**Rationale and design of the colchicine for the prevention of perioperative atrial fibrillation in patients undergoing major noncardiac thoracic surgery (COP-AF) trial**

David Conen MD MPH,1,2,3, Ekaterine Popova MD,4,5, Michael Ke Wang MD,1,2,3, Matthew T.V. Chan MBBS MMed PhD,6, Giovanni Landoni MD,7,8, Cara Reimer MD MSc,9, Sadeesh K. Srinathan MD MSc,10, Juan P. Cata MD,11, Sean R. McLean MD,12,13, Juan Carlos Trujillo Reyes MD PhD,14, Ascensión Martín Grande MD,15, Anna Gonzalez Tallada MD PhD,16, Daniel I. Sessler MD,17, Edith Fleischmann MD,18, Donna E. Maziak MDCM MSc,19, Barbara Kabon MD,18, Luca Voltolini MD PhD,20, Laura Gutiérrez-Soriano MD,21, Vikas Tandon MD,2, Deborah DuMerton RN,9, Biniam Kidane MD MSc,22, Ravi Rajaram MD MSc,23, Yaron Shargall MD,24, John D. Neary MD,2, Jennifer R. Wells MSc,1, William F. McIntyre MD PhD,1,2,3, Steffen Blum MD PhD,1,25, Sandra N. Ofori MBBS MSc,1,2,26,Jessica Vincent MSc,1, Lizhen Xu PhD,1,2, Zhuoru Li MSc,1, Jeff S. Healey MD MSc,1,2, Amit X. Garg MD PhD,1,3,27, PJ Devereaux MD PhD,1,2,3, on behalf of the COP-AF Investigators\*

1. Population Health Research Institute, Hamilton, ON, Canada
2. Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
3. Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
4. Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain
5. Iberoamerican Cochrane Centre, 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. Vita-Salute San Raffaele University, Milan, Italy
9. Kingston Health Sciences Centre, Kingston, ON, Canada
10. Department of Surgery, University of Manitoba, Winnipeg, MB, Canada
11. Department of Anesthesiology and Perioperative Medicine, The University of Texas – MD Anderson Cancer Center, Houston, TX, United States
12. Department of Anesthesia, Vancouver Acute (Vancouver General Hospital and UBC Hospital), The University of British Columbia, Vancouver, BC, Canada
13. Department of Anesthesia, Pharmacology and Therapeutics, The University of British Columbia, Vancouver, BC, Canada
14. Department of Thoracic Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
15. Hospital Universitario Ramón y Cajal, Madrid, Spain
16. Department of Anesthesiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
17. Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, United States
18. Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria
19. University of Ottawa, Ottawa, ON, Canada
20. Thoracic Surgery Unit, Careggi University Hospital, Florence, Italy
21. Department of Anesthesiology, Fundación CardioInfantil - Instituto de Cardiología, Bogotá, Colombia
22. Departments of Surgery, Physiology and Pathophysiology, University of Manitoba, Winnipeg, MB, Canada
23. Department of Cardiothoracic Surgery, The University of Texas – MD Anderson Cancer Center, Houston, TX, United States
24. Division of Thoracic Surgery, Department of Surgery, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
25. Cardiovascular Research Institute Basel, University Hospital Basel, Basel, Switzerland
26. University of Port Harcourt, Choba, Nigeria
27. Departments of Medicine, Epidemiology and Biostatistics, Western University, London, ON, Canada

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

Word count: 6,273 words

Short title: Rationale and Design of COP-AF

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)

**Abstract**

Background

Perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS) are common complications after noncardiac surgery. Inflammation has been implicated in the pathogenesis of both disorders. The COP-AF trial tests the hypothesis that colchicine reduces the incidence of perioperative AF and MINS in patients undergoing major noncardiac thoracic surgery.

Design

The ‘COlchicine for the Prevention of Perioperative Atrial Fibrillation’ (COP-AF) trial is an international, blinded, randomized trial that compares colchicine to placebo in patients aged at least 55 years and undergoing major noncardiac thoracic surgery with general anesthesia. Exclusion criteria include a history of AF and a contraindication to colchicine (e.g., severe renal dysfunction). Oral colchicine at a dose of 0.5 mg or matching placebo is given within 4 hours before surgery. Thereafter, patients receive colchicine 0.5 mg or placebo twice daily for a total of 10 days. The two independent co-primary outcomes are clinically important perioperative AF (including atrial flutter) and MINS during 14 days of follow-up. The main safety outcomes are sepsis or infection and non-infectious diarrhea. We aim to enroll 3,200 patients from approximately 40 sites across 11 countries to have at least 80% power for the independent evaluation of the two co-primary outcomes.

