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Effect of a Perioperative Hypotension-Avoidance Strategy Versus a Hypertension-Avoidance Strategy on the Risk of Acute Kidney Injury: A Clinical Research Protocol for a Substudy of the POISE-3 Randomized Clinical Trial

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Abstract

Background: Most patients who take antihypertensive medications continue taking them on the morning of surgery and during the perioperative period. However, growing evidence suggests this practice may contribute to perioperative hypotension and a higher risk of complications. This protocol describes an acute kidney injury substudy of the Perioperative Ischemic Evaluation-3 (POISE-3) trial, which is testing the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy in patients undergoing noncardiac surgery.

Objective: To conduct a substudy of POISE-3 to determine whether a perioperative hypotension-avoidance strategy reduces the risk of acute kidney injury compared with a hypertension-avoidance strategy.

Design: Randomized clinical trial with 1:1 randomization to the intervention (a perioperative hypotension-avoidance strategy) or control (a hypertension-avoidance strategy).

Intervention: If the presurgery systolic blood pressure (SBP) is $<$130 mmHg, all antihypertensive medications are withheld on the morning of surgery. If the SBP is $\geq$130 mmHg, some medications (but not angiotensin receptor blockers [ACEIs], angiotensin receptor blockers [ARBs], or renin inhibitors) may be continued in a stepwise manner. During surgery, the patients' mean arterial pressure (MAP) is maintained at $\geq$80 mmHg. During the first 48 hours after surgery,

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some antihypertensive medications (but not ACEIs, ARBs, or renin inhibitors) may be restarted in a stepwise manner if the SBP is ≥130 mmHg.
Control: Patients receive their usual antihypertensive medications before and after surgery. The patients' MAP is maintained at ≥60 mmHg from anesthetic induction until the end of surgery.
Setting: Recruitment from 108 centers in 22 countries from 2018 to 2021.
Patients: Patients (~6800) aged ≥45 years having noncardiac surgery who have or are at risk of atherosclerotic disease and who routinely take antihypertensive medications.
Measurements: The primary outcome of the substudy is postoperative acute kidney injury, defined as an increase in serum creatinine concentration of either ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours of randomization or ≥50% within 7 days of randomization.
Methods: The primary analysis (intention-to-treat) will examine the relative risk and 95% confidence interval of acute kidney injury in the intervention versus control group. We will repeat the primary analysis using alternative definitions of acute kidney injury and examine effect modification by preexisting chronic kidney disease, defined as a prerandomization estimated glomerular filtration rate <60 mL/min/1.73 m^2.
Results: Substudy results will be analyzed in 2022.
Limitations: It is not possible to mask patients or providers to the intervention; however, objective measures will be used to assess acute kidney injury.
Conclusions: This substudy will provide generalizable estimates of the effect of a perioperative hypotension-avoidance strategy on the risk of acute kidney injury.

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Abrégé

Contexte : La plupart des patients qui prennent des médicaments antihypertenseurs continuent de les prendre le matin d'une intervention chirurgicale et pendant la période périopératoire. De plus en plus de preuves suggèrent que cette pratique pourrait entraîner l'hypotension périopératoire et augmenter le risque de complications. Ce protocole décrit une sous-étude sur l'insuffisance rénale aiguë (IRA) découlant de l'essai *Perioperative Ischemic Evaluation-3* (POISE-3). Cet essai teste l'effet d'une stratégie d'évitement de l'hypotension périopératoire par rapport à une stratégie d'évitement de l'hypertension chez des patients qui subissent une chirurgie non cardiaque.

Objectifs : Cette sous-étude de l'essai POISE-3 vise à déterminer si une stratégie d'évitement de l'hypotension périopératoire réduit le risque d'IRA comparativement à la stratégie d'évitement de l'hypertension.

Type d'étude : Essai clinique randomisé à répartition 1:1 au groupe intervention (stratégie d'évitement de l'hypotension périopératoire) ou au groupe témoin (stratégie d'évitement de l'hypertension).

