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Hypotension-Avoidance Versus Hypertension-Avoidance Strategies in Noncardiac Surgery

An International Randomized Controlled Trial

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Background: Among patients having noncardiac surgery, perioperative hemodynamic abnormalities are associated with vascular complications. Uncertainty remains about what intraoperative blood pressure to target and how to manage long-term antihypertensive medications perioperatively.

Objective: To compare the effects of a hypotension-avoidance and a hypertension-avoidance strategy on major vascular complications after noncardiac surgery.

Design: Partial factorial randomized trial of 2 perioperative blood pressure management strategies (reported here) and tranexamic acid versus placebo. (ClinicalTrials.gov: NCT03505723)

Setting: 110 hospitals in 22 countries.

Patients: 7490 patients having noncardiac surgery who were at risk for vascular complications and were receiving 1 or more long-term antihypertensive medications.

Intervention: In the hypotension-avoidance strategy group, the intraoperative mean arterial pressure target was 80 mm Hg or greater; before and for 2 days after surgery, renin–angiotensin–aldosterone system inhibitors were withheld and the other long-term antihypertensive medications were administered only for systolic blood pressures 130 mm Hg or greater, following an algorithm. In the hypertension-avoidance strategy group, the intraoperative mean arterial pressure target was 60 mm Hg or greater; all antihypertensive medications were continued before and after surgery.

Measurements: The primary outcome was a composite of vascular death and nonfatal myocardial injury after noncardiac surgery, stroke, and cardiac arrest at 30 days. Outcome adjudicators were masked to treatment assignment.

Results: The primary outcome occurred in 520 of 3742 patients (13.9%) in the hypotension-avoidance group and in 524 of 3748 patients (14.0%) in the hypertension-avoidance group (hazard ratio, 0.99 [95% CI, 0.88 to 1.12]; $P = 0.92$). Results were consistent for patients who used 1 or more than 1 antihypertensive medication in the long term.

Limitation: Adherence to the assigned strategies was suboptimal; however, results were consistent across different adherence levels.

Conclusion: In patients having noncardiac surgery, our hypotension-avoidance and hypertension-avoidance strategies resulted in a similar incidence of major vascular complications.

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* For a list of POISE-3 Trial Investigators and Study Groups, see the **Supplement** (available at Annals.org).

During noncardiac surgery, approximately 25% of patients experience clinically significant hypotension (1). Postoperative hypotension on surgical wards is also common and is often prolonged (1–3). Preoperative, intraoperative, and postoperative hypotension is associated with an increased risk for death and vascular complications at 30 days after noncardiac surgery (1, 2, 4–8).

Perioperative hypertension is also associated with vascular complications after noncardiac surgery (9–12). Half of adults having major noncardiac surgery have a history of hypertension, and most use antihypertensive medication (1, 13).

Physicians in preoperative clinics make recommendations about the perioperative management of patients' long-term antihypertensive medications. A large international cohort study reported that most physicians continued

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long-term antihypertensive medications perioperatively (that is, usual practice was consistent with a hypertension-avoidance strategy) (1). Observational studies and small trials suggest that withholding angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) may reduce perioperative hypotension and vascular complications (1, 14–16). Other observational studies have suggested that withholding β-blockers may increase perioperative complications (17, 18). No large trial informs how long-term antihypertensive medications should be managed perioperatively.

Anesthesiologists have to decide for each patient what minimal intraoperative mean arterial pressure (MAP) they will accept. Although MAP targets of 60 mm Hg or greater are commonly used, it has been questioned whether MAP targets of 80 mm Hg or greater would improve outcomes (8, 19). Only 3 small randomized controlled trials (RCTs) have tested alternative intraoperative blood pressure targets and they produced conflicting results (20–22).

We undertook the POISE-3 (PeriOperative ISchemic Evaluation-3) Trial to evaluate the effect of 2 perioperative blood pressure management strategies (that is, a hypotension-avoidance and a hypertension-avoidance strategy) on the 30-day risk for major vascular complications in patients undergoing noncardiac surgery who were using long-term antihypertensive therapy.

METHODS

Study Design and Oversight

POISE-3 was an international RCT that allowed separate evaluation of the effects of a hypotension-avoidance versus a hypertension-avoidance strategy (reported here), and of tranexamic acid versus placebo, in patients having noncardiac surgery. POISE-3 used a partial factorial design, whereby every patient in POISE-3 was randomly assigned in the tranexamic acid trial and only patients who met additional eligibility criteria were also randomly assigned in the blood pressure management trial. Details of the trial objectives, design, and methods are reported elsewhere (23). The full protocol and statistical analysis plan are provided (available at Annals.org). All centers obtained ethics approval before commencing recruitment.

