Research Square

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Achieved Blood Pressure or the Need to Achieve It in Acute Traumatic Spinal Cord Injury

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Research Article

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Abstract

Background

Guidelines recommend raising mean arterial pressure (MAP) after acute traumatic spinal cord injury, but the only randomized trial found no neurologic benefit from a target above 85 mmHg. Observational studies that favor higher MAP cannot separate pressure achieved from the illness that prevents it. We emulated the trial in routinely collected intensive care data and tested whether any benefit of a higher MAP survives once vasopressor need is taken into account.

Methods

Adults with acute traumatic spinal cord injury admitted to intensive care within 72 hours of hospital admission were identified in MIMIC-IV (one center) and eICU-CRD (58 centers). Time zero was the sixth hour of intensive care. Using clone, censor and weight methods, we compared a strategy of daily mean MAP of 85 mmHg or more with 65 to 85 mmHg over 72 hours. The primary outcome was discharge home or to rehabilitation. Post hoc analyses used nurse charted limb strength as a negative control outcome and split each strategy by vasopressor use.

Results

Of 738 patients, 316 of 683 (46.3%) reached a day 1 mean MAP of 85 mmHg or more. Favorable discharge was 71.8% with the higher strategy and 58.2% with the conventional strategy (risk difference 13.6 percentage points, 95% CI 3.6 to 22.7), and in hospital death 6.2% and 12.2%. The strategies were balanced for baseline motor strength. When vasopressor status was held fixed, the MAP difference fell to 6.7 points (95% CI, minus 6.5 to 19.7), whereas needing a vasopressor at the same MAP was associated with 33.1 points fewer favorable discharges (95% CI, minus 59.8 to minus 7.4). Phenylephrine and norepinephrine as first agent gave similar outcomes.

Conclusions

A higher MAP was associated with better hospital outcomes mainly when it occurred without vasopressors. The apparent benefit of MAP augmentation in observational data may reflect the need for support rather than the pressure achieved, which agrees with the neutral randomized trial.

Introduction

Acute traumatic spinal cord injury often causes loss of sympathetic tone below the level of injury, and hypotension in the first days is common. Since 2013, guidelines have recommended keeping mean arterial pressure (MAP) between 85 and 90 mmHg for seven days to protect the injured cord from

secondary ischemia [1]. The 2024 AO Spine guideline relaxed this to a lower limit of 75 to 80 mmHg and an upper limit of 90 to 95 mmHg for three to seven days, and it graded the evidence as very low and the recommendation as weak [2]. It made no recommendation on the choice of vasopressor [2].

The case for MAP augmentation rests on observational studies. Patients who spent more time above 85 mmHg recovered more motor function in several single center cohorts [3, 5, 6], whereas others found no relation between MAP goals and motor recovery [4]. In routine care the target is often missed, and much of the recorded pressure falls outside the intended range [5, 7]. In 2025 the first randomized trial compared a MAP target above 85 to 90 mmHg with a target above 65 to 70 mmHg in 92 patients at 13 trauma centers [8]. Motor and sensory scores at six months did not differ, and the augmented group had higher organ dysfunction scores [8]. The trial was small, and the two lines of evidence now point in different directions.

One explanation is confounding by illness severity. A patient whose MAP stays high without support differs from a patient whose MAP is low despite norepinephrine, and observational studies rarely separate the pressure achieved from the effort needed to achieve it. Target trial emulation applies the design of a randomized trial to routine data and removes immortal time and selection biases that affect earlier analyses [9]. However, it cannot by itself correct for severity that is not recorded. We therefore emulated the randomized trial in two intensive care databases covering 59 hospitals, and we tested its result with prespecified sensitivity analyses and with post hoc falsification tests. Our aim was to estimate the effect of a higher MAP strategy on hospital outcomes and to find out whether any benefit depends on vasopressor need.