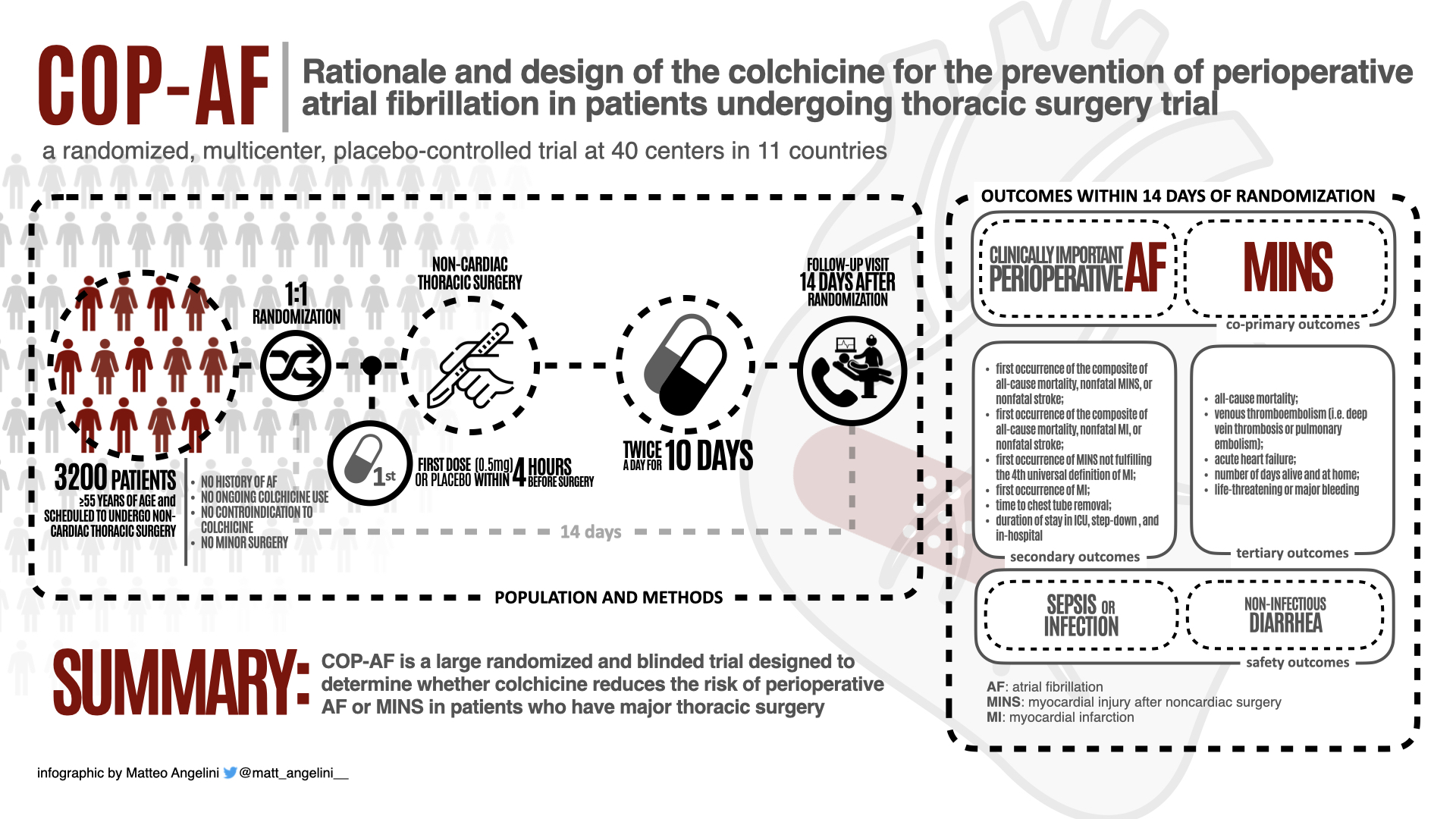
Summary

COP-AF is a large randomized and blinded trial designed to determine whether colchicine reduces the risk of perioperative AF or MINS in patients who have major noncardiac thoracic surgery.

**Keywords**

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

**Graphical abstract**



**Introduction**

Atrial fibrillation (AF) is among the most common cardiovascular complications occurring after noncardiac thoracic surgery and is the most common perioperative cardiac arrhythmia (1, 2). The incidence of perioperative AF after major noncardiac thoracic surgery usually ranges between 10 and 20% (3-10). Perioperative AF is associated with multiple complications, including adverse hemodynamic changes and an increased length of stay. For example, in a large international trial, perioperative AF was independently associated with an increase in the length of hospital stay by 6 days (95% confidence interval (CI), 3.4 - 8.4 days) (11). Increasing evidence also suggests that perioperative AF is associated with a 2-3-fold higher risk of mortality (12-15) and a 2-4-fold higher risk of stroke (11, 16, 17) during short- and long-term follow-up.

Another common adverse perioperative outcome is myocardial injury after noncardiac surgery (MINS), defined as a postoperative troponin elevation of presumed ischemic origin (2). MINS occurs in approximately 16-27% of patients after noncardiac surgery (18-23). Patients with MINS have an increased risk of death (18, 24, 25) and adverse cardiovascular events (24, 26), during both short- and long-term follow-up. This increased risk in patients with MINS is similar whether or not patients fulfill the criteria for the universal definition of myocardial infarction (MI) (24, 27).