The Population Health Research Institute coordinated the study and was responsible for the randomization, database, data validation, analyses, and center coordination. The steering committee designed the trial and vouches for the accuracy of the data, analyses, and adherence of the study to the protocol. The writing committee finalized the statistical analysis plan before any investigator was unblinded to the trial results and the database was locked. The first author wrote the initial draft of the manuscript, and the writing committee made revisions and decided to submit the manuscript for publication.

Study Participants

We recruited patients from June 2018 through July 2021 at 110 hospitals in 22 countries. Eligible patients were aged 45 years or older, were undergoing inpatient noncardiac surgery, had a history of vascular disease or a combination of vascular risk factors, and were receiving 1 or more antihypertensive medications for at least 30 days in the 6 weeks preceding randomization. **Supplement Methods 1** (available at Annals.org) reports all eligibility criteria.

Procedures

After obtaining written informed consent from the patient or substitute decision maker, study personnel randomly assigned patients on the day of surgery before the procedure, using a central web randomization system, to the hypotension-avoidance or hypertension-avoidance strategy using a 1:1 ratio. The randomization process used randomly variable block sizes stratified by center. Patients, health care providers, and study personnel were aware of the allocation to the blood pressure management strategies. Outcome adjudicators were masked to treatment allocation. Study personnel instructed eligible patients not to take their evening antihypertensive medications the night before surgery or their morning antihypertensive medications the morning of surgery and to bring these medications to the hospital. Patients were to withhold antihypertensive medications the night before surgery to minimize the risk for any long-acting antihypertensive medication affecting the treatment interventions on the day of surgery.

Both blood pressure management strategies addressed the preoperative, intraoperative, and postoperative periods. They were labeled as hypotension-avoidance and hypertension-avoidance to distinguish the dominant hemodynamic abnormality they preferentially intended to avoid.

In the hypotension-avoidance group, on the day of surgery before the procedure and during the first 2 days after surgery, the patient's long-term antihypertensive medications were managed on the basis of an algorithm that continued medications in a stepwise manner only for a systolic blood pressure (SBP) 130 mm Hg or greater and prioritized continuation of β-blockers. Patients in this group were not to take any ACEIs, ARBs, or direct renin inhibitors starting the night before surgery until day 3 after surgery. **Supplement Methods 2** (available at Annals.org) presents the detailed algorithm.

In the hypotension-avoidance group, anesthesiologists targeted an intraoperative MAP of 80 mm Hg or greater from the time of anesthetic induction until the end of surgery. The anesthesiologist decided how to achieve the intraoperative MAP target (for example, fluids, vasopressors).

In the hypertension-avoidance group, on the morning of surgery before the operation, patients received all their long-term antihypertensive medications. The intraoperative blood pressure target was a MAP of 60 mm Hg or greater. Patients resumed their antihypertensive medications immediately after surgery.

We undertook central monitoring of site adherence with the assigned strategies throughout the study. For monitoring purposes, we used a definition of adherence solely based on the adherence of each patient to the assigned strategy, without a different qualification of nonadherence depending on the reasons, which we did not collect.

Outcomes

The primary outcome was a major vascular complication—a composite of vascular death and nonfatal myocardial injury after noncardiac surgery (MINS), stroke, and cardiac arrest at 30 days after randomization. Secondary outcomes were MINS, MINS not fulfilling the universal definition of myocardial infarction, myocardial infarction, stroke, vascular death, and all-cause death. The **Supplement** (available at Annals.org) reports the tertiary outcomes, definitions, and the adjudication process (**Supplement Methods 3** to **5**, available at Annals.org). **Supplement Methods 6** (available at Annals.org) reports the follow-up process.

Statistical Analysis

The initial sample size (10 000 patients) of POISE-3 was established for the tranexamic acid versus placebo trial. We conservatively estimated that 65% of the patients in the tranexamic acid trial would be eligible for the blood pressure management factorial (that is, 6500 patients). We designed the 2 strategies expecting to produce a differential effect on hemodynamics that would lead to a hazard ratio (HR) of 0.75 with the hypotension-avoidance strategy, compared with the hypertension-avoidance strategy, for the 30-day incidence of the primary outcome (1, 6). We estimated that 6500 patients would provide 95% power to detect a HR of 0.75, at a 2-sided α level of 0.05, assuming an 11.0% outcome rate in the hypertension-avoidance strategy (24–26). An independent data monitoring committee reviewed interim analyses when 25%, 50%, and 75% of the 30-day data were available (**Supplement Methods 7**, available at Annals.org). POISE-3 was terminated when 9535 patients were enrolled in the tranexamic acid trial, at which time 7490 patients were enrolled in the blood pressure management trial.

