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ORIGINAL CLINICAL RESEARCH REPORT

Intraoperative Hypotension and Myocardial Injury After Noncardiac Surgery in Adults With or Without Chronic Hypertension: A Retrospective Cohort Analysis

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BACKGROUND: The risk of myocardial injury progressively increases at intraoperative mean arterial pressures (MAPs) ≤65 mm Hg. Higher pressures might be required in chronically hypertensive patients. We aimed to test the hypothesis that the harm threshold is higher in patients with chronic hypertension than in normotensive patients.

METHODS: We conducted a single-center retrospective cohort analysis of adults >45 years old who had noncardiac surgery between 2010 and 2018 and scheduled, rather than symptom-driven, postoperative troponin measurements. The MAP thresholds under which risk started to increase were compared between patients with chronic hypertension (baseline MAP ≥110 mm Hg) and normotensive patients (baseline MAP <110 mm Hg). The primary outcome was a composite of in-hospital mortality and myocardial injury within 30 days, defined by any postoperative 4th-generation troponin T measurement ≥0.03 ng/mL apparently due to cardiac ischemia. Multivariable logistic regression and moving average smoothing methods were used to evaluate confounder-adjusted associations between the composite outcome and the lowest intraoperative MAP sustained for either 5 or 10 cumulative minutes, and whether the relationship depended on baseline pressure (normotensive versus hypertensive).

RESULTS: Among 4576 eligible surgeries, 2066 were assigned to the normotensive group with mean (standard deviation [SD]) baseline MAP of 100 (7) mm Hg, and 2510 were assigned to the hypertensive group with mean baseline MAP of 122 (10) mm Hg. The overall incidence of the composite outcome was 5.6% in normotensive and 6.0% in hypertensive patients ($P = .55$). The relationship between intraoperative hypotension and the composite outcome was not found to depend on baseline MAP in a multivariable mixed effects logistic regression model. Furthermore, no statistical change points were found for either baseline MAP group.

CONCLUSIONS: Baseline blood pressure of the hypertensive patients was only moderately increased on average, and the event rate was low. Nonetheless, we were not able to demonstrate a difference in the harm threshold between normotensive and chronically hypertensive patients. Our results do not support the theory that hypertensive patients should be kept at higher intraoperative pressures than normotensive patients. (Anesth Analg 2022;00:00–00)

KEY POINTS

- **Question:** Do patients with chronic hypertension have a higher threshold for intraoperative hypotension below which the risks for myocardial injury or mortality start to increase?
- **Findings:** In a single-center cohort of >4500 patients who had noncardiac surgery with routine troponin measurements, patients with chronic hypertension did not have a higher threshold for intraoperative hypotension compared to normotensive patients.
- **Meaning:** Our results do not support the practice of keeping hypertensive patients at higher intraoperative blood pressures than normotensive patients.

GLOSSARY

ACE = angiotensin converting enzyme; **ASA** = American Society of Anesthesiologists; **AUC** = area under the curve; **BMI** = body mass index; **CCF** = Cleveland Clinic Foundation; **CI** = confidence interval; **DBP** = diastolic blood pressure; **eGFR** = estimated glomerular filtration rate; **GI** = gastrointestinal; **IRB** = institutional review board; **MAP** = mean arterial pressure; **MINS** = myocardial injury after noncardiac surgery; **OR** = operating room; **POISE-2** = PeriOperative ISchemic Evaluation-2 Trial; **SBP** = systolic blood pressure; **SD** = standard deviation; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **TnT** = troponin T; **TWA** = time-weighted average; **VISION** = Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study; **WHO** = World Health Organization

Although preventable intraoperative mortality is now rare, postoperative mortality is not. Thirty-day mortality for inpatients >45 years of age is 1% to 2% after noncardiac surgery[1–3], therefore contributing about 200,000 deaths annually in the United States alone.[4] Seventy percent of 30-day mortality after noncardiac surgery occurs during the initial hospitalization, and it is most strongly associated with myocardial injury, major surgical bleeding, and sepsis.[5]

Myocardial injury after noncardiac surgery (MINS), defined by increased plasma troponin concentrations judged to be of ischemic etiology, is associated with roughly a 3-fold increase in 30-day mortality.[2,3] Baseline morbidity is the strongest predictor of postoperative cardiovascular complications, but intraoperative hypotension is also associated with MINS and is of special interest since it is potentially modifiable.[6–11]

Hypotension can be defined by reductions relative to preoperative baseline pressures or on the basis of absolute thresholds.[12,13] Across the noncardiac surgical population, relative and absolute intraoperative hypotension comparably predict myocardial and renal injuries,[14] but absolute thresholds are easier to use because baseline blood pressure is often unavailable and pressures measured shortly before surgery often overestimate true baseline values.[15]

Absolute thresholds imply that harm begins to accrue at similar pressures in all patients, which seems inconsistent with the theory that hypertensive patients have shifted autoregulation curves that better accommodate their normal pressure range.[16] It is, therefore, plausible, and perhaps likely, that patients with chronic hypertension require higher intraoperative pressures to avoid myocardial injury. We, therefore, tested the hypothesis that the absolute intraoperative hypotensive threshold below which the odds of worse outcome begin to increase for the average patient is higher in chronically hypertensive patients than in normotensive patients.

METHODS

The study was approved by the Cleveland Clinic Foundation (CCF) institutional review board (IRB) with waived individual consent (CCF IRB #19-038, approved on March 12, 2019, IRB executive director Bridget Howard). This report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies. We evaluated a retrospective cohort of adults at least 45 years old who had noncardiac surgery at the Cleveland Clinic between 2010 and 2018 and had scheduled (rather than for-cause) postoperative 4th-generation troponin-T measurements. Troponin was evaluated either by clinical routine for colorectal surgical inpatients or because patients participated in 1 of 4 clinical studies: PeriOperative ISchemic Evaluation-2 Trial (POISE-2),[17,18] addition of nitrous oxide to general anesthesia in at-risk patients having major noncardiac surgery (ENIGMA-II),[19] Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study (VISION),[2] or the Balanced Anesthesia Study (BALANCED).[20] The routine in all these patients was to sample blood for troponin on the first 2 postoperative mornings while patients remained hospitalized, and in many cases, also 6 to 12 hours after surgery and on the third postoperative day.

