ORIGINAL INVESTIGATIONS

Targeting Higher Intraoperative Blood Pressures Does Not Reduce Adverse Cardiovascular Events Following Noncardiac Surgery

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ABSTRACT

BACKGROUND Intraoperative arterial hypotension is strongly associated with postoperative major adverse cardio-vascular events (MACE); however, whether targeting higher intraoperative mean arterial blood pressures (MAPs) may prevent adverse events remains unclear.

OBJECTIVES This study sought to determine whether targeting higher intraoperative MAP lowers the incidence of postoperative MACE.

METHODS This single-center randomized controlled trial assigned adult patients at cardiovascular risk undergoing major noncardiac surgery to an intraoperative MAP target of $\geq$60 mm Hg (control) or $\geq$75 mm Hg (MAP $\geq_{75}$). The primary outcome was acute myocardial injury on postoperative days 0-3 and/or 30-day MACE/acute kidney injury (AKI) (acute coronary syndrome, congestive heart failure, coronary revascularization, stroke, AKI, and all-cause mortality). The secondary outcome was 1-year MACE.

RESULTS In total, 458 patients were randomized (intention-to-treat population: 451). The cumulative intraoperative duration with MAP <65 mm Hg was significantly shorter in the MAP $\geq_{75}$ group (median 9 minutes [interquartile range: 3 to 24 minutes] vs 23 minutes [interquartile range: 8-49 minutes]; $P < 0.001$). The primary outcome incidence was 48% for MAP $\geq_{75}$ and 52% for control (risk difference -4.2; 95% CI: -13% to $+5\%$), the primary contributor being AKI (incidence 44%). Acute myocardial injury occurred in 15% (MAP $\geq_{75}$) and 19% (control) of patients. The secondary outcome incidence was 17% for MAP $\geq_{75}$ and 15% for control (risk difference $+2.7$; 95% CI: -4% to $+9.5\%$).

CONCLUSIONS These findings do not support universally targeting higher intraoperative blood pressures to reduce postoperative complications. Despite a 60% reduction in hypotensive time with MAP <65 mm Hg, no significant reductions in acute myocardial injury or 30-day MACE/AKI could be found. (Biomarkers, Blood Pressure, BIS: Risk Stratification/ Management of Patients at Cardiac Risk in Major Noncardiac Surgery [BBB]; NCT02533128) (J Am Coll Cardiol 2021;78:1753–1764) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Founda-tion. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Major adverse cardiovascular events (MACE) and myocardial injury are leading causes of morbidity and mortality following noncardiac surgery, with up to one-third of 30-day mortality potentially attributable to myocardial injury [1,2]. Intraoperative hypotension has been found to be strongly associated with postoperative cardiovascular morbidity and all-cause mortality [3-5].

However, it remains unclear whether targeting higher intraoperative blood pressures (BPs) may improve postoperative outcomes—ie, whether intraoperative hypotension is a marker or mediator of disease. Given the paucity of interventional trials [6] to date, this remains an important yet unanswered question in perioperative medicine [7]. Particularly, no studies have yet examined the isolated effect of targeting higher intraoperative BPs during major noncardiac surgery in a population at high cardiovascular risk—the patients who have the highest risk for postoperative complications and potentially stand to gain the most from avoidance of hypotensive episodes.

With this study, we sought to elucidate whether targeting a higher intraoperative mean arterial blood pressure (MAP) in all patients at cardiovascular risk reduces the incidence of postoperative complications following major noncardiac surgery at 30 days and 1 year postoperatively.

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METHODS

STUDY DESIGN AND PATIENTS. Our study was a pragmatic single-center, randomized controlled trial (RCT) comparing 2 intraoperative BP targets with regard to postoperative complications. This RCT was part of a larger cohort study (BBB Study [Biomarkers, Blood pressure and BIS]), examining the association of perioperative factors with MACE at a referral center in Switzerland.

We studied adult patients over 45 years of age at cardiovascular risk undergoing major noncardiac surgery. Cardiovascular risk was defined as meeting at least 1 of the following 6 criteria: history of coronary artery disease, peripheral artery disease, stroke, or congestive heart failure; undergoing major vascular surgery (excluding arteriovenous shunt, vein stripping procedures, and carotid endarterectomies); or fulfilment of any 3 of the 7 Lee criteria (Supplemental Material). Major noncardiac surgery was defined as vascular, intraperitoneal, intrathoracic, or major orthopedic surgery.