Groupe intervention : Si la pression artérielle systolique (PAS) avant l'opération est $<$130 mmHg, tous les médicaments antihypertenseurs sont suspendus le matin de la chirurgie. Si la PAS est $\geq$130 mmHg, certains médicaments (excluant les inhibiteurs de l'enzyme de conversion de l'angiotensine [IECA], les antagonistes du récepteur de l'angiotensine [ARA] ou les inhibiteurs de la rénine) peuvent être poursuivis de façon graduelle. Pendant la chirurgie, la pression artérielle moyenne (PAM) du patient est maintenue à $\geq$80 mmHg. Dans les 48 heures suivant l'intervention chirurgicale, certains médicaments antihypertenseurs (excluant les IECA, les ARA ou les inhibiteurs de la rénine) peuvent être réintroduits par étapes si la PAS est $\geq$130 mmHg.

Groupe témoin : Les patients reçoivent leurs médicaments antihypertenseurs habituels avant et après la chirurgie. La PAM du patient est maintenue à $\geq$60 mmHg de l'induction de l'anesthésie à la fin de l'intervention chirurgicale.

Cadre : Recrutement à partir de 108 centres dans 22 pays entre 2018 à 2021.

Sujets : Des patients (~6 800) âgés de 45 ans et plus atteints d'athérosclérose, ou présentant un risque de l'être, devant subir une chirurgie non cardiaque et prenant des médicaments antihypertenseurs sur une base régulière.

Mesures : Le principal critère d'évaluation de cette sous-étude est une IRA postopératoire définie par une hausse d'au moins 26,5 μmol/L ($\geq$0,3 mg/dL) de la créatinine sérique dans les 48 heures suivant la randomisation ou d'au moins 50 % dans les 7 jours suivant la randomisation.

Méthodologie : L'analyse primaire (par intention de traiter) examinera le risque relatif d'une IRA et l'intervalle de confiance à 95 % dans le groupe intervention par rapport au groupe témoin. Nous répéterons l'analyse primaire en utilisant d'autres définitions de l'IRA et nous examinerons la modification de l'effet en présence d'une insuffisance rénale préexistante (définie par un DFGe prérandomisation $<$60 ml/min/1,73 m^2).

Résultats : Les résultats de cette sous-étude seront analysés en 2022.

Limites : Il n'est pas possible de procéder à l'insu des patients ou des prestataires de soins pour cette intervention; des mesures objectives seront toutefois utilisées pour évaluer l'IRA.

Conclusion : Cette sous-étude fournira des estimations généralisables de l'effet d'une stratégie visant à éviter l'hypotension périopératoire sur le risque d'insuffisance rénale aiguë.

Keywords

acute kidney injury, antihypertensive medication, hypotension, mean arterial pressure, noncardiac surgery

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What was known before

Both perioperative hypotension and hypertension are independently associated with adverse outcomes; however, hypotension is more common and may be more dangerous.

What this adds

We are conducting an acute kidney injury substudy of Perioperative Ischemic Evaluation-3 (POISE-3), a multinational randomized clinical trial of patients on antihypertensive medications having noncardiac surgery; the trial is testing the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy.

Introduction

Most patients who take antihypertensive medications continue taking them on the morning of surgery and during the perioperative period.[1] However, growing evidence suggests that this practice may contribute to perioperative hypotension and a higher risk of complications.[1-7] This has led to debate about optimal perioperative blood pressure targets and whether antihypertensive medications should be withheld during the perioperative period and how they should be reintroduced postoperatively.[1,8] The effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on cardiovascular outcomes is currently being tested in the Perioperative Ischemic Evaluation-3

(POISE-3) trial, a partial 2 × 2 factorial trial (factor 1 is testing the effect of tranexamic acid vs placebo). The trial started recruitment in June 2018 and is expected to enroll ~7000 patients aged ≥45 years undergoing noncardiac surgery with an overnight hospital stay who have or are at risk of atherosclerotic disease and who routinely take antihypertensive medications.

