Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery (COP-AF)

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LIST OF ABBREVIATIONS

AF: Atrial fibrillation/atrial flutter
ARR: Absolute risk reduction
CABG: Coronary artery bypass graft
CI: Confidence interval
CRF: Case report form
CRP: C-reactive protein
CT: Computed tomography
cTn: Cardiac troponin
DSMC: Data and safety monitoring committee
ECG: Electrocardiogram
eGFR: Estimated glomerular filtration rate
GCP: Good clinical practice
GCS: Glasgow Coma Scale
GI: Gastrointestinal
HIV: Human immunodeficiency virus
HR: Hazard ratio
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU: Intensive care unit
IEC: Independent ethics committee
IL: Interleukin
IL-1β: Interleukin-1 beta
IRB: Institutional review board
LBBB: Left bundle branch block
MI: Myocardial infarction
MINS: Myocardial injury after noncardiac surgery
MRI: Magnetic resonance imaging
NS: Non-significance
OR: Odds ratio
PCI: Percutaneous coronary intervention
PHRI: Population Health Research Institute
PI: Principal investigator
POD: Postoperative day
PPS: Post-pericardiotomy syndrome
PreOD: Preoperative day
qSOFA: quick Sequential Organ Failure Assessment
RCT: Randomized controlled trial
RRR: Relative risk reduction
SAE: Serious adverse event
SD: Standard deviation
SUSAR: Suspected unexpected serious adverse reactions
URL: Upper reference limit
WBC: White blood cell

STUDY/TRIAL ACRONYMS

COLCOT: Colchicine Cardiovascular Outcomes Trial
COP-AF: Colchicine for the Prevention of Perioperative Atrial Fibrillation
COPPS: Colchicine for the Prevention of the Post-pericardiotomy Syndrome
COPPS-2: Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation
HIP ATTACK: Hip Fracture Accelerated Surgical Care and Treatment Track
LoDoCo2: Low Dose Colchicine 2
MANAGE: Management of Myocardial Injury after Noncardic Surgery
POISE: Perioperative Ischemic Evaluation
POISE-2: Perioperative Ischemic Evaluation 2
VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation
VISION Cardiac Surgery: Vascular Events in Surgery Patients Cohort Evaluation – Cardiac Surgery

STUDY SYNOPSIS

Title	**CO**lchicine for the **P**revention of perioperative **A**trial **F**ibrillation in patients undergoing major noncardiac thoracic surgery (COP-AF)
Project Office	COP-AF Study Project Office; Population Health Research Institute; Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Room C1-239, Hamilton, Ontario, Canada L8L 2X2 Email: copaf@phri.ca
Study Size	3,200 patients
Study Design	Multi-centre, blinded, randomized controlled trial
Primary Objectives	To determine whether the administration of colchicine compared with placebo reduces the occurrence of 1) perioperative atrial fibrillation/atrial flutter (AF), and 2) myocardial injury after noncardiac surgery (MINS), both within 14 days of randomization.
Secondary Objectives	The secondary trial objectives are to determine whether the administration of colchicine compared with placebo reduces the following within 14 days of 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 myocardial infarction (MI), or nonfatal stroke; 3. MINS not fulfilling the 4th universal definition of MI; 4. MI; 5. time to chest tube removal; and 6. duration of stay in ICU, step-down, and in-hospital.
Main Safety Outcomes	The two main safety outcomes are the occurrence of sepsis/infection and non-infectious diarrhea within 14 days of randomization.
Inclusion Criteria	Patients are eligible if they: 1. are undergoing thoracic surgery with general anesthesia; 2. are ≥55 years of age at randomization; 3. are expected to require at least an overnight hospital admission after surgery; and 4. provide written informed consent.
Exclusion Criteria	Patients are excluded if they fulfill any of the following criteria: 1. have a prior history of documented AF; 2. are currently taking anti-arrhythmic medication; 3. are undergoing minor thoracic interventions/procedures; 4. have contraindications to colchicine; 5. are not expected to take oral medications for >24 hours after surgery; 6. are scheduled for lung transplantation; 7. are currently taking non-study colchicine before surgery; 8. have severe hepatic dysfunction; 9. have aplastic anemia; 10. women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding; 11. took within the last 14 days or scheduled to take during the first 10 days after surgery clarithromycin, erythromycin, telithromycin, cyclosporine, ketoconazole or itraconazole; 12. HIV patients treated with antiretroviral therapy; or 13. are scheduled for thoracoscopic wedge resection only.
Treatment Regimen	Oral colchicine at a dose of 0.5 mg or matching placebo will be given within 4 hours before surgery. The second dose will be given in the evening after surgery. Thereafter, patients will continue to receive colchicine 0.5 mg or placebo twice daily for a total of 10 days.
Follow-up	Patients will be followed while in hospital and at 14 days after randomization
Statistical Considerations	The co-primary outcomes will be presented using cumulative incidence curves and be compared between groups using a log rank test. Cox regression models will be used to obtain hazard ratios and confidence intervals.

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1.0 INTRODUCTION

During the last few decades, substantial advances in noncardiac surgery have improved disease treatment and patients' quality of life. As a result, the number of patients undergoing surgery, including thoracic surgery, continues to grow (1). Based on recent estimates, and confidential data from the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, an observational study of a representative sample of 40,000 patients undergoing noncardiac surgery, it is estimated that 5 million major thoracic surgical procedures are undertaken annually around the world (2, 3).

Complications such as atrial fibrillation/atrial flutter (AF) and myocardial injury after noncardiac surgery (MINS) occur commonly after thoracic surgery and adversely affect patient outcomes and significantly increase health care costs. Effective prevention of these complications is expected to shorten length of hospital stay and re-admissions and may reduce the incidence of stroke and other adverse outcomes.

Colchicine, an anti-inflammatory agent, has been effective in preventing perioperative AF and post-pericardiotomy syndrome (PPS) in the cardiac surgery setting. After successful completion of a pilot study, we will undertake a large randomized controlled trial (RCT) to determine the efficacy of colchicine for the prevention of new onset AF and MINS in patients undergoing thoracic surgery. This is the "**CO**lchicine for the **P**revention of perioperative **A**trial **F**ibrillation in patients undergoing major noncardiac thoracic surgery" **(COP-AF)** Trial.

2.0 BACKGROUND

2.1 Colchicine and perioperative AF

In a study of surgical data from 56 countries around the world, it was estimated that globally over 230 million major surgical procedures are undertaken annually (1). Confidential, unpublished data from the VISION Study suggest that around 5 million of these surgeries are major thoracic surgical procedures. Despite the undisputed benefits of thoracic surgery, it is also associated with major cardiovascular complications.

AF is one of the most common serious complications occurring after thoracic surgery and is the most common perioperative cardiac arrhythmia (4). The incidence of AF in patients undergoing major thoracic surgery ranges from 1 in 10 in low-risk patients to as high as 1 in 5 in high-risk patients (5-12). Age has consistently been identified as the strongest risk predictor of perioperative AF in surgery patients, including those undergoing thoracic surgery (10, 13, 14). Due to the overall ageing of the society, the enhanced survival of patients with cardiovascular disease, which allows them to live long enough to develop conditions that require thoracic surgery, and the shift in practice patterns to provide advanced care (including surgery) for the elderly, the age of patients undergoing thoracic surgery will further increase in the future. It is therefore likely that the incidence of perioperative AF and its associated complications will continue to grow, and there is an urgent need for trials trying to prevent perioperative AF.

