Rationale and design of the COlchicine for Prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation (COPPS-2 trial): A randomized, placebo-controlled, multicenter study on the use of colchicine for the primary prevention of the postpericardiotomy syndrome, postoperative effusions, and postoperative atrial fibrillation

Background

The postpericardiotomy syndrome (PPS), postoperative effusions, and postoperative atrial fibrillation (POAF) are common complications of cardiac surgery, which may lead to prolonged hospital stay, readmissions, or need for invasive interventions (ie, pericardiocentesis and thoracentesis).\(^1\)\(^-\)\(^5\) Preventive strategies, especially if combined, may be useful to improve perioperative management and reduce costs.

Colchicine, administered primarily for gout, has been in use in gout-associated arthritis for nearly 4,000 years.\(^6\) Additional indications include familial Mediterranean fever (FMF)\(^7\) and, more recently, also for recurrent pericarditis.\(^8\)\(^-\)\(^13\)

The PPS and postoperative effusions

Mild pericarditis and low-grade fever, often associated with pericardial/pleural effusion, are common after cardiac surgery and are generally related to the amount of pericardial/pleural manipulation.\(^1\) The PPS has been reported in 10% to 40% of patients after cardiac surgery.\(^1\)\(^-\)\(^5\) The disease develops days to a few months after surgery and may have a prolonged and disabling course.\(^1\)\(^4\) Treatment includes aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. Corticosteroids are generally limited to patients with NSAID contraindications, or who are intolerant or unresponsive to NSAID. Few randomized clinical trials have examined the management of the PPS and, especially, its prevention.\(^1\)\(^5\)\(^-\)\(^18\) Preliminary data have suggested that colchicine may be useful for the treatment for patients with PPS. In this setting, colchicine is often considered for treatment as adjunct to NSAID or corticosteroids to reduce the dosage of associated drugs and thus possible adverse effects.\(^3\)\(^,\)\(^5\)

Different strategies have been considered for PPS prevention including aspirin, corticosteroids, and colchicine. The most relevant clinical trials included a total of 894 patients: 3 studies were double-blind randomized controlled trials (RCTs). Treatment comparisons were as follows: colchicine versus placebo (2 RCTs enrolling a total of 471 patients), methylprednisolone versus placebo (a single RCT of 246 pediatric patients), and aspirin versus historical controls (a single nonrandomized study on 177 pediatric patients).\(^1\)\(^5\)\(^-\)\(^18\) Colchicine was protective against PPS (odds ratio [OR] 0.38, 95% CI 0.22-0.65), whereas study findings on methylprednisolone (OR 1.13, 95% CI 0.57-2.25) and aspirin (OR 1.00, 95% CI 0.16-6.11) were negative but inconclusive because they were based on 1 study and/or a nonrandomized design.\(^1\)\(^9\)

COPPS trial

At present, the COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS)\(^1\)\(^8\) is the largest clinical trial to test the ability of colchicine to safely prevent PPS. This multicenter, double-blind trial, randomized 360 consecutive patients (mean age 65.7 ± 12.3 years, 66% men, 180 in each treatment arm), on the third postoperative day to receive either placebo or colchicine for 1
month (1.0 mg twice daily for the first day, followed by a maintenance dose of 0.5 mg twice daily in patients weighing ≥70 kg and halved doses for patients weighing <70 kg). The incidences of PPS and postoperative effusions were evaluated in each study group. Colchicine significantly reduced the incidence of PPS at 12 months compared with placebo (8.9% vs 21.1%; P = .002, respectively; number needed to treat [NNT] 8) and the incidence of postoperative pericardial (12.8% vs 22.8%, P = .019, relative risk reduction 43.9%, NNT 10) and pleural effusions (12.2% vs 25.6%, P = .002, relative risk reduction 52.3%, NNT 8). The incidence of adverse effects (only gastrointestinal intolerance) and drug withdrawal was similar between the study groups, with a trend toward an increased rate of both events in patients receiving colchicine.\textsuperscript{18,20}