A Kidney Substudy of POISE-3

Approximately 10% of patients who undergo noncardiac surgery will develop perioperative acute kidney injury, with 0.5% receiving dialysis as a result.[6,9,10] Acute kidney injury is associated with longer hospital stays, increased health care costs, and death.[10,11] Perioperative hypotension can cause ischemia-reperfusion injury to the kidney.[12] We, and others, have shown that the risk for acute kidney injury increases progressively with the severity and duration of perioperative hypotension.[2,3,6,13] In a recent trial of 678 elderly hypertensive patients having gastrointestinal surgery, patients randomized to an intraoperative mean arterial pressure (MAP) of 80 to 95 mmHg had less acute kidney injury than those randomized to a lower or higher target MAP (65-79 and 96-110 mmHg, respectively)—the incidence of acute kidney injury in these groups was 6.3%, 13.5%, and 12.9%, respectively ($P = .03$).[9] Whether these findings generalize to a broader patient group undergoing other types of noncardiac surgery remains unknown.[9]

This protocol describes a planned kidney substudy of POISE-3 to examine the effect of a perioperative hypotension-avoidance strategy on the risk of acute kidney injury compared with a hypertension-avoidance strategy. We will also examine whether the intervention has a larger absolute benefit in patients with preexisting chronic kidney disease, which is the most prominent risk factor for acute kidney injury.[14]

Main Questions in the POISE-3 Kidney Substudy

Primary question. Does a perioperative hypotension-avoidance strategy reduce the risk of acute kidney injury compared with a hypertension-avoidance strategy in patients having noncardiac surgery who routinely take antihypertensive medication and who have or are at risk of atherosclerotic disease?

Secondary question. Does the presence of preexisting chronic kidney disease modify the effect of a perioperative hypotension-avoidance strategy on the risk of acute kidney injury?

Method

Overview of the POISE-3 Main Trial

POISE-3 (NCT03505723) is a randomized clinical trial being conducted in 108 centers in 22 countries. Enrollment began in June 2018 and will continue until December 2021. POISE-3 is designed as a partial 2 × 2 factorial trial. In factor 1, the tranexamic acid factorial, 10 000 patients ≥45 years having noncardiac surgery with an overnight hospital stay who have or are at risk of atherosclerotic disease (the full list of inclusion criteria is provided in Appendix I in the Supplement) will be randomized to receive intravenous tranexamic acid or placebo during surgery. In factor 2, the blood pressure management factorial, an estimated 7000 patients who are routinely taking at least 1 antihypertensive drug will also be randomized to receive a perioperative hypotension-avoidance strategy or a hypertension-avoidance strategy. The acute kidney injury substudy will analyze patients enrolled in factor 2.

Patient Recruitment and Informed Consent

Study personnel screen the patient list in the preoperative assessment clinic to identify eligible patients. A variety of screening approaches are used to identify patients who do not attend the preoperative assessment clinic, including screening the daily surgical list in the operating room and reviewing patient lists on surgical wards and intensive care units. At each center, the services of anesthesia, surgery, and medicine are asked to page study personnel to notify them of admissions through the emergency department and ward patients requiring surgery. Study personnel approach all eligible patients to obtain written informed consent before surgery. Where possible, research personnel inform patients about the trial in preoperative clinics. Patients who are not identified or approached in the preoperative clinic are contacted before surgery to discuss the trial and their potential participation.

