Colchicine for prevention of post-pericardiotomy syndrome and post-operative atrial fibrillation: the COPPS-2 randomized clinical trial.

Massimo Imazio, MD, FESC on behalf of the COPPS-2 Investigators
Cardiology Dpt. Maria Vittoria Hospital and
University of Torino, Torino, Italy
massimo_imazio@yahoo.it
massimo.imazio@unito.it

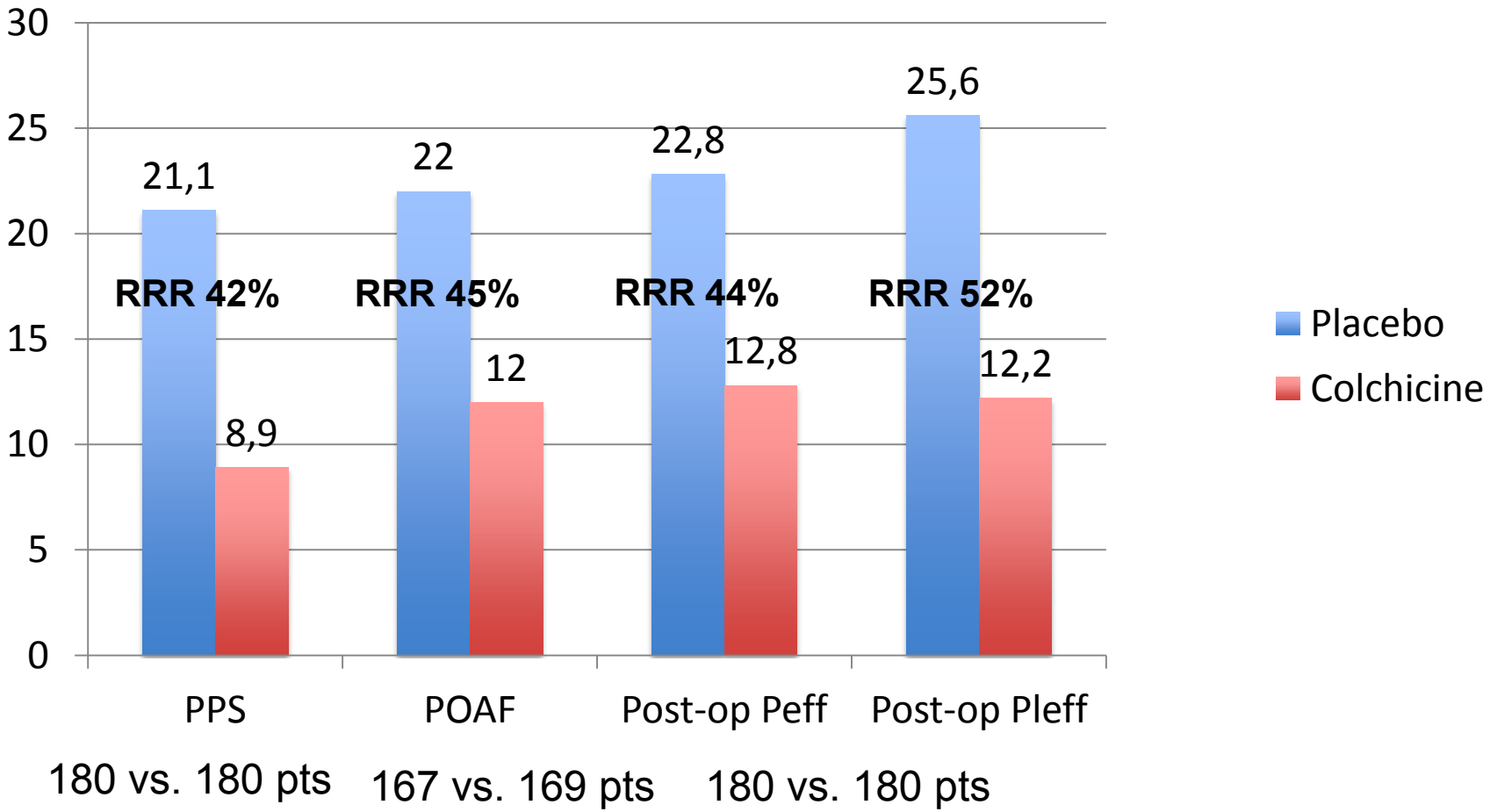
Disclosures:

- The COPPS-2 trial was supported by former Azienda Sanitaria 3 of Torino (now ASLTO2) within the Italian National Health Service.
- Acarpia (Madeira, Portugal) provided the study drug and placebo as an unrestricted institutional grant and had no role in planning of the study, analysis of data, or writing of the manuscript.
- FAR.G.IM. srl (Catania, Italy) provided funding to support insurance costs for the trial.