2.2 Impact of perioperative AF

a) Mortality

Prior studies have shown an association between perioperative AF and mortality. In a retrospective cohort of 583 patients undergoing esophagectomy, 11% developed perioperative AF. The 1-year mortality rate was 25% in the perioperative AF group and 10% in the non-AF group. The adjusted hazard ratio (HR) for death in the perioperative AF group was 2.56 (95% confidence interval (CI) 1.43-4.57, p=0.002) (15). The VISION study included patients undergoing thoracic surgery and showed a significant association of perioperative AF with 30-day mortality (16). Another study conducted in Ontario of 6,038 patients undergoing carotid endarterectomy found that AF was an independent predictor for stroke within 30 days

(odds ratio (OR) 1.83; 95% CI, 1.18-2.83) and death or stroke within 30 days (OR 1.89; 95% CI, 1.29-2.76) (17). Brathwaite et al. prospectively monitored the outcome in a surgical intensive care unit (ICU) of 462 patients who underwent non-cardiothoracic surgery. In the 6% of patients who had new onset AF, the mortality rate at one year after surgery was 29%, as compared to 9% in patients with pre-existing AF, and 4% in patients not suffering perioperative AF ($p<0.005$) (18).

b) Increased risk of stroke

During hospitalization for surgery, patients with known AF have a much greater risk of developing stroke than patients without AF. In a large cohort of 371,641 patients undergoing noncardiac surgery (including 39,339 thoracic surgery patients), patients with known AF had a fourfold increased risk of perioperative stroke than those without AF (OR 3.98; 95% CI, 3.57-4.45) (19). In the Perioperative Ischemic Evaluation (POISE) Trial, a large RCT of over 8,000 patients undergoing noncardiac surgery (including patients undergoing thoracic surgery), patients who developed new perioperative AF had a higher risk of stroke within 30-days after surgery (multivariable adjusted OR 3.51; 95% CI, 1.45-8.52). These perioperative strokes were generally devastating and a majority of these patients either died, were left incapacitated or severely limited in their ability to perform activities of daily living (20). These data suggest that both new perioperative AF and chronic preoperative AF significantly increase the risk of perioperative stroke and AF occurring during the hypercoagulable postoperative period may be particularly risky.

The impact of perioperative AF may be even greater than what is suggested by the incidence of major strokes. Subclinical strokes are often missed and manifest as a deterioration in cognitive function, postoperative confusion, memory deficits, and seizures with no evidence of focal neurological injury (21). These events occur more commonly in patients who develop dysrhythmias after cardiac surgery (5.7 vs. 2.5%; OR 1.97; 95% CI, 1.12-3.46) (22). The impact of perioperative covert brain injury further highlights the potential benefit of preventing perioperative AF.

A meta-analysis of 5,479 patients undergoing cardiac surgery showed that anti-arrhythmic treatments to prevent perioperative AF may reduce the incidence of perioperative stroke (85 events; OR 0.63; 95% CI, 0.41-0.98), thereby demonstrating that preventing perioperative AF may be an effective method to lower the risk of perioperative stroke after cardiac surgery (23). However, 2 surveys among 216 cardiac surgeons show that anti-arrhythmic drugs are rarely used for perioperative AF prevention, and the fear of anti-arrhythmic drug complications was one of the key reasons for not using these drugs (24, 25). For example in these surveys, only 18-19% of surgeons used amiodarone to prevent perioperative AF (24, 25). Moreover, in the COP-AF pilot study none of the 100 participants received perioperative prophylaxis with amiodarone (26). These data clearly demonstrate that in clinical practice, antiarrhythmic medications are not used for perioperative AF prevention, and that no established clinical standard of care exists.

c) Prolongation of ICU and hospital stay

Perioperative AF is commonly associated with prolonged hospital and ICU stays. Patients undergoing noncardiac surgery who developed supraventricular arrhythmias (including AF) had a 33% increase in their length of hospital stay (10, 11, 20). In POISE, perioperative AF was independently associated with an increase in the length of hospital stay by 6 days (risk adjusted 95% CI, 3.4-8.4 days) (20). Patients who developed perioperative AF after thoracic surgery had a mean hospital stay of 17 days (standard deviation [SD]±18.6) compared to 8 days (SD±11) in those who did not develop perioperative AF ($p<0.001$) (10). In a second study, the average length of stay was 23 days for patients with new-onset perioperative AF, 17 days for those with pre-existing AF, and 13 days for those with no AF. Moreover, the length of ICU stay was 9, 3, and 2 days, respectively (18).

Consequently, hospitalization cost was greater in patients with perioperative AF ($56,426 vs. $28,325, $p<0.001$) (10), even when this cost was adjusted for the presence of other perioperative complications

($27,859 vs. $21,425, p<0.001) (10). Importantly, preventing perioperative AF with colchicine in a randomized trial of patients undergoing cardiac surgery shortened the mean length of overall hospitalization by three days (27).

d) Risks associated with the use of postoperative anticoagulation

Although perioperative AF is associated with an increased risk of stroke, the decision to start anticoagulation in patients who have recently undergone surgery is difficult. For perioperative AF, no risk-prediction model exists to select those patients who would benefit from anticoagulation at an acceptable risk of postoperative bleeding. When faced with this decision, clinicians often chose to avoid the immediate risk of bleeding; this may expose their patients to an increased stroke risk and contribute to the burden of postoperative strokes (20). Given the inevitable trade-off between the risks of stroke and bleeding with anticoagulation it is clear that prevention of perioperative AF is highly preferable.

2.3 Inflammation, colchicine and perioperative AF

Colchicine is an inexpensive drug with potent anti-inflammatory effects. It inhibits leukocyte migration, interferes with kinin formation and prevents beta tubulin binding (28). This slows mitosis in granulocytes, thereby suppressing the inflammatory response (29). Colchicine also impairs the cellular apparatus required for the assembly of the inflammasome, thereby reducing the release of interleukin-1 beta (IL-1β) and other interleukins (ILs) (30, 31). 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 PPS (28, 32-37).

Colchicine prevents the occurrence of perioperative AF after cardiac surgery. The Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial randomized 360 cardiac surgery patients to receive colchicine or placebo on postoperative day (POD) 3 (36, 38). Colchicine significantly reduced the incidence of PPS (8.9% (n=16) vs. 21.1% (n=38); p=0.002). As a secondary endpoint, colchicine reduced the incidence of perioperative AF (12.0 (n=20) vs. 22.0% (n=35); relative risk reduction (RRR)=45%; 95% CI, 34.0–94.0, p=0.021). Duration of perioperative AF was 3±1 vs. 8±3 days (p=0.001), suggesting that colchicine may also induce faster conversion to sinus rhythm. Colchicine significantly shortened the length of hospital stay (21 vs. 24 days; p=0.030) (38).

Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation (COPPS-2) was another trial of 360 cardiac surgery patients, where colchicine was started 2 days before surgery. Again, colchicine significantly reduced the incidence of the PPS (19.4 (n=35) vs. 29.4% (n=53)). Colchicine non-significantly reduced perioperative AF incidence (33.9% (n=61) vs. 41.7% (n=75)) (37). When COPPS and COPPS-2 are meta-analyzed, colchicine significantly reduces the absolute risk of perioperative AF by 8% (95% CI, 2%-15%; p=0.01).

In a study of 170 AF patients undergoing pulmonary vein isolation, the administration of colchicine significantly reduced C-reactive protein (CRP) levels on postprocedural day 4 (3.6 vs. 4.6 mg/L, p<0.01) and significantly lowered AF recurrences within 3 months of the procedure (16.0% vs. 33.5%, p=0.01) (39).