### Postoperative atrial fibrillation

Postoperative atrial fibrillation is the most common complication after cardiac surgery affecting up to 65% of patients, depending on the type of surgery (coronary artery bypass graft surgery, valve surgery, or combined coronary artery bypass graft/valve surgery), patient characteristics, definition of arrhythmia, and surveillance. Postoperative atrial fibrillation is increasingly common because of the increasing number of cardiac surgery operations and the advanced age of the operated population. Postoperative atrial fibrillation increases patient morbidity, length of hospital stay, and health care costs.\textsuperscript{21}

The pathophysiologic basis for the development of POAF is likely multifactorial. Pericardial inflammation, autonomic imbalance during the postoperative time, excessive production of catecholamines, and fluid shifts may all contribute.\textsuperscript{22,23} Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are significantly decreased by corticosteroids,\textsuperscript{24} suggesting that anti-inflammatory therapy may be beneficial for the prevention of POAF. In the COPPS-POAF substudy, patients on colchicine had a reduced incidence of POAF (12.0% vs 22.0%, respectively; P = .021; relative risk reduction 45%; NNT 11) with a shorter inhospital stay (9.4 ± 3.7 days vs 10.3 ± 4.3 days, P = .040) and rehabilitation stay.\textsuperscript{25}

Microtubules have a significant role in numerous cellular cytoskeletal and intracellular transport activities. Colchicine blocks microtubule assembly and can actively disrupt microtubules. Thus, microtubules regulate the localization and interaction of adrenergic receptors and adenylate cyclase and may modulate the phosphorylation of calcium channels and, as a result, the response of the atria to autonomic stimulation. Because autonomic balance is altered in the postoperative state, agents that attenuate sympathetic activity (eg, adrenergic receptor blockers) or the response to sympathetic activity (eg, colchicine) increase parasympathetic activity, which may decrease the risk of calcium overload–induced ectopy.\textsuperscript{26} In addition, colchicine attenuates neutrophil activation, endothelial cell adhesion, and migration to injured tissues.\textsuperscript{11,18}

In light of these positive initial research findings on the role of colchicine in postcardiac surgery patients, confirmatory studies are urgently needed before its routine administration can be recommended for the prevention of several relevant perioperative complications (PPS, postoperative effusions, and POAF). Both efficacy and safety should be evaluated, especially in the perioperative period, preferably with administration of the drug before cardiac surgery to assess its full beneficial effect in the immediate perioperative period, when most of the studied complications are more likely to occur. A limitation of the COPPS trial was that colchicine was begun on postoperative day 3; whether the beneficial effects are similar when colchicine is started before surgery is uncertain.
Methods

Trial design

The COlchicine for the Prevention of the Post-pericardiotomy Syndrome and postoperative Atrial Fibrillation (COPPS-2) trial is a prospective, multicenter, randomized, double-blind, placebo-controlled study, that will evaluate the efficacy and safety of colchicine for the primary prevention of PPS, postoperative effusions, and POAF. The trial design is depicted in the following figure.

![COPPS-2 trial design](image)

Study population

The study population will consist of 360 patients enrolled at 11 hospitals in Italy. All consecutive adult patients who undergo cardiac surgery in any of the study sites will be approached for enrollment. All patients must provide informed consent and be able to comply with study procedures and follow-up. Inclusion and exclusion criteria are reported in Table I.
Randomization and study drug administration.

Patients will be randomized to receive placebo or colchicine between 48 and 72 hours before surgery and continued for 1 month after surgery. Participants will be randomly assigned to treatment groups by a central computer–based automated sequence. Randomization will be based on permuted blocks, with a block size of 4. The random allocation sequence will be implemented by using sequentially numbered containers. All participants and trial investigators will be blinded to randomized treatment. Colchicine will be given as 0.5 mg twice daily in patients weighing ≥70 kg or colchicine 0.5 mg once daily (in patients weighing <70 kg) without a loading dose. Colchicine will be provided by gastric tube in unconscious postoperative patients in intensive care units. Adherence will be determined on the basis of counts of pills in dispensed boxes with a target of at least 80% adherence.