Unlabeled use of drugs:

- Colchicine for PPS and POAF prevention

Background: COPPS Trial

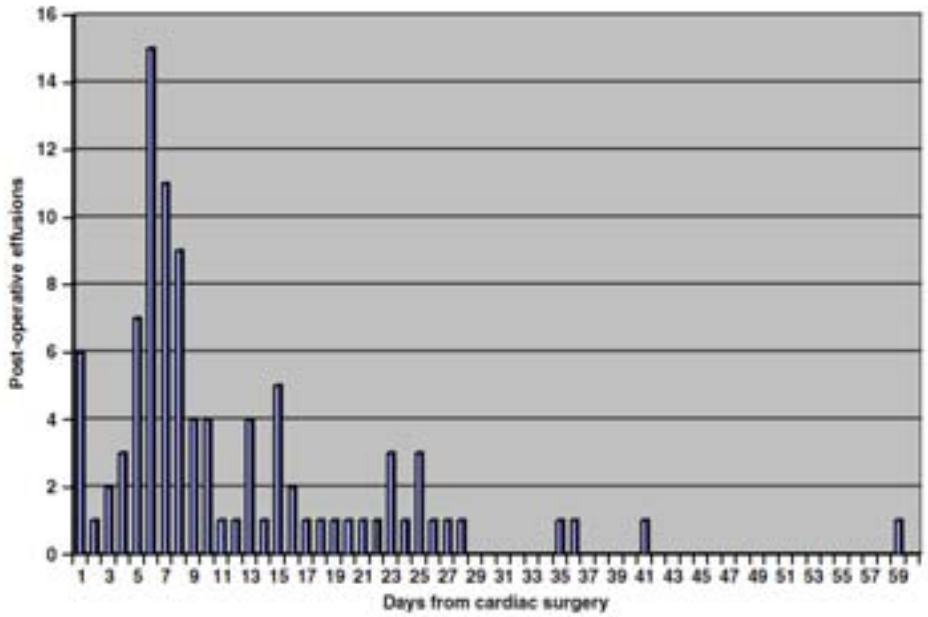


Eur Heart J. 2010 Nov;31(22):2749-54
Circulation. 2011 Nov 22;124(21):2290-5
Am Heart J. 2011 Sep;162(3):527-32.e1

PPS and POAF

COPPS: PPS incidence

90% in 60 days

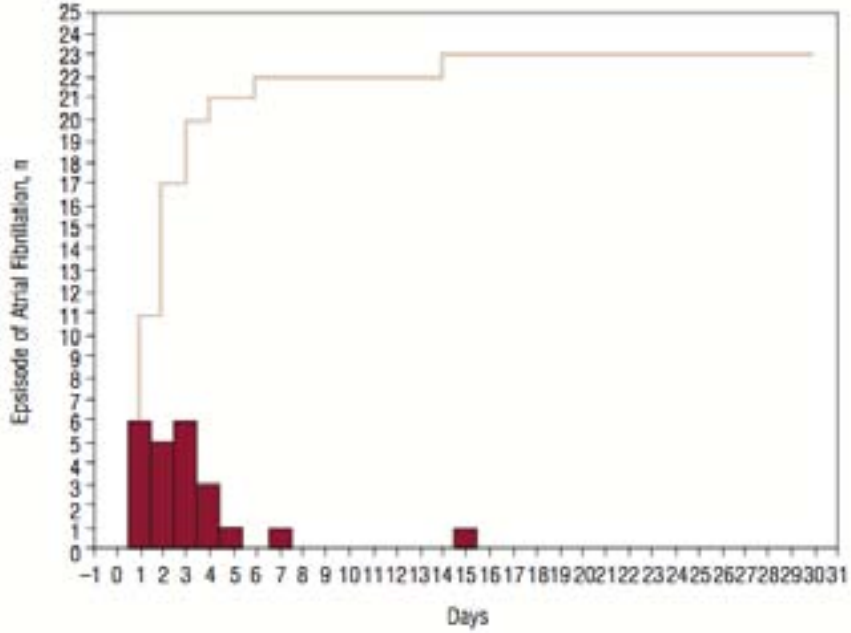


Time course of postoperative effusions after cardiac surgery.

