A sub-study of the POISE-3 randomized trial examined effects of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on the risk of acute kidney injury

see commentary on page 15

OPEN

POISE-3 Trial Investigators and Study Groups[1]

In this pre-specified sub-study of the POISE-3 trial, we examined the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on the risk of postoperative acute kidney injury (AKI). Altogether, 7307 patients were included from 110 hospitals in 22 countries. Patients were 45 years and older, had or were at risk of atherosclerotic disease, took at least one antihypertensive medication, and were scheduled for noncardiac surgery. Hypotension-avoidance strategy: (i) target intraoperative mean arterial pressure (MAP) 80 mm Hg or over, (ii) on day of surgery and for two days after, hold renin-angiotensin-aldosterone system inhibitors and use other antihypertensives in stepwise fashion if systolic blood pressure (SBP) 130 mm Hg or more. Hypertension-avoidance strategy: (i) target intraoperative MAP 60 mm Hg or more, (ii) continue all antihypertensives before and after surgery. Primary outcome: postoperative AKI, an increase in serum creatinine concentration of either 26.5 μmol/L or more (0.3 mg/dL or more) within 48 hours of randomization or 50% or more within seven days of randomization. The hypotension-avoidance group (3654 patients) used fewer antihypertensive medications than the hypertension-avoidance group (3653 patients); specifically, 6% vs. 38% used an ACEI or ARB on the day of surgery, and 6% vs. 47% and 7% vs. 50% one and two days after surgery, respectively. Patients also spent about half as much intraoperative time with a MAP under 80 mm Hg (27 vs. 60 minutes, respectively), but had little difference in average BP before or after surgery. There was no significant difference in AKI risk (15.1% vs. 14.4%). Results were consistent with other definitions of AKI and in patients with preexisting chronic kidney disease. Thus, a hypotension-avoidance strategy targeting a MAP greater than 80 mm Hg in the operating room and discontinued blood pressure medication during the perioperative period did not confer a lower risk of AKI compared to a hypertension avoidance strategy.

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Editor's Note

The online publication of this article coincided with the Late Breaking Clinical Trials session at ASN Kidney Week 2024. This article provides cutting-edge insight into a recent clinical trial and the implications for kidney care.

Lay Summary

During surgery, a patient's blood pressure can sometimes become too low. This can starve the body's organs of blood and oxygen and cause organ injury. Perioperative Ischemic Evaluation-3 (POISE-3), an international randomized clinical trial, tested a new strategy to keep blood pressure from falling too low during the surgical period. We conducted a substudy of POISE-3 to examine whether this strategy reduced the risk of kidney injury. This is an important question because each year, 20 million patients who have surgery experience acute kidney injury and 20,000 develop kidney failure. We compared the risk of acute kidney injury in 7,307 patients randomized to receive the new strategy to prevent low blood pressure versus a usual care strategy. We found no difference between the groups. Preventing acute kidney injury during the surgical period continues to be a challenge.

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Perioperative blood pressure is strongly associated with cardiovascular complications after noncardiac surgery.[1–7] It remains uncertain whether to continue or withhold chronic antihypertensive medications during the perioperative period and what should be the ideal mean arterial pressure (MAP) target during surgery.[1,4,8–12]

The Perioperative Ischemic Evaluation-3 (POISE-3) trial (NCT03505723) was an international randomized clinical trial that compared the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on cardiovascular outcomes in mid- to older-age adults who had noncardiac surgery and routinely took antihypertensive medication.[13,14] The risk of the primary outcome (a composite of vascular death, nonfatal myocardial injury, stroke, or cardiac arrest at 30 days after surgery) did not differ between study groups.

A KIDNEY SUBSTUDY OF POISE-3

We conducted a prespecified kidney substudy of POISE-3 to examine the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on the risk of postoperative acute kidney injury (AKI).[15] AKI occurs in over 10% of noncardiac surgeries and is associated with longer hospital stays, increased health care costs, kidney failure, and death.[16,17] We hypothesized the perioperative hypotension-avoidance strategy would reduce the risk of AKI compared to the hypertension-avoidance strategy, because perioperative hypotension may cause ischemia-reperfusion injury,[18] and the risk for AKI is reported to increase progressively with the severity and duration of perioperative hypotension.[6,19–21] In this substudy, we estimated the treatment effect and examined it separately in patients with and without preexisting chronic kidney disease—a prominent risk factor for AKI.[22]

METHODS

Overview of the POISE-3 main trial

The POISE-3 study design and intervention are described elsewhere.[13,14] POISE-3 was an international randomized clinical trial conducted in 110 hospitals in 22 countries from June 27, 2018, to July 15, 2021. POISE-3 was designed as a partial 2 × 2 factorial trial. In the first factorial, 9535 patients aged ≥45 years having noncardiac surgery with an overnight hospital stay who had or were at risk for atherosclerotic disease were randomized to receive intravenous tranexamic acid or placebo during surgery. In the second factorial, 7490 patients who routinely took at least 1 antihypertensive medication were also randomized to a perioperative hypotension-avoidance strategy or a hypertension-avoidance strategy. All participating centers obtained ethics approval to conduct the trial, and all participants provided written informed consent before enrollment.

The kidney substudy was performed in the second factorial.

Patient selection and recruitment

Supplementary Table S1 lists the complete eligibility criteria for POISE-3. Because tranexamic acid is mainly eliminated through the kidney and could be unsafe in patients with very low kidney function, patients with a creatinine clearance <30 ml/min (Cockcroft-Gault formula) or receiving chronic dialysis were excluded from the trial.

Randomized group assignment

The Population Health Research Institute coordinated the trial and administered the randomization system. Randomization occurred before surgery after a patient was deemed eligible and provided written informed consent. Patients were randomized using a concealed, centralized web randomization system, stratified according to center. Patients, health care providers, and study personnel were aware of each patient's blood pressure management strategy after it was randomly allocated.