Higher levels of inflammatory biomarkers have been associated with a higher risk of both perioperative AF and MINS (28-32), but it is unclear whether anti-inflammatory treatment can decrease the incidence of these complications. Colchicine is an inexpensive drug with potent anti-inflammatory effects. It inhibits leukocyte migration, interferes with kinin formation and prevents beta tubulin binding. This slows mitosis in granulocytes, thereby suppressing the inflammatory response (33). Colchicine also impairs the cellular apparatus required for the assembly of the inflammasome, thereby reducing the release of interleukin 1β and other interleukins (34, 35). Its efficacy as an anti-inflammatory agent has been demonstrated in patients with gout, pericarditis, and Familial Mediterranean Fever, and in patients after cardiac surgery to prevent the post-pericardiotomy syndrome (36-41). Colchicine decreased the occurrence of perioperative AF after cardiac surgery (40, 42). More recently, the Low Dose Colchicine 2 (LoDoCo2) trial randomized 5,522 patients with ischemic heart disease to colchicine or placebo, and demonstrated a significant reduction in cardiovascular events (6.8% vs. 9.6%; hazard ratio [HR] 0.69; 95% CI, 0.57-0.83). Colchicine also reduced the incidence of MI (1.1% vs. 1.5%; HR 0.70; 95% CI, 0.53-0.93) (43). The Colchicine Cardiovascular Outcomes Trial (COLCOT) randomized 4,745 patients to receive colchicine or placebo within 30 days of an MI and found that colchicine reduced the incidence of cardiovascular events (5.5% vs. 7.1%; HR 0.77; 95% CI, 0.61-0.96) (44). In a meta-analysis of four randomized trials of patients with ischemic heart disease, colchicine reduced the relative risk of MI by 22% (95% CI, 6-36%) (45).

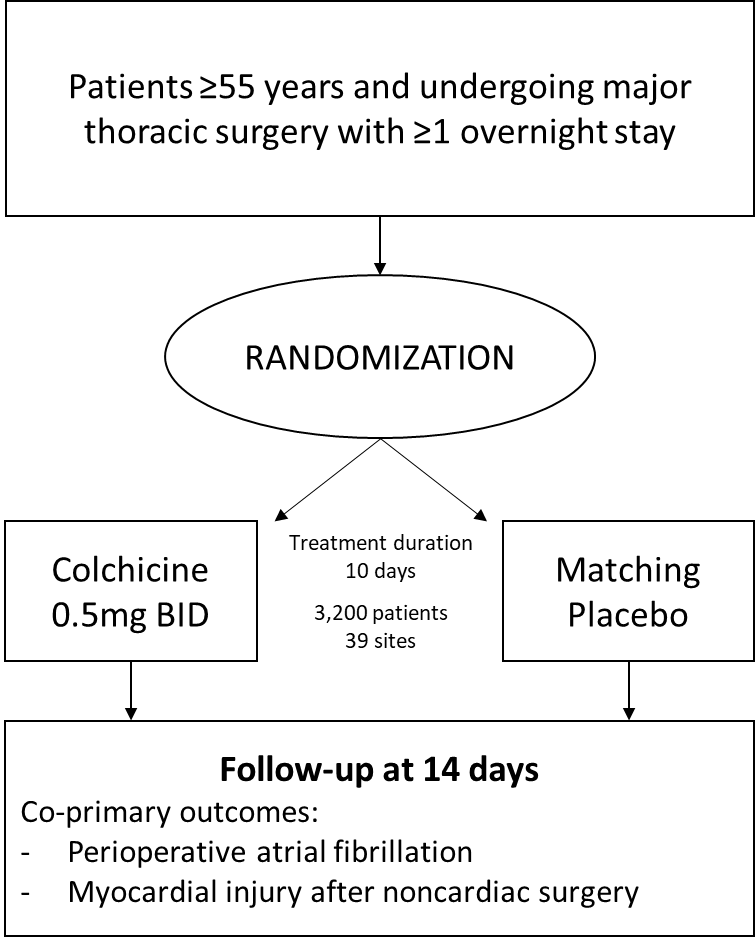
The COP-AF trial was originally designed to evaluate whether low-dose colchicine prevents the occurrence of perioperative AF after major noncardiac thoracic surgery. After the publication of LoDoCo2 and COLCOT, the study leadership decided to add MINS as a co-primary outcome, to test the hypothesis that administration of colchicine reduces perioperative ischemic events, independent of perioperative AF.

**Methods**

Study design

COP-AF (clinicaltrials.gov; NCT03310125) is a randomized placebo-controlled clinical trial. The study was approved by local ethics committees and regulatory authorities in all involved jurisdictions. After providing written informed consent, eligible patients are randomized to colchicine 0.5mg twice daily or placebo. Patients, healthcare providers, data collectors and managers, as well as outcome adjudicators are blinded to study drug allocation. The trial involves approximately 40 sites across 11 countries. A flow diagram of the study is provided in Figure 1.

