Original Article

Mean Arterial Pressure Goal in Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials

Sauradeep Sarkar[a, d], Sahib Singh[b], Amit Rout[c]

Abstract

Background: Current guidelines recommend targeting a mean arterial pressure (MAP) goal of 65 mm Hg or more in critically ill medical patients. Prospective studies have shown that a higher MAP goal can improve survival and decrease end-organ damage. However, randomized controlled trials (RCTs) have failed to show similar results. Thus, we performed this meta-analysis to evaluate whether a high MAP goal compared to a standard or low MAP goal will improve clinical outcomes in critically ill medical patients.

Methods: We searched electronic databases for RCTs comparing standard MAP goals versus high MAP goals in critically ill medical patients. A standard MAP goal was defined as a MAP of 60 - 70 mm Hg, and a MAP of 70 mm Hg or more was considered a high MAP goal. Outcomes of interest were mortality, duration of mechanical ventilation, and intensive care unit (ICU) length of stay. Subgroup analysis was performed based on the type of critically ill patients: cardiac arrest and septic shock. We used random-effects meta-analysis to estimate risk ratio (RR) with a 95% confidence interval (CI) for a dichotomous outcome. For continuous outcomes, the inverse variance method was used to calculate the standardized mean difference (SMD) with 95% CI. A P value of 0.05 or less was considered significant.

Results: Six RCTs with a total of 3,753 patients (standard MAP goal: n = 1,872 and high MAP goal: n = 1,881) were included in the final analysis. Both standard/low MAP goal and high MAP goal were associated with similar risk for mortality (RR 0.94, 95% CI (0.87, 1.01), P = 0.11), duration of mechanical ventilation (SMD 0.51, 95% CI (-0.29, 1.31), P = 0.21) and ICU length of stay (SMD 0.22, 95% CI (-0.07, 0.5), P = 0.14). Subgroup analysis in cardiac arrest patient showed decreased ICU stay (SMD 0.55, 95% CI (0.31, 0.80), P < 0.000001) in patients with higher MAP goal compared to the stand-

ard MAP goal group without any difference in mortality or duration of mechanical ventilation. Subgroup analysis of patients with septic shock had similar outcomes in both MAP targets.

Conclusions: In critically ill patients, a higher MAP goal of > 70 mm Hg was associated with a similar risk of mortality, duration of mechanical ventilation, and ICU length of stay when compared with a standard MAP goal of 60 - 70 mm Hg.

Keywords: Mean arterial pressure; Septic shock; Cardiac arrest

Introduction

Septic shock or vasodilatory shock and post-cardiac arrest patients contribute to the majority of critically ill patients in the medical intensive care unit (ICU). The current surviving sepsis guidelines recommend targeting a mean arterial pressure (MAP) of 65 mm Hg with no benefit of targeting a higher MAP in septic shock patients [1]. Similarly, the 2010 American Heart Association guidelines recommend a MAP of more than 65 mm Hg for cardiac arrest patients [2]. However, several prospective studies have shown that targeting higher MAP goals were associated with improved neurological outcomes as well as survival among cardiac arrest patients [3-5]. Several studies have shown that a MAP greater than 70 mm Hg may avoid acute kidney injury and improve microcirculation in the setting of septic shock [6-9]. However, randomized controlled trials (RCTs) in critically ill patients so far have failed to show any benefits. We, therefore, performed this meta-analysis of all the available RCT to evaluate whether a higher MAP goal will improve outcomes in critically ill patients.

Materials and Methods

Two reviewers (SS and SS) independently searched electronic databases for RCTs comparing standard MAP goals versus a high MAP goal in critically ill medical patients. The studies were included if they met the following criteria: RCTs of adult human subjects, reporting clinical outcomes in critically ill patients who were treated with a higher MAP goal versus a standard MAP goal, reporting at least one clinical outcome of interest. The main exclusion criteria were nonrandomized control trials. A standard MAP goal was defined as a MAP of

Table 1. Baseline Characteristics of the Patients and Characteristics of Trials Included