We analyzed patients according to the group to which they were assigned, censoring data for patients who were lost to follow-up on the last day their status was known. For the primary outcome analysis, we used Cox proportional hazards models with stratification according to the randomization to tranexamic acid or placebo, after assessing for the proportionality assumption. We calculated the HR and corresponding 95% CI and associated *P* value. We adopted a similar approach for the secondary and most tertiary outcomes. We used a 2 × 2 table to analyze the outcome cancellation or postponement of surgery on the day of surgery because of blood pressure concerns; we used quantile regression to analyze length of hospital stay and number of days alive and at home.

Supplement Methods 8 (available at Annals.org) reports the details of the prespecified subgroup analyses for the primary outcome; each subgroup effect was assessed on the basis of an interaction term in the Cox proportional hazards model.

For each participant, adherence to the assigned strategy was defined and calculated separately for the intraoperative component and the pre- and postoperative components. In both strategies, the intraoperative adherence was defined on the basis of the percentage of intraoperative time spent according to the assigned MAP targets (**Supplement Table 2**, available at Annals.org). The pre- and postoperative adherence was calculated separately for each day of the intervention (**Supplement Table 3**, available at Annals.org). Because the intent was that patients assigned to the hypertension-avoidance strategy received all their long-term antihypertensive medications, in this group the percent adherence each day was defined as the proportion of their daily long-term medications the patient received on that day. For the hypotension-avoidance strategy group, we developed a percent adherence definition on the basis of the study algorithm (**Supplement Methods 2**). The patient percent adherence increased for each medication that the patient was supposed to take and the patient received, and for each medication that the patient was not supposed to take and the patient did not receive. In contrast, the patient percent adherence decreased for each medication that the patient was supposed to take and the patient did not receive, and for each medication that that the patient was not supposed to take and the patient did receive.

Statistical analyses were done using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The funders had no role in the study design, conduct, analyses, or manuscript preparation.

RESULTS

Patient Characteristics

In the blood pressure management trial ($n = 7490$), 3742 patients were randomly assigned to the hypotension-avoidance strategy and 3748 to the hypertension-avoidance strategy (**Figure 1**). The 30-day follow-up was complete for 99.9% of participants. The baseline characteristics (**Table 1**) and the type of surgery and anesthesia (**Supplement Table 1**, available at Annals.org) were similar between groups. Participants' mean age was 69.8 years; 44.3% were women. Medications taken in the long term included ACEIs or ARBs (71.7%) and β-blockers (43.6%).

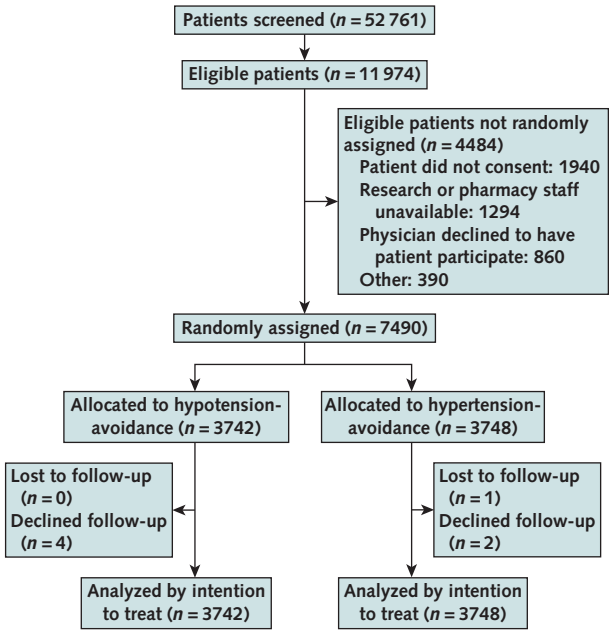
Adherence

Supplement Table 2 provides detailed information on adherence to the assigned intraoperative MAP targets. The hypotension-avoidance group spent more intraoperative minutes with a MAP of 80 mm Hg or greater than the hypertension-avoidance group (absolute difference, 31 minutes). The hypertension-avoidance group spent more intraoperative minutes with a MAP of 60 to 79 mm Hg than the hypotension-avoidance group (absolute difference, 31 minutes).

