Advisory board work for Paion. **Markus Skrifvars:** Speaker fees from BARD Medical.'.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109862.

Author details

[a]*Department of Anaesthesia and Intensive Care, Helsinki University Hospital and University of Helsinki, Helsinki, Finland* [b]*Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark* [c]*Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium* [d]*Department of Cardiology, University Hospitals Leuven, Leuven, Belgium* [e]*Faculty of Medicine and Life Sciences, University Hasselt, Diepenbeek, Belgium* [f]*Department of Anaesthesiology and Intensive Care, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland* [g]*Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark* [h]*Department of Anaesthesiology and Intensive Care, Tampere University Hospital and Tampere University, Tampere, Finland* [i]*Intensive Care Unit, Liverpool Hospital, South Western Sydney Local Health District, South Western Clinical School, University of New South Wales, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia* [j]*Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland* [k]*Lund University and Department of Clinical Sciences Lund, Anaesthesia and Intensive Care, Helsingborg Hospital, Lund, Sweden* [l]*Skåne University Hospital, Clinical Studies Sweden – Forum South, Lund, Sweden* [m]*Anaesthesia and Intensive Care, Helsingborg Hospital, Lund, Sweden* [n]*Department of Clinical Sciences Lund, Cardiology, Skåne University Hospital, Lund University, Lund, Sweden* [o]*Department of Neuroanaesthesiology, The Neuroscience Centre, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark* [p]*South Western Clinical School, University of New South Wales, Sydney, Australia* [q]*Critical Care Division, The George Institute for Global Health, University of New South Wales, Sydney, Australia* [r]*Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Denmark* [s]*Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland*

REFERENCES

1. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 2013;39:1972–80.
2. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. Lancet 2021;398:1269–78.
3. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47:369–421.
4. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017;21:90.
5. Ameloot K, Jakkula P, Hastbacka J, et al. Optimum blood pressure in patients with shock after acute myocardial infarction and cardiac arrest. J Am Coll Cardiol 2020;76:812–24.
6. Jakkula P, Pettila V, Skrifvars MB, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 2018;44:2091–101.
7. Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J 2019;40:1804–14.
8. Kjaergaard J, Møller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med 2022;387:1456–66.
9. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. Eur Heart J 2019;40:2671–83.
10. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370:1583–93.
11. Grand J, Wiberg S, Kjaergaard J, Wanscher M, Hassager C. Increasing mean arterial pressure or cardiac output in comatose out-of-hospital cardiac arrest patients undergoing targeted temperature management: Effects on cerebral tissue oxygenation and systemic hemodynamics. Resuscitation 2021;168:199–205.
12. Bogaerts E, Ferdinande B, Palmers PJ, et al. The effect of fluid bolus administration on cerebral tissue oxygenation in post-cardiac arrest patients. Resuscitation 2021;168:1–5.
13. O'Connor ME, Prowle JR. Fluid overload. Crit Care Clin 2015;31:803–21.
14. https://clinicaltrials.gov/ct2/show/NCT05564754. In: Editor (ed) Book https://clinicaltrials.gov/ct2/show/NCT05564754. City, pp.
15. Grand J, Meyer AS, Kjaergaard J, et al. A randomised double-blind pilot trial comparing a mean arterial pressure target of 65 mm Hg

versus 72 mm Hg after out-of-hospital cardiac arrest. Eur Heart J Acute Cardiovasc Care 2020;9:S100–9.
16. Skrifvars MB, Ameloot K, Grand J, et al. Protocol for an individual patient data meta-analysis on blood pressure targets after cardiac arrest. Acta Anaesthesiol Scand 2022;66:890–7.
17. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: An advisory statement from the international liaison committee on resuscitation. Circulation 2018;137:e783–801.
18. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) adopts consolidated guideline on good clinical practice in the conduct of clinical trials on medicinal products for human use. Int Dig Health Legis 2019;48:231–34.
19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366 l4898.
20. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:Ed000142.
21. Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance - a five-step procedure for evaluation of intervention effects in randomised clinical trials. BMC Med Res Methodol 2014;14:34.
22. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384:2283–94.
23. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol 2017;17:162.
24. Nielsen EE, Nørskov AK, Lange T, et al. Assessing assumptions for statistical analyses in randomised clinical trials. BMJ Evid Based Med 2019;24:185–9.
25. Nørskov AK, Lange T, Nielsen EE, et al. Assessment of assumptions of statistical analysis methods in randomised clinical trials: the what and how. BMJ Evid Based Med 2021;26:121–6.
26. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;61:64–75.
27. Beylin ME, Perman SM, Abella BS, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive Care Med 2013;39:1981–8.
28. Bro-Jeppesen J, Annborn M, Hassager C, et al. Hemodynamics and vasopressor support during targeted temperature management at 33 degrees C Versus 36 degrees C after out-of-hospital cardiac arrest: a post hoc study of the target temperature management trial*. Crit Care Med 2015;43:318–27.
29. Grand J, Hassager C, Winther-Jensen M, et al. Mean arterial pressure during targeted temperature management and renal function after out-of-hospital cardiac arrest. J Crit Care 2019;50:234–41.
30. Laurikkala J, Wilkman E, Pettila V, et al. Mean arterial pressure and vasopressor load after out-of-hospital cardiac arrest: Associations with one-year neurologic outcome. Resuscitation 2016;105:116–22.
31. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between elevated mean arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest: Results from a multicenter prospective cohort study. Crit Care Med 2019;47:93–100.
32. Carayannopoulos KL, Pidutti A, Upadhyaya Y, et al. Mean arterial pressure targets and patient-important outcomes in critically Ill adults: A systematic review and meta-analysis of randomized trials. Crit Care Med 2023;51:241–53.
33. Strand K, Soreide E, Kirkegaard H, et al. The influence of prolonged temperature management on acute kidney injury after out-of-hospital cardiac arrest: A post hoc analysis of the TTH48 trial. Resuscitation 2020;151:10–7.
34. Mah KE, Alten JA, Cornell TT, et al. Acute kidney injury after in-hospital cardiac arrest. Resuscitation 2021;160:49–58.
35. Lamontagne F, Day AG, Meade MO, et al. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. Intensive Care Med 2018;44:12–21.
36. Ameloot K, Genbrugge C, Meex I, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets? Resuscitation 2015;90:121–6.
37. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: A randomized clinical trial. Jama 2020;323:938–49.
38. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation 2015;131:e29–e322.
39. Wihersaari L, Ashton NJ, Reinikainen M, et al. Neurofilament light as an outcome predictor after cardiac arrest: a post hoc analysis of the COMACARE trial. Intensive Care Med 2021;47:39–48.