Study (year)	N (patients[a])	Follow-up (months)	Major inclusion criteria	Major exclusion criteria	Age (years ± SD)/range	MAP target (mm Hg)
Afsar et al, 2014 (SEPSISPAM) [13]	H: 388	3	Septic shock refractory to fluid resuscitation, vasopressor use < 6 h	Pregnancy, decision not to resuscitate	H: 65 ± 13	H: 80 - 85
	S: 388				S: 65 ± 15	S: 65 - 70
Lamontagne et al, 2016 (OVATION) [14]	H: 58	1	Vasodilatory shock, adequate fluid resuscitation, vasopressor use ≥ 6 h	Vasopressors ≥ 24 h, expected to die within 48 h, other shock etiology	H: 63 ± 13	H: 75 - 80
	S: 60				S: 66 ± 13	S: 60 - 65
Lamontagne et al, 2020 (65 Trial) [15]	H: 1,300	3	Vasodilatory shock, adequate fluid resuscitation, vasopressor use ≥ 6 h	Vasopressors use for bleeding, cardiac failure, post-CABGs vasoplegia, brain or spinal cord injury	H: 74.8 (70.1 - 80.8)	H: > 70
	S: 1,283				S: 75.2 (70.4 - 80.5)	S: 60 - 70
Jakkula et al, 2018 (COMACARE) [17]	H: 60	6	Resuscitation after VT or VF OHCA	Intracranial pathology, severe respiratory failure	H: 58 ± 14	H: 80 - 100
	S: 60				S: 61 ± 11	S: 65 - 75
Ameloot et al, 2019 (Neuroprotect) [16]	H: 52	6	Resuscitated OHCA from presumed cardiac cause	Intracranial pathology, refractory shock on vasopressors	H: 64 ± 12	H: 85 - 100
	S: 55				S: 65 ± 13	S: 65
Grand et al, 2020 [18]	H: 23	6	Resuscitated OHCA from presumed cardiac cause	Unwitnessed OHCA asystole primary rhythm, intracranial pathology	H: 63 ± 10	H: 72
	S: 26				S: 59 ± 13	S: 65

[a])Number of patients include all the patients initially randomized in trial. H: high mean arterial pressure; S: standard mean arterial pressure; OHCA: out-of-hospital cardiac arrest; VT: ventricular tachycardia; VF: ventricular fibrillation; MAP: mean arterial pressure; SD: standard deviation; CABG: coronary artery bypass grafting.

60 - 70 mm Hg, and a MAP of 70 mm Hg or more was considered a high MAP goal. From the eligible RCTs, study characteristics including study design, year of publication, inclusion and exclusion criteria, sample size, follow-up period, baseline patient characteristics, treatment data, and clinical outcomes at the longest available follow-up were collected. Outcomes of interest were mortality, duration of mechanical ventilation, and ICU length of stay. Subgroup analysis was performed based on the type of critical care admission; cardiac arrest and septic shock/vasodilatory shock patients.

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. We used Cochrane review manager, version 5.4 RevMan for study analysis [11]. For dichotomous clinical data, pooled risk ratio (RR) and 95% confidence intervals (CIs) were calculated using the random-effects models with the Mantel-Haenszel method. For continuous variables, we computed standardized mean difference (SMD) with 95% CI using the inverse variance method. A P value of 0.05 or less was considered statistically significant. Study heterogeneity was assessed by calculating I-squared statistic; heterogeneity was considered significant in the case of $I^2 > 50\%$. Mean

and standard deviations were extrapolated from median and range using the statistical method outlined by Hozo et al [12]. Forest plots were generated to demonstrate the relative effect size of high MAP goals versus standard MAP goals for individual clinical endpoints.

