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Effect of Colchicine on the Risk of Perioperative Acute Kidney Injury: Clinical Protocol of a Substudy of the Colchicine for the Prevention of Perioperative Atrial Fibrillation Randomized Clinical Trial

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Abstract

Background: Inflammation during and after surgery can lead to organ damage including acute kidney injury. Colchicine, an established inexpensive anti-inflammatory medication, may help to protect the organs from pro-inflammatory damage. This protocol describes a kidney substudy of the colchicine for the prevention of perioperative atrial fibrillation (COP-AF) study, which is testing the effect of colchicine versus placebo on the risk of atrial fibrillation and myocardial injury among patients undergoing thoracic surgery.

Objective: Our kidney substudy of COP-AF will determine whether colchicine reduces the risk of perioperative acute kidney injury compared with a placebo. We will also examine whether colchicine has a larger absolute benefit in patients with pre-existing chronic kidney disease, the most prominent risk factor for acute kidney injury.

Design and Setting: Randomized, superiority clinical trial conducted in 40 centers in 11 countries from 2018 to 2023.

Patients: Patients (~3200) aged 55 years and older having major thoracic surgery.

Intervention: Patients are randomized 1:1 to receive oral colchicine (0.5 mg tablet) or a matching placebo, given twice daily starting 2 to 4 hours before surgery for a total of 10 days. Patients, health care providers, data collectors, and outcome adjudicators will be blinded to the randomized treatment allocation.

Methods: Serum creatinine concentrations will be measured before surgery and on postoperative days 1, 2, and 3 (or until hospital discharge). The primary outcome of the substudy is perioperative acute kidney injury, defined as an increase (from the prerandomization value) in serum creatinine concentration of either $\geq$26.5 μmol/L ($\geq$0.3 mg/dL) within 48 hours of surgery or $\geq$50% within 7 days of surgery. The primary analysis (intention-to-treat) will examine the relative risk of acute kidney injury in patients allocated to receive colchicine versus placebo. We will repeat the primary analysis using alternative definitions of acute kidney injury and examine effect modification by pre-existing chronic kidney disease, defined as a prerandomization estimated glomerular filtration rate (eGFR) $<$60 mL/min per 1.73 m^2.

Limitations: The substudy will be underpowered to detect small effects on more severe forms of acute kidney injury treated with dialysis.

Results: Substudy results will be reported in 2024.

Conclusions: This substudy will estimate the effect of colchicine on the risk of perioperative acute kidney injury in older adults undergoing major thoracic surgery.

Clinical trial registration number: NCT03310125

Abrégé

Contexte: L'inflammation pendant et après une intervention chirurgicale peut causer des lésions aux organes, notamment de l'insuffisance rénale aiguë (IRA). La colchicine, un médicament anti-inflammatoire reconnu et bon marché, peut contribuer à protéger les organes contre les lésions pro-inflammatoires. Le présent protocole décrit une sous-étude rénale de l'essai *Colchicine for the Prevention of Perioperative atrial fibrillation* (COP-AF), qui examine l'effet de la colchicine, par rapport à un placebo, sur le risque de fibrillation auriculaire et de lésion myocardique chez les patients qui subissent une chirurgie thoracique.

Objectif: Notre sous-étude rénale de l'essai COP-AF permettra de vérifier si la colchicine réduit le risque d'IRA périopératoire par rapport à un placebo. Nous tenterons également de déterminer si la colchicine présente un plus grand bénéfice absolu pour les patients atteints d'une insuffisance rénale chronique préexistante, laquelle constitue le plus important facteur de risque pour l'IRA.

Cadre et type d'étude: Essai clinique à répartition aléatoire visant à démontrer une supériorité. L'étude, qui s'étend de 2018 à 2023, est menée dans 40 centers situés dans 11 pays.

Sujets: Des patients (~3200) âgés de 55 ans et plus subissant une chirurgie thoracique majeure.

Interventions: Les patients sont répartis 1:1 de façon aléatoire pour recevoir de la colchicine par voie orale (comprimé de 0.5 mg), ou un placebo correspondant, deux fois par jour à partir de 2 à 4 heures avant l'intervention chirurgicale, pour un total de 10 jours. Les patients, les prestataires de soins de santé, les personnes qui collectent les données et celles qui évaluent les résultats ne seront pas informés de l'attribution du traitement.

