COLCHICINE TO PREVENT PERIOPERATIVE ATRIAL FIBRILLATION

COLCHICINE FOR PREVENTION OF PERIOPERATIVE ATRIAL FIBRILLATION IN PATIENTS UNDERGOING THORACIC SURGERY: PILOT STUDY

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TITLE: Colchicine For Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery (COP-AF): Pilot Study

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LAY ABSTRACT

In patients undergoing thoracic surgery, as many as 1 in 5 patients will develop atrial fibrillation (fast disorganized chaotic heart beats). This may lead to complications including death, stroke (clot in the brain), and longer hospital stay. One theory is that atrial fibrillation is due to excessive inflammation in the body after surgery. The purpose of this pilot study is to determine whether it is feasible to conduct a large study to test the effect of colchicine, an anti-inflammatory drug, on the risk of developing atrial fibrillation after thoracic surgery. Participants were randomly assigned to take either colchicine or placebo starting on the day of the surgery for 10 consecutive days. We documented the presence or absence of atrial fibrillation after surgery. We demonstrated feasibility of enrolment, application of the intervention, and follow up of 100 participants. The results of this study will be useful in developing a larger multicentre trial.

ABSTRACT

BACKGROUND: Up to 20% of patients will develop postoperative atrial fibrillation (POAF) or atrial flutter after thoracic surgery. These arrhythmias have been associated with serious complications such as death, stroke, and increased hospital length of stay.

OBJECTIVES: This study aimed to determine: the feasibility of recruiting patients undergoing thoracic surgery to a randomized controlled trial (RCT) comparing colchicine and placebo for the prevention of POAF, the resources required to conduct a large trial, and compliance with the study drug. The main efficacy outcome was POAF or atrial flutter within 30 days of randomization.

METHODS: Patients aged 55 years and older undergoing a resection of tumor in the lung were recruited from two Canadian centers. Participants were randomly assigned to receive colchicine 0.6mg or placebo orally within 4 hours before surgery. Postoperatively, patients received colchicine 0.6mg or placebo twice daily for 10 days. Troponin measurement and an electrocardiogram were performed daily during the first 3 days after surgery. Patients' follow-up occurred in hospital and at 30-days.

RESULTS: One hundred patients were randomized (49 to colchicine and 51 to placebo) over a period of 12 months. All patients completed the 30-day follow-up. The mean staff time required to recruit and follow-up each patient was 165 minutes. 71% of patients completed the study drug course without interruption. New POAF or atrial flutter

occurred in 5 (10.2%) of the patients in the colchicine group and 7 (13.7%) of the patients in the placebo group (adjusted hazard ratio 0.69; 95% confidence interval, 0.20-2.34; p= 0.55).

CONCLUSION: These results show the feasibility of COP-AF pilot study. This pilot study will serve as the foundation for the large multicentre COP-AF RCT.

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ABBREVIATIONS

ACS: Acute coronary syndrome
AE: Adverse event
AF: Atrial fibrillation
aHR: Adjusted hazard ratio
ARDS: Acute respiratory distress syndrome
CABG: Coronary artery bypass graft
CCU: Critical care unit
CI: Confidence interval
CK- MB: Creatinine kinase (muscle and brain)
COP-AF: COlchicine For Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery
COPPS: Colchicine for the Prevention of the Postpericardiotomy Syndrome
COPPS POAF: Colchicine for the Prevention of the Postpericardiotomy Syndrome Atrial Fibrillation sub-study
CRF: Case report form
DIC: Disseminated intravascular coagulopathy
DMC: Data monitoring committee
DVT: Deep venous thrombosis
EAC: Event adjudication committee
ECG: Electrocardiogram
eGFR: Estimated glomerular filtration rate
Hb: Haemoglobin
HR: Hazard ratio
ICU: Intensive care unit
IEC: Independent ethics committee
IRB: Institutional review board
IWRS: Interactive web randomization system
LBBB: Left bundle branch block
MI: Myocardial infarction
MINS: Myocardial injury after noncardiac surgery
NNT: Number needed to treat
NSAIDs: Nonsteroidal anti-inflammatory drugs
NSTEMI: Non-ST elevation myocardial infarction
OR: Odds ratio
PAR: Population attributable risk
PCI: Percutaneous coronary intervention
PE: Pulmonary embolism
PHRI: Population Health Research Institute
PI: Principal investigator
PO: Per os (by mouth)
POAF: Postoperative atrial fibrillation
POISE: Perioperative Ischemic Evaluation Study

PPS: Postpericardiotomy syndrome
RCT: Randomized controlled trial
RR: Relative risk
RRR: Relative risk reduction
SD: Standard deviation
SAE: Serious adverse events
SIRS: Steroids in cardiac surgery trial
STEMI: ST elevation myocardial infarction
TIA: Transient ischemic attack
URL: Upper reference limit
VISION: Vascular events in Noncardiac Surgery Patients Cohort Evaluation
VTE: Venous thromboembolism

DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary writer of this manuscript. I am also primarily responsible for the interpretation of the statistical analyses and reporting of the results. Patient data were collected by qualified teams led by Dr. P.J. Devereaux and Dr. Sadeesh Srinathan.

INTRODUCTION

Over 230 million people undergo surgery each year across the world.(1) Substantial advances in surgery, safer anesthetic approaches, and a shift towards advanced care of the elderly have contributed to the rise in the number of patients undergoing surgery. Consequently, older patients are now having surgery when compared to a decade ago. In fact, it is estimated that 40% of American patients undergoing surgery are ≥65 years of age.(2) Age is associated with substantial postoperative morbidity and mortality. As a result, the incidence of postoperative cardiovascular complications is increasing. It is estimated that 8 million patients will develop a major cardiovascular complications within 30 days of inpatient noncardiac surgery.(1)

Postoperative atrial fibrillation (POAF) and atrial flutter are the most common cardiac arrhythmias after surgery.(3) Development of new POAF and atrial flutter is associated with an increased risk of postoperative death, stroke, and prolonged hospitalization.(4) Thus, preventing these arrhythmias is fundamental for patient's best care in addition to reducing healthcare system costs.(4)

Trials have demonstrated that colchicine, an anti-inflammatory drug, prevents postpericardiotomy syndrome (PPS) and potentially prevents POAF following cardiac surgery.(5) In this pilot randomized controlled trial (RCT), we evaluated the feasibility of conducting a large trial to evaluate whether colchicine can prevent POAF and atrial flutter

in patients undergoing thoracic surgery. The trial is entitled **CO**lchicine for the **P**revention of perioperative **A**trial **F**ibrillation **(COP-AF)** Pilot Trial.

This manuscript will be divided in four chapters: **Chapter 1**: Atrial Fibrillation after noncardiac surgery and pleural effusion after thoracic surgery: Background; **Chapter 2**: Pilot study of Colchicine for prevention of perioperative atrial fibrillation after thoracic surgery: Study rationale and methodology; **Chapter 3**: Pilot study of Colchicine for prevention of perioperative atrial fibrillation after thoracic surgery: Results and discussion; **Chapter 4**: Conclusion and future research directions.

CHAPTER 1:

ATRIAL FIBRILLATION AFTER NONCARDIAC SURGERY AND PLEURAL EFFUSION AFTER THORACIC SURGERY: BACKGROUND

1.0 INTRODUCTION

Approximatively 4.8 million people undergo noncardiac thoracic surgery every year worldwide.(6) In over 70% of these cases, thoracic surgery is indicated for resection of a tumor.(7) Therefore, thoracic surgery is performed to address an urgent condition, most of the time. This category of surgery carries substantial risk for death (i.e., 3%) and cardiovascular and pulmonary complications.(8) Up to 1 in 5 patients undergoing thoracic surgery will develop postoperative atrial fibrillation (POAF).(7, 9) Also, patients having major thoracic surgery typically require hospital admission. This is partially explained by the need to drain pleural fluids that accumulate after surgery. Pleural effusion drainage can take several days, contributing to a prolonged hospital stay. Therefore, therapeutic strategies are needed to prevent postoperative atrial arrhythmia and to reduce pleural effusion output after thoracic surgery.

1.1 Postoperative atrial fibrillation

The most common supraventricular tachyarrhythmias after surgery are POAF and atrial flutter, conditions that commonly co-exist. POAF is far more frequent than atrial flutter.(10) Therefore, previous research has focused on POAF. In this section, a comprehensive review of POAF will be presented. Given that the pathophysiology and the outcomes associated with atrial flutter are thought to be similar to atrial fibrillation in

the non-surgical setting,(11) it is plausible that the postoperative findings observed with POAF can also be seen in postoperative atrial flutter.

The incidence of POAF ranges between 0.4% to 19% following noncardiac surgery.(4, 6, 7, 9, 12-17) The incidence of POAF varies according to the type of surgery. For example, POAF occurs in 3 to 12% of patients undergoing lower risk surgery, such as elective genital-urinary surgery.(4, 6, 12) On the other hand, it is reported that up to 19% of patients undergoing thoracic surgery will develop new POAF.(9) It is possible that these reported incidences are an underestimation for several reasons. Frequently, cardiac arrhythmia, in particular atrial fibrillation, is asymptomatic.(18) During the postoperative period, most patients are not connected to telemetry to capture transient runs of arrhythmia. Hence, they are not adequately monitored to detect POAF. Additionally, over 65% of new POAF occurs within the first 3 days after surgery,(3, 14) a period during which patients are receiving substantial amount of analgesia that can mask cardiac symptoms that may accompany POAF (*e.g.*, chest pain, palpitation, dyspnea). Therefore, POAF is likely more common than reported. Following a comprehensive review of several databases (Medline, PubMed, Embase), we identified studies of all designs involving at least 300 patients who underwent noncardiac surgery and that reported incidences of POAF. Table 1 integrates the results of the 13 eligible studies.