Methods

Data sources and ethics

We used MIMIC-IV version 3.1, which holds intensive care admissions to Beth Israel Deaconess Medical Center, Boston, from 2008 to 2022 [10], and eICU-CRD version 2.0, which holds admissions to 208 United States hospitals in 2014 and 2015 [11]. Both databases are deidentified, and their use was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center with a waiver of consent. Access was obtained through PhysioNet credentialing. For this type of study, formal consent is not required. The Northwestern ICU database was screened but held only 19 eligible patients and was not analyzed. The study is reported according to the TARGET statement for target trial emulation [13] and the STROBE statement.

Target trial and its emulation

Table 2 sets out the protocol of the target trial and how each element was mapped to the data. Eligible patients were adults with an acute traumatic spinal cord injury who were admitted to intensive care within 72 hours of hospital admission. In MIMIC-IV we identified injury by ICD-9 codes 806 and 952 and

by ICD-10 codes S14.0, S14.1, S24.0, S24.1, S34.0 and S34.1 for the initial encounter, and we kept the first intensive care stay of each admission. In eICU-CRD we used the same codes or a diagnosis string of traumatic spinal cord injury entered within 24 hours of unit admission, together with an APACHE admission diagnosis of trauma or spinal cord injury, and we kept the first stay of each patient. Injury level was coded as cervical, thoracic or lumbosacral. A complete lesion was taken from the ICD code in MIMIC-IV and from the diagnosis string in eICU-CRD.

Table 2
Protocol of the target trial and its emulation

Component	Target trial	Emulation
Eligibility	Adults with acute traumatic spinal cord injury in intensive care	ICD codes or diagnosis string for acute injury, ICU within 72 hours of hospital admission, in ICU at hour 6
Strategies	Daily mean MAP 85 mmHg or more vs 65 to 85 mmHg for 3 days	Same, from hourly charted MAP, days with adequate measurement only
Assignment	Randomized	Clone, censor at first deviation, inverse probability of adherence weights
Time zero	Randomization	Hour 6 of intensive care
Follow-up	Until hospital discharge	Until hospital discharge
Primary outcome	Discharge home or to rehabilitation	Same, from discharge location
Causal contrast	Per protocol effect	Per protocol effect
Analysis	Risk difference and ratio	Weighted risks, 300 patient-level bootstrap samples

Time zero was the sixth hour of intensive care, and patients had to be in the unit at that time. This gave six hours to record baseline values, which matches the window in which a trial would randomize. Follow-up started at time zero and was divided into 24-hour days.

Exposure strategies

The exposure was the daily mean of hourly MAP values, using invasive pressure when available and noninvasive pressure otherwise. A day counted when it had at least six hourly values covering at least half of the hours spent in the unit that day. The augmented strategy required a daily mean MAP of 85 mmHg or more on every counted day of the first three days. The conventional strategy required a daily mean of at least 65 and below 85 mmHg. These limits match the two arms of the randomized trial [8]. Days after intensive care discharge and days without enough measurements did not count as deviations.

Outcomes

The primary outcome was favorable discharge, defined as being alive at hospital discharge and discharged home or to inpatient rehabilitation. Secondary outcomes were in-hospital death, acute kidney injury of stage 2 or higher within seven days by creatinine criteria, and length of intensive care stay. Neurologic scores are not recorded in either database, so discharge destination was used as the closest available measure of function.

Statistical analysis

Because a patient can follow both strategies at time zero, we used the clone, censor and weight approach [12]. Each patient was copied into both arms and censored on the first day the observed MAP left the range of that arm. To correct the selection created by censoring, we fitted a pooled logistic model for adherence on each day. The model included age, sex, injury level, complete lesion, head injury, chest injury, database, baseline MAP, minimum heart rate, vasopressor use, mechanical ventilation, arterial line, lactate, creatinine and hemoglobin, and the previous day's MAP, vasopressor use, ventilation and minimum heart rate. Missing values were set to the median with a missing indicator. Each uncensored clone received the inverse of its cumulative probability of adherence, and weights were truncated at the 99th percentile. Weighted risks were compared as risk differences and risk ratios. Confidence intervals came from 300 bootstrap samples drawn at the patient level.