The Institutional Review Board (IRB) approval was not applicable. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Six RCTs with a total of 3,753 patients (standard MAP goal: n = 1,872 and high MAP goal: n = 1,881) were included in the final study analysis [13-18]. Three studies included septic/vasodilatory shock patients [13-15], and three included post-cardiac arrest patients [16-18]. The 65 Trial (Lamontagne et al, 2020) contributed to 65% of the total study population (2,463 patients) [15]. The duration of follow-up ranged from 1 month to 6 months. Baseline patient characteristics and study inclusion and exclusion criteria are shown in Table 1 [13-18]. The
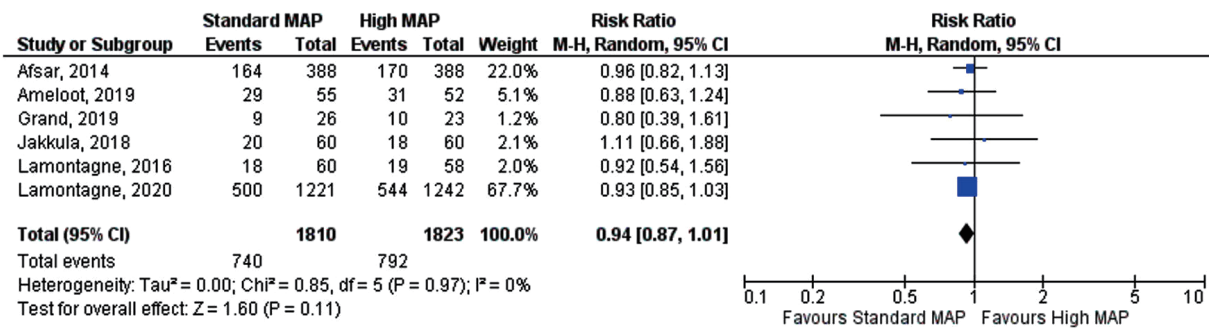
Study or Subgroup	Standard MAP Events	Total	High MAP Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Afsar, 2014	164	388	170	388	22.0%	0.96 [0.82, 1.13]
Ameloot, 2019	29	55	31	52	5.1%	0.88 [0.63, 1.24]
Grand, 2019	9	26	10	23	1.2%	0.80 [0.39, 1.61]
Jakkula, 2018	20	60	18	60	2.1%	1.11 [0.66, 1.88]
Lamontagne, 2016	18	60	19	58	2.0%	0.92 [0.54, 1.56]
Lamontagne, 2020	500	1221	544	1242	67.7%	0.93 [0.85, 1.03]
Total (95% CI)		**1810**		**1823**	**100.0%**	**0.94 [0.87, 1.01]**
Total events	740		792			

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)

Figure 1. Forest plot showing risk ratio of overall mortality. MAP: mean arterial pressure; CI: confidence interval.

mean age of the study population was 65 in both groups and almost 70% were male. All six trials reported mortality, while four trials reported the duration of mechanical ventilation, and five trials reported ICU length of stay. Out of 3,753, a total of 1,532 patients died, with 740 in the standard MAP group and 792 in the MAP group. Both standard MAP goals and high MAP goals were associated with similar risk for mortality (RR 0.94, 95% CI (0.87, 1.01), P = 0.11) with no evidence of heterogeneity between studies (I² = 0%) (Fig. 1) [13-18]. Similarly, there was no difference in the duration of mechanical ventilation (SMD 0.51, 95% CI (-0.29, 1.31), P = 0.21) (Fig. 2) [15-18], and ICU length of stay (SMD 0.22, 95% CI (-0.07, 0.5), P = 0.14) (Fig. 3) [13, 15-18], between standard MAP versus high MAP goal but with significant heterogeneity between studies.

Subgroup analysis was performed based on type of critical care admission with 3,357 patients in the septic shock subgroup and only 276 patients included in the cardiac arrest subgroup. Post-cardiac arrest patients with higher MAP goal had a lower duration of ICU stay (SMD 0.55, 95% CI (0.31, 0.80), P < 0.000001, I² = 2%) when compared to the standard MAP goal (Fig. 4) [13, 15-18]. However, both MAP goals had

similar risk of mortality (RR 0.92, 95% CI (0.71, 1.2), P = 0.55) and duration of mechanical ventilation (SMD 0.69, 95% CI (-0.31, 1.69), P = 0.21) (Figs. 5, 6) [13-18]. In patients with septic shock both standard and high MAP goals had a similar risk of mortality (RR 0.92, 95% CI (0.87, 1.02), P = 0.55) and ICU length of stay (SMD -0.10, 95% CI (-0.28, 0.08), P = 0.26) (Figs. 4, 5) [13-18].

