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Chronic Hypertension and the Effect of Mean Arterial Pressure Strategies in Septic Shock: A Two-Cohort Target Trial Emulation Using Bayesian g-Computation

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Abstract

Background

Chronic hypertension shifts renal autoregulation rightward, and in the SEPSISPAM trial, a higher mean arterial pressure (MAP) target reduced renal-replacement therapy (RRT) in hypertensive patients. We tested whether chronic hypertension modifies the effect of sustained higher versus lower MAP strategies on new RRT and mortality in septic shock.

Methods

We performed a Bayesian target trial emulation in 13,714 adults with sepsis receiving vasopressors from MIMIC-IV (n = 7,181) and eICU-CRD (n = 6,533). From 6 hours after vasopressor initiation, two sustained 48-hour strategies were compared: interval-mean MAP ≥ 73 mmHg versus 65–72 mmHg, followed by usual care to day 28, using a Bayesian parametric g-formula with time-varying confounders and competing risks. The prespecified estimand was the strategy × hypertension interaction.

Results

For RRT, the interaction odds ratio was 1.20 (95% credible interval [CrI] 0.88–1.65); for mortality, 1.04 (0.73–1.48). Additive interactions were + 0.5 (− 1.1 to 2.1) and − 1.3 (− 2.6 to − 0.1) percentage points. The posterior probability of an RRT interaction as protective as SEPSISPAM implied (odds ratio ≤ 0.53) was below 0.01%, and the probability that it lay between 0.80 and 1.25 was 59%. Estimates were stable across 17 sensitivity analyses, including a prior centred on the SEPSISPAM subgroup (0.89, 0.69–1.16).

Conclusion

Chronic hypertension did not modify the renal or mortality effect of sustained MAP strategies in septic shock; a history of hypertension alone does not support a higher MAP target for renal protection.

Introduction

Guidelines recommend an initial mean arterial pressure (MAP) target of 65 mmHg during resuscitation of septic shock (1), yet this consensus value rests on limited comparative evidence. Chronic arterial hypertension shifts the renal pressure–flow autoregulation curve rightward, so that a pressure sufficient for a normotensive kidney may leave a hypertensive kidney hypoperfused (2). This mechanism gained clinical weight in SEPSISPAM, in which a higher target (80–85 vs 65–70 mmHg) did not change mortality but, in the prespecified chronic-hypertension stratum, reduced the need for renal-replacement therapy (RRT) from 42.2% to 31.7% (3). That result still underpins suggestions to individualize the target upward in hypertensive patients (4).

Subsequent randomized evidence has not supported the signal. A pooled individual-patient analysis of two trials found no subgroup, including chronic hypertension, that benefited from a higher target (5); permissive hypotension was not harmful in older patients (6); OPTPRESS, targeting 80–85 mmHg in older patients with septic shock, was stopped early for ineffectiveness and possible harm, with no benefit in the half with known hypertension (7); and a post hoc analysis of SEPSISPAM found no heterogeneity of the treatment effect across baseline characteristics and a harm pathway through norepinephrine requirement (8). The question has only been examined in randomized subgroups of trials assigning a target at one time point, whereas the autoregulatory rationale concerns pressure sustained over the resuscitation period; observational data can address sustained strategies but achieved MAP and vasopressor dose influence each other over time, a feedback conventional regression cannot handle.

We therefore emulated a target trial (9) contrasting sustained higher- and lower-MAP strategies in two independent septic-shock cohorts, estimated with a Bayesian parametric g-formula (10), to test the prespecified hypothesis that the effect of the MAP strategy on new RRT and mortality differs between patients with and without chronic hypertension.

Methods

Study design and reporting

We followed the target trial emulation framework (9) and report according to STROBE (11) and TARGET (12); both checklists are in Electronic Supplementary Material (ESM) 1, and the target trial components and their operationalization are tabulated in ESM 2. The two databases were analysed as one cohort. The estimand and analysis plan were prespecified before the g-formula analysis was run.

Data sources

MIMIC-IV contains 94,458 ICU stays at Beth Israel Deaconess Medical Center, Boston, from 2008 to 2022 (13); the eICU Collaborative Research Database (eICU-CRD) contains 200,859 ICU stays from 208 U.S. hospitals in 2014 and 2015 (14). Operational definitions, diagnosis codes, text strings, and item identifiers are listed in ESM 3.

Eligibility and time zero

Eligible patients were adults with a sepsis diagnosis (International Classification of Diseases codes in MIMIC-IV; diagnosis strings in eICU-CRD) who received a vasopressor infusion (norepinephrine, epinephrine, phenylephrine, vasopressin, or dopamine), which defined the septic-shock phenotype. Only the first ICU stay per patient was used. Time zero was 6 hours after the first vasopressor infusion, a landmark that follows initial resuscitation, as in SEPSISPAM (3), and lets hours 0–6 define the baseline hemodynamic state; patients had to be alive and in the ICU at the landmark. Patients with pre-existing end-stage renal disease, and those already receiving RRT before the landmark, were excluded from the RRT analysis.