Prespecified secondary analyses were a three-arm comparison (below 75, 75 to 85, and 85 mmHg or more), follow-up windows of five and seven days, and subgroups by database, cervical level, vasopressor use at baseline, absence of head injury and exclusion of transfers. We also report an unweighted comparison of patients grouped by their three-day mean MAP, which mirrors the design of earlier studies. In an exploratory analysis we compared phenylephrine with norepinephrine as the first vasopressor started within 24 hours, using inverse probability of treatment weighting with propensity scores truncated at 0.05 and 0.95.

Post hoc falsification analyses

The following analyses were added after the primary result was seen and are reported as post hoc. In MIMIC-IV, nurses chart the strength of each limb on a six-point scale (no movement, contraction without movement, movement not against gravity, lift against gravity, some resistance, full resistance), scored 0 to 5. We took the first value of each limb recorded between six hours before and 24 hours after unit admission and averaged the four limbs. First, we used this baseline motor score and the presence of any limb with no movement as negative control outcomes [14]. A strategy that starts later cannot change a score measured before it, so a difference between arms would show residual confounding. Second, we added motor strength to the weight model. Third, we split each MAP strategy by whether a vasopressor was given on each day, creating four strategies. We also calculated the E-value for the primary result [15].

Analyses used Python 3.12 with DuckDB and scikit-learn. Patient-level data stayed on the local computer as required by the data use agreements. Code is available as supplementary material.

Results

Patients and blood pressure in practice

We included 738 patients, 354 from MIMIC-IV and 384 from 58 eICU-CRD hospitals (median 3 patients per hospital, range 1 to 40). The median age was 59 years (interquartile range 40 to 71), 532 (72.1%) were men, and 449 (60.8%) had a cervical injury (Table 1). At baseline, 158 (21.4%) received a vasopressor and 181 (24.5%) were mechanically ventilated. Overall, 450 of 732 patients with a known destination (61.5%) had a favorable discharge and 87 (11.9%) died in hospital. The MIMIC-IV cohort was sicker than the eICU-CRD cohort, with more vasopressor use at baseline (35.6% vs 8.3%) and more deaths (17.5% vs 6.6%).

Table 1
Baseline characteristics and hospital outcomes

Characteristic	All (n = 738)	MIMIC-IV (n = 354)	eICU-CRD (n = 384)
Age, years, median (IQR)	59 (40 to 71)	60.5 (45 to 72)	57 (38 to 71)
Men, n (%)	532 (72.1)	261 (73.7)	271 (70.6)
Cervical injury, n (%)	449 (60.8)	249 (70.3)	200 (52.1)
Thoracic injury, n (%)	123 (16.7)	79 (22.3)	44 (11.5)
Complete lesion, n (%)	64 (8.7)	42 (11.9)	22 (5.7)
Head injury, n (%)	172 (23.3)	101 (28.5)	71 (18.5)
Chest injury, n (%)	201 (27.2)	135 (38.1)	66 (17.2)
Baseline MAP, mmHg, median (IQR)	82.7 (75.7 to 91.6)	82.2 (75.4 to 90.8)	83.4 (76.4 to 92.9)
Baseline heart rate, per min, median (IQR)	72 (62 to 84)	70 (59 to 82)	74 (64 to 85)
Vasopressor at baseline, n (%)	158 (21.4)	126 (35.6)	32 (8.3)
Mechanical ventilation at baseline, n (%)	181 (24.5)	108 (30.5)	73 (19.0)
Arterial line at baseline, n (%)	257 (34.8)	172 (48.6)	85 (22.1)
Lactate, mmol/L, median (IQR), n measured	1.9 (1.3 to 2.8), 270	1.9 (1.4 to 2.7), 180	2.1 (1.2 to 3.0), 90
Creatinine, mg/dL, median (IQR), n measured	0.9 (0.7 to 1.1), 617	0.9 (0.7 to 1.1), 278	0.9 (0.7 to 1.1), 339
Day 1 mean MAP, mmHg, median (IQR)	83.5 (75.8 to 90.9)	82.8 (75.4 to 89.2)	84.6 (76.6 to 92.8)
Favorable discharge, n (%)	450 (61.5)	217 (61.3)	233 (61.6)
Discharged to rehabilitation, n (%)	256 (35.0)	169 (47.7)	87 (23.0)
Discharged home, n (%)	194 (26.5)	48 (13.6)	146 (38.6)
In-hospital death, n (%)	87 (11.9)	62 (17.5)	25 (6.6)
Kidney injury stage 2 or higher, n (%) of measured	22 (3.8)	14 (5.2)	8 (2.6)
ICU stay, days, median (IQR)	3.1 (1.5 to 7.5)	4.0 (1.9 to 9.6)	2.4 (1.3 to 5.4)

