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Proactive vs Reactive Treatment of Hypotension During Surgery The PRETREAT Randomized Clinical Trial

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IMPORTANCE Intraoperative hypotension is associated with adverse postoperative outcomes, but whether a proactive strategy to prevent intraoperative hypotension improves outcomes is uncertain.

OBJECTIVE To determine whether intraoperative blood pressure management stratified by risk of hypotension reduces postoperative functional disability compared with usual care in adults undergoing noncardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial, adults undergoing elective noncardiac surgery at 2 tertiary hospitals in the Netherlands were enrolled from June 17, 2021, to February 7, 2024. The date of last follow-up was October 24, 2024.

INTERVENTION Patients were randomized 1:1 to proactive blood pressure management with mean arterial pressure targets based on risk of intraoperative hypotension (low risk, ≥ 70 mm Hg; intermediate risk, ≥ 80 ; high risk, ≥ 90) or usual management at their anesthesiologist's discretion, generally aiming to avoid a mean arterial pressure of less than 65 mm Hg without higher predefined targets.

MAIN OUTCOMES AND MEASURES The primary outcome was functional disability at 6 months, assessed with the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0; scale range, 0-100; higher scores indicate more disability). A minimally clinically important difference of 5 points was prespecified. There were 23 secondary outcomes, including quality of life, complications, and mortality within 6 months.

RESULTS The trial was stopped early for futility after 3247 of 5000 planned patients (median age, 59 years [IQR, 44-69]; 1738 female [53.5%]) were enrolled. A total of 677 patients (21%) were low risk; 1814 (56%), intermediate risk, and 756 (23%), high risk. Baseline median WHODAS scores were 12.5 [IQR, 4.2-29.2] in proactive group and 14.6 [IQR, 4.2-29.2] in standard group. At 6 months, mean (SD) WHODAS scores were 17.7 (20.1) in the proactive group and 18.2 (20.5) in the standard group (mean difference, -0.5; 95% credible interval, -1.9 to 0.9). There were no significant differences in any of the 23 secondary outcomes.

CONCLUSIONS AND RELEVANCE Intraoperative blood pressure management with mean arterial pressure goals stratified by risk of hypotension did not improve functional disability at 6 months postoperatively compared with standard intraoperative blood pressure management.

TRIAL REGISTRATION Overview of Medical Research in the Netherlands (CCMO): [NL-OMON55117](#)

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Intraoperative hypotension, defined as a mean arterial pressure of less than 65 mm Hg, affects more than 75% of patients undergoing surgery and is associated with adverse clinical outcomes, including myocardial ischemia, kidney failure, and mortality.¹⁻⁹ However, it remains uncertain whether hypotension during anesthesia should be corrected. Studies aiming to prevent intraoperative hypotension have primarily focused on identifying the lowest threshold of blood pressure not associated with adverse outcomes. Several randomized trials have been conducted, although they were limited by small sample sizes, or failure to report or achieve substantial differences in blood pressures between intervention and control groups.^{8,10-15}

Patients determined preoperatively to be at higher risk of intraoperative hypotension may experience more rapid or severe blood pressure declines intraoperatively and thus may benefit from a higher mean arterial pressure (MAP) target higher than the commonly used threshold of 65 mm Hg. Based on this rationale, we hypothesized that stratified blood pressure targets—adjusted to a patient's expected risk of intraoperative hypotension—could reduce intraoperative hypotension and improve outcomes.

To evaluate this hypothesis, the PRETREAT trial (Proactive vs Reactive Treatment of Hypotension), a pragmatic randomized trial comparing a proactive, risk-stratified approach to intraoperative blood pressure management vs usual care, was conducted.¹⁶ The primary outcome was functional disability at 6 months, measured using the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0),^{17,18} which evaluates functional impairment across 6 domains: cognition, mobility, self-care, interpersonal relationships, life activities, and participation.^{17,19,20} A 6-month time point was selected to capture both persistent complications and downstream effects of perioperative events, including those that may have clinically resolved but affect long-term recovery. This time point aligns with recommendations from the Standardized Endpoints in Perioperative Medicine (STEP) initiative, which identified 6-month patient-reported disability, measured with WHODAS, as an important functional outcome for perioperative trials.¹⁹

Methods

Design, Organization, and Oversight

This was a randomized clinical trial conducted at the University Medical Center Utrecht and Amsterdam University Medical Center, the Netherlands. The trial was registered with the Overview of Medical Research in the Netherlands registry (NL-OMON55117, first registration March 3, 2021).²¹ The trial protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht (reference No. 20-749) and has been published previously (Supplement 1).¹⁶ All participants provided written informed consent before enrollment. The trial used an adaptive 2-phase design, which incorporated a first adaptive phase allowing for iterative adaptations of the intervention strategy, and a successive trial phase studying the effect of the intervention strategy on patient out-

Key Points

Question Does intraoperative blood pressure management with a mean arterial pressure goal stratified by preoperatively determined risk of intraoperative hypotension improve postoperative functional disability at 6 months in patients undergoing elective noncardiac surgery?

Findings In this randomized clinical trial including 3247 adults undergoing elective noncardiac surgery, targeting a mean arterial pressure of at least 70 mm Hg for patients at low risk, at least 80 mm Hg for those at intermediate risk, and at least 90 mm Hg for those at high risk of intraoperative hypotension did not improve postoperative disability at 6 months as measured by the World Health Organization Disability Assessment Schedule (range, 0 to 100; minimal clinically important difference, 5 percentage points) compared with usual intraoperative management that aimed to maintain a mean arterial pressure of at least 65 mm Hg at the discretion of the treating anesthesiologist (mean score, 17.7 vs 18.2, respectively).