Am Heart J. 2011 Sep;162(3):527-32.e1.

POAF incidence

70% POAF in ICU



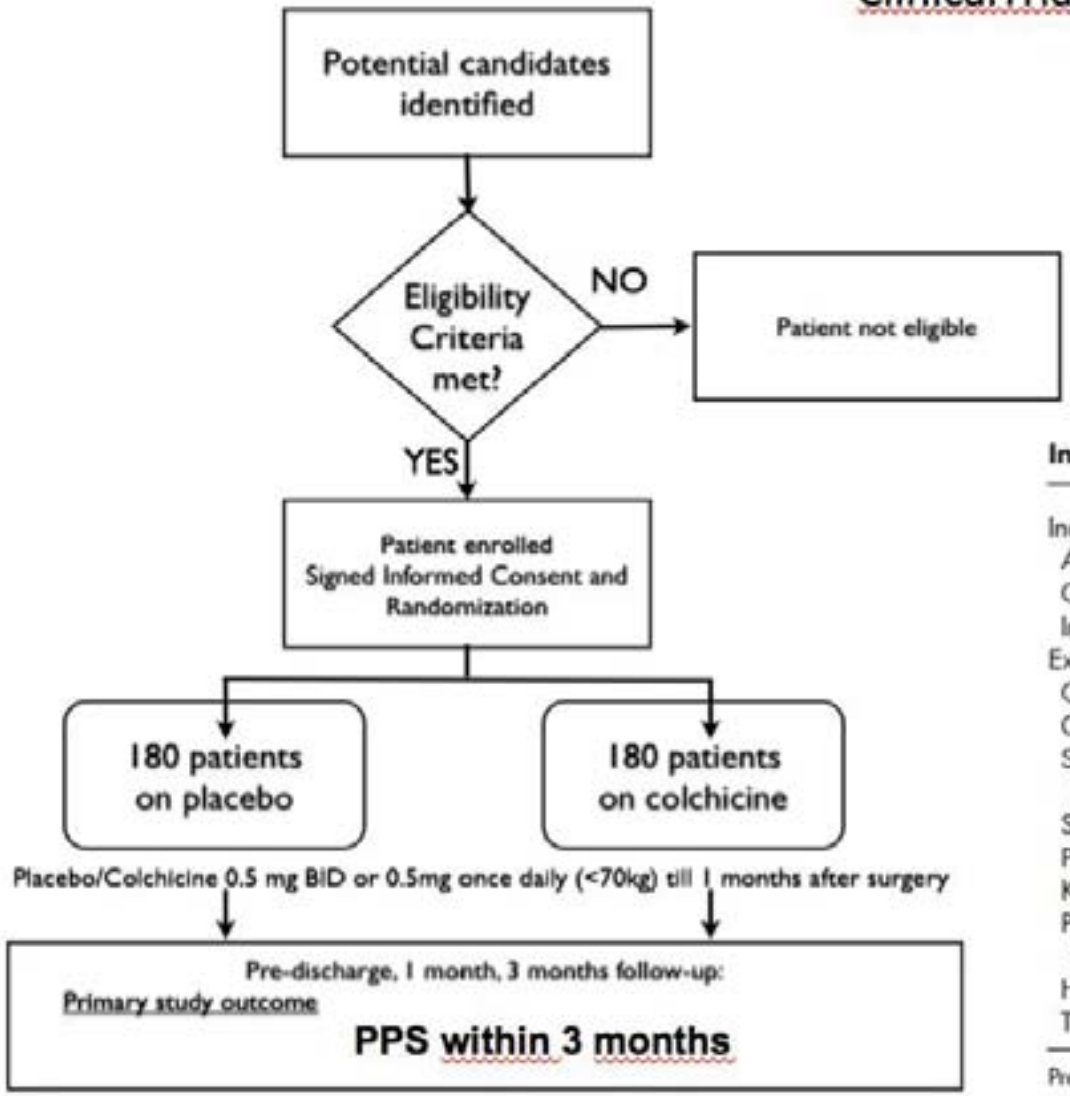
Rev Esp Cardiol. 2007;60(8):841-7

Objective

- To determine the efficacy and safety of perioperative administration of oral colchicine to reduce:
  - post-pericardiotomy syndrome (PPS),
  - post-operative AF (POAF),
  - post-operative effusions (pleural and/or pericardial).