Baseline values were taken in the first six hours of intensive care, laboratory values from 24 hours before to six hours after admission. Percentages of discharge outcomes use patients with a known destination as denominator. IQR, interquartile range; MAP, mean arterial pressure.

Of 683 patients with an adequate MAP record on day 1, 316 (46.3%) had a daily mean of 85 mmHg or more, 214 (31.3%) had 75 to 85 mmHg, 122 (17.9%) had 65 to 75 mmHg and 31 (4.5%) were below 65 mmHg. The median daily MAP stayed between 80 and 86 mmHg over the first week in both databases. Patients with a lower day 1 MAP were more often ventilated (33.6% in the 65 to 75 mmHg group vs 19.6% in the group at 85 mmHg or more) and more often had a complete lesion (14.8% vs 7.6%). On day 3, 109 patients were still in the unit with a daily mean of 85 mmHg or more.

Primary analysis

After cloning, 282 patients remained adherent to the augmented strategy and 285 to the conventional strategy at the end of day 3. The effective sample sizes after weighting were 129 and 206. Favorable discharge was 71.8% (95% CI, 64.9 to 78.7) under the augmented strategy and 58.2% (51.8 to 65.0) under the conventional strategy, a risk difference of 13.6 percentage points (3.6 to 22.7) and a risk ratio of 1.23 (1.06 to 1.43) (Table 3). In-hospital death was 6.2% and 12.2% (risk difference minus 6.0 points, 95% CI, minus 10.7 to minus 0.3). Kidney injury of stage 2 or higher was rare (22 events) and was not more frequent with the augmented strategy (1.5% vs 6.1%). Length of intensive care stay did not differ (6.8 vs 6.7 days). The E-value for the primary risk ratio was 1.76, and 1.31 for its lower confidence limit. The unweighted comparison by three-day mean MAP gave a smaller difference (favorable discharge 61.5% at 85 mmHg or more vs 52.0% at 75 to 85 mmHg).

Table 3
Primary and secondary outcomes under the two strategies (72 hours)

Outcome	MAP 85 mmHg or more, % (95% CI)	MAP 65 to 85 mmHg, % (95% CI)	Risk difference, points (95% CI)	Risk ratio (95% CI)
Favorable discharge	71.8 (64.9 to 78.7)	58.2 (51.8 to 65.0)	13.6 (3.6 to 22.7)	1.23 (1.06 to 1.43)
In-hospital death	6.2 (3.3 to 10.4)	12.2 (8.1 to 15.8)	minus 6.0 (minus 10.7 to minus 0.3)	0.51 (0.27 to 0.96)
Kidney injury stage 2 or higher	1.5 (0.0 to 3.6)	6.1 (2.0 to 11.0)	minus 4.7 (minus 9.7 to 0.0)	0.24 (0.00 to 1.02)
ICU stay, days, mean	6.8 (5.1 to 7.9)	6.7 (5.7 to 7.7)	0.1 (minus 1.8 to 1.6)	1.01 (0.74 to 1.27)
Effective sample sizes after weighting were 129 for the higher and 206 for the conventional strategy.				