Concomitant medications. Additional medical therapy will be provided according to comorbidities and existing practice guidelines.

Study hypothesis

The primary hypothesis of the COPPS-2 trial is that the early use of colchicine as adjunct to conventional treatment, compared with placebo, will reduce the incidence of PPS, postoperative effusions, and POAF at 3 months after cardiac surgery. This time frame was selected because almost all such events in the COPPS trial occurred in the first 3 months after cardiac surgery. Postpericardiotomy syndrome developed in 54 patients (15.0%; mean age 66 ± 12 years, 48.1% women): 79.6% in the first month, 13.0% in the second month, and 7.4% in the third month. Secondary hypotheses are that colchicine will reduce the incidence of cardiac tamponade, the need for pericardiocentesis or thoracentesis, recurrences of PPS, and disease-related readmissions. Additional analyses will evaluate overall mortality and stroke incidence.
Study outcomes

The primary study end point will be the incidence of PPS within 3 months. Secondary study end points will include postoperative effusions and POAF within 3 months after cardiac surgery, the incidence of cardiac tamponade, the need for pericardiocentesis or thoracentesis, recurrences of PPS, disease-related readmissions, overall mortality, and stroke incidence.

Diagnostic criteria for the diagnosis of PPS will include the following: (1) fever without alternative causes, (2) pleuritic chest pain, (3) friction rub, (4) evidence of new or worsening pericardial, and/or (5) pleural effusion with evidence of systemic inflammation assessed by elevation of C-reactive protein.\(^{17,18,27}\)

A semiquantitative assessment of pericardial effusion will be adopted: a small effusion will be considered as an echo-free space (anterior plus posterior) of less than 10 mm, a moderate effusion will be an echo-free pericardial space of 10 to 20 mm, and a large effusion will be an echo-free space >20 mm. Pericardial effusion echo-free spaces will be measured at the onset of the QRS complex (end of diastole).\(^{5,12,28}\)

Quantitative assessment of pleural effusions will not be performed. The study will assess the presence or absence of pleural effusion and the need for thoracentesis. Criteria for the diagnosis of recurrent pericarditis will include the following: (1) documented first attack of acute pericarditis according to definitive diagnostic criteria and (2) evidence of pericarditis symptoms/signs recurrence (with a symptom-free interval >6 weeks). Incessant or persistent pericarditis will be diagnosed with continued activity of pericarditis (with a symptom-free interval of ≤6 weeks). Recurrence will be documented by recurrent pain and one or more of the following signs: pericardial friction rub, electrocardiogram (ECG) changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count or erythrocyte sedimentation rate.\(^{30}\)

A patient will be considered in remission if symptom-free with disappearance of clinical, electrocardiographical, and echocardiographical signs of disease. On the contrary, we will consider treatment failure in case of persistence of fever, pericardial effusion appearance or worsening, and general illness lasting more than 7 days.\(^{30}\)

Postoperative atrial fibrillation will be defined as atrial fibrillation lasting for more than 30 seconds. Continuous electrocardiographic monitoring will be adopted for at least 5 days postsurgery. Twelve-lead ECGs are recommended daily and more frequently at the discretion of the treating physicians for symptoms or clinically suspected arrhythmia. Clinical data (eg, onset time, symptoms, treatments, and duration) and confirmatory rhythm strips or 12-lead ECGs will be collected for all postoperative arrhythmias of at least 30 seconds’ duration. Use of chronic or prophylactic antiarrhythmic drugs, history of AF, and planned AF ablation are not exclusions, given the similar or higher risk of postoperative AF in these patients and no known biologic interaction that might reduce the efficacy of colchicine in such patients.

A blinded clinical end point committee will adjudicate all events (Appendix).