Design, Setting, Participants, Intervention

ClinicalTrials.gov Identifier: NCT01552187



Inclusion and exclusion criteria

Inclusion criteria
- Age >18 y
- Candidate to cardiac surgery
- Informed consent

Exclusion criteria
- Current atrial fibrillation
- Candidate to cardiac transplantation
- Severe liver disease or elevation of serum transaminases (>1.5 times the upper reference limit)
- Serum creatinine >2.5 mg/dL
- Preoperative elevation of CK or known myopathy
- Known chronic intestinal diseases or blood dyscrasias
- Pregnancy, lactation, or women of childbearing potential not protected by a contraception method
- Hypersensitivity to colchicine
- Treatment with colchicine for any cause

Preoperative elevation of CK beyond upper limit of reference interval.

Main Outcome Measures

PPS within 3 month (primary end point):

At least 2 of these criteria should be present for the diagnosis

1. Fever without alternative causes
2. Pleuritic chest pain
3. Friction rub
4. Evidence of new or worsening pleural effusion
5. Evidence of new or worsening pericardial effusion

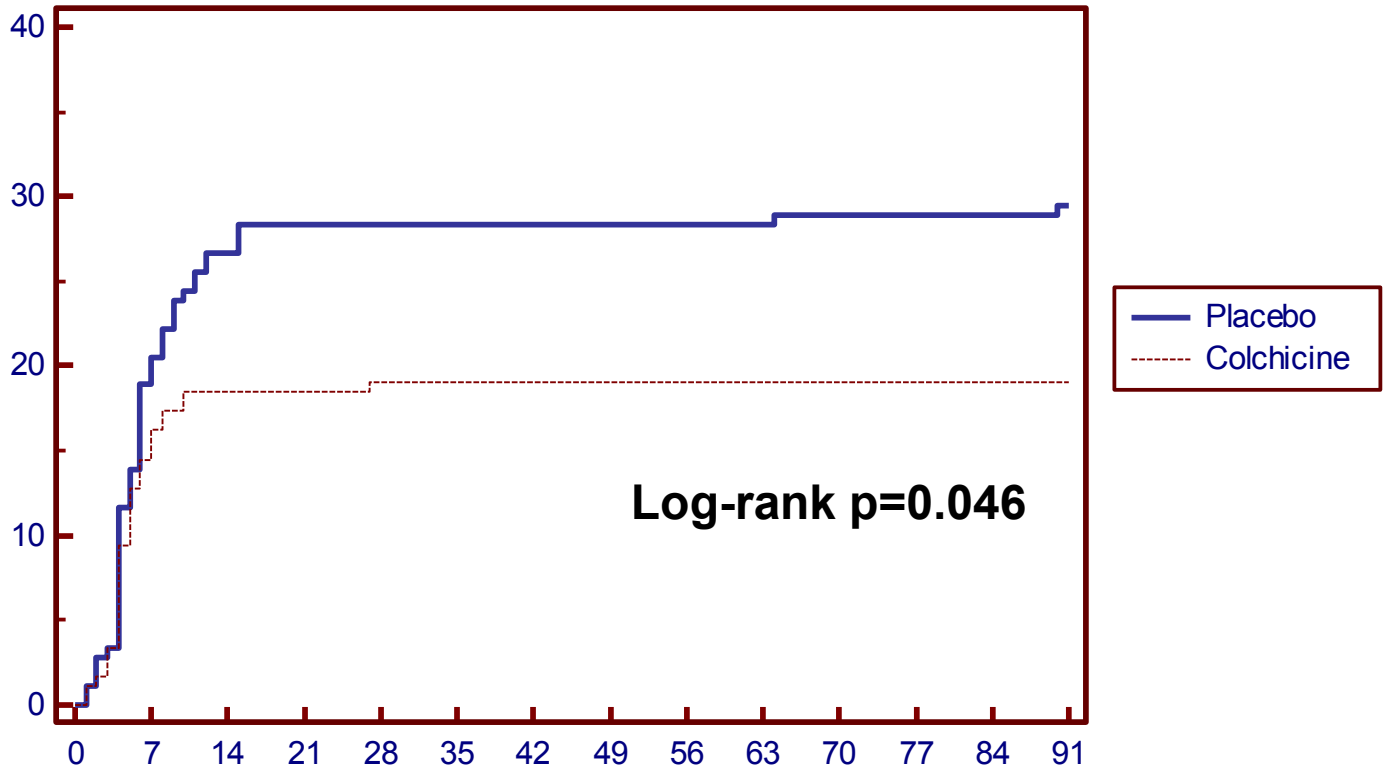
POAF within 3 months (secondary end point):
Post-operative AF was defined as AF lasting for more than 30 seconds. Continuous ECG monitoring at least 5 days post-surgery then daily ECG and symptoms-guided.