Treatment strategies

The 48-hour window after the landmark was divided into twelve 4-hour intervals, and the mean MAP in each interval (invasive or noninvasive) was classified as 73 mmHg or higher, 65–72 mmHg, or below 65 mmHg. The higher strategy sustained 73 mmHg or higher in every interval; the lower strategy sustained 65–72 mmHg, the guideline band. The 73-mmHg threshold is the pressure the lower-target arm of SEPSISPAM achieved (3) and 65 mmHg the guideline minimum (1) ; a MAP below 65 mmHg is an observed state that informed the models but was not an arm, so refractory hypotension does not define the lower strategy. Because adherence is judged on achieved MAP, the emulated contrast is the per-protocol analogue of sustained adherence to a target; the intention-to-treat effect of assigning a target is not estimable.

Outcomes and follow-up

The primary outcome was new RRT within 28 days of the landmark, with death and discharge alive as competing events; the secondary outcome was in-hospital death within 28 days, with discharge alive as a competing event. RRT was ascertained from the MIMIC-IV derived dialysis table and from eICU-CRD treatment records (modalities in ESM 3), death from hospital discharge status and time. Follow-up continued on the 4-hour grid to discharge, death, or day 28.

Covariates and missing data

Baseline covariates were age, sex, illness severity (first-day Sequential Organ Failure Assessment score in MIMIC-IV, APACHE IV score in eICU-CRD), chronic kidney disease, the Charlson comorbidity index (MIMIC-IV only), and the hemodynamic state at the landmark: mean MAP over hours 0–6, the last lactate and creatinine, and the mean norepinephrine-equivalent (NEE) dose over hours 0–6. Time-varying confounders in each interval were the NEE dose (15) (conversion and sources in ESM 3), an indicator of ongoing vasopressor infusion, the highest lactate, and the highest creatinine. Chronic hypertension and comorbidities were defined from diagnosis codes (MIMIC-IV) or diagnosis and past-history strings (eICU-CRD). Within the window, MAP, lactate, and creatinine were carried forward from the last measurement, a missing first interval took the landmark value, and the few remaining missing values were replaced by the cohort median (ESM 4).

Statistical analysis

Estimand. The prespecified estimand was the modification by chronic hypertension of the per-protocol effect of sustaining the higher versus the lower strategy for 48 hours, expressed as (i) the strategy × hypertension interaction on the discrete-time cause-specific hazard during the window, reported as an odds ratio that approximates a ratio of cause-specific hazard ratios (16); and (ii) the difference between strata of the 28-day risk difference (higher minus lower), the additive-scale interaction (17). Under the autoregulation hypothesis the RRT interaction lies below 1.

Estimation. We used a Bayesian parametric g-formula (10). Conceptually, the g-formula asks what would have happened to the same patients had their MAP been held in one band or the other for 48 hours: fitted models for the confounders and the hazards are used to simulate each patient's course under each strategy, and the Bayesian fit turns the uncertainty of those models into posterior probabilities for the comparison. Per outcome we fitted models for the time-varying confounders (Gaussian for log-lactate and log-creatinine; a two-part model for ongoing vasopressor infusion and log NEE dose given infusion), each conditional on the lagged state, the lagged MAP category, baseline covariates, a database indicator, and a cubic function of time; logistic models for the cause-specific hazards of the event and of the competing event within the window, conditional on the MAP category, chronic hypertension, their interaction, the concurrent confounders, baseline covariates, the database indicator, and time; and logistic models for both hazards after the window, conditional on baseline covariates, the database indicator, the 48-hour state, and time (ESM 5). The database indicator is the centre effect of a stratified multicentre analysis; the severity scores (SOFA, APACHE IV) and the Charlson index entered as database-specific terms. Models were fitted by Hamiltonian Monte Carlo in Stan (18) with four chains of 1,000 post-warm-up iterations and weakly informative Normal(0, 2.5) priors on standardized slopes (19). For each of 1,000 posterior draws the covariate and event processes were simulated forward under each sustained strategy, within each hypertension stratum over that stratum's pooled baseline covariate distribution, giving the standardized competing-risk cumulative incidence to day 28 (20), the within-stratum risk differences, and the additive interaction; component posteriors were combined assuming independence across models. The fitted model was also standardized to each database's population.

Model validation. Convergence required a potential scale-reduction factor below 1.01, a bulk effective sample size above 400, and no divergent transitions (ESM 7). We checked the covariate models by posterior predictive checks and the full model set by a natural-course simulation (21), drawing the MAP category from a fitted treatment model and comparing simulated with observed cumulative incidence and covariate trajectories by stratum and database (ESM 8); the treatment model also quantified positivity as the share of patients with a modelled probability below 0.10 of the higher category in the first interval (22). Observed cumulative incidence was estimated with the nonparametric Aalen–Johansen estimator on the same 4-hour grid, accounting for the competing events.

Inference. We report posterior medians with 95% credible intervals (CrI), the posterior probabilities that the interaction odds ratio was below 1, at most 0.75, and at most 0.53 (the SEPSISPAM value), and the probability that it lay within a region of practical equivalence of 0.80–1.25 (23, 24). Heterogeneity between databases was examined by adding strategy × database and strategy × hypertension × database terms to the hazard models.