Meaning Proactive, risk-stratified blood pressure management did not improve postoperative disability at 6 months.

come. During the adaptive phase, data on the incidence of hypotension were monitored every 3 weeks (≈ 8 times) to accommodate necessary adaptations to the intervention strategy. At the end of the adaptive phase (at 6 months) an interim assessment of intervention efficacy was conducted, with a 30% or more relative risk reduction in intraoperative hypotension as the criterion to continue with the trial, no longer allowing any adaptations to the intervention strategy. The trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

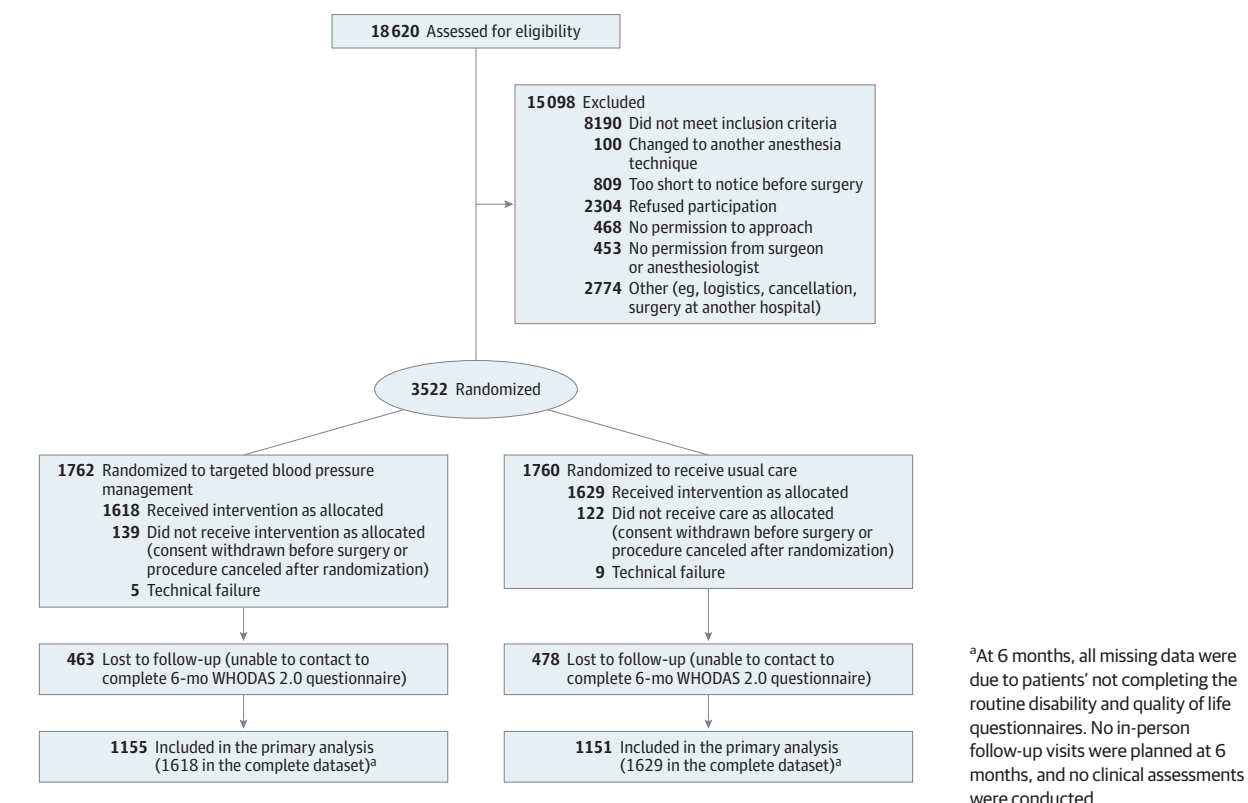
Trial Population

Adult patients (≥ 18 years) undergoing elective noncardiac surgery under general or central-neuraxial anesthesia with an expected hospital stay of at least 1 night after surgery were eligible for inclusion (Figure 1). Patients undergoing low-risk surgeries (eg, ophthalmic), obstetric procedures, or organ transplant; participating in other clinical trials; being unable to meet study requirements (eg, legal incapacity); and having an American Society of Anesthesiologists (ASA) physical status of 5 were excluded.

Trial Procedures

Patients were randomized 1:1 to a proactive blood pressure management strategy (intervention) or usual care (control), using concealed, computer-generated permuted blocks (sizes 4, 6, 8) in Castor EDC software,²² stratified by predicted intraoperative hypotension risk. Randomization was performed through the Castor EDC system with concealed allocation. Although the same research team member could also coordinate follow-up, patients completed outcome questionnaires digitally, ensuring that outcome assessment remained blinded to treatment allocation. Patients were not informed of their allocation until after completion of the 6-month follow-up questionnaires to avoid influencing self-reported outcomes. Treating anesthesiologists in the intervention group were aware of

Figure 1. Recruitment, Randomization, and Follow-Up of Patients in the PRETREAT Trial



allocation to deliver the proactive strategy, whereas anesthesiologists in the control group were not informed that their patients were participating in the trial to minimize changes in usual care behavior.

Prior to randomization, a trained researcher calculated each patient's predicted risk of intraoperative hypotension using a prespecified, center-specific model based on historical data (eAppendix 1 in Supplement 2). Patients were classified into low-, intermediate-, or high-risk groups, which determined their assigned MAP target in the intervention group. Anesthesia teams were provided a locally developed clinical guideline (Appendix 2 of the study protocol in Supplement 1) via email the day before surgery and as printed material in the operating room, including flowcharts with risk stratum-specific treatment options. The choice of vasopressor, dosing, and timing remained at the discretion of the attending anesthesiologist.