Exclusion criteria were pregnancy, inclusion in another clinical trial with common endpoints (high-sensitivity cardiac troponin I [hs-cTnI], any component of the composite outcome MACE), previous enrollment in this clinical trial, emergent surgery, presence of any active cardiac conditions (unstable coronary syndromes, decompensated heart failure, significant arrhythmias, severe valvular disease) [8], and any transplantation.
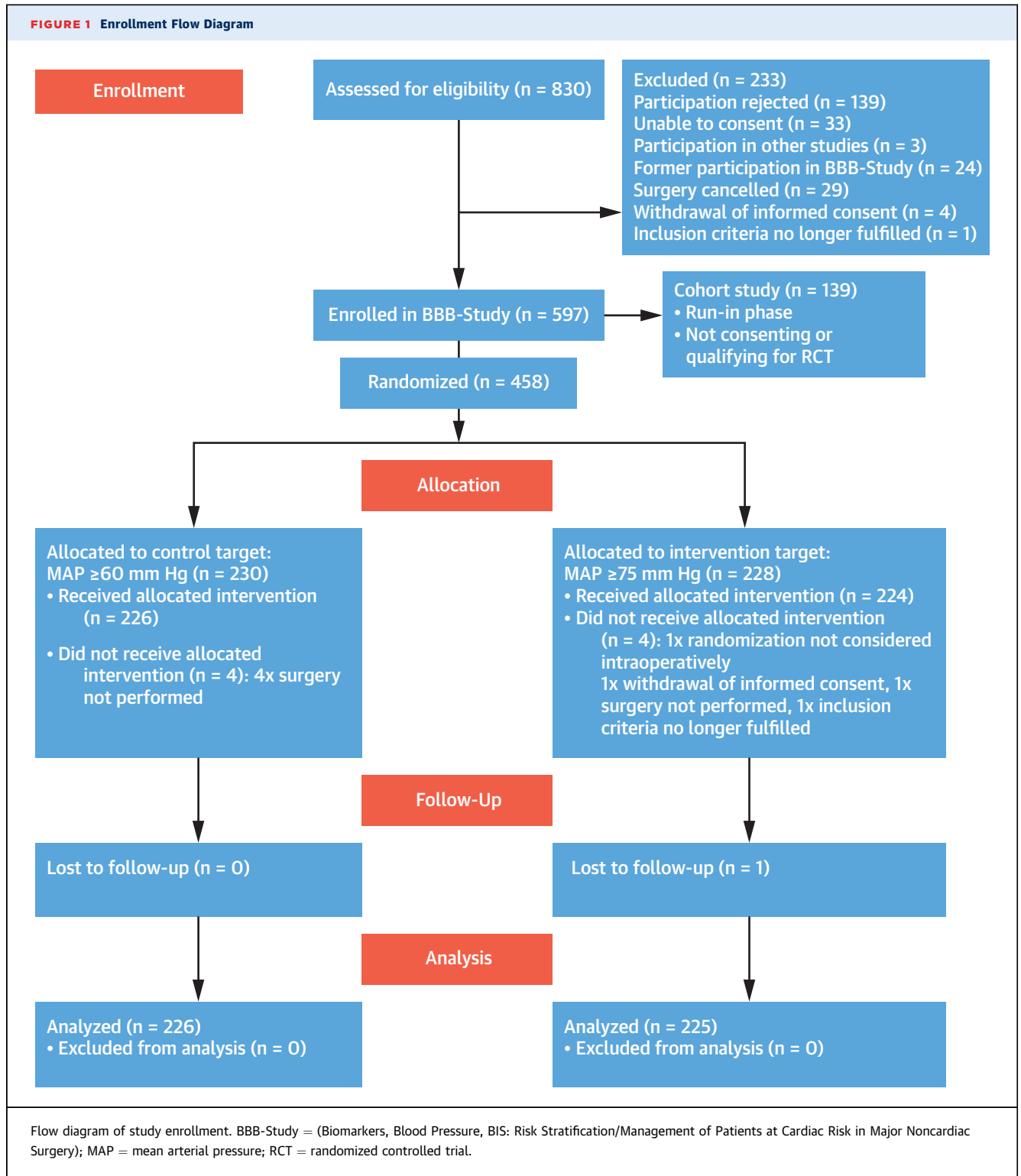
RANDOMIZATION. Patients were randomized preoperatively in the preoperative anesthesia clinic in a 1:1 ratio using computerized block randomization to either the MAP ≥75 mm Hg group (*MAP* $\geq_{75}$) or control group.

BLINDING. The postoperative treatment teams and patients remained blinded to the randomization. Until completion of the primary outcome analysis, the statistical analysis team remained blinded to the randomization.

PROCEDURES. Intervention. In the intervention group (MAP $\geq_{75}$) a MAP ≥75 mm Hg was targeted intraoperatively. In the control group, a MAP ≥60 mm Hg was targeted intraoperatively (per the current ESC/ESA Clinical Practice Guidelines on Noncardiac Surgery [9]). Deviations below the prescribed targets were allowed when deemed medically indicated (eg, active surgical bleeding).

Intraoperative anesthetic management. All patients had general anesthesia, provided with either a target-controlled infusion (TCI) of propofol using the Schnider pharmacokinetic model [10,11] or with volatile anesthetics (sevoflurane or desflurane). Analgesia was provided with a combination of fentanyl and a TCI of remifentanil using the Minto pharmacokinetic model [12,13]. Anesthetic depth was titrated to a bispectral index (BIS) (Anandic Medical Systems AG; BIS VISTA, version: platform 2.03, software 3.22) between 45 and 60 confirmed by adequate frontal EEG traces. Muscle relaxants were given to facilitate orotracheal intubation and intraoperatively as indicated. When indicated, general anesthesia was supplemented with regional/neuraxial analgesia. All patients had controlled ventilation.

Intraoperative hemodynamic management. Intraoperative hemodynamics were managed per an institutional algorithm (Supplemental Figure 1) placing an emphasis on treatment of reversible causes (hypovolemia and anesthetic overdose indicated by a BIS <45) before administration of vasopressors (ephedrine and/or norepinephrine, depending on clinical scenario) and on maintenance of adequate end-organ perfusion. Clinical implementation of the institutional hemodynamic management algorithm

FIGURE 1 Enrollment Flow Diagram

Flow diagram of study enrollment. BBB-Study = (Biomarkers, Blood Pressure, BIS: Risk Stratification/Management of Patients at Cardiac Risk in Major Noncardiac Surgery); MAP = mean arterial pressure; RCT = randomized controlled trial.

was at the discretion of the anesthesiologist in charge.

Postoperative management. Postoperatively, patients were cared for in the postanesthesia care unit or surgical intensive care unit with—unless medically

indicated otherwise—a MAP ≥65 mm Hg targeted, consistent with consensus statements (14).

Data collection. Intraoperative parameters were automatically collected and saved electronically (LOWTeq anesthesia digital anesthetic protocol,