**Figure 1** Study flow chart



BID=Twice daily

Study population

COP-AF aims to enroll 3,200 patients and follow them for 14 days. Inclusion and exclusion criteria are listed in Table 1. Eligible patients are at least 55 years of age and scheduled to undergo major noncardiac thoracic surgery with at least one overnight stay. Patients with a prior history of AF or those undergoing minor procedures are excluded, as are patients currently taking colchicine or those with a contraindication to colchicine (e.g., creatinine clearance <30ml/min, drug interactions as listed in table 1).

**Table 1** Eligibility criteria

|  |
| --- |
| **Inclusion criteria** |
|  |
| 1. patient is undergoing thoracic surgery with general anesthesia; |
| 1. patient is ≥55 years of age at the time of randomization; |
| 1. patient is expected to require at least an overnight hospital admission after surgery; AND |
| 1. patient provides written informed consent to participate. |
|  |
| **Exclusion criteria** |
|  |
| 1. patients with a prior history of documented atrial fibrillation; |
| 1. patients currently taking anti-arrhythmic medication other than β-blockers, calcium channels blockers or digoxin; |
| 1. patients undergoing minor thoracic interventions/procedures (e.g., isolated thoracoscopic lung wedge resection, minor chest-wall surgeries, chest tube insertions, or needle pleural/lung biopsies); |
| 1. patients with contraindications to colchicine (e.g., allergy to colchicine, myelodysplastic disorders, or an estimated glomerular filtration rate <30 mL/min/1.73m); |
| 1. patients not expected to take oral medications for >24 hours after surgery (e.g., esophagectomy); |
| 1. patients scheduled for lung transplantation; |
| 1. patients currently taking non-study colchicine before surgery; |
| 1. patients with severe hepatic dysfunction; |
| 1. patients with aplastic anemia; |
| 1. women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding; |
| 1. patients who took within the last 14 days or scheduled to take during the first 10 days after surgery clarithromycin, erythromycin, telithromycin, cyclosporine, ketoconazole, or itraconazole; OR |
| 1. HIV patients treated with antiretroviral therapy. |

Randomization, intervention and follow-up

Eligible patients who provide written informed consent are randomized before surgery. Randomization occurs via a 24-hour interactive web-based system maintained by the coordinating center at the Population Health Research Institute, McMaster University, Hamilton, Canada. Patients are randomized in a 1:1 ratio to colchicine or placebo. Randomization is stratified by center with variable block sizes that are unknown to site personnel.

The first dose of oral colchicine, at a dose of 0.5 mg, or matching placebo is given preoperatively within 4 hours of surgery. This timing was chosen because it increases the feasibility of the trial, because patients undergoing pulmonary vein isolation had an early reduction in AF recurrence when colchicine was initiated on the day of the intervention (46), and because pharmacokinetic data showed peak colchicine blood levels after a single dose of 0.6 mg of colchicine within 1-2 hours, suggesting rapid onset of action (47). Thereafter all patients receive their assigned treatment twice daily for a total of 10 days. We chose twice daily dosing to counteract the substantial inflammatory response after surgery (48), and because many 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 (41, 42, 46). A study drug administration period of 10 days was chosen based on pre-existing data showing that virtually all perioperative AF events occur in the first 10 days (9). In the COP-AF pilot, all perioperative AF events occurred within 9 days after surgery (49). Similarly, most MINS events occur within the first 3 days after surgery (13), suggesting that this treatment algorithm is also appropriate for testing the hypothesis that colchicine prevents the occurrence of MINS.

Patients are followed daily during their hospitalization until discharge. After surgery, 3 daily troponin and creatinine measurements are obtained, as long as patients are still in the hospital (50). Patients discharged home before completing the study medication are given a bottle with enough pills to complete 10 days of treatment. The final follow-up visit occurs 14 days after randomization, either during a clinic visit or via the phone. Outcome ascertainment was set-up as close to usual clinical practice as possible, even if this means that some asymptomatic post-discharge outcome events may be missed. Study drug adherence is assessed in all patients in the case report forms, where dates and times of permanent and temporary study drug interruptions are noted, as well as the main reason for the interruption.

Study objectives and outcomes

The *primary objective* of this trial is to determine whether the administration of colchicine compared with placebo independently reduces the occurrence of the co-primary outcomes within 14 days of randomization.

The first co-primary outcome is clinically important perioperative AF (including atrial flutter), defined as AF that results in angina, heart failure, or symptomatic hypotension, or that requires treatment with a rate-controlling drug, antiarrhythmic drug, or electrical cardioversion. This definition has previously been validated as prognostically relevant (11, 51), and helps to avoid counting short, asymptomatic AF episodes of unknown clinical significance as events (52).

The second co-primary outcome is MINS, defined as any MI, and any elevated troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology [e.g. chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 14 days after the initiation of surgery.

