

COlchicine for Post-Pericardiotomy Syndrome (COPPS) and Post-Operative Atrial Fibrillation (POAF) prevention study: a multicenter, double-blind randomized controlled trial.

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1861 > 2011 >
150° anniversario Unità d'Italia



Disclosure: None

Role of the Funding Source:

- Independent study founded and performed within the Italian National Healthcare System.
- Approval by the relevant institutional ethical review boards, written informed consent by participants.
- The steering committee designed and oversaw the trial.
- All data were received, checked, and analyzed independently at the Coordinating Centre (Cardiology Dpt, Maria Vittoria Hospital, Torino, Italy) following blinded adjudication of clinical events and side effects.
- Acarpia Lda (Madeira, Portugal) provided supply of drug/placebo as unrestricted grant.

Background

1. Postoperative atrial fibrillation (POAF) is common after cardiac surgery (10%-65%), depending on the surgery type, patient features, definition of arrhythmia, and surveillance*;
2. Inflammation and pericarditis may be contributing factors for POAF;
3. both are potentially affected by antiinflammatory drugs and colchicine, which has been shown to be safe and efficacious for pericarditis prevention[°]

**Ann Intern Med.* 2001;135:1061–1073;

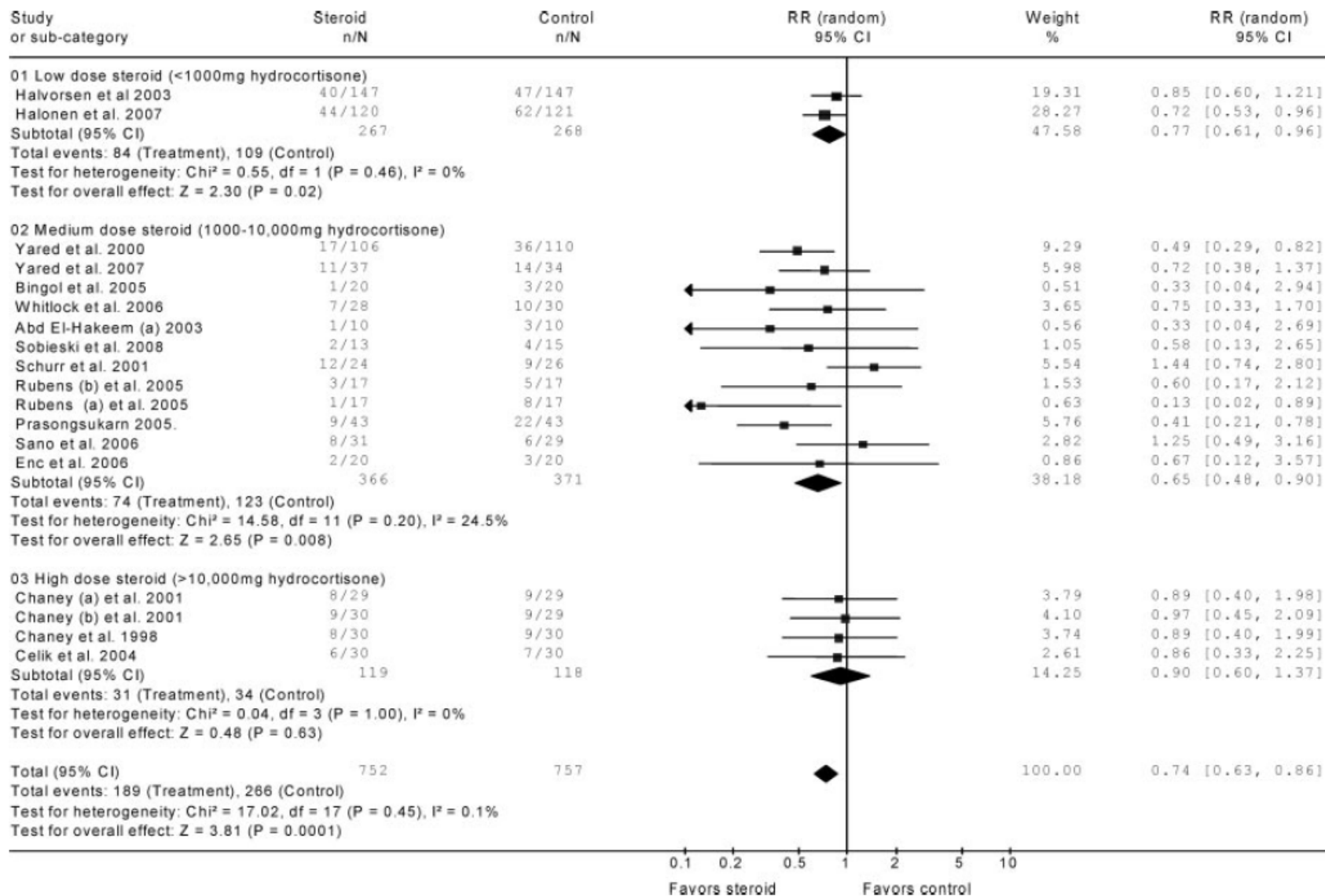
[°]CORP trial- *Ann Intern Med.* 2011;155:409-414