IL-1 related pathways may be of particular importance for AF prevention. As indicated above, colchicine significantly interferes with the release of IL-1β (30, 31). We recently completed a small, randomized pilot study of 24 patients, comparing the IL-1β inhibitor canakinumab with placebo to prevent AF recurrences after electrical cardioversion. After 6 months of follow-up, canakinumab lowered CRP levels (3.0 versus 4.8 mg/L) and demonstrated a trend towards a reduced risk of AF recurrence (HR 0.36; 95% CI, 0.11, 1.15; p=0.086) (confidential, unpublished data). Patients undergoing surgical procedures including thoracic surgery have a marked increase in markers of inflammation in the postoperative period (3). Many studies have shown that the incidence of perioperative AF is strongly related to elevations in

inflammatory markers such as CRP, white blood cell (WBC) count, and ILs (40-44). For example, patients with perioperative AF had greater WBC elevations after thoracic surgery than patients without perioperative AF (77% vs. 48%; p<0.001) (41). In another study, patients with arrhythmias after cardiac surgery had higher levels of complement activation on the second day after surgery than those without arrhythmias (800 vs. 525; p=0.004) (42).

2.4 Colchicine dosing and safety

The efficacy and safety outcomes of clinical trials for colchicine to prevent perioperative AF, PPS or pericarditis are shown in Appendix I (Tables 2 and 3). The maintenance dose for colchicine in different studies ranges from 0.5 to 1.5 mg per day. Doses of 1 mg produced similar results to 1.5 mg for the reduction of PPS (RRR 57.9% vs. 51.5%) (27, 45). The 1 mg dose used in the COPPS Trial reduced the relative risk for perioperative AF by 45% (27). A maintenance dose of 1.5 mg was associated with a higher rate of drug discontinuation (22.7 vs. 8%) compared to a 1 mg dose (27, 45). A meta-analysis suggested that a loading dose does not increase efficacy but reduces tolerability (46).

The dose used in the COPPS Trials (0.5 mg twice daily) reduced the absolute risk of perioperative AF by 8% (27, 37). These trials also showed that 43% of all perioperative AF events are missed when the study medication is started on the 3rd POD and that pre-treatment for 48 to 72 hours is not more effective in preventing perioperative AF and PPS (27, 37). Moreover, patients undergoing pulmonary vein isolation had an early benefit on a reduced risk of AF recurrence even though colchicine was initiated on the day of the intervention (39). These observations are in line with pharmacokinetic data showing that peak colchicine blood levels after a single dose of 0.6 mg of colchicine are achieved within 1 to 2 hours, suggesting rapid onset of action (47).

Despite the large number of patients who took colchicine within clinical trials, none reported serious side effects (32-35). The most common complaints occurring with colchicine relate to gastrointestinal (GI) symptoms, mainly diarrhea (Appendix I, Table 3). All these GI symptoms resolved upon discontinuation of the study drug (27, 28, 34, 37, 39, 45, 47-50). Single dose studies in patients with gout suggested that these side effects are dose-dependent (47).

Considering these data, we have established the following dosing algorithm for COP-AF. Oral colchicine at a dose of 0.5 mg or matching placebo will be given within 4 hours before surgery. The second dose of 0.5 mg or matching placebo will be given between 6:00PM and 11:59PM after surgery. Thereafter all patients will continue to receive colchicine 0.5 mg or matching placebo twice daily for a total of 10 days. No loading dose of colchicine will be administered given that a previous meta-analysis of pericarditis trials showed no increased efficacy for a loading dose but reduced tolerability (46).

This dosing regimen has been tested in the completed COP-AF pilot, a randomized trial of 100 patients who underwent thoracic surgery with similar eligibility criteria to the full COP-AF Trial. The incidence of perioperative AF at 30 days was 10% in the colchicine group and 14% in the placebo group (p=NS) (26). All perioperative AF events occurred in the first 14 days after surgery. Study drug discontinuation was similar in both groups, 85% of participants took all study medication during the first 4 days after surgery. These data suggest that the proposed dosing regimen is feasible and may reduce the risk of perioperative AF in this patient population.

2.5 MINS prevention and other potential cardiovascular benefits of colchicine

One of the most common adverse outcomes is MINS, occurring in 18% of patients after noncardiac surgery (51) (up to 27% after thoracic surgery (52-56)). Patients with MINS have an increased risk of short-term and long-term mortality (51, 57, 58), as well as adverse cardiovascular events (57, 59). The risk of adverse outcomes in patients with MINS is similar whether or not patients are symptomatic (57) and thereby fulfill the criteria for the Universal Definition of Myocardial Infarction (MI) (60). These data

highlight the important implications MINS has for patients, healthcare providers, hospitals, and society. These implications have recently been recognized and emphasized in a prominent scientific statement of the American Heart Association (61). MINS is strongly associated with elevations in inflammatory markers, including CRP, WBC count, and ILs (62-66). For example, patients undergoing noncardiac surgery with a neutrophil-lymphocyte ratio greater than four had a higher odds of having MINS (OR 2.56; 95% CI, 1.92-3.41) (62). In a small RCT of 400 patients undergoing percutaneous coronary intervention (PCI), patients receiving a single dose of colchicine on the day of the intervention had a 6.9% absolute risk reduction in myocardial injury compared with patients receiving placebo (67). While this large absolute risk difference was not statistically significant (p=0.19), these data nevertheless suggest that an adequately powered RCT may have shown a clinically important reduction in myocardial injury associated with colchicine.

Data in nonsurgical patients suggest that colchicine can prevent ischemic events. A randomized trial of colchicine 0.5 mg daily in patients with coronary artery disease showed that compared with placebo colchicine reduced the incidence of acute coronary syndrome, cardiac arrest or stroke (5.3% vs. 16.0%; HR 0.33; 95% CI, 0.18-0.59) (68). In a large randomized trial of 10,061 patients with previous MI, 150 mg of canakinumab injected every 3 months significantly reduced the risk of major cardiovascular events (3.9% per year vs. 4.5% per year; HR 0.85; 95% CI, 0.74-0.98) (69). Colchicine may also reduce infarct size among patients with ST segment elevation MI (70). 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% [n=187] vs. 9.6% [n=264]; HR 0.69; 95% CI, 0.57-0.83; p<0.001). Colchicine also reduced the incidence of MI (1.1% [n=83] vs. 1.5% [n=116]; HR 0.70; 95% CI, 0.53-0.93; p=0.01) (71). 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% [n=131] vs. 7.1% [n=170]; HR 0.77; 95% CI, 0.61-0.96; p=0.02) (72). There was no between group difference in overall adverse events. In a meta-analysis of four RCTs of patients with ischemic heart disease, colchicine reduced the RR of MI by 22% (95% CI, 6-36%; p=0.01) (73). Finally, in a randomized trial of diabetic patients undergoing PCI, colchicine reduced angiographic in-stent restenosis (16% colchicine vs. 33% control; OR 0.38; 95% CI, 0.18-0.79; p=0.007) (74). Although further studies are needed to confirm the cardiovascular benefits of colchicine, these findings suggest that colchicine may have additional cardiovascular benefits in patients undergoing thoracic surgery.

