**Effect of colchicine on perioperative atrial fibrillation and myocardial injury after noncardiac surgery in patients undergoing major thoracic surgery – the COP-AF randomised controlled trial**

David Conen MD,1,2,3 Michael Ke Wang MD,1,2 Ekaterine Popova MD,4,5 Prof Matthew TV Chan PhD,6 Prof Giovanni Landoni MD,7,8 Juan P. Cata MD,9 Cara Reimer MD,10 Sean R. McLean MD,11 Sadeesh K. Srinathan MD,12 Juan Carlos Trujillo Reyes PhD,13 Ascension Martín Grande MD,14 Anna Gonzalez Tallada MD,15 Prof Daniel I. Sessler MD,16 Edith Fleischmann MD,17 Barbara Kabon MD,17 Luca Voltolini PhD,18 P. Cruz PhD,19 Prof Donna E. Maziak MDCM,20 Prof Laura Gutiérrez-Soriano MD,21 William F. McIntyre MD,1,2,3 Vikas Tandon MD,2 Elisabeth Martínez-Téllez MD,13 Juan Jose Guerra-Londono MD,9 Deborah DuMerton RN,22 Prof Randolph HL Wong MD,23 Anna L. McGuire MD,24 Biniam Kidane MD,12 Diego Parise Roux MD,14 Prof Yaron Shargall MD,25 Jennifer R. Wells MSc,1 Sandra N. Ofori MBBS,1,2 Jessica Vincent MSc,1 Lizhen Xu PhD,1,2 Zhuoru Li MSc,1 Prof John W. Eikelboom MBBS,1,2 Prof Sanjit S. Jolly MD,1,2,3 Prof Jeff S. Healey MD,1,2 Prof PJ Devereaux MD;1,2,3 on behalf of the COP-AF Investigators\*

1. Population Health Research Institute, Hamilton, ON, Canada
2. Department of Medicine, McMaster University, Hamilton, ON, Canada
3. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
4. IIB SANT PAU, Institut d’Investigació Biomèdica Sant Pau, Barcelona, Spain
5. Centro Cochrane Iberoamericano, Barcelona, Spain
6. The Chinese University of Hong Kong, Shatin, Hong Kong Special Administrative Region, China
7. Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
8. School of Medicine, Vita-Salute University San Raffaele, Milan, Italy
9. Department of Anesthesiology and Perioperative Medicine, The University of Texas – MD Anderson Cancer Center, Houston, TX, United States
10. Department of Anesthesiology, Queen's University, Kingston Health Sciences Centre, Kingston, ON, Canada
11. Vancouver Acute Department of Anesthesia and Perioperative Medicine, Vancouver General Hospital, Vancouver, BC, Canada
12. Department of Surgery, University of Manitoba, Winnipeg, MB, Canada
13. Department of Thoracic Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
14. Hospital Universitario Ramón y Cajal, Madrid, Spain
15. Department of Anesthesiology, Vall d'Hebron Hospital Universitari, Spain
16. Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, United States
17. Department of Anesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria
18. Thoracic Surgery Unit, University Hospital Careggi, Florence, Italy
19. Service of Anesthesiology and Reanimation, General University Hospital Gregorio Marañón, Madrid, Spain
20. University of Ottawa, The Ottawa Hospital, Dept of Surgery, Division of Thoracic Surgery, Ottawa, ON, Canada
21. Anesthesiology Department, Anesthesiology Research Group, Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, Colombia
22. Kingston Health Sciences Centre, Kingston, ON, Canada
23. Division of Cardiothoracic Surgery, Department of Surgery, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
24. Division of Thoracic Surgery, Vancouver General Hospital, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada
25. Division of Thoracic Surgery, Department of Surgery, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

\* Names of all COP-AF investigators are listed in the supplementary appendix

Short title: Colchicine for the prevention of perioperative AF and MINS

Address for correspondence:

David Conen

Population Health Research Institute

237 Barton Street East

Hamilton Ontario, Canada

Phone: +1 905 522-1155

Email: [David.conen@phri.ca](mailto:David.conen@phri.ca)

**Research in context**

Evidence before the study

Perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS) are common complications after noncardiac thoracic surgery, and affected patients have a worse prognosis. Higher levels of inflammatory biomarkers are associated with both entities. Colchicine is an anti-inflammatory drug that lowered the incidence of perioperative AF after cardiac surgery in several small randomised trials. Two large randomised trials demonstrated that low-dose colchicine compared to placebo reduced the incidence of major adverse cardiovascular events (MACE) in patients with stable coronary artery disease (LoDoCo2; 5522 patients; 6·8% versus 9·6%; hazard ratio [HR] 0·69; 95% confidence interval [CI], 0·57-0·83), and in those recruited within 30 days after an acute myocardial infarction (MI) (COLCOT; 4745 patients; 5·5% versus 7·1%; HR 0·77; 95% CI, 0·61-0·96). We did a systematic search of MEDLINE, EMBASE and CENTRAL for randomised trials using colchicine to prevent adverse cardiovascular events in patients undergoing noncardiac surgery. With the exception of our COP-AF pilot trial, we did not identify any study.

Added value of this study

COP-AF is the largest randomised trial to assess the efficacy and safety of colchicine 0·5mg twice daily in patients undergoing major noncardiac thoracic surgery to date. Colchicine did not significantly reduce the incidence of clinically important perioperative AF or MINS. Colchicine did, however, reduce the post-hoc composite of clinically important perioperative AF or MINS, and the composite of vascular death, nonfatal MINS, nonfatal stroke, and clinically important perioperative AF. Colchicine increased the risk of non-infectious diarrhoea, but not the composite of sepsis or infection.