Corticosteroids for the Prevention of Atrial Fibrillation After Cardiac Surgery

A Randomized Controlled Trial

Intervention Patients were randomized to receive either 100-mg hydrocortisone or matching placebo as follows: the first dose in the evening of the operative day, then 1 dose every 8 hours during the next 3 days. In addition, all patients received oral metoprolol (50-150 mg/d) titrated to heart rate.

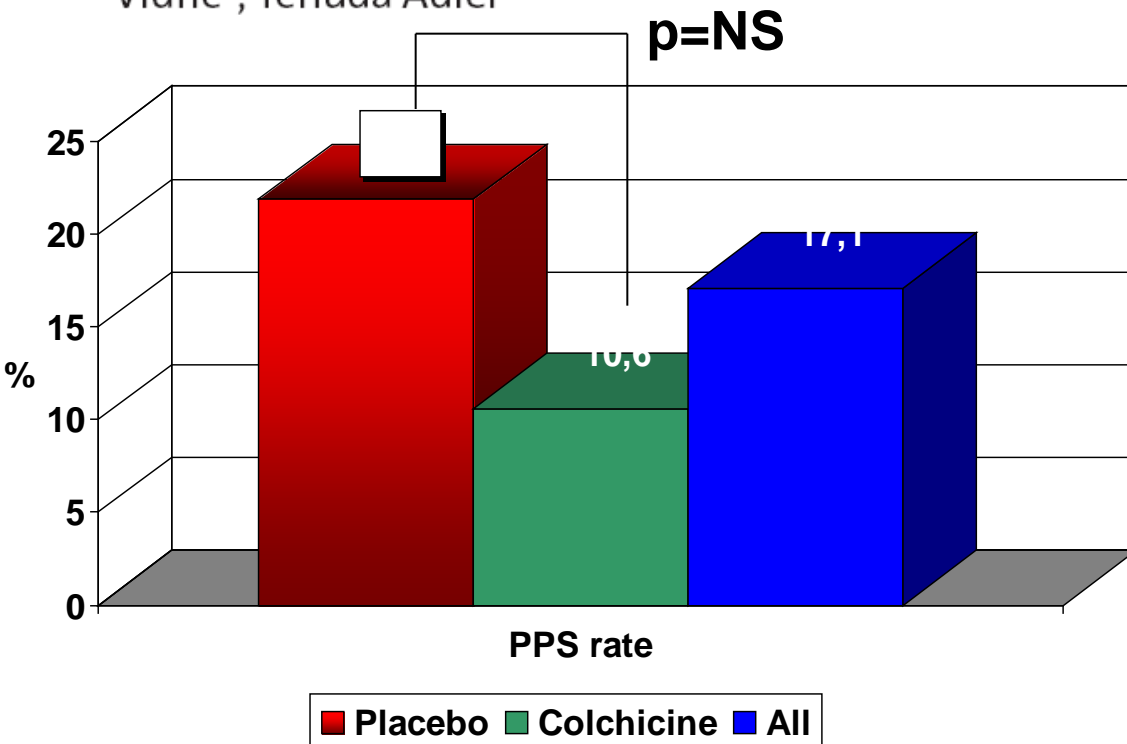
Characteristics	Placebo (n = 121)	Hydrocortisone (n = 120)	Univariate P Value
AF during first 84 hours after cardiac surgery	58 (47.9)	36 (30.0)	.01
Onset of AF (hours after operation), mean (SD)	21.3 (25.4)	16.0 (24.6)	.10
In-hospital AF	62 (51.7)	44 (36.)	.02
In-hospital mortality	1 (0.83)	1 (0.83)	>.99