The daily mean adherence to patients' long-term antihypertensive medications according to allocated strategies ranged between 68.3% and 74.6% in the hypotension-avoidance group and between 56.7% and 70.4% in the hypertension-avoidance group (**Supplement Table 3**).

Supplement Table 4 (available at Annals.org) describes the frequency of administration of antihypertensive medications on different intervention days in the 2 study groups. The number of patients who received an ACEI or ARB on the day of surgery was 199 (5.3%) in the hypotension-avoidance group versus 1432 (38.3%) in the hypertension-avoidance group; on day 1 after surgery,

Figure 1. Patient flow diagram.



237 (6.4%) versus 1746 (47.3%); and on day 2 after surgery, 227 (7.4%) versus 1526 (50.0%). Fewer patients received 1 or more antihypertensive medications in the hypotension-avoidance group than in the hypertension-avoidance group on the day of surgery (absolute difference, 33.7 percentage points), on day 1 after surgery (40.3 percentage points), and on day 2 after surgery (41.4 percentage points). At discrete times after randomization, patients in the hypotension-avoidance strategy group had on average higher SBPs (1.1 to 1.7 mm Hg) (**Supplement Table 5**, available at Annals.org) and heart rates (1.2 to 1.4 beats/min) (**Supplement Table 6**, available at Annals.org) than patients in the hypertension-avoidance strategy group.

Study Outcomes

The primary outcome occurred in 520 of 3742 patients (13.9%) in the hypotension-avoidance group and 524 of 3748 patients (14.0%) in the hypertension-avoidance group, with an HR in the hypotension-avoidance strategy group of 0.99 (95% CI, 0.88 to 1.12; $P = 0.92$) (**Table 2** and **Supplement Figure 1**, available at Annals.org) and an absolute risk difference of 0.08 percentage points (CI, −1.65 to 1.48 percentage points). There was no difference between the 2 groups on any secondary or tertiary outcome (**Table 2**).

Prespecified Subgroup Analyses

The effect of the hypotension-avoidance strategy compared with the hypertension-avoidance strategy was consistent whether patients were receiving long-term therapy with ACEIs or ARBs or not, whether they were receiving 1 or more long-term antihypertensive medications, and for different preoperative SBP or *N*-terminal pro–B-type natriuretic peptide values (**Supplement Figure 2**, available at Annals.org).

The results of the primary outcome analysis were not modified by the status of randomization to the tranexamic acid or placebo group.

Post Hoc Analyses

Post hoc subgroup analyses showed that the treatment effect on the primary outcome was similar whether patients were receiving long-term β-blocker therapy or not, and for the type of noncardiac surgery (**Supplement Figure 2**). There was no dose–response relationship between the effect of the hypotension-avoidance versus the hypertension-avoidance strategies on the primary outcome and the adherence to the assigned strategies (that is, there was no trend of a treatment effect with increasing adherence, whether adherence was computed at the center [**Figure 2**] or at the patient level) (**Supplement Table 7**, available at Annals.org). Similarly, the effect of the hypotension-avoidance strategy compared with the hypertension-avoidance strategy on SBP and heart rate was consistent across centers based on their adherence to the intervention (**Supplement Tables 8** and **9**, available at Annals.org).

Through review of medical records, we retrospectively collected events of clinically significant hypotension and bradycardia occurring between randomization and day 4 after surgery or discharge, whichever came first. We obtained data for 7140 (95.3%) study participants. Overall, fewer patients in the hypotension-avoidance group than in the hypertension-avoidance group had clinically significant hypotension (807 [22.6%] vs. 1016 [28.4%] patients; odds ratio, 0.74 [CI, 0.66 to 0.82]) (**Table 3**). Most of these events (80%) occurred during surgery, and the study groups differed only for the incidence of clinically significant hypotension intraoperatively, and not preoperatively or postoperatively (**Table 3**). **Supplement Table 10** (available at Annals.org) reports interventions used during episodes of intraoperative clinically significant hypotension. Groups did not differ for the incidence of clinically significant bradycardia, at any time (**Supplement Table 11**, available at Annals.org).