Randomized Group Assignment

Randomization occurs on the day of surgery (before surgery) after a patient has been deemed eligible and has provided written informed consent. To ensure that the randomization sequence is concealed from participating centers and patients, randomization is generated centrally online via an Interactive Web Randomization System (maintained by the POISE-3 Project Office at the Population Health Research Institute in Hamilton, ON, Canada). The randomization process uses variable-block randomization, stratified by center. Study personnel who randomize patients do not know the block size. In this partial factorial trial, all patients are first randomized 1:1 to the tranexamic acid intervention or placebo, which is factor 1. Those who are eligible for factor 2 and consent to participate (conservatively estimated to be 65% of 10 000, described in the sample size and statistical power section below) are randomized 1:1 to a hypotension-avoidance strategy or a hypertension-avoidance strategy. Patients and providers are notified of the factor 2 assignment after it is randomly assigned to a given patient.

Intervention

All patients who are eligible to participate in factor 2, the blood pressure management factorial, are instructed to not take their antihypertensive medication the night before and/or on the morning of surgery (before coming to the hospital) and to bring their antihypertensive medications to the hospital. Patients who do not have their antihypertensive medications with them on the day of surgery, or who already took their antihypertensive medications on the day of surgery, are still eligible for randomization to this factorial. They continue to receive the intraoperative and postoperative components of the trial as described below.

Hypotension-avoidance strategy (intervention). On the morning of surgery, all antihypertensive medications are withheld if the presurgery systolic blood pressure (SBP) is $<$130 mmHg. If the SBP is $\geq$130 mmHg, some medications may be continued in a stepwise manner (see Appendix II in the Supplement); however, no patient will take an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or a renin inhibitor, alone or in combination, on the day of surgery.

Intraoperatively, the attending anesthetist is asked to maintain the patient's MAP to $\geq$80 mmHg, from anesthetic induction until the end of surgery. Methods to achieve this target (fluids, vasopressors, inotropes, etc) are left to the discretion of the anesthetist.

During the first 48 hours after surgery, some antihypertensive medications may be restarted (in a stepwise manner) if the SBP is $\geq$130 mmHg (except no ACEIs, ARBs, or renin inhibitors). Starting on postoperative day 3, the management of blood pressure and antihypertensive medication is left to the discretion of the treating physician.

Hypertension-avoidance strategy (control). Patients receive their usual antihypertensive medications before and after surgery. Intraoperatively, the anesthetist is asked to maintain the patient's MAP to $\geq$60 mmHg, from anesthetic induction until the end of surgery.

This strategy mirrors what typically occurs in routine care as documented in the literature.[1,8,15-17] In the VISION study (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation), more than 70% of patients on chronic antihypertensive medications continued these medications in the 24 hours before noncardiac surgery.[1] Although there is no standard, the existing literature documents that usual care typically consists of maintaining the intraoperative MAP above 60 mmHg.[15,16]

Methods Used in the POISE-3 Kidney Substudy

Patient selection. Eligibility criteria for the POISE-3 main trial are fully detailed in Appendix I in the Supplement. Briefly, eligible patients include those having noncardiac surgery with at least one expected night in hospital after surgery, those aged $\geq$45 years, and those who have or are at risk of atherosclerotic disease. To be eligible to participate in factor 2 (the blood pressure management factorial), patients need also to be treated for $\geq$30 days in the 6 weeks before randomization with at least 1 antihypertensive medication of any class (ie, ACEIs, ARBs, renin inhibitors, β-blockers, calcium channel blockers, central α2-agonists, α-blockers, direct vasodilators, long-acting nitrates, thiazide diuretics, loop diuretics, or potassium-sparing diuretics).