Herz. 2002;27:791-4

Colchicine for the Prevention of Postpericardiotomy Syndrome

Yaron Finkelstein¹, Joseph Shemesh², Kerem Mahlab², Dan Abramov³, Yaron Bar-El⁴, Alex Sagie¹, Erez Sharoni³, Gideon Sahar³, Aram Kurt Smolinsky⁴, Taly Schechter¹, Bernard A. Vidne³, Yehuda Adler²



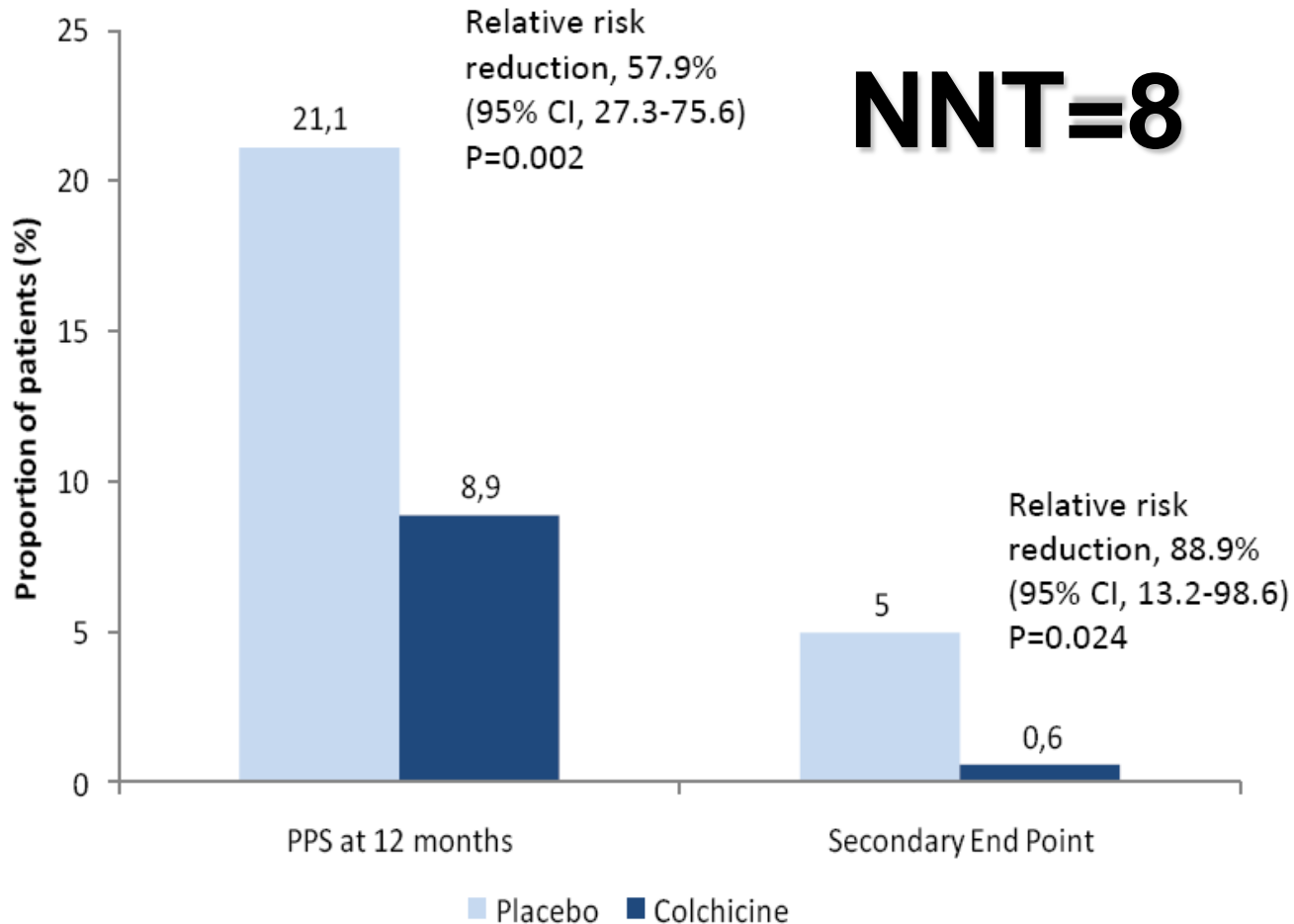
- Prospective, double-blind design
- 163 patients; colchicine 1.5mg/day for 1 month
- 52/163 (31%) excluded (complications, intolerance, non-compliance)
- PPS at 3 months (placebo vs. colchicine: 14/64 vs.5/47; p= NS)