Intervention

Patients in the second factorial were instructed not to take their antihypertensive medication(s) the night before and/or on the morning of surgery and to bring them to the hospital. Patients who did not have their antihypertensives with them on the day of surgery or who already took their antihypertensives on the day of surgery were still eligible for randomization. They continued receiving the trial's intraoperative and postoperative components as described herein.

Hypotension-avoidance strategy (intervention). Target intraoperative MAP ≥80 mm Hg; the anesthesiologist was asked to maintain a MAP ≥80 mm Hg from anesthetic induction until the end of surgery. The methods to achieve this target (e.g., fluids, vasopressors, inotropes) were left to the discretion of the anesthesiologist.

On the day of surgery and for 2 days after, aim to withhold renin-angiotensin-aldosterone system inhibitors (RASIs: angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or renin inhibitor), and during this period use other long-term antihypertensives in a stepwise fashion if the systolic blood pressure is ≥130 mm Hg (see Supplementary Table S2 for the algorithm).

Hypertension-avoidance strategy (control). Target intraoperative MAP ≥60 mm Hg; intraoperatively, the anesthesiologist was asked to maintain a MAP ≥60 mm Hg from anesthetic induction until the end of surgery. This strategy mirrors what typically occurs in routine care as documented in the literature.[1,4,23–25]

Continue all usual antihypertensive medications on the day of surgery and for 2 days after surgery.

In both groups, the attending physician determined blood pressure management from postoperative day 3 onward.

Methods used in the POISE-3 kidney substudy

This substudy received separate grant funding from the Kidney Foundation of Canada in 2019. The protocol and analysis plan were published before POISE-3 completion,[15] and the analysis was performed after the publication of POISE-3 main results.[14] Minor changes to the substudy protocol were made during analysis and are documented in Supplementary Table S3. Study reporting follows recommended guidelines (Supplementary Table S4).[26]

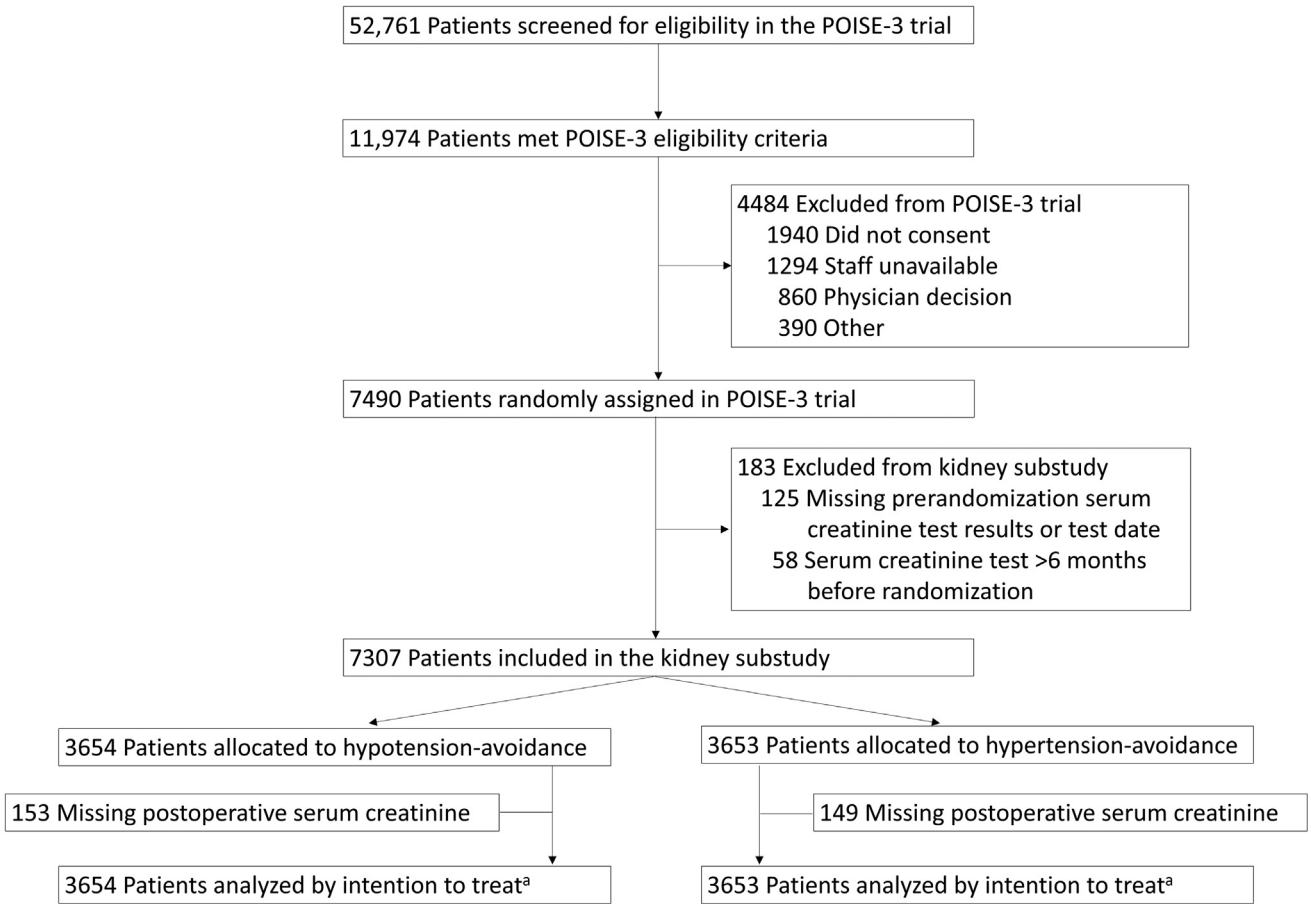


Figure 1 | Patient flow diagram. [a]Missing data on postoperative serum creatinine was imputed using fully conditional specification multiple imputation. For an additional 109 patients (1.5%) whose postrandomization serum creatinine was not obtained until 8 or more days after randomization (mostly due to delayed surgery), acute kidney injury was coded as absent, and a sensitivity analysis was conducted using the date of surgery rather than the date of randomization as the start of follow-up (Supplementary Table S11). POISE-3, Perioperative Ischemic Evaluation-3.