Table 1: Summary of reported incidences of POAF after noncardiac surgery in eligible studies

First author	Year	Study design	Incidence of POAF n/N (%)	POAF ascertained	Population
Devereaux (POISE-2) (19)	2014	Cohort study of RCT	203/10,010 (2.0) (patients from both aspirin and placebo groups)	No systematic monitoring was performed	Patients undergoing noncardiac surgery and at risk of vascular complications randomized to receive aspirin or placebo, 591 patients underwent thoracic surgery
Bhave (4)	2012	Retrospective cohort using administrative database of 375 US hospitals	10,957/370,447 (3.0)	ICDM-9-CM codes	Patients who underwent major noncardiac surgery Among 8,047 patients who underwent thoracic surgery, 465 patients developed POAF (5.8%)
Burris* (20)	2010	Retrospective review of hospital ICU database	30/354 (8.5)	Review of charts and ECG(s) obtained for clinical indications	Patients admitted to surgical ICU after non-cardiothoracic surgery
Sohn (17)	2009	Retrospective cohort – charts reviews	30/7,756 (0.39)	Review of charts and ECG(s) obtained for clinical indications	Patients who underwent non-cardiothoracic surgery

Devereaux (POISE) (21)	2008	Cohort study of RCT	211/8,351 (2.5) (patients from both metoprolol and placebo groups)	After surgery, an ECG was obtained 6-12 hours postoperatively and daily for 3 days	Patients who underwent noncardiac surgery with, or at risk of atherosclerotic disease randomized to receive metoprolol or placebo
Juul (DIPOM) (22)	2006	Cohort study of RCT	8/921 (0.87) (patients randomized to both metoprolol and placebo arms)	No systematic monitoring was performed	Patient with diabetes and who underwent noncardiac surgery randomized to metoprolol or placebo, 37 patients underwent thoracic surgery
Christians (16)	2001	Retrospective cohort – chart review	51/13,696 (0.37)	Review of charts and ECG(s) obtained for clinical indications	Patients who underwent noncardiac nonthoracic surgery
Polanczyk‡ (14)	1998	Prospective cohort	317/4,181 (7.6)	ECG immediately after surgery, then on POD #1, #3, and #5.	Patients who were in sinus rhythm before surgery and underwent major noncardiac surgery, 502 patients underwent thoracic surgery

Brathwaite‡ (3)	1998	Prospective cohort	47/462 (10.2)	Continuous telemetry until ICU discharge, then ECG obtained if clinical indications	Patients underwent non-cardiothoracic surgery and were admitted to a surgical ICU
Thoracic surgery					
Onaitis (13)	2010	Retrospective cohort (National database of Society of Thoracic Surgery)	1,755/13,906 (12.6)	Review of notes and ECG(s) obtained for clinical indications	Patients having undergone lobectomy or greater for primary lung cancer resection
Roselli (9)	2005	Retrospective cohort (Hospital initiated thoracic surgery database)	113/604 (18.7)	All patients had telemetry during hospital stay (hospital stay median: 8 days)	Patients who underwent lung cancer resection surgery
Vaporciyan (7)	2004	Prospective data collection for database of department of surgery	319/2,588 (12.3)	All patients had telemetry for at least 72 hours after surgery	Patients who underwent thoracic surgery
Amar (23)	2000	Cohort study of RCT	60/330 (18.2) (patients from both diltiazem and placebo groups)	Continuous dual-lead ECG recording for 72 to 96 hours after surgery	Patients who underwent thoracic surgery randomized to diltiazem or placebo immediately after thoracic surgery

*Postoperative arrhythmia reported; ‡Supraventricular/atrial arrhythmia reported. ICDM-9-CM: International Classification of Diseases, 9th edition, Clinical Modification; ECG: Electrocardiogram; ICU: Intensive care unit; POD: postoperative day; RCT: Randomized controlled trial; US: United States of America.

1.1.1 Causes of POAF

Mechanisms leading to POAF are still not fully elucidated.(24) Several conditions are thought to trigger POAF after noncardiac surgery. Autonomic stimulation, electrolyte imbalances, anemia, hypervolemia, hypovolemia, hypoxia, metabolic alternations are some of the proposed causes of POAF.(24) Another important mechanism described to lead to POAF is inflammation.(24)

The development of POAF have been associated with increased inflammatory markers such as C-reactive protein (CRP), white blood cells (WBC), interleukin-6 (IL-6),(25) and complements.(12, 26-30) In a prospective cohort study performed by Amar et al. including 272 patients in sinus rhythm and undergoing elective thoracic surgery, patients who developed POAF had higher WBC counts from preoperative baseline to postoperative days 1 to 3, than those without POAF ($p < 0.001$).(27) Further, a two-fold increase of WBC from pre-surgery to postoperative day 1 was associated with a 3.3 fold increase of risk of POAF (OR 3.3; 95%CI, 2.0-8.3).(27) Similarly, Bruins et al. conducted a small prospective study of 19 patients having cardiopulmonary bypass surgery and demonstrated that patients developing cardiac arrhythmia postop had increased CRP, complements 3 & 4, and IL-6 levels.(12) Peaks levels of complements 4 on postoperative day 2 correlated with the occurrence of arrhythmia on this same day ($p = 0.0065$).(12) This study did not address whether inflammation is an independent predictor of postoperative arrhythmia. Despite limited available evidence, it seems plausible that perioperative inflammation predisposes to POAF.

In cardiac surgery, several studies have evaluated the impact of anti-inflammatory drugs on POAF. Firstly, the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) was examined in an open labeled randomized trial by Cheruku et al. Patients undergoing CABG surgery were randomized to receive ibuprofen 600mg orally three times a day for 7 days or no ibuprofen (control group). Among 100 patients recruited, 5 patients in the ibuprofen group and 14 patients in the control group developed POAF (9.8% versus 28.6%, p = 0.017).(28) Further, in 2009, a meta-analysis including 50 randomized controlled trials (RCTs) and 3,323 patients showed that corticosteroids prophylaxis before cardiac surgery reduce the risk of POAF (25.1% versus 35.1%; number needed to treat= 10; RR 0.74; 95%CI, 0.63-0.86, p < 0.01).(31) Subsequently, in 2015, the Steroids in cardiac surgery (SIRS) study by Whitlock et al. reached a different conclusion. This large international RCT of 7,507 patients undergoing cardiopulmonary bypass evaluated the impact of methylprednisolone versus placebo, given at anesthetic induction and at initiation of cardiopulmonary bypass, on 30-day mortality and other 30-day morbidities. The incidence of new POAF was similar is both arms (22% in methylprednisolone group versus 23% in placebo group; RR 0.97; 95%CI, 0.89-1.06; p= 0.48).(32) A potential limitation of this trial is that methylprednisolone was only given around the time of surgery and this may not have been adequate to prevent inflammation in the days after surgery. The causal effect of inflammation on POAF development is very plausible and deserves further exploration.

1.1.2 Impact of POAF

POAF is associated with increased morbidity and mortality after surgery. In addition of risk of death, stroke, and increased hospital length of stay, POAF is a burden on healthcare systems.(4)

Several studies have observed a direct association between POAF and increased mortality. A large retrospective cohort study of 20,022 patients undergoing carotid endarterectomy showed that 1,451 patients (7.2%) developed POAF, and these patients had significantly higher risk of death (adjusted OR 2.94; $p = 0.0021$).(33) Likewise, in a prospective observational study of 462 consecutive patients having noncardiac surgery, Brathwaite et al. demonstrated that new postoperative atrial arrhythmia was associated with a 23.4% in-hospital mortality rate, compared to 4% in those with no atrial arrhythmia ($p < 0.05$). Most arrhythmia started within the first 2 days of surgery and death occurred days after onset of the new arrhythmia. Lastly, among patients undergoing thoracic surgery for lung cancer, risk of mortality at discharge was higher in patients with new postoperative atrial arrhythmia (5.6% versus 1.6%, $p < 0.0001$).(13) Hence, avoiding development of POAF is fundamental to decrease postoperative mortality.

Outside the surgical setting, atrial fibrillation is clearly associated with an increased risk of ischemic embolic stroke due to intra-cardiac thrombus formation.(34) As for POAF, it is typically transient and self-limited, which has led some clinicians to underestimate its risk of stroke. Despite it short duration, patients with POAF have an increased incidence

of ischemic stroke. In the POISE trial, a large RCT of over 8,000 patients undergoing noncardiac surgery and receiving metoprolol or placebo, new clinically significant POAF was an independent predictor of stroke within 30-days after surgery (OR 3.52; 95%CI, 1.45-8.52). Most interestingly, new POAF population attributable risk (PAR) was 6.9% (95%CI, 2.1-20.4). In other words, 6.9% of all strokes were potentially due to POAF. Moreover, this may be an underestimation as most POAF is asymptomatic and transient. Therefore, more patients who suffered a perioperative stroke may have had POAF that resulted in stroke. These perioperative strokes were generally devastating and a majority of these patients either died or were left incapacitated with severe limitations in their ability to perform activities of daily living.(21)

In addition to the short-term risk of stroke, the stroke risk seems to persist throughout the year following hospital discharge. A retrospective cohort study examined the association between POAF and the long-term risk of stroke in 24,711 patients undergoing surgery.(35) At 1 year after hospital admission for noncardiac surgery, cumulative rates of stroke were 1.47% (95% CI, 1.24-1.75%) in those with POAF and 0.36% (95%CI, 0.35%-0.37%) in those without POAF. Cox proportional hazards analyses suggested POAF was an independent predictor of stroke at 1 year (HR 2.0; 95%CI, 1.7-2.3).(35) Overall, there are data suggesting that new POAF increases the risk of ischemic stroke acutely and long-term.