Implications of all the available evidence

While colchicine did not significantly reduce the incidence of perioperative AF or MINS individually, it did have a beneficial effect on the composite of the two co-primary outcomes. These potential benefits associated with colchicine are in line with previous studies in patients with coronary artery disease. Future trials should further investigate the role of colchicine in the prevention of adverse cardiovascular outcomes in patients undergoing surgery.

**Abstract**

Background

Higher levels of inflammatory biomarkers are associated with an increased risk of perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS). Colchicine is an anti-inflammatory drug that may prevent these complications.

Methods

We performed an international, randomised trial at 45 sites in 11 countries. Patients aged ≥55 years and undergoing major noncardiac thoracic surgery were randomised to receive oral colchicine 0·5mg twice daily or matching placebo, starting within four hours before surgery and continuing for ten days. Healthcare providers, patients, data collectors, and adjudicators were blinded to treatment assignment. The co-primary outcomes were clinically important perioperative AF and MINS during 14 days of follow-up. This trial is registered at ClinicalTrials.gov (NCT03310125).

Findings

We enrolled 3209 patients between February 14, 2018, and June 27, 2023. Clinically important AF developed in 103 of 1608 (6·4%) patients assigned to colchicine, and 120 of 1601 (7·5%) patients assigned to placebo, hazard ratio (HR) 0·85 (95% confidence interval [CI] 0·65-1·10), absolute risk reduction (ARR) 1·1%, 95% CI -0·7-2·8, p=0.22. MINS occurred in 295 (18·3%) patients assigned to colchicine, and 325 (20·3%) patients assigned to placebo, HR 0·89 (95% CI 0·76-1·05), ARR 2·0%, 95% CI -0·8-4·7, p=0.16. Non-infectious diarrhoea was more common in the colchicine group, 134 (8·3%) versus 38 (2·4%) events, HR 3·64 (95% CI 2·54-5·22), but did not prolong median length of hospital stay and led to only one readmission..

Interpretation

In patients undergoing major noncardiac thoracic surgery, administration of colchicine did not significantly reduce the incidence of the co-primary outcomes clinically important AF or MINS. While colchicine increased the risk of mostly benign non-infectious diarrhoea, there was an encouraging trend of fewer cardiovascular events with colchicine that requires further research.

Funding

Canadian Institutes of Health Research, Accelerating Clinical Trials Consortium, and others.

**Keywords**

Colchicine; inflammation; thoracic surgery; atrial fibrillation; myocardial injury; prevention

**Introduction**

Colchicine is an inexpensive drug with anti-inflammatory effects. 1-3 Its efficacy has been demonstrated in multiple inflammatory diseases, such as gout, pericarditis, and Familial Mediterranean Fever. 4-6 Small randomised trials suggest that in patients undergoing cardiac surgery, low-dose colchicine reduces the risk of the post-pericardiotomy syndrome and perioperative atrial fibrillation (AF). 7-9 Two large randomised trials, Low Dose Colchicine 2 (LoDoCo2) and Colchicine Cardiovascular Outcomes Trial (COLCOT), found that low-dose colchicine significantly reduced the incidence of major cardiovascular outcomes in patients with coronary artery disease. 10,11

Higher levels of inflammatory biomarkers have been associated with an increased risk of perioperative AF and myocardial injury after noncardiac surgery (MINS), 12-14 two cardiovascular complications commonly occurring after noncardiac thoracic surgery. 15,16 Whether anti-inflammatory treatment effectively reduces the incidence of these two complications is currently unclear. Given the poor prognosis of patients with perioperative AF and MINS, 17,18 preventing these complications is an important unmet clinical need.

We performed the ‘Colchicine for the prevention of perioperative atrial fibrillation’ (COP-AF) trial to evaluate the effect of low-dose colchicine on the occurrence of perioperative AF and MINS after major noncardiac thoracic surgery.

**Methods**

Study design

COP-AF was an investigator-initiated, randomised, placebo-controlled, clinical trial performed at 45 sites across 11 countries. Details of the study design and methodology were published previously. 19 The trial was approved by local ethics committees and regulatory authorities in participating jurisdictions. All patients provided written informed consent before enrolment in COP-AF.

Patients

Eligible patients were ≥55 years old, scheduled for noncardiac thoracic surgery with general anaesthesia, and were expected to require at least one overnight hospital stay after surgery. We excluded patients fulfilling any of the following criteria: history of documented AF; patients currently taking anti-arrhythmic medication other than β-blockers, calcium channels blockers, or digoxin; patients undergoing minor thoracic interventions; patients with contraindications to colchicine (e.g., severe renal dysfunction); patients not expected to take oral medications for >24 hours after surgery; patients scheduled for lung transplantation; patients currently taking non-study colchicine; patients with severe hepatic dysfunction; patients who took clarithromycin, erythromycin, telithromycin, cyclosporine, ketoconazole, or itraconazole in the preceding 14 days; or patients currently treated with antiretroviral medications against the human immunodeficiency virus.

Randomisation and masking

Eligible patients who provided written informed consent were randomised in a 1:1 ratio to colchicine 0·5mg twice daily or matching placebo. Patients, healthcare providers, data collectors, data managers, and outcome adjudicators were blinded to study drug allocation. We used a central, computerised, web-based, randomisation system to allocate patients to colchicine or placebo. Randomisation was stratified by centre with variable block sizes unknown to study personnel.