The *secondary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the following outcomes within 14 days after randomization:

1. first occurrence of the composite of all-cause mortality, nonfatal MINS, or nonfatal stroke;
2. first occurrence of the composite of all-cause mortality, nonfatal MI, or nonfatal stroke;
3. first occurrence of MINS not fulfilling the 4th universal definition of MI;
4. first occurrence of MI;
5. time to chest tube removal;
6. duration of stay in intensive care unit, step-down, and in-hospital.

The *tertiary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the following outcomes within 14 days of randomization:

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;
5. life-threatening or major bleeding.

The main *safety outcomes* of COP-AF during the 14-day period after randomization are:

1. sepsis or infection;
2. non-infectious diarrhea.

The adjudication committee is composed of a committee of clinicians with expertise in perioperative outcomes. The committee is blinded to treatment allocation and adjudicates the co-primary endpoints and other outcomes according to an adjudication plan. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Detailed definitions for all outcome events are provided in the appendix.

Sample size calculations

Based on data from 2,100 randomized patients, we estimate an overall incidence of perioperative AF of approximately 9%, and a permanent discontinuation rate of 10.5% in week 1 and 2.7% in week 2 of the trial. Also assuming a relative risk reduction of 30%, and a 2-sided alpha of 0.0324, 3,200 patients will provide 83% power for the first co-primary outcome.

Based on data from 2,100 randomized patients, the overall incidence of elevated troponin measurements after major noncardiac thoracic surgery is approximately 25%. Assuming that 10-15% of these events are nonischemic in origin (24), the overall incidence of MINS will be around 22%, which is consistent with the unblinded results from the pilot trial (20). Assuming 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 of the trial, 3,200 patients will provide a power of 80% for the co-primary outcome of MINS.

Statistical analysis

All statistical analyses will follow the trial completion according to a separate statistical analysis plan, to be written before the termination of the trial and unblinding. For both co-primary outcomes, we will plot the cumulative incidence curves between the two treatment groups and compare them using log-rank tests. We will use Cox proportional-hazards models with treatment group as an independent variable to obtain HRs and 95% CIs. If needed, the competing risk of death will be taken into account using subdistribution hazards models proposed by Fine and Gray (53). Colchicine will be considered effective if either of the two co-primary efficacy analyses is significant. To address the multiplicity problem that might occur, we will use the ‘fallback procedure’ (54), and we will partition the total alpha of 0.05 among the two co-primary outcomes, with a significance level of 0.0324 for the first co-primary outcome and 0.0176 for the second co-primary outcome before adjustment for potential overlap. According to the ‘fallback procedure’, if the first co-primary outcome is found to be significant at the 0.0324 alpha level, then this alpha is “unused”, and is passed to the second co-primary outcome. Therefore, if the first co-primary outcome is found to be significant, the second co-primary outcome will be evaluated at the 0.05 alpha level. If the first co-primary outcome is found to be non-significant, we are still able to test the second co-primary, but at the overlap-accounted-for alpha level. We will evaluate the actual amount of overlap between the two co-primary outcomes at the end of the trial, and we will adjust the alpha of the second co-primary outcome accordingly.

For all secondary, tertiary, or safety outcomes other than duration of stay and the number of days alive and at home, a similar time to event analysis method will be used, but without the fallback procedure. For outcomes such as duration of stay and number of days alive and at home, a two-sample t-test or Wilcoxon rank sum test will be used depending on the distribution of the variables. The alpha levels for all secondary, tertiary, and safety outcomes will be 0.05 unless specified otherwise. We will follow the intention-to-treat principle. All efforts will be made to collect information about the clinical outcomes for participants lost to follow-up. In case of no contact, the participant will be censored on their last day of available contact.

Cox proportional-hazards models assessing each co-primary outcome provide the basis for evaluating subgroup effects. We will consider the possibility that a subgroup effect is present if the interaction term of treatment and subgroup is statistically significant at a p-value less than alpha 0.05. We will also consider other credibility criteria to judge the truthfulness of a subgroup effect (55). Prespecified subgroups for the two co-primary outcomes are age, type of surgery (non-thoracoscopic versus thoracoscopic surgery) and renal function. We expect that colchicine has a stronger effect in older patients, in those undergoing non-thoracoscopic surgery, and in those with lower renal function.

Trial Organization

The international Steering Committee consists of experts in perioperative medicine, anesthesiology, cardiology, internal medicine, statistics and thoracic surgery. It convenes regularly by teleconference and oversees the conduct of the trial. For each participating country, a member of the Steering Committee is appointed to act as the national principal investigator.

A data and safety monitoring committee (DSMC) reviews all reported serious adverse events. During the trial, 2 interim efficacy analyses have occurred based on the original primary outcome of perioperative AF, when 50% and 75% of the 14-day data were available. The DSMC follows the modified Haybittle-Peto rule of 4 standard deviations (α = 0.0001) when 50% of the data are analyzed, and 3 standard deviations (α = 0.0027) for analyses in the second half of the trial (56, 57). For a finding to be considered significant, these predefined boundaries have to be exceeded in at least 2 consecutive analyses, 3 or more months apart. Given these stringent criteria, the α-level for the final analysis for each co-primary outcome will remain unchanged. We did not add additional interim analyses after the change in sample size and primary outcome.