The intervention strategy required anesthesiologists to maintain a minimum intraoperative MAP of at least 65 mm Hg, with goals of at least 70 mm Hg for low-risk, at least 80 mm Hg for intermediate-risk, or at least 90 mm Hg for high-risk patients. A detailed description of this strategy is provided in the published protocol.¹⁶ The control group received usual care, in which anesthesiologists sought to avoid sustained MAP values lower than 65 mm Hg, consistent with current standards of practice and the European Society of Cardiology guideline recommendations.²³

Preoperative antihypertensive medications were managed according to institutional policy, which aligns with international recommendations.²³ Angiotensin-converting en-

zyme inhibitors, angiotensin receptor blockers, and diuretics were withheld on the day of surgery, except for patients with heart failure with reduced ejection fraction, in whom continuation of these medications was advised. Patients taking β -blockers and calcium channel blockers preoperatively continued these medications, and other antihypertensive agents were managed at the discretion of the treating physician.

For patients with intraarterial catheters in place, arterial blood pressure values were recorded—1 every minute. For patients with intermittent noninvasive blood pressure monitoring, MAP was typically measured every 3 to 5 minutes. Hypotension was defined as a MAP value lower than 65 mm Hg for at least 2 consecutive measurements for arterial blood pressure or 1 noninvasive reading to reduce misclassification from transient fluctuations.²⁴

The WHODAS 2.0 and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaires were obtained preoperatively (between the preoperative assessment visit and the day of surgery), at 30 days, and 6 months after surgery as part of routine clinical care at both locations.

Trial Outcomes

The primary outcome was postoperative disability 6 months after surgery, measured with the 12-item WHODAS 2.0 (score range, 0-100; higher scores indicate greater disability; minimally clinically important difference [MCID], 5 percentage points).¹⁷ Interpretation of the primary outcome was prespecified to be meaningful only if the intervention achieved both a measurable change in treatment behavior (guideline-adherent

initiation of vasopressors) and a reduction in intraoperative hypotension, defined as at least a 30% reduction in the area under the threshold for MAP of lower than 65 mm Hg.

There were 23 prespecified secondary outcomes. Patient-centered outcomes included WHODAS score at 30 days, EQ-5D-5L score at 30 days and 6 months, in-hospital mortality, mortality within 48 hours, and all-cause mortality within 6 months. Additional clinical outcomes were length of stay, postoperative troponin and creatinine values (≤ 7 days), acute kidney injury defined by Kidney Disease: Improving Global Outcomes criteria, intensive care unit admission, use of non-prophylactic antibiotics, hospital readmission, and reoperation. Perioperative complications included hemorrhage requiring transfusion, new-onset atrial fibrillation within 24 hours, and new-onset heart failure within 24 hours. A composite secondary outcome was life-threatening events, defined as any of the following: shock, venous thromboembolism (deep vein thrombosis or pulmonary embolism), myocardial infarction, stroke, or acute kidney injury. Full definitions of all secondary outcomes are provided in eAppendix 3 in [Supplement 2](#).

Sample Size Calculation and Power

Based on baseline WHODAS scores observed in the participating centers, we expected an absolute reduction in mean disability score from 17% to 12% (corresponding to an MCID of 5 percentage points) at 6 months in the intermediate-risk stratum between the study groups. Accounting for an anticipated 20% loss to follow-up at 6 months, we estimated that a total of 2500 patients per group would provide sufficient power (eAppendix 2 in [Supplement 2](#)).¹⁶

Statistical Analysis

All analyses were conducted using a bayesian framework, which allowed us to estimate credible treatment effects given the observed data. Patients were analyzed according to the group to which they were randomized, and those who withdrew consent or did not have the anticipated surgery were excluded from the analyses. Baseline characteristics of participants are described using frequencies with percentages for categorical variables and medians with interquartile ranges for continuous variables. Preoperative WHODAS and EQ-5D-5L missing data were imputed by using the median value of the corresponding variable because missingness of baseline covariates was minimal and median imputation was considered sufficient and more transparent than more complex methods.

Bayesian regression models were planned for analysis of the effect of the intervention on treatment, intraoperative blood pressures, and the outcome at 6 months, considering randomization, hypotension risk stratum, and their interaction. Because there were only 2 centers, we deemed it more efficient and transparent to model study center as a dichotomous fixed effect rather than including a random effect for 2 centers. Unless otherwise noted, all parameter estimates are reported as means with 95% credible intervals (CrIs). All models were fitted using weakly informative or noninformative default priors and using the Markov Chain Monte Carlo method.

Disability at 6 months was analyzed with bayesian linear regression, with baseline WHODAS scores as an additional independent variable. Superiority was defined as a posterior probability of at least 0.95 that WHODAS scores were at least 5 percentage points lower in the intervention group.¹⁷

Treatment changes, ie, the proportion of procedures in which vasoactive medication was initiated according to the clinical guidelines of the intervention strategy, were analyzed with bayesian logistic regression. Superiority was defined as a posterior probability at least 0.95 or higher guideline adherence in the proactive group compared with usual care.

Reduction in intraoperative hypotension, measured by the area under the threshold for a MAP value lower than 65 mm Hg, was assessed using bayesian linear regression. Superiority was defined as a posterior probability of at least 0.95 that the area under the threshold in the proactive group was at least 30% lower than in usual care.