Discussion

This meta-analysis of RCTs shows that targeting a high MAP goal in critically ill patients with septic shock and post-cardiac arrest was associated with a similar risk of mortality, duration of mechanical ventilation, and ICU length of stay when compared with standard MAP goal. In patients with chronic hypertension, higher MAP targets have been shown to reduce the rate of acute kidney injury as well as renal replacement therapy [13]. Retrospective studies have shown that MAP less than 80 mm Hg may worsen the myocardial injury and acute kidney injury [19]. A large-scale retrospective study in more than 5,000 patients showed the prolonged duration of MAP be-
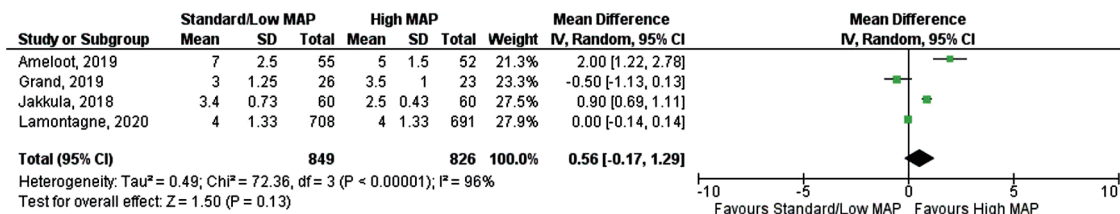
Study or Subgroup	Standard/Low MAP Mean	SD	Total	High MAP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ameloot, 2019	7	2.5	55	5	1.5	52	21.3%	2.00 [1.22, 2.78]
Grand, 2019	3	1.25	26	3.5	1	23	23.3%	-0.50 [-1.13, 0.13]
Jakkula, 2018	3.4	0.73	60	2.5	0.43	60	27.5%	0.90 [0.69, 1.11]
Lamontagne, 2020	4	1.33	708	4	1.33	691	27.9%	0.00 [-0.14, 0.14]
Total (95% CI)			**849**			**826**	**100.0%**	**0.56 [-0.17, 1.29]**

Heterogeneity: Tau² = 0.49; Chi² = 72.36, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.50 (P = 0.13)

Figure 2. Forest plot showing risk ratio of the duration of mechanical ventilation. MAP: mean arterial pressure; CI: confidence interval.

Study or Subgroup	Standard/Low MAP Mean	SD	Total	High MAP Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Afsar, 2014	8	2.3	388	8	1.8	388	24.8%	0.00 [-0.14, 0.14]
Ameloot, 2019	8	3	55	7	1.5	52	17.9%	0.42 [0.03, 0.80]
Grand, 2019	5	1.5	26	4.5	1	23	13.0%	0.38 [-0.19, 0.95]
Jakkula, 2018	4.5	0.9	60	3.9	0.65	60	18.3%	0.76 [0.39, 1.13]
Lamontagne, 2020	4.3	1.6	1283	4.6	1.7	1300	25.9%	-0.18 [-0.26, -0.10]
Total (95% CI)			**1812**			**1823**	**100.0%**	**0.22 [-0.07, 0.50]**

Heterogeneity: Tau² = 0.08; Chi² = 36.44, df = 4 (P < 0.00001); I² = 89%
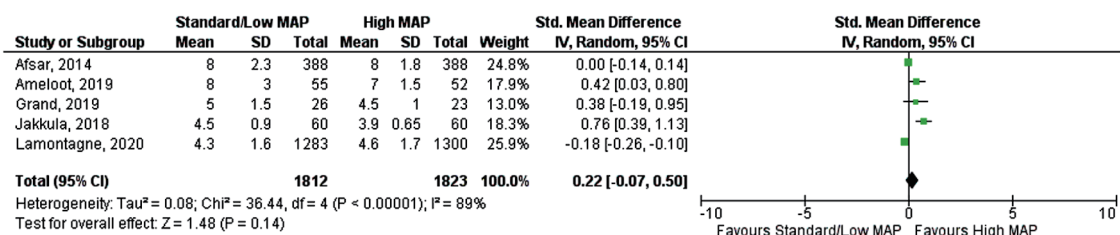Test for overall effect: Z = 1.48 (P = 0.14)