COPPS study questions

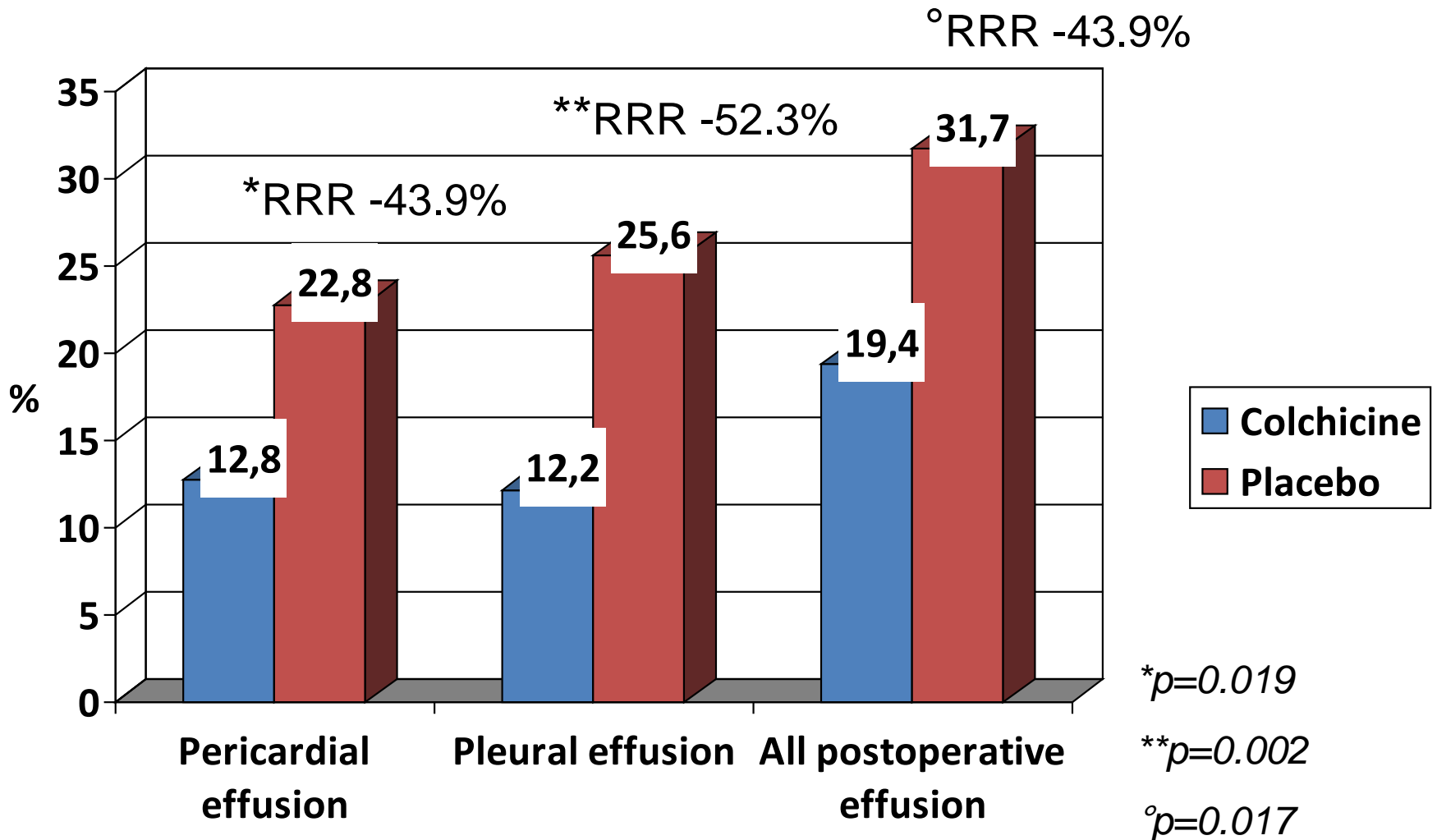
Is colchicine efficacious and safe to prevent:

1. The post-pericardiotomy syndrome?
2. Post-operative effusions (pericardial and/or pleural)?
3. Post-operative atrial fibrillation?