Sensitivity analyses (ESM 11–12) used the two-cohort estimator, models fitted separately in each database and the interaction posteriors combined by precision-weighted fixed-effect pooling, which is also reported for the primary specification. We varied the design (the original threshold design, MAP ≥ 73 vs < 73 mmHg from vasopressor initiation with controlled standardization; the band strategies applied from the first vasopressor without a landmark; thresholds of 70, 75, and 80 mmHg; 24- and 72-hour windows; a 2-hour grid), the estimation (controlled standardization; positivity trimming to modelled probabilities of 0.10–0.90; prior scales of 1 and 10; SEPSISPAM-centred and skeptical priors on the interaction, Normal(− 0.64, 0.31) and Normal(0, 0.35) on the log scale), and the data (invasive MAP only; double-strength eICU-CRD infusion concentrations; 28-day all-cause mortality in MIMIC-IV). Sensitivity analyses used two chains of 500 iterations and 400 simulation draws (details and diagnostics in ESM 11). Analyses used Python 3 with DuckDB, cmdstanpy, and Stan.

Results

Cohorts

Of 26,886 and 22,256 vasopressor-treated ICU stays in MIMIC-IV and eICU-CRD, 7,181 and 6,533 adults with sepsis in their first ICU stay, alive and in the ICU at the 6-hour landmark, formed the analysis cohort of 13,714 patients (Fig. 1). After exclusion of 593 and 502 patients with end-stage renal disease and 122 and 119 with RRT before the landmark, 6,466 and 5,912 patients (12,378) entered the RRT analysis. Chronic hypertension was present in 4,521 (63.0%) and 3,338 (51.1%) patients (7,859; 57.3%). Hypertensive patients were older and had more chronic kidney disease and higher creatinine, but similar acute illness severity, landmark MAP, lactate, and vasopressor dose, and similar crude outcomes (Table 1). In the first interval after the landmark, 41% of patients in each cohort had a mean MAP of 73 mmHg or higher, 37–38% were in the 65–72 mmHg band, and 21% were below 65 mmHg, with identical distributions in the two strata (Table 1); patients spent on average 46–48% of the window at 73 mmHg or higher, and the modelled probability of the higher category in the first interval was below 0.10 in 21% of patients (ESM 6).

Table 1

Baseline characteristics, hemodynamic state at the 6-hour landmark, strategy categories, and crude outcomes of the two cohorts, overall and by chronic-hypertension status

Characteristic	MIMIC-IV Overall	No chronic hypertension	Chronic hypertension	SMD	eICU-CRD Overall	No chronic hypertension	Chronic hypertension	SMD
No. of ICU stays	7,181	2,660	4,521		6,533	3,195	3,338	
Age, mean (SD), y	65.2 (15.2)	59.2 (16.6)	68.7 (13.1)	+ 0.64	66.6 (15.1)	62.9 (16.5)	70.1 (12.7)	+ 0.49
Female, %	44.5	45.6	43.8	−0.04	47.7	48.4	47.1	−0.02
Chronic kidney disease, %	29.0	14.0	37.9	+ 0.57	14.0	9.1	18.8	+ 0.28
End-stage renal disease, %	8.3	3.5	11.0	+ 0.29	7.7	6.9	8.4	+ 0.06
Charlson comorbidity index, median [IQR]	6 [4–8]	5 [2–7]	6 [5–8]	+ 0.61	—	—	—	—
Illness severity, median [IQR][b]	8 [6–11]	8 [6–11]	8 [6–11]	−0.03	81 [65–100]	81 [65–99]	81 [65–100]	+ 0.02
MAP, hours 0–6, mean (SD), mmHg	71.8 (8.5)	71.6 (8.3)	71.9 (8.6)	+ 0.04	70.7 (8.7)	70.6 (8.6)	70.8 (8.7)	+ 0.02
Lactate at hour 6, median [IQR], mmol/L	2.0 [1.4–3.0]	2.0 [1.5–3.1]	2.0 [1.4–3.0]	−0.04	2.2 [1.5–3.2]	2.2 [1.5–3.4]	2.2 [1.5–3.1]	−0.06
Creatinine at hour 6, median [IQR], mg/dL	1.5 [1.0–2.4]	1.3 [0.8–1.9]	1.5 [1.1–2.7]	+ 0.35	1.6 [1.0–2.7]	1.5 [0.9–2.4]	1.7 [1.1–2.9]	+ 0.19
NEE dose, hours 0–6, median [IQR], µg/kg/min	0.10 [0.05–0.21]	0.10 [0.05–0.22]	0.10 [0.05–0.20]	−0.07	0.10 [0.04–0.22]	0.09 [0.04–0.22]	0.10 [0.04–0.22]	0.00
MAP ≥ 73 mmHg in first interval, %	40.8	40.7	40.9	0.00	41.2	40.8	41.5	+ 0.01
MAP 65–72 mmHg in first interval, %	38.2	38.6	37.9	−0.01	37.1	37.9	36.3	−0.03

Data are mean (SD), median [interquartile range], or percentage. SMD, standardized mean difference comparing the chronic-hypertension and no-chronic-hypertension strata; MAP, mean arterial pressure; NEE, norepinephrine-equivalent dose. [a]Excludes patients with pre-existing end-stage renal disease and patients receiving renal-replacement therapy before the landmark (MIMIC-IV n = 6,466; eICU-CRD n = 5,912). [b]First-day Sequential Organ Failure Assessment score in MIMIC-IV and APACHE IV score in eICU-CRD; the scales are not comparable.