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 on chronic dialysis are excluded from POISE-3. We expect 15% to 20% of patients enrolled in POISE-3 will have chronic kidney disease defined by a prerandomization estimated glomerular filtration rate (eGFR) $<$60 mL/min per 1.73 m^2 (975-1300 patients)[18] as assessed by the CKD-EPI equation.[19]

In addition, we will exclude patients missing a prerandomization serum creatinine because these data are needed to define acute kidney injury. Less than 2% of participants are expected to be excluded for this reason.[6]

Substudy data collection. The most recent test result for serum creatinine before randomization was the baseline value. These data were obtained from a review of medical records. The date of randomization is used to identify the start of follow-up in this substudy. We expect $>$95% of enrolled patients to have surgery within 3 days of randomization. In our substudy of POISE-2, the median time from randomization to surgery was 2 hours (25th, 75th percentile: 1-3 hours) and we expect a similar distribution in POISE-3.[6] All centers receive substudy funds to measure and record a daily serum creatinine value on postoperative days 1, 2, and 3 (or until hospital discharge) in all randomized patients. This schedule is expected to minimize any ascertainment bias related to the assessment of acute kidney injury (ie, if the intervention alters the incidence of another event such as myocardial infarction, this could influence the likelihood of serum creatinine measurement). Centers are also asked to record all other serum creatinine measurements performed as a part of routine care (and their dates) during the hospital stay. No urine output data are used in this substudy given difficulties with accurately measuring this variable outside of the intensive care unit. Receipt of new dialysis for kidney failure is recorded at hospital discharge and 30 days after randomization.

This data collection schedule is informed by our experience collecting kidney function data in our substudy of POISE-2 and we expect to capture most events of acute kidney injury.[6,18] In a prior study where we collected daily serum creatinine values in the first 5 days after surgery, we noted that 93% of postoperative acute kidney injury events occurred in the first 3 days after surgery.[20] At the time of the final

analysis, we will compare the characteristics of patients who did and did not provide at least one serum creatinine measurement during the week following randomization and will examine the number of measurements by treatment group (and measurement dates) to confirm there is no differential outcome ascertainment between groups. We expect <1% of patients will die in the operating room or within 48 hours after surgery, which may result in no serum creatinine measurement after randomization.[6] In the POISE-2 substudy,[6] more than 95% of patients had at least 1 serum creatinine measurement within the 7 days following surgery and the median number of postoperative serum creatinine measurements was identical in the intervention and placebo groups (3 measurements; interquartile range [IQR] = 2-4) along with the specific postoperative days of these measurements. The median duration of hospital stay was identical in each group (4 days; IQR = 3-7 days).

Substudy outcomes. The *primary outcome* of the POISE-3 kidney substudy is postoperative acute kidney injury, defined 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.[21]

Secondary definitions of acute kidney injury. Seven secondary definitions of acute kidney injury will be examined to assess whether the primary results are robust:

1. A composite outcome of acute kidney injury (primary definition) or death within 48 hours of randomization (to account for the potential impact of early deaths on outcome ascertainment).
2. Acute kidney injury (primary definition) for at least 2 days within 7 days of randomization.
3. 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.
4. 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 4.0 mg/dL or more (≥353.6 μmol/L) 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.
5. Receipt of dialysis within 30 days of randomization.
6. 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.
7. 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. The main POISE-3 trial is planning to enroll 10 000 patients in factor 1 (the tranexamic acid factorial) and it is expected that at least 80% of these patients will be taking preoperative maintenance antihypertensive medications (based on estimates from the POISE-2 trial).[5] As a conservative estimate, at least 70% of the patients in factor 1 are expected to be eligible for and consent to participate in factor 2 (the blood pressure management factorial) and we expect that 98% of these 7000 patients will be eligible for inclusion in the kidney substudy, providing an expected sample size of at least 6800 patients in the substudy.

For the kidney substudy, a sample of 6800 patients will provide >80% power to detect a 20% relative risk (RR) reduction for the primary outcome of postoperative acute kidney injury (2-sided $\alpha = 0.05$), assuming an incidence of acute kidney injury of 10% in the control group.

Statistical analysis plan. In the primary analysis (intention-to-treat), a modified Poisson regression model (accounting for center) will be used to estimate the RR and 95% confidence interval (CI) for postoperative acute kidney injury comparing the intervention group with the control group.[22,23] Missing data on postoperative serum creatinine (expected for <5% of surviving patients)[6] will be imputed using multiple imputation; parameters will be estimated using standard methods while allowing for extra imputation variability.[24] A 2-tailed P value of ≤.05 will be considered statistically significant.