Follow-up

Postoperative follow-up visits will be scheduled at 1 day, 3 days, discharge day from cardiac surgery, weekly during rehabilitation time, 1 month, and 3 months. Each follow-up visit will include physical examination, blood chemistry, ECG, echocardiography aimed at the identification and semiquantitative assessment of pericardial effusion, and echo study to assess the presence of...
pleural effusion. At least 1 chest-x-ray will be performed during cardiac surgery stay before discharge and then as clinically indicated. Incidence of POAF will be assessed by means of ECG monitoring during intensive care and overall cardiac surgery stay, ECG at the time of follow-up visits, or symptomatic AF recorded by ECG. The study will especially focus on the prevention of symptomatic AF or AF requiring new or escalating therapy. A potential study limitation is the possible missing reporting of episodes of asymptomatic POAF by means of implantable loop recorders or continuous ECG monitoring beyond the first 5 postoperative days. However, such interventions would not be justified or feasible in an unselected patient population for the scheduled 3-month follow-up.

Sample size and statistical significance

Sample size calculations are based on previous data from the COPPS trial.\textsuperscript{18,25} Assuming a PPS rate of 22\% in the placebo group at 3 months and a 2-sided test at the .05 level, a total enrollment of 360 patients will be needed to attain a power of 0.80 to detect a reduction in the recurrence rate to 11\% in the colchicine group.

The study hypothesis was that colchicine could halve the PPS rate. Analyses will be performed by intention to treat. An additional on-treatment analysis will be also performed based on patients who will be both tolerant and compliant to colchicine.

Independent data safety monitoring board and clinical events validation

Data will be collected using standardized case report forms, clinical events committee adjudication forms, and study database. Data will be managed blinded to treatment assignments. Safety endpoints will be examined including colchicine adverse effects and postoperative infections rates. An adverse event will be considered severe if the event is either fatal or life-threatening, or requiring hospitalization, or significantly or permanently disabling or medically significant (ie, an event that jeopardized the patient or required medical or surgical intervention to prevent an adverse outcome). An adverse event will be filed according to whether it is discovered by patient-reported symptoms or blood chemistry monitoring during follow-up visits. A data safety monitoring committee (DSMC) whose members will be blinded to treatment assignment will perform an interim analysis after enrolment of 50\% of patients. Unmasking of the randomization code will be allowed only in case of a severe adverse event.

Prespecified criteria for early termination of the trial will include the finding of a difference in the primary outcome in favor of placebo of 4 SD in the first half of the trial or 3 SD in favor of the second half. For harm, a 2.6-SD excess in the first half and 2-SD excess in the second half against the therapy for severe adverse effects would be a statistical boundary to consider early termination of the trial. These boundaries should remain crossed on a second look of the data at least 3 months later.

Study organization

Executive committee. The executive committee (online Appendix) will evaluate the progress of the study and review recommendations of the DSMC regarding the safety of trial participants. The executive committee will make decisions regarding early termination or continuation of the trial upon recommendation from the DSMC after interim data analyses.

Steering committee. The steering committee (online Appendix) will provide clinical guidance on protocol development, study implementation and conduct, and interpretation of results.
Data and safety monitoring committee. The DSMC (online Appendix) will monitor the trial progress, review data from one interim efficacy analysis, and ensure the safety of patients being enrolled in the study.

Event adjudication committee. An independent committee (online Appendix) blinded to treatment assignment, and consisting of geographically diverse group of academicians and clinicians with expertise in pericardial disease management will systematically identify and adjudicate suspected end point events according to prespecified criteria.

Subgroup analysis and substudies

The clinical effect of colchicine will be further evaluated in different subgroups including age (b65 years vs ≥65 years), gender, serum C-reactive protein (nonelevated or elevated), and presence/absence of pericardial effusion.

Discussion

Few randomized clinical trials have examined the management of PPS and, especially, its prevention.15-18 As a result, treatment of PPS and postoperative effusions is largely empirical. However, these postoperative complications (PPS, postoperative effusions, and POAF) are a source of considerable morbidity and are often challenging to treat.