Post-operative eff. within 3 months (secondary end point):
Pericardial and/or Pleural by ultrasonography.

Outcome	Placebo (n=180)	Colchicine (n=180)	Absolute differences (95% CI) %
Primary End Point within 3 months Post-Pericardiotomy Syndrome	53 (29.4%)	35 (19.4%)	10.0 (1.1 to 18.7)
Main Secondary end points:			
Post-Operative Atrial Fibrillation	75 (41.7%)	61 (33.9%)	7.8 (-2.2 to 17.6)
POAF (on-treatment):	61 (41.2%)	38 (27.0%)	14.2 (3.3 to 24.7)
Post-operative effusions	106 (58.9%)	103 (57.2%)	1.7 (-8.5 to 11.7)
Cardiac Tamponade	3 (1.7%)	1 (0.6%)	1.1 (-1.6 to 4.3)
Pericardiocentesis or thoracentesis	13 (7.2%)	13 (7.2%)	0.0 (-5.6 to 5.6)
PPS recurrence	3 (1.7%)	3 (1.7%)	0.0 (-3.3 to 3.3)
Disease-related readmissions	2 (1.1%)	2 (1.1%)	0.0 (-2.7 to 2.7)
Overall mortality°	2 (1.1%)	6 (3.3%)	2.2 (-1.6 to 6.1)
Stroke	1 (0.6%)	2 (1.1%)	0.50 (-2.1 to 3.4)

Results

Kaplan-Meier incidence of post-pericardiotomy syndrome according to treatment groups.



Number at risk

Group: Placebo	180	143	131	128	128	128	128	128	128	127	126	126	125	81
Group: Colchicine	180	147	141	141	139	139	139	139	139	139	139	139	139	91

Safety

Feature	Placebo (n=180)	Colchicine (n=180)	Absolute differences (95% CI) %
Adverse events	21 (11.7%)	36 (20.0%)	8.3 (0.76 to 15.9)
Gastrointestinal intolerance*	12 (6.7%)	26 (14.4%)	7.7 (1.4 to 14.3)
Hepatotoxicity°	2 (1.1%)	1 (0.6%)	0.50 (-2.1 to 3.4)
Drug discontinuation	32 (17.8%)	39 (21.7%)	3.9 (-4.4 to 12.5)

Reported data represent the number of affected individuals.
No serious adverse events (any fatal or life-threatening event, requiring hospitalization, or significantly or permanently disabling or medically significant, that could have jeopardized the patient or required medical or surgical intervention to prevent an adverse outcome) were reported, as well as myotoxicity, alopecia or other side effects beyond those reported in the table.
*= Diarrhea, nausea, cramping, abdominal pain, or vomiting.
°= Any elevation of aminotransferase levels above the normal reference range.

Conclusions

- Among patients undergoing cardiac surgery, the perioperative use of colchicine compared with placebo reduced the incidence of post-pericardiotomy syndrome but not of post-operative AF or postoperative effusions.
- The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.