Méthodologie: Les concentrations sériques de créatinine seront mesurées avant l'intervention et aux jours postopératoires 1, 2, et 3 (ou jusqu'au congé de l'hôpital). Le principal critère d'évaluation de cette sous-étude est une IRA périopératoires définie par une hausse (par rapport à la valeur mesurée avant la répartition aléatoire) d'au moins 26.5 μmol/L (≥0.3 mg/dL) de la créatinine sérique dans les 48 heures suivant l'intervention ou d'au moins 50% dans les 7 jours suivants. L'analyze primaire (intention de traiter) examinera le risque relatif d'IRA chez les patients recevant de la colchicine par rapport au placebo. L'analyze primaire sera répétée 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 débit de filtration glomérulaire estimé (DFGe) inférieur à 60 mL/min/1.73 m^2 avant la répartition aléatoire.

Limites: Cette sous-étude ne sera pas assez puissante pour détecter de petits effets sur les formes plus graves d'insuffisance rénale aiguë traitées par dialyze.

Résultats: Les résultats de cette sous-étude feront l'objet d'un rapport en 2024.

Conclusion: Cette sous-étude permettra d'estimer l'effet de la colchicine sur le risque d'insuffisance rénale aiguë périopératoire chez les adultes âgés qui subissent une chirurgie thoracique majeure.

Numéro d'enregistrement de l'essai clinique: NCT03310125

Keywords

acute kidney injury, colchicine, noncardiac surgery

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What was known before

Inflammation during and after surgery associates with organ damage including acute kidney injury. Colchicine is an established inexpensive anti-inflammatory medication that is now being investigated for its ability to prevent perioperative events associated with inflammation during thoracic surgery.

What this adds

Our substudy of a multinational randomized clinical trial of approximately 3200 patients having major thoracic surgery will examine the effect of colchicine versus placebo on the risk of perioperative acute kidney injury.

Background

Colchicine is a natural alkaloid commonly used to treat inflammatory conditions including gout, pericarditis, Familial Mediterranean Fever, and coronary artery disease,[1-6] and it also prevents postpericardiotomy syndrome after cardiac surgery.[7,8] Colchicine inhibits leukocyte migration, interferes with kinin formation and beta-tubulin binding, and reduces the release of inflammatory cytokines.[6,9,10] Colchicine is now being investigated for its ability to prevent perioperative events associated with inflammation, including atrial fibrillation during thoracic surgery.[11-13] Thoracic surgery can induce a pro-inflammatory state caused by the acute stress of surgery and its associated mechanical tissue injury.[14-16]

A new trial, "Colchicine for the prevention of perioperative atrial fibrillation in patients undergoing thoracic surgery," is currently underway at 40 centers in 11 countries until 2023 (NCT03310125).[17] Colchicine for the prevention of perioperative atrial fibrillation is planning to enroll 3200 patients. Patients are randomly assigned to receive colchicine (0.5 mg) or placebo, twice daily starting 2 to 4 hours before surgery for a total of 10 days. The 2 co-primary outcomes are clinically significant perioperative atrial fibrillation and myocardial injury after noncardiac surgery (MINS) within 14 days of randomization. Outcome definitions are provided below.

A Kidney Substudy of Colchicine for the Prevention of Perioperative Atrial Fibrillation

This protocol describes a planned kidney substudy of COP-AF to determine the effect of colchicine versus placebo on the risk of perioperative acute kidney injury (AKI). Each year, 20 million patients globally have their kidneys injured during surgery, and 20 000 develop kidney failure.[18-21] Ischemia-reperfusion injury commonly occurs during surgery and triggers inflammation in the kidney that leads to an abrupt decline in kidney function (AKI),[22] but therapies to prevent this adverse outcome have remained elusive.[23] Well-powered clinical trials are needed to test interventions that show promise for mitigating AKI.[24] Through its multiple anti-inflammatory mechanisms, colchicine is an excellent candidate to prevent perioperative AKI (Figure 1), but this hypothesis needs to be tested. To date, long-term use of low-dose colchicine has not been shown to have a beneficial effect on kidney function.[39,40] Our substudy will examine the effect of low-dose colchicine on perioperative AKI. We hypothesize that colchicine will have a larger absolute benefit in patients with pre-existing chronic kidney disease (CKD), which is the most prominent risk factor for developing perioperative AKI.[41]

Main Questions in the Colchicine for the Prevention of Perioperative Atrial Fibrillation Kidney Substudy

Primary question. Does oral colchicine (0.5 mg twice daily for 10 days) versus placebo reduce the risk of perioperative AKI in patients having major thoracic surgery?