Procedures

The first 0·5mg dose of oral colchicine or matching placebo was administered within 4 hours before the start of surgery. This timing was chosen to increase trial feasibility, as most patients are admitted on the day of surgery, and longer pre-treatment would have created major logistical challenges. Previous colchicine studies suggested rapid onset of action, 20 and pre-treatment for 2-3 days before cardiac surgery was not more effective in preventing perioperative AF and the post-pericardiotomy syndrome compared with initiating colchicine after cardiac surgery 7,21 supporting the decision to initiate study treatment on the day of surgery. Thereafter all patients received their assigned treatment twice daily for a total of ten days. Twice daily dosing was chosen to counteract the substantial inflammatory response after thoracic surgery, 22 and because several prior studies assessing the efficacy and safety of colchicine for the prevention of perioperative AF (including the COP-AF pilot study) used twice daily dosing. 7,23 A 10-day treatment period was selected because previous studies showed that most perioperative AF and MINS events occur in the first ten days after surgery. 18,23,24

Study personnel followed patients daily until discharge. Daily cardiac troponin levels were obtained during the first three postoperative days. The duration and type of rhythm monitoring was conducted as per routine practices at each site, but the protocol strongly recommended daily electrocardiograms on the first three postoperative days as long as the patients was still admitted, or whenever a patient reported symptoms potentially caused by AF. The final follow-up visit occurred 14 days after randomisation, where no electrocardiogram was required.

Outcomes

The first co-primary outcome was clinically important perioperative AF, defined as AF or atrial flutter that results in angina, heart failure, or symptomatic hypotension, or that requires treatment with a rate-controlling drug, antiarrhythmic drug, or electrical cardioversion. This outcome definition was chosen because of its prognostic relevance, 17 and to avoid adding short asymptomatic AF episodes of unknown clinical relevance to the primary outcome. The second co-primary outcome was MINS, defined as myocardial infarction (MI), or an elevated postoperative troponin judged to be due to myocardial ischemia. Secondary outcomes were 1) a composite of all-cause mortality, nonfatal MINS, or nonfatal stroke; 2) a composite of all-cause mortality, nonfatal MI, or nonfatal stroke; 3) MINS not fulfilling the fourth universal definition of MI; 4) MI; 5) time to chest tube removal; and 6) length of stay in hospital, in intensive care unit, and in step-down unit. Tertiary outcomes were 1) all-cause mortality; 2) venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism); 3) acute heart failure; 4) number of days alive and at home; and 5) a composite of life-threatening or major bleeding. The main safety outcomes were 1) a composite of sepsis or infection; and 2) non-infectious diarrhoea. Post-hoc analyses assessed 1) a composite of clinically important perioperative AF or MINS; 2) a composite of vascular mortality, nonfatal MINS, nonfatal stroke, or clinically important perioperative AF; 3) stroke; 4) all reported perioperative AF events whether or not they fulfilled the criteria for clinically important AF; and 5) infection and sepsis separately.

Definitions for all outcome events are provided in the appendix. Trained physicians formed the adjudication committee and adjudicated all reported events related to perioperative AF, MINS, MI, and stroke. All unrefuted events were included in the statistical analyses.

Statistical analysis

COP-AF was initially designed to recruit 2800 patients to evaluate clinically important perioperative AF as the only primary outcome. In 2022, following the publication of LoDoCo2 and COLCOT, 10,11 the Steering Committee decided to add MINS as an independent co-primary outcome, as troponin levels had been systematically obtained in all COP-AF patients for the entire duration of the trial. This decision was made without knowledge of any unblinded trial results. To have sufficient power for both co-primary outcomes, a sample size of 3200 patients was needed. We assumed an overall incidence of perioperative AF of 9·0%, a permanent discontinuation rate of 10·5% in the first week of follow-up and 2·7% in the second week, a relative risk reduction of 30%, and a 2-sided alpha of 0·0324, such that 3200 patients provided 83% power for the first co-primary outcome. Assuming an incidence of MINS of 22%, a 20% relative risk reduction in the colchicine group, a 2-sided alpha of 0·0176, and a permanent discontinuation rate of 10·5% in week 1 and 2·7% in week 2, 3200 patients provided 80% power for the co-primary outcome of MINS.

A data and safety monitoring committee performed two interim efficacy analyses for the original primary outcome of clinically important perioperative AF, when 50% and 75% of the original 14-day data were available. The committee followed a modified Haybittle-Peto rule of four standard deviations (SD) (α = 0·000067) when 50% of the data were analysed, and three SDs (α = 0·0027) for analyses when 75% of the data were available.

Unless stated otherwise, all statistical analyses followed a statistical analysis plan that was finalised before the completion of the trial and before unblinding. We used the intention-to-treat principle for all analyses. Patients lost to follow-up without an outcome of interest were censored on their last day of available contact.

For the two co-primary outcomes, we plotted cumulative incidence curves between the two treatment groups and compared them using log-rank tests. Cox proportional-hazards models with treatment group as an independent variable were used to obtain hazard ratios (HRs), 95% confidence intervals (CIs) and p values. We used the fallback procedure to address the issue of multiplicity, 25 and partitioned the total alpha of 0·05 among the two co-primary outcomes, with α=0·0324 for the first co-primary outcome and an overlap adjusted α=0·018 for the second co-primary outcome. If the first co-primary outcome was significant at α=0·0324, then this alpha would be unused and passed to the second co-primary outcome, which would then be evaluated at α=0·05. If the first co-primary outcome was not significant, the second co-primary would be assessed at α=0·018.

All secondary, tertiary, safety, and post-hoc outcomes with an event date were evaluated using Cox proportional-hazards models. For length of stay, we used a Wilcoxon rank sum test, and number of days alive and at home was compared with quantile regression. Given the small number of events, the stroke incidence was compared using the Fisher exact test.