COPPS trial: Main results



Colchicine reduces post-operative effusions



COPPS-POAF study

Objective

- To evaluate the efficacy and safety of colchicine for the prevention of post-operative atrial fibrillation;
- Specific condition to test: occurrence of POAF on intervention (from the 3rd post-operative day).

Study design and setting

- Design: Prospective, randomized, double-blind, placebo-controlled, multicenter trial;
- Setting: 6 general hospital in North of Italy-urban areas (Maria Vittoria Hospital, Torino; Ospedali Riuniti, Bergamo; Mauriziano Hospital, Torino; Niguarda Hospital, Milano; San Maurizio Regional Hospital, Bolzano; and Ospedale degli Infermi, Rivoli);

Inclusion/Exclusion Criteria

Inclusion criteria

Candidate for cardiac surgery

Age ≥ 18 years

Informed consent

Exclusion criteria

Known severe liver disease or current transaminases >1.5 times the upper normal limit

Current serum creatinine >2.5 mg/dl

Known myopathy or elevated baseline preoperative creatine kinase

Known blood dyscrasias or gastrointestinal disease

Pregnant and lactating women

Women of childbearing potential not protected by a contraceptive method

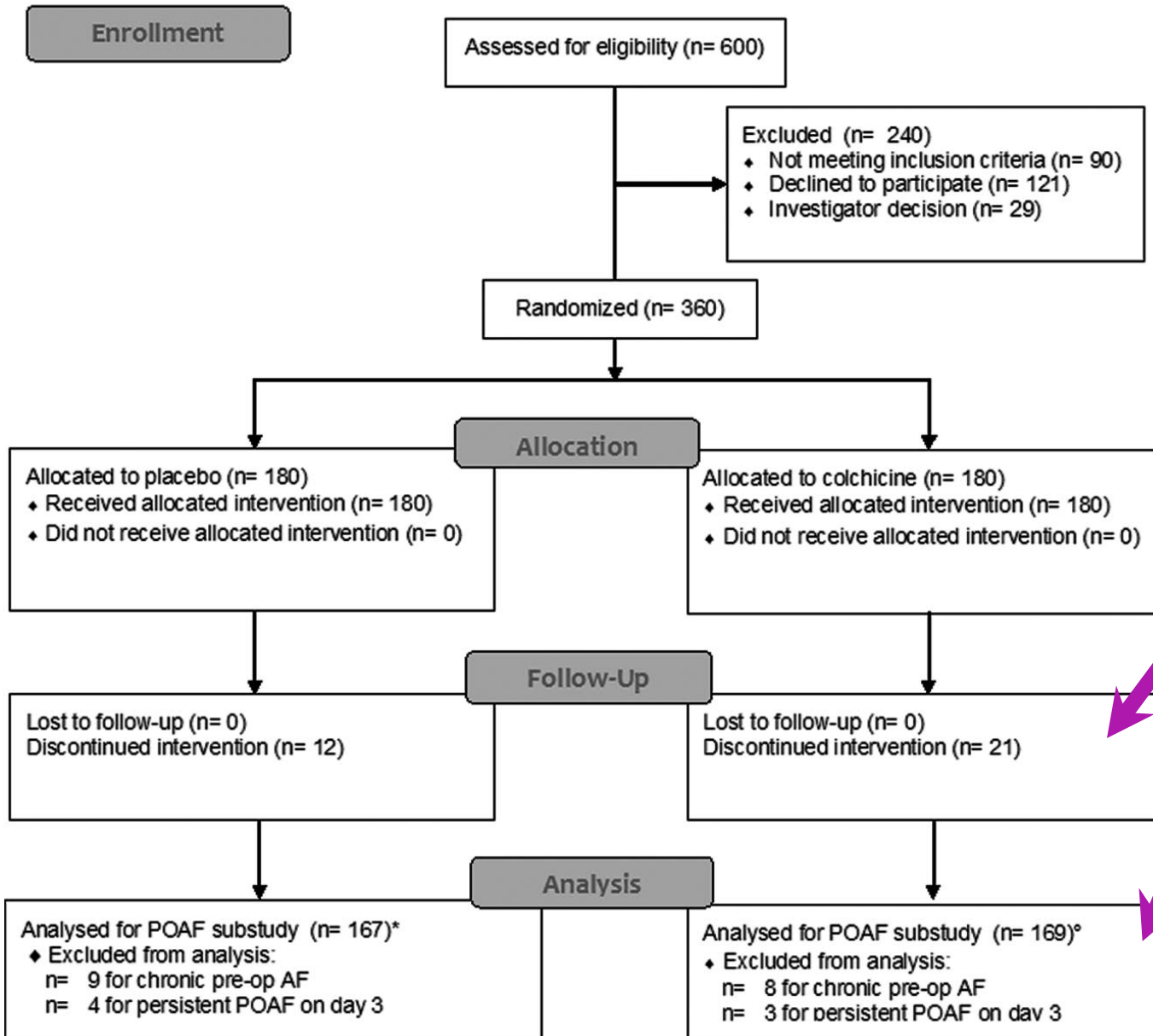
Known hypersensitivity to colchicine

Current treatment with colchicine for any indications