In addition to area under the threshold of less than 65 mm Hg, we also calculated area under the threshold for MAP values lower than 100 mm Hg, higher than 100 mm Hg, and higher than 130 mm Hg. The area under the threshold lower than 100 mm Hg was predefined to capture the overall burden of blood pressure exposure below a physiological MAP threshold and was used both descriptively and in an exploratory association analysis (eAppendix 4 in [Supplement 2](#)). In contrast, MAP of at least 100 mm Hg and at least 130 mm Hg was predefined as safety end points to assess potential overtreatment with vasopressors and possible harm from excessive blood pressure elevations. These thresholds were selected based on clinical concerns that both hypotension and hypertension may contribute to adverse outcomes.

Patient-level secondary outcomes, such as postoperative complications and quality of life, were also analyzed using bayesian linear or logistic regression models. Nonpatient-centered secondary outcomes, such as process-level outcomes, were summarized descriptively.

At the start of the study, 2 interim analyses were prespecified with the following stopping criteria: (1) a relative risk reduction of less than 30% in the incidence of intraoperative hypotension (MAP < 65 mm Hg) at 6 months (the end of the adaptive phase); and (2) a 5 percentage point difference on the WHODAS scale at 30 days after the inclusion of 2500 patients (50% of the total sample size).

In June 2023, the data and safety monitoring board (DSMB) recommended to add futility criteria to the interim analysis at 2500 patients and include the primary outcome of WHODAS at 6 months (eAppendix 2, eTable 1 in [Supplement 2](#)). Several futility boundaries were defined, all based on an MCID of 5 percentage points on the WHODAS scale. Futility was defined if (1) the posterior probability percentage point difference of 5 or more at 6 months was 10% or less in all risk strata, or (2) the posterior probability percentage point difference of 5 or more at 30 days was 5% or less within each stratum and simultaneously 20% or less at 6 months.

Markov Chain Monte Carlo sampling was performed in R with the brms package (via Stan).^{25,26} Six chains were run with 10 000 iterations each, including 5000 warm-up iterations.

Table 1. Baseline Patient Characteristics

Characteristic	Intervention (n = 1618)	Control (n = 1629)
Age, median (IQR), y	59 (44-69)	59 (45-69)
Sex, No. (%)		
Men	764 (47.2)	745 (45.7)
Women	854 (52.8)	884 (54.3)
ASA classification, No. (%)		
1 (Healthy)	277 (17.1)	275 (16.9)
2 (Mild systemic disease)	932 (57.6)	941 (57.8)
3 or 4 (Severe systemic disease)	409 (25.3)	413 (25.4)
Type of surgery, No. (%)		
General	526 (32.5)	462 (28.4)
Gynecologic	247 (15.3)	291 (17.9)
Orthopedics	227 (14.0)	242 (14.9)
ENT or head and neck	228 (14.1)	216 (13.3)
Neurosurgery	191 (11.8)	198 (12.2)
Urologic	146 (9.0)	160 (9.8)
Plastic	53 (3.3)	59 (3.6)
Duration, median (IQR), min		
Planned	165 (105-225)	160 (105-225)
Realized	162 (103-250)	164 (104-245)
Type of blood pressure measurement		
Arterial (invasive)	301 (18.6)	279 (17.1)
Noninvasive	1317 (81.4)	1350 (82.9)
Baseline MAP, median (IQR), mm Hg	104 (93-114)	104 (93-115)
Preexisting conditions, No. (%) ^a		
Hypertension	470 (29.0)	480 (29.5)
Pulmonary	223 (13.8)	195 (12.0)
Cardiac	178 (11.0)	148 (9.1)
Diabetes	121 (7.5)	121 (7.4)
Kidney failure	53 (3.3)	69 (4.2)
Preoperative medication use		
ACE inhibitors or angiotensin receptor blockers	225 (13.9)	218 (13.4)
β-Blockers	170 (10.5)	154 (9.5)
Calcium antagonists	161 (10.0)	158 (9.7)
Diuretics	128 (7.9)	135 (8.3)
Antidiabetics	102 (6.3)	94 (5.8)
Type of anesthesia, No. (%)		
General ^b	1569 (97.0)	1589 (97.5)
Spinal	49 (3.0)	40 (2.5)
Preoperative WHODAS 2.0 score, median (IQR) ^{c,d}	12.5 (4.2-29.2) (n = 1517)	14.6 (4.2-29.2) (n = 1526)
Preoperative EQ-5D-5L score, median (IQR) ^{d,e}	0.8 (0.5-0.9) (n = 1517)	0.8 (0.5-0.9) (n = 1526)

Abbreviations: ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; ENT, ear, nose, and throat; EQ-5D-5L, EuroQol 5-Dimension 5-Level; MAP, mean arterial pressure; WHODAS, World Health Organization Disability Assessment Schedule.

^a Based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, codes provided in eAppendix 6 in Supplement 2.

^b Combined with epidural in 153 patients in the intervention group and 149 in the control group.

^c WHODAS score ranges from 0 to 100, with higher scores indicating greater disability. A score of around 12.5 reflects mild disability. A between-group difference of 5 points is considered the minimal clinically important difference.

^d Completed preoperative questionnaires; for the primary analysis, missing values were imputed using the sample median.

^e EQ-5D-5L index scores range from -0.59 to 1.00, with 1.00 indicating full health. A median score of 0.8 reflects moderate health-related quality of life.

Convergence was assessed using trace plots and with the Gelman-Rubin statistic. Posterior predictive checks evaluated model fit, ensuring consistency between observed and predicted data.

To assess robustness of the primary outcome to deviations from the missing-at-random assumption, we performed a delta-based sensitivity analysis applying fixed shifts to imputed WHODAS scores in the context of multiple imputation (eAppendix 5 in Supplement 2).

Interim Analyses

The prespecified interim analysis after the first 6 months demonstrated a more than 30% relative risk reduction in intraoperative hypotension and the trial was continued accordingly.