Horneffer et al15 studied 149 cases of PPS after cardiac surgery at the Johns Hopkins Hospital. Patients were randomized to receive either ibuprofen 600 mg 4 times a day, indomethacin 25 mg 4 times a day, or placebo for 10 days. The rates of PPS resolution were 91% in the ibuprofen group, 88% in the indomethacin group, and 59% in the placebo group, respectively. Treatment discontinuation was reported in 17% for ibuprofen, 20% for indomethacin, and 18% in the placebo group. Relapses at 1 month were reported in 25% for both ibuprofen and indomethacin and 50% for placebo. The authors concluded that NSAIDs were a safe and effective treatment of PPS and recurrence prevention.

Mott et al16 reported a double-blind randomized trial of 246 pediatric patients undergoing cardiac surgery at Texas Children's Hospital. Patients were randomized to receive either solumedrol (1mg/kg intravenously for 1 dose preoperatively and 1 mg/kg every 6 hours for 4 doses postoperatively) or placebo to prevent the PPS. Although the rate of the uncomplicated PPS was lower in the treatment group (62% vs 94%), the overall incidence of the PPS was similar in the 2 study groups: 17% for solumedrol and 15% for placebo. A complicated PPS (defined as requiring readmission, thoracentesis, or pericardiocentesis) was more common in the placebo group (38% vs 6%). This study suggested that prophylactic administration of solumedrol does not prevent the PPS.

Finkelstein et al17 reported a double-blind randomized trial of 163 patients who underwent cardiac surgery in 2 centers in Israel (Rabin and Sheba Medical Centers). The initial study group included 163 patients who were randomly assigned to receive colchicine (1.5mg daily) or placebo for 1 month, starting on the third postoperative day. All patients were evaluated for the development of PPS within the first 3 months after cardiac surgery. Unfortunately, 52 (31.9%) of 163 patients were excluded because of postoperative complications, noncompliance, or gastrointestinal adverse effects. Postpericardiotomy syndrome was diagnosed in 19 (17.1%) of 111 patients who completed the study: 5 (10.6%) of 47 patients in the colchicine group and 14 (21.9%) of 64 patients in the placebo group, showing a favorable trend but not statistical significance (P = .135). The authors concluded that colchicine may be efficacious for the prevention of PPS after cardiac surgery, but further evaluation is needed in larger clinical trials. In the COPPS trial and COPPS-POAF substudy, colchicine halved the incidence of PPS, postoperative effusions, and POAF.18,20,25
In an editorial in Circulation, Van Wagoner wrote that results of the trial are promising and that it would be of great interest to prospectively evaluate the use of perioperative colchicine treatment as a prophylactic approach, beginning at the time of surgery or before. Such treatment can reduce the morbidity associated with common postsurgical complications. If colchicine is effective in preventing POAF, this treatment would constitute an important new indication for the use of a very old drug. Thus, there is a need for a new clinical trial that will assess the efficacy and safety of colchicine for the primary prevention of PPS, postoperative effusions, and POAF in the perioperative period. The COPPS-2 trial is specifically designed for this task. Colchicine will be started 48 to 72 hours before surgery and administered for 1 month using weight-adjusted doses (0.5 or 1 mg daily), without a loading dose to reduce gastrointestinal adverse effects and improve compliance.

**Summary**

The COPPS-2 study will address an important knowledge gap in prevention of common postcardiac surgery complications. It will be the first large randomized placebo-controlled clinical trial to evaluate the efficacy and safety of colchicine for the primary prevention of several postoperative complications (PPS, postoperative effusions, and POAF) in the perioperative period. This trial will evaluate the possible benefit of the early use of colchicine, starting before cardiac surgery.