Unfavourable short-term outlook for any causes

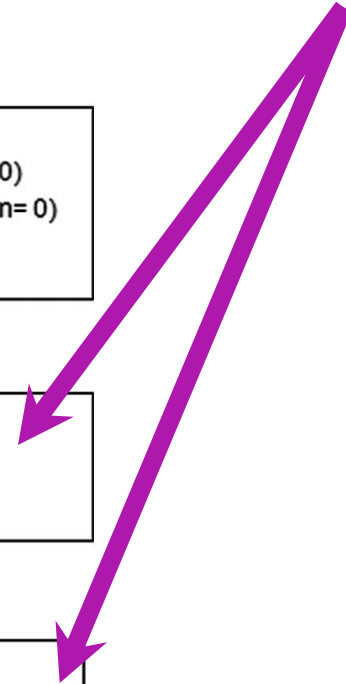
For the COPPS POAF substudy, POAF events limited to days 1 and 2 were excluded from the analysis because the effect of colchicine could not be evaluated (the drug was administered starting on day 3). The protocol excluded patients with chronic AF and those with persistent POAF on day 3 before starting colchicine.

COPPS-POAF CONSORT Flow Diagram



No patients lost to follow-up

All patients analysed for outcomes



Baseline features

Characteristic	Placebo (n=167)	Colchicine (n=169)	<i>P</i>
Age (mean±SD), y	66.6±11.0	64.8±13.7	0.21
Age >65 y (n=196), n (%)	102 (61.1)	94 (55.6)	0.32
Male sex (n=230), n (%)	112 (67.1)	118 (69.8)	0.64
Medical history, n (%)			
Previous history of AF (n=19)	11 (6.6)	8 (4.7)	0.49
Previous congestive HF (n=40)	22 (13.2)	18 (10.7)	0.50
Previous cardiac surgery (n=18)	10 (6.0)	8 (4.7)	0.64
Hypertension (n=231)	116 (69.5)	115 (68.1)	0.81
Diabetes mellitus (n=77)	43 (25.7)	34 (20.1)	0.24
COPD (n=26)	15 (9.0)	11 (6.5)	0.51
Cardiac surgery type, n (%)			
CABG (n=167)	76 (45.5)	91 (53.8)	0.16
Valvular surgery (n=92)	49 (29.3)	43 (25.4)	0.16
Aorta surgery (n=11)	7 (4.2)	4 (2.4)	0.16
Combined surgery (n=60)	32 (19.2)	28 (16.6)	0.16
Other (n=6)	3 (1.8)	3 (1.8)	0.16