2.6 Why we need a trial of colchicine in patients undergoing thoracic surgery

From the data summarized above, it is clear colchicine is a highly effective anti-inflammatory agent that holds great potential for preventing perioperative AF and ischemic cardiovascular events in patients undergoing thoracic surgery. The effective prevention of perioperative AF and MINS is a clear unmet clinical need as it has the potential to significantly reduce mortality, stroke, and hospital stays in patients undergoing thoracic surgery. Data from patients undergoing cardiac surgery suggest colchicine prevents perioperative AF, and studies in nonsurgical patients showed that colchicine prevents ischemic events in patients with coronary artery disease; however, a large trial is now needed to determine if colchicine can prevent perioperative AF and MINS in patients undergoing thoracic surgery.

An additional potential advantage of colchicine is that it may prevent the occurrence of other inflammatory complications after thoracic surgery. Given the profound impact of colchicine on PPS and pericarditis recurrence, it is reasonable to assume that colchicine may also lower the total amount of fluid drained or the time until chest tube removal after thoracic surgery. In the COP-AF pilot study, colchicine 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, while the time to chest tube removal did not differ significantly between groups (75).

Reducing the time to chest tube removal is an important outcome, as it may lower hospital stay, reduce the incidence of postoperative infections, and improve patient's well-being.

3.0 METHODS

3.1 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 clinically important perioperative AF and MINS within 14 days of randomization.

The first co-primary outcome is time to clinically important perioperative AF which will be defined as AF developing after randomization until the end of follow-up 14 days after randomization, and that results in angina, heart failure, or symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug or electrical cardioversion (see Appendix II). This definition has been validated in previous perioperative studies (20, 76). Its criteria ensure short, asymptomatic AF episodes of unknown clinical significance are not considered events (57).

The second co-primary outcome is time to MINS, defined as an elevated troponin occurring between the initiation of surgery and the end of the 14-day follow-up period and that is considered to have resulted from myocardial ischemia.

The *secondary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the following outcomes within 14 days of 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. MINS not fulfilling the Fourth Universal Definition of MI;
4. MI;
5. time to chest tube removal; and
6. duration of stay in ICU, step-down, and in-hospital.

The *tertiary trial objectives* are to determine whether the administration of colchicine compared with placebo reduces the occurrence of 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; and
5. first occurrence of the composite of life-threatening or major bleeding.

Details about some secondary and tertiary outcomes may not be reported in the main manuscript.

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

1. first occurrence of the composite of sepsis or infection; and
2. noninfectious diarrhea.

Definitions of all secondary, tertiary and safety endpoints are given in Appendix II.

3.2 Design

This is a Phase III randomized placebo-controlled trial. Patients will be randomized to colchicine or placebo. Patients, healthcare providers, data collectors, and outcome adjudicators will be blinded to study drug allocation.

3.3 Enrollment and randomization

We will recruit 3,200 patients. All patients undergoing thoracic surgery will be screened for eligibility and all eligible patients will be approached for consent.

All eligible patients for whom written informed consent is obtained will be randomized before surgery. Research personnel will randomize patients via a 24-hour interactive web-based randomization system maintained by the coordinating centre at the Population Health Research Institute (PHRI). Patients will be randomized in a 1:1 ratio to colchicine or placebo. Randomization will be stratified by centre with block sizes of two and four. Block sizes will be unknown to site study personnel.

3.4 Sample size

Based on the blinded data from 2,100 randomized patients, we estimated an overall incidence of perioperative AF of approximately 9%. We therefore expect a perioperative AF event rate of 11% in the placebo group and 7.7% in the colchicine group (RRR 30%). Assuming a 2-sided alpha of 0.0324 and permanent discontinuation rate of 10.5% in week one and 2.7% in week two of the trial, a total of 3,200 patients (1,600 patients in each study arm) will provide 83% power for the first co-primary outcome (Appendix III).

Based on this same blinded data set, the overall incidence of elevated troponin measurements after thoracic surgery is approximately 25%. Assuming 10 to15% of these events are nonischemic in origin (57), the overall incidence of MINS will be around 22%, which is consistent with the unblinded results from the pilot trial (53). A meta-analysis of nonsurgical RCTs found that colchicine led to a 22% RRR in the risk of MI (95% CI, 6-36%; p=0.01) (73). Assuming an event rate of 24.5% in the placebo group, a 20% RRR in the colchicine group, a 2-sided alpha of 0.0176, and a permanent discontinuation rate of 10.5% in week one and 2.7% in week two of the trial, a total of 3,200 patients will provide a power of 80% for the co-primary outcome of MINS (Appendix III).

3.5 Intervention

Oral colchicine at a dose of 0.5 mg or matching placebo will be given after randomization, within 4 hours before surgery. The second dose of 0.5 mg of colchicine or matching placebo will be given between 6:00PM and 11:59PM after surgery. Thereafter all patients will continue to receive colchicine 0.5 mg or matching placebo twice daily for a total of 10 days. If the study medication is halted because of diarrhea, treatment should be resumed upon resolution of the diarrhea using 0.5 mg of colchicine or matching placebo once daily.

A study drug administration period of 10 days was chosen based on the following data. Polanczyk et al. reported that 66% of perioperative supraventricular arrhythmias (including perioperative AF) occurred in the first 3 days, and 96% occurred during the first 10 days (11). In the COP-AF pilot, all perioperative AF events occurred within 2 weeks of follow-up. Furthermore, the inflammatory response is greatest around the time of surgery (3).

Patients discharged home before completing the study medication will be given a package containing colchicine 0.5 mg or placebo to complete 10 days of treatment. In the event that the surgery is postponed the patient will continue to receive colchicine or placebo for 9 days after their surgery or until the end of follow-up 14 days after randomization, whichever occurs first.

3.6 Eligibility

Inclusion criteria

Patients are eligible if they:

1. are undergoing thoracic surgery with general anesthesia;

2. are ≥55 years of age at the time of randomization;
3. are expected to require at least an overnight hospital admission after surgery; and
4. provide written informed consent to participate.

Exclusion criteria

We will exclude patients who meet any of the following criteria:

1. patients with a prior history of documented AF;
2. patients currently taking anti-arrhythmic medication other than β-blockers, calcium channels blockers or digoxin;
3. patients undergoing minor thoracic interventions/procedures (i.e., minor chest-wall surgeries, chest tube insertions, or needle pleural/lung biopsies);
4. patients with contraindications to colchicine (i.e., allergy to colchicine, myelodysplastic disorders, or an estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m);
5. patients not expected to take oral medications for >24 hours after surgery (e.g., esophagectomy);
6. patients scheduled for lung transplantation;
7. patients currently taking non-study colchicine before surgery;
8. patients with severe hepatic dysfunction;
9. patients with aplastic anemia;
10. women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding;
11. 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[*];
12. human immunodeficiency virus (HIV) patients treated with antiretroviral therapy; or
13. patients scheduled for thoracoscopic lung wedge resection only[†].

[*] While systemic administration of these medications is contraindicated, patients with local administration only (e.g., eye drops, creams) are eligible for the trial.

[†] Patients scheduled for multiple thoracoscopic lung wedge resection only are eligible for inclusion.

3.7 Recruitment

Trial participants will be recruited through pre-operative assessment clinics and by systematic screening of thoracic surgery lists. All patients undergoing elective or urgent thoracic surgery who meet the inclusion criteria will be considered for potential enrollment. Study personnel will interview and consent patients before their planned surgery and before randomization.

Study personnel will also collect data on recruitment rates and complete weekly recruitment case report forms (CRFs) documenting the number of patients eligible, randomized, and reasons for not enrolling.