Substudy patient selection. The substudy included all patients enrolled in the second factorial of POISE-3 who had an available prerandomization serum creatinine (97% of the main study population; Figure 1).

Serum creatinine measurement. *Baseline prerandomization/preoperative serum creatinine.* The single most recent test result for serum creatinine before randomization within the last 6 months before surgery was the baseline value. Patients were followed for outcomes from the time of randomization.

Postoperative serum creatinine. All centers received substudy funds to measure and record a daily serum creatinine value on postoperative days 1, 2, and 3 (or until hospital discharge if it occurred before day 3). This schedule was chosen to minimize biased ascertainment of AKI (i.e., if the intervention altered the incidence of another event, such as myocardial infarction, this could influence the likelihood of serum creatinine measurement). Centers were also asked to record all other serum creatinine measurements performed during routine care (and their dates) during the hospital stay. Information on urine output was not collected because it is challenging to measure accurately outside the intensive care unit. Any receipt of new dialysis for kidney failure was recorded at hospital discharge and 30 days after randomization.

Substudy outcomes

The primary outcome was postoperative AKI. AKI was defined using Kidney Disease: Improving Global Outcomes[27] (KDIGO) criteria as an increase in the postrandomization serum creatinine concentration (from the prerandomization value) of ≥26.5 μmol/l (≥0.3 mg/dl) within 48 hours of randomization or an increase of ≥50% within 7 days of randomization.

The following 7 alternative definitions of AKI were examined as secondary outcomes to assess whether the primary results were robust:

(i) A composite outcome of AKI (primary definition) or death within 48 hours of randomization (to account for the potential impact of early deaths on outcome ascertainment).
(ii) AKI (primary definition) for at least 2 days within 7 days of randomization.
(iii) Stage 2 AKI (or higher), defined as a postrandomization increase in serum creatinine of ≥100% from the prerandomization value within 7 days of randomization, or

an increase to an absolute value of 354 μmol/l or more (≥4.0 mg/dl) within 7 days of randomization (when the primary outcome definition of AKI is met), or receipt of dialysis within 30 days of randomization.

(iv) Stage 3 AKI, defined as a postrandomization increase in serum creatinine of ≥200% from the prerandomization value within 7 days of randomization, or an increase to an absolute value of 354 μmol/l or more (≥4.0 mg/dl) within 7 days of randomization (when the primary outcome definition of AKI is met), or receipt of dialysis within 30 days of randomization.

(v) Receipt of dialysis within 30 days of randomization.

(vi) Percentage change in serum creatinine in the first 7 days of randomization, defined as (peak postrandomization serum creatinine – prerandomization serum creatinine)/ prerandomization serum creatinine × 100.

(vii) Absolute change in serum creatinine in the first 7 days of randomization, defined as peak postrandomization serum creatinine – prerandomization serum creatinine.

Sample size and statistical power

POISE-3 planned to enroll 10,000 patients in the tranexamic acid factorial.[3] We estimated at least 70% would be eligible for and consent to participate in the blood pressure management factorial and expected 98% of these 7,000 patients to be eligible for inclusion in the AKI substudy. A sample of 6,800 provides >80% power to detect a 20% relative risk reduction in postoperative AKI with hypotension-avoidance (2-sided $\alpha = 0.05$), assuming an AKI incidence of 10% in the hypertension-avoidance group.[15]

Statistical analysis

All analyses adhered to the intention-to-treat principle and were done using SAS version 9.4 (SAS Institute Inc). Continuous variables are summarized as mean (SD) or median (interquartile range [IQR]) as appropriate.

Analysis of the primary and secondary outcomes. The risk of the primary outcome and the 5 binary secondary outcomes were examined using risk ratios (RRs) and risk differences (RDs), comparing the hypotension-avoidance group to the hypertension-avoidance group. RRs and 95% confidence intervals (CIs) were obtained from a modified Poisson regression model, and RDs and 95% CIs from a binomial regression model with an identity link function.[28] The 2 continuous secondary outcomes were analyzed using linear regression models. All models accounted for potential within-center correlation using cluster-robust standard errors.

Treatment of missing data. Missing data on postoperative serum creatinine up until 7 days after randomization, which occurred in 301 surviving patients (4.1%), was imputed using fully conditional specification multiple imputation with 100 imputed datasets; parameters and standard errors were estimated using standard methods allowing for extra imputation variability.[29,30] Prerandomization patient characteristics, treatment group, center of randomization, and outcomes measured within 30 days of randomization, including death and receipt of dialysis, were included in the imputation model. In the primary analysis, 1 patient who died within 48 hours after randomization without contributing a serum creatinine measurement was included in the analysis and assumed not to have AKI. AKI was coded as absent for an additional 109 patients (1.5%) whose postrandomization serum creatinine was not obtained until 8 or more days after randomization (primarily due to delayed surgery). A sensitivity analysis was conducted using the date of surgery rather than the date of randomization as the start of follow-up.

Prespecified subgroup analyses. The risk of postoperative AKI was examined in 4 subgroup analyses as follows (hypotheses for these analyses are described in the published protocol[15] and in Supplementary Table S5): (i) Preexisting chronic kidney disease (defined as an estimated glomerular filtration rate [eGFR] <60 vs. ≥60 ml/min per 1.73 m^2 at baseline; calculated using the 2021 Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] creatinine equation[31]), (ii) prerandomization eGFR, where eGFR was modeled as a continuous variable with restricted cubic splines to allow for nonlinearity, (iii) random allocation to tranexamic acid versus placebo, and (iv) prerandomization use of an ACEI or ARB. For binary subgroups, multiplicative interaction was assessed by including an interaction term (treatment group × subgroup) in a modified Poisson regression, and additive interaction was assessed by including an interaction term in a regression model with a binary distribution and an identity link. For the analyses of prerandomization eGFR as a continuous variable, we used a likelihood ratio test in a logistic regression model to test for multiplicative interaction between eGFR and the intervention. We did not adjust for effect of the center or prerandomization variables, and only participants with complete data were included.