The second interim analysis—including the futility analysis—was conducted on December 12, 2023, at 2975 randomized patients rather than at approximately 2500 patients as planned. This delay was the result of the recommendation to add futility criteria by the DSMB requiring additional preparations

Table 2. Primary Outcome and Efficacy Requirements

	Mean (SD) [No. of patients]		Mean Difference (95% credible interval)		Odds ratio (95% credible interval) ^c
Data or outcome measure	Intervention	Control	Absolute ^a	Relative, % ^b	
Primary outcome					
WHODAS 2.0 score at 6 mo					
Overall ^d	17.7 (20.1) [1155]	18.2 (20.5) [1151]	-0.5 (-1.9 to 0.9)	-2.8 (-10.5 to 5.0)	
Low risk ^e	13.1 (15.8) [209]	13.9 (15.7) [202]	-0.4 (-3.7 to 2.9)	-2.5 (-26.4 to 21.0)	
Intermediate risk ^e	17.1 (18.6) [657]	17.9 (19.7) [651]	-0.9 (-2.8 to 0.9)	-5.0 (-15.4 to 5.2)	
High risk ^e	22.5 (24.7) [289]	21.8 (24.0) [298]	0.5 (-2.3 to 3.2)	2.2 (-10.4 to 14.7)	
Secondary outcomes					
Vasopressor initiation according to guidelines, % (No./total)					
Overall ^f	60.1 (973/1618)	29.5 (481/1629)	30.6 (28.3 to 34.9)	86.4 (72.9 to 101.6)	3.73 (3.21 to 4.31)
Low risk ^g	37.2 (124/333)	12.5 (43/344)	29.0 (21.7 to 36.0)	177.6 (109.0 to 276.1)	4.26 (2.89 to 6.30)
Intermediate risk ^g	62.0 (563/908)	30.7 (278/906)	32.2 (27.8 to 36.5)	82.1 (66.0 to 101.0)	3.87 (3.18 to 4.72)
High risk ^g	75.9 (286/377)	42.2 (160/379)	31.0 (24.8 to 37.1)	58.8 (43.1 to 78.0)	4.60 (3.35 to 6.34)
Area under the threshold for mean arterial pressure <65 mm Hg (minute × mm Hg)					
Overall ^h	28.5 (80.9) [1618]	70.6 (133.8) [1629]	-42.3 (-49.8 to -34.8)	-48.4 (-55.5 to -41.1)	
Low risk ⁱ	32.0 (66.4) [333]	95.6 (155.8) [344]	-64.6 (-80.8 to -48.1)	-58.3 (-69.4 to -46.2)	
Intermediate risk ⁱ	23.4 (78.8) [908]	63.4 (129.8) [906]	-40.1 (-50.0 to -30.0)	-50.1 (-60.0 to -39.6)	
High risk ⁱ	37.8 (95.3) [377]	65.6 (118.7) [379]	-27.3 (-43.1 to -11.9)	-32.8 (-48.0 to -15.6)	

^a Adjusted mean difference (continuous outcomes) or adjusted risk difference (binary outcomes) between intervention and control groups.

^b For continuous outcomes (World Health Organization Disability Assessment Schedule 2.0 [WHODAS 2.0] area under the threshold), the adjusted mean difference expressed as a percentage of the control group mean; for binary outcomes (vasopressor initiation), the adjusted risk difference expressed as a percentage of the control group event rate.

^c Adjusted odds ratio of the outcome comparing intervention and control groups.

^d The overall WHODAS effect was estimated in a bayesian linear regression model including randomization group, baseline WHODAS score, and study center.

^e The WHODAS risk group effects were estimated in a bayesian linear regression

model including randomization group, hypotension risk stratum, their interaction, baseline WHODAS score, and study center.

^f The overall vasopressor effect was estimated in a bayesian logistic regression model including randomization group and study center.

^g The vasopressor risk group effects were estimated in a bayesian logistic regression model including randomization group, hypotension risk stratum, their interaction, and study center.

^h The overall area under the threshold effect was estimated in a bayesian linear regression model including randomization group and study center.

ⁱ The area under the threshold risk group effects were estimated in a bayesian linear regression model including randomization group, hypotension risk stratum, their interaction, and study center.

including submitting revisions of the study protocol and the DSMB plan to the medical ethics committee.

For the second interim analysis, WHODAS data were available for 2474 patients at 30 days and 1896 patients at 6 months. The mean between-group difference in WHODAS score at 30 days was 0.6 (95% CrI, -2.3 to 3.5) and at 6 months was 2.0 (95% CrI, -1.8 to 5.7). The posterior probability of the intervention exceeding the MCID of 5 percentage points was less than 5%. Based on these results the DSMB concluded there was no harm, but recommended early termination of the trial for futility, so the trial was stopped. During the time required to conduct the analysis, review the results, and obtain the DSMB recommendation, the trial continued recruiting and additional patients were randomized, bringing the total enrollment to 3522 of the planned 5000.