We excluded patients without at least 1 clinic blood pressure during the 3 months preceding surgery, patients with American Society of Anesthesiologists physical status 5, patients with elevated preoperative troponin T (TnT) concentration, patients with missing intraoperative blood pressure recording for >20 consecutive minutes, and patients with TnT elevation potentially from noncardiac origin (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D823).

Baseline blood pressure was defined as the average of all mean arterial pressure (MAP) measurements during the 3 months preceding surgery, excluding measurements during hospitalizations. Patients were grouped by average baseline MAP. Specifically, we considered ambulatory mean pressures <110 mm Hg to be normotensive and pressures ≥110 mm Hg to represent baseline hypertension. We chose the MAP threshold to be 110 mm Hg since it is close to the mean pressure corresponding with the World Health Organization (WHO) definition of hypertension, 140/90 mm Hg (the exact arithmetic MAP is 106.67 mm Hg, but we chose to use the clinically more meaningful value of 110 mm Hg).[21]

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Conflicts of Interest: See Disclosures at the end of the article.

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Intraoperative MAPs recorded in the Perioperative Health Documentation System cannot be modified by clinicians but can be identified as artifacts. Invasive pressures were recorded at 1-minute intervals; noninvasive pressures were recorded at 1- to 5-minute intervals. We removed artifacts using the following rules, in order: (1) blood pressures documented as artifacts; (2) pressures out-of-range defined by (a) systolic blood pressure (SBP) ≥300 or SBP ≤20 mm Hg, (b) SBP less than or equal to diastolic blood pressure (DBP) + 5 mm Hg, or (c) DBP ≤5 mm Hg or DBP ≥225 mm Hg; (3) abrupt changes defined by SBP change ≥80 mm Hg within 1 minute in either direction or ≥40 mm Hg within 2 minutes in both directions. Pressures between measurements were linearly interpolated.

Our primary outcome was a collapsed composite outcome of in-hospital mortality and MINS, the latter defined as at least one 4th-generation serum TnT concentration ≥0.03 ng·mL^{-1} during the initial 30 postoperative days that was judged to be of ischemic origin. The secondary outcome was MINS only.

Statistical Analysis

We used a convenience sample of all eligible patients in the relevant period. Potential confounding variables are listed in Table 1. We defined preexisting medical conditions using International Classification of Diseases, Ninth Revision procedure codes and included only those fulfilling at least 1 of the following: (1) appeared in the patient's "problem list" with a date preceding the date of surgery; (2) appeared in procedure code list before the index surgery; or (3) were flagged as a chronic condition based on Healthcare Cost and Utilization Project definitions. Since there were many types of surgical procedures, we characterized each procedure code into 1 of 231 clinically meaningful categories using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures.[22] We then aggregated low-frequency-event or nonevent categories (N < 10) into 1 group and used that as the reference group (a low-risk group).

Our primary MAP exposures of interest were the lowest intraoperative MAP for a cumulative case total of 5 and 10 minutes. Secondarily, we report time-weighted average MAP (TWA-MAP) and area under an MAP-threshold (area under the curve [AUC]) to describe the normotensive and hypertensive groups. An AUC-MAP below each threshold was calculated as the cumulative sum of the areas below the given threshold for a patient, using the trapezoid rule. Technically, the AUC for a patient is calculated by first obtaining the product of the time between 2 adjacent MAP measurements and the average of the 2 MAP measurements for each measurement below the threshold, and then summing these areas across episodes. TWA-MAP below a threshold for a patient was derived as AUC-MAP divided by the time interval between the first and the last MAP measurements.

For the primary outcome of the collapsed composite outcome of in-hospital mortality and MINS, we did the following primary, secondary, and sensitivity analyses.

Primary Analysis of the Primary Outcome. We used multivariable mixed effects logistic regression to assess whether a relationship between the lowest intraoperative MAP exposures and the composite outcome depends on baseline MAP category (normotensive and hypertensive) while adjusting for the potential confounding factors in Table 1 by testing the interaction between baseline MAP and the lowest MAP exposures. In this mixed effects model, a compound symmetry within-subject correlation structure was assumed to account for the possible correlation among multiple surgeries within the same patient; a linearity test between each MAP threshold and response was modeled by a restricted cubic spline function with 3 knots, located at the 10th, 50th, and 90th percentiles. We also evaluated the same interaction while considering baseline MAP pressure as a continuous variable. If no interaction was found for either of these models (defined a priori as $P \geq .15$), the relationship between the composite outcome and the lowest MAP exposures was assessed by a main effects multivariable mixed effects logistic regression adjusted for baseline MAP and the other potential confounding variables in Table 1.

Moving-average smoothing plots of the univariable relationship between the composite outcome and each MAP exposure and smoothed cubic spline curves from the above multivariable mixed effects logistic regression models were used to visualize threshold pressures below which the odds of poor outcome appeared to begin to increase.

Secondary Analyses of the Primary Outcome. Based on the observed visual trends, we conducted 2 sets of secondary analyses: first, estimated change points or thresholds of minimum MAP using statistical methods, and second, assessing relationships with outcome while assuming a change point of 65 mm Hg.