Prespecified additional analyses. We conducted the following additional analyses and looked for concordance with the results of the primary outcome analysis. Results are presented as point estimates with 95% CIs (without *P* values) and should be interpreted as exploratory because multiple comparisons can potentially increase type I error.

- A complete-case analysis restricted to 7006 patients with at least 1 postoperative serum creatinine measurement (95.9% of patients in the primary analysis).
- An adjusted analysis that included the random allocation of tranexamic acid versus placebo and the following prespecified covariates (measured before randomization) based on their known association with AKI: age (in years, modeled with restricted cubic splines), biological sex, cardiovascular disease (any coronary artery disease, peripheral vascular disease, or stroke), diabetes, prerandomization eGFR (as a continuous variable modeled with restricted cubic splines), a history of smoking within 2 years of surgery, urgent or emergency surgery, and type of surgery (major vascular surgery, major thoracic surgery, or other surgery); missing data on these variables was 0.6%.
- An analysis excluding patients who underwent urgent or emergent surgery (in case some developed AKI before randomization).

- An analysis where the start of follow-up was the date of surgery (rather than the date of randomization), excluding patients who did not undergo surgery (0.6% of patients).

RESULTS

Patient enrolment and characteristics

Figure 1 shows the flow of patients from enrolment, allocation, follow-up, and analysis. The first patient was randomized on June 27, 2018, and 7307 of 7490 patients randomized into POISE-3 (97.6%) were included in this substudy: 3654 randomly allocated to the hypotension-avoidance strategy and 3653 to the hypertension-avoidance strategy. The last patient was randomized on July 15, 2021. Table 1 shows baseline (prerandomization) patient characteristics. The mean age of patients was 70 years, 44% were women, and 38% had diabetes requiring medication. The prerandomization serum creatinine was obtained a median of 5 (IQR: 1, 16) days before surgery; the mean eGFR was 76 (SD: 19) ml/min per 1.73 m^2, and 1552 (21%) had an eGFR <60 ml/min per 1.73 m^2. Seventy-two percent of patients used an ACEI or ARB and 29% a thiazide, thiazide-like, or loop diuretic. The mean blood pressure measured on the morning of surgery, before induction, and before administration of any antihypertensive medications in the hospital was 140/78 mm Hg. There were no significant baseline differences between the 2 groups.

Follow-up blood pressure values and antihypertensive medication use

The hypotension-avoidance group (n = 3654) used fewer antihypertensive medications after randomization than the hypertension-avoidance group (n = 3653) did (Supplementary Table S6, which includes the absolute differences with 95% CIs). At least 1 antihypertensive medication was used by 36% of patients in the hypotension-avoidance group versus 70% in the hypertension-avoidance group on the day of surgery, 39% versus 70% 1 day after surgery, and 42% versus 83% 2 days after surgery. An ACEI or ARB was used by 6% versus 38% of patients on the day of surgery, 6% versus 47% 1 day after surgery, and 7% versus 50% 2 days after surgery. A thiazide, thiazide-like, or loop diuretic was used by 5% versus 15% of patients on the day of surgery, 7% versus 23% 1 day after surgery, and 7% versus 24% 2 days after surgery.

The median operative time was similar in both groups (145 minutes). The hypotension-avoidance group spent less intraoperative time with a MAP <80 mm Hg than the hypertension-avoidance group (median 27 vs. 60 minutes) did (shown in Supplementary Table S7, along with other measures of intraoperative MAP). The median intraoperative time spent with a MAP <60 mm Hg was 0 minutes in both groups (Supplementary Table S7). Also, there was little to no difference in average blood pressure values before surgery and during the 2 days after surgery (Figure 2).

Primary outcome: AKI

There was no significant difference in the risk of postoperative AKI between the hypotension-avoidance group versus the hypertension-avoidance group (15.1% vs. 14.4%; RR: 1.05 [95% CI: 0.93 to 1.19] and RD: 0.7% [95% CI: −0.9% to 2.4%]; Table 2). Results for the secondary outcomes were consistent with the primary analysis (Table 2). Using the peak value in the first 7 days after randomization compared to the prerandomization value, the mean percentage change in serum creatinine in the 2 groups was 15% versus 14% (difference: 0.5% [95% CI: −1.6 to 2.7]). The absolute change was 11.9 versus 11.5 μmol/l (difference: 0.3 μmol/l [95% CI: −1.6 to 2.2]). The 2 groups had a similar number of postoperative serum creatinine measures (median: 3 per patient [IQR: 1, 4] in both groups).

Chronic kidney disease subgroup

The lack of effect was consistent regardless of preexisting chronic kidney disease (Table 3) and across the range of eGFR when analyzed as a continuous variable ($P = 0.92$).

Prespecified additional analyses

Effect estimates were not modified by randomization to the tranexamic acid or placebo group, nor by the prerandomization use of ACEI or ARBs (Table 3). Results were also consistent in all additional analyses (Supplementary Tables S8–S11).

Post hoc analyses

The intervention's effect on AKI did not consistently increase (or decrease) with greater adherence to the assigned strategy across the analyses of adherence computed at the center level (Supplementary Table S12) or the patient level (Supplementary Table S13).

DISCUSSION

In this planned kidney substudy of POISE-3, patients having noncardiac surgery who took at least 1 long-term antihypertensive medication were randomized to receive a perioperative hypotension-avoidance strategy or a hypertension-avoidance strategy. The primary outcome, postoperative AKI, did not significantly differ between the randomized groups. Results were consistent for multiple definitions of AKI and in subgroups of high-risk patients, including those with preexisting chronic kidney disease.