Across studies, length of hospital stay is significantly longer in patients who develop POAF.(3, 13, 14, 33) Brathwaite et al. observed in a prospective study that the mean ICU length of stay was higher in patients with atrial arrhythmia compared to those without atrial arrhythmia (8.5 ± 17.4 versus 2.0 ± 4.5 days; $p < 0.05$).(3) A similar observation was made when assessing mean total hospital length of stay: 23.3 ± 23.6 days in the new onset atrial arrhythmia group versus 13.3 ± 17.7 in those with no arrhythmia ($p < 0.05$). Following thoracic surgery, POAF significantly increased the mean length of hospital stay compared to patients who did not develop POAF (16.6 ± 18.6 days versus 8.2 ± 11.0 days; $p < 0.001$).(7) Studies have consistently demonstrated that new POAF prolongs hospital length of stay. Consequently, it is not surprising that mean hospital charges are higher in people with new POAF compared to patients without POAF ($56,426.57 ± $88,924.53 versus $28,325.98 ± $40,126.15; $p < 0.001$).(7) Similarly, Bhave et al. demonstrated that POAF after noncardiac surgery resulted in increased hospitalization costs with an adjusted difference of $4,177 (95% CI, $3,764 - $4,590).(4) Additional charges related to outpatient treatment of POAF (*e.g.*, beta-blockers and anticoagulation) and to complications of anticoagulation were not including in the cost assessments. Hence, the negative financial repercussions of POAF on healthcare systems are likely even higher than reported.

1.2 Pleural effusion after thoracic surgery

Pleural fluid is continuously produced in the pleural cavity, and a constant balance between formation and absorption is maintained under physiological conditions.(36)

After lung surgery or major lung resection, the amount of pleural effusion production increases, mainly due to the inflammatory response and to lymph node dissection.(37) In fact, the body naturally reacts by using the mesothelium and pleural surface cells to recruit a wide variety of immunological compounds including eosinophils, neutrophils, leukocytes, and cytokines.(38) This may result in the accumulation of a large amount of pleural effusion, where fluids like empyema, chyle, and blood may collect in the pleural space and induce respiratory difficulties.(39) The pleural effusion must be drained by chest tubes, which are routinely placed in the pleural cavity after every major thoracic surgery. Patients will have their chest tubes in- situ for several days before removal, based on "large amounts" of drainage. These chest tubes are heavily invasive, can cause related pain and are a possible route of infection to the pleural space. Also, pleural effusion formation and drainage usually leads to either a prolonged length of hospital stay or post-operative re-admission.(40) Although the process of inserting chest tubes following a major lung resection is so far indispensable, reducing the degree of inflammation within the pleural space may lead to a subsequent reduction in the volume of chest fluid extracted, consequently expediting discharge and reducing the risk of device related infections.

While the thoracic surgery literature is scarce about the role of anti-inflammatory drugs in preventing the excessive formation of postoperative pleural effusion, the cardiac surgery literature has for years suggested that perioperative use of steroids and NSAIDs might attenuate the inflammatory process after cardiac surgery. In fact, previous studies

suggested a role for NSAIDs in reducing the size of postoperative pericardial effusion and in the prevention of tamponade. Consequently, NSAIDs are used in this setting.(41) Likewise, it is reported that the use of NSAIDs in patients undergoing coronary artery bypass surgery might also lessen the amount of pleural effusion.(42) The SIRS trial, large multi-center RCT evaluating the effect of perioperative methylprednisolone in patients undergoing cardiopulmonary bypass, reported a significantly reduced chest tube output in the methylprednisolone arm when compared to placebo (440 ml versus 480 ml; p= 0.0007).(32) Given the similarity in pathophysiology between pericardial and pleural effusion formation after cardiac surgery and pleural fluid development after thoracic surgery, one can postulate that the administration of anti-inflammatory agents such as colchicine in patients undergoing major thoracic surgery might be beneficial in reducing the amount of postoperative pleural effusion, and hence in reducing the time to chest tube removal and overall length of hospital stay.

1.3 Colchicine

Colchicine is extracted from plants and has been used as a therapeutic agent for decades. Throughout the years, colchicine has been used to treat inflammation in conditions such as gout and pericarditis, and certain auto-immune disease (*e.g.,* familial Mediterranean fever).(43) More recently, colchicine's anti-inflammatory properties have led researchers to examine it role in treatment and prevention of cardiovascular diseases.

Colchicine mechanism of action is not completely elucidated. Nevertheless, it is well described that colchicine has an effect on the immune system by acting on neutrophils

and macrophages. Colchicine inhibits neutrophil adhesion and mobilization to inflamed tissue.(43) Further, this agent prevents macrophages from releasing various substances including nitric oxide and tumor necrosis factor α, resulting in decrease inflammation.(43) Lastly, recent work in dogs has demonstrated that colchicine inhibits intimal hyperplasia and leucocyte vascular endothelial growth factor expression, preventing endothelial dysfunction.(43) Research testing the role of colchicine in the management of cardiovascular diseases is ongoing.

1.3.1 Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation in cardiac surgery

First described in 1958, PPS occurs in up to 17.8% of patients undergoing cardiac surgery.(44) Symptoms typically begin days to months postoperatively. The syndrome is characterized by pericarditis with fever, leukocytosis, chest pain that worsens with inspiration and lying supine, pericardial rub, and pleural effusion. Although PPS is typically self-limited, it can evolve to cardiac tamponade and premature coronary artery bypass graft closure.(44) Despite uncertain physiopathology of PPS, anti-inflammatory drugs such as aspirin may be effective in treating this condition and are the current mainstay therapy. Further, patients with PPS are more likely to have a prolonged hospitalization or to require re-admission.(44) Multiple agents including colchicine have been tested as a prophylactic therapy.

POAF following cardiac surgery is far more common than after noncardiac surgery. Aging patients and the type of cardiac surgery influence the incidence of POAF, which varies from 10% to 65%.(45) Similar to POAF in noncardiac surgery, POAF after cardiac surgery is associated with increased morbidity, length of hospital stay, and healthcare system costs.(46) Two major drugs categories are being evaluated to attenuate the incidence of POAF in cardiac surgery patients: anti-arrhythmic agents and anti-inflammatory agents. Currently, colchicine is one of few anti-inflammatory drugs that researchers are evaluating.(47)

Several studies have evaluated the effect of colchicine in cardiac surgery. Therefore, to ensure proper appraisal of the current literature, we performed a scoping review. We searched for RCTs assessing the impact of colchicine on PPS and/or POAF in adults. The search was conducted using three databases: PubMed, Medline, and Embase. Five RCTs, all among cardiac surgery patients, were identified and are summarized in Table 2. The first RCT evaluating the effect of colchicine on PPS was completed by Finkelstein in 2002.(48) Colchicine or placebo were administered on the third day following cardiac surgery and was given for 1 month. This study of only 111 patients was underpowered and failed to demonstrate significant effect of colchicine on PPS (10.6% in colchicine group versus 21.9% in placebo arm; $p< 0.135$; RRR 51.4%; 95% CI, -25.6-81.2).

In 2010, Imazio et al. conducted a slightly larger multi-center RCT (the COPPS trial) that included 360 patients undergoing cardiac surgery. Colchicine 0.5mg bid was started on

postoperative day 3 until 1 month after surgery. The incidence of PPS at 12 months was significantly reduced in the colchicine group (8.9% versus 21.1%; p= 0.002; RRR 57.9%; 95% CI, 27.3-75.6).(49) Then, in 2011, a sub-study of COPPS study (i.e., the COPPS POAF study) was performed to assess the impact of colchicine on POAF. The incidence of POAF in the colchicine group was 12.0% and 22.0% in the placebo group (p= 0.021), colchicine reducing the risk of developing POAF (RRR 45.5%; 95% CI, 34.0-94.0). In addition, it was observed that colchicine resulted in faster conversion to sinus rhythm (average duration of POAF 3 ± 1.2 versus 8 ± 2.5 days). Four years later, the same team conducted a slightly different trial of 360 patients where instead of starting colchicine after surgery, it was initiated 48 to 72 hours before cardiac surgery and continued for 1 month after surgery.(5) Here again, PPS within 3 months following surgery occurred significantly less in colchicine patients (19.4% versus 29.4%; RRR 34.0%; 95% CI, 4.1-54.5). Although there were numerically less POAF in the colchicine group, the difference was not statistically significant (33.9% versus 41.7%; RRR 18.7%; 95% CI, -6.3-37.8). Similarly, Sarzaeem et al. showed that preoperative colchicine administration reduced the incidence of POAF in an RCT of 216 patients undergoing CABG (14.8% versus 30.6%, p= 0.006; RRR 51.5%; 95% CI, 17.3-71.6).(50)

In summary, three RCTs reported the impact of colchicine on PPS, among which two studies (COPPS trial and Finkelstein et al.) administered colchicine postoperatively and one trial (COPPS-2 trial) administered colchicine 48 to 72 hours before surgery. A meta-analysis of these tree trials showed that PPS occurred in 56 patients among 407 patients

who received colchicine and in 105 patients among 424 patients randomised to placebo (risk ratio 0.56; 95% CI 0.42-0.76) (Figure 1). As for POAF, three RCTs reported it and results were inconsistent. COPPS POAF trial and Sarzaeem et al. initiated colchicine after surgery and both studies clearly showed that colchicine prevented POAF (RRR 45.5%; 95% CI, 34.0-94.0; and; RRR 51.5%; 95% CI, 17.3-71.6; respectively).(50, 51) However, in COPPS-2 trial, colchicine was given preoperatively and the results failed to demonstrate preventative effect of colchicine (33.9% versus 41.7%, RRR 18.7%; 95% CI, -6.3-37.8).(5) In a meta-analysis of these three studies, POAF occurred in 97 patients among 457 patients randomized to colchicine and in 145 patients among 455 patients who received placebo (risk ratio 0.63; 95% CI, 0.44-0.90) (Figure 2). These findings bring us to postulate that colchicine may prevent POAF after thoracic surgery.