Prespecified supporting analyses. As outlined below, we will conduct several supporting analyses and examine whether the results are concordant with the results of the primary analysis. We will also examine 7 secondary definitions of acute kidney injury and conduct a subgroup analysis of patients with preexisting chronic kidney disease.

Complete-case analysis. We will perform a complete-case analysis restricted to patients with at least one postoperative serum creatinine measurement (expected to be ~95% of patients in the primary analysis). If there are centers with <90% complete serum creatinine measurements (or periods in some centers before initiating the kidney substudy), we will analyze only those centers (or periods of time in those centers) with over 90% completed measurements.

Adjusted analyses. In our experience with previous kidney substudies, the unadjusted and adjusted results were virtually

identical;[18,25] nonetheless, to potentially increase the precision of our estimates,[26] we will use a generalized estimating equation approach for binary outcome data, accounting for within-center correlation, adjusting for 9 covariates (measured before randomization) based on their known association with acute kidney injury: age (in years, modeled with restricted cubic splines), 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 (~6%-7% of POISE-2 participants),[6] and type of surgery (major vascular surgery, major thoracic surgery, or other surgery). We will also adjust for the random allocation of tranexamic acid versus placebo. Adjusted RRs and 95% CIs will be reported. We expect missing data on these variables to be <0.5%.[6]

Alternative definitions of acute kidney injury. We will examine 7 secondary definitions of acute kidney injury (5 categorical and 2 continuous, as described above). Binary outcomes will be assessed using modified Poisson regression models, and continuous outcomes using linear regression models. We will visually inspect the point estimates and 95% CIs and assess concordance with the primary analysis. Despite the large sample size, supplementary analyses of severe acute kidney injury will have limited statistical power for small effects.

Subgroup analysis. Compared with patients with preserved kidney function, patients with an eGFR below 60 mL/min per 1.73 m^2 have a higher risk of acute kidney injury and may be more vulnerable to the ischemic effects of hypotension.[14] We hypothesize that the hypotension-avoidance intervention may confer a larger absolute benefit to patients with preexisting chronic kidney disease, defined by a prerandomization eGFR <60 mL/min per 1.73 m^2 as assessed with the 2021 CKD-EPI equation.[27,28] To examine the presence of additive interaction, we will calculate the absolute difference in risk (and 95% CI) between the intervention and control groups in patients with and without preexisting chronic kidney disease; a *P* value for the interaction term will be assessed in a regression model for binary outcome data. We will also conduct a test for multiplicative interaction between eGFR and the intervention group, where eGFR is a continuous variable modeled with restricted cubic splines to allow for nonlinearity. We do not expect prerandomization eGFR will modify the RR of acute kidney injury with a strategy of hypotension-avoidance compared with hypertension-avoidance.

Additional analyses. We anticipate that the treatment effects of tranexamic acid and the hypotension-avoidance strategy will act independently, but will explore this by reporting cell-by-cell results (ie, for each of the 4 treatment groups) and will test for multiplicative interaction using a modified Poisson regression. We will also examine the between-group difference in adherence. As well, because patients who undergo urgent or emergent surgery may be more likely to develop acute kidney injury before randomization, we will repeat the primary analyses after excluding these categories of surgery. An additional subgroup analysis will examine the treatment effect in patients who are taking versus not taking an ACEI or ARB before randomization; we hypothesize that the hypotension-avoidance strategy may confer a greater benefit (both in relative and absolute terms) in preventing acute kidney injury in patients taking versus not taking an ACEI or ARB before randomization. Finally, we expect <5% of randomized patients to have delayed surgery (>3 days after randomization) or not undergo surgery at all. We will examine concordance with the primary intention-to-treat analysis when the date of surgery (rather than the date of randomization) is used as the start of follow-up, excluding those who did not undergo surgery.