Evidence from cohort studies consistently shows that exposure to perioperative hypotension is a strong risk factor for AKI.[6,19,21,32,33] AKI is associated with MAPs <50 to 55 mm Hg (even for less than a minute), MAPs 65 to 80 mm Hg (on average and/or over time), and with percentage drops in MAP from baseline (e.g., 20% or greater).[6,21,32] In a recent meta-analysis of 5 randomized clinical trials comprising 1485 patients undergoing noncardiac surgery, a strict intraoperative blood pressure management strategy (to achieve a MAP ≥70 mm Hg or a MAP decrease of less than 30% from the baseline) was associated with a reduced risk of postoperative AKI compared with conventional therapy (RR: 0.73 [95% CI: 0.58–0.92]).[34] Only 1 of these trials defined AKI using KDIGO criteria. In that trial, which included 678 older

Table 1 | Baseline characteristics

	Hypotension-avoidance strategy (n = 3654)	Hypertension-avoidance strategy (n = 3653)
Demographics		
Age, mean (SD), yr	69.8 (9.2)	69.7 (9.3)
Age ≥70 yr	2053 (56)	2013 (55)
Biological sex		
Male	2035 (56)	2050 (56)
Female	1619 (44)	1603 (44)
Weight, mean (SD), kg	80.8 (20.2)	80.6 (19.9)
Year of randomization		
2018	215 (6)	215 (6)
2019	1473 (40)	1463 (40)
2020	1303 (36)	1294 (35)
2021	663 (18)	681 (19)
Location		
Europe	1491 (41)	1484 (41)
North America	1126 (31)	1135 (31)
Asia	655 (18)	653 (18)
Australia and New Zealand	299 (8)	303 (8)
South America	74 (2)	69 (2)
Africa	9 (<1)	9 (<1)
Medical history		
Hypertension	3573 (98)	3571 (98)
Diabetes requiring medication	1439 (39)	1349 (37)
Coronary artery disease	1142 (31)	1121 (31)
Active cancer	1020 (28)	1048 (29)
Smoked within 2 yr before surgery	809 (22)	806 (22)
Peripheral artery disease	563 (15)	548 (15)
Congestive heart failure	517 (14)	524 (14)
Atrial fibrillation	367 (10)	338 (9)
Stroke	302 (8)	306 (8)
Transient ischemic attack	198 (5)	199 (5)
Surgical characteristics		
Major surgery[a]	2928 (80)	2916 (80)
Emergent/urgent surgery	361 (10)	365 (10)
Surgery type		
Major general surgery	1106 (30)	1100 (30)
Major urological or gynecological surgery	455 (12)	494 (14)
Major vascular surgery	392 (11)	416 (11)
Major thoracic surgery	89 (2)	78 (2)
Kidney function and blood pressure		
Preoperative serum creatinine, μmol/l		
Mean (SD)	87 (29)	88 (31)
Median (25th, 75th percentiles)	82 (69, 100)	83 (70, 99)
Preoperative serum creatinine >175 μmol/l (>2.0 mg/dl)	48 (1)	52 (1)
Preoperative eGFR, ml/min per 1.73 m^2[b]		
Mean (SD)	76 (19)	76 (19)
Median (25th, 75th percentiles)	78 (62, 92)	78 (63, 92)
eGFR category		
<15	3 (<1)	7 (<1)
15–29	30 (1)	23 (1)
30–44	208 (6)	216 (6)
45–59	536 (15)	529 (14)
60–89	1808 (49)	1799 (49)
≥90	1069 (29)	1079 (30)
Preoperative blood pressure, mm Hg		
Systolic blood pressure, mean (SD)[c]	139.7 (20.0)	139.9 (20.0)
Diastolic blood pressure, mean (SD)[c]	77.6 (11.1)	77.4 (11.3)
Preoperative heart rate, mean (SD), beats/min	74.4 (12.7)	74.3 (12.7)
Antihypertensive medication		
No. long-term antihypertensive medications		
Mean (SD)	2.0 (1.0)	2.0 (1.0)
Patients on 1 medication, n/n (%)	1299/3642 (36)	1345/3641 (37)
Patients on 2 medications, n/n (%)	1326/3642 (36)	1306/3641 (36)
Patients on 3 medications, n/n (%)	1017/3642 (28)	990/3641 (27)
Type of long-term antihypertensive medications		
ACEI or ARB	2620 (72)	2617 (72)
β-blocker	1634 (45)	1560 (43)
Dihydropyridine calcium-channel blocker	1318 (36)	1242 (34)
Thiazide, thiazide-like, or loop diuretic	1047 (29)	1080 (30)
Thiazide or thiazide-like diuretic	801 (22)	834 (23)
Loop diuretic	272 (7)	267 (7)
α-Blocker	253 (7)	256 (7)
Rate-controlling calcium-channel blocker	122 (3)	145 (4)
Other potassium-sparing diuretic	106 (3)	102 (3)
Long-acting nitrate	60 (2)	76 (2)
Aldosterone antagonist	54 (1)	67 (2)
α2-adrenergic agonist	38 (1)	41 (1)
Hydralazine	21 (1)	24 (1)