Statistical Estimation of Change Points. The smoothed cubic spline curves were consistent with the exposure-outcome relationships being either a segmented straight line effect or quadratic effect (like a U-shaped curve) within each baseline MAP level. We, therefore, used the threshold multivariable logistic regression method developed by Fong et al[23] to statistically estimate a threshold, or change point, and its 95% confidence interval (CI) for each

Table 1. Demographic Characteristics, Intraoperative Factors, and Postoperative Outcomes by Baseline MAP

Factor	Baseline MAP < 110 mm Hg (n = 2066)	Baseline MAP ≥ 110 mm Hg (n = 2510)	*P* value[a]
Demographic characteristics			
Age (y)	60 ± 9	63 ± 10	**<.001**
Female, n (%)	1095 (53)	1127 (45)	**<.001**
BMI (kg·m^{-2})	28 ± 6.8	30 ± 6.7	**<.001**
Race, n (%)			
White	1855 (90)	2196 (88)	**.046**
Black	142 (7)	218 (9)	
Other	69 (3)	96 (4)	
Preoperative conditions			
ASA physical status, n (%)			
1	4 (0)	3 (0)	.78
2	473 (23)	552 (22)	
3	1448 (70)	1788 (71)	
4	141 (7)	167 (7)	
Preoperative creatinine (mg·dL^{-1})	0.85 ± 0.17	0.85 ± 0.17	.17
Preoperative hemoglobin (g·dL^{-1})	12.8 ± 1.7	13.4 ± 1.9	**<.001**
Baseline eGFR (mL·min^{-1}·1.73 m^{-2})	84 ± 13	83 ± 13	**.010**
Baseline MAP (mm Hg)	100 ± 7	122 ± 10	**<.001**
Year of surgery, n (%)			
2010	24 (1)	12 (1)	**<.001**
2011	139 (5)	68 (3)	
2012	438 (17)	232 (11)	
2013	341 (14)	178 (9)	
2014	48 (2)	27 (1)	
2015	381 (15)	372 (18)	
2016	422 (17)	432 (21)	
2017	439 (17)	423 (20)	
2018	278 (11)	322 (16)	
Preoperative use of cardiac medications, n (%)			
ACE inhibitor	519 (25)	827 (33)	**<.001**
Angiotensin receptor blockers	232 (11)	453 (18)	**<.001**
Beta blockers	966 (47)	1172 (47)	.97
Calcium channel blockers	358 (17)	671 (27)	**<.001**
Diuretics	697 (34)	1010 (40)	**<.001**
Previous medical history, n (%)			
Congestive heart failure	92 (4)	79 (3)	**.020**
Valvular disease	74 (4)	115 (5)	.091
Pulmonary circulation disease	13 (1)	18 (1)	.72
Peripheral vascular disease	120 (6)	149 (6)	.85
Chronic pulmonary disease	254 (12)	316 (13)	.76
Diabetes	323 (16)	490 (20)	**<.001**
Intraoperative			
Surgical duration (h)	4.1 ± 2.1	4.3 ± 2.1	**<.001**
Blood loss (mL)	75 (25–200)	100 (30–250)	**<.001**
Use of arterial catheter, n (%)	528 (26)	799 (32)	**<.001**
Surgical procedure, n (%)			
Ileostomy and other enterostomy	193 (9)	177 (7)	**<.001**
Colorectal resection	606 (29)	736 (29)	
Other GI therapeutic procedures in the OR	511 (25)	428 (17)	
Arthroplasty knee	38 (2)	90 (4)	
Hip replacement, total and partial	43 (2)	102 (4)	
Spinal fusion	59 (3)	110 (4)	
Other[b]	616 (30)	867 (35)	
Postoperative outcome			
Composite, n (%)	115 (6)	150 (6)	.55
MINS	77 (4)	104 (4)	.47
In-hospital mortality	46 (2)	55 (2)	.94

Data presented as means ± SDs, medians (Q1–Q3), or n (column %), *P* values from the *t* test or Wilcoxon rank sum test for continuous variables, and χ^2 test for categorical variables, as appropriate.

Abbreviations: ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index; CCS, Clinical Classification Software; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MAP, mean arterial pressure; MINS, myocardial injury after noncardiac surgery; OR, operating room; SD, standard deviation.

[a]Statistically significant if *P* <.05.

[b]Low-frequency-event or nonevent CCS categories (n < 10) were aggregated into 1 group (a low-risk reference group).

of these scenarios.[22] We evaluated each effect in a separate threshold regression, with the segmented effect modeled as follows: $\eta = \alpha_1 + \alpha_2^T z + \gamma x + \beta_1 (x - e)_+$ and the quadratic effect as follows: $\eta = \alpha_1 + \alpha_2^T z + \gamma x + \beta_{2,-} (x - e)^2_- + \beta_{2,+} (x - e)^2_+$, where η denotes the logit of the composite outcome, e denotes the threshold parameter, x is the lowest MAP exposure with threshold effect, z denotes a vector of additional predictors, and $(x - e)_+ = x - e$ if $x > e$ and 0 otherwise, and $(x - e)_- = x - e$ if $x \le e$ and 0 otherwise.[23]

Since the current "chngpt" R package for this method does not permit an interaction term to estimate and compare the change points within each baseline MAP group simultaneously, we fitted threshold multivariable logistic regressions for each group separately. Due to only 115 events of the composite outcome in the normotensive group and 150 in the hypertensive group, we could not include all potential cofounding variables from Table 1. We therefore conducted univariable analysis between the composite outcome and each potential confounding variable in Table 1 and selected those predictors that were strongly associated with the composite outcome with $P < .001$ within both baseline MAP groups. If significant change points were found, we would use a Z score test to compare thresholds between the 2 baseline MAP groups.