3.8 Follow-up

Patients will be followed daily during their hospitalization until discharge. They will have a daily troponin and creatinine measurement for the first 3 days after surgery, if they are still in hospital (78). They will remain on colchicine or placebo for a total of 10 days after randomization. Patients who are discharged before the end of their trial treatment will be given a package containing colchicine or placebo to complete a total of 10 days. After discharge, patients will be followed during their visits to the surgical clinics at 14 days after randomization. Patients who do not attend the surgical clinics will be contacted via the phone. Number of days alive and at home, length of stay and re-admission occurrences will be extracted from patient charts and recorded on patient data collection forms. With the current follow-up practice at our divisions and our previous experience in performing large, randomized trials, we expect minimal loss of follow-up in this study. We will use the same mechanisms for ensuring full follow-up as in our previous large international perioperative trials (99.8% complete follow-up in POISE, 99.9% complete follow-up

in POISE-2). The end of the trial will coincide with the completion of the last visit by all patients randomized, excluding those who have withdrawn consent or been lost to follow-up.
Table 1: Study procedure schedule

	Enrollment	Baseline Assessment	POD 1-3	Hospital Discharge	14 Day/Final Follow-up
Inclusion/exclusion criteria	X				
Written informed consent	X				
Randomization	X				
Study drug dispensation	X				
Demographics		X			
Vital signs and physical measures*		X			
Concomitant medications		X		X	X
Daily troponin†			X		
Daily creatinine‡			X		
Daily 12-lead ECG§			X		
Clinical events				X	X
Serious adverse events				X	X
Study drug compliance					X

* Includes blood pressure, heart rate, hemoglobin, serum creatinine, height and weight measurements

† Daily troponin measurements must be done on PODs 1 to 3 or until hospital discharge, whichever comes first.

‡ Daily creatinine measurements must be done on PODs 1 to 3 or until hospital discharge, whichever comes first.

§ Daily 12-lead electrocardiograms (ECGs) are strongly recommended on PODs 1 to 3 or until hospital discharge, whichever comes first.

3.9 Outcome monitoring

To maximize the generalizability of this trial, we will interfere as little as possible with the usual heart rhythm monitoring practices in the local centres. Patients will undergo continuous heart rhythm monitoring intraoperatively, in recovery rooms, ICUs, and step-down units according to local standards. If perioperative AF is observed on a cardiac monitor, a 12-lead ECG will be obtained. We strongly recommend daily 12-lead ECGs will be performed for the first 3 days after surgery. Physicians will be encouraged to obtain a 12-lead ECG if patients report palpitations, chest pain or shortness of breath, or if the treating physician feels it is indicated. We will not conduct any additional heart rhythm monitoring (i.e., Holter monitoring) on study participants, as the primary endpoint of this trial is clinically important perioperative AF as defined in section 3.1 and Appendix II.

Daily troponin will be recorded in the first 3 days after surgery to measure the impact of colchicine on MINS (78). Daily creatinine will also be recorded in the first 3 days after surgery to measure the impact of colchicine on renal function.

3.10 Outcome adjudication

The adjudication committee will be composed of a committee of clinicians who have expertise in perioperative outcomes. The committee will be blinded to treatment allocation and will adjudicate the co-primary endpoints and other outcomes according to a separate adjudication plan. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Study definitions for this trial can be found in Appendix II.

3.11 Patient safety and reporting of adverse events

3.11.1 Definitions serious adverse event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event.

A suspected unexpected serious adverse reactions (SUSAR) is an event which is:

- suspected to be causally associated with colchicine;
- unexpected in its nature, severity, or outcome (i.e., the reaction(s) is not consistent with the reference information in the product monograph for colchicine);
- serious (as defined above for an SAE); and
- not an efficacy or safety outcome as defined in the protocol (including events resulting in death).

3.11.2 Safety reporting

Efficacy or safety outcomes will not be considered as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional for this medical condition. All events considered as part of the primary, secondary, tertiary, or safety events as outlined in Sections 3.1 and 3.11 should be reported on the appropriate pages in the CRFs but not as SAE, unless considered exceptional for this medical condition.

The Site Principal Investigator (PI) (or qualified delegate) is responsible for reporting all SAEs in DFexplore, regardless of whether the event is considered related or not related to the study drug. Qualified site study personnel should report all SAEs immediately and no later than 24 hours of their knowledge of the event. The Project Office will perform expedited reporting of SUSARs classified as life-threatening to regulatory authorities as soon as possible and no later than seven calendar days of first knowledge by the PHRI (unless otherwise specified by regulatory authorities). All other SUSARs will be reported as soon as possible and no later than 15 calendar days of first knowledge by the PHRI.

The PHRI is responsible for notifying sites of a SUSAR by distributing an Investigator Notification to them to forward to their respective ethics committees. This will be done in parallel with the aforementioned submissions to regulatory authorities.

3.11.3 Safety monitoring and emergency unblinding

Patients' safety will be monitored through the Data and Safety Monitoring Committee (DSMC). The DSMC will review all SAEs.

Legitimate situations such as a large overdose of the study drug may require unblinding. We will avoid unblinding when appropriate through the use of the following strategy. Prior to unblinding, the attending

physician will have to complete a detailed checklist to document the reason for unblinding and whether alternatives have been explored. Stopping the study medication, skipping a dose, or giving open label medication will be adequate for the management of most situations. If, after these steps, the local study investigator believes emergency unblinding is essential for the patient's management, then it can be undertaken. We recommend that all unblinding decisions be made jointly with the Project Office.

3.12 Statistical analysis

Statistical analysis will follow the trial completion according to a separate statistical analysis plan. This plan will be written before the termination of the trial and before unblinding. We will plot the cumulative incidence curves between the two treatment groups for the co-primary outcomes and compare them using a log-rank test. We will use Cox regression models to obtain HRs and 95% CIs, 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. If needed, the competing risk of death will be taken into account using subdistribution hazards models proposed by Fine and Gray (79). As this trial has two co-primary outcomes, the 'fallback procedure' will be used to determine if the outcomes are statistically significant (80). The overall alpha-level will be set to 0.05 and will be divided between the two co-primary outcomes in the final analysis. At the end of the trial, we will evaluate a potential overlap between the two co-primary outcomes, and we will adjust the alpha of the second co-primary outcome to reflect the actual amount of overlap at that time. 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.

For all secondary, tertiary and safety outcomes other than number of days alive and at home and length of hospital stay, we will use the same approach, but without fallback procedure and a significance level of 0.05. We will follow the intention-to-treat principle (i.e., patients will be analyzed within the group they were allocated). All efforts will be made to collect information about the clinical outcomes for those participants lost to follow-up. In case of no contact, the participant will be censored on their last day of available contact during the study.

3.13 Subgroup analyses

Cox proportional hazards models assessing each co-primary outcome will 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 take into account other credibility criteria to judge the likelihood of a subgroup effect (81).

We will assess age, type of surgery (non-thoracoscopic versus thoracoscopic surgery) and renal function as prespecified subgroups for the two co-primary outcomes. We expect that colchicine has a stronger effect in older patients, in those undergoing non-thoracoscopic surgery, and in those with lower renal function.

3.14 Interim analyses

Two interim efficacy analyses based on the primary outcome will occur when 50% and 75% of the 14-day data are available. The DSMC will employ the modified Haybittle-Peto rule of 4 SDs (α=0.0001) when 50% of the data are analyzed, and 3 SDs (α=0.0027) for analyses in the second half (82, 83). For a finding to be considered significant, these predefined boundaries have to be exceeded in ≥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.