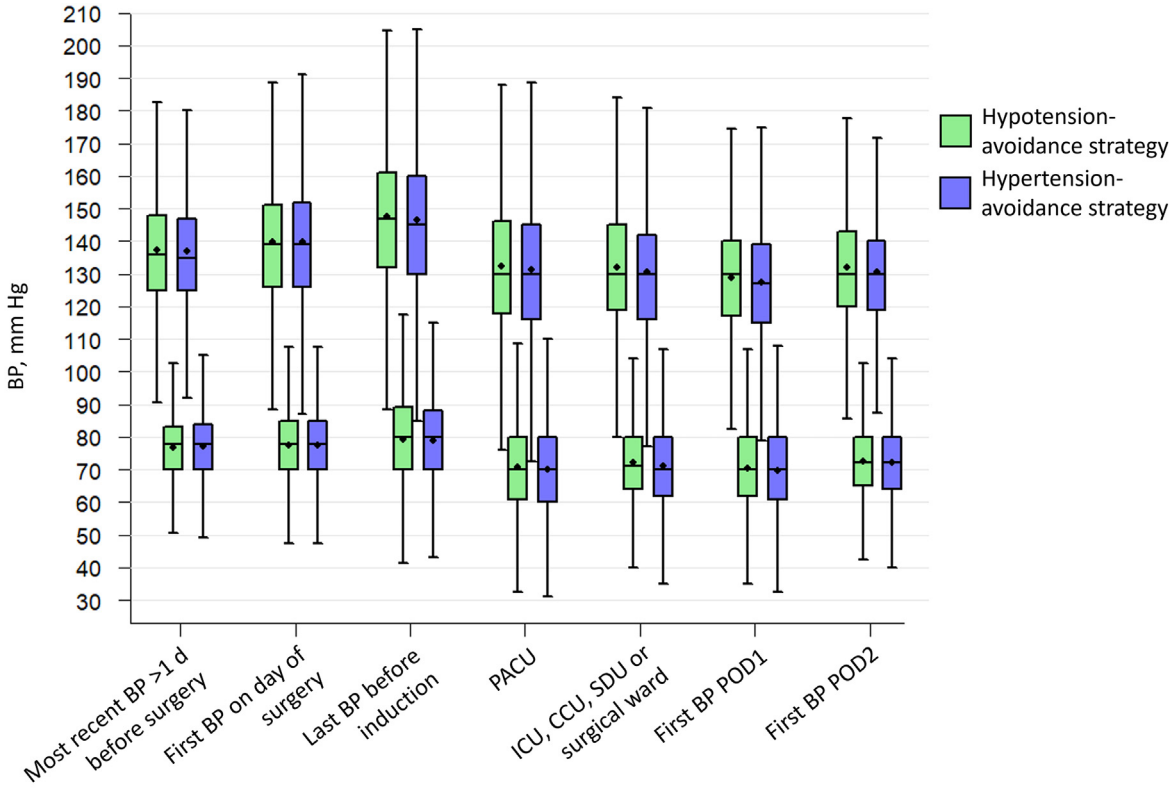
(*Continued*)

Table 1 | (Continued)

Antihypertensive medication		
Other vasodilator (e.g., minoxidil)	17 (<1)	20 (1)
Direct renin inhibitor	13 (<1)	11 (<1)

ACEI angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; eGFR estimated glomerular filtration rate; POISE-3, Perioperative Ischemic Evaluation-3.
[a]Defined as per POISE-3 inclusion criteria (Supplementary Table S1); type of surgery included general (noncardiac), orthopedic, vascular, urological, spinal, gynecological, thoracic, and plastic; more details in Marcucci *et al.*[14]
[b]eGFR was calculated using the 2021 Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation using serum creatinine, age, and sex.[31]
[c]First measured on the morning of surgery, before induction and before administration of any antihypertensive medication.
Results are presented as n (%) unless otherwise specified.

hypertensive patients having gastrointestinal surgery, patients randomized to an intraoperative MAP target of 80 to 95 mm Hg had fewer AKI events than those randomized to a lower or higher target MAP (65–79 and 96–110 mm Hg, respectively); the incidence of AKI in the middle target group was 6.3%, compared with 13.5% and 12.9% in the lower and higher target groups, respectively ($P = 0.03$).[35] Most recently, the Stop-or-Not Randomized Clinical Trial, which included 2222 patients, examined the effect of continuing versus discontinuing RASIs before major noncardiac surgery.[36] The primary outcome was death or major postoperative complications, and other outcomes included hypotension during surgery and AKI (defined using KDIGO criteria). Episodes of intraoperative hypotension occurred in 41% of the patients in the RASI discontinuation group and in 54% of the patients in the RASI continuation group (RR: 1.31 [95% CI: 1.19–1.44]); however, the between-group absolute difference in the duration of hypotension was only 4 minutes between the 2 treatment groups, and there were no differences in other trial outcomes, including AKI. As we previously demonstrated in the VISION study, it is postoperative hypotension that is associated with major vascular complications, and analyses that include postoperative hypotension demonstrate that intraoperative hypotension is not associated with major vascular complications.[1] This finding is supported by the fact that



No. observations							
Hypotension-avoidance	3500	3638	3625	2594	3299	3591	3011
Hypertension-avoidance	3476	3624	3624	2571	3269	3601	2973

Figure 2 | Systolic and diastolic blood pressure at preoperative and postoperative time points. Tukey boxplot circles show the mean blood pressure (BP); boxes show the median, 25th percentile (P25), and 75th percentile (P75) blood pressure; and whiskers show the minimum and maximum values (truncated to the lower and upper adjacent values where applicable [P25 − 1.5 × IQR and P75 + 1.5 × IQR]; outliers not shown). [a]For the category *Most recent BP >1 d before surgery*, 95% of BPs were measured before randomization. CCU, critical care unit; ICU, intensive care unit; IQR, interquartile range; PACU, postanesthesia care unit; POD1, postoperative day 1; POD2, postoperative day 2; SDU, step down unit.

Table 2 | Effect of a hypotension-avoidance versus hypertension-avoidance strategy on the risk of acute kidney injury in patients receiving noncardiac surgery

	Events, n (%)[a]				
	Hypotension-avoidance strategy (n = 3654)	Hypertension-avoidance strategy (n = 3653)	Risk difference, % (95% CI)[b]	Relative risk (95% CI)[c]	*P* value[b]
Primary outcome					
Acute kidney injury[d]	530/3502 (15.1)	505/3504 (14.4)	0.7 (−0.9, 2.4)	1.05 (0.93, 1.19)	0.43
Secondary outcomes					
Acute kidney injury or 48 h death[e]	531/3502 (15.2)	505/3504 (14.4)	0.8 (−0.9, 2.4)	1.05 (0.93, 1.19)	0.42
Acute kidney injury for ≥2 d[f]	178/3502 (5.1)	180/3504 (5.1)	−0.1 (−1.1, 1.0)	0.99 (0.80, 1.22)	0.92
Stage 2 acute kidney injury[g]	90/3502 (2.6)	101/3504 (2.9)	−0.3 (−1.1, 0.4)	0.89 (0.67, 1.18)	0.42
Stage 3 acute kidney injury[h]	33/3502 (0.9)	45/3504 (1.3)	−0.4 (−0.9, 0.1)	0.72 (0.46, 1.12)	0.15
Received dialysis, 30 d	14 (0.4)	14 (0.4)	0.0 (−0.3, 0.3)	1.00 (0.51, 1.96)	0.99

CI, confidence interval.