At any time during the trial if safety concerns arise the DSMC chairperson assembles a formal meeting of the full committee. The DSMC makes their recommendations to the Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered, the DSMC invites the Operations Committee to explore all possibilities before making a decision.

Trial Progress

The first COP-AF patient was randomized on February 14, 2018. As of January 3, 2023, 2,600 patients have been enrolled. Ongoing recruitment involves approximately 40 centers across 11 countries. The current version of the study protocol was submitted before study recruitment was completed and before the completion of the last patient/last visit. Some protocol amendments have been implemented during the course of the trial. The most recent version of the protocol reported here has been finalized close to the end of the recruitment.

Funding and responsibilities

COP-AF was funded by grants from the Canadian Institutes of Health Research (PJT-162458, PJT-165842), Hamilton Academic Health Sciences Organization (HAHSO), Population Health Research Institute, Hamilton Health Sciences, the Division of Cardiology at McMaster University, all in Hamilton, Canada; the Hanela Foundation, Switzerland; and the General Research Fund (14121720), Research Grants Council, Hong Kong Special Administrative Region, China. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

**Discussion**

Reducing the risk of perioperative AF and MINS is an unmet clinical need in patients who have major noncardiac thoracic surgery, and if causally related to these events such an intervention may also reduce mortality, stroke, and the duration of hospitalization. Colchicine is an inexpensive and effective anti-inflammatory agent that holds promise in reducing the incidence of these two perioperative complications. The COP-AF trial will provide clear evidence about its benefits and risks in this setting.

Although colchicine has effectively reduced the occurrence of perioperative AF after cardiac surgery in several relatively small randomized trials (41, 42), it is not widely employed in these patients according to our experience. One reason could be that knowledge translation efforts were insufficient. We will work with knowledge translation experts to effectively disseminate our findings. Another reason for the lack of colchicine use in cardiac surgery patients could be that previous studies were relatively small, and experience in many areas has shown that large international trials such as COP-AF providing precise answers are needed to change clinical practice. COP-AF will also show if the benefits observed in cardiac surgery patients can be extended to patients undergoing noncardiac surgery. COP-AF focuses on patients undergoing major noncardiac thoracic surgery because the incidence of perioperative AF in this population is higher than in other types of noncardiac surgery (4), and therefore the clinical need is greatest. Prior studies have documented a more than 10-15-fold increase in inflammatory biomarker levels in the first 48 to 72 hours after major noncardiac thoracic surgery, corresponding to the same time period where most perioperative AF events tend to occur (48). We are not aware of any studies suggesting a differential inflammatory response between men and women in this context.

Patients with MINS are at increased risk of death within 30 days after surgery (13). The risk of death is increased regardless of whether patients had ischemic features (i.e., symptoms or ischemic changes on the electrocardiogram) (adjusted HR 5.04; 95% CI, 3.56-7.12) or not (adjusted HR 3.20; 95% CI, 2.37-4.32) (24). While there is a need to prevent MINS, no such treatment is currently available. MINS is strongly associated with elevations in inflammatory markers, including C-reactive protein, white blood cell count, and interleukins (28-32). Recent studies in patients with coronary artery disease have underscored the potential of colchicine in preventing ischemic cardiovascular events (43, 44). Given the ischemic origin of MINS, it is plausible that colchicine has the ability to prevent MINS after noncardiac thoracic surgery. As all patients enrolled in COP-AF systematically get their postoperative troponin measured, it was decided to test this important hypothesis, and add MINS as a coprimary outcome to COP-AF.

Colchicine may prevent other postoperative inflammatory complications. Colchicine has a profound impact on post-pericardiotomy syndrome and pericarditis recurrence (36-41), and in the COP-AF pilot study it significantly reduced the total amount of fluid drained at 48 hours (584 ml vs. 763 ml, p=0.04) and at various other time points (58). Therefore, it is plausible that colchicine may reduce the time to chest tube removal in COP-AF. This is an important outcome, as it may shorten the length of hospital stay, reduce the incidence of postoperative infections, and improve patient’s well-being.

**Conclusions**

COP-AF is a large randomized trial that will determine whether colchicine, a potent anti-inflammatory drug, lowers the risk of perioperative AF and MINS in patients who have major noncardiac thoracic surgery. Finding a safe, effective and inexpensive intervention that prevents postoperative cardiovascular complications addresses an unmet clinical need.