The DSMC will monitor for an adverse impact of colchicine on sepsis or mortality. For these analyses, a 3 SDs excess in the first half and a 2.6 SDs excess in the second half of the trial would trigger discussions about stopping for harm. At any time during the trial if safety concerns arise the DSMC chairperson will assemble a formal meeting of the full committee. The DSMC will make 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 will invite the Operations Committee to explore all possibilities before a decision is made.

3.15 Substudies

Substudies may be added based on the recommendation of the Project Office Operations Committee. These substudies will not be part of the main protocol and the analysis and reporting of these substudies will be separate from the main study.

4.0 TRIAL MANAGEMENT

David Conen is the PI of the COP-AF trial. He has substantial experience in setting up and conducting large scale multicenter studies. PJ Devereaux is the Trial Chair. He has led, and is leading, large international perioperative trials (e.g., POISE, POISE-2, HIP ATTACK, MANAGE), and observational studies (e.g., VISION, VISION Cardiac Surgery).

The randomization and organization of the trial will be conducted at the PHRI. The Project Office at PHRI is responsible for the day-to-day running of the trial. The Program Manager of the trial has extensive experience in running large cardiovascular trials and will work part-time on the trial and oversee the full-time Study Coordinator who has experience in perioperative RCTs. The Study Coordinator is responsible for the daily conduct of the trial. Prior to initiating the trial, investigator site research personnel will conduct in-services for the nurses on the relevant floors and clinics (e.g., pre-admission clinic, surgical floors); and the local trial investigators will review the protocol with the relevant physician groups (e.g., anesthesia). All centres will display posters of the eligibility criteria throughout the hospitals. Centres will also distribute pocket cards of the trial eligibility criteria and protocol to relevant physicians and allied health care workers. The posters and pocket cards will contain the contact information of the site investigator and research personnel. Investigators and research personnel will receive regular enrollment reports to review study progress. Research personnel will keep daily screening records of all patients who were eligible but not enrolled in the trial and the reason why. They will submit these records to the Project Office weekly.

The Project Office Operations Committee will meet bi-monthly to review trial progress and all pertinent issues related to the conduct of COP-AF. The Project Office Operations Committee will report directly to the International Operations Committee. This committee will include broad international representation, and members may be added as the trial progresses. The International Operations Committee will hold conference calls annually to review the progress of the trial, discuss international COP-AF issues, and strategize to ensure the successful conduct and completion of the trial.

The International Operations Committee will report to the international Steering Committee, consisting of experts in perioperative medicine, cardiology, intensive care, internal medicine, statistics and thoracic surgery. The Steering Committee will oversee the conduct of the trial. For each participating country, the Project Office will appoint a member of the Steering Committee to act as the National PI. At each Steering Committee meeting the National PIs will provide a brief report to the Steering Committee regarding the country's progress in COP-AF, goals for the coming year, and any issues that require input. The Steering Committee will include a broad international representation, and we may add members as the trial progresses.

All participating centres will have a Centre PI, and this individual is responsible for: (1) obtaining ethics approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and forwarding this to the Project Office; (2) ensuring study approval is obtained before recruitment starts; (3) ensuring the protocol is followed; (4) ensuring all physicians and nurses involved in the perioperative care of patients undergoing thoracic surgery are aware and informed about the COP-AF Trial (this will involve organizing and presenting educational in-services about the trial and distributing posters and pocket protocols); (5) ensuring that all surgical patients are screened for the trial; (6) ensuring that all enrolled patients have their troponin levels, creatinine levels, ECGs and echocardiograms obtained when appropriate; (7) ensuring that all enrolled patients are followed appropriately; (8) ensuring that all CRFs are promptly and accurately completed and submitted to the Project Office, and that all inquiries from the Project Office regarding patient forms or other matters are addressed promptly; (9) ensuring that a simple screening log is kept of all eligible thoracic surgery patients who are not enrolled in COP-AF and the primary reason they were not enrolled; (10) ensuring they maintain the list of patient identification numbers and patient names to enable identification of hospital records at a later date according to local regulation.

5.0 ETHICAL CONSIDERATIONS

This trial will be conducted in compliance with the protocol, principles laid down in the Declaration of Helsinki, Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), and all applicable laws and regulations of the countries in which the study is performed. Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, and subject recruitment materials/process. Amendments to the protocol will require IRB/IEC approval. The Investigator also agrees to provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.

All patient information will be stored in a high security computer system and kept strictly confidential. Subject confidentiality will be further ensured by utilizing subjects' identification code numbers to correspond to treatment data in the computerized files. Only the DSMC and the trial statistician who reports to the DSMC will be aware of the unblinded data until the trial is completed. The DSMC will be composed of individuals with substantial trial experience and perioperative medicine knowledge and will be responsible to ensure patients' safety and the accuracy of the data.

Patients' medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited. Medical information may be given to patients' personal physicians or to other appropriate medical personnel responsible for the patients' welfare. Data generated as a result of the trial are to be available for inspection on request by the participating physicians, IRB/IEC and competent authorities.

6.0 ENSURING DATA QUALITY

Several procedures will ensure data quality including:

1. All research personnel will undergo a training session prior to trial initiation to ensure consistency in trial procedures including data collection and reporting;
2. All centres will have a detailed trial Manual of Operations that will outline each step of the protocol;
3. Investigators can use a toll-free phone number to a help line at the Project Office to resolve any problems or questions that arise;
4. Project Office personnel will validate data using quality control checks to identify errors or omissions; then the Project Office personnel will notify the sender of any such issues with data validation via secure internet, email, telephone, or visit if necessary;

5. Project Office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, consistency, thoroughness, completeness of data collection and event rates, and they will immediately address any identified issues;
6. The Programmer will create internal validity and range checks using the DFexplore Database System which will identify any errors or omissions and notify the sender and Research Assistants of any such issues;
7. The Research Assistants will undertake multi-level data validation of the trial CRFs;
8. The Research Coordinator (or delegate) will (a) send investigators regular quality control reports; and (b) obtain from the trial statistician and present to the PI reports on internal validity and range checks using the DFexplore Database System;
9. The Study Statistician will undertake statistical monitoring as requested by the Project Office to identify outliers through comparing centre and data collector variables (e.g., rates of reported primary outcomes); and
10. Data already collected from participants requesting withdrawal will be maintained to protect the integrity of the study.

7.0 IMPORTANCE OF THE TRIAL

Perioperative AF and MINS are among the most common serious complications occurring in patients undergoing thoracic surgery. This large, randomized trial will determine whether colchicine, a potent anti-inflammatory drug, lowers the risk of perioperative AF, MINS, and other inflammatory complications in patients undergoing thoracic surgery. Finding a safe, effective, and low-cost intervention to prevent cardiovascular complications holds great potential and addresses a major unmet clinical need, as it may decrease length of ICU and hospital stay, improve the quality of perioperative care, lower costs, and reduce the risk of stroke or death.