[a]A postrandomization serum creatinine was missing for 153 patients (4%) in the hypotension-avoidance group and for 149 patients (4%) in the hypertension-avoidance group. The denominator for each outcome (e.g., n = 3502) is the number of patients with nonmissing acute kidney injury status (i.e., the number of patients who provided at least 1 postrandomization creatinine, or who died within 48 hours of randomization without providing a postrandomization creatinine). For an additional 60 patients (2%) in the hypotension-avoidance group and 49 (1%) in the hypertension-avoidance group, the postrandomization serum creatinine was not obtained until 8 or more days after randomization (mostly due to delayed surgery); acute kidney injury was coded as absent in these patients. For 1 patient who died within 48 hours of randomization with no postoperative serum creatinine test result (hypotension-avoidance group), acute kidney injury was coded as absent for all stages.

[b]The risk difference was obtained from a binomial regression model (accounting for center) with an identity link function. Missing data on acute kidney injury was imputed using multiple imputation.

[c]A modified Poisson regression model (accounting for center) was used to estimate the relative risk and 95% CI for the outcome comparing the hypotension-avoidance group to the hypertension-avoidance group. Missing data on acute kidney injury was imputed using multiple imputation.

[d]The primary definition of acute kidney injury was an increase in the postrandomization serum creatinine concentration (from the prerandomization value) of ≥26.5 μmol/l (≥0.3 mg/dl) within 48 hours of randomization or an increase of ≥50% within 7 days of randomization. There were 3 patients who did not meet the definition of stage 1 acute kidney injury (for 2 because their creatinine levels were measured after the first 7 days), but they received dialysis.

[e]Acute kidney injury (primary definition) or death within 48 hours of randomization.

[f]Acute kidney injury (primary definition) for at least 2 days within 7 days of randomization.

[g]Stage 2 acute kidney injury (or higher), defined as a postrandomization increase in serum creatinine of ≥100% from the prerandomization value within 7 days of randomization, or an increase to an absolute value of 353.6 μmol/l or more (≥4.0 mg/dl) within 7 days of randomization (when the primary outcome definition of acute kidney injury is met), or receipt of dialysis within 30 days of randomization.

[h]Stage 3 acute kidney injury, defined as a postrandomization increase in serum creatinine of ≥200% from the prerandomization value within 7 days of randomization, or an increase to an absolute value of 353.6 μmol/l or more (≥4.0 mg/dl) within 7 days of randomization (when the primary outcome definition of acute kidney injury is met), or receipt of dialysis within 30 days of randomization.

postoperative hypotension commonly lasts for more than an hour, whereas intraoperative hypotension typically lasts for 15 minutes.[3]

With 7307 patients, the POISE-3 kidney substudy is the largest existing trial to examine the effect of a perioperative hypotension-avoidance strategy on AKI. We hypothesized that a hypotension-avoidance strategy during noncardiac surgery would protect against postoperative AKI, particularly in patients with chronic hypertension and chronic kidney disease, who may have less autoregulatory capacity and may be more susceptible to ischemia-reperfusion injury from hypotension.[11,22,37,38] We did not observe any intervention effect, even in patients with preexisting chronic kidney disease. Given that adherence to the intervention was reasonable, and better adherence was not consistently associated with fewer AKI events, the lack of an intervention effect is likely due to the 2 strategies producing an insufficient difference in hemodynamics as evidenced by the lack of a difference in systolic blood pressure and diastolic blood pressure outside of the operating room (Figure 2). Patients allocated to the hypotension-avoidance group did use substantially fewer blood pressure medications than patients in the hypertension-avoidance group on the day of surgery and in the following 2 days (including ACEIs, ARBs, and diuretics; Supplementary Table S6). Also, they spent about half as much intraoperative time with a MAP <80 mm Hg, recognizing that the median intraoperative time spent with a MAP <60 mm Hg was 0 minutes in both groups (Supplementary Table S7). In this substudy, we did not examine whether interventions used during episodes of intraoperative clinically significant hypotension differed between the groups. However, in the main POISE-3 trial, the intervention groups did not differ in the proportion of patients who received more intravenous crystalloid or colloid fluids or initiated inotrope or vasopressor agents.[14]

This substudy has some limitations. Very few participants had an eGFR <30 ml/min per 1.73 m^2 due to the trial's eligibility restrictions for the tranexamic factorial and, therefore, we do not know whether the intervention is beneficial in those with more advanced chronic kidney disease. It was not possible to mask patients or providers to the intervention. However, any resulting ascertainment bias was likely minimal as patients in both groups had the same prespecified schedule for serum creatinine measurements, and the groups had a similar number of postoperative serum creatinine measures (median 3 per patient). The protocol for avoiding hypotension in POISE-3 recommended holding ACEI or ARB on the day of surgery. Considering the half-life of these drugs, results might have varied if patients had

Table 3 | Hypotension-avoidance versus hypertension-avoidance strategy and the risk of acute kidney injury in patients receiving noncardiac surgery: subgroup analysis