Table 2: Summary of randomized controlled trials examining the effect of colchicine on PPS and POAF after cardiac surgery*

First author Year	N	Surgery type	Intervention - Colchicine	Comparator	Intervention duration	Results
Imazio COPPS-2 trial 2014 (5)	360	Cardiac surgery*	0.5mg bid	Placebo	Start 48-72 h preop and continued for 1 month postop	**PPS:** Colchicine 19.4% Placebo 29.4% RRR 34.0%; 95% CI, 4.1-54.5 **POAF:** Colchicine 33.9% Placebo 41.7% RRR 18.7%; 95% CI, -6.3-37.8 **Pericardial or pleural effusions:** Colchicine 57.2% Placebo 58.9% RRR 2.8%; 95% CI, -15.8-18.5

Sarzaeem 2014 **(50)**	216	CABG	1mg night before surgery, 1mg the morning of surgery, then 0.5mg bid	Placebo	Start the night preop and continued for 5 days postop	**POAF:** Colchicine 14.8% Placebo 30.6% p= 0.006 RRR 51.5%; 95% CI, 17.3-71.6 **ICU stay:** Colchicine 2.4 days Placebo 3.1 days p< 0.001 **Hospital length of stay:** Colchicine 6.6 days Placebo 8.1 days p< 0.001
Imazio COPPS POAF sub-study 2011 **(51)**	336	Cardiac surgery*	1mg bid on the first day then 0.5mg bid	Placebo	Start 3rd days postop and continued for 1 month	**POAF:** Colchicine 12.0% Placebo 22.0% P= 0.021 RRR 45.5%; 95% CI, 34.0-94.0 **Hospital length of stay:** Colchicine 9.4±3.7 days Placebo 10.3±4.3 days P= 0.040

Imazio** COPPS trial 2010 **(49)**	360	Cardiac surgery*	1mg bid on the first day then 0.5mg bid	Placebo	Start 3rd days postop and continued for 1 month	**PPS:** Colchicine 8.9% Placebo 21.1% p= 0.002 RRR 57.9%; 95% CI, 27.3-75.6 **Combined endpoints** (disease related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses): Colchicine 0.6% Placebo 5.0% p= 0.024 RRR 88.9%; 95% CI, 13.2-98.6
Finkelstein** 2002 **(48)**	111	Cardiac surgery	1.5mg/day	Placebo	Start 3rd day postop and continued for 1 month	**PPS:** Colchicine 10.6% Placebo 21.9% p< 0.135 RRR 51.4%; 95% CI -25.6-81.2

* Cardiac surgery includes CABG and valve repair surgery; ** POAF not assessed.

CABG: coronary artery bypass graft; CI: confidence interval; COPPS: Colchicine for the prevention of the postpericardiotomy syndrome; ICU: intensive care unit; POAF: postoperative atrial fibrillation; PPS: postpericardiotomy syndrome, RRR: relative risk reduction.

1.3.2 Colchicine safety

Colchicine is a substrate for intestinal and hepatic cytochrome P450 3A4. This drug is mostly eliminated by the hepato-biliary system and the rest of it is excreted through the kidneys (10-20%).(43) In general, colchicine is well tolerated. The most common adverse effects of colchicine are abdominal pain, diarrhea, nausea, and vomiting. These effects are typically transient and reversible with lowering the dose. Blood dyscrasias, myopathy, and rhabdomyolysis have been reported in patients on colchicine and are uncommon.(43)

Many clinical trials have reported on the safety of colchicine. In the COPPS-2 trial, patients on colchicine developed significantly more gastrointestinal symptoms including diarrhea, nausea, vomiting or abdominal pain (14.4% in the colchicine group versus 6.7% in the placebo group; RR 2.17; 95% CI, 1.13-4.16).(5) None of these symptoms led to hospital admission. Rate of hepatotoxicity was mild and comparable in both groups (0.6% in colchicine arm versus 1.1% in placebo arm; RR 0.5; 95% CI, 0.05-5.47). No serious adverse event, fatal or life-threatening event requiring hospital admission, were reported. The drug discontinuation rate was similar in both arms (21.7% in the colchicine group versus 17.8% in the placebo arm; RR 1.29; 95% CI, 0.80-1.85). Overall, colchicine is a safe and well tolerated.

CHAPTER 2:

PILOT STUDY OF COLCHICINE FOR PREVENTION OF PERIOPERATIVE ATRIAL FIBRILLATION AFTER THORACIC SURGERY: STUDY RATIONALE AND METHODOLOGY

2.1 STUDY RATIONALE

Following thoracic surgery, postoperative atrial fibrillation (POAF) occurs in up to 20% of patients and is associated with poor outcomes. Patients developing new POAF are at higher risk of stroke and death. Also, POAF leads to a prolong length of hospital stay, which adds to healthcare system costs. Given that postoperative inflammation might contribute to the development of POAF, anti-inflammatory drugs, such as colchicine, may prevent POAF. Although this hypothesis is supported by the results of trials in patients undergoing cardiac surgery, this remains to be tested in patients undergoing thoracic surgery.

We ultimately want to conduct a trial to investigate the following research question: "In patients undergoing thoracic surgery, does administration of colchicine 0.6mg before surgery followed by 0.6mg PO BID for 10 days, compared to placebo, reduce the incidence of new atrial fibrillation or atrial flutter at 30 days after randomization?" Our hypothesis is that colchicine will attenuate the occurrence of POAF after thoracic surgery. Before conducting a large RCT to address this question, we performed a pilot RCT to

determine whether a large multi-center RCT was feasible and the resources required for its completion.

2.2 METHODS

2.2.1 Trial Design

A placebo-controlled, randomized controlled trial was conducted to test the feasibility of comparing colchicine to placebo in patients undergoing general thoracic surgery and establish the foundation for a large, multi-centre, clinical trial. Patients were recruited from April 28th, 2014 to April 7th, 2015.

2.2.2 Participants

2.2.2.1 Eligibility criteria

Inclusion criteria

All patients ≥55 years of age in sinus rhythm undergoing a resection of tumor in the lung (malignant, benign, or unknown) during the study period were eligible for inclusion in the trial.

Exclusion criteria

Patients with any of the following conditions were excluded:

1) Patient in AF or atrial flutter just prior to surgery.
2) Patient undergoing only minor thoracic interventions or procedures (i.e., chest tube insertion, needle pleural/lung biopsy, minor chest-wall surgeries, or mediastinoscopy).

3) Patient with contraindications to colchicine (i.e., allergy, myelodysplastic disorders, pregnancy, or estimated glomerular filtration rate [e-GFR] <30 ml/min/1.73m^2).
4) Patient not expected to take oral medications for >24 hours after surgery (*e.g.*, esophagectomy).
5) Patient taking non-study colchicine before surgery.

2.2.2.2 Setting

The trial was conducted at St. Joseph Healthcare, Hamilton, Ontario; and the University of Manitoba Health Sciences Centre, Winnipeg, Manitoba. The randomization, data management, statistical analysis and the oversight of the trial were performed at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario. With the agreement of thoracic surgeons, patients were approached in the thoracic surgery clinic, days to weeks before their surgery. All patients provided informed consent. Study personnel randomized patients on the day of surgery.

2.2.3 Intervention

On the day of surgery, patients received 0.6mg of colchicine or placebo within a window of 4 hours before surgery. The second dose of colchicine 0.6mg or placebo was given between 6:00PM and 11:59PM after surgery. Patients continued to receive colchicine 0.6mg or placebo twice daily for an additional 9 days (for a total duration of treatment of 10 days). The placebo group received a placebo capsule that was identical in appearance

to the active study drug. In the event that the surgery was postponed, the study drug was held and resumed when the participant presented back to the surgery. At that moment, another dose of study drug was given before surgery and patient continued to receive colchicine or placebo after surgery as per protocol.

Colchicine was purchased from Pharmascience. Bay Area Research Laboratory (BARL) undertook drug over-encapsulation and making of an identical appearing placebo, labeling, and packaging. Patients discharged home prior to completing the study medication (i.e. within 10 days of surgery) were given a package containing colchicine 0.6mg or placebo to complete 10 days of treatment.

2.2.4 Outcomes

2.2.4.1 Feasibility outcomes

The feasibility outcomes of this pilot study were the following:

1) To determine the feasibility of recruiting patients undergoing thoracic surgery to an RCT of colchicine versus placebo for the prevention of perioperative AF.
2) To determine the human and financial resources required to conduct a full scale trial.
3) To assess the compliance with the study drug.

We decided a priori that we would deem a large trial feasible if the following pre-set criteria were fulfilled:

1) recruit 100 patients within 18 months and obtain final follow-up of at least 95% of

participants;

2) collect time required to identify, consent, and follow patients; and
3) achieve a study drug compliance of 90%.

2.2.4.2 Efficacy outcomes

The primary efficacy outcome consisted of collecting preliminary data on the incidence of new onset perioperative AF or atrial flutter within 30-day after randomization. Secondary efficacy outcomes were the 30-day incidence of death, myocardial injury after noncardiac surgery (MINS), myocardial infarction (MI), stroke or transient ischemic attack (TIA), clinically important bradycardia, clinically important hypotension, sepsis/infection, amount of pleural fluid drainage, as well as the duration of ICU, step-down unit and in-hospital stays. Safety outcomes were to assess the 30-day incidence of life-threatening bleeding, major bleeding, and non-infectious diarrhea. Outcomes definitions are available in Appendix B.