Results

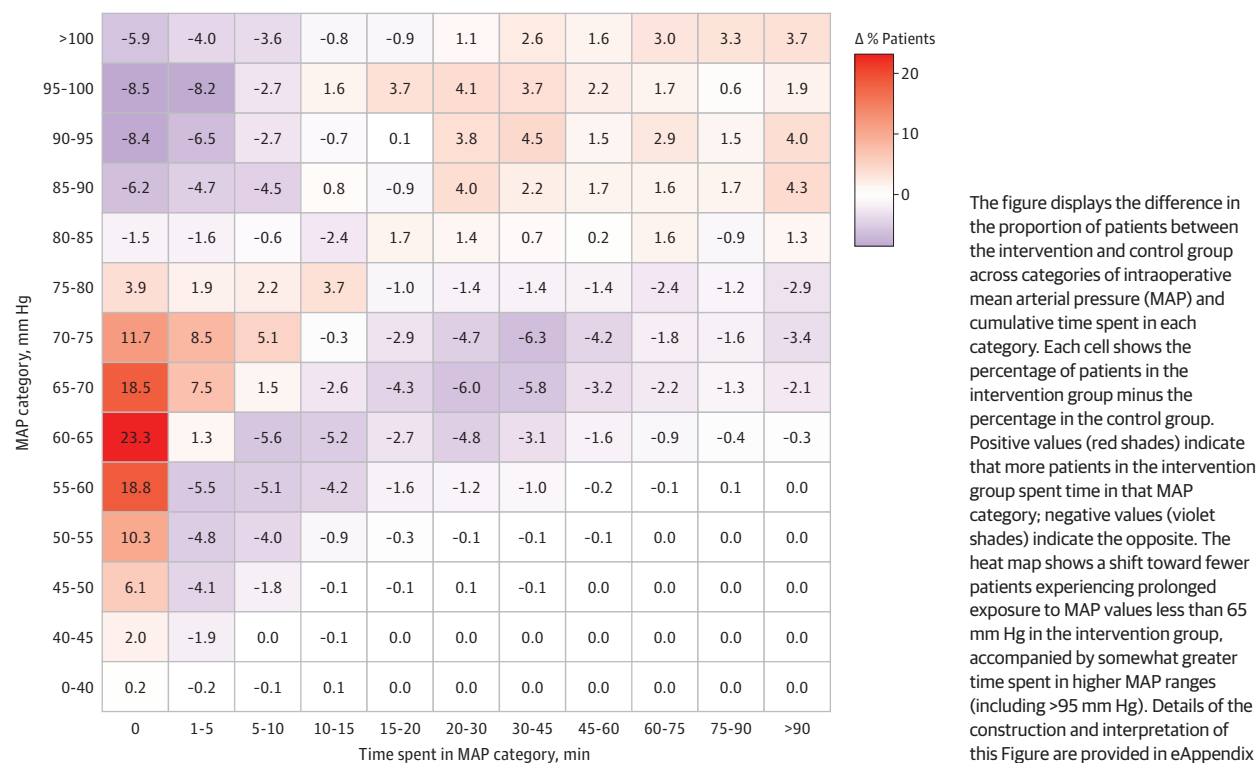
Trial Participants

Between June 17, 2021, and February 7, 2024, 18 620 patients were screened for eligibility. The trial was stopped early for

futility based on the DSMB recommendation after 3522 of 5000 planned patients were randomized: 1762 to the intervention group and 1760 to the usual care group (Figure 1). Of these, 1618 patients in the intervention group and 1629 in the usual care group received the allocated intervention and were included in the primary analysis population (Figure 1). The median age of participants was 59 years (IQR, 44-69), 1738 (53.5%) were female, and 3158 (97.3%) received general anesthesia (Table 1). The baseline characteristics were comparable between the groups. The date of last follow-up was October 24, 2024.

A preoperative clinical risk score stratified 677 patients (21%) as being at low risk; 1814 (56%), intermediate risk; or 756 (23%), high risk of intraoperative hypotension. Of the 3247 randomized patients who had received the allocated intervention, 580 (17.9%) received invasive blood pressure monitoring and 2667 (82.1%) received noninvasive measurements. At 6 months, 2306 patients (71.0%) completed WHODAS follow-up (1151 in the intervention group and 1155 in the control group). eTables 2 through 4 in Supplement 2 show baseline characteristics for each risk group.

Figure 2. Heat Map of Between-Group Differences in Intraoperative Mean Arterial Pressure Exposure



Primary Outcome

The mean (SD) WHODAS score at 6 months was 17.7 (20.1) in the intervention group and 18.2 (20.5) in the control group. The between-group difference was -0.5% (95% CrI, -1.9% to 0.9%), corresponding to a relative difference of -2.8% (95% CrI, -10.5% to 5.0%). The posterior probability of benefit of the intervention was 0.1% (Table 2; eFigure 1 in Supplement 2). Results were consistent across prespecified risk strata.

In low-risk patients, the mean (SD) WHODAS score was 13.1 (15.8) in the intervention group and 13.9 (15.7) in the control group, with a between-group difference of -0.4 (95% CrI, -3.7 to 2.9). In intermediate-risk patients, the mean (SD) scores were 17.1 (18.6) and 17.9 (19.7), respectively; difference -0.9 (95% CrI, -2.8 to 0.9). In high-risk patients, scores were 22.5 (24.7) vs 21.8 (24.0), with a difference of 0.5 (95% CrI, -2.3 to 3.2).

Treatment Behavior and Intraoperative Hypotension

As prespecified, interpretation of the primary outcome required demonstration of both a behavioral change (vasopressor initiation) and a reduction in intraoperative hypotension. Both conditions were met: vasopressor use according to clinical guidelines increased, and intraoperative hypotension was reduced (see the Trial Outcomes subsection in the Methods section). Compared with the control group, vasopressors were administered more frequently according to the clinical guidelines in the intervention group (odds ratio [OR], 3.73; 95% CrI, 3.21-4.31), with a 100% posterior probability of superiority across all risk strata (Table 2; eFigure 1 in Supplement 2).