Secondary question. Does the presence of pre-existing CKD modify the effect of colchicine on the risk of perioperative AKI?

Methods

Overview of the Colchicine for the Prevention of Perioperative Atrial Fibrillation Main Trial

The COP-AF is a phase III randomized clinical trial scheduled to enroll 3200 patients undergoing major thoracic surgery (NCT03310125).[17] The COP-AF is funded by the Canadian Institutes of Health Research and is being coordinated by the Population Health Research Institute (Hamilton ON). Enrollment began in February 2018 and will continue until late 2023. Patients will be enrolled from 40 centers in 11 countries. All patients undergoing major thoracic surgery who meet the trial's eligibility criteria are considered for enrollment. Study personnel interview patients and obtain their consent before randomization, which occurs before surgery.

The primary objective of COP-AF is to determine whether colchicine versus placebo reduces the risk of clinically important perioperative atrial fibrillation or MINS within 14 days of randomization—atrial fibrillation will be considered clinically important if it results in angina, heart failure, symptomatic hypotension, or treatment with a rate-controlling drug, anti-arrhythmic drug, or electrical cardioversion. Myocardial injury after noncardiac surgery is a postoperative troponin elevation that is considered due to myocardial ischemia. Patients, health care providers, data collectors, and outcome adjudicators will be blinded to the treatment allocation.