TABLE 1 Characteristics of Patients at Baseline		
	Control (n = 226)	MAP Target ≥75 mm Hg (n = 225)
Age, y	69 ± 10	70 ± 8
Sex		
Male	182 (81)	186 (83)
Female	44 (19)	39 (17)
ASA physical status		
2	81 (36)	76 (34)
3	142 (63)	144 (64)
4	3 (1)	5 (2)
Charlson comorbidity index		
0	44 (19)	37 (16)
1	52 (23)	33 (15)
2	40 (18)	62 (28)
3	40 (18)	44 (20)
4	32 (14)	31 (14)
5	12 (5)	6 (3)
6	1 (0)	6 (3)
7	2 (1)	2 (1)
8	0 (0)	2 (1)
9	2 (1)	2 (1)
10	1 (0)	0 (0)
Revised cardiac risk index		
0	2 (1)	2 (1)
1	109 (48)	95 (42)
2	81 (36)	94 (42)
3	29 (13)	29 (13)
4	4 (2)	5 (2)
5	1 (0)	0 (0)
Fulfilment of ≥3 Lee criteria	38 (17)	34 (15)
History of coronary artery disease	84 (37)	111 (49)
History of peripheral artery disease	94 (42)	110 (49)
History of congestive heart failure	1 (0)	2 (1)
History of stroke	23 (10)	11 (5)
History of transient ischemic attack	7 (3)	9 (4)
Preoperative serum creatinine >175 μmol/L	33 (15)	34 (15)
Insulin-dependent diabetes mellitus	24 (11)	19 (8)
Preoperative brain-type natriuretic peptide	52 (29-102)	54 (28-108)
Preoperative high-sensitivity cardiac troponin I	10 (10-11)	10 (10-10)
ACE inhibitor		
None	160 (71)	147 (65)
Continued perioperatively	66 (29)	78 (35)
Stopped perioperatively	0 (0)	0 (0)
Angiotensin receptor blocker		
None	154 (68)	165 (73)
Continued perioperatively	71 (31)	59 (26)
Stopped perioperatively	1 (0)	1 (0)
Beta-blocker		
None	114 (50)	116 (52)
Continued perioperatively	112 (50)	108 (48)
Stopped perioperatively	0 (0)	1 (0)

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LOWTeq GmbH, Cologne, Germany), with the intraoperative period defined as the interval between beginning and end of anesthetic care (including induction of general anesthesia). Further study-related patient data were stored in a secure, centralized Filemaker 16 database (Claris International Inc) with regular auditing by local monitors of the Clinical Trials Unit St. Gallen.

Biomarker assays. hs-cTnI was measured using the Beckman Coulter ACCESS AccuTn+3 assay (Beckman Coulter Inc). Brain-type natriuretic peptide (BNP) was measured using the Biosite Triage BNP assay (Quidel Corp).

Biomarker measurements. Perioperative biomarker measurements were performed in all patients (hs-cTnI preoperatively and on postoperative days [PODs] 0-3, BNP preoperatively and on POD 0).

OUTCOMES. The primary outcome was a composite of hs-cTnI rise on POD 0-3 and/or 30-day MACE/acute kidney injury (AKI). A relevant hs-cTnI rise was defined as a value over 40 ng/L (99th percentile of the upper reference limit) and a relative increase of ≥35% compared with the preoperative value (15-17). The 30-day MACE/AKI was a composite of acute coronary syndrome, new or worsening congestive heart failure, coronary revascularization, stroke, AKI (18), or all-cause mortality (Supplemental Appendix).

The secondary outcome was 1-year MACE, a composite identical to 30-day MACE/AKI except for the inclusion of new or progressive chronic kidney disease in place of *AKI*.

STATISTICAL ANALYSIS AND DATA HANDLING.
Sample size calculation. All randomized patients who had surgery were analyzed as intention-to-treat. With an expected incidence of 39.5% in the control group (20% troponin elevation, 19.5% MACE) and 27% in the intervention group, a power of 80%, a 2-sided significance level of 0.05, and a drop-out rate of 10%, we estimated a sample size of 458 patients.
Primary statistical analysis. The primary and secondary outcomes were compared between groups using a chi-square test of stochastic independence. All CIs for risk differences were calculated based on the normal approximation.
Sensitivity and post hoc statistical analyses. An analogue Bayesian analysis was performed post hoc to further characterize any treatment effects. A Bayes Factor was derived on the basis of a multinomial model with fixed group sizes using the software JASP (JASP Team [2019], JASP version 0.11.1) (19). To assess comparability of our study population with previous studies, we performed analyses examining the association of hypotensive time with both short- and long-term MACE, including time-to-event analyses and proportional hazards regression (R packages survival 3.2.3 and survminer 0.4.8). Finally, sensitivity analyses of the primary endpoint were performed with AKI defined per protocol, defined purely

by creatinine rise, without AKI stage 1 and without AKI altogether.

Data handling. Data preparation/analysis and statistical analysis were performed with R version 3.5.1 (R Core Team, R Foundation for Statistical Computing). For analysis of hemodynamic data, MAPs ≤30 mm Hg and ≥250 mm Hg, heart rates ≤30 and ≥200 beats/min, and BIS ≤10 and ≥80 were considered physiologically implausible and were removed from the dataset; this approach is similar to previous studies (20). Missing laboratory values were considered to be within normal limits.

ETHICS APPROVAL, STUDY REGISTRATION, AND MONITORING. This study was approved by the Cantonal Ethics Committee of St. Gallen, Switzerland (EKSG 15/003). Prior to patient recruitment, this trial was registered with ClinicalTrials.gov (NCT02533128) and the Swiss National Clinical Trials Portal (SNCTP000001512). Data and study monitoring were performed by the Clinical Trials Unit of the Cantonal Hospital St. Gallen.

RESULTS

STUDY POPULATION. Patients were enrolled from March 7, 2016, to April 17, 2019, at the Cantonal Hospital St. Gallen, a Swiss referral center, with the last follow-up on April 17, 2020. Of 830 eligible patients, 139 were included solely in our run-in/parallel cohort study and 458 were included and randomized in the RCT. With 7 patients not undergoing surgery and 1 patient lost to follow-up (0.2%), our intention-to-treat population had 451 patients (**Figure 1**). The measured baseline parameters were well balanced between the study groups and can be found in **Table 1**.

INTRAOPERATIVE ANESTHETIC MANAGEMENT. All 451 patients had general anesthesia, of which 171 (38%) additionally received epidural analgesia. Analgesia was provided with fentanyl, supplemented by a remifentanil TCI. General anesthesia consisted of a propofol TCI in 431 patients (95.6%), a combination of a propofol TCI and volatile anesthetics in 12 patients (2.7%), and exclusively volatile anesthetics in 8 patients (1.7%). The mean BIS was 47 in the MAP $\geq_{75}$ group and 46 in the control group ($P = 0.001$) (Supplemental Figure 2). Invasive BP monitoring was instituted in 86% of patients.