Characteristic	MIMIC-IV	No chronic hypertension	Chronic hypertension	SMD	eICU-CRD	No chronic hypertension	Chronic hypertension	SMD
	Overall				Overall			
MAP < 65 mmHg in first interval, %	20.8	20.5	21.0	+ 0.01	21.1	20.7	21.5	+ 0.02
Fraction of window at ≥ 73 mmHg, mean (SD)	0.46 (0.33)	0.45 (0.33)	0.47 (0.33)	+ 0.05	0.48 (0.35)	0.47 (0.35)	0.49 (0.35)	+ 0.06
In-hospital mortality, %	34.3	33.1	35.1	+ 0.04	31.3	30.2	32.3	+ 0.05
New renal-replacement therapy, %[a]	12.4	12.5	12.4	−0.01	9.0	9.2	8.8	−0.01

Data are mean (SD), median [interquartile range], or percentage. SMD, standardized mean difference comparing the chronic-hypertension and no-chronic-hypertension strata; MAP, mean arterial pressure; NEE, norepinephrine-equivalent dose. [a]Excludes patients with pre-existing end-stage renal disease and patients receiving renal-replacement therapy before the landmark (MIMIC-IV n = 6,466; eICU-CRD n = 5,912). [b]First-day Sequential Organ Failure Assessment score in MIMIC-IV and APACHE IV score in eICU-CRD; the scales are not comparable.

Effect modification by chronic hypertension

For new RRT, the strategy × hypertension interaction odds ratio was 1.20 (95% CrI, 0.88–1.65) (Table 2, Fig. 2). The posterior probability that the interaction was below 1 was 13%; that it was at most 0.75, 0.2%; that it was at most 0.53, below 0.01%; and that it lay within 0.80–1.25, 59%. For mortality, the interaction was 1.04 (0.73–1.48), with a 78% probability of lying within 0.80–1.25. On the additive scale, the between-stratum difference in the 28-day risk difference was + 0.5 (− 1.1 to 2.1) percentage points for RRT and − 1.3 (− 2.6 to − 0.1) percentage points for mortality. Within strata, the 28-day risk of new RRT was 3.0 and 3.5 percentage points lower under the higher strategy in patients with and without chronic hypertension, and the day-7 risk differences, the horizon of the SEPSISPAM renal outcome, were likewise similar between strata (Table 2). The database-specific RRT interactions were 1.21 (0.80–1.79) in MIMIC-IV and 1.18 (0.77–1.80) in eICU-CRD (difference in log odds ratio, − 0.03 [− 0.49 to 0.45]) and the mortality interactions 1.12 (0.71–1.82) and 0.91 (0.59–1.43) (− 0.20 [− 0.74 to 0.31]) (Table 2).

Table 2

Standardized 28-day cumulative incidence under the sustained higher (MAP ≥ 73 mmHg) and lower (MAP 65–72 mmHg) strategies, within-stratum risk differences, and effect modification by chronic hypertension in the pooled cohort and in each database's population

Outcome and population	Patients (events)	28-d risk, higher strategy, % (95% CrI)	28-d risk, lower strategy, % (95% CrI)	Risk difference, pp (95% CrI)	Day-7 risk difference, pp (95% CrI)	Interaction OR (95% CrI)	Additive interaction, pp (95% CrI)
New renal-replacement therapy							
Chronic hypertension	6,947	10.3 (9.2–11.3)	13.2 (11.6–15.0)	−3.0 (− 5.3 to − 1.0)	−2.3 (− 4.2 to − 0.5)	1.20 (0.88–1.65)	+ 0.5 (− 1.1 to 2.1)
No chronic hypertension	5,431	9.4 (8.4–10.5)	12.9 (11.5–14.4)	−3.5 (− 5.4 to − 1.6)	−2.9 (− 4.6 to − 1.3)		
All patients	12,378 (1,354)					P(OR < 1) = 13%; P(OR ≤ 0.75) = 0.2%; P(OR ≤ 0.53) < 0.01%; P(0.80–1.25) = 59%	
MIMIC-IV population[a]	6,466 (812)	11.4 / 10.9	14.7 / 14.6	−3.3 (− 5.8 to − 1.0) −3.8 (− 5.8 to − 1.6)		1.21 (0.80–1.79)[b]	+ 0.5 (− 1.4 to 2.2)
eICU-CRD population[a]	5,912 (542)	8.7 / 8.1	11.2 / 11.3	−2.5 (− 4.6 to − 0.7) −3.2 (− 5.1 to − 1.5)		1.18 (0.77–1.80)[b]	+ 0.7 (− 0.8 to 2.3)
Between-database difference[b]						Δ log-OR − 0.03 (− 0.49 to 0.45); P(Δ > 0) = 44%	
In-hospital mortality							
Chronic hypertension	7,859	23.8 (22.4–25.4)	35.8 (33.6–38.2)	−12.0 (− 15.1 to − 8.9)	−6.2 (− 8.2 to − 4.2)	1.04 (0.73–1.48)	−1.3 (− 2.6 to − 0.1)
No chronic hypertension	5,855	20.6 (19.2–	31.3 (29.3–	−10.7 (− 13.5 to −	−5.6 (− 7.3 to − 3.8)		