Discussion

This protocol describes our planned acute kidney injury substudy and statistical analysis plan of the POISE-3 randomized clinical trial, which is testing the effect of a perioperative hypotension-avoidance strategy versus a hypertension-avoidance strategy on patients ≥45 years having noncardiac surgery who have or are at risk of atherosclerotic disease, and who routinely take antihypertensive medications.

Although both perioperative hypotension and hypertension are independently associated with adverse outcomes,[29] hypotension is more common, occurring in approximately 40% of noncardiac surgeries.[2,3,13,30] Intraoperative hypotension may also be more dangerous.[7] In the last decade, both observational[1-3,7,13,31-33] and experimental studies[9,34] demonstrated that perioperative hypotension is an independent predictor of vascular events and death. This association is seen for MAPs <50 to 55 mmHg (even for less than a minute), for MAPs 65 to 80 mmHg (on average and/or over time), and for percentage drops in MAP from baseline (eg, 20% or greater). These data suggest that the optimal perioperative blood pressure target may be higher than previously thought, particularly in patients with chronic hypertension, who may have less autoregulatory capacity and may be more susceptible to ischemia-reperfusion injury from hypotension.[29,34,35]

By adding additional serum creatinine measurements to POISE-3, we can efficiently and reliably determine whether a perioperative hypotension-avoidance strategy reduces the risk of acute kidney injury compared with a hypertension-avoidance strategy. Our substudy has some limitations. It will not be possible to mask patients or providers to the intervention; however, any resulting ascertainment bias should be minimal as patients in both groups have the same prespecified schedule for serum creatinine measurements. Furthermore, as shown in POISE-2, we anticipate no difference in the number of postoperative serum creatinine

measures between treatment arms.[6,21] The primary outcome of this kidney substudy is postoperative acute kidney injury, defined as an acute rise in serum creatinine concentration from the prerandomization value.[36] While many prevention trials of acute kidney injury follow this definition, this outcome is a surrogate endpoint that may not directly impact how a patient feels, functions, or survives. Unfortunately, detailed information on long-term permanent kidney function after hospital discharge will not available for most patients enrolled in POISE-3. However, even small decreases in kidney function after surgery are associated with poor short- and long-term outcomes[10,11] and our definition of acute kidney injury follows international clinical practice guidelines and is a defensible approach for our primary outcome.[36] We will also examine whether intervention effects are consistent for stage 2 and 3 acute kidney injury; despite being less frequent, these events are more important to patients and health care providers. Our definition of acute kidney injury does not include oliguria given the difficulty of accurately measuring urine output in an international setting; however, any resulting outcome misclassification would be expected to be nondifferential between groups. Finally, the prerandomization measure of serum creatinine will be the most recently obtained measure before randomization and we expect it to be obtained within 1 week before surgery for most patients. Depending on why the patient needs surgery, a serum creatinine test obtained at the time of hospital admission may be unstable or elevated. Although such error may impede the detection of an acute rise in postrandomization serum creatinine, which is needed for the identification of acute kidney injury, we expect this error to be similar between randomized groups. We will report the prerandomization serum creatinine concentration for each group and examine if it differs for patients whose baseline measurement was obtained at the time of hospital admission versus earlier. We will also conduct an adjusted analysis that controls for patients' prerandomization eGFR and receipt of urgent or emergency surgery.

Conclusions

Our substudy of POISE-3 will determine whether a perioperative hypotension-avoidance strategy reduces the risk of acute kidney injury compared with a hypertension-avoidance strategy. We will also conduct a subgroup analysis by preoperative chronic kidney disease, which is a strong risk factor for acute kidney injury.[14] Conducting this study with a sample size of 6800 patients in 108 centers in 22 countries with the use of randomized trial methodology will help generate results that are accurate, precise, and broadly generalizable.

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.

Availability of Data and Materials

Not available.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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