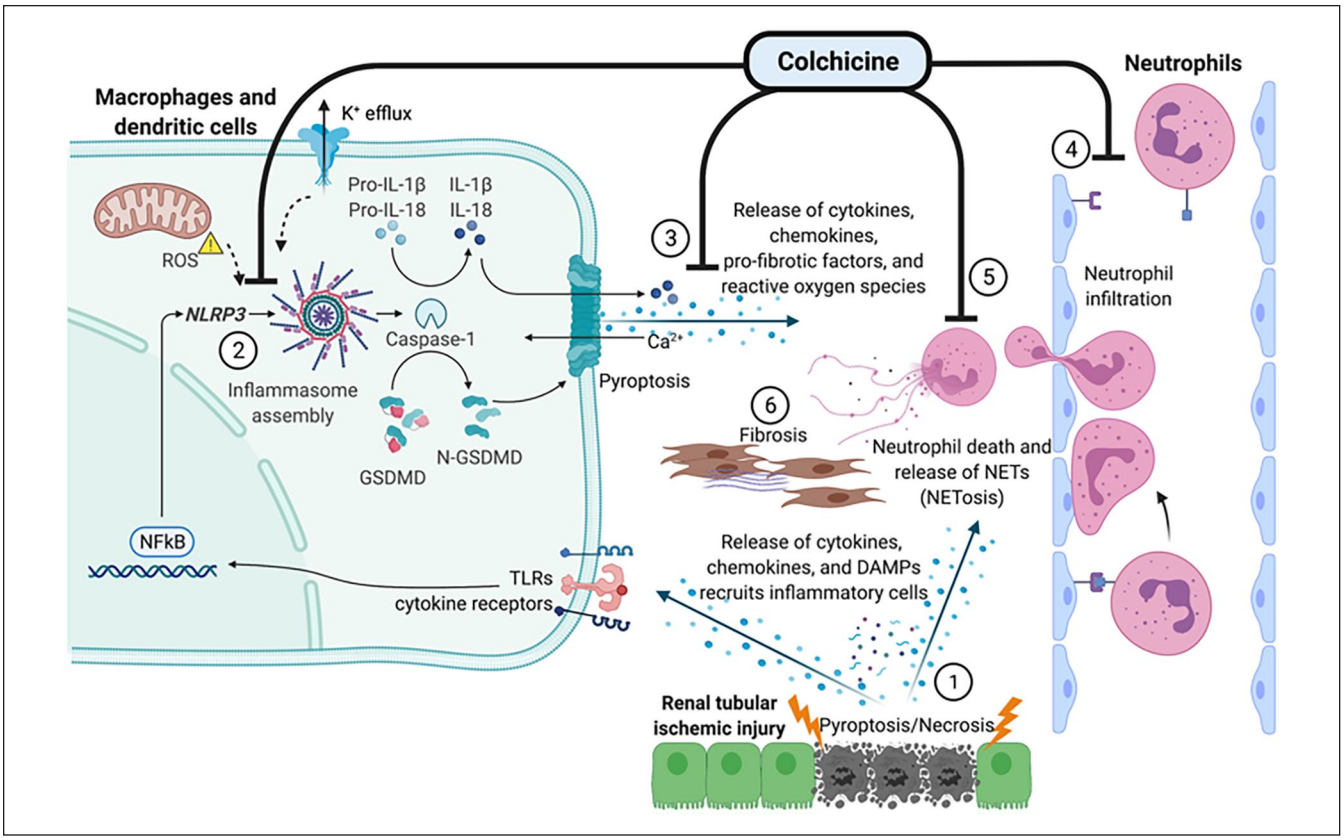

Figure 1. Mechanisms by which colchicine may prevent perioperative acute kidney injury.
Note. LRR = Leucine-rich repeat; NLRP3 = Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; NOD = Nucleotide-binding oligomerization domain. (1) Ischemia from perioperative hypotension results in necrosis/pyroptosis of renal tubular cells.[25] These dying cells release cytokines and damage-associated molecular patterns (DAMPs) that recruit inflammatory cells. Macrophages and dendritic cells signal NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) to assemble the NLRP3 inflammasome. (2) Given this first signal and a second signal from reactive oxygen species (ROS) and ion efflux, NLRP3 assembles the NLRP3 inflammasome, which leads to caspase 1-dependent maturation of the pro-inflammatory cytokines IL-1β and IL-18, as well as gasdermin D (GSDMD).[26-29] Activated GSDMD goes on to form pores in the macrophage cell membrane and initiate pyroptosis, a process by which the inflammatory cytokines are released and the macrophage may die. NLRP3 also exerts inflammasome-independent effects by mediating mitochondrial function and increasing ROS in kidney epithelial cells.[30,31] Colchicine inhibits the NLRP3 inflammasome as well as downstream interleukin maturation, pyroptosis, and neutrophil recruitment.[10] Colchicine may also inhibit the microtubule polymerization needed for inflammasome assembly. (3) Colchicine reduces cytokines, chemokines, and profibrotic factors not known to be related to the NLRP3 inflammasome.[32] (4) Colchicine decreases neutrophil infiltration of the kidneys by inhibiting adhesion molecules.[33] Blocking neutrophil infiltration can protect against ischemia-reperfusion injury and cisplatin-induced kidney injury.[34,35] (5) Colchicine inhibits neutrophil extracellular trap (NET) formation, which is a major mechanism by which neutrophils exert damage in inflammation.[36] (6) The inflammatory response to kidney injury stimulates fibrosis.[37] Colchicine has demonstrated antifibrotic effects in the kidney and may protect patients who experience acute kidney injury from developing a chronic decrement in kidney function.[38]

Participant Recruitment, Eligibility, and Informed Consent

Trial participants will be recruited through preoperative assessment clinics and by systematic screening of thoracic surgery lists. Eligible patients are those aged ≥55 years undergoing major, nonemergency thoracic surgery (elective or urgent) with general anesthesia and at least 1 overnight stay, no history of documented atrial fibrillation, not currently taking anti-arrhythmic medication, not undergoing minor thoracic interventions/procedures, a preoperative eGFR >30 mL/min per 1.73 m^2, and no contraindication to colchicine; the complete list of eligibility criteria for the COP-AF main trial are listed elsewhere (NCT03310125).[17] Study personnel will interview and obtain written, informed consent from patients before their planned surgery and before randomization.

Randomized Group Assignment

Enrolled patients are randomized on the day of surgery (before surgery). To ensure that allocation is concealed from participating centers and patients, randomization is done online via a central interactive web randomization system maintained by the coordinating center at the Population Health Research Institute. Patients are randomized 1:1 to

colchicine or placebo. Randomization is stratified by center with varying block sizes (study personnel who randomize patients do not know the block size). Patients, health care providers, data collectors, outcome adjudicators, and investigators are blinded to the treatment allocation.