Risks are posterior medians of the standardized competing-risk cumulative incidence from the Bayesian g-formula fitted to the two databases as one cohort, each hypertension stratum standardized over its pooled baseline covariate distribution. The interaction OR is the strategy × chronic-hypertension coefficient on the discrete-time cause-specific hazard during the 48-hour window (odds ratio approximating a ratio of cause-specific hazard ratios); the additive interaction is the between-stratum difference of the 28-day risk differences. Posterior probabilities are from the 1,000 posterior draws; values below their resolution are from the Normal approximation of the posterior. The within-stratum risk differences for mortality are confounded by the severity that determines whether a higher pressure can be sustained and are not interpreted as effects of a target (see Discussion). [a]The same fitted model standardized to that database's own baseline covariate distribution; risks and risk differences are given as chronic hypertension / no chronic hypertension. [b]Database-specific interaction from the heterogeneity model (strategy × database and strategy × hypertension × database terms added to the hazard models); Δ log-OR, eICU-CRD minus MIMIC-IV. CrI, credible interval; OR, odds ratio; pp, percentage points.

Outcome and population	Patients (events)	28-d risk, higher strategy, % (95% CrI)	28-d risk, lower strategy, % (95% CrI)	Risk difference, pp (95% CrI)	Day-7 risk difference, pp (95% CrI)	Interaction OR (95% CrI)	Additive interaction, pp (95% CrI)
		22.0)	33.5)	8.0)			
All patients	13,714 (4,286)					P(OR < 1) = 42%; P(OR ≤ 0.75) = 3.5%; P(0.80–1.25) = 78%	
MIMIC-IV population[a]	7,181 (2,296)	24.3 / 20.3	36.7 / 30.8	−12.3 (− 15.7 to − 9.1) −10.5 (− 13.3 to − 7.7)		1.12 (0.71–1.82)[b]	−1.8 (− 3.1 to − 0.5)
eICU-CRD population[a]	6,533 (1,990)	23.0 / 20.9	34.6 / 31.7	−11.6 (− 14.5 to − 8.6) −10.9 (− 13.7 to − 8.2)		0.91 (0.59–1.43)[b]	−0.8 (− 2.2 to 0.8)
Between-database difference[b]						Δ log-OR − 0.20 (− 0.74 to 0.31); P(Δ > 0) = 23%	

Risks are posterior medians of the standardized competing-risk cumulative incidence from the Bayesian g-formula fitted to the two databases as one cohort, each hypertension stratum standardized over its pooled baseline covariate distribution. The interaction OR is the strategy × chronic-hypertension coefficient on the discrete-time cause-specific hazard during the 48-hour window (odds ratio approximating a ratio of cause-specific hazard ratios); the additive interaction is the between-stratum difference of the 28-day risk differences. Posterior probabilities are from the 1,000 posterior draws; values below their resolution are from the Normal approximation of the posterior. The within-stratum risk differences for mortality are confounded by the severity that determines whether a higher pressure can be sustained and are not interpreted as effects of a target (see Discussion). [a]The same fitted model standardized to that database's own baseline covariate distribution; risks and risk differences are given as chronic hypertension / no chronic hypertension. [b]Database-specific interaction from the heterogeneity model (strategy × database and strategy × hypertension × database terms added to the hazard models); Δ log-OR, eICU-CRD minus MIMIC-IV. CrI, credible interval; OR, odds ratio; pp, percentage points.

Within-stratum contrasts and sensitivity analyses

The modelled 28-day mortality was 11 to 12 percentage points lower under the higher than under the lower strategy in both strata (Table 2), far larger than any trial has observed and opposite in direction to OPTPRESS (7). We interpret these within-stratum contrasts, for RRT as for mortality, as confounded by the severity that determines whether a higher pressure can be sustained (see Discussion).

With the two-cohort estimator, the primary specification gave pooled interactions of 1.21 (0.87–1.67) for RRT and 1.03 (0.70–1.50) for mortality, the same as the one-cohort estimates, and the interaction estimates were stable across the sensitivity analyses (ESM 11, Table S11.1 and Fig. S11.1). The pooled RRT interaction ranged from 0.93 (0.69–1.26) without the landmark to 1.26 (0.94–1.68) with a 72-hour window; it was 1.03 (0.78–1.37) under the original threshold design and 1.16–1.27 across the other variants, unchanged by controlled standardization and positivity trimming. In no analysis did the posterior probability of an RRT interaction at most 0.75 exceed 9.3%, or of one at most 0.53 exceed 0.03%. With a prior centred on the SEPSISPAM subgroup, the RRT interaction was 0.95 (0.65–1.41) in MIMIC-IV and 0.85 (0.57–1.21) in eICU-CRD (pooled, 0.89 [0.69–1.16]; probability of at most 0.53, 0.02%), and the skeptical prior gave 1.13 (0.86–1.50). The pooled

mortality interaction ranged from 0.86 (0.61–1.22) to 1.24 (0.84–1.83) across variants, was 0.76 (0.56–1.03) under the SEPSISPAM prior, and 0.84 (0.47–1.50) for 28-day all-cause mortality in MIMIC-IV. Additive interactions stayed within 1.1 percentage points of zero for RRT, except in the smaller eICU-CRD arterial-line subcohort (+ 2.5; −2.2 to 6.9), and between − 2.5 and + 0.3 percentage points for mortality.