INTRAOPERATIVE HEMODYNAMIC MANAGEMENT. All patients experienced hypotensive episodes with MAP <75 mm Hg. However, patients in the MAP $\geq_{75}$ group experienced significantly less cumulative duration with MAP <75 mm Hg (median 72 minutes [interquartile range (IQR): 41-138 minutes] vs

TABLE 1 Continued		
	Control (n = 226)	MAP Target ≥75 mm Hg (n = 225)
Calcium-channel blocker		
None	169 (75)	163 (72)
Continued perioperatively	57 (25)	60 (27)
Stopped perioperatively	0 (0)	2 (1)
Operations		
Gynecological surgery	4 (2)	1 (0)
Orthopedic surgery	6 (3)	7 (3)
Thoracic surgery	11 (5)	18 (8)
Urological surgery	15 (7)	31 (14)
Vascular surgery	161 (71)	142 (63)
Visceral surgery	29 (13)	26 (12)

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists.

121 minutes [IQR: 70-210 minutes]; $P < 0.001$) and less cumulative hypotensive time with MAP <65 mm Hg (median 9 minutes [IQR: 3 to 24 minutes] vs 23 minutes [IQR: 8-49 minutes]; $P < 0.001$) (**Figure 2**). Patients in the MAP $\geq_{75}$ group spent a median 23% of the time with a MAP <75 mm Hg compared with 41% in the control group. Further, in the MAP $\geq_{75}$ group, hypotensive episodes were shorter (median 80 seconds [IQR: 53-145 seconds] vs 116 seconds [IQR: 81-240 seconds]; $P < 0.001$) and less pronounced (average minimal MAP of hypotensive episodes median 60 mm Hg [IQR: 55-63 mm Hg] vs 57 mm Hg [IQR: 51-62 mm Hg]; $P < 0.001$) compared with the control group (Supplemental Figure 3).

Patients in the MAP $\geq_{75}$ group received significantly higher cumulative doses of ephedrine compared with the control group, and vasopressors were given at higher BPs (Supplemental Figure 4). There were no significant differences in the infused doses of norepinephrine; in median, minimum, or maximum heart rates; or in blood losses (median 400 mL [IQR: 150-1,000 mL] vs 500 mL [IQR: 150-1,160 mL]; $P = 0.18$) between the 2 groups. The cumulative fluid balance (median +1,455 mL [IQR: +600 to +2,645 mL]) and the amount of administered crystalloids, colloids, and blood products did not differ significantly between the 2 groups.

MISSING LABORATORY DATA. A total of 1.9% of hs-cTnI and 1.5% of creatinine measurements were missing and assumed to be normal. One patient declined all blood draws.

PRIMARY OUTCOME: ACUTE MYOCARDIAL INJURY ON PODs 0-3 AND/OR 30-DAY MACE/AKI. The primary outcome occurred in 108 patients (48%) in the MAP $\geq_{75}$ and 118 patients (52%) in the control group

(risk difference −4.2%; 95% CI: −13% to +5%; P = 0.42) (**Central Illustration**). Acute myocardial injury was present in 33 (15%) vs 43 (19%) (risk difference −4.4%; 95% CI: −11% to +2.5%) and MACE/AKI in 101 (45%) vs 105 (46%), with acute kidney injury present in 96 (43%) vs 104 (46%) (risk difference −3.4%; 95% CI: −13% to +5.8%) in the MAP $\geq_{75}$ and control groups, respectively (**Figure 3A**).

SECONDARY OUTCOME: 1-YEAR MACE. The secondary outcome occurred in 39 patients (17%) in the MAP $\geq_{75}$ and 33 patients (15%) in the control group (risk difference +2.7; 95% CI: -4% to 9.5%) (**Figure 3B**).

SENSITIVITY AND POST HOC ANALYSES. A post hoc Bayesian analysis yielded a Bayes Factor (BF$_{01}$) of 5.7 for the primary outcome and 8.5 for the secondary outcome, indicating substantial evidence in favor of the absence of a treatment effect in the whole study population with regard to both endpoints (21).

Longer cumulative intraoperative hypotensive time with MAP <65 mm Hg was significantly associated with the primary composite endpoint (risk difference +21%; 95% CI: +12% to +30%) and 1-year MACE (risk difference +9.8%; 95% CI: +3.1% to +17%). The association with 1-year MACE was further confirmed using proportional hazards regression (HR: 1.98; 95% CI: 1.22-3.21) (Supplemental Figure 5).

Due to the high incidence of AKI (46% control group) sensitivity analyses were performed, showing no significant differences in the primary outcome with 30-day MACE defined without AKI (risk difference −4.4%; 95% CI: −11% to +2.7%), using laboratory criteria (risk difference −2.5%; 95% CI: −11% to +6.5%), or when defined per protocol (risk difference −4.2%; 95% CI: −13% to +5%) (**Figure 4**).

Finally, a post hoc analysis examining the prognostic relevance of the study endpoints found both postoperative AKI and acute myocardial injury to be significantly and independently associated with 1-year mortality in the whole study population (AKI OR: 4.96 [95% CI: 1.48-22.5], acute myocardial injury OR: 3.19 [95% CI: 0.15-26.3]) in a multivariate logistic regression model correcting for the Charlson comorbidity index.