Assuming a Theoretical Change-Point of 65 mm Hg. Second, we also observed a possible MAP threshold of 65 mm Hg from the smoothed cubic spline curves for both baseline MAP groups. Since the relationship between the lowest MAP and the composite outcome did not depend on the baseline MAP in the primary analyses, for this analysis, we combined the 2 groups together. We fit a multivariable piecewise mixed effects logistic regression, adjusted for the potential confounding variables in Table 1, to evaluate slopes before and after the MAP threshold of 65 mm Hg and compare the slopes. Here, the exposure of the lowest MAP for a patient for a cumulative 5 or 10 minutes ("lowest pressure") was partitioned into 2 intervals determined by the threshold, and a separate line segment was fit to each interval (piecewise regression). Odds ratios were estimated for each segment (ie, odds of outcome for a decrease of specified amounts from the threshold), and the odds ratios were compared between segments with a ratio of odds ratios (95% CI).

Sensitivity Analysis of the Primary Outcome. We also defined baseline blood pressure groups using baseline MAP <100 mm Hg and MAP ≥110 mm Hg for the normotensive and hypertensive groups, respectively, to explore the association between the lowest MAP and the composite outcome using multivariable mixed effects logistic regression and change-point analysis.

Analyses of the Secondary Outcome (MINS). Using similar statistical methods as those used for the primary outcome, we also assessed the relationship between the lowest MAP and the risk of MINS.

Sample Size Considerations. We conducted a post hoc power calculation using univariable logistic regression to estimate the strength of association that we could detect with 90% power at the 0.05 significance level with the given data. Considering 4576 surgeries available for this analysis, with an overall 5.7% incidence of the composite outcome of MINS and mortality and an estimated mean (SD) lowest intraoperative MAP of 65 (8) mm Hg for a cumulative case total of 5 minutes, we had 90% power to detect an odds ratio as small as 1.03 per 1 mm Hg decrease in the lowest MAP for 5 minutes.

For all analyses of primary and secondary outcomes, Bonferroni correction was used to adjust for 2 exposures (ie, the lowest MAP for cumulative 5 or 10 minutes), with $P < .025$ (ie, $P < .05/2 = .025$) considered statistically significant. Interactions between baseline MAP and exposures were considered significant if $P < .05$. All analyses were performed with SAS Statistical Software, version 9.4 (SAS Institute), and R 3.4.4 software (Institute for Statistics and Mathematics).

RESULTS

Among 12,120 patients who had 16,720 noncardiac surgeries and participated in the 4 underlying studies or had colorectal surgery between 2014 and 2018, 4061 patients having 4576 surgeries met our enrollment criteria (Figure 1), 36% of whom participated in 1 of the 4 studies and the rest from the colorectal surgery database. Among these, the normotensive group included 2066 surgeries with an average ±SD clinic MAP of 100 ± 7 mm Hg, and the baseline hypertensive group included 2510 surgeries with an average clinic MAP of 122 ± 10 mm Hg. There was at least 1 troponin measurement during the initial 2 postoperative days in 98% of cases. Only about 9% of cases were discharged within a day of surgery.

Patients' baseline, preoperative, and intraoperative characteristics along with incidence of the composite outcome are presented in Tables 1 and 2 according to baseline blood pressure. Patients in the baseline hypertension group were more likely to be older, men, have a higher body mass index (BMI), prescribed with antihypertensive medications, and to have diabetes. They also had slightly higher baseline hemoglobin concentrations and greater estimated intraoperative blood loss. Additionally, they had higher intraoperative minimal MAPs, therefore, less intraoperative hypotension (smaller area and shorter duration under any MAP threshold, $P < .001$).