Discussion

In two independent ICU databases analysed as one cohort, a target trial emulation of sustained higher- and lower-MAP strategies in septic shock found no evidence that chronic hypertension modifies the effect on new RRT or mortality. The RRT interaction, the direct test of the hypothesis that a higher pressure protects the hypertensive kidney, lay above 1, the posterior probability of an interaction as protective as the SEPSISPAM subgroup implied was below 0.01%, and the additive interaction was within one percentage point of zero; the mortality interaction was 1.04 on the hazard scale and − 1.3 percentage points on the additive scale.

These findings extend the randomized evidence accumulated since SEPSISPAM (3, 5–8). Across randomized subgroups, an individual-patient synthesis, a formal search for heterogeneity, and now an emulation of sustained strategies in 13,714 patients, the renal-protection signal has not reproduced. The wider randomized evidence points the same way: in a meta-analysis of 28 trials and 15,672 critically ill and surgical patients, lower blood-pressure targets were associated with lower mortality, the effect was carried by the critically ill trials, and acute kidney injury did not differ between targets (25).

Our emulation adds two things the trials could not: it contrasts sustained achievement of a pressure over 48 hours, the exposure the autoregulatory mechanism implicates, rather than assignment to a target at one moment; and it quantifies how far the data are from the hypothesis, since even a prior that fully adopted the SEPSISPAM subgroup estimate was pulled to a pooled RRT interaction of 0.89 (0.69–1.16), leaving a 0.02% posterior probability of the SEPSISPAM value.

Any benefit of a higher target has to be weighed against the vasopressor exposure needed to achieve it, which in randomized trials was associated with more arrhythmia (3), fewer RRT-free days (7), and harm mediated through the norepinephrine requirement (8). This trade-off is the premise of “protective hemodynamics”, which proposes lowering the pressure target when vasopressor requirements rise rather than escalating catecholamines to hold a number, and which regards a higher target for hypertensive patients as unsupported by trial evidence (26).

The within-stratum contrasts must not be read as effects of a target. The strategies are defined by achieved MAP, and no clinician can assign a patient to a sustained pressure below a threshold: the modelled 11- to 12-percentage-point mortality advantage of the higher strategy measures the severity that determines whether a pressure can be sustained, not the benefit of sustaining it. In the data a high achieved MAP is followed by weaning, so under the simulated higher strategy the vasopressor dose falls rather than rises; the g-formula learns the clinician's response to pressure, not the physiology that produces it. Our estimand was chosen to be robust to this structure: a bias shared by both strata cancels in the between-stratum interaction, and the MAP distribution, time at target, and positivity profile were identical in the two strata.

Our findings do not argue against individualizing the pressure target; they argue against individualizing it on a history of hypertension. Expert guidance frames personalization as a response-guided process, a transient “MAP challenge” with reassessment of perfusion indices and de-escalation when they do not improve, rather than a target assigned from a baseline characteristic (27), and testing such a strategy, rather than another fixed-target comparison, is the natural next step.

Strengths include two independent databases, analysed as one cohort and giving concordant database-specific estimates; a sustained-strategy estimand with explicit handling of the feedback between achieved MAP and vasopressor dose; competing events handled for both outcomes; a single posterior from which all quantities are read coherently; and validation of the component models by posterior predictive checks and a natural-course simulation. Bayesian g-computation has rarely been used for target trial emulation in critical care (28), and the Bayesian framing serves the question directly: it yields the

probability that the interaction is as large as prior studies implied, or lies within a range of practical equivalence, rather than a verdict on a null hypothesis (24).

The study has limitations. It is observational, and identification rests on no unmeasured confounding of the achieved MAP given the modelled covariates and on correctly specified models; the g-formula trades the weight-model assumptions of inverse-probability methods for outcome-model assumptions and extrapolates where few patients sustained a strategy for 48 hours. Both cohorts are U.S. ICUs, and the strategies tested fixed thresholds rather than targets individualized to premorbid pressure. Finally, the credible intervals, particularly for RRT, do not exclude moderate effect modification in either direction, although they exclude the magnitude the SEPSISPAM subgroup implied.

Conclusion

In 13,714 patients from two independent ICU databases, a target trial emulation estimated with Bayesian g-computation found no evidence that chronic hypertension modifies the renal or mortality effect of sustained MAP strategies in septic shock and excluded an interaction of the size the SEPSISPAM subgroup implied. Concordant with contemporary randomized evidence, these data do not support targeting a higher MAP for renal protection on the basis of a hypertension history alone.

Declarations

Ethics approval: Both databases are de-identified. MIMIC-IV was accessed under PhysioNet credentialing; the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved the data collection and waived informed consent. eICU-CRD is released under the HIPAA safe-harbor provisions. No additional ethical approval was required.

Consent for publication: All co-authors have reviewed the final manuscript and given their formal consent for its submission and publication

Availability of data and material: MIMIC-IV and eICU-CRD are available to credentialed users at https://physionet.org.

Conflicts of interest: The authors declare no conflicts of interest.

Funding: No funding.