We conducted additional subgroup analyses to explore whether the effects of the interventions on the primary outcome (**Supplement Table 12**, available at Annals.org) and on clinically significant hypotension (**Supplement Table 13**, available at Annals.org) differed in participants receiving long-term ACEI or ARB therapy who were or were not adherent to the administration of ACEIs or ARBs according to the assigned strategy; the results did not differ from the main analyses. We found no difference in vascular outcomes when only patients who were adherent to withholding ACEIs or ARBs (hypotension-avoidance) and to continuing ACEIs or ARBs (hypertension-avoidance) were compared, whether adherence was assessed only on the day of surgery or on every day of the intervention.

DISCUSSION

In patients having noncardiac surgery who were receiving long-term antihypertensive therapy, a perioperative

Table 1. Baseline Characteristics

Characteristic	Hypotension-Avoidance Strategy (*n* = 3742)	Hypertension-Avoidance Strategy (*n* = 3748)
Mean age (SD), *y*	69.8 (9.3)	69.8 (9.3)
Sex, *n* (%)		
Male	2075 (56)	2096 (56)
Female	1667 (44)	1652 (44)
Eligibility criteria met, *n* (%)*		
Preoperative *N*-terminal pro–B-type natriuretic peptide ≥200 ng/L	439 (12)	441 (12)
History of coronary artery disease	1116 (31)	1149 (31)
History of peripheral artery disease	570 (15)	562 (15)
History of stroke	309 (8)	311 (8)
Undergoing major vascular surgery	396 (11)	425 (11)
Risk criteria†		
Undergoing major surgery‡	3000 (80)	2990 (80)
History of congestive heart failure	530 (14)	542 (14)
History of transient ischemic attack	202 (5)	205 (5)
Diabetes requiring medication	1470 (39)	1392 (37)
Age ≥70 y	2106 (56)	2077 (55)
History of hypertension	3656 (98)	3663 (98)
Preoperative serum creatinine >175 μmol/L (>2.0 mg/dL)	45 (1)	49 (1)
History of smoking within 2 y before surgery	820 (22)	825 (22)
Undergoing emergent/urgent surgery	403 (11)	406 (11)
Other medical history, *n* (%)		
History of atrial fibrillation	382 (10)	353 (9)
Active cancer	1035 (28)	1064 (28)
Preoperative creatinine		
μmol/L	87.3 (28.7)	87.6 (30.9)
mg/dL	0.99 (0.32)	0.99 (0.35)
Number of long-term antihypertensive medications		
Mean (SD)	2.0 (1.0)	2.0 (1.0)
Patients on 1 medication, *n* (%)	1326 (36)	1388 (37)
Patients on 2 medications, *n* (%)	1366 (37)	1337 (36)
Patients on ≥3 medications, *n* (%)	1038 (28)	1011 (27)
Type of long-term antihypertensive medications, *n* (%)		
ACEI or ARB	2684 (72)	2684 (72)
β-Blocker	1668 (45)	1601 (43)
Dihydropyridine calcium-channel blocker	1342 (36)	1271 (34)
Thiazide or thiazide-like diuretic	820 (22)	851 (23)
Rate-controlling calcium-channel blocker	127 (3)	147 (4)
Loop diuretic	287 (8)	277 (7)
Aldosterone antagonist	56 (1)	69 (2)
Other potassium-sparing diuretic	110 (3)	101 (3)
α-Blocker	260 (7)	263 (7)
Hydralazine	22 (1)	25 (1)
Long-acting nitrate	62 (2)	76 (2)
Other vasodilator (e.g., minoxidil)	18 (<1)	20 (<1)
α2-adrenergic agonist	39 (1)	41 (1)
Direct renin inhibitor	13 (<1)	11 (<1)
Preoperative systolic blood pressure, *mm Hg*§	139.7 (20.0)	140.0 (20.0)
Preoperative diastolic blood pressure, *mm Hg*§	77.6 (11.1)	77.4 (11.3)
Preoperative heart rate, *beats/min*§	74.5 (12.7)	74.3 (12.7)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.
* Patients were eligible for enrollment in the study if they met ≥1 of the eligibility criteria.
† Meeting this eligibility criterion involved meeting at least 3 of the 9 risk criteria listed here.
‡ Defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.
§ First measured on the morning of surgery, before induction and before the administration of any antihypertensive medication.