Patients were followed during their hospitalization until discharge. Troponin was measured and ECG was performed once a day for the first 3 days after surgery, if patients were still in hospital. Troponin measurements were drawn as the same time as the routine postoperative blood work by the ward nurse. Additional troponin measurements or ECGs ordered by the treatment team during the admission were also noted. Pleural fluid drainage was recorded every 8 hours for the first 48 hours. Time of chest tube removal was also noted.

After discharge, patients were seen at their pre-planned visits in the surgical clinics, 30 days after surgery. Patients who were not assessed in the surgical clinics were contacted via telephone. Length of stay and re-admission occurrences were extracted from patient charts and recorded on patient data collection forms. All data collection was completed by the research assistants, under the supervision of site investigators.

2.2.5 Sample size

We decided to recruit 100 patients. This was a convenience sample that should give us enough experience to assess our pilot objectives and to enable a sample size calculation in the subsequent larger trial.(52) Assuming a POAF event rate of 20%, a 2-sided alpha of 0.05, power of 0.80, and that colchicine would reduce this event rate by 25%, a total of 903 patients would be required in each arm of a full trial.

2.2.6 Randomization

Once a patient was deemed eligible and written informed consent was obtained, randomization occurred a few hours before surgery. Research personnel randomized patients via an Interactive Web Randomization System (IWRS). The IWRS is a 24-hour computerized randomization internet system maintained by the coordinating centre at the PHRI.

The randomization process used block randomization stratified by centre. Study personnel and investigators were unaware of the block size. Patients were randomized in a 1:1 fashion to receive colchicine or placebo.

2.2.7 Blinding

Patients, healthcare providers, data collectors, and outcome adjudicators were blinded to treatment allocation. Study drugs appearance was identical. All trial patients received the same structured follow-up. The outcome adjudicators (expert physicians) were blinded to treatment allocation, and the following outcomes were adjudicated: death, perioperative AF, new onset atrial flutter, MINS, MI, stroke, TIA, and postoperative infection. The decisions of the adjudication committee were used for all statistical analyses involving these outcomes.

2.2.8 Statistical methods

Analyses include all randomized patients. We followed the intention-to-treat principle (i.e., patients were analyzed within the group they were allocated). We used alpha = 0.05 level of significance (two-sided).

Standard methods were used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of continuous variables included the number of subjects (N), mean, standard deviation, median, quartiles 1 and 3, or minimum and maximum. Frequency distributions (N and %) were given for categorical data.

We reported descriptive statistics of the number of recruited patients and of the eligible not-recruited patients. Also, we reported number of eligible participants, number of

randomized participants, number of days recruiting, number of months recruiting and recruitment rate was calculated by dividing the number of randomized participants with the numbers of total months recruiting. We included all events that the centres reported and the adjudication committee did not refute. We tested the incidence of the binary efficacy event by allocation group using a chi-squared test or Fisher's exact test, as appropriate. We compared the hospitalization and critical care length of stay durations using an independent Students t test.

Drug compliance and adverse events were assessed and presented with descriptive statistics. Data completeness was summarized by the number of troponin measurements and the 12-lead ECG performed during the first 3 days after surgery. Also, we assessed the research personnel workload (time by task per patient).

We used Cox proportional hazards models to estimate the effect of colchicine on the hazard ratio for the primary and secondary efficacy outcomes and their associated 95% confidence intervals (CI). First occurrence of each event were used in the calculation.

2.2.9 Ethical considerations

Institutional review board (IRB) approval was obtained in both centres before the start of recruitment. A clinical trial application (CTA) was submitted to Health Canada to obtain permission to use colchicine for a new medical condition. Health Canada approved this trial (protocol number: COPAF131001). We registered COP-AF pilot study at clinicaltrials.gov (the identifier was NCT01985425).

2.2.10 Funding

This pilot study was supported by grants from the Canadian Institutes of Health Research, the Division of General Internal Medicine at McMaster University, and Physicians Services Incorporated.

CHAPTER 3:

PILOT STUDY OF COLCHICINE FOR PREVENTION OF PERIOPERATIVE ATRIAL FIBRILLATION AFTER THORACIC SURGERY: RESULTS AND DISCUSSION

3.1 RESULTS

3.1.1 Recruitment

Prior to the start of recruitment, initiation visits were organized at both study centres with site research personnel including surgeons. During these meetings, a detailed overview of the protocol and recruitment strategies was presented. We separately met with thoracic surgery ward nurses to explain the study protocol while putting the emphasis on the schedule of study drug administration and pleural drainage output recording.

The study was launched on April 15th 2014. The first patient was enrolled on April 28th 2014 and the last patient on April 7th 2015. One hundred patients were recruited in 345 days (i.e., 11 months and 11 days), a recruitment rate of 9 participants per month. 30-day follow-up were completed in 100% of trial participants.

3.1.2 Participant flow

Among the 205 eligible patients for COP-AF pilot study, 55 patients (26.8%) declined to participate, physicians declined participation of 4 patients (2.0%), 30 patients were not identified before surgery, and 16 patients (7.8%) were not included for other reasons. One hundred patients were randomized (48.8% of eligible patients). Following the

randomization process, 49 patients were allocated to receive colchicine and 51 to receive placebo. In the placebo group, one patient had his surgery cancelled. Consequently, this patient did not receive the study drug. This patient was nevertheless included in the analysis based on the intention-to-treat principle. Forty-nine patients from the colchicine group and 51 patients from the placebo arm were included in the statistical analyses. Figure 3 is a participant flow diagram.

3.1.3 Baseline data

Among enrolled patients, the mean age was 69 years in both groups. More women were randomized to receive colchicine arm (33 [68.8%] compared to placebo 22 [43.1%], p= 0.010). Table 3 reports the medical history of patients in both groups. In the placebo group, there were more patients with a history of coronary artery disease (15 [29.4%] versus 5 [10.2%], p= 0.016) and patients with hypertension (34 [66.7%] versus 21 [42.9%], p= 0.017). 7% of patients had an active malignancy.

3.1.4 Outcomes

3.1.4.1 Feasibility outcomes

COP-AF pilot study was successfully completed in a timely fashion. One hundred patients were recruited in less than 12 months. Moreover, staff time required per patient was captured. On average, assessing patient eligibility and baseline history taking took 30 minutes to the research personnel, 50 minutes for in-hospital follow up, and 85 minutes to complete 30-day follow-up. Totalling 165 minutes required from the research staff to enrol and follow each patient in COP-AF pilot study.

Among the 99 patients who underwent surgery, 71 (71.7%) patients completed the study drug course without interruption (35 patients in colchicine arm and 36 patients in placebo group). Three additional patients completed study drug course with interruption. Overall, 74.7% of patients completed study drug course. There were 25 (25.3%) patients that did not complete the full study drug course. Please refer to Table 4 for drug compliance data. Patient refusal to continue to participate to the study was the main reason for permanent drug discontinuation (8 patients). Only three patients developed potential drug related side effects (i.e., non-infectious diarrhea, nausea, and vomiting) that led to drug interruption. Overall, 77% of patients completed >85% of their study drug course (38 patients in the colchicine arm and 39 in the placebo group, p= 0.615). Table 5 presents a summary of the reasons for drug discontinuation.

For outcomes assessments, troponin measurements and 12-lead ECG were performed on the first three days after surgery. On postoperative day 1, troponin was measured in 98 (98%) patients. On the following day, 96 patients had troponin measured (96%). Then, on the third day, this blood test was performed in only 79 patients (79%). This is primarily explained by the fact that 13 patients were discharged on the 3rd day after surgery and consequently blood tests were not drawn on that day. For the remaining 8 patients, there was no documented reason for not measuring troponin. As for the serial ECG, 94 (94%) patients had it done on the first postoperative day. On the 2nd day, ECG was performed on 89 (89%) patients. Finally, 71 (71%) patients had ECG on

postoperative day 3. Here again, 13 patients were discharged on the 3rd day after surgery, preventing the completion of 12-lead ECG on that day and the remaining 16 patients did not have ECG for an unclear reason.

Overall, the primary feasibility objectives were achieved. In less than 12 months, one hundred patients were randomized in COP-AF pilot study across two Canadian sites. Further, we determine the workload per patient to conduct the study. Finally, over 77% of patient completed >85% of the study drug course.

3.1.4.2 Efficacy outcomes

Five patients in the colchicine arm developed new atrial fibrillation (AF) or atrial flutter and 7 patients developed AF or atrial flutter in the placebo group (10.2% versus 13.7%, p= 0.760). The Cox-regression model demonstrated that perioperative colchicine intake did not significantly reduce the risk of atrial arrhythmia development (aHR 0.69; 95% CI 0.20-2.34; p= 0.55) (Figure 4). Cox-regression model was adjusted for gender, hypertension, CAD status at baseline, as these baseline variables were not balanced between the two arms and are thought to be risk factors for development of AF.(53, 54) New atrial arrhythmia consisted of atrial fibrillation in five patients assigned to the colchicine group and six patients randomized to the placebo arm. The mean time to the first occurrence of atrial fibrillation or flutter after surgery was a mean of 3.7 days and median of 3.4 days.