Consent to participate: Not applicable (de-identified databases; consent waived by the source institutions).

Code availability: The analysis code is available will be deposited in a public repository with a DOI on acceptance.

Authors' contributions: Conceptualization: NS, PZ; Methodology: NS, JP; Formal analysis and investigation: NS, CK; Writing - original draft preparation: PZ; Writing - review and editing: SS, CK, JP; Supervision: NS;

Declaration of Artificial Intelligence assisted technologies: During the preparation of this work the author(s) used Claude Opus 5.5 (Anthropic, San Francisco, Californa) in order to improve the readability of the text and formatting. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article

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Figures

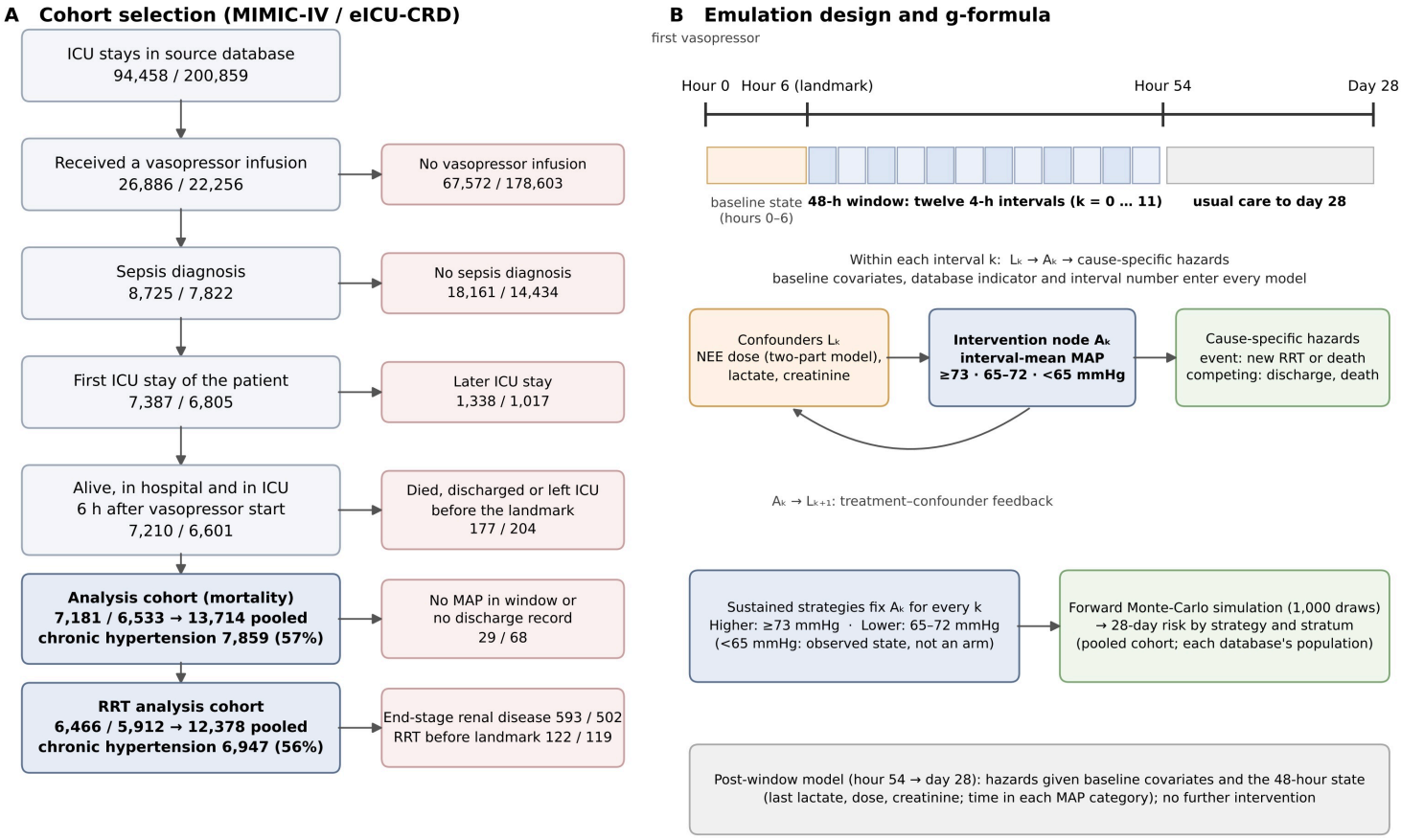


Figure 1

Cohort selection and emulation design. (A) Flow of ICU stays in MIMIC-IV and eICU-CRD from the source databases to the analysis cohorts and the renal-replacement-therapy (RRT) cohorts; counts are shown as MIMIC-IV / eICU-CRD. (B) Design of the emulation: time zero is 6 hours after the first vasopressor infusion; the 48-hour exposure window is divided into twelve 4-hour intervals in which the mean arterial pressure (MAP) category (≥73, 65–72, or <65 mmHg) is the intervention node and norepinephrine-equivalent dose, lactate, and creatinine are the simulated time-varying confounders; cause-specific hazards of the event and the competing event are modelled within the window and, conditional on the 48-hour state, to day 28 under usual care. Arrows from the intervention node back to the confounders mark the treatment–confounder feedback that the g-formula simulates forward.