Table 2. Effects of the Hypotension-Avoidance Strategy Versus the Hypertension-Avoidance Strategy on 30-Day Outcomes

Outcomes	Hypotension-Avoidance Strategy (*n* = 3742)	Hypertension-Avoidance Strategy (*n* = 3748)	Hazard Ratio (95% CI)	*P* Value
Primary composite outcome: vascular death and nonfatal MINS, stroke, and cardiac arrest, *n* (%)	520 (13.9)	524 (14.0)	0.99 (0.88 to 1.12)	0.92
Secondary outcomes, *n* (%)				
MINS	474 (12.7)	481 (12.8)	0.99 (0.87 to 1.12)	
MINS not fulfilling the universal definition of myocardial infarction	424 (11.3)	439 (11.7)	0.97 (0.85 to 1.10)	
Myocardial infarction	54 (1.4)	46 (1.2)	1.18 (0.80 to 1.75)	
Stroke	17 (0.5)	17 (0.5)	1.00 (0.51 to 1.96)	
Vascular death	25 (0.7)	24 (0.6)	1.04 (0.60 to 1.83)	
All-cause death	50 (1.3)	43 (1.1)	1.17 (0.78 to 1.75)	
Tertiary outcomes, *n* (%)				
Hemorrhagic stroke	0 (0.0)	1 (<0.1)	–	
Nonhemorrhagic stroke	17 (0.5)	16 (0.4)	1.07 (0.54 to 2.11)	
Acute congestive heart failure	21 (0.6)	18 (0.5)	1.17 (0.62 to 2.19)	
New clinically important atrial fibrillation	62 (1.7)	44 (1.2)	1.42 (0.96 to 2.08)	
Sepsis	47 (1.3)	57 (1.5)	0.88 (0.60 to 1.29)	
Surgery cancelled or postponed because of blood pressure concerns	6 (0.2)	6 (0.2)	1.00 (0.32 to 3.11)	
Other tertiary outcomes*				
Length of hospital stay, *d*	4.0 (2.1 to 7.1)	4.0 (2.1 to 7.0)	0.05 (−0.05 to 0.14)	
Days alive and at home	25.0 (21.0 to 28.0)	25.0 (21.0 to 28.0)	>−0.01 (−0.29 to 0.29)	

MINS = myocardial injury after noncardiac surgery.
* For these outcomes, the median (IQR) is reported for each group; the effect size is shown as median difference between groups (95% CI).

hypotension-avoidance strategy did not differ from a hypertension-avoidance strategy regarding the effects on a composite of vascular death and nonfatal MINS, stroke, and cardiac arrest. Results also proved similar between the 2 strategies for other outcomes, including death, myocardial infarction, new atrial fibrillation, acute congestive heart failure, and sepsis.

Three RCTs evaluated alternative strategies of intraoperative blood pressure management in high-risk patients undergoing noncardiac surgery. Wanner and colleagues (22) randomly assigned 458 patients to a MAP target of 60 mm Hg or greater or 75 mm Hg or greater. Futier and colleagues (20) randomly assigned 298 patients to an individualized management strategy aiming at SBP within 10% of the patient's baseline, or to a standard management strategy (targeting SBP ≥80 mm Hg or ≥40% of the baseline). Wu and colleagues (21) randomly assigned 678 patients to a MAP target of 65 to 79, 80 to 95, or 96 to 110 mm Hg. These trials reported conflicting results (20–22). None of these trials showed differences in major vascular complications, but they were limited by inadequate sample size to show plausible effects (20–22).

A meta-analysis of 3 small RCTs (total *n* = 188) (14–16) comparing preoperative discontinuation versus continuation of ACEI or ARB therapy in patients undergoing noncardiac surgery found that preoperative continuation of ACEIs or ARBs was associated with an increased risk for intraoperative hypotension (pooled relative risk, 2.53 [CI, 1.08 to 5.93]) (27). A subsequent small RCT (*n* = 275) found similar results but also that withholding ACEIs results in more postoperative hypertension (SBP >180 mm Hg) (28).

Adequately powered to show important effects on major vascular outcomes, POISE-3 did not show any benefit of the alternative strategies: intraoperative MAP target of 80 mm Hg or greater, discontinuing ACEI or ARB therapy, and administering antihypertensive medications on the basis of patients' SBP, versus intraoperative MAP target of 60 mm Hg or greater and continuing all antihypertensive medications.

There are at least 2 potential explanations for the lack of difference in the primary outcome in POISE-3. One is that the suboptimal adherence to the planned strategies decreased the effects that optimal adherence may have made evident. A second is that the interventions differed insufficiently in their effect on hemodynamics—and would have differed insufficiently even with optimal adherence—to lead to a difference in effects on vascular outcomes.