For each co-primary outcome, we performed prespecified subgroup analyses according to age (<65 versus ≥65 years), type of surgical incision (non-thoracoscopic versus thoracoscopic) and renal function (creatinine clearance <45, 45-60, and ≥60ml/min). We expected a stronger colchicine effect in older patients, in those undergoing non-thoracoscopic surgery, and in those with worse renal function. We also performed a post-hoc subgroup analysis according to sex. We included a treatment by subgroup interaction term in the non-stratified Cox models to formally test for a subgroup effect, and used α<0·05 for statistical significance.

All analyses were performed in SAS, version 9·4 (SAS Institute, Inc., Cary, NC). This trial was registered with ClinicalTrials.gov (NCT03310125).

Role of the funding source

The funders of this trial had no role in the trial design; the collection, analysis, and interpretation of data; the writing of the report; or in the decision to submit the paper for publication.

**Results**

Between February 14, 2018, and June 27, 2023, we screened 15,368 patients, of which 7969 were eligible for COP-AF. Of these, 3209 patients provided informed consent and were randomised to receive colchicine (n=1608) or matching placebo (n=1601) (Figure 1). One patient declined further follow-up before the final visit, such that follow-up was >99·9% complete.

Baseline characteristics are shown in Table 1. Mean (SD) age of the participants was 68 (7) years, 1656 (51·6%) were male, 687 (21·4%) were current smokers, 595 (18·5%) had a history of diabetes, and 1668 (52·0%) had a history of hypertension. The most common procedures were pulmonary resections, including lobe resections (n=2041, 63·6%), wedge resections (n=651, 20·3%), and segment resections (n=487, 15·2%). 2981 (92·9%) of all patients had surgery for confirmed or presumed malignancy, and 2397 (74·7%) of surgeries used a thoracoscopic approach. The pericardium was resected in 47 (1·5%) patients.

At least one dose of study drug was administered to 3174 (98·9%) patients. During follow-up, 474 (14·9%) patients permanently discontinued study medication, 272 (16·9%) in the colchicine group, and 202 (12·6%) in the placebo group. Median time to study drug discontinuation was 5 days (interquartile range [IQR] 3-7 days) in the colchicine group and 4 days (IQR 2-7 days) in the placebo group. By day 5, 180 of 203 (81%) clinically important perioperative AF events and 606 of 620 (98%) MINS events had already occurred. The most common reasons for study drug discontinuation were non-infectious diarrhoea (79 patients [29·0%] in the colchicine group versus 18 [8·9%] in the placebo group) and patient refusal to continue study drug (73 patients [26·8%] versus 85 patients [42·1%]).

The number of patients who had at least one electrocardiogram on postoperative days 1, 2, and 3 was 2619 (81·6%), 2103 (65·5%) and 1585 (49·4%), respectively, and 2775 (86·5%) patients had at least one ECG, with no differences by treatment group. Clinically important perioperative AF occurred in 103 (6·4%) patients in the colchicine group and 120 (7·5%) patients in the placebo group, HR 0·85 (95% CI 0·65-1·10), absolute risk reduction (ARR) 1·1%, 95% CI -0·7-2·8, p=0·22 (Table 2, Figure 2). MINS was diagnosed in 295 (18·3%) patients in the colchicine group, and 325 (20·3%) patients in the placebo group, HR 0·89 (95% CI 0·76-1·05), ARR 2·0%, 95% CI -0·8-4·7, p=0·16.

Directionally consistent but non-significant effects were observed for the key secondary outcomes, including the composite outcome of all-cause mortality, nonfatal MINS, and nonfatal stroke, HR 0·88, 95% CI 0·75-1·03; the composite of all-cause mortality, nonfatal MI, and nonfatal stroke, HR 0·67 (95% CI 0·39-1·17); MINS not fulfilling the fourth universal definition of MI, HR 0·90, 95% CI 0·76-1·06); and MI, HR 0·86, 95% CI 0·41-1·81 (Table 2). Colchicine had no significant effect on time to chest tube removal or length of stay.

We report the results from several post-hoc analyses. The composite outcome of clinically important perioperative AF or MINS occurred in 360 (22·4%) patients in the colchicine group and in 415 (25·9%) patients in the placebo group, HR 0·84 (95% CI 0·73-0·97). The composite outcome of vascular mortality, nonfatal MINS, nonfatal stroke or clinically important perioperative AF occurred in 364 (22·6%) patients in the colchicine group versus 422 (26·4%) in the placebo group, HR 0·83 (95% CI, 0·72-0·96). Six patients had a stroke, 1 (0·1%) in the colchicine group and 5 (0·3%) in the placebo group (p=0.12). There was a total of 248 (7·7%) AF events, 116 (7·2%) in the colchicine group and 132 (8·2%) in the placebo group, HR 0·87 (95% CI 0·67-1·11).

The HRs of colchicine for the tertiary outcomes were 0·63 (95% CI 0·25-1·63) for all-cause mortality, 2·50 (95% CI 0·97-6·44) for venous thromboembolism, 0·88 (95% CI 0·59-1·31) for the composite of life-threatening or major bleeding, and not estimable for acute heart failure, as shown in Table 2. Colchicine had no significant effect on number of days alive and at home.