DISCUSSION

STATEMENT OF PRINCIPAL FINDINGS. In this pragmatic, single-center RCT, we found no significant differences in short- or long-term cardiovascular outcomes when targeting an intraoperative MAP $\geq$75 mm Hg compared with an MAP $\geq$60 mm Hg. Neither the incidence of acute myocardial injury on
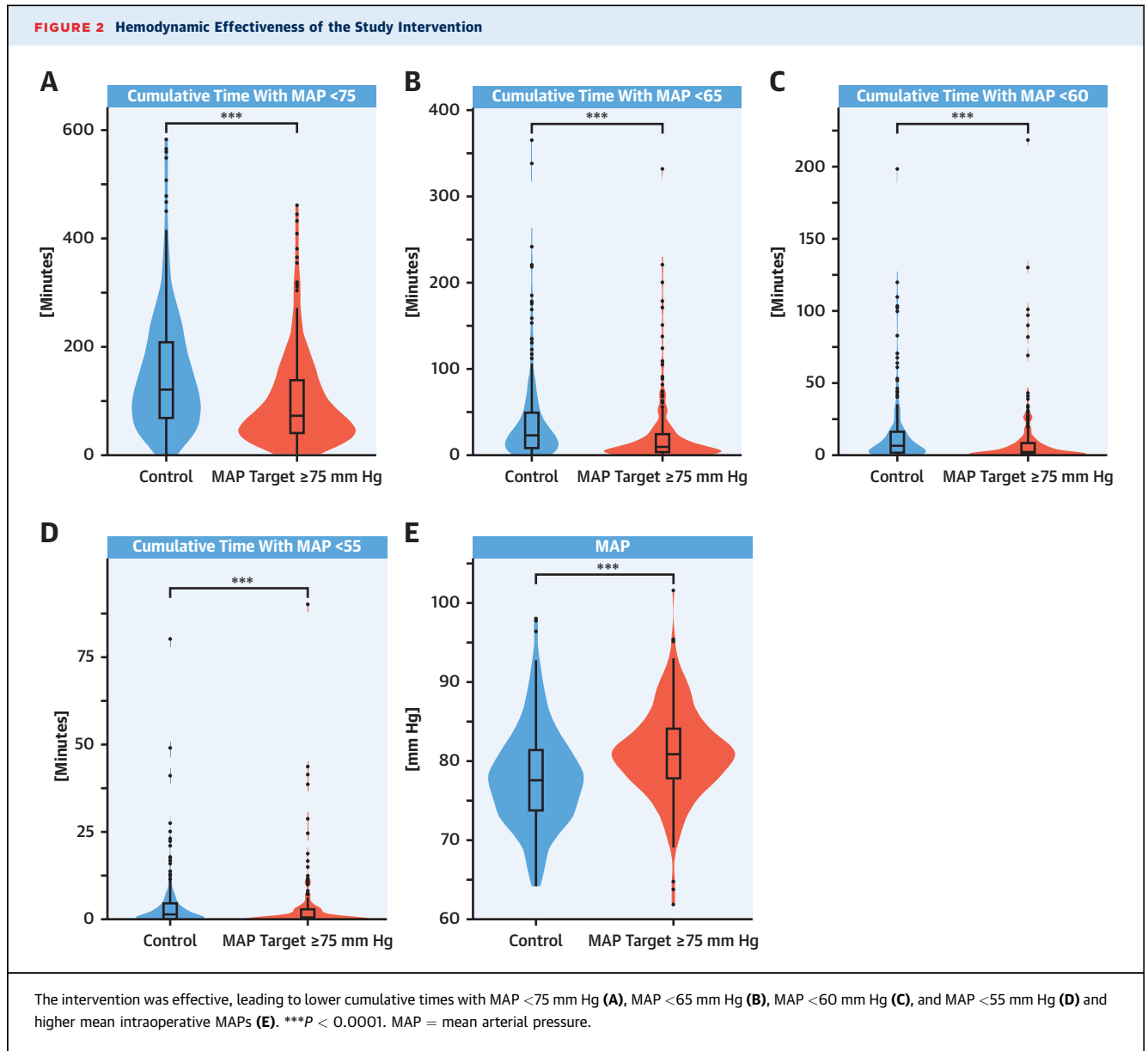
PODs 0-3 and/or 30-day MACE/AKI, nor the incidence of 1-year MACE were significantly different in the 2 study arms, despite over halving intraoperative hypotensive time with MAP <65 mm Hg.

JUSTIFICATION OF STUDY METHODOLOGY. Study population. The inclusion criteria for our study are based on previous landmark trials on perioperative MACE in noncardiac surgery (22) and consistent with the definition of a high-risk patient population (23). The incidences of postoperative acute myocardial injury of 17% and myocardial infarction at 30 days of 3.5% in the control group further underline the high perioperative cardiovascular risk of the studied population.

Study intervention. Our choice to use an MAP target $\geq$75 mm Hg in the intervention group is supported by the best available evidence. Most large cohort studies with over 10,000 patients have used absolute BP thresholds (3). In the largest study (57,315 patients) to compare absolute with relative BP thresholds of which we are aware (24), relative BP cutoffs were not superior to absolute cutoffs for prediction of myocardial injury after noncardiac surgery (MINS) or AKI. Further, although MAPs as high as 80 mm Hg have been associated with MACE (25), it has been suggested that the risk of overall organ injury only begins to rise rapidly below a MAP of 65 mm Hg (strongly prognostically relevant hypotension) (3,7), leading to the proposition to use excursions below this BP threshold as part of an intraoperative quality metric (26). By targeting an MAP $\geq$75 mm Hg, we were able to achieve a 60% reduction in strongly prognostically relevant hypotensive time.

Study endpoints. We strived to align our definition of MACE with previous landmark studies in perioperative medicine (1,22). Our choice to integrate both acute myocardial injury and AKI into our primary endpoint is supported by the fact that AKI and myocardial injury are the 2 adverse events most strongly associated with intraoperative hypotension (3-5), and that both AKI (27-29) and myocardial injury (17,30) have considerable prognostic importance in the postoperative period. This is underlined by a cohort study of 50,314 patients undergoing major surgery, in whom isolated AKI was shown to be an independent risk factor for postoperative mortality with a risk-adjusted 90-day mortality rate (3.5%; 95% CI: 2.8%-4.1%) similar to that of isolated cardiovascular complications (3.4%; 95% CI: 2.9%-3.9%), with even AKI stage RIFLE Risk conferring increased risk for 90-day mortality (31). We were able to reproduce these findings in our study population,

FIGURE 2   Hemodynamic Effectiveness of the Study Intervention

The intervention was effective, leading to lower cumulative times with MAP <75 mm Hg **(A)**, MAP <65 mm Hg **(B)**, MAP <60 mm Hg **(C)**, and MAP <55 mm Hg **(D)** and higher mean intraoperative MAPs **(E)**. ***$P < 0.0001$. MAP = mean arterial pressure.

with both AKI at 30 days and acute myocardial injury on PODs 0-3 independently associated with 1-year MACE.