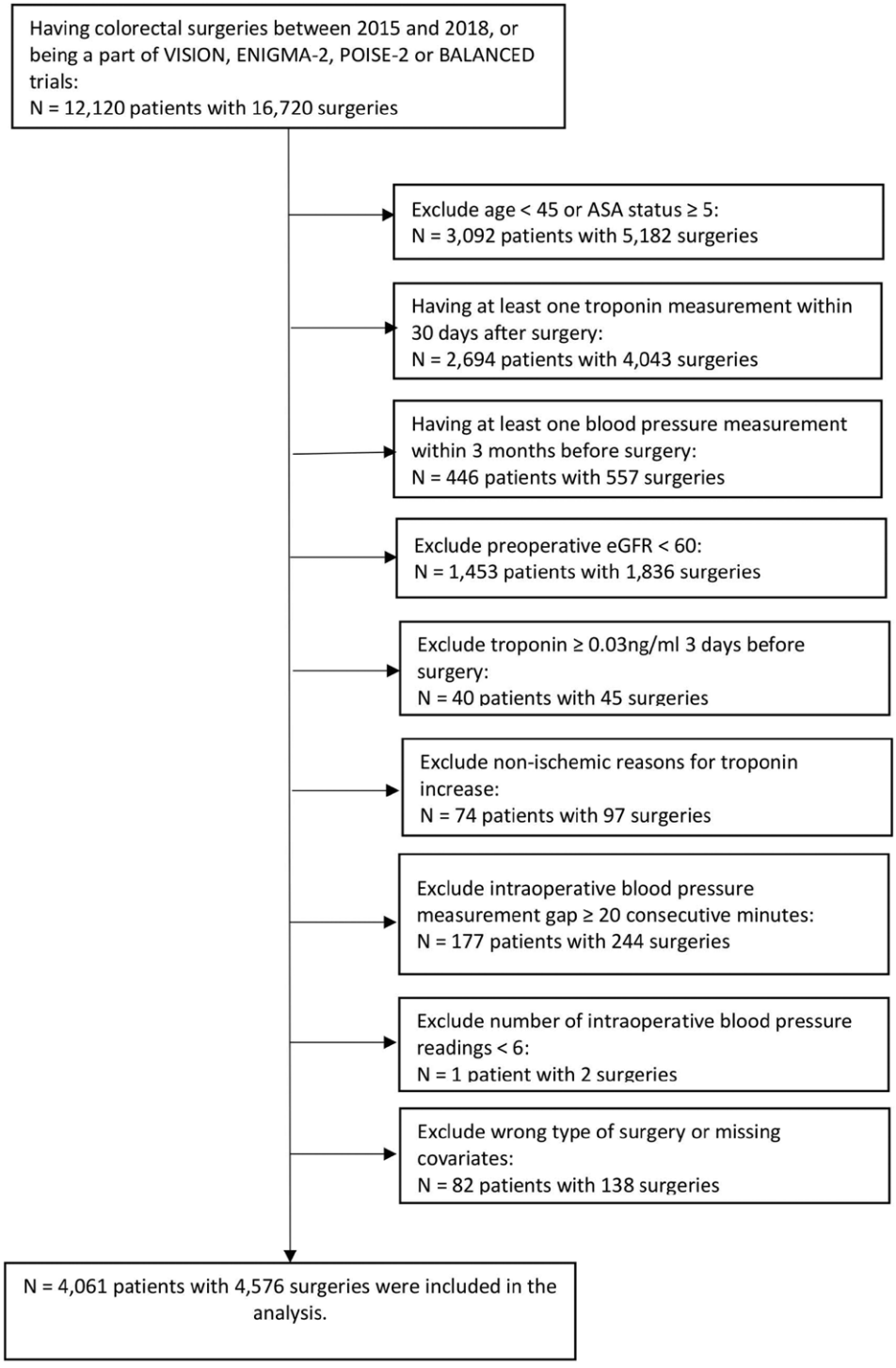

Figure 1. Flow chart. ASA indicates American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; POISE-2, PeriOperative ISchemic Evaluation-2 Trial; VISION, Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study.

Primary Outcome: Composite of MINS and In-Hospital Mortality

The overall incidence of the composite outcome was 5.6% (115 of 2066) in patients who were normotensive at baseline and 6.0% (150 of 2510) in those who were hypertensive at baseline ($P = .55$). Baseline, preoperative, and intraoperative variables are presented in Supplemental Digital Content, Table 2, http://links.lww.com/AA/D823 according to outcome. Univariable analyses showed that patients experiencing the composite outcome had lower minimal MAP values and longer duration and greater area under the hypotension thresholds than those without events (all $P < .001$; Table 3). There were no clinically important associations between baseline MAP or intraoperative TWA-MAP (ie, without using thresholds) and the composite outcome. Patients experiencing the composite outcome were not found to have higher

Table 2. Intraoperative Blood Pressure Characteristics by Baseline MAP

Factor	Baseline MAP < 110 mm Hg (n = 2066)	Baseline MAP ≥ 110 mm Hg (n = 2510)	*P* value
Intraoperative TWA-MAP (mm Hg)	85 ± 9	88 ± 9	**<.001**
Lowest MAP (mm Hg) for cumulative minutes			
≥5	64 ± 8	66 ± 9	**<.001**
≥10	67 ± 7	69 ± 8	**<.001**
AUC under MAP (mm Hg·min)			
<75 mm Hg	271 (101–562)	186 (58–419)	**<.001**
<70 mm Hg	98 (24–227)	64 (11–168)	**<.001**
<65 mm Hg	21 (1–72)	13 (0–56)	**<.001**
<60 mm Hg	1.0 (0–19)	0 (0–15)	**<.001**
<55 mm Hg	0 (0–2.0)	0 (0–1.0)	**.048**
Minutes under MAP			
<75 mm Hg	43 (19–82)	32 (12–64)	**<.001**
<70 mm Hg	20 (7–43)	13 (3–31)	**<.001**
<65 mm Hg	6 (1–16)	4 (0–11)	**<.001**
<60 mm Hg	1 (0–5)	0 (0–4)	**<.001**
<55 mm Hg	0 (0–1)	0 (0–1)	.052
TWA under MAP (mm Hg)			
<75 mm Hg	1 (0–3)	1 (0–2)	**<.001**
<70 mm Hg	0 (0–1)	0 (0–1)	**<.001**
<65 mm Hg	0 (0–0)	0 (0–0)	**<.001**
<60 mm Hg	0 (0–0)	0 (0–0)	**<.001**
<55 mm Hg	0 (0–0)	0 (0–0)	**.024**

Data presented as means ± SDs or medians (Q1–Q3).
Abbreviations: AUC, area under the curve; MAP, mean arterial pressure; MINS, myocardial injury after noncardiac surgery; TWA, time-weighted average.

Table 3. Univariable Association Between Intraoperative MAP Exposures and a Composite of MINS and In-Hospital Mortality

Factor	Composite outcome (n = 265)	Nonevent (n = 4311)	*P* value
Intraoperative TWA-MAP (mm Hg)	86 ± 9	86 ± 9	.66
Lowest MAP (mm Hg) for cumulative minutes			
≥5	63 ± 9	65 ± 8	**<.001**
≥10	66 ± 9	68 ± 8	**<.001**
AUC under MAP (mm Hg·min)			
<75 mm Hg	317 (107–704)	219 (75–463)	**<.001**
<70 mm Hg	116 (26–307)	75 (16–190)	**<.001**
<65 mm Hg	37 (2–108)	15 (0–62)	**<.001**
<60 mm Hg	5 (0–31)	0 (0–15)	**<.001**
<55 mm Hg	0 (0–9)	0 (0–1)	**<.001**
Minutes under MAP			
<75 mm Hg	50 (20–87)	36 (15–71)	**<.001**
<70 mm Hg	23 (7–48)	16 (5–35)	**<.001**
<65 mm Hg	7 (1–23)	5 (0–13)	**<.001**
<60 mm Hg	2 (0–7)	0 (0–4)	**<.001**
<55 mm Hg	0 (0–2)	0 (0–1)	**<.001**
TWA under MAP (mm Hg)			
<75 mm Hg	1 (0–2)	1 (0–2)	**.014**
<70 mm Hg	0 (0–1)	0 (0–1)	**.002**
<65 mm Hg	0 (0–0)	0 (0–0)	**<.001**
<60 mm Hg	0 (0–0)	0 (0–0)	**<.001**
<55 mm Hg	0 (0–0)	0 (0–0)	**<.001**