**Disclosures**

The COPPS-2 trial is registered with the ClinicalTrials.gov Identifier NCT01552187. The trial is an independent study founded and performed in the Italian National Healthcare System. The executive and steering committees designed and oversaw the trial and will have the final decision on the contents of the manuscript. All data will be received, checked, and analyzed at the Cardiology Department, Maria Vittoria Hospital, Torino, Italy, as the Coordinating Center, after blinded adjudication of clinical events and adverse effects. Acarpia (Madeira, Portugal) will provide the drug and placebo as unrestricted grant. FAR.G.IM. srl (Catania, Italy) will provide funding to support insurance costs for the trial. No other extramural funding will be used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

**References**


Appendix

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**Acquisition of data**: All authors

**Analysis and Interpretation**: Massimo Imazio, Alberto Pullara

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**Critical revision of the manuscript for important intellectual content**: All authors

**Statistical Analysis**: Massimo Imazio, Alberto Pullara

**Conflict of interest**: None

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**Recruiting centers**

1. Cardiology Department, Maria Vittoria Hospital, ASLTO2 Torino, Italy
2. Cardiac Surgery and Internal Medicine Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy
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6. Cardiac Surgery, ospedale San Camillo, Roma, Italy
7. Cardiology and Cardiac Surgery Department, Ca’ Forcello Hospital, Treviso, Italy
Protocol changes for COPPS-2 trial. Summary of all amendments.

Criteria for the post-pericardiotomy-syndrome. Evidence of systemic inflammation (i.e. C-reactive protein elevation) is included in case of pericardial and pleural effusions without other criteria.

Diagnostic criteria for the diagnosis of PPS will include the following: (1) fever without alternative causes, (2) pleuritic chest pain, (3) friction rub, (4) evidence of new or worsening pericardial, and/or (5) pleural effusion with evidence of systemic inflammation assessed by elevation of C-reactive protein.
Statistical plan of the COPPS-2 trial.

Sample size and data analysis
Sample size calculations are based on previous data from the COPPS trial. Assuming a PPS rate of 22% in the placebo group at 3 months and a 2-sided test at the .05 level, a total enrollment of 360 patients is needed to attain a power of 0.80 to detect a reduction in the recurrence rate to 11% in the colchicine group. The study hypothesis is that colchicine could halve the PPS rate.

The main analysis will be by intention-to-treat, including all patients according to treatment assigned at randomization. All patients who will withdraw or die will be included in all analyses until their date of death or withdrawal. An additional on-treatment analysis is planned on patients who will be both tolerant and compliant to colchicine (including those patients with at least 80% adherence over the course of the study until the onset of the primary end point or the end of the assigned treatment, whichever will occur first).

The clinical effect of colchicine will be further evaluated in different prespecified subgroups including age (<65 years vs ≥65 years), gender, serum C-reactive protein (non-elevated or elevated), and presence/absence of pericardial effusion.

Data will be expressed as means and standard deviations. Patient groups will be compared by the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. A two-sided p value <0.05 will indicate statistical significance. Time to event distributions will be estimated by the Kaplan-Meier method and compared by the log-rank test. Analyses will be performed with SPSS version 13.0 (SPSS, Chicago, Illinois) and MedCalc Version 12.7.2 (MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium).

Outcomes
The primary study end point was the incidence of PPS within 3 months. Secondary study end points were postoperative effusions and POAF within 3 months after cardiac surgery, the incidence of cardiac tamponade, the need for pericardiocentesis or thoracentesis, recurrences of PPS, disease-related readmissions, stroke incidence, and overall mortality.

**Planned analyses**

1. Comparison of baseline characteristics
2. Outcomes comparison in the 2 study groups (colchicine vs. placebo)
3. Kaplan-Meier incidence of post-pericardiotomy syndrome according to treatment groups
4. On-treatment analysis based on patients who will be both tolerant and compliant to colchicine (including those patients with at least 80% adherence over the course of the study until the onset of the primary end point or the end of the assigned treatment, whichever occurred first).
5. The clinical effect of colchicine will be evaluated in different pre-specified subgroups including age (<65 years vs. ≥65 years), gender, serum C-reactive protein (non-elevated or elevated), and presence/absence of pericardial effusion.
6. Safety analyses: comparison of adverse events and drug discontinuation rates