Statistical power. Our study was powered to detect a risk difference of 13% in our primary composite outcome with an assumed baseline incidence of 39.5% in the control group (20% for acute myocardial injury and 19.5% for 30-day MACE/AKI), a realistic effect estimate based on pooled observational data on the association of varying degrees of intraoperative hypotension with postoperative MACE (3). Our incidence of acute myocardial injury of 19% in the control group was in line with our sample size calculation and comparable to previous

landmark studies, with the VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study) 2 finding a MINS incidence of 17.9% (17). However, our incidence of 30-day MACE/AKI was higher than expected (46% in the control group), predominantly driven by AKI. It must be underlined that although our study is adequately powered to detect a relevant treatment effect on acute myocardial injury and acute kidney injury, further conclusions pertaining to the remaining subcomponents of 30-day MACE (acute coronary syndrome, coronary revascularization, congestive heart failure, stroke, death) cannot be drawn because of their low incidences.
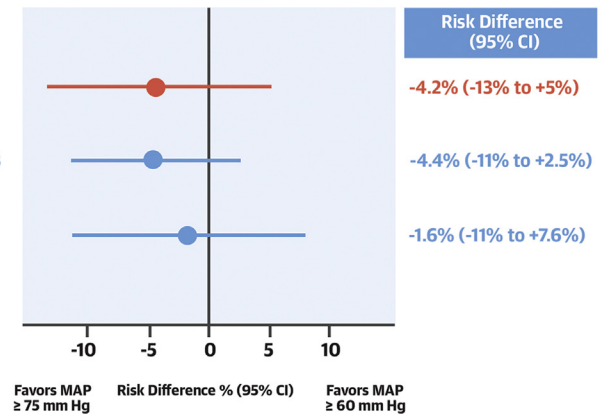
CENTRAL ILLUSTRATION Intraoperative Blood Pressure Targets and Postoperative Major Adverse Cardiovascular Events

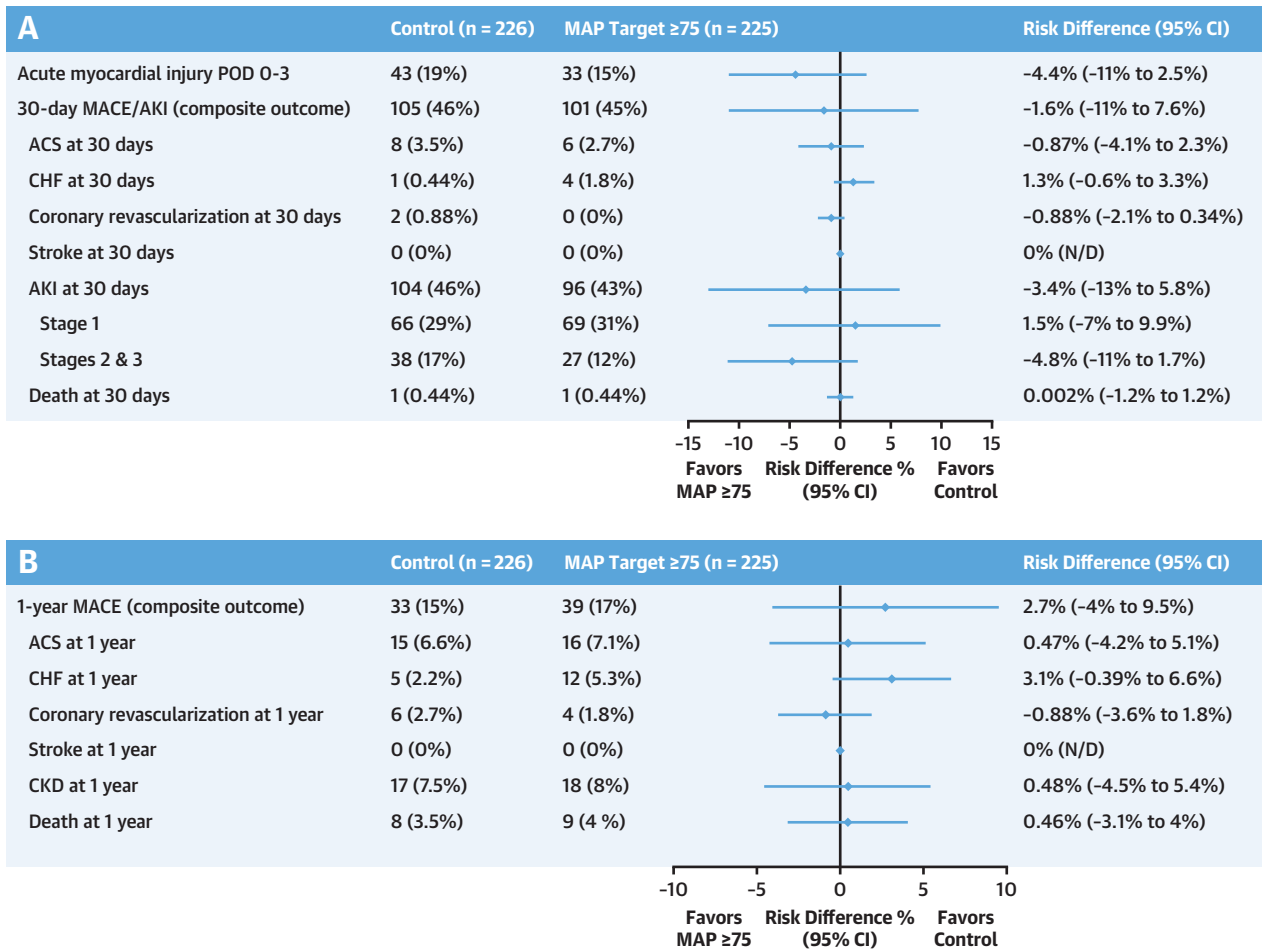Wanner, P.M. et al. J Am Coll Cardiol. 2021;78(18):1753–1764.

Despite clinically important reductions in intraoperative hypotension, targeting higher intraoperative blood pressures during major noncardiac surgery was not associated with a significant difference in the incidence of acute myocardial injury or 30-day major adverse cardiovascular events/acute kidney injury. AKI = acute kidney injury; CI = confidence interval; MACE = major adverse cardiovascular event; POD = postoperative day.