The composite outcome of sepsis or infection occurred in 103 (6·4%) patients in the colchicine group and 83 (5·2%) patients in the placebo group, HR 1·24 (95% CI 0·93-1·66). In a post-hoc analysis, the HR was 1·55 (95% CI 0·67-3·58) for sepsis, and it was 1·19 (95% CI 0·87-1·61) for infection. Colchicine increased the incidence of non-infectious diarrhoea, 134 (8·3%) versus 38 (2·4%) patients, HR 3·64 (95% CI 2·54-5·22). No treatment was required in 66 (38·4%) cases of diarrhoea, only 15 (8·7%) patients needed intravenous hydration, 2 (1·2%) received antibiotics, and 1 (0·7%) patient required readmission for diarrhoea. The median (IQR) duration of diarrhoea was 3 (2-4) days in the colchicine group versus 3 (2-4) days in the placebo group. Study treatment was interrupted for at least two doses in 94 (72·3%) patients with diarrhoea in the colchicine group and 22 (62·9%) patients in the placebo group. In the colchicine group, the median (IQR) length of stay was 5 (4-7) days in patients with diarrhoea and 5 (3-7) days in those without diarrhoea.

Results from prespecified subgroup analyses for both co-primary outcomes are shown in Figure 3. We found no evidence of effect modification according to age or renal function for both co-primary outcomes. With regard to the type of surgical incision, there were statistically significant interactions for both co-primary outcomes. Colchicine demonstrated a reduced risk of clinically important perioperative AF in patients undergoing thoracoscopic surgery (n=2397; HR 0·53, 95% CI 0·36-0·77), whereas it increased the risk in patients having open surgery (n=784; HR 1·59, 95% CI 1·07-2·35) (p for interaction <0·0001). Colchicine had a beneficial effect on the incidence of MINS among patients having thoracoscopic surgery (n=2397; HR 0·80, 95% CI 0·66-0·98) but no effect among patients having open surgery (n=784; HR 1·15, 95% CI 0·87-1·53) (p for interaction 0·04). The results of the post-hoc subgroup analyses according to sex are shown in the Supplementary Table.

**Discussion**

A 10-day course of colchicine 0·5mg twice daily did not significantly reduce the risk of the co-primary outcomes clinically important perioperative AF and MINS. In post-hoc analyses, colchicine demonstrated a significant reduction in the composite of clinically important perioperative AF and MINS, HR 0·84 (95% CI 0·73-0·97), and the composite of vascular mortality, nonfatal MINS, nonfatal stroke, or clinically important perioperative AF, HR 0·83 (95% CI, 0·72-0·96). Colchicine had no effect on the risk of sepsis or infection, but increased the incidence of non-infectious diarrhoea, HR 3·64 (95% CI 2·54-5·22).

Our demonstrated HR for clinically important perioperative AF was consistent with prior findings from LoDoCo2 and COLCOT, where the HRs for AF were 0·84 (95% CI 0·66-1·07) and 0·93 (95% CI 0·59-1·46), respectively. 10,11 The event rate in our trial was lower than anticipated, and we may have missed a small to moderate but clinically important effect of colchicine. Looking at all AF events slightly increased the number of outcome events, but the colchicine effect size remained similar. Continuous rhythm monitoring would most likely have further increased the number of AF events detected but it is unlikely it would have increased the identification of clinically important perioperative AF. In addition, the clinical relevance of short subclinical AF events is currently unclear. 26

Our results seem to differ from randomised trials in cardiac surgery patients. In a meta-analysis of eight randomised trials including 1885 patients, the relative risk for colchicine to reduce perioperative AF was 0·70, 95% CI 0·59-0·82. 9 Several potential explanations may explain the observed difference in these results with COP-AF including the following: 1. it is possible that perioperative AF after cardiac surgery is more strongly associated with inflammation than AF after thoracic surgery; 2. publication bias in the cardiac surgery trials remains a concern given the small size of the included trials; and 3. the overlap in the CIs for the treatment effects across the cardiac surgery meta-analysis and COP-AF results suggests that colchicine may have a similar moderate effect size in reducing the risk of clinically important AF in both settings.

We found a significant reduction in perioperative AF events with colchicine in patients undergoing thoracoscopic surgery, but an increased risk of AF in patients undergoing open surgery (p for interaction <0·0001). The observed effect modification was inconsistent with our a priori hypothesis that colchicine would be more beneficial in patients undergoing open surgery. However, it is possible that the stronger inflammatory response after open surgery is not effectively counteracted by colchicine, or inflammation-induced AF cases may be more common after thoracoscopic surgery compared to open thoracic surgery. Both hypotheses would not explain a potentially harmful effect of colchicine in open thoracic surgery.

Colchicine significantly reduced two post-hoc vascular composite outcomes. Directionally consistent but non-significant effects were observed for other ischemia-related outcomes, including MINS, the composite of all-cause mortality, nonfatal MINS or nonfatal stroke, the composite of all-cause mortality, nonfatal MI or nonfatal stroke, as well as MI and stroke. These results are also in line with randomised trials showing a significant reduction of major adverse cardiovascular events in patients with coronary artery disease. 10,11 It is therefore possible that colchicine prevents cardiovascular events after major noncardiac thoracic surgery.

The effect of colchicine on MINS was stronger among patients undergoing thoracoscopic surgery, again raising the possibility that troponin elevations in less invasive surgeries are more frequently caused by inflammation rather than direct surgical manipulation. The observed effect modification was inconsistent with our a priori hypothesis that colchicine would be more beneficial in patients undergoing open surgery.

Colchicine did not shorten the time to chest tube removal or reduce length of stay. In the COP-AF pilot study colchicine reduced the total amount of fluid drained at different time points, suggesting that the colchicine dose used in COP-AF reduces pleural inflammation. 27 The lack of effect on time to chest tube removal likely reflects the fact that other mechanisms are more important drivers of this outcome after thoracic surgery (e.g., air leaks).