Data presented as mean ± SD or median (Q1–Q3), *P* values from the *t* test or Wilcoxon rank sum test for continuous variables.
Abbreviations: AUC, area under the curve; CI, confidence interval; MAP, mean arterial pressure; MINS, myocardial injury after noncardiac surgery; SD, standard deviation; TWA, time-weighted average.

baseline MAP (mean ± SD of 114 ± 16 vs 112 ± 14 mm Hg; $P = .10$).

Main Results: Comparing Baseline BP Groups Using Splines and Multivariable Modeling. Univariable moving-average and multivariable spline smoothing plots of the lowest observed MAP for each patient are shown in Figure 2. The moving-average plots for neither baseline MAP group had a clear visual change point. Spline smoothing plots (Figure 2) from the mixed effects multivariable logistic regression models assessing the interaction between the baseline MAP group and the lowest MAP indicated that the relationships between the lowest intraoperative MAP and the composite outcome did not depend on their baseline pressures, Supplemental Digital Content, Table 3, http://links.lww.com/AA/D823; the interaction *P* values between the baseline MAP group and the lowest cumulative 5 and 10 minutes of MAP were 0.96 and 0.86,

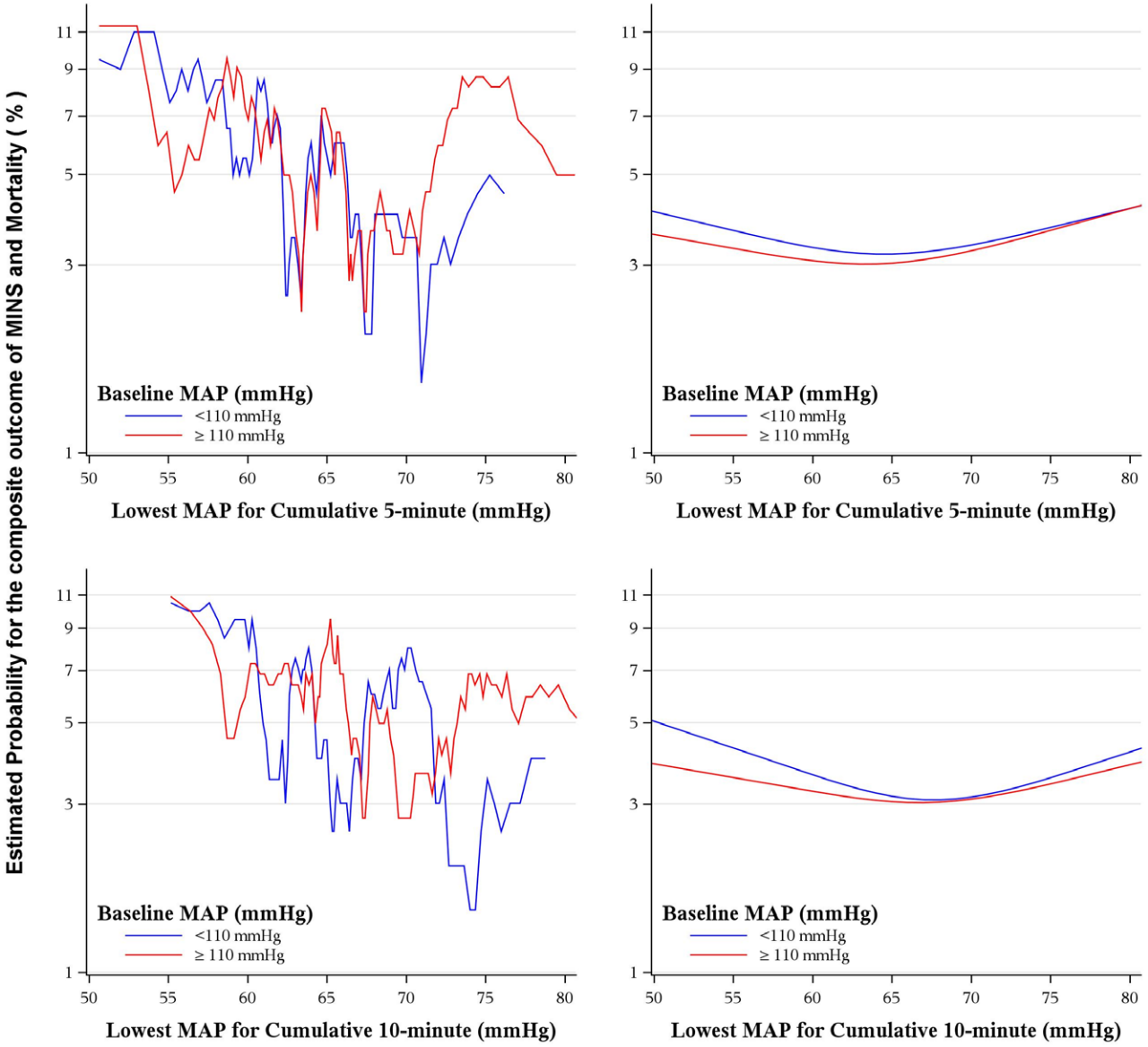

Figure 2. Intraoperative lowest MAP thresholds for a composite outcome of MINS and in-hospital mortality, according to baseline MAP groups (<110 and ≥110 mm Hg). Univariable and multivariable relationships between MINS/mortality and absolute lowest MAP thresholds. Left, Estimated probability of MINS/mortality from the univariable moving-window smoothing with the width of 10% data as a window size and 1% data as a moving size. Right, Estimated probability from multivariable logistic regression smoothed by restricted cubic spline with 3 degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. Multivariable models adjusted for covariates in Table 1. The Y-axis was on the logit scale of log $(\frac{p}{1-p})$ and labeled as probability (p%). The smoothed plots do not identify a constant change point (ie, distinct change in slope), presumably due to small sample size and low incidence. Multivariable logistic regressions identified a change point near 65 mm Hg, but testing the change point of 65 mm Hg using piecewise regressions showed no significant relationship within either segment. There were no interaction effects between baseline MAP groups and intraoperative lowest MAP thresholds for 5 min (P = .96) or 10 min (P = .86). MAP indicates mean arterial pressure; MINS, myocardial injury after noncardiac surgery.

respectively. After excluding the interaction term from the models, main effect multivariable logistic models suggested that the lowest MAP was not associated with the composite outcome in models either assuming a restrict cubic spline relationship or a linear relationship (ie, all type III F test's $P > .05$; Supplemental Digital Content, Table 3, http://links.lww.com/AA/D823). No interaction was found while modeling the lowest MAP as a continuous predictor, and the continuous predictor was also not associated with the composite outcome in the main effects model.

Statistical Change-Point Analysis. In the first set of secondary analyses, no estimated change point within either baseline MAP group was statistically significant (ie, such that the relationship between the exposure and outcome differed in patients above versus below the estimated change point) while assuming a segmented (straight line) effect and using Bonferroni correction (Table 4).