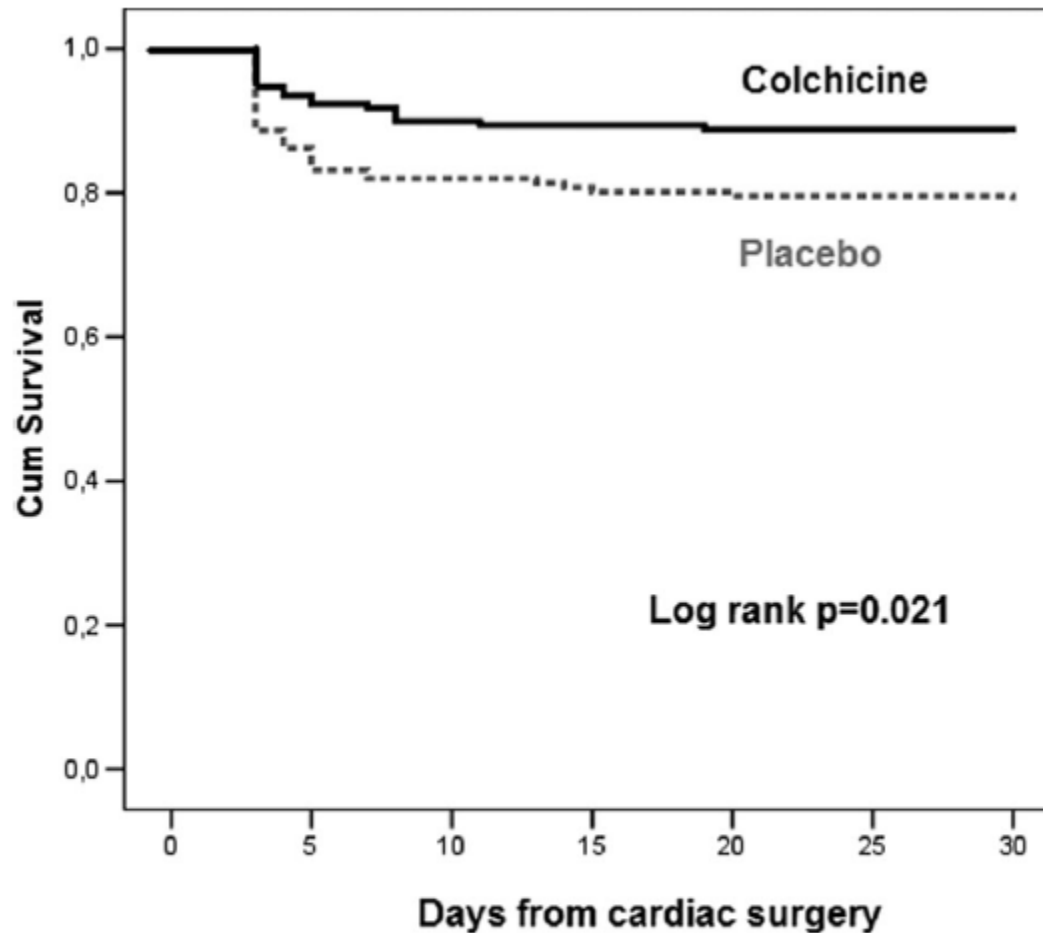
COPPS POAF study primary end point

Event	Placebo (n=167)	Colchicine (n=169)	<i>P</i>	RRR, % (95% CI)
Primary end point				
POAF on placebo/ colchicine, %*	22.0	12.0	0.021	45.5 (34.0–94.0)
Additional items				
Cardiac surgery stay, d	10.3±4.3	9.4±3.7	0.040	
Rehabilitation stay, d	13.9±6.5	12.1±6.1	0.009	
Overall hospital stay, d	24.2±8.9	21.4±7.9	0.030	
Death or stroke, n (%)	2 (1.2%)	2 (1.2%)	0.616	

RRR indicates relative risk reduction with colchicine; CI, confidence interval; and POAF, postoperative atrial fibrillation.

*Calculated by means of Cox regression analysis.

Kaplan-Meier POAF-free survival after postoperative day 3 according to treatment groups.