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9.0 APPENDIX I: TABLES

Table 2: **Summary of clinical trials for colchicine to prevent post-pericardiotomy syndrome, pericarditis or atrial fibrillation**

Study	Colchicine Dose	Number of Patients	Time Treatment Initiated	Treatment Duration	Follow-up Duration	Primary Outcome	Colchicine vs. Placebo	Secondary Outcomes
Finkelstein (2002)	1.5 mg/day (divided in 3 doses)	163[a] (enrolled) 111 (analyzed)	POD 3	1 month	3 months	PPS after cardiac surgery	10.6% vs. 21.9%; RRR=51.5%; p=0.135	Pericarditis[b]: 4.5% vs. 12.6%; RRR=64.2%
COPE (2005)[c]	1-2 mg first day then 0.5-1 mg/day[d]	120	Day of presentation with pericarditis	3 months	24 months	Recurrent pericarditis	11.7% vs. 33.3%; RRR=64.8%; p=0.009	Persistence of symptoms after 3 days of therapy: 11.7% vs. 36.7%; RRR=68.1%; p=0.003
CORE (2005)[c]	1-2 mg first day then 0.5-1 mg/day[d]	84	Day of presentation with pericarditis	6 months	20 months	Recurrent pericarditis	24% vs. 50.6%; RRR=52.5%; p=0.02	Persistence of symptoms after 3 days of therapy: 10% vs. 31%; RRR=67.7%; p=0.03
COPPS (2010)	1 mg twice on first day then 0.5 mg twice daily[e]	360	POD 3	1 month	12 months	PPS after cardiac surgery	8.9% vs. 21.1%; RRR=57.9%; p=0.002	Pleural effusion: 12.2% vs. 25.6%; RRR=52.3%; p=0.002 Pericardial effusion: 12.8% vs. 22.8%; RRR=43.8%; p=0.019
COPPS-AF (2010)	Same as COPPS	All patients in sinus rhythm on POD3 (336/360)	POD 3	1 month	12 months	Development of AF	12% vs. 22%; RRR=45%; p=0.021	Duration of postoperative AF: 3±1.2 days vs. 7.7±2.5 days; p<0.001 Hospital stay[f]: 21 days vs. 24 days; p=0.030
CORP (2011)	1-2 mg first day then 0.5-1 mg/day[d]	120	Day of presentation with pericarditis	6 months	18 months	Recurrent pericarditis	24% vs. 55%; RRR=56%; p<0.001	Persistence of symptoms after 3 days of therapy: 23% vs. 53%; RRR=56%; p=0.001
Defteros et al. (2012)	1 mg/day	170[g]	Day of AF ablation	3 months	3 months	AF recurrence	16% vs. 34%; p=0.01; RRR=53%	Postinterventional CRP: 3.6 mg/L vs. 4.6 mg/L; p<0.01

ICAP (2013)	0.5-1 mg/day	240	Day of presentation with pericarditis	3 months	18 months	Incessant or recurrent pericarditis	17% vs. 38%; RRR=56%; p<0.001	Persistence of symptoms after 3 days of therapy: 19% vs. 40%; p=0.001
COPPS-2 (2014)	0.5-1 mg/day	360	PreOD 2-3	1 month	3 months	PPS after cardiac surgery	19.4% vs. 29.4%; Absolute risk reduction (ARR)=10.0%; 95% CI, 1.1, 18.7	Postop AF: 33.9% vs. 41.7%; ARR 7.8; 95% CI, 2.2, 17.6 Pleural/pericardial effusion: 57.2% vs. 58.9%; p=NS
CORP-2 (2014)	0.5-1 mg/day	240	Day of presentation with pericarditis	6 months	18 months	Recurrent pericarditis	21.6% vs. 42.5%; RRR=51%; p=0.0009	Persistence of symptoms after 3 days of therapy: 19% vs. 44%; p=0.0001
POPE-2 (2015)	1 mg/day	197	7-30 days post cardiac surgery	14 days	14 days	Difference in pericardial effusion	p=0.23	-
COP-AF pilot (2016)	1.2 mg/day	100	Day of surgery	10 days	10 days	Periop AF	10% vs. 14%; RRR=31%	Infection/sepsis: 12% vs. 16%; p=0.62

POD: Postoperative day; PreOD: Preoperative day; PPS: Post-pericardiotomy syndrome; AF: Atrial fibrillation; RRR: Relative risk reduction

[a] Analysis on 111 patients only; excluded 52 patients because of postoperative complications, non-compliance (10.4%), GI side effects (11.7%), corticosteroid therapy (5.5%), renal failure (1.2%), stroke (1.8%), pancreatitis (0.6%) and allergic reaction (0.6%).

[b] Pericarditis: the colchicine group had a total of six events of pericarditis (four patients had one event, and one patient two), and the placebo group 17 events (twelve patients had one event, one patient two, and one patient three)

[c] Open label RCT, comparing aspirin alone to aspirin and colchicine for prevention of recurrent pericarditis.

[d] The lower dose (1 mg on first day then 0.5 mg daily, all divided in two doses) was given to patients who weigh <70 kg or those intolerant to the high dose regimen, all patients received aspirin 800-1000 mg (or ibuprofen 600 mg in COPPS) orally every 6 or 8 hours for 7 to 10 days with gradual tapering over 3 to 4 weeks.

[e] Dose was halved in patients weighing <70 kg

[f] Total hospital stay includes in-hospital (9.4±3.7 vs. 10.3±4.3 days; p=0.040) and rehabilitation stay (12.1±6.1 vs. 13.9±6.5 days)

[g] A total of 9 patients (4 in the colchicine arm) did not present at any follow-up visit and were therefore excluded from the analysis

Table 3: **Summary of adverse events reported for colchicine to prevent post-pericardiotomy syndrome, pericarditis or atrial fibrillation**

Study	Colchicine Dose	Discontinuation of Colchicine vs. Placebo	Adverse Events
Finkelstein (2002)*	1.5 mg/day (divided in 3 doses)	Not reported#	Not reported
COPE (2005)	1-2 mg first day then 0.5-1 mg/day	8.3% vs. 0.0%	8.3% diarrhea (n=5/60)
CORE (2005)	1-2 mg first day then 0.5-1 mg/day	7% vs. 0.0%	7% diarrhea (n=3/42) all resolved after withdrawal. 2 patients had a relapse of pericarditis after discontinuing colchicine
COPPS (2010)	1 mg twice on first day then 0.5 mg twice daily	11.7% vs. 6.7%; p=0.145	GI: 8.9% vs. 4.4% No severe side effects reported
CORP (2011)	1-2 mg first day then 0.5-1 mg/day (twice daily dosing)	8% vs. 7%	GI intolerance: 7% colchicine vs. 5% placebo
Defteros et al. (2012)	0.5 mg twice daily	12.3% vs. 6.3%; p=0.18	Diarrhea 8.6% vs. 1.3%; p=0.03
ICAP (2013)	0.5 mg once daily if <70kg 0.5 mg twice daily if ≥70kg	11.7% vs. 8.3%; p=0.52	GI intolerance: 9% colchicine vs. 8% placebo
COPPS-2 (2014)	0.5 mg once daily if <70kg 0.5 mg twice daily if ≥70kg	17.8% vs. 21.7%; p=NS	GI 14.4% colchicine vs. 6.7% placebo
CORP-2 (2014)	0.5 mg once daily if <70kg 0.5 mg twice daily if ≥70kg	6.7% vs. 5.8%	Overall: 11.7% colchicine vs. 8.3% placebo GI: 7.5% vs. 7.5%
POPE-2 (2015)	1 mg/day#	9.8% vs. 3.0%	Not reported
COP-AF pilot (2016)	0.6 mg twice daily	29% vs. 29%	Diarrhea: 10% vs. 2%, p=0.11

GI: Gastrointestinal includes nausea, abdominal pain, vomiting or cramps.

* The authors did not report adverse events by treatment group, only for the overall patient population. Twenty two percent of all patients enrolled in the trial (placebo and colchicine groups) were excluded for the following reasons: 11.7% due to GI symptoms; 10.4% due to non-compliance; 5.5% due to steroid therapy; 1.8% due to stroke; 1.2% due to renal failure; 0.6% due to allergic reaction; and 0.6% due to acute pancreatitis. These patients were excluded after randomization, however their allocation was not reported.