In the second set of secondary analyses, results from piecewise logistic regression for the combined baseline MAP groups indicated that the relationship

Table 4. Results of Change-Point Tests for the Composite Outcome of MINS and In-Hospital Mortality[a]

	Baseline MAP < 110 mm Hg (n = 2066)		Baseline MAP ≥ 110 mm Hg (n = 2510)	
Lowest MAP	**Change point (97.5% CI)**	***P* value**	**Change point (97.5% CI)**	***P* value**
Assuming a segmented effect				
Cumulative ≥5 min	72 (61–83)	0.182	67 (56–78)	.196
Cumulative ≥10 min	76 (66–86)	0.117	69 (59–79)	.0499
Assuming a quadratic effect				
Cumulative ≥5 min	58 (48–68)	0.200	56 (43–69)	.789
Cumulative ≥10 min	59 (49–69)	0.332	73 (62–84)	.873
Sensitivity analysis	Baseline MAP < 100 mm Hg (n = 864)		Baseline MAP ≥ 110 mm Hg (n = 2510)	
Assuming a segmented effect				
Cumulative ≥5 min	63 (53–73)	0.636	67 (56–78)	.196
Cumulative ≥10 min	66 (56–76)	0.528	69 (59–79)	.0499
Assuming a quadratic effect				
Cumulative ≥5 min	54 (43–65)	0.916	56 (43–69)	0.790
Cumulative ≥10 min	58 (47–69)	0.924	73 (62–84)	0.873

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; MAP, mean arterial pressure; MINS, myocardial injury after noncardiac surgery.

[a]For each baseline MAP group, a change point was estimated from a multivariable continuous threshold logistic regression model with the composite outcome as outcome and the "lowest MAP" variables as exposure, adjusting for age, ASA status, year of surgery, use of arterial line, preoperative hemoglobin, preoperative ace inhibitor, beta blocker, calcium channel blockers, diuretics, chronic heart failure, diabetes, and valvular disease. *P* values compare the 2 segmented slopes or 2 quadratic curves above versus below the estimated change point. Segmented effect: $\eta = \alpha_1 + \alpha_2^T z + \gamma x + \beta_1 (x - e)_+$; quadratic effect: $\eta = \alpha_1 + \alpha_2^T z + \gamma x + \beta_{2,-} (x - e)^2_- + \beta_{2,+} (x - e)^2_+$, where *e* denote the threshold parameter, *x* is the lowest MAP exposure with threshold effect, *z* a vector of additional predictors, and $(x - e)_+ = x - e$ if $x > e$ and 0 otherwise, and $(x - e)_- = x - e$ if $x \le e$ and 0 otherwise (Fong et al[23]). Bonferroni correction was used to adjust for 2 exposures (ie, the lowest MAP for a cumulative 5 or 10 min, with $P < .025$ (ie, $P < .05/2 = .025$) considered statistically significant.

between MAP and outcome was not statistically significant within any of the segments above or below a threshold of MAP of 65 mm Hg (all $P > .20$) (Supplemental Digital Content, Table 4, http://links.lww.com/AA/D823). Furthermore, there was no difference between the slopes above versus below MAP of 65 mm Hg for the lowest cumulative 5 minutes (odds ratios [95% CI] of 1.22 [0.98–1.51]; $P = .069$) or the lowest cumulative 10 minutes (odds ratios [95% CI] of 1.27 [1.01–1.63]; $P = .044$) while using Bonferroni correction with a significance level of 0.025.

In a sensitivity analysis, the exposure was defined as baseline MAP <100 mm Hg or ≥110 mm Hg. The normotensive group (baseline MAP <100) included 890 surgeries, and the incidence of the composite outcome was 5.96% (53 of 960). Results also showed that the intraoperative lowest MAP was not associated with the composite outcome (Table 4; Supplemental Digital Content, Tables 3 and 4, http://links.lww.com/AA/D823).