Figure 3. Forest plot showing risk ratio of ICU length of stay. MAP: mean arterial pressure; CI: confidence interval; ICU: intensive care unit.
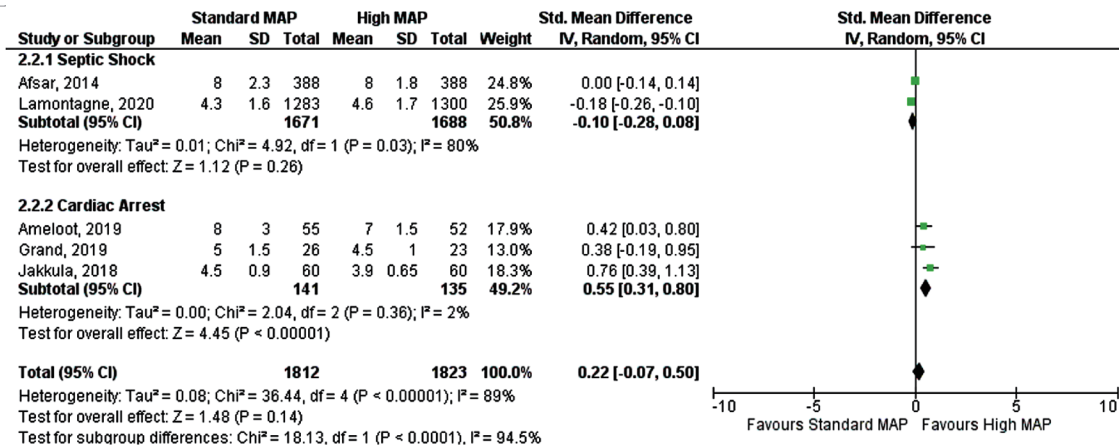
Figure 4. Forest plot showing ICU length of stay by subgroup analysis. MAP: mean arterial pressure; CI: confidence interval; ICU: intensive care unit.
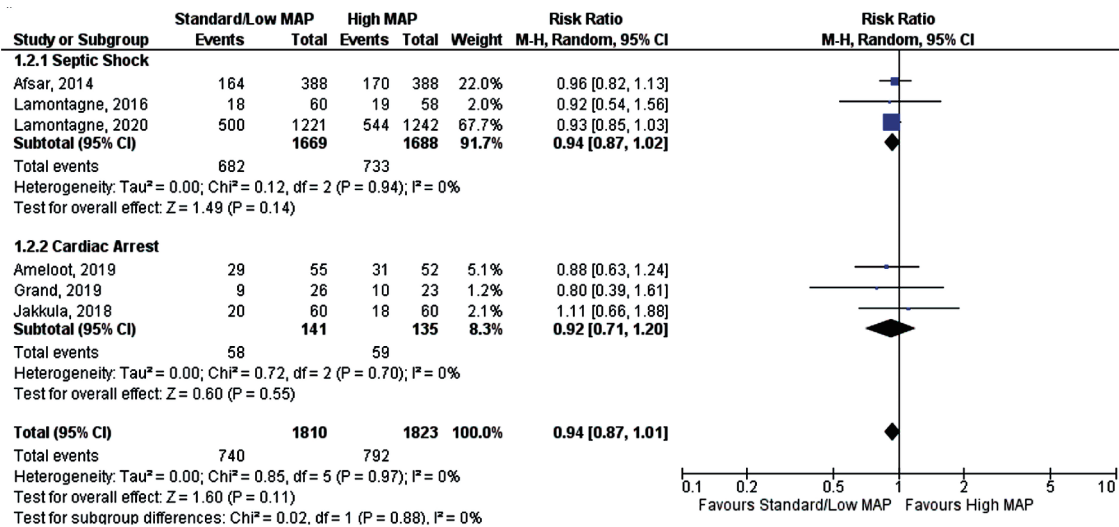

Figure 5. Forest plot showing mortality by subgroup analysis. MAP: mean arterial pressure; CI: confidence interval.
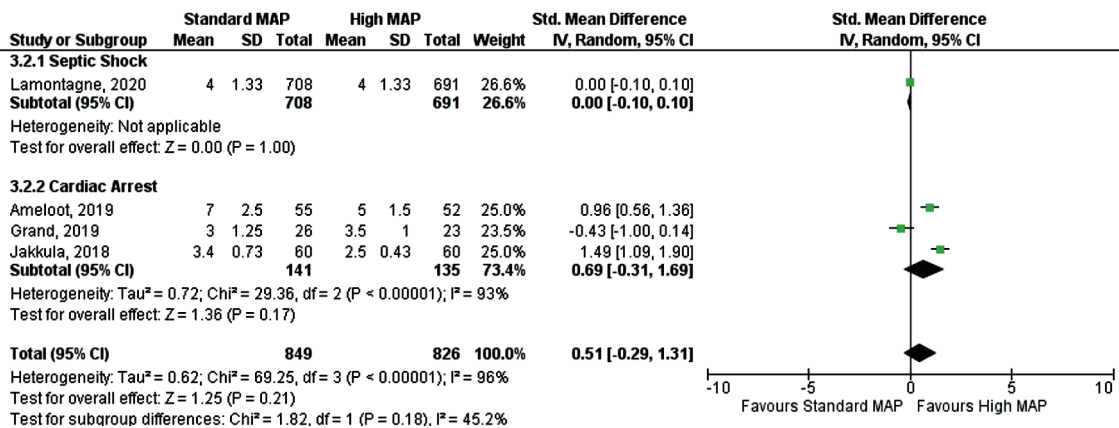