The intervention effectively reduced intraoperative hypotension. The area under the threshold for MAP less than

65 mm Hg was 28.5 mm Hg × minutes in the intervention group vs 70.6 mm Hg × minutes in the control group, corresponding to a 48.4% relative reduction (95% CrI, -55.5% to -41.1%). The effect was most pronounced in low-risk patients (32.0 vs 95.6 mm Hg × minutes; relative reduction, -58.3%; 95% CrI, -69.4% to -46.2%). Across all risk strata, the relative risk reduction exceeded the prespecified 30% threshold, indicating shorter and/or less severe episodes of hypotension. The median average MAP was 86.9 mm Hg (IQR, 82.0-92.9) in the intervention group vs 81.1 mm Hg (IQR, 75.3-87.1) in the control group. Any MAP less than 65 mm Hg occurred in 47.7% of intervention patients vs 71.0% in controls (eTable 5 in Supplement 2).

Figure 2 displays a heat map of the difference in patient distribution across MAP and time categories. Fewer intervention patients experienced prolonged MAP less than 65 mm Hg, with a visible shift toward higher MAP ranges. Details on heat map construction are in eAppendix 4 in Supplement 2.

Secondary Outcomes

There were no significant differences in any of the 23 secondary outcomes. Compared with the control group, the intervention group showed no improvement in the 30-day WHODAS score (mean difference, -0.3; 95% CrI, -1.6 to -1.1), the 30-day EQ-5D-5L (mean difference, 0; 95% CrI, -0.01 to 0.02), or the 6-month EQ-5D-5L (mean difference, 0.01; 95% CrI, -0.01 to 0.03; Table 3; eAppendix 7 in Supplement 2). There were no significant differences between groups in 6-month all-cause mortality (1.8% vs 2.3%; OR, 0.77; 95% CrI, 0.46 to 1.25), in-hospital mortality (0.3% vs 0.4%; OR, 0; 95% CrI, 0 to 1.45),

Table 3. Secondary Patient-Level Outcomes

Outcome	No. (%) of patients		Regression coefficient or odds ratio (95% CrI)
	Intervention group (n = 1618)	Control group (n = 1629)	
Disability scores, median (IQR)			
30-d WHODAS 2.0 (n = 2523)	22.9 (10.4 to 39.6)	25.0 (10.4 to 41.7)	-0.3 (-1.6 to 1.1)
30-d EQ-5D-5L (n = 2523)	0.74 (0.57 to 0.85)	0.75 (0.55 to 0.86)	0 (-0.01 to 0.02)
6-mo EQ-5D-5L (n = 2306)	0.81 (0.68 to 0.89)	0.81 (0.66 to 0.89)	0.01 (-0.01 to 0.03)
Mortality, No. (%)			
In-hospital	5 (0.3)	7 (0.4)	0 (0 to 1.45) ^a
In-hospital ≤48 h	0	2 (0.1)	0 (0 to 1.11) ^a
All-cause mortality ≤6 mo	29 (1.8)	38 (2.3)	0.77 (0.46 to 1.25)
Length of stay, median (IQR), d (n = 3231)	3.0 (1.0 to 5.0)	3.0 (2.0 to 5.0)	-0.06 (-0.52 to 0.39)
Troponin, median (IQR), ng/L (n = 387) ^b	10.5 (5.0 to 22.0)	8.0 (4.0 to 16.0)	-171.93 (-506.11 to 161.02)
Creatinine, μmol/L (n = 774) ^b	71.0 (59.0 to 89.0)	72.0 (61.0 to 89.0)	-0.06 (-0.52 to 0.39)
Intensive care admission ^c	59 (3.6)	47 (2.9)	1.29 (0.87 to 1.91)
Nonprophylactic antibiotics ^b	273 (16.9)	290 (17.8)	0.93 (0.77 to 1.13)
Readmission in same hospital	533 (32.9)	584 (35.9)	0.88 (0.76 to 1.02)
Reoperation ^c	63 (3.9)	60 (3.7)	1.06 (0.74 to 1.52)
Hemorrhage requiring transfusion	51 (3.2)	41 (2.5)	1.27 (0.83 to 1.93)
New onset atrial fibrillation within 24 h	2 (0.1)	1 (0.1)	2.32 (0.20 to 41.86) ^a
New onset heart failure within 24 h	0	0	
Life-threatening events (patients) ^{c,d}			
Acute kidney injury ^{b,d}	49 (3.0)	58 (3.6)	0.84 (0.57 to 1.25)
Deep vein thrombosis or pulmonary embolism	7 (0.4)	9 (0.6)	3.71 (0.40 to 69.96) ^a
Myocardial infarction	5 (0.3)	11 (0.7)	0.77 (0.27 to 2.11) ^a
Cerebrovascular accident	3 (0.2)	1 (0.1)	0.44 (0.14 to 1.23) ^a
Shock	3 (0.2)	1 (0.1)	3.78 (0.42 to 66.64) ^a
Overall	62 (3.8)	75 (4.6)	0.82 (0.58 to 1.16)

Abbreviations: EQ-5D-5L, EuroQol 5-Dimension 5-Level; WHODAS, World Health Organization Disability Assessment Schedule.

SI conversion factor: To convert creatinine from μmol/L to mg/dL, divide by 88.4.

^a Unreliable credibility interval due to rare outcome.

^b In-hospital within 7 days.

^c Within hospital stay.

^d Both the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, registration codes reported in eAppendix 6 in Supplement and the Kidney Disease Improving Global Outcomes criteria were used to determine kidney injury, both of which produced the same results. Using only creatinine, in case creatinine was not determined, it was assumed that patients did not have acute kidney injury.

intensive care unit admission (3.6% vs 2.9%; OR, 1.29; 95% CrI, 0.87 to 1.91), hospital readmission (32.9% vs 35.9%; OR, 0.88; 95% CrI, 0.76 to 1.02), reoperation (3.9% vs 3.7%; OR, 1.06; 95% CrI, 0.74 to 1.52), or new-onset atrial fibrillation or heart failure (<0.1%; OR, 2.32; 95% CrI, 0.20 to 41.86).