INTERPRETATION OF FINDINGS IN THE CONTEXT OF PREVIOUS STUDIES. Our study contrasts with the INPRESS (Intraoperative Norepinephrine to Control Arterial Pressure Study), a multicenter RCT of 298 patients undergoing abdominal surgery in which individualized BP management led to a reduced incidence of postoperative organ dysfunction compared with standard management, primarily driven by a lower incidence of altered consciousness without any significant differences in acute kidney injury, myocardial ischemia or infarction, stroke, acute heart failure, or 30-day mortality (6). Importantly, INPRESS delivered a hemodynamic care bundle involving administration of colloid boluses to optimize stroke volume index and blood transfusion to maintain serum hemoglobin >10 g/dL, in addition to targeting the randomized BP target (systolic BP within 10% reference vs above 80 mm Hg or within 40% of reference). Further, the 2 study arms in INPRESS received different vasopressors (primarily ephedrine boluses in the standard vs norepinephrine infusion in the individualized arm). Finally, the high incidence of postoperative severe sepsis/septic shock (13.7%) and the low incidence of myocardial ischemia/infarction (0.3%) raise questions about the studied population. These factors complicate drawing definitive conclusions pertaining to intraoperative BP targets in major noncardiac surgery, and suggest that INPRESS set out to answer a different research question in a different population. Hence, we believe our study delivers novel interventional data on the isolated effect of BP management on established short- and long-term cardiovascular endpoints in major noncardiac surgery.

MEANING OF THE STUDY. There is an abundance of observational data stemming from dozens of cohort studies in hundreds of thousands of patients demonstrating a strong association between intraoperative hypotension and postoperative adverse cardiovascular outcomes (3-5). This has raised the question whether this association could be of a causal nature and, hence, whether hemodynamic intervention could help prevent postoperative adverse events (7,9,32). Our study is the first RCT of which we are aware to examine whether targeting higher intraoperative BPs in a high-risk population during major noncardiac surgery may reduce the incidence of postoperative short- and long-term MACE. Our finding that more than halving strongly prognostically relevant hypotensive time (MAP <65 mm Hg) is not associated with any significant differences in short- or long-term adverse cardiovascular outcomes

FIGURE 3 Effect of Targeting Higher Intraoperative Blood Pressures on MACE

A	Control (n = 226)	MAP Target ≥75 (n = 225)		Risk Difference (95% CI)
Acute myocardial injury POD 0-3	43 (19%)	33 (15%)		-4.4% (-11% to 2.5%)
30-day MACE/AKI (composite outcome)	105 (46%)	101 (45%)		-1.6% (-11% to 7.6%)
ACS at 30 days	8 (3.5%)	6 (2.7%)		-0.87% (-4.1% to 2.3%)
CHF at 30 days	1 (0.44%)	4 (1.8%)		1.3% (-0.6% to 3.3%)
Coronary revascularization at 30 days	2 (0.88%)	0 (0%)		-0.88% (-2.1% to 0.34%)
Stroke at 30 days	0 (0%)	0 (0%)		0% (N/D)
AKI at 30 days	104 (46%)	96 (43%)		-3.4% (-13% to 5.8%)
Stage 1	66 (29%)	69 (31%)		1.5% (-7% to 9.9%)
Stages 2 & 3	38 (17%)	27 (12%)		-4.8% (-11% to 1.7%)
Death at 30 days	1 (0.44%)	1 (0.44%)		0.002% (-1.2% to 1.2%)

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Favors   Risk Difference %   Favors
MAP ≥75   (95% CI)   Control

B	Control (n = 226)	MAP Target ≥75 (n = 225)		Risk Difference (95% CI)
1-year MACE (composite outcome)	33 (15%)	39 (17%)		2.7% (-4% to 9.5%)
ACS at 1 year	15 (6.6%)	16 (7.1%)		0.47% (-4.2% to 5.1%)
CHF at 1 year	5 (2.2%)	12 (5.3%)		3.1% (-0.39% to 6.6%)
Coronary revascularization at 1 year	6 (2.7%)	4 (1.8%)		-0.88% (-3.6% to 1.8%)
Stroke at 1 year	0 (0%)	0 (0%)		0% (N/D)
CKD at 1 year	17 (7.5%)	18 (8%)		0.48% (-4.5% to 5.4%)
Death at 1 year	8 (3.5%)	9 (4 %)		0.46% (-3.1% to 4%)

-10 -5 0 5 10
Favors   Risk Difference %   Favors
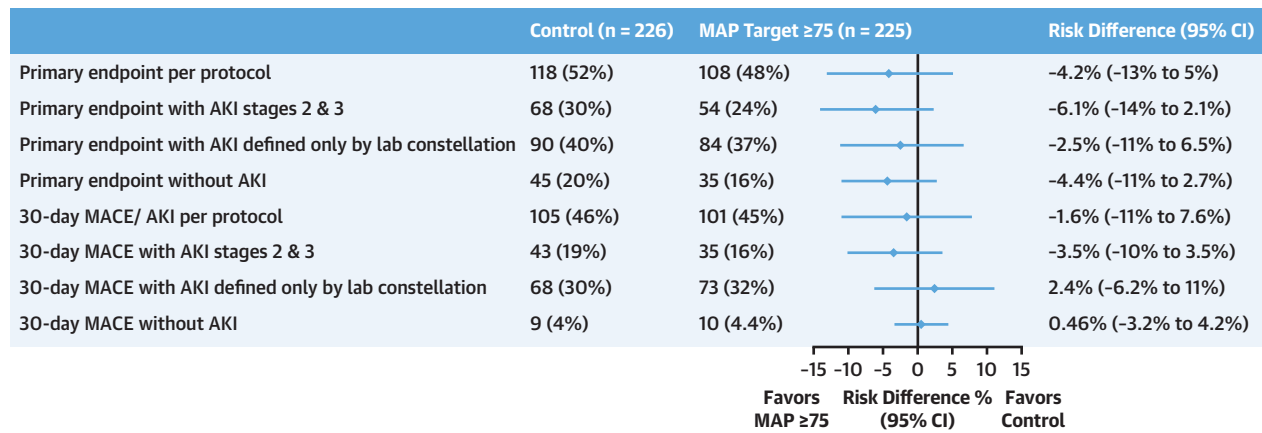MAP ≥75   (95% CI)   Control