Likewise, there was no statistical difference in the incidence of myocardial injury after noncardiac surgery (MINS) (colchicine 20.4% versus placebo 23.5%, p= 0.706). Among patients with MINS, two patients in the colchicine group had an myocardial infarction (MI) and three in the placebo group had an MI. Clinically important bradycardia occurred more frequently in patients who received placebo (2.0% versus 17.6%, p= 0.016). No difference was observed among patients who developed clinically important hypotension (colchicine 46.9% versus placebo 47.1%, p= 0.990).

Patients on colchicine reported more non-infectious diarrhea (colchicine 10.2% versus placebo 2.0%, p= 0.108), although this was not statistically significant. Other safety outcomes were comparable in both arms: major bleeding (colchicine 2.0% versus placebo 5.9%, p= 0.618), serious adverse event (colchicine 6.1% versus placebo 5.9%, p= 1.000), infection or sepsis (colchicine 12.2% versus placebo 15.7%, p= 0.620) and pulmonary embolism (colchicine 4.1% versus placebo 0.0%, p= 0.238). At 30-day follow-up, we report no death, stroke or transient ischemic attack, life threatening bleeding, deep venous thrombosis, or new acute renal failure requiring dialysis. Efficacy and safety outcomes are presented in Table 6.

Finally, patients in both groups had similar mean hospital length of stay (colchicine 7.4 ± 5.3 days versus placebo 6.8 ± 3.4 days; p= 0.771). Likewise, duration of critical care unit stay was comparable in both arms (colchicine 3.3 ± 5.1 days versus placebo 2.7 ± 2.3 days; p= 0.725).

Pleural drainage results will be reported in a separate manuscript.

3.1.5 Unblinding

One patient was unblinded. This was a 62 year old woman. On postoperative day 3, she developed acute respiratory failure requiring positive pressure ventilation. Although a pneumonia was thought to be the cause of her acute respiratory distress syndrome (ARDS), the patient's respirologist raised the possibility that colchicine induced pneumonitis may be the cause. Due to respirologist's concerns, we permanently discontinued the study drug and unblinded the patient. The patient was randomized to active colchicine. On postoperative day 11, the patient was discharged home.

A thorough review of the literature and drug monographs failed to find a case report of pneumonitis induced by low dose colchicine. Colchicine causing multi-organ dysfunction syndrome in acute overdose is well described. When ingested at high dose (>0.5mg/kg), colchicine can induce ARDS and disseminated intravascular coagulopathy (DIC), that may lead to death.(55, 56) However, at usual and low doses as used in COP-AF pilot study, acute respiratory failure has not been described. In fact, colchicine was previously considered for treatment of fibrotic interstitial lung disease.(57) Moreover, colchicine toxicity can result from the interaction between colchicine and other drugs that inhibit CYP 3A4.(56) These drugs include erythromycin, clarithromycin, and ketoconazole. No CYP 3A4 inhibitor was part of this patient's medication list. In brief,

given the lack of reported cases of respiratory failure in patients taking low dose colchicine, COP-AF pilot study investigators thought that it is unlikely that colchicine had caused pneumonitis or respiratory distress in this patient.

3.2 DISCUSSION

3.2.3 Interpretation

Recruitment for COP-AF pilot study was successfully completed. One hundred patients were recruited in less than 12 months, which was faster than the expected period of 18 months. Among the eligible patients not recruited, the main reasons for declining was refusal to participate and patients not identified. The latter was remediated by ensuring the presence of a research assistant at the thoracic surgery clinic to screen patients and to remind surgeons of eligibility criteria. Follow up was completed in all patients. Moreover, research personnel recorded the time required to complete each task related to the study completion. An average of 165 minutes per participant was necessary. This information will be extremely useful to determine the amount of personnel required to conduct the full scale trial and to calculate a well estimated budget. Lastly, adherence to study drug was assessed. We were hoping that 90% of participants complete study drug course. 74.7% completed the study drug course and 77.8% of patients took >85% of their assigned study drug. Various reasons led to permanent drug discontinuation (refer to Table 5). By far, patient refusal to continue to take study drug was the most common reason. Therefore, it is important to ensure that patient who initially agree to participate are fully committed to contribute to the trial. Only 3 patients experienced adverse events

that led to drug interruption. Consequently, the study drug regimen was well tolerated by the majority of participants.

In COP-AF pilot study, patients' baseline characteristics were comparable, except for gender, history of coronary artery disease, and hypertension. Despite randomization, variability among the two populations was explained by the small sample size. Consequently, cox-regression model was adjusted for gender, hypertension, and coronary artery disease status at baseline. Further, overall, only 7% of patients recruited had active cancer. One could have expected a higher proportion of patients with active cancer as most thoracic surgery involves tumor resection. This is mainly due to the definition used for active cancer: patients with a malignancy and had received chemotherapy within the last 6 months before randomization. For the full scale trial, one should consider using a different and more inclusive definition of active cancer such as patients with malignancy diagnosed by tissue biopsy.

Although we did not demonstrate a benefit with the study drug on the efficacy outcomes, the trial was underpowered. We demonstrated that colchicine had an aHR of 0.69 (95% CI, 0.20-2.34) for preventing POAF or atrial flutter. This point estimate of effect is plausible since other studies that investigated colchicine properties in the perioperative setting after cardiac surgery showed similar findings. Both Imazio et al. and Sarzaeem et al. showed that perioperative colchicine statistically decreases the incidence of POAF (RR 0.55; 95% CI, 0.33-0.90; RR 0.49; 95% CI, 0.28-0.83; respectively).(50, 51)

Although COP-AF pilot study is testing postoperative atrial fibrillation (POAF) in thoracic surgery, we believe that the surgical approach in thoracic surgery is similar to the one used in cardiac surgery (i.e., thoracotomy and possible pericardium irritation).

Additionally, in our study, colchicine reduced the risk of clinically important bradycardia of 87% (HR 0.11; 95%CI, 0.01-0.87; p= 0.036; aHR 0.13; 95%CI, 0.02-1.07, p= 0.057), which, at first glance, seems contradicting given it effect on preventing POAF. However, colchicine is an anti-inflammatory agent and POAF is triggered by inflammation, therefore it is plausible that colchicine prevents POAF but does not induce bradycardia. Also, it is unknown whether the placebo group received different medications or anesthetic modalities that have induced more bradycardia. Lastly, given the very small events number (1 in colchicine arm and 9 in placebo arm), this observation could be due to chance.

Colchicine's anti-platelet properties raised concerns from surgeons and anesthetists because of possible risk of bleeding, as observed in patients on non-steroidal anti-inflammatory drugs. According to colchicine monographs, colchicine can lead to blood dyscrasias including thrombocytopenia. In our study, one patient experienced major bleeding in the colchicine group and 2 in the placebo arm. No patient had life threatening bleed. Although small events number, COP-AF pilot study did not demonstrate more

bleeding events in patients on colchicine. Other safety adverse events were few and similar in both groups. Finally, it is important to note that COP-AF pilot study detected only a small number of events and one should not draw meaningful clinical conclusions from it.

3.2.2 Limitations

Although COP-AF pilot study fulfilled feasibility outcomes, it is possible that the resources required to conduct such a trial were underestimated. Research staff role consisted of screening, enrolling and ensuring in-hospital and 30-day follow-up. Performing ECG, blood drawing, and frequent chest tube output recording was completed by the supportive thoracic surgery nursing team. For the full scale international trial, these tasks will probably have to be fulfilled by the research staff, as support from most surgical nursing teams is unclear. If necessary, these added responsibilities will increase the staff time by approximately 30 minutes per patient.

The compliance to study drug was not achieved (pre-set objective of 90%) but over 74% of participants completed the study course. Nevertheless, compliance could have been better. To enhance drug adherence, we could ensure application of strategies demonstrated to have a positive impact on compliance. Atreja et al. performed a quantitative systematic review of strategies to improve patient adherence.(58) Six strategies were described including simplifying drug regimen, ensuring patient understanding of the goal of the study, addressing patient's beliefs or concerns regarding

study drug, refining patient-research team communication by sending emails or telephonic reminders or by involving patients families in the dialogue, and routinely evaluating drug compliance.

Postoperative troponin measurements and ECG was completed in the majority of the participants on the first two days but not on the 3rd day. In the full scale trial, emphasis should be put on obtaining troponin measurements and ECG on the 3rd day after surgery before participant's hospital discharge on that day.

The aim of this study was to establish feasibility rather than assessing clinical outcomes. With a small sample size, it was unlikely to observe statistically significant findings. As explained in the statistical analysis section, in order to detect significant results, a larger sample size would have been required to ensure enough power.

Outcome assessment can be challenging in the postoperative period. The primary clinical outcome consisted of assessing the development of atrial arrhythmia. In this case, ECG was performed daily for the first three postoperative days. This method was the most feasible one but may have missed arrhythmia in some patients. Firstly, atrial fibrillation or flutter was diagnosed on average between the 3rd and the 4th day after surgery (all available ECG in chart were recorded for outcome assessment). Therefore, since ECG were performed only on the first three days after surgery, it is possible this diagnosis of arrhythmia was missed on day 3 or later. Also, atrial arrhythmia can be transient and of

short duration. In addition, most patients in the postoperative setting do not have symptoms when atrial fibrillation or flutter occurs (*e.g.*, palpitation, chest pain, or dyspnea). Consequently, an ECG captures a brief period in time and the incidence of POAF and atrial flutter could have been underestimated. In view of these results, for the full trial, performing ECG for a longer period of time after surgery or offering continuous telemetry would certainly improve primary efficacy outcome assessment, although this would be costly. Given that the overall mean length of hospital stay is 7.1 ± 4.4 days and that most atrial arrhythmia were diagnosed between the 3rd and the 4th day after surgery, serial ECG or continuous telemetry for 5 days after surgery (instead of 3 days in COP-AF pilot study) would not delay discharge and might capture more arrhythmia. For patients discharged earlier, ECG data for the first three days will still be available.