Figure 6. Forest plot showing duration of mechanical ventilation by subgroup analysis. MAP: mean arterial pressure; CI: confidence interval.

low 65 mm Hg to be associated with increased mortality [20]. Despite this, our meta-analysis failed to show any benefits of a high MAP goal in survival. The results of our meta-analysis are in line with the RCTs included in this study. This shows that a specific MAP goal or a one-size-fits-all approach might not be clinically beneficial.

A prior meta-analysis that pooled data from two septic shock RCTs [11, 13] did not find any improvement in overall 28-day survival in the higher MAP group; however, it showed increased mortality with higher MAP group in the elderly patients exposed to vasopressors greater than 6 h [21]. We did not find any increased mortality with a high MAP goal; however, there was a numerical but non-significant increase in mortality in the high MAP group. Further, we were not able to perform age-related analysis because of a lack of data. Subgroup analysis based on the type of ICU admission showed no significant difference in mortality with different MAP goals but there was again a numerical non-significant increase in mortality in the septic shock group. This increase was mainly driven by the 65 Trial (Lamontagne et al, 2020 [15]), which was designed as permissive hypotension versus usual care and found no difference between them. Two of the included post-cardiac arrest RCTs reported improved cerebral oxygenation in the higher MAP group [16, 17]. In one *post hoc* analysis of these trials, patients with cardiogenic shock-related cardiac arrest with higher MAP goals had a lower area under the troponin T curve suggesting lesser myocardial injury [22]. Though, despite evidence of some benefits the results failed to translate into a significant improvement in clinical outcomes. In the cardiac arrest subgroup, we found that patients with higher MAP had a shorter length of ICU stay compared to patients with standard MAP goals. These results should be interpreted cautiously as the number of patients in this subgroup was limited, length of stay was not a standardized outcome and depend on individual centers. However, this is hypothesis-generating and future studies should aim to identify possible subgroups where higher MAP goals might be beneficial.

The 2015 American Heart Association guidelines modified its recommendation for MAP goal of 65 mm Hg, stating that different organs and individuals may have different optimal pressures leading to the concept of patient-specific optimal MAP goals [23]. Recently a systematic review investigated the concept of cerebral autoregulation to study the role of optimal MAP goals in improving cerebral oxygenation in post-cardiac arrest patients but failed to show any improvement in neurological outcomes [24]. Our findings support current guidelines for targeting a MAP goal of 65 mm Hg in critically ill medical patients [1, 2]. Studies with a focus on improved hemodynamic monitoring and specific end-organ perfusion outcomes are necessary to provide more consistent data. This meta-analysis has some limitation which includes, the presence of a heterogeneous trial population including different MAP goals in both the groups, non-standardized blood pressure monitoring, and a lack of data on end-organ outcomes and biomarkers. Future trials might benefit from more precise hemodynamic monitoring and strict adherence to MAP goals [25]. Newer ongoing RCT, like Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65 trial) will evaluate the impact of MAP goals specifically on biological markers of end organs, which will likely improve our understanding further [26].

Conclusions

Targeting a high MAP goal in critically ill patients offers no benefits over the current standard MAP goal in terms of mortality, duration of mechanical ventilation, and ICU length of stay.

Acknowledgments

None to declare.

Financial Disclosure

No financial disclosures to declare.

Conflict of Interest

This article has no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Sauradeep Sarkar: conception, design, acquisition of data, and draft writing. Sahib Singh: acquisition of data and draft revising. Amit Rout: statistical analysis and interpretation of data, draft revising.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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