Intervention

The first dose of oral colchicine (0.5 mg) or matching placebo is given after randomization, 2 to 4 hours before surgery. Pharmacokinetic data show that colchicine blood levels peak 1 to 2 hours after a single dose.[42] The second dose of 0.5 mg colchicine or matching placebo is given between 6:00 pm and 11:59 pm after surgery. Thereafter, all patients continue to receive colchicine (0.5 mg) or matching placebo twice daily for a total of 10 days. If the study medication is halted because of diarrhea, treatment is resumed upon resolution of diarrhea using 0.5 mg/day of colchicine or matching placebo during the remainder of the 10-day intervention period. Patients discharged home before completing the study medication are given a package containing colchicine 0.5 mg or placebo to complete 10 days of treatment. In the event, the surgery is postponed, and the patient continues to receive colchicine or placebo for 9 days after their surgery or until the end of follow-up 14 days after randomization, whichever occurs first.

Methods used in the colchicine for the prevention of perioperative atrial fibrillation kidney substudy. Key aspects of the COP-AF protocol that are relevant to the kidney substudy are described below.

Patient Selection

All patients enrolled in COP-AF will be included in the substudy once a study center initiates follow-up data collection of serum creatinine. We expect >95% of patients in the main trial to be included in the substudy.

Data Collection

Baseline, prerandomization serum creatinine. Patients have their serum creatinine tested during hospital admission as part of routine care. Patients in COP-AF also need a serum creatinine test within 6 weeks before randomization to assess trial eligibility. The most recent result available before randomization will serve as the baseline value.

Postoperative serum creatinine. 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 for all randomized patients. Centers will also receive funding to record all other serum creatinine measurements (and their dates) done as a part of routine care during the patient's hospital stay. This data collection schedule is informed by our experience in collecting kidney function data in our previous substudies,[43-47] and we expect to capture most AKI events with this schedule. In a prior study where we collected daily serum creatinine values in the first 5 days after surgery, 93% of perioperative AKI events occurred in the first 3 days.[48] A fixed collection schedule will also minimize biased ascertainment of AKI; for example, if the intervention altered the incidence of myocardial infarction or another event, it could influence the number of serum creatinine measurements done. At the time of the final analysis, we will compare the characteristics of patients who did and did not provide at least 1 serum creatinine measurement during the week following surgery, and examine the number of measurements by treatment group (and measurement dates) to confirm there is no differential outcome ascertainment between groups. No urine output data will be used in this substudy given difficulties with accurately measuring this variable outside of the intensive care unit.

Receipt of new dialysis for kidney failure will be recorded at hospital discharge and the final follow-up visit 14 days after surgery. We expect <1% of patients will die in the operating room or within 48 hours after surgery, which may result in no serum creatinine measurements.[45] Study personnel will contact patients who miss their 14-day surgical clinic follow-up visit by phone.

The start of follow-up in the substudy will be the date of randomization (we expect the median time from randomization to surgery to be <20 hours).[45,46] The trial end date will be the date the last randomized patient completes their final study visit on postoperative day 14.

Substudy Outcomes

The primary outcome of the COP-AF kidney substudy is perioperative AKI, 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.[49]

A total of 8 secondary outcomes (alternative definitions of AKI) will be examined to assess whether the primary results are robust:

1. 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).
2. Acute kidney injury (primary definition) for at least 2 days within 7 days of randomization.
3. 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 353.6

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 14 days of randomization.
4. 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 ≥353.6 μmol/L (≥4.0 mg/dL) within 7 days of randomization (when the primary outcome definition of AKI is met), or receipt of dialysis within 14 days of randomization.
5. Receipt of dialysis within 14 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.
8. Baseline-adjusted between-group difference in the absolute peak postoperative serum creatinine value.

Sample Size and Statistical Power for the Colchicine for the Prevention of Perioperative Atrial Fibrillation Kidney Substudy

Colchicine for the prevention of perioperative atrial fibrillation is scheduled to enroll 3200 patients, and we expect >95% of these patients to be eligible for inclusion in the kidney substudy. A sample size of 3000 patients will provide 85% power to detect a 25% relative risk (RR) reduction for the primary outcome of perioperative AKI (2-sided $\alpha = 0.05$), comparing the intervention and placebo groups, assuming an incidence of AKI of 15% in the placebo group and a minimal amount of missing data (<1% missing data due to death and <1% missing data due to loss to follow-up).[44,46] In previous studies, the incidence of AKI in patients undergoing thoracic surgery has ranged from 5% to 40%, depending on surgery type and AKI definition.[18,46,50,51]

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 the primary outcome of perioperative AKI comparing the intervention group to the control group (ie, colchicine versus placebo).[52,53] Missing data on postoperative serum creatinine, expected for <1% of surviving patients,[44,46] will be imputed using fully conditional specification multiple imputation with 100 imputed datasets; parameters and standard errors will be estimated using standard methods allowing for extra imputation variability.[54,55] A 2-tailed P value $< .05$ will be considered statistically significant.