3.2.3 Generalizability

The number of major thoracic surgery cases continues to grow. Also, older patients are nowadays undergoing thoracic surgery. Although this is a feasibility trial, it is important to highlight the potential value of COP-AF full scale trial. This trial will address an important question that affects a large number of patients. POAF not only is associated with increase mortality and stroke, it had a direct impact on healthcare system resources and healthcare cost. The patients involved in this large trial will represent an accurate reflection of the majority of thoracic surgery patients, ensuring the generalizability of it results.

CHAPTER 4: CONCLUSION AND FUTURE RESEARCH DIRECTIONS

4.0 CONCLUSION AND FUTURE DIRECTIONS

Older patients are undergoing surgery and consequently, a growing number of postoperative cardiac complications are observed. Postoperative atrial fibrillation (POAF) is one of the most common conditions encountered after thoracic surgery. COP-AF pilot study demonstrated the feasibility of conducting a large RCT to assess the effect of colchicine on the incidence of POAF after thoracic surgery. Although underpowered, the trial suggests that the impact of colchicine on POAF is promising.

COP-AF pilot study demonstrated that the completion of a full scale multi-center COP-AF trial is possible. Based on the findings of COP-AF pilot study, several changes to the protocol should be considered. Strategies to improve study drug compliance should be applied. Further, in order to adequately monitor for the primary outcome (POAF and atrial flutter), a longer period of monitoring for arrhythmia is required. ECG or telemetry monitoring for the first 5 days after surgery will certainly increase the detection rate of postoperative atrial arrhythmia. An adequately powered trial will allow investigators to determine the actual effect of colchicine on POAF in thoracic surgery. The full scale trial will need to include at least 2,526 participants (1,263 patients per arm) to detect statistical difference. This sample size was calculated using a POAF incidence of 10%, a risk reduction of 31% (aHR 0.69 from COP-AF pilot trial), and a power of 80%. It is important to note that POAF incidence in COP-AF pilot study is based on a very small events number and one could reassessed the sample size using both COP-AF pilot results

and previous works. In order to enrol this amount of patients, we estimate that the participation of 60 to 80 centres will be necessary. Finally, the full scale COP-AF trial is feasible and is a novel and important study that can answer a crucial clinical question affecting a large number of patients.

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APPENDIX A

Figure 1: Risk ratio for postpericardiotomy syndrome

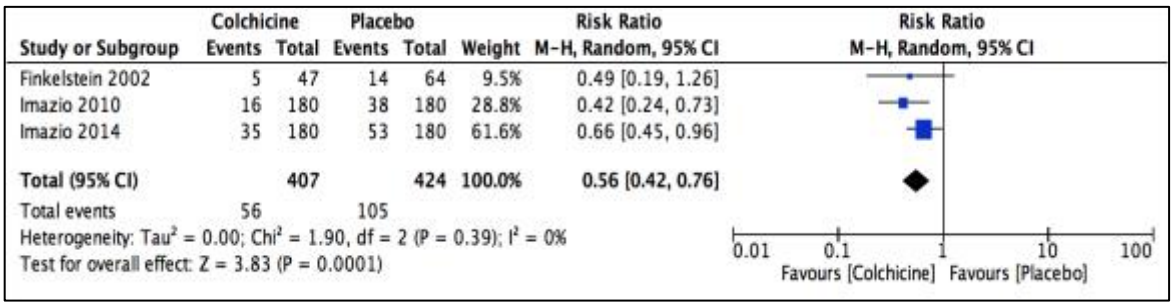


Figure 2: Risk ratio for postoperative atrial fibrillation

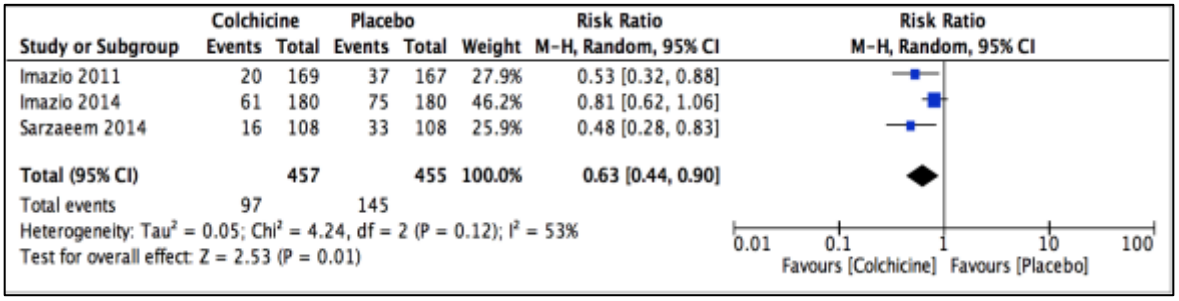


Figure 3: Participant flow chart

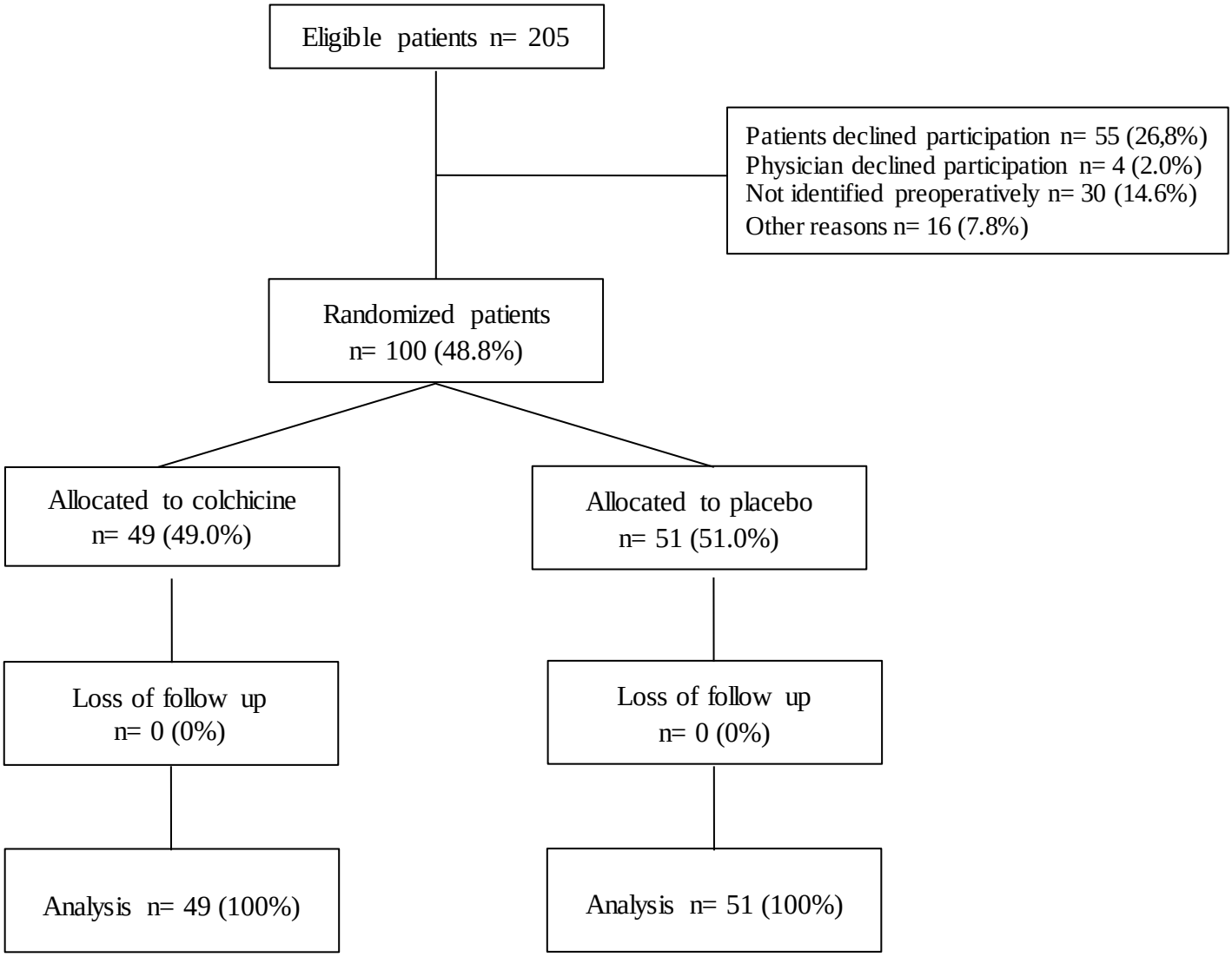


Table 3: Baseline characteristics

	Colchicine N (%) (N=49)	Placebo N (%) (N=51)	P-value
Age, mean(SD)	68.89 (7.5)	68.26 (7.4)	0.674
Female	33 (68.8%)	22 (43.1%)	0.010
MEDICAL HISTORY			
AF/A. Flutter	0.0	0.0	0.0
Stroke/TIA	7 (14.3%)	3 (5.9%)	0.196
CHF	1 (2.0%)	0.0	0.490
DVT/PE	3 (6.1%)	3 (5.9%)	1.000
CAD	5 (10.2%)	15 (29.4%)	0.016
Cardiac arrest	0.0	0.0	0.0
PVD	3 (6.1%)	3 (5.9%)	1.000
Diabetes on treatment	8 (16.3%)	9 (17.6%)	0.861
Hypertension	21 (42.9%)	34 (66.7%)	0.017
COPD	23 (46.9%)	25 (49.0%)	0.835
ILD	2 (4.1%)	0.0	0.238
Home oxygen therapy	0.0	0.0	0.0
Active cancer	3 (6.1%)	4 (7.8%)	1.000
History of tobacco use	43 (87.8%)	45 (88.2%)	0.941