Targeting a MAP ≥75 mm Hg intraoperatively was not associated with any significant differences in the primary endpoint of acute myocardial injury on PODs 0-3 and/or 30-day MACE/AKI **(A)** or of the secondary endpoint of 1-year MACE **(B)**. Note: 30-day and 1-year MACE differed in definitions, the former using AKI and the latter taking new/progressive CKD as renal endpoints. ACS = acute coronary syndrome; AKI = acute kidney injury; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; MACE = major adverse cardiovascular events; MAP = mean arterial pressure; N/D = not defined; POD = postoperative day.

suggests that simply targeting higher intraoperative BPs in all patients will most likely not lead to meaningful widespread improvements in postoperative outcomes. Based on the available pooled population data (3), a reduction in hypotensive time of this magnitude would be expected to lead to a clinically relevant—and with our sample size, detectable—decrease in the incidence of postoperative acute myocardial injury and AKI. The link between intraoperative hypotension and postoperative MACE is likely more complex than previously assumed and will require further investigation before evidence-based recommendations on intraoperative BP management may be made.

UNANSWERED QUESTIONS AND FUTURE RESEARCH.
Clearly, below a certain threshold, hypotension must have a direct and strong causal relationship with morbidity and mortality; however, where this limit may lie in individual patients remains unclear. Hence, future studies will need to focus on determining the point at which hypotension transitions from mere marker to potent mediator of disease, ie, the point at which the correct hemodynamic intervention would be expected to positively affect outcome. A key development in this direction could be a move away from population-based to individualized definitions of hypotension, which could open the door to a paradigm of personalized intraoperative

FIGURE 4 Sensitivity Analysis of Primary Outcome and 30-Day MACE

	Control (n = 226)	MAP Target ≥75 (n = 225)	Risk Difference (95% CI)
Primary endpoint per protocol	118 (52%)	108 (48%)	-4.2% (-13% to 5%)
Primary endpoint with AKI stages 2 & 3	68 (30%)	54 (24%)	-6.1% (-14% to 2.1%)
Primary endpoint with AKI defined only by lab constellation	90 (40%)	84 (37%)	-2.5% (-11% to 6.5%)
Primary endpoint without AKI	45 (20%)	35 (16%)	-4.4% (-11% to 2.7%)
30-day MACE/ AKI per protocol	105 (46%)	101 (45%)	-1.6% (-11% to 7.6%)
30-day MACE with AKI stages 2 & 3	43 (19%)	35 (16%)	-3.5% (-10% to 3.5%)
30-day MACE with AKI defined only by lab constellation	68 (30%)	73 (32%)	2.4% (-6.2% to 11%)
30-day MACE without AKI	9 (4%)	10 (4.4%)	0.46% (-3.2% to 4.2%)

-15 -10 -5 0 5 10 15

Favors   Risk Difference %   Favors
MAP ≥75   (95% CI)   Control

Sensitivity analyses were performed to ascertain the effect of AKI definitions (per protocol, only stages 2 and 3, only lab constellation, without AKI) on the primary composite outcome (acute myocardial injury and/or 30-day MACE) and 30-day MACE alone, showing no significant differences in the study results. Abbreviations as in Figure 3.

BP targets (33), as has been successfully demonstrated in other clinical contexts (34). Furthermore, the effect of minimizing hypotension postoperatively remains unclear and requires further investigation. Finally, equally as important as the choice of intraoperative hemodynamic targets are the hemodynamic interventions used to reach these targets—further research exploring the interplay of these important factors is needed.

STUDY STRENGTHS AND LIMITATIONS. To our knowledge, this is the first RCT in patients at elevated cardiovascular risk undergoing major noncardiac surgery examining the isolated effect of targeting higher intraoperative BPs on both the short- and long-term incidence of MACE. However, our study has several important limitations. First, our choice of a universal MAP target ≥75 mm Hg in the intervention arm, although based on the best available evidence at the time (20), could very well have been inadequate in individual patients. Hence, our study does not rule out a benefit of targeting higher BPs in certain subgroups of patients, but only that doing so in a whole population at cardiovascular risk unlikely carries a widespread clinically relevant benefit. Second, we must underline that this was a pragmatic study comparing 2 MAP targets—not 2 BPs. Third, the high incidence of AKI led to imbalance in the incidences of our composite primary outcome. This can be explained by an overly conservative estimate of the incidence of AKI in our population (35). Considering that 67% of the study patients had vascular surgery, the 46% AKI incidence is in line with the expected incidence in this patient population (36). Fourth, with the heterogeneity in the effects of the intervention on the components of the composite outcome, caution should be exercised in the interpretation of the individual subcomponents of the composite endpoint, particularly of those with low incidences. Finally, we must emphasize that our study was not powered to detect a treatment effect on 1-year outcomes and that our findings pertaining to long-term outcomes are of an exploratory nature.

CONCLUSIONS

Targeting an MAP ≥75 mm Hg universally in patients at cardiovascular risk undergoing major noncardiac surgery was not associated with a reduction in the incidence of 30-day MACE/AKI and/or acute myocardial injury on PODs 0-3 or the incidence of 1-year MACE compared with standard intraoperative BP management per the current 2014 ESC/ESA Clinical Practice Guidelines on Noncardiac Surgery (9). Despite the strong association of intraoperative hypotension with postoperative adverse cardiovascular outcomes, our data are not indicative of a large reduction in the incidence of such events and cannot rule out the absence of a reduction in postoperative MACE/AKI when universally targeting higher intraoperative BPs. Further studies examining the interplay of intraoperative hypotension, perioperative hemodynamic intervention, and postoperative outcomes with a focus on individualization are needed. Only once the mechanisms underlying perioperative cardiovascular complications are better understood

will we be able to design meaningful interventions that could one day benefit our patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: Despite the strong association between intraoperative hypotension and postoperative MACE, targeting higher intraoperative BPs has uncertain implications for these events.

TRANSLATIONAL OUTLOOK: Future studies focusing on the point at which hypotension transitions from marker to mediator of adverse events could set in motion a transition from a population-based to an individualized definition of hypotension.

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KEY WORDS blood pressure, hypotension, intraoperative, MACE, myocardial injury, organ injury

APPENDIX For an expanded Methods section and supplemental figures, please see the online version of this paper.