The risk of sepsis or infection was similar in the two groups. The risk of non-infectious diarrhoea was significantly higher in patients receiving colchicine, with an absolute risk increase of 5·9%. Our data suggest that colchicine induced diarrhoea was temporary, rarely needed intravenous treatments, and did not prolong hospitalisation. These findings are similar to LoDoCo2, where colchicine once daily did not increase the risk of hospitalisations for gastrointestinal reasons. 10 The incidence of diarrhoea was not reported in LoDoCo2. In COLCOT, the incidence of nausea and flatulence but not diarrhoea was increased among patients receiving colchicine. 11

There was a non-significant increased risk of venous thromboembolism among patients receiving colchicine. One previous trial reported a similar trend, 28 but no increased risk of venous thromboembolism was found in other large colchicine trials. 10,11,29 As the number of venous events in all of these trials was small and there is no good mechanistic explanation, we consider chance – as suggested by the 95% CI – to be the most likely explanation for this finding. In order to further explore this outcome, it will be informative to collect and report detailed information about venous thromboembolism in future colchicine trials.

COP-AF is the largest randomised trial of perioperative colchicine administration conducted to date. The adherence to the study medication was excellent and complete follow-up was available in all but 1 (>99·9%) participants. Almost 50% of participants were female, and the trial was conducted in 11 countries on four continents, such that our findings should be widely generalisable to patients undergoing major noncardiac thoracic surgery. The event rate of clinically important perioperative AF was lower than anticipated, and our trial may have missed a small to moderate but clinically important effect of colchicine on this outcome. Continuous monitoring was not systematically used in COP-AF, because our trial focussed on clinically important perioperative AF. While this strategy is consistent with usual clinical practice, we may have missed some asymptomatic AF episodes of potential clinical relevance. The significant interactions for larger effects in patients having thoracoscopic surgery for both co-primary outcomes are hypothesis generating, and should ideally be confirmed in future trials. The incidence of some events (e.g., stroke, MI) was low, and their exact effect sizes will need to be determined in future studies.

In patients undergoing major noncardiac thoracic surgery, a 10-day course of colchicine did not reduce the risk of clinically important perioperative AF or MINS compared with placebo. Colchicine did increase the risk of non-infectious diarrhoea, which seems to be temporary and benign. Despite these findings, several results provide an encouraging signal of potential benefit for colchicine in these patients. Further trials are warranted of colchicine in patients undergoing noncardiac surgery.

**Contributors**

DC, EP, MTVC, GL, SKS, DIS, EF, JWE, SSJ, JSH and PJD contributed to the design of the study. DC, MKW, EP, MTVC, GL, JPC, CR, SRM, SKS, JCTR, AMG, AGT, BK, LV, PC, DEM, LGS, WFM, VT, EMT, JJGL, DD, RHLW, ALM, BK, DPR, YS, JRW, SNO, JV, and PJD contributed to data collection. LX and ZL did the data analyses. All authors contributed to the interpretation of the data. DC wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript before seeing and approving the final version. DC and PJD had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

**Declaration of Interests**

Dr. Conen received research grants from the Canadian Institutes of Health Research (CIHR), speaker fees from Servier, and advisory board fees from Roche Diagnostics and Trimedics, all outside of the current study. Dr. Popova is funded by a research contract (SLT017/20/000089) supported by the Department of Health of the Generalitat de Catalunya, Spain. Dr. Sessler serves on advisory boards and has equity interests in Calorint (Philadelphia, PA), TransQtronics (Philadelphia, PA), the Health Data Analytics Institute (Dedham, Mass), Medasense (Tel Aviv, Israel), and Perceptive Medical (Newport Beach, CA. The Department of Outcomes Research which Dr. Sessler chairs has research grants from dozens of companies. Dr McIntyre received speaker fees from Bayer, Servier and Eli Lilly, and consulting fees from AtriCure and Trimedics, all outside the current study. Dr. Jolly received grant support from Boston Scientific, and speaker fees from Pendopharm and Penumbra. Dr. Healey received research grants and speaker fees from Boston Scientific, BMS/Pfizer, and Medtronic. Dr. Devereaux is a member of a research group with a policy of not accepting honorariums or other payments from industry for own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions Dr. Devereaux originated and grants he has written, he has received grants from Abbott Diagnostics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Cloud DX, Coviden, Octapharma, Philips Healthcare, Roche Diagnostics, Siemens, and Stryker. He has also participated in an advisory board meeting for GlaxoSmithKline and an expert panel meeting with AstraZeneca, Boehringer Ingelheim, and Roche. None of the other authors reported any disclosures.

**Data sharing**

The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. PHRI prioritises 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. 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 upon request and approval of the proposed use of the data by a review committee. Data are available to The Lancet for evaluation of reported analyses. Data requests from other non-COP-AF investigators will not be considered until 5 years after the close of the trial.

**Acknowledgements**

This study was funded by grants from the CIHR (PJT-162458, PJT-165842), the Accelerating Clinical Trials (ACT) Consortium, the Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario, the Population Health Research Institute, Hamilton Health Sciences, the Division of Cardiology at McMaster University, all in Canada; the Hanela Foundation, Switzerland; and the General Research Fund (14121720), Research Grants Council, Hong Kong Special Administrative Region, China.

**References**

1. Dinarello CA, Chusid MJ, Fauci AS, Gallin JI, Dale DC, Wolff SM. Effect of prophylactic colchicine therapy on leukocyte function in patients with familial Mediterranean fever. *Arthritis Rheum* 1976; **19**: 618-22.

2. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. *Clin Ther* 2014; **36**: 1465-79.

3. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; **440**: 237-41.

4. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005; **112**: 2012-6.