Acknowledgment: COPPS-2 Investigators

Steering and Executive committee: Massimo Imazio, MD (Chairman and Principal Investigator) (Ospedale Maria Vittoria and University of Torino, Torino, Italy), Riccardo Belli, MD (Co-chairman), (Ospedale Maria Vittoria, Torino, Italy), Antonio Brucato, MD (Ospedale Papa Giovanni XXIII, Bergamo, Italy), and Paolo Ferrazzi, MD, (Ospedale Papa Giovanni XXIII, Bergamo, Italy). **Data and safety monitoring committee**: Yaron Finkelstein, MD (Hospital for Sick Children, Toronto, Canada), Anna Leggieri, MD (Ospedale Maria Vittoria, Torino, Italy), Bernhard Maisch, MD (University of Marburg, Germany), Bongani Mayosi, MD (University of Cape Town, South Africa), Jae K. Oh, Rochester, MD (Mayo Clinic, Rochester, USA), Arsen D. Ristic, MD and Petar Seferovic, MD (University of Belgrade, Belgrade, Serbia). **Clinical events committee**: Yehuda Adler, MD (Cham Sheba Medical Center, Tel Hashomer and Sackler University, Tel Aviv, Israel), Brian Hoit, MD (Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, USA), David H. Spodick, MD (St Vincent Hospital, Worcester, USA) and Alberto Pullara, MD, (Ospedale Maria Vittoria and University of Torino, Torino, Italy). **Centers (Italy): Cardiac Surgery and Internal Medicine Department, Ospedale Papa Giovanni XXIII, Bergamo** (103 patients enrolled): Antonio Brucato, MD (center principal investigator, PI), Paolo Ferrazzi, MD, Diego Cugola, MD, Davide Cumetti, MD, Silvia Maestroni MD, Francesco Innocente, MD, Anna Valenti, MD; **Cardiac Surgery and Rehabilitation, Villa Maria Pia Hospital, Torino** (56 patients enrolled): Chiara Comoglio, MD (center PI), Oleksandr Dyrda, MD, Stefania Trimboli, MD, Elisabetta Lardone, MD, Paolo Sorrentino, MD, Ingignoli Biagio, MD, Roberto Valesio, MD, Annarita Zeoli, MD; **Cardiology Department, Maria Vittoria Hospital, ASLTO2 Torino** (54 patients enrolled): Massimo Imazio, MD (center PI), Riccardo Belli, MD, Alessandra Chinaglia, MD, Enrico Cecchi, MD, Luisella Coda, MD, Brunella Demichelis, MD, Silvia Ferro, MD, Davide Forno, MD; **Cardiac Surgery, Ospedale Niguarda, Milano** (34 patients enrolled): Alberto Barosi, MD (center PI), Anna Gandino, MD (center co-PI), Luigi Martinelli, MD, Gianna Attanasio, MD; **Cardiac Surgery, ospedale Mauriziano, Torino** (27 patients enrolled): Roberto Flocco, MD (center PI), Riccardo Casabona, MD; **Cardiology and Cardiac Surgery Department, Ca' Forcello Hospital, Treviso** (26 patients enrolled): Fabio Chirillo, MD (center PI), Marcio Scorsin, MD, Zoran Olivari, MD, Elvio Polesel, MD; **Cardiac Surgery, Ospedale San Camillo, Roma** (24 patients enrolled): Vincenzo Polizzi, MD (center PI), Emanuela Belmonte, MD, Francesco Musumeci, MD, Amedeo Pergolini, MD; **Cardiology Department, Ospedale Regionale San Maurizio, Bolzano and Cardiac Surgery, Ospedale Santa Chiara, Trento** (15 patients enrolled): Roberto Cemin, MD (center PI), Angelo Graffigna, MD; **Cardiology Department, Ospedale degli Infermi, Rivoli** (9 patients enrolled): Stefania Ferrua, MD (center PI), Ferdinando Varbella, MD; **Cardiology and Cardiac Surgery Dept of Cardiological Thoracic and Vascular Sciences, University of Padova** (9 patients enrolled): Alida L Caforio (center PI), Vincenzo Tarzia (center co-PI), Sabino Iliceto, MD, Gino Gerosa, MD; **Cardiology Department, San Giovanni Bosco Hospital, ASLTO2 Torino** (3 patients enrolled): Piera Costanzo, MD (center PI), Massimo Minelli, MD.

Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation

The COPPS-2 Randomized Clinical Trial

Massimo Imazio, MD; Antonio Brucato, MD; Paolo Ferrazzi, MD; Alberto Pullara, MD; Yehuda Adler, MD; Alberto Barosi, MD; Alida L. Caforio, MD; Roberto Cemin, MD; Fabio Chirillo, MD; Chiara Comoglio, MD; Diego Cugola, MD; Davide Gunetti, MD; Oleksandr Dyrda, MD; Stefania Ferrua, MD; Yaron Finkelstein, MD; Roberto Piccco, MD; Anna Gandino, MD; Brian Hoit, MD; Francesco Innocente, MD; Silvia Maestrini, MD; Francesco Musumeci, MD; Jae Oh, MD; Amedeo Pergolini, MD; Vincenzo Polizzi, MD; Arsen Ristić, MD; Caterina Simon, MD; David H Spodick, MD; Vincenzo Tarzia, MD; Stefania Trinkoll, MD; Anna Valenti, MD; Riccardo Belli, MD; Fiorenzo Gaita, MD; for the COPPS-2 Investigators

Supplemental content at jama.com

IMPORTANCE Postpericardiotomy syndrome, postoperative atrial fibrillation (AF), and postoperative effusions may be responsible for increased morbidity and health care costs after cardiac surgery. Postoperative use of colchicine prevented these complications in a single trial.

OBJECTIVE To determine the efficacy and safety of perioperative use of oral colchicine in reducing postpericardiotomy syndrome, postoperative AF, and postoperative pericardial or pleural effusions.

DESIGN, SETTING, AND PARTICIPANTS Investigator-initiated, double-blind, placebo-controlled, randomized clinical trial among 360 consecutive candidates for cardiac surgery enrolled in 11 Italian centers between March 2012 and March 2014. At enrollment, mean age of the trial participants was 67.5 years (SD, 10.6 years), 69% were men, and 36% had planned valvular surgery. Main exclusion criteria were absence of sinus rhythm at enrollment, cardiac transplantation, and contraindications to colchicine.

INTERVENTIONS Patients were randomized to receive placebo (n=180) or colchicine (0.5 mg twice daily in patients >70 kg or 0.5 mg once daily in patients <70 kg, n=180) starting between 48 and 72 hours before surgery and continued for 1 month after surgery.

MAIN OUTCOMES AND MEASURES Occurrence of postpericardiotomy syndrome within 3 months; main secondary study end points were postoperative AF and pericardial or pleural effusion.

RESULTS The primary end point of postpericardiotomy syndrome occurred in 35 patients (19.4%) assigned to colchicine and in 53 (29.4%) assigned to placebo (absolute difference, 10.0%; 95% CI, 1.1%-18.7%; number needed to treat = 10). There were no significant differences between the colchicine and placebo groups for the secondary end points of postoperative AF (colchicine, 61 patients [33.9%]; placebo, 75 patients [41.7%]; absolute difference, 7.8%; 95% CI, −2.2% to 17.6%) or postoperative pericardial/pleural effusion (colchicine, 103 patients [57.2%]; placebo, 106 patients [58.9%]; absolute difference, 1.7%; 95% CI, −8.5% to 11.7%), although there was a reduction in postoperative AF in the prespecified on-treatment analysis (placebo, 61/148 patients [41.2%]; colchicine, 38/141 patients [27.0%]; absolute difference, 14.2%; 95% CI, 3.3%-24.7%). Adverse events occurred in 21 patients (11.7%) in the placebo group vs 36 (20.0%) in the colchicine group (absolute difference, 8.3%; 95% CI, 0.76%-15.9%; number needed to harm = 12), but discontinuation rates were similar. No serious adverse events were observed.

CONCLUSIONS AND RELEVANCE Among patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion. The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01552187

JAMA. doi:10.1001/jama.2014.10206
Published online August 30, 2014

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The COPPS-2 Investigators are listed at the end of this article.

Corresponding Author: Massimo Imazio, MD, Department of Cardiology, Maria Vittoria Hospital and University of Torino, Via Cibrario 72, Torino, Torino 10141, Italy (massimo.imazio@yahoo.it, massimo.imazio@unito.it).

JAMA®

The Journal of the American Medical Association

Imazio M and coauthors

Colchicine for Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation: the COPPS-2 Randomized Clinical Trial

Published online August 30, 2014

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

The JAMA Network