Dosing schedule not reported (once vs. twice a day)

10.0 APPENDIX II: EVENTS DEFINITIONS

Atrial fibrillation/atrial flutter (AF):
AF is defined as the replacement of the consistent P waves on 12-lead ECG, rhythm strip or documented telemetry tracing, by rapid oscillation or fibrillatory/flutter waves.

Clinically important perioperative atrial fibrillation/atrial flutter (AF):
Clinically important perioperative AF is defined as AF developing after randomization until the end of follow-up 14 days after randomization, that is documented on an ECG, rhythm strip or telemetry tracing, and that results in angina, heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug or electrical cardioversion.

Sub-classification of death:
Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction (MI), cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g., trauma, infection, malignancy).

Myocardial Injury after Noncardiac Surgery (MINS):
MINS is defined as any MI (as defined below) 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 only exceptions to the definition of an elevated troponin will be to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L.

Myocardial Injury after Noncardiac Surgery not fulfilling the Fourth Universal Definition of Myocardial Infarction:
Using the MINS definition above, MINS not fulfilling the fourth Universal Definition of MI includes all MINS events that do not fulfil the definition of MI below (i.e., MINS without ischemic signs or symptoms, ischemic changes on the ECG, and evidence of new loss of viable myocardium or new regional wall motion abnormality on non-invasive tests).

Myocardial infarction (Fourth Universal Definition):
The diagnosis of MI requires any one of the following criteria:

1. Detection of a rise or fall of a cardiac troponin value (cTn) with at least one value above the 99th percentile of the upper reference limit (URL) with at least one of the following:
    a. Ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort, shortness of breath, pulmonary edema).
    b. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds.
    c. New, or presumed new, ECG changes indicative of ischemia (i.e., ST elevation [≥2mm in leads V1, V2, or V3 and ≥1mm in the other leads], ST segment depression [≥1mm], or symmetric inversion of T waves ≥1mm in at least two contiguous leads, or development of new left bundle branch block (LBBB).
    d. Imaging evidence of new loss of viable myocardium or new or presumed new, cardiac regional wall motion abnormality in a pattern consistent with an ischemic etiology.
    e. Identification of a coronary thrombus by angiography or autopsy (Post-mortem

demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large, circumscribed area of necrosis with or without intramyocardial hemorrhage).

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cTn were obtained, or before cTn values would be increased.
3. PCI related MI is defined by elevation of a cTn value (>5 x 99th percentile URL) in patients with a normal baseline cTn value (≤99th percentile URL) or a rise of a cTn measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
4. Stent thrombosis or restenosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cTn values with at least one of value above the 99th percentile URL (as defined under 1).
5. CABG related MI is defined by elevation of cTn values (>10 x 99th percentile URL) in patients with a normal baseline cTn value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
6. Isolated development of new pathological Q waves with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Myocardial infarction <u>after MINS</u>:

MI after MINS requires the following criteria:

1. Detection of a rise or fall of a cardiac biomarker with at least one value above the 99th percentile of the URL and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
    a. Ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
    b. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds;
    c. New or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [>2 mm in leads V1, V2, or V3 or >1 mm in the other leads], ST segment depression [>1mm], or symmetric inversion of T waves >1 mm) in at least two contiguous leads;
    d. New LBBB;
    e. New cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or
    f. Identification of intracoronary thrombus on angiography or autopsy.

Stroke:

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to focal ischemia of the brain, retina, or spinal cord and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours, unless supported by clear evidence of infarction on neurologic imaging (magnetic resonance imaging [MRI] or computerized tomography [CT]). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke, or uncertain (used when no imaging is available to exclude hemorrhage). Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary

transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction (see above, this excludes flow related infarcts distal to stenosis) and as documented by CT scan/MRI that is consistent with infarction.
2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.
    a. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (i.e., a decrease of at least 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.
    b. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.
3. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs. hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage vs. severe hemorrhagic transformation); these stroke events will be classified as undetermined.
4. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage.
    a. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e., hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e., contusions) due to trauma, or microbleeds detected by MRI.
    b. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.

Acute heart failure:

Acute heart failure is defined as a clinical sign (i.e., at least one of the following: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following:

1. Radiographic findings (i.e., at least one of the following: vascular redistribution, interstitial pulmonary edema, frank alveolar pulmonary edema, or multiple and diffuse bilateral B lines on ultrasonography);
2. Elevated levels of natriuretic peptides; or
3. Heart failure treatment implemented with diuretics with documented clinical improvement.

Pulmonary embolism:

The diagnosis of pulmonary embolism requires any one of the following:

1. A high probability ventilation/perfusion lung scan;
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan;

3. An intraluminal filling defect on pulmonary angiography; or
4. A positive diagnostic test for deep vein thrombosis and one of the following:
    a. Non-diagnostic (i.e., indeterminate or intermediate probability) ventilation/perfusion lung scan; or
    b. Non-diagnostic (i.e., subsegmental defect or technically inadequate study) helical CT scan.

Deep venous thrombosis of leg or arm:
The diagnosis of deep venous thrombosis requires any one of the following:
1. A persistent intraluminal filling defect on contrast venography;
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.

Life-threatening bleeding:
Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy/vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Major bleeding:
Major bleeding is defined as bleeding that is not specified under "life-threatening bleeding" above, and
1. Results in a postoperative hemoglobin ≤70g/L and the patient receiving a transfusion of ≥2 units of red blood cells;
2. Results in a hemoglobin drop of ≥50 g/L and the patient receiving a transfusion of ≥2 units of red blood cells;
3. Results in the patient receiving a transfusion of ≥4 units of red blood cells within a 24 hour period;
4. Leads to one of the following interventions: embolization, superficial vascular repair, nasal packing; or
5. Is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

Sepsis/infection:
Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

The Third International Consensus Definitions Task Force defines sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, sepsis will require a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system:
1. Glasgow Coma Scale (GCS) score of 13 or less (1 point);
2. Systolic blood pressure of 100 mm Hg or less (1 point); and
3. Respiratory rate of 22 breaths/min or more (1 point).

Noninfectious diarrhea:
Noninfectious diarrhea is defined as a new onset of >3 loose bowel movements per day. The diarrhea should not be caused by an infectious organism.

11.0 APPENDIX III: POWER AND SAMPLE SIZE CALCULATIONS

Clinically important atrial fibrillation

Power	Sample Size	Control Event Rate	Hazard Ratio	Alpha
80	2,717	0.12	0.7000	0.0324
85	3,079	0.12	0.7000	0.0324
90	3,567	0.12	0.7000	0.0324
80	2,993	0.11	0.7000	0.0324
85	3,392	0.11	0.7000	0.0324
90	3,929	0.11	0.7000	0.0324
80	3,323	0.10	0.7000	0.0324
85	3,767	0.10	0.7000	0.0324
90	4,364	0.10	0.7000	0.0324

Myocardial injury after noncardiac surgery

Power	Sample Size	Control Event Rate	Hazard Ratio	Alpha
80	2,924	0.225	0.78	0.0176
85	3,287	0.225	0.78	0.0176
90	3,773	0.225	0.78	0.0176
80	3,631	0.222	0.80	0.0176
85	4,082	0.222	0.80	0.0176
90	4,687	0.222	0.80	0.0176
80	2,595	0.247	0.78	0.0176
85	2,917	0.247	0.78	0.0176
90	3,349	0.247	0.78	0.0176
80	3,201	0.245	0.80	0.0176
85	3,598	0.245	0.80	0.0176
90	4,132	0.245	0.80	0.0176