Post-Hoc Sensitivity Analysis

Results were stable across all delta scenarios, with estimated treatment effects consistently close to zero and 95% CrIs remaining within the prespecified MCID (eAppendix 5 in Supplement 2).

Discussion

This trial demonstrated that a strategy of proactively selecting MAP targets based on preoperative assessment of risk of intraoperative hypotension did not lead to a clinically relevant impact on functional disability at 6 months or any secondary outcome compared with a strategy based on standard intraoperative blood pressure management.

These findings align with a recent meta-analysis²⁷ of 10 randomized trials involving 9359 patients that reported no meaningful differences in complications or mortality between proactive and usual care strategies, aside from a modest reduction in atrial fibrillation and length of stay. This meta-analysis used

mortality as a primary outcome, which likely does not capture mild organ injury potentially resulting from intraoperative hypotension. Notably, the meta-analysis was largely driven by the Perioperative Ischemic Evaluation-3 (POISE-3),¹⁵ which included 7490 patients, in which intraoperative MAP targets were implemented together with a protocol for perioperative antihypertensive drug management. This combined approach makes it difficult to determine to what extent the observed effects were attributable to the blood pressure targets themselves vs the medication strategy. The PRETREAT trial¹⁶ sought to address this by choosing postoperative functional disability at 6 months as the primary outcome to assess longer-term consequences of perioperative events.¹⁹

The results herein suggest that usual care, in which clinicians typically aim to prevent MAP from being lower than 65 mm Hg but often fail to fully avoid such episodes, does not result in worse outcomes than proactively maintaining higher intraoperative targets. However, the safe lower limit of MAP remains uncertain, especially given concerns that vasopressors used to raise blood pressure may increase the risk of acute kidney injury.^{28,29}

The intervention in the current study used risk-stratified blood pressure targets based on a preoperative intraoperative hypotension prediction model. Although this approach reflects real-life decision-making and reduces overtreatment, it may have lacked sufficient individualization. Within each risk

group, there may have been heterogeneous treatment effects, with some patients benefiting and others not, resulting in a net neutral effect. Additionally, although the intervention reduced hypotension, the mean MAP difference between groups was 5.8 mm Hg (86.9 mm Hg vs 81.1 mm Hg), which may not have been large enough to affect functional recovery. However, the heat map analysis (Figure 2) more clearly revealed a shift away from prolonged or deep hypotension in the intervention group, accompanied by somewhat greater time spent at higher MAP values, including higher than 95 mm Hg. Although this hypothetically raises concern that benefits of avoiding hypotension might be offset by increased hypertension, no signal of excess major complications such as myocardial infarction, stroke, hemorrhage, or acute heart failure was observed.

The relatively high MAP values in the control group likely reflect current practice in which a MAP of less than 65 mm Hg is avoided, although not always successfully. A recent survey of 146 Canadian anesthesiologists, perfusionists, and cardiac surgeons found that 88% of anesthesiologists reported avoiding MAP values less than 65 mm Hg, and most indicated initiating vasopressor therapy when pressures approached this threshold.³⁰ This supports the interpretation that the control group in the current study, in which vasopressors were frequently administered, represents a realistic and clinically relevant comparator.

Although some patients experienced limited hypotension, the median area under the threshold of less than 65 mm Hg in the control group (23.7 mm Hg × minutes) was comparable with prior studies linking intraoperative hypotension to adverse outcomes.⁹

Previous studies on perioperative blood pressure management, including a meta-analysis,²⁷ yielded conflicting results highlighting the challenges in this field.¹⁻¹⁵ To address these, PRETREAT incorporated several design features. First, the adaptive design incorporated explicit stopping rules that allowed interim assessment of intervention efficacy, ensuring that the trial would only proceed to full enrollment if the intervention achieved a meaningful reduction in intraoperative hypotension. Second, the intervention included clear, expert-developed guidelines to support implementation and ad-

herence, which has reportedly been difficult in previous trials.¹⁵ Third, the control group reflected contemporary clinical practice, unlike earlier randomized clinical trials with possibly undertreated controls.^{10,11} Fourth, a WHODAS evaluation at 6 months was chosen as the primary outcome because it captures long-term functional disability that may result from early postoperative complications. The consistency of findings at 30 days and across in-hospital outcomes supports its validity as a long-term end point.

Limitations

This study has several limitations. First, the stratified MAP targets were based on preoperative intraoperative hypotension risk and may not fully reflect patients' intraoperative susceptibility, which could have led to heterogeneous effects within risk groups. Second, although the WHODAS 2.0 is validated and widely used, it may not identify isolated subclinical organ dysfunction. Third, 29% of patients lacked primary outcome data, which introduces potential attrition bias despite consistent findings at 30 days and across secondary outcomes. Fourth, anesthesiologists in the intervention group were not blinded, although those in the control group were not informed about trial participation, which likely minimized performance bias. Fifth, preoperative antihypertensive medication use in this analyses was not accounted for. Although perioperative management was standardized across sites according to institutional policies aligned with international recommendations, residual effects of these medications on intraoperative hemodynamic stability cannot be excluded. Sixth, postoperative hypotension was not targeted, which may also affect long-term outcomes. Seventh, early stopping for futility reduced statistical power and precluded robust subgroup analyses.

Conclusions

Intraoperative blood pressure management with a MAP goal stratified by risk of intraoperative hypotension did not improve functional disability at 6 months postoperatively compared with standard intraoperative blood pressure management.

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