Secondary analyses

In the three-arm comparison, the difference between 85 mmHg or more and 75 to 85 mmHg was 12.0 points (95% CI, minus 2.1 to 26.3), and a MAP below 75 mmHg did not differ from 75 to 85 mmHg (minus 2.2 points, minus 26.2 to 15.7). The difference grew with longer follow-up, to 12.8 points (1.0 to 22.3) at five days and 20.6 points (10.2 to 31.0) at seven days. The direction was the same in both databases (MIMIC-IV 14.9 points, minus 0.3 to 31.1; eICU-CRD 13.0 points, minus 0.3 to 25.4), in cervical

injury (14.1 points, 1.9 to 26.3) and after excluding transfers (11.2 points, 1.5 to 21.0) (Fig. 1). The difference was present in patients without a vasopressor at baseline (14.6 points, 4.6 to 25.8; n = 580) but not in patients who already received one (1.4 points, minus 26.0 to 40.7; n = 158).

As first vasopressor, phenylephrine was started in 115 patients and norepinephrine in 68. Favorable discharge (53.7% vs 50.4%; difference 3.3 points, minus 10.5 to 18.9), death (21.7% vs 23.8%) and bradycardia below 50 beats per minute within 72 hours (28.0% vs 27.4%) did not differ.

Post hoc falsification analyses

Limb strength was charted for 218 of 354 MIMIC-IV patients (61.6%), at a median of 1.0 hour after unit admission. It was strongly prognostic. In-hospital death was 31.7% when the mean score was 1.5 or less, 8.1% between 1.5 and 3.5, and 1.8% above 3.5.

The two strategies were balanced on this negative control outcome. The weighted mean baseline motor score was 2.65 in the augmented arm and 2.67 in the conventional arm (difference minus 0.01, 95% CI, minus 0.52 to 0.53), and the share with a limb that did not move was 40.8% and 39.5%. Adding motor strength to the weight model changed the primary estimate little (in all MIMIC-IV patients from 14.9 to 12.3 points, 95% CI, minus 2.9 to 29.4).

Splitting the strategies by vasopressor use changed the picture (Fig. 2). Among patient days without a vasopressor, favorable discharge was 74.1% with a MAP of 85 mmHg or more and 67.4% with 65 to 85 mmHg, a difference of 6.7 points (95% CI, minus 6.5 to 19.7). At 65 to 85 mmHg, receiving a vasopressor was associated with 33.1 points fewer favorable discharges (34.4% vs 67.4%; 95% CI for the difference, minus 59.8 to minus 7.4). The arms that included vasopressors were small after weighting (effective sample sizes 18 and 7), and their estimates are imprecise.

Discussion

In 738 patients with acute traumatic spinal cord injury from 59 hospitals, a strategy of keeping daily mean MAP at 85 mmHg or more for three days was associated with more favorable discharges and fewer deaths than a strategy of 65 to 85 mmHg. The association held in both databases, in cervical injury and with longer follow-up. However, it was largely confined to patients who reached the higher pressure without vasopressors. When vasopressor use was held fixed, the difference attributable to MAP fell by half and its confidence interval included zero, whereas needing a vasopressor at the same MAP was associated with a large deficit. Our data therefore do not show that raising MAP improves outcome. They suggest that a high MAP reached spontaneously marks a less severe injury.

This reading explains why observational and randomized evidence disagree. Earlier cohorts related the share of time above 85 mmHg to motor recovery [3, 5, 6], and our unweighted analysis reproduced that pattern. Such analyses compare patients by the pressure they achieved, not by the strategy they were given. Hypotension after spinal cord injury partly reflects loss of supraspinal sympathetic control, so a patient who stays above 85 mmHg without support probably has less autonomic and therefore less

overall cord damage. The randomized trial assigned the target and not the pressure, and it found no difference in six-month motor or sensory scores [8]. Our four-strategy analysis approaches the trial's question from the observational side and reaches a compatible answer.