	Events, n (%)[a]					
	Hypotension-avoidance strategy (n = 3654)	Hypertension-avoidance strategy (n = 3653)	Risk difference[b] (95% CI)	*P* value[b]	Relative risk (95% CI)[c]	*P* value[c]
Chronic kidney disease[d]						
Yes	129/740 (17.4)	125/744 (16.8)	0.6 (−3.2, 4.7)	0.96	1.04 (0.81, 1.32)	0.91
No	401/2762 (14.5)	380/2760 (13.8)	0.7 (–1.1, 2.6)		1.05 (0.92, 1.21)	
ACEI or ARB before randomization[e]						
Yes	395/2502 (15.8)	367/2500 (14.7)	1.1 (−0.9, 3.1)	0.47	1.07 (0.93, 1.24)	0.53
No	135/1000 (13.5)	138/1004 (13.8)	−0.2 (−3.2, 2.8)		0.98 (0.78, 1.25)	
Tranexamic acid group						
Tranexamic acid	265/1749 (15.2)	260/1754 (14.8)	0.3 (−2.0, 2.7)	0.65	1.02 (0.86, 1.21)	0.66
Placebo	265/1753 (15.1)	245/1750 (14.0)	1.1 (−1.2, 3.4)		1.08 (0.91, 1.28)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.
[a]A postrandomization serum creatinine was missing for 153 patients (4%) in the hypotension-avoidance group and for 149 patients (4%) in the hypertension-avoidance group. For an additional 60 patients (2%) in the hypotension-avoidance group and 49 (1%) in the hypertension-avoidance group, the postrandomization serum creatinine was not obtained until 8 or more days after randomization (mostly due to delayed surgery); acute kidney injury was coded as absent in these patients. For 1 patient who died within 48 hours of randomization with no postoperative serum creatinine test result, acute kidney injury was coded as absent for all stages. The denominator for each subgroup (e.g., n = 740) is the number of patients with nonmissing acute kidney injury status (i.e., the number of patients who provided at least 1 postrandomization creatinine, or who died within 48 hours of randomization without providing a postrandomization creatinine).
[b]The risk difference was obtained using a generalized estimating equation with an identity link and binomial distribution, accounting for center. Missing acute kidney injury was imputed using multiple imputation which accounted for the subgroup; estimates were combined using standard methods. A separate analysis was performed for each subgroup. The *P* value for additive interaction was obtained using a similar model, with an interaction term between treatment group assignment and an indicator variable for the subgroup of interest.
[c]A modified Poisson regression model (accounting for center) was used to estimate the relative risk and 95% CI for the outcome comparing the hypotension-avoidance strategy group to the hypertension-avoidance strategy group. Missing acute kidney injury was imputed using multiple imputation, which accounted for the subgroup; estimates were combined using standard methods. A separate analysis was performed for each subgroup. The *P* value for the interaction was obtained using a similar model, with an interaction term between treatment group assignment and an indicator variable for the subgroup of interest.
[d]Defined by a prerandomization eGFR <60 ml/min per 1.73 m^2 as assessed with the 2021 Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation.[31]
[e]ACEI or ARB use before randomization (for at least 30 days in the 6 weeks preceding randomization) was missing in 5 patients in the hypotension-avoidance group and in 5 patients in hypertension-avoidance group; we imputed "no ACEI/ARB use" for these patients.

stopped taking these medications for several days before surgery. The primary substudy outcome, postoperative AKI, was defined as an acute rise in serum creatinine concentration from the prerandomization value.[27] While many AKI prevention trials follow this definition, this outcome is a surrogate endpoint that may not directly impact how a patient feels, functions, or survives. There is emerging interest in phenotyping AKI beyond changes in serum creatinine, including biomarkers of tubular damage.[39–41] Nonetheless, our definition of AKI follows current international clinical practice guidelines, and the primary results were consistent with the analyses of more severe manifestations of AKI, including stages 2 and 3 AKI and receiving dialysis. Our definition of AKI did not include oliguria, given the difficulty of accurately measuring urine output. The prerandomization serum creatinine measurement was typically taken within a week before surgery (median: 5 days). Depending on the reason for the surgery, this value may be unstable, making it challenging to accurately detect any acute rise in postsurgery creatinine levels. However, results were consistent in analyses that controlled for the prerandomization eGFR and when we excluded patients who underwent urgent or emergency surgery (those more likely to have unstable baseline values; Supplementary Tables S9 and S10, respectively).

The strengths of this substudy include its randomized trial methodology with concealed allocation, enrollment of 7307 patients from 110 centers in 22 countries, and standardized collection of postrandomization serum creatinine. The primary outcome and statistical analysis plan were prespecified, the effect estimates were precise, and multiple sensitivity analyses supported the primary results.

Relevance to clinical practice

Our findings suggest that targeting a MAP >80 mm Hg in the operating room does not reduce the risk of AKI compared with targeting a MAP >60 mm Hg. Our findings also suggest that from a kidney perspective, it is safe to continue blood pressure medications during the perioperative period, recognizing that physicians should continue to make individualized judgments.

Conclusions

In this international, randomized clinical trial of patients undergoing noncardiac surgery, the risk of postoperative AKI did not differ between patients randomized to receive a hypotension-avoidance strategy versus a hypertension-avoidance strategy.

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(*Continued on following page*)

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DISCLOSURE

CSM is the founder of a start-up company, WARD24/7 ApS, with the aim of pursuing the regulatory and commercial activities of the WARD-project (Wireless Assessment of Respiratory and circulatory Distress, a project developing a clinical support system for continuous wireless monitoring of vital signs). WARD24/7 ApS has obtained license agreement for any WARD-project software and patents. One patent has been filed: "Wireless Assessment of Respiratory and circulatory Distress (WARD), EP 21184712.4 and EP 21205557.8". DC reports speaker fees from Servier and consulting fees from Trimedics. All the other authors declared no competing interests.

DATA STATEMENT

The data for this substudy are held by the Population Health Research Institute (PHRI). The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. The PHRI prioritizes access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. The PHRI balances the length of the research study and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only on request and approval of the proposed use of the data by a review committee. Data will be available to the journal for evaluation of reported analyses. Data requests from other non–POISE-3 investigators will not be considered until 5 years after the close of the trial.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

An appropriately authorized ethics committee approved the trial in all the participating centers. Written informed consent was obtained from all the participants before enrollment.

CONSENT FOR PUBLICATION

Consent for publication was obtained from all authors.

AUTHOR CONTRIBUTIONS

All the authors reviewed the manuscript drafts for important intellectual content and provided approval of the final version for submission. AXG is the guarantor and corresponding author and accepts full responsibility for the overall content of the work and conduct of the study, had access to the data, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Supplementary material is available online at www.kidney-international.org.

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