Prespecified supporting analyses. We will examine 8 secondary outcomes (alternative definitions of AKI) and conduct the following supporting analyses to determine whether there is concordance with the primary analysis. We will also conduct a subgroup analysis of patients with preoperative CKD.

Complete-case analysis. We will perform a complete-case analysis restricted to centers with >90% completed measurements and patients with at least 1 postrandomization serum creatinine measurement (expected to be 99% of patients in the primary analysis).

Fully adjusted analyses. In our experience with previous kidney substudies, the unadjusted and adjusted results were virtually identical[45,56]; nonetheless, to potentially increase the precision of our estimates, we will use a generalized estimating equation approach for binary outcome data, accounting for within-center correlation, adjusting for the following prespecified covariates (measured before randomization) based on their known association with AKI: 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 before surgery, and age × prerandomization eGFR.[57] Adjusted RRs and 95% CIs will be reported. We expect missing data on these variables to be <0.5%.[45] Fully conditional specification multiple imputation will be used to impute missing covariate and outcome data, and parameters and standard errors will be estimated using standard methods allowing for extra imputation variability.[54,55]

Alternative definitions of acute kidney injury. We will examine 8 alternative definitions of AKI (5 categorical and 3 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 (P values will not be reported). Despite the large sample size, supplementary analyses of severe AKI will have limited statistical power for small effects.

Subgroup analysis. Pre-existing CKD is one of the strongest risk factors for developing perioperative AKI.[58-60] Patients with CKD are particularly vulnerable to superimposed renal sequelae due to vascular insufficiency, maladaptive repair mechanisms, and reduced nephron number.[41] In a post hoc analysis of the Dexamethasone for Cardiac Surgery randomized clinical trial, intraoperative dexamethasone (a glucocorticoid) versus placebo significantly reduced the risk of

in-hospital dialysis; however, this event occurred only in patients with pre-existing CKD.[61] For these reasons, we hypothesize that colchicine may confer a larger absolute benefit to patients with pre-existing CKD (defined by a prerandomization eGFR <60 mL/min per 1.73 m^2).[62] To examine the presence of additive interaction, we will calculate the absolute risk difference (and 95% CI) between intervention groups in each subgroup; a *P* value for the interaction term will be obtained from a logistic regression model. We will also conduct a test for interaction between eGFR and intervention group, where eGFR is a continuous variable modeled with restricted cubic splines to allow for nonlinearity.

Additional analyses. We will examine the between-group difference in adherence as the percentage of patients who received the randomly allocated treatment as intended during the hospital stay. We will conduct a per-protocol analysis of the primary and secondary outcomes using this definition and examine concordance with the intention-to-treat analyses. Finally, we expect $<1\%$ of randomized patients will have delayed surgery (eg, >24 hours after randomization) or not undergo surgery. We will examine concordance with the primary intention-to-treat analysis when we exclude patients who did not undergo surgery within 24 hours after randomization.

Recognized Limitations

The primary outcome of this kidney substudy is perioperative AKI, defined as an acute rise in serum creatinine concentration from prerandomization values.[49] While virtually all prevention trials of AKI follow this definition, this outcome is a surrogate endpoint that may not directly impact how a patient feels, functions, or survives. Unfortunately, data on long-term kidney function will not be available for most patients enrolled in COP-AF (except in regions where linkage to administrative health care databases is possible). However, even small decreases in kidney function after surgery are associated with poor short- and long-term outcomes,[18,63] and our definition of AKI follows international clinical practice guidelines.[49] We will also examine whether intervention effects are consistent for stage 2 and 3 AKI; despite being less frequent, these events are more relevant to patients and health care providers.

Conclusions

Acute kidney injury is a common and serious complication of surgery. The COP-AF trial will provide strong evidence on whether colchicine can mitigate this outcome in patients undergoing major thoracic surgery. Conducting this substudy with a sample size of >3000 patients from more than 40 centers in 11 countries with the use of randomized trial methodology will help generate results that are accurate, precise, and generalizable.

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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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.

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