The weighted analysis did not remove this bias, although the strategies were balanced on baseline limb strength. Limb strength measures motor completeness, which is a different construct from autonomic completeness, and two patients with the same motor score can differ widely in sympathetic function. The negative control test therefore rules out one form of confounding but not all forms. The E-value of 1.76 means that an unmeasured factor associated with both MAP and outcome by a risk ratio of 1.76 could explain the primary result. Autonomic injury severity could plausibly reach that size. This is the main lesson for future observational work, in which vasopressor need should be treated as part of the exposure and not as a covariate.

Our data also describe current practice. Fewer than half of patients reached a daily mean of 85 mmHg on day 1, and the median daily MAP stayed between 80 and 86 mmHg, which is close to the lower limit of 75 to 80 mmHg in the 2024 guideline [2]. A MAP below 75 mmHg was not associated with worse outcomes than 75 to 85 mmHg, but this comparison rested on an effective sample of 29 patients. We found no excess of kidney injury with the higher strategy, unlike the higher organ dysfunction scores in the randomized trial [8], but kidney injury was rare in our cohort. Phenylephrine and norepinephrine gave similar results, and the question of vasopressor choice, on which the guideline makes no recommendation [2], remains open.

Strengths and limitations

The study is about eight times larger than the randomized trial, includes 59 hospitals and avoids immortal time bias by aligning eligibility, assignment and start of follow-up. It reports a negative control analysis and a decomposition by vasopressor use. It also has important limitations. Neither database records the ASIA impairment scale, so neurologic recovery could not be measured, and discharge destination depends on rehabilitation access and insurance as well as on function. Injury and its completeness were identified from administrative codes. Daily means do not capture brief hypotensive episodes, and noninvasive pressure was used when no arterial line was present. eICU-CRD data date from 2014 and 2015, and its infusion records are incomplete. The falsification analyses were added after the primary result was known, limb strength was available only in MIMIC-IV and in 62% of its patients, and the vasopressor arms had small effective sample sizes. Finally, residual confounding by autonomic injury severity cannot be excluded.

Future trials of MAP targets could stratify randomization by vasopressor requirement at enrollment, because the patients in whom the target matters most may be those who cannot reach it unaided. Observational studies should report achieved pressure separately for patients with and without vasopressor support.

Conclusions

In this emulation of the randomized trial of MAP targets after acute traumatic spinal cord injury, a higher MAP was associated with better hospital outcomes mainly when it was reached without vasopressors. Once vasopressor need was accounted for, we found no clear benefit of the higher target, which agrees with the neutral trial. The apparent benefit of MAP augmentation in observational data may reflect the severity of injury that determines the need for support rather than the pressure achieved.

Declarations

Compliance with instructions The manuscript complies with the Neurocritical Care instructions to authors.

Author contributions HBT and EE conceived and designed the study, acquired and analyzed the data, interpreted the results and drafted the manuscript. Both authors approved the final version and agree to be accountable for the work.

Authorship and prior publication All authors meet ICMJE criteria. The manuscript has not been published and is not under consideration elsewhere.

Ethics MIMIC-IV and eICU-CRD are deidentified public databases approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center with a waiver of informed consent. Access was granted after PhysioNet credentialing and completion of human research training. For this type of study, formal consent is not required.

Conflicts of interest The authors declare that they have no conflicts of interest.

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Reporting checklists The STROBE checklist is appended at the end of the manuscript, and the target trial protocol is reported in Table 2 following the TARGET statement.

Use of artificial intelligence Claude (Anthropic) was used to help write the data extraction and analysis code and to draft and edit the manuscript text. The authors reviewed all code and output, ran every analysis on the original data, verified all numbers and references, and take full responsibility for the content.

Data availability MIMIC-IV and eICU-CRD are available through PhysioNet to credentialed users. The analysis code is provided as supplementary material.