**Disclosures**

Dr. Conen received speaker fees from Servier and BMS/Pfizer, as well as 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 is a consultant for Pacira biosciences (Parsippany, NJ). He serves on advisory boards and has equity interests in Calorint (Philadelphia, PA), TransQtronics (Philadelphia, PA, the Health Data Analytics Institute (Boston, Mass), Medasense (Tel Aviv, Israel), Serenno (Yokneam, Israel), Sensifree (Cupertino, CA), Perceptive Medical (Newport Beach, CA), and Neuroindex (Tel Aviv, Israel). He serves on the Board of the Foundation for Anesthesia Education and Research. The Department of Outcomes Research, which Dr. Sessler chairs, has research grants from dozens of companies. Dr Blum received funding from the Swiss National Science Foundation, the Mach-Gaensslen Foundation and the Bangerter-Rhyner Foundation outside the submitted work. Dr. Healey received research grants and speaking fees from Boston Scientific, BMS/Pfizer, Servier, and Bayer. Dr. Garg is supported by the Dr. Adam Linton Chair in Kidney Health Analytics. 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 endeavors 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.

**References**

1. Frendl G, Sodickson AC, Chung MK, Waldo AL, Gersh BJ, Tisdale JE, et al.2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. J Thorac Cardiovasc Surg. 2014;148(3):e153-93.

2. Borges F, Ofori S, Marcucci M**.** Myocardial Injury after Noncardiac Surgery and Perioperative Atrial Fibrillation: From Evidence to Clinical Practice. Canadian Journal of General Internal Medicine. 2021;16(SP1):18-26.

3. Ai D, Xu G, Feng L, Yu J, Banchs J, Vaporciyan AA, et al.Dexmedetomidine does not reduce atrial fibrillation after lung cancer surgery. J Cardiothorac Vasc Anesth. 2015;29(2):396-401.

4. Cardinale D, Sandri MT, Colombo A, Salvatici M, Tedeschi I, Bacchiani G, et al.Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery: The PRESAGE Trial. Ann Surg. 2016;264(2):244-51.

5. Mc Cormack O, Zaborowski A, King S, Healy L, Daly C, O'Farrell N, et al.New-onset atrial fibrillation post-surgery for esophageal and junctional cancer: incidence, management, and impact on short- and long-term outcomes. Ann Surg. 2014;260(5):772-8; discussion 8.

6. Onaitis M, D'Amico T, Zhao Y, O'Brien S, Harpole D**.** Risk factors for atrial fibrillation after lung cancer surgery: analysis of the Society of Thoracic Surgeons general thoracic surgery database. Ann Thorac Surg. 2010;90(2):368-74.

7. Roselli EE, Murthy SC, Rice TW, Houghtaling PL, Pierce CD, Karchmer DP, et al.Atrial fibrillation complicating lung cancer resection. J Thorac Cardiovasc Surg. 2005;130(2):438-44.

8. Vaporciyan AA, Correa AM, Rice DC, Roth JA, Smythe WR, Swisher SG, et al.Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: analysis of 2588 patients. J Thorac Cardiovasc Surg. 2004;127(3):779-86.

9. 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(4):279-85.

10. Fernando HC, Jaklitsch MT, Walsh GL, Tisdale JE, Bridges CD, Mitchell JD, et al.The Society of Thoracic Surgeons practice guideline on the prophylaxis and management of atrial fibrillation associated with general thoracic surgery: executive summary. Ann Thorac Surg. 2011;92(3):1144-52.

11. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al.Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008;371(9627):1839-47.

12. Chin JH, Moon YJ, Jo JY, Han YA, Kim HR, Lee EH, et al.Association between Postoperatively Developed Atrial Fibrillation and Long-Term Mortality after Esophagectomy in Esophageal Cancer Patients: An Observational Study. PLoS One. 2016;11(5):e0154931.

13. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, et al.Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. Jama. 2017;317(16):1642-51.

14. Tu JV, Wang H, Bowyer B, Green L, Fang J, Kucey D**.** Risk factors for death or stroke after carotid endarterectomy: observations from the Ontario Carotid Endarterectomy Registry. Stroke. 2003;34(11):2568-73.

15. Brathwaite D, Weissman C**.** The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest. 1998;114(2):462-8.

16. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF**.** Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. Anesthesiology. 2009;110(2):231-8.

17. Conen D, Alonso-Coello P, Douketis J, Chan MTV, Kurz A, Sigamani A, 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(5):645-51.

18. Smilowitz NR, Redel-Traub G, Hausvater A, Armanious A, Nicholson J, Puelacher C, et al.Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. Cardiol Rev. 2019;27(6):267-73.

19. Gonzalez-Tallada A, Borrell-Vega J, Coronado C, Morales P, de Miguel M, Ferreira-Gonzalez I, et al.Myocardial Injury After Noncardiac Surgery: Incidence, Predictive Factors, and Outcome in High-Risk Patients Undergoing Thoracic Surgery: An Observational Study. J Cardiothorac Vasc Anesth. 2020;34(2):426-32.

20. Bessissow A, Agzarian J, Shargall Y, Srinathan S, Neary J, Tandon V, et al.Colchicine for Prevention of Perioperative Atrial Fibrillation in patients undergoing lung resection surgery: a pilot randomized controlled study. Eur J Cardiothorac Surg. 2018;53(5):945-51.