With respect to adherence, intraoperative protocol MAP adherence was high: The 2 treatment groups showed significant differences in the intraoperative time spent with MAPs between 60 and 79 mm Hg, or 80 mm Hg or greater. With respect to perioperative adherence to the antihypertensive medications, although overall suboptimal, there were substantial differences in the use of ACEIs or ARBs on the day of surgery (absolute difference, 33 percentage points) and day 1 (absolute difference, 41 percentage points) and day 2 after surgery (absolute difference, 43 percentage points). There were also substantial differences in the proportion of patients receiving 2 or more antihypertensive medications on the day of surgery (absolute difference, 26 percentage points) and day 1 (absolute difference, 32 percentage points) and day 2 after

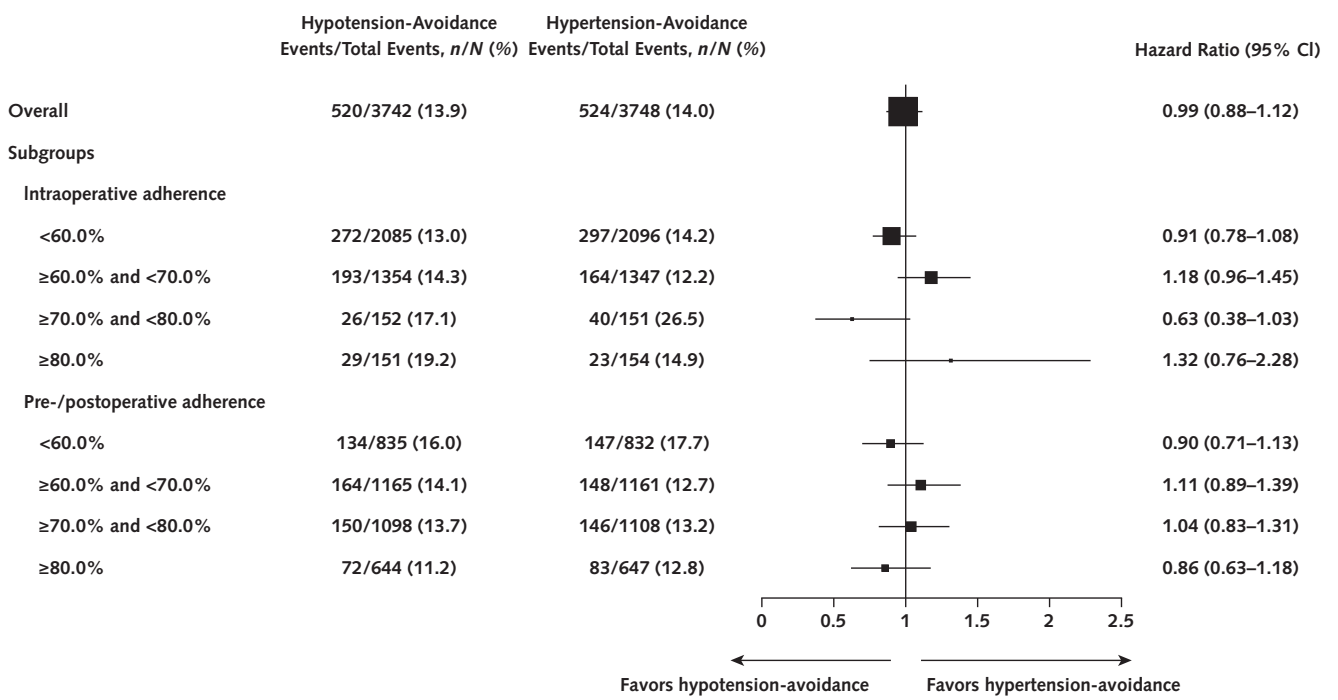
surgery (absolute difference, 33 percentage points). Despite these differences, outside the operating room, the between-group differences in SBP (1.1 to 1.7 mm Hg) and heart rate (1.2 to 1.4 beats/min) were on average small and clinically irrelevant. Moreover, our analyses of the effects of the strategies on the primary outcome, SBP, and heart rate by adherence did not show any "dose-effect." There was no clinically meaningful difference between the 2 groups in centers or patients with greater adherence.

There was a 6-percentage point absolute difference between the 2 groups in the incidence of intraoperative clinically significant hypotension; however, there was no difference in clinically significant hypotension after surgery, which may explain why our intervention did not affect major vascular complications. Through multivariable analyses, including both intraoperative and postoperative clinically significant hypotension, the VISION (Vascular Events in Noncardiac Surgery Cohort Evaluation) study showed that only postoperative hypotension was associated with an increased risk for major vascular events (1). The biological plausibility of this finding is supported by data showing that clinically significant hypotension lasts a median of 15 minutes intraoperatively and a median of 180 minutes postoperatively (2), and that the duration of hypotension shows a dose-response in its relationship with major vascular complications (29).