5. Imazio M, Brucato A, Cemin R, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med* 2011; **155**: 409-14.

6. Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long-term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum* 1991; **34**: 973-7.

7. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. *Circulation* 2011; **124**: 2290-5.

8. Imazio M, Trinchero R, Brucato A, et al. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J* 2010; **31**: 2749-54.

9. Agarwal S, Beard CW, Khosla J, et al. Safety and efficacy of colchicine for the prevention of post-operative atrial fibrillation in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Europace* 2023; **25**.

10. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med* 2020; **383**: 1838-47.

11. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019; **381**: 2497-505.

12. Ackland GL, Abbott TEF, Cain D, et al. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. *Br J Anaesth* 2019; **122**: 180-7.

13. Martins OM, Fonseca VF, Borges I, Martins V, Portal VL, Pellanda LC. C-Reactive protein predicts acute myocardial infarction during high-risk noncardiac and vascular surgery. *Clinics (Sao Paulo)* 2011; **66**: 773-6.

14. Amar D, Goenka A, Zhang H, Park B, Thaler HT. Leukocytosis and increased risk of atrial fibrillation after general thoracic surgery. *Ann Thorac Surg* 2006; **82**: 1057-61.

15. Cardinale D, Sandri MT, Colombo A, et al. Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery: The PRESAGE Trial. *Ann Surg* 2016; **264**: 244-51.

16. Uchoa RB, Caramelli B. Troponin I as a mortality marker after lung resection surgery - a prospective cohort study. *BMC Anesthesiol* 2020; **20**: 118.

17. Conen D, Alonso-Coello P, Douketis J, et al. Risk of stroke and other adverse outcomes in patients with perioperative atrial fibrillation 1 year after non-cardiac surgery. *Eur Heart J* 2020; **41**: 645-51.

18. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *Jama* 2017; **317**: 1642-51.

19. Conen D, Popova E, Wang MK, et al. Rationale and design of the colchicine for the prevention of perioperative atrial fibrillation in patients undergoing major noncardiac thoracic surgery (COP-AF) trial. *Am Heart J* 2023; **259**: 87-96.

20. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010; **62**: 1060-8.

21. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. *Jama* 2014; **312**: 1016-23.

22. Craig SR, Leaver HA, Yap PL, Pugh GC, Walker WS. Acute phase responses following minimal access and conventional thoracic surgery. *Eur J Cardiothorac Surg* 2001; **20**: 455-63.

23. Bessissow A, Agzarian J, Shargall Y, et al. Colchicine for Prevention of Perioperative Atrial Fibrillation in patients undergoing lung resection surgery: a pilot randomized controlled study. *Eur J Cardiothorac Surg* 2017.

24. Polanczyk CA, Goldman L, Marcantonio ER, Orav EJ, Lee TH. Supraventricular arrhythmia in patients having noncardiac surgery: clinical correlates and effect on length of stay. *Ann Intern Med* 1998; **129**: 279-85.

25. Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of hypotheses. *J Biopharm Stat* 2005; **15**: 929-42.

26. Svendsen JH, Diederichsen SZ, Hojberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet* 2021; **398**: 1507-16.

27. Agzarian J, Bessissow A, Srinathan S, et al. The effect of colchicine administration on postoperative pleural effusion following lung resection: a randomized blinded placebo-controlled feasibility pilot study. *Eur J Cardiothorac Surg* 2017.

28. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med* 2021; **9**: 924-32.

29. Eikelboom JW, Jolly SS, Belley-Cote EP, et al. Colchicine and aspirin in community patients with COVID-19 (ACT): an open-label, factorial, randomised, controlled trial. *Lancet Respir Med* 2022; **10**: 1160-8.