21. Hua A, Pattenden H, Leung M, Davies S, George DA, Raubenheimer H, et al.Early cardiology assessment and intervention reduces mortality following myocardial injury after non-cardiac surgery (MINS). J Thorac Dis. 2016;8(5):920-4.

22. Lucreziotti S, Conforti S, Carletti F, Santaguida G, Meda S, Raveglia F, et al.Elevaciones de la troponina I cardiaca tras la cirugía torácica. Incidencia y correlaciones con las características clínicas basales, la proteína C reactiva y los parámetros perioperatorios. Revista Española de Cardiología. 2007;60(11):1159-66.

23. Muley T, Kurz M, Männle C, Alekozai A, Winteroll S, Dienemann H, et al.Comparison of serum cardiac specific biomarker release after non-cardiac thoracic surgery. Clin Lab. 2011;57(11-12):925-32.

24. Writing Committee for the VSI, Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, et al.Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA. 2017;317(16):1642-51.

25. Yu J, Lim B, Lee Y, Park JY, Hong B, Hwang JH, et al.Risk factors and outcomes of myocardial injury after non-cardiac surgery in high-risk patients who underwent radical cystectomy. Medicine (Baltimore). 2020;99(43):e22893.

26. Gualandro DM, Puelacher C, Lurati Buse G, Glarner N, Cardozo FA, Vogt R, et al.Incidence and outcomes of perioperative myocardial infarction/injury diagnosed by high-sensitivity cardiac troponin I. Clin Res Cardiol. 2021;110(9):1450-63.

27. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al.Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):e618-e51.

28. Ackland GL, Abbott TEF, Cain D, Edwards MR, Sultan P, Karmali SN, 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(2):180-7.

29. Larmann J, Handke J, Scholz AS, Dehne S, Arens C, Gillmann HJ, et al.Preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with major adverse cardiovascular and cerebrovascular events in coronary heart disease patients undergoing non-cardiac surgery. BMC Cardiovasc Disord. 2020;20(1):230.

30. Sanders RD, Craigova L, Schessler B, Casey C, White M, Parker M, et al.Postoperative troponin increases after noncardiac surgery are associated with raised neurofilament light: a prospective observational cohort study. Br J Anaesth. 2021;126(4):791-8.

31. 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(5):773-6.

32. Crispi V, Isaac E, Abah U, Shackcloth M, Lopez E, Eadington T, et al.Surgical factors associated with new-onset postoperative atrial fibrillation after lung resection: the EPAFT multicentre study. Postgrad Med J. 2020.

33. 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(3):618-22.

34. Dalbeth N, Lauterio TJ, Wolfe HR**.** Mechanism of action of colchicine in the treatment of gout. Clin Ther. 2014;36(10):1465-79.

35. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J**.** Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440(7081):237-41.

36. Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, et al.Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112(13):2012-6.

37. Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al.Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med. 2005;165(17):1987-91.

38. Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, et al.Colchicine for recurrent pericarditis (CORP): a randomized trial. Ann Intern Med. 2011;155(7):409-14.

39. Zemer D, Livneh A, Danon YL, Pras M, Sohar E**.** Long-term colchicine treatment in children with familial Mediterranean fever. Arthritis Rheum. 1991;34(8):973-7.

40. Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, 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(22):2749-54.

41. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, et al.Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. Jama. 2014;312(10):1016-23.

42. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, 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(21):2290-5.

43. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al.Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383(19):1838-47.

44. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al.Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381(26):2497-505.

45. Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC, et al.Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. Eur Heart J. 2021;42(28):2765-75.

46. Deftereos S, Giannopoulos G, Kossyvakis C, Efremidis M, Panagopoulou V, Kaoukis A, et al.Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol. 2012;60(18):1790-6.

47. 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(4):1060-8.

48. 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(3):455-63.

49. Bessissow A, Agzarian J, Shargall Y, Srinathan S, Neary J, Tandon V, 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.

50. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al.Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. Can J Cardiol. 2017;33(1):17-32.

51. Alonso-Coello P, Cook D, Xu SC, Sigamani A, Berwanger O, Sivakumaran S, et al.Predictors, Prognosis, and Management of New Clinically Important Atrial Fibrillation After Noncardiac Surgery: A Prospective Cohort Study. Anesth Analg. 2017;125(1):162-9.

52. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS**.** Management of atrial high-rate episodes detected by cardiac implanted electronic devices. Nat Rev Cardiol. 2017.

53. Fine JP, Gray RJ**.** A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509.

54. Wiens BL, Dmitrienko A**.** The fallback procedure for evaluating a single family of hypotheses. J Biopharm Stat. 2005;15(6):929-42.

55. Sun X, Briel M, Walter SD, Guyatt GH**.** Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117.

56. Haybittle JL**.** Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.

57. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al.Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976;34(6):585-612.

58. Agzarian J, Bessissow A, Srinathan S, Devereaux PJ, Neary J, Decher W, 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.