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Figures

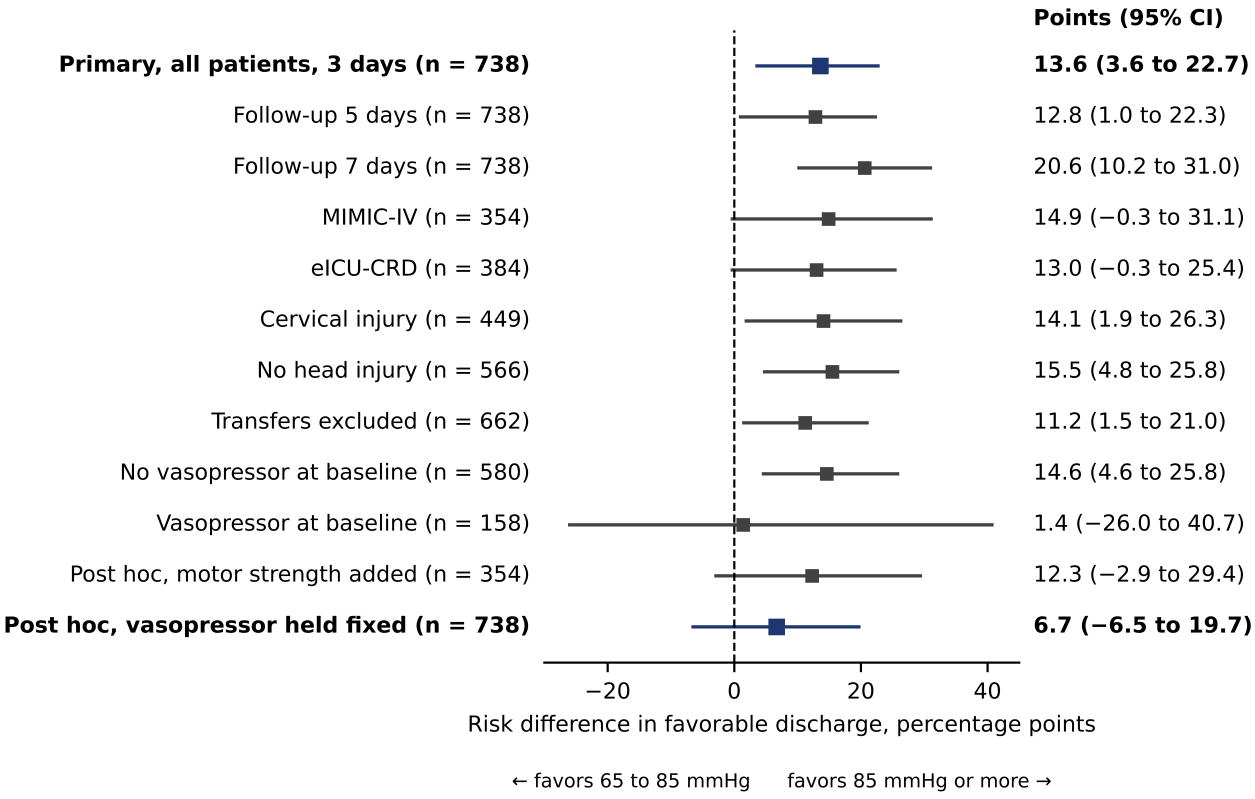

Figure 1

Risk difference in favorable discharge between the higher and the conventional MAP strategy across analyses. Squares show weighted risk differences in percentage points and lines their 95% confidence intervals from 300 patient-level bootstrap samples. Positive values favor a daily mean MAP of 85 mmHg or more. The first row is the primary analysis over 72 hours. The last two rows are post hoc analyses, one adding baseline limb strength to the weight model in MIMIC-IV and one holding vasopressor status fixed. CI, confidence interval; MAP, mean arterial pressure.