**Table 1** Baseline characteristics

| **Characteristics** | **Colchicine (N=1608)** | **Placebo (N=1601)** |
| --- | --- | --- |
| **Demographics** |  |  |
| Age, mean (SD) | 68·3 (7·3) | 68·3 (7·1) |
| Male, N (%) | 831 (51·7) | 825 (51·5) |
| Ethnicity |  |  |
| White/Caucasian, N (%) | 1332 (82·8) | 1331 (83·1) |
| Black/African descent, N (%) | 11 (0·7) | 14 (0·9) |
| Hispanic/Latino, N (%) | 49 (3·0) | 48 (3·0) |
| Asian, N (%) | 163 (10·1) | 160 (10·0) |
| Other, N (%) | 16 (1·0) | 13 (0·8) |
| **Medical History** |  |  |
| Stroke, N (%) | 46 (2·9) | 39 (2·4) |
| Heart failure, N (%) | 15 (0·9) | 18 (1·1) |
| Coronary artery disease, N (%) | 142 (8·8) | 144 (9·0) |
| Myocardial infarction, N (%) | 90 (5·6) | 73 (4·6) |
| Peripheral vascular disease, N (%) | 83 (5·2) | 87 (5·4) |
| Diabetes mellitus, N (%) | 301 (18·7) | 294 (18·4) |
| Hypertension, N (%) | 836 (52·0) | 832 (52·0) |
| Chronic obstructive pulmonary disease, N (%) | 390 (24·3) | 341 (21·3) |
| Current tobacco use, N (%)1 | 351 (21·8) | 336 (21·0) |
| Serum creatinine (µmol/L), mean (SD) | 77·9 (20·7) | 78·5 (20·5) |
| Calculated creatinine clearance (mL/min), mean (SD)2 | 83·5 (27·3) | 83·3 (27·1) |
| Body mass index (kg/m2) | 27·0 (5·3) | 27·2 (5·4) |
| **Medications taken within 24 hours before surgery** |  |  |
| Aspirin, N (%) | 155 (9·6) | 141 (8·8) |
| ACEI or ARB, N (%) | 310 (19·3) | 305 (19·1) |
| Beta-blocker, N (%) | 232 (14·4) | 224 (14·0) |
| Rate-controlling calcium channel blocker, N (%) | 28 (1·7) | 23 (1·4) |
| Statin, N (%) | 551 (34·3) | 498 (31·1) |
| **Type of surgery3** |  |  |
| Wedge resection, N (%) | 314 (19·5) | 337 (21·0) |
| Segment resection, N (%) | 245 (15·2) | 242 (15·1) |
| Lobe resection, N (%) | 1028 (63·9) | 1013 (63·3) |
| Pneumonectomy, N (%) | 44 (2·7) | 44 (2·7) |
| Decortication, N (%) | 60 (3·7) | 58 (3·6) |
| Mediastinal mass resection, N (%) | 88 (5·5) | 91 (5·7) |
| Pericardium resected, N (%) | 24 (1·5) | 23 (1·4) |
| Other | 363 (22·6) | 358 (22·4) |
| Surgery performed on the initial scheduled date, N (%) | 1581 (98·3) | 1564 (97·7) |
| Surgery not performed within 14 days of randomisation, N (%) | 14 (0·9) | 13 (0·8) |
| **Surgical approach** |  |  |
| Thoracoscopic, N (%) | 1219 (75·8) | 1178 (73·6) |
| Thoracoscopic converted to open, N (%) | 98 (6·1) | 106 (6·6) |
| Open (Non-thoracoscopic), N (%) | 276 (17·2) | 304 (19·0) |
| **Type of anaesthesia in addition to general anesthesia4** |  |  |
| General anaesthesia only, N (%) | 268 (16·7) | 256 (16·0) |
| Thoracic epidural, N (%) | 361 (22·5) | 389 (24·3) |
| Paravertebral, N (%) | 402 (25·0) | 413 (25·8) |
| Intercostal, N (%) | 592 (36·8) | 587 (36·7) |
| Local, N (%) | 213 (13·2) | 198 (12·4) |

SD=standard deviation; ACE-I= Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker

1: Defined as having used tobacco within 6 weeks prior to randomisation

2: Using the Cockcroft-Gault formula

3: More than one selection can be made per patient

4: More than one selection can be made per patient if “General anaesthesia only” is not selected

**Table 2** Effects of colchicine on efficacy and safety outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Colchicine  (N=1608) | Placebo  (N=1601) | Hazard Ratio  (95% CI) | P Value |
| **Co-primary outcomes** **– N (%)**  Clinically important perioperative atrial fibrillation | 103 (6·4) | 120 (7·5) | 0·85 (0·65-1·10) | 0·22 |
| Myocardial injury after noncardiac surgery | 295 (18·3) | 325 (20·3) | 0·89 (0·76-1·05) | 0·16 |
| **Secondary outcomes – N (%)**  Composite of all-cause mortality, nonfatal MINS and nonfatal stroke  Composite of all-cause mortality, nonfatal MI and nonfatal stroke  MINS not fulfilling the fourth universal definition of MI  Myocardial infarction  Chest tube removal1  Days in hospital – median (interquartile range)  Nights in step down unit – median (interquartile range)  Nights in intensive care unit – median (interquartile range) | 293 (18·2)  21 (1·3)  285 (17·7)  13 (0·8)  1476 (93·5)  5·0 (3·0-7·0)  1·0 (0·0-3·0)  0·0 (0·0-0·0) | 334 (20·9)  31 (1·9)  311 (19·4)  15 (0·9)  1470 (94·1)  5·0 (3·0-7·0)  1·0 (0·0-3·0)  0·0 (0·0-0·0) | 0·88 (0·75-1·03)  0·67 (0·39-1·17)  0·90 (0·76-1·06)  0·86 (0·41-1·81)  1·02 (0·94-1·11) | 0·11  0·16  0·22  0·69  0·58  0·462  0·572  0·912 |
| **Tertiary outcomes – N (%)**  All-cause mortality  Deep venous thrombosis or pulmonary embolism  Acute heart failure  Composite of life-threatening or major bleeding  Days alive and at home – median (interquartile range) | 7 (0·4)  15 (0·9)  0  45 (2·8)  10·0 (8·0-12·0) | 11 (0·7)  6 (0·4)  3 (0·2)  51 (3·2)  10·0 (8·0-12·0) | 0·63 (0·25-1·63)  2·50 (0·97-6·44)  -  0·88 (0·59-1·31) | 0·35  0·06  -  0·52  >0·993 |
| **Safety outcomes – N (%)**  Composite of sepsis and infection  Non-infectious diarrhoea | 103 (6·4)  134 (8·3) | 83 (5·2)  38 (2·4) | 1·24 (0·93-1·66)  3·64 (2·54-5·22) | 0·14  <0·0001 |

MINS= Myocardial injury after noncardiac surgery; MI= Myocardial infarction;

1: Analysis based on 3141 patients who had at least one chest tube inserted

2: Wilcoxon rank sum test

3: P value based on quantile regression

**Figure legends**

**Figure 1** Patient flow diagram

**Figure 2** Cumulative incidence curves for the co-primary outcomes

1. Clinically important perioperative atrial fibrillation
2. Myocardial injury after noncardiac surgery

HR=Hazard ratio; CI=Confidence intervals.

**Figure 3** Prespecified subgroup analyses for the two co-primary outcomes

1. Clinically important perioperative atrial fibrillation
2. Myocardial injury after noncardiac surgery

HR=Hazard ratio; CI=Confidence intervals. Creatinine clearance calculated using the Cockcroft-Gault formula.