As a whole, these analyses suggest that the lack of effect in POISE-3 was more likely due to the failure of the interventions to result in substantial and clinically important changes in hemodynamics, as opposed to suboptimal adherence being responsible for failure of the intervention to show the expected effect on clinical outcomes. In contrast, a previous large international trial (POISE-1) randomly assigned patients undergoing noncardiac surgery who were previously not receiving a β-blocker to receive extended-release metoprolol succinate or placebo treatment started 2 to 4 hours before surgery and continued for 30 days (4). Patients randomly assigned to metoprolol compared with placebo had a substantially lower heart rate (mean difference, 7.0 beats/min) and a lower risk for myocardial infarction (HR, 0.73 [CI, 0.60 to 0.89]; $P = 0.002$); they also had a statistically significant higher incidence of postoperative clinically significant hypotension (15.0% vs. 9.7%; odds ratio, 1.55 [CI, 1.55 to 1.74]; $P < 0.001$), stroke (HR, 2.17 [CI, 1.26 to 3.74]; $P = 0.005$), and death (HR, 1.33 [CI, 1.03 to 1.74]; $P = 0.032$) (4). These results suggest that perioperative interventions that substantially alter hemodynamic measures can affect patient-important outcomes.

Strengths of POISE-3 include participation of 110 hospitals in 22 countries and greater than 99% follow-up rate. A limitation is that patients, health care providers,

Figure 2. Analyses of the primary outcome on the basis of the center-average percent adherence to the study blood pressure management strategies.



Center-average percent adherence intraoperatively (intraoperative adherence) was calculated as the average percent adherence to the intraoperative mean arterial pressure target in either strategy, across all participants randomly assigned in that center. Center-average adherence preoperatively and postoperatively (pre-/postoperative adherence) was calculated as the average of the daily mean percent adherence to the preoperative and postoperative phases of the assigned strategy of administration of antihypertensive medications, across all participants randomly assigned in that center. Primary outcome was a composite of vascular death and nonfatal myocardial injury after noncardiac surgery, stroke, and cardiac arrest.

Table 3. Effects of the Hypotension-Avoidance Strategy Versus the Hypertension-Avoidance Strategy on Clinically Significant Hypotension

Outcomes	Hypotension-Avoidance Strategy (*n* = 3562)	Hypertension-Avoidance Strategy (*n* = 3578)	Odds Ratio (95% CI)
Clinically significant hypotension at any time between randomization and day 4 after surgery or discharge, *n* (%)*	807 (22.6)	1016 (28.4)	0.74 (0.66–0.82)
Clinically significant hypotension at different times after randomization, *n* (%)*			
Before surgery	26 (0.7)	31 (0.9)	0.84 (0.50–1.42)
During surgery	682 (19.1)	892 (24.9)	0.71 (0.64–0.80)
After surgery	170 (4.8)	167 (4.7)	1.02 (0.82–1.27)

* Clinically significant hypotension was defined as a systolic blood pressure <90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, inotropic agent, or vasopressor agent.

and study personnel were aware of the treatment allocation. If investigators were biased toward one group, this did not result in detection of a treatment effect. We collected data on clinically significant hemodynamic events only retrospectively by reviewing medical records, which may have limited our ability to capture all of the events. Moreover, we did not collect data on the duration of these events. Despite these limitations, we did observe a difference in intraoperative but not postoperative clinically significant hypotension. Patients were not randomly assigned to the various approaches to achieve intraoperative MAP targets; therefore, we cannot reliably inform the relative merits of the various approaches (for example, fluids, vasopressors, and inotropes).

In conclusion, in patients having noncardiac surgery and receiving long-term antihypertensive therapy, POISE-3 showed no difference in effects on major vascular complications between 2 alternative blood pressure management strategies. POISE-3 addressed common questions that confront perioperative care physicians and showed that intraoperative MAPs of 80 mm Hg or greater versus 60 mm Hg or greater and perioperative withholding or continuing of long-term antihypertensive medications did not substantially affect perioperative hemodynamics or vascular complications. Further research is needed to identify and evaluate perioperative interventions that can modify hemodynamics to an extent and in the direction that will lead to a favorable effect on major clinical outcomes.

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