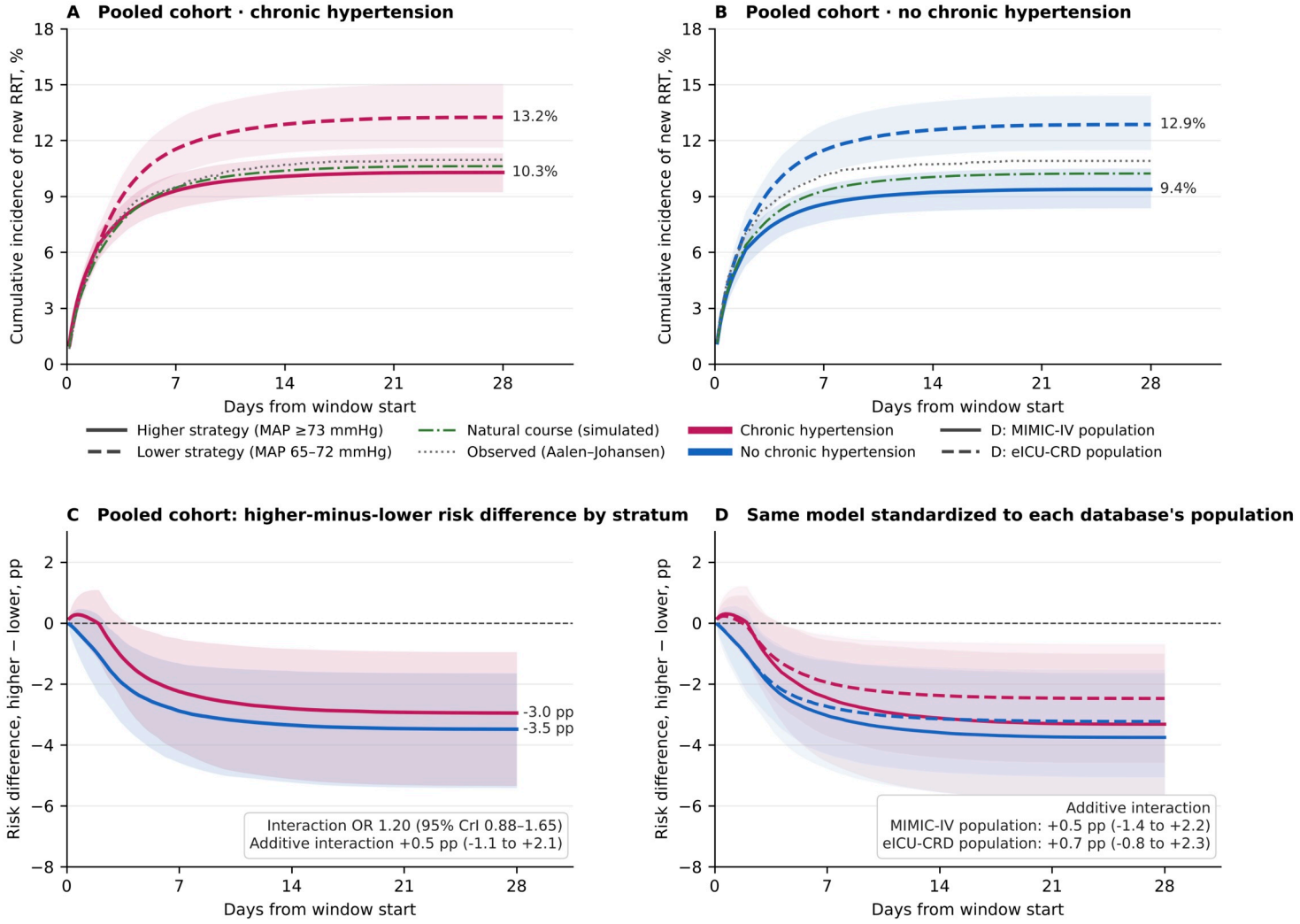


Figure 2

Effect of the sustained MAP strategies on new renal-replacement therapy (RRT) by chronic-hypertension status in the pooled cohort. (A, B) Standardized cumulative incidence of new RRT under the higher (solid) and lower (dashed) strategies in patients with (A) and without (B) chronic hypertension, with the simulated natural course (green dash-dot) and the observed Aalen–Johansen estimate (grey dotted) for reference; 28-day values are labelled. The within-stratum contrasts are per-protocol comparisons of achieved pressure and are subject to the confounding by severity discussed in the text; the natural course lies close to the higher-strategy curve, and only 1.1% of patients sustained the lower strategy for all twelve intervals (ESM 6), so that curve rests largely on model extrapolation. (C) Within-stratum difference in cumulative incidence (higher minus lower, percentage points) in patients with and without chronic hypertension; the gap between the curves is the

additive interaction, and the strategy × hypertension interaction odds ratio and additive interaction are given in the panel. (D) The same fitted model standardized to the MIMIC-IV (solid) and eICU-CRD (dashed) populations. Colour encodes the stratum (chronic hypertension, magenta; no chronic hypertension, blue); shaded areas are 95% posterior credible intervals. The mortality counterpart is shown in ESM 9.

Supplementary Files

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- ESMOnlineResource1.docx