The Secondary Outcome of MINS

The relationships between the lowest intraoperative MAP and MINS did not depend on patients' baseline blood pressures, with the interaction *P* values between the baseline MAP group and the lowest cumulative 5 and 10 minutes of MAP of 0.305 and 0.126, respectively (Supplemental Digital Content, Table 5, http://links.lww.com/AA/D823). Main effect multivariable logistic models suggested that the lowest MAP was not associated with the composite outcome while modeling cumulative 5 and 10 minutes of MAP as a restrict cubic spline item (ie, all type III F tests' $P > .05$; Supplemental Digital Content, Table 4, http://links.lww.com/AA/D823). No interaction effect was found while modeling the lowest MAP as a continuous predictor, and the continuous predictor was also not associated with the composite outcome in the main effects model.

Furthermore, the moving-average plots for neither baseline MAP group had a clear visual change point. Although there was a possible change point around MAP of 65 mm Hg from main effect multivariable logistic models, results from the change-point analysis and the multivariable piecewise mixed effects logistic regression showed that no significant change point was found (Supplemental Digital Content, Tables 6 and 7 and Figure 1, http://links.lww.com/AA/D823).

DISCUSSION

Patients with chronic hypertension were generally less exposed to intraoperative hypotension, as characterized by the time under any predefined hypotensive threshold, lowest intraoperative MAP, area under any threshold, or TWA-MAP. This could be explained either by their baseline tendency toward hypertension or by caregivers' practice to target higher pressures intraoperatively. They nonetheless comparably experienced the composite outcome, presumably because they were at greater baseline cardiovascular risk, as indicated by their older age, male sex, higher BMI, and more comorbidities.

Both normotensive and chronically hypertensive patients showed similar associations between intraoperative hypotension at various thresholds and

harm. Similar thresholds are in distinct contrast to the common belief that chronically hypertensive patients have upshifted autoregulation curves that accommodate their typically high pressures. This belief is largely based on animal research of cerebral blood flow, showing that both the upper and the lower limits of cerebral autoregulation increase with the degree of induced chronic hypertension.[24,25] Overall, our results suggest that the MAP below which myocardial harm accrues is similar in normotensive patients and those with chronic hypertension.

We only included patients who had scheduled, rather than symptom-driven, postoperative troponin assessments, due to either participation in a trial or to clinical routine. Compliance was excellent, with an average of 98% of cases having troponin measured during the initial 2 postoperative days while hospitalized. Troponin was assessed for at least 2 days while hospitalized because 94% of myocardial injury occurs within this period.[3] Unlike previous studies, we did not assume that patients without a troponin measurement did not have MINS. Our cohort, therefore, consists of a relatively small sample, but one with highly reliable assessment of myocardial injury. While applying the enrollment criteria on the entire population of surgical patients ≥45 years having noncardiac surgery, we excluded nearly 7000 patients. Excluded patients were generally similar to included patients, with some small differences in comorbidities and a shorter duration of surgery (Supplemental Digital Content, Table 8, http://links.lww.com/AA/D823).

The overall incidence of the composite outcome, MINS or mortality, was only 5.6%, which is considerably lower than in previous reports, presumably because we did not include urgent operations or vascular surgery. A consequence of sparse outcomes and only 4576 operations is that we lacked power to evaluate varying degrees of baseline hypertension. We, therefore, divided the population into patients who did or did not have chronic hypertension, rather than considering gradations of hypertension. The threshold we selected was an MAP of 110 mm Hg because it is close to the common definition of hypertension (140/90 mm Hg), which corresponds to an MAP of about 107 mm Hg.[21] However, an MAP of 110 mm Hg is not especially high, and it remains likely that there is some degree of baseline hypertension that requires higher intraoperative pressures to prevent myocardial injury.

Another consequence of sparse outcomes and our relatively small cohort was wide CIs around our point estimates of potential MAP harm thresholds. Thus, while there was no clear evidence that chronic hypertension increased the mean pressure at which hypotensive injury started, considerable uncertainty remains and future analyses are warranted. Also, due to the small number of observed outcome events, when conducting threshold logistic regression, we were only able to include a subset of cofounding variables when estimating change points within baseline MAP levels. However, a strength of our primary analysis was that with a mixed effects logistic regression model, we were able to estimate both linear and nonlinear associations for the relationship between low intraoperative MAP exposures and outcome as well as test the interaction between these associations and baseline MAP levels, all the while thoroughly adjusting for confounding and the potential within-patient correlation across multiple surgeries.

The inclusion of patients from a single center, many of whom participated in 1 of 4 clinical studies along about 10 years, presumably limits generalizability of our conclusions to other setups. The relatively low incidence of the composite outcome in our cohort (5.6%) limited our ability to test more thresholds or to consider baseline blood pressure as a continuous variable. Future analyses are warranted, but such data are currently not available. Furthermore, patients with chronic hypertension were generally less exposed to intraoperative hypotension, which risks our analysis with confounding by indication. Nonetheless, it seems that despite smaller exposure to hypotension, these patients experienced similar rates of the outcome, suggesting that their risk is at least as high as that of normotensive patients.

Despite the relatively low incidence of the composite outcome, mortality was somewhat high at 2.2%. Although 30-day mortality after adult noncardiac surgery is often reported at 1.2% to 1.8%, it is highly variable depending on patients' age and comorbidities, surgical complexity, and country.[3,26] Considering our patients' age and comorbidities, as well as the relatively sicker patients seeking medical care in the Cleveland Clinic, this mortality rate is not surprising.

In summary, no clear hypotensive threshold indicating an increase in the odds of major complications was found for surgical patients either with or without chronic hypertension. We were not able to demonstrate a difference in the harm threshold between normotensive and chronically hypertensive patients. Our results do not support the concept that chronically hypertensive patients generally need to be kept at an MAP much higher than 65 mm Hg to avoid increasing the risk of myocardial injury or mortality.

DISCLOSURES

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Conflicts of Interest: D. I. Sessler is a consultant for Edwards Lifesciences, Sensifree, and Perceptive Medical.
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