Table 4: Drug compliance

	Colchicine N (%) (N=49)	Placebo N (%) (N=51)	P-value
Completed study drug course WITHOUT interruption	35 (71.4%)	36 (70.6%)	0.926
Completed study drug course WITH interruption	1 (2.0%)	2 (4.0%)	1.000
Did not completed study drug course	13 (26.5%)	10 (20.0%)	0.458
Patients received >85% of study drug course	38 (77.6%)	39 (78.0%)	0.615

Table 5: Drug discontinuation

Reason for Discontinuation	Number of patients
Permanent Discontinuation (# patients = 23)	
Patient refusal to take study medication	8
Patient unable to locate study medication	3
Development of serious adverse event	2
Development of outcome event – non-infectious diarrhea	2
Drug discontinued after surgeon request	2
Patient unable to take oral medication	2
Patient unable to swallow study drug capsule	1
Development of new renal failure	1
Other reasons	2
Temporary Discontinuation (# patients = 3)	
Development of nausea and vomiting	1
Patient refusal to take study medication	1
Drug discontinued after surgeon request	1

Table 6: Efficacy and safety outcomes

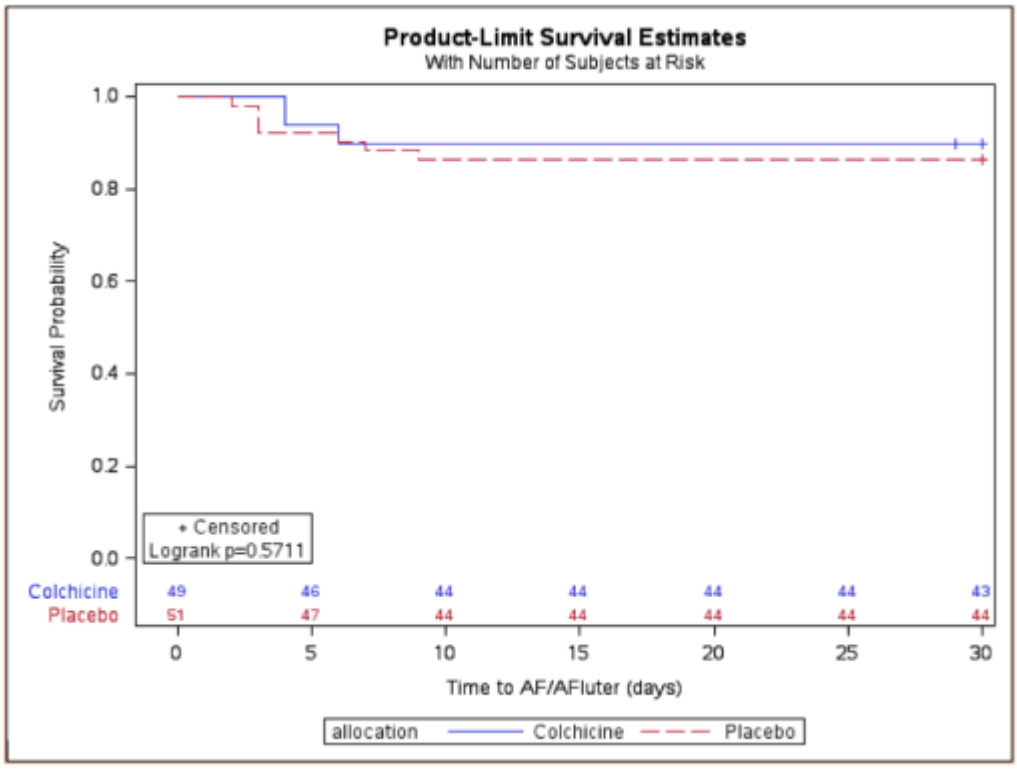
	Colchicine N (%) (N=49)	Placebo N (%) (N=51)	P-value
New AF/A. Flutter	5 (10.2%)	7 (13.7%)	0.760
New AF	5 (10.2%)	6 (11.8%)	1.000
New A. Flutter	0.0	1 (2.0%)	1.000
All-cause death	0.0	0.0	0.0
MINS	10 (20.4%)	12 (23.5%)	0.706
MI	2 (20.0%)	3 (25.0%)	1.000
Stroke/TIA	0.0	0.0	0.0
Clinically important bradycardia	1 (2.0%)	9 (17.6%)	0.016
Clinically important hypotension	23 (46.9%)	24 (47.1%)	0.990
Life threatening bleeding	0.0	0.0	0.0
Major bleeding	1 (2.0%)	3 (5.9%)	0.618
Serious adverse event	3 (6.1%)	3 (5.9%)	1.000
Infection/Sepsis	6 (12.2%)	8 (15.7%)	0.620
Non-infectious diarrhea	5 (10.2%)	1 (2.0%)	0.108
DVT	0.0	0.0	0.0
PE	2 (4.1%)	0.0	0.238
New ARF requiring dialysis	0.0	0.0	0.0
Hospital length of stay (days), mean (SD)	7.4 (5.3)	6.8 (3.4)	0.771

Table 7: Cox-regression models, Colchicine versus Placebo

	Unadjusted HR			Adjusted HR		
	HR	**95%CI**	**P-value**	**HR**	**95%CI**	**P-value**
New AF/A. Flutter	0.72	0.23-2.27	0.576	0.69	0.20-2.34	0.548
AF	0.84	0.26-2.76	0.776	0.77	0.21-2.74	0.682
Troponin elevation	0.96	0.42-2.18	0.926	1.26	0.50-3.15	0.627
MINS	0.87	0.38-2.01	0.742	1.08	0.42-2.74	0.878
Clinically important bradycardia	0.11	0.01-0.87	0.036	0.13	0.02-1.07	0.057
Clinically important hypotension	0.98	0.55-1.73	0.874	1.07	0.57-2.01	0.841
Major bleeding	0.35	0.04-3.34	0.359	2.36	0.11-50.9	0.585
Serious adverse event	1.06	0.21-5.27	0.940	0.84	0.16-4.52	0.838
Infection/Sepsis	0.78	0.27-2.25	0.645	1.36	0.38-4.86	0.640

*Adjusted for gender, hypertension, and CAD status at baseline.

Figure 4: Kaplan-Meier curves of the primary efficacy outcome



APPENDIX B: EVENTS DEFINITIONS

Atrial fibrillation:

Replacement of the consistent P waves on 12-lead ECG, or documented telemetry tracing, by rapid oscillation or fibrillatory waves and an irregular ventricular response.

Atrial flutter:

Replacement of the consistent P waves on 12-lead ECG, or documented telemetry tracing, by saw-tooth flutter waves.

Postoperative atrial fibrillation (POAF):

New-onset atrial fibrillation developing after induction of anesthesia until the end of follow-up.

Sub-classification of death:

Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, 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 infarction (MI) prior to surgery:

The diagnosis of MI prior to surgery or MI occurring beyond 30 days after surgery requires any one of the following criteria:

1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) 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) within 24 hours of Troponin T elevation.
    b. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds.
    c. 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. Coronary artery intervention (i.e., PCI or CABG surgery) within 2 weeks of Troponin T elevation or ischemic symptoms.
    e. New or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging.

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Myocardial injury after noncardiac surgery (MINS):

The diagnosis of myocardial injury after noncardiac surgery requires one of the following criteria:

1. Within the first 30 days after noncardiac surgery, peak Troponin T ≥0.03 ng/mL, peak Troponin I ≥0.04 ng/mL or, elevation of Troponin or CK-MB measurement with one or more of the following defining features:
    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. 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 [>1 mm], OR symmetric inversion of T waves >1 mm) in at least two contiguous leads;
    d. New LBBB;
    e. New or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; or

f. Identification of intracoronary thrombus on angiography or autopsy

2. Within the first 30 days after noncardiac surgery, peak Troponin T ≥0.03 ng/mL or, elevation of Troponin or CK-MB measurement with no alternative explanation (e.g., pulmonary embolism, sepsis, cardioversion, a known troponin antibody or known chronically elevated troponin measurements, or another known non ischemic etiology) to myocardial injury.

Myocardial infarction after MINS within 30 days of surgery:

Myocardial infarction after MINS and within 30 days of surgery requires the following criteria:

1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) 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:

New focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours and cerebral imaging consistent with acute stroke.

Transient ischemic attack (TIA):

New focal neurological deficit thought to be vascular in origin with signs and symptoms lasting less than 24 hours.

Clinically important bradycardia:

Clinically important bradycardia is defined as a heart rate < 55 beats per minute requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.

Clinically important hypotension:

Clinically important hypotension is defined as a systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.

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

- results in a postoperative hemoglobin $\leq$ 70g/L and the patient receiving a transfusion of $\geq$ 2 units of red blood cells
- results in a hemoglobin drop of $\geq$ 50 g/L and the patient receiving a transfusion of $\geq$ 2 units of red blood cells
- results in the patient receiving a transfusion of $\geq$ 4 units of red blood cells within a 24 hour period
- leads to one of the following interventions: embolization, superficial vascular repair, nasal packing **OR**
- is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

Serious adverse events:

Serious adverse events are those events that are fatal, immediately life threatening, cause or prolong hospitalization, result in persistent or significant disability or incapacity, result in a congenital anomaly or birth defect, or fulfill other comparable medical criteria.

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. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38^{o}C or < 36^{o}C; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^{9}/L or < 4 x 10^{9}/L.

Non-infectious diarrhea:

This outcome is defined by new onset >3 loose bowel movements per day. The diarrhea should not be caused by an infectious organism.