Patients at risk:

Colchicine:

169 164 159 154 149 144 139

Placebo:

167 162 157 152 147 142 137

Feature	POAF, n (%)		<i>P</i>
	No (n=281)	Yes (n=55)	
Mean age, y	66±11	67±13	0.677
Age >65 y (n=196)	161 (57.3)	35 (63.6)	0.455
Male sex (n=230)	196 (69.8)	34 (61.8)	0.313
Previous history of AF (n=19)	14 (5.0)	5 (9.1)	0.213
Previous congestive HF (n=40)	31 (11.0)	9 (16.4)	0.260
Previous cardiac surgery (n=18)	13 (4.6)	5 (9.1)	0.303
Hypertension (n=231)	193 (68.7)	38 (69.1)	1.000
Diabetes mellitus (n=77)	65 (23.1)	12 (21.8)	1.000
COPD (n=26)	23 (8.2)	3 (5.5)	0.781
LA anteroposterior diameter >45 mm (n=81)	43 (15.3)	18 (32.7)	0.004
Ejection fraction <40% (n=42)	32 (11.4)	10 (18.2)	0.185
Surgery other than CABG (n=169)	134 (47.7)	35 (63.6)	0.039
Postpericardiotomy syndrome (n=50)	38 (13.5)	12 (21.8)	0.145
Pericardial effusion (n=59)	44 (15.7)	15 (27.3)	0.051
Pleural effusion (n=60)	47 (16.7)	13 (23.6)	0.248
Perioperative β -blocker use (n=174)	156 (55.5)	18 (32.7)	0.003
Perioperative use of amiodarone* (n=49)	42 (14.9)	7 (12.7)	0.830
Perioperative ACEI/ARB use (n=126)	104 (37.0)	22 (40.0)	0.761
Colchicine (n=169)	149 (53.0)	20 (36.4)	0.027

Clinical Characteristics Comparison Between Patients With and Without Postoperative Atrial Fibrillation (POAF)

Hazard Ratios for POAF on Placebo/Colchicine Treatment in the Cox Proportional Hazards Model

Factor	Hazard Ratio	95% Confidence Interval	<i>P</i>
LA anteroposterior diameter >45 mm	2.31	1.15–4.63	0.019
Perioperative β -blocker use	0.47	0.25–0.88	0.019
Colchicine	0.52	0.28–0.96	0.036

The presented variables were determined with a stepwise selection procedure from variables included in Table 3. A value of $P < 0.05$ was considered the significance level for variable entry.

Side Effects and Drug Withdrawal

Event	Placebo (n=167), n (%)	Colchicine (n=169), n (%)	<i>P</i>
Side effects	8 (4.8)	16 (9.5)	0.137
Severe side effects	0 (0.0)	0 (0.0)	
Other side effects			
Gastrointestinal	7 (4.2)	16 (9.5)	0.082
Alopecia	0 (0.0)	0 (0.0)	
Anorexia	0 (0.0)	0 (0.0)	
Hepatotoxicity	0 (0.0)	0 (0.0)	
Myotoxicity	1 (0.6)	0 (0.0)	0.497
Bone marrow toxicity	0 (0.0)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	
Drug withdrawal			
Overall	11 (6.6)	20 (11.8)	0.131
Related to side effects	8 (4.8)	16 (9.5)	0.145
Patient or medical decision	3 (1.8)	4 (2.4)	0.998

Limitations

- **Colchicine is not registered for the prevention of pericarditis in North America or Europe and its use as such is off-label;**
- Our limited sample size might have precluded the identification of certain adverse effects;
- **Colchicine was given starting on the postoperative day 3. On this basis, the potential beneficial effect of the drug is limited from postoperative day 3, with the potential to miss early POAF cases in the first 2 days;**
- Only Caucasian adults (may not apply to paediatric populations and other ethnicities);
- **Patients with transaminases elevation, or severe liver disease, elevated creatinine, and patients with myopathy, blood dyscrasias or gastrointestinal disease were excluded;**
- Women who are pregnant, lactating, or women of childbearing potential without sufficient contraceptive protection were excluded.

Conclusions

Following cardiac surgery, colchicine, as empiric anti-inflammatory therapy, appears to be an in-expensive and safe means

- to reduce the incidence of POAF and hospitalization length;
- to reduce the incidence of the PPS and post-operative effusions.

COPPS Steering Committee, Recruiting centres and investigators

Steering Committee:

Chairman: Rita Trincherò, MD, Torino, Italy.

Co-chairman and Principal Investigator: Massimo Imazio, MD. Torino. Italy.

Nucleus Members of the Study Group on “Heart and Infectious diseases” of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO).

COPPS recruiting centres and investigators:

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Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Colchicine Reduces Postoperative Atrial Fibrillation Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy

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Published online today