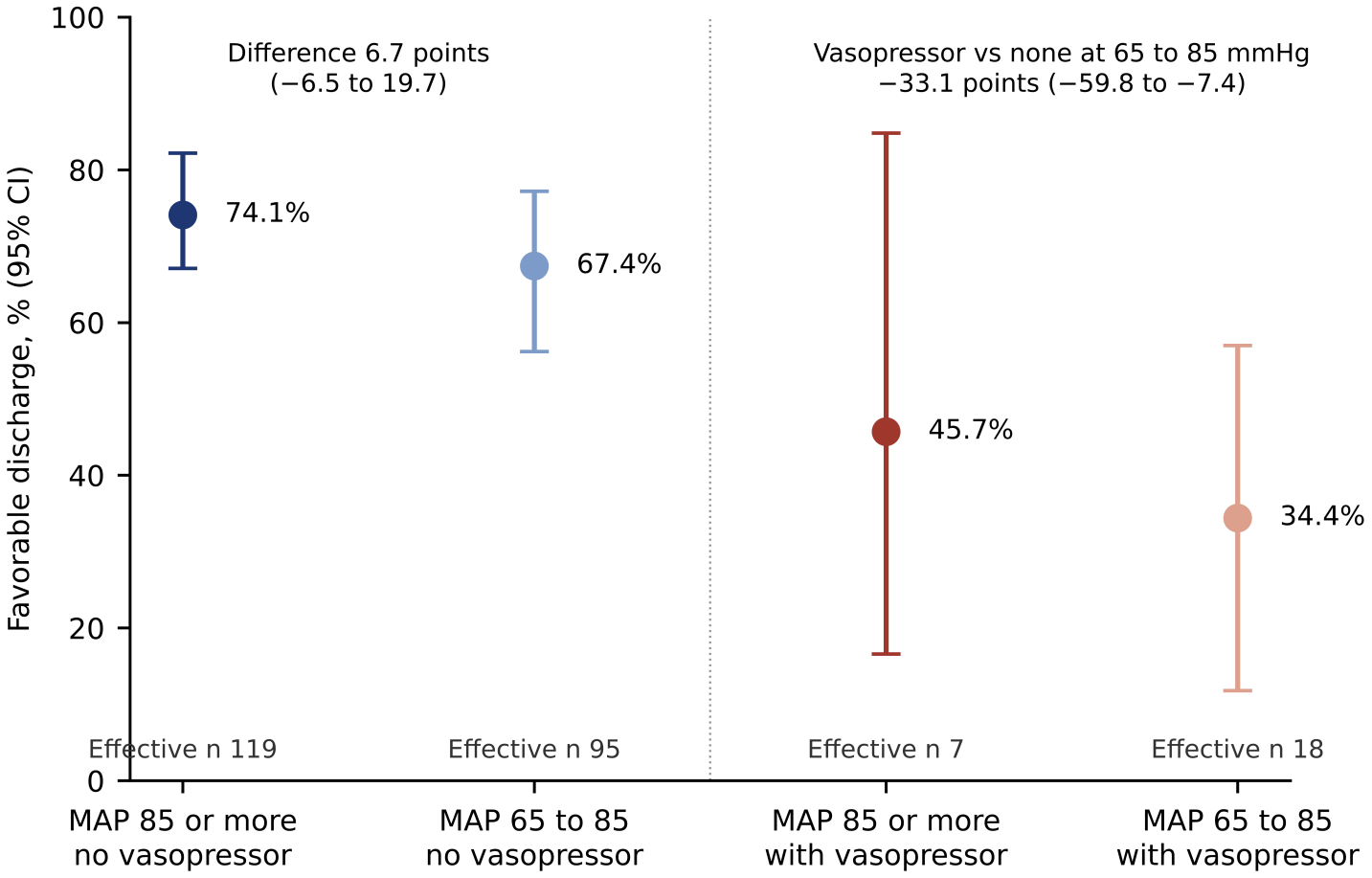

Figure 2

Favorable discharge under four strategies defined by MAP range and vasopressor use over 72 hours. Points show weighted risks and bars their 95% confidence intervals. Effective sample sizes after weighting are shown above the axis. The arms that include vasopressors are small and imprecise. MAP, mean arterial pressure.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklist.docx