DECLARATION OF CONFLICT OF INTEREST

Disclosure: None

- 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.

COlchicine for Recurrent Pericarditis (CORP): a multicenter, double-blind randomized controlled trial.

Presenter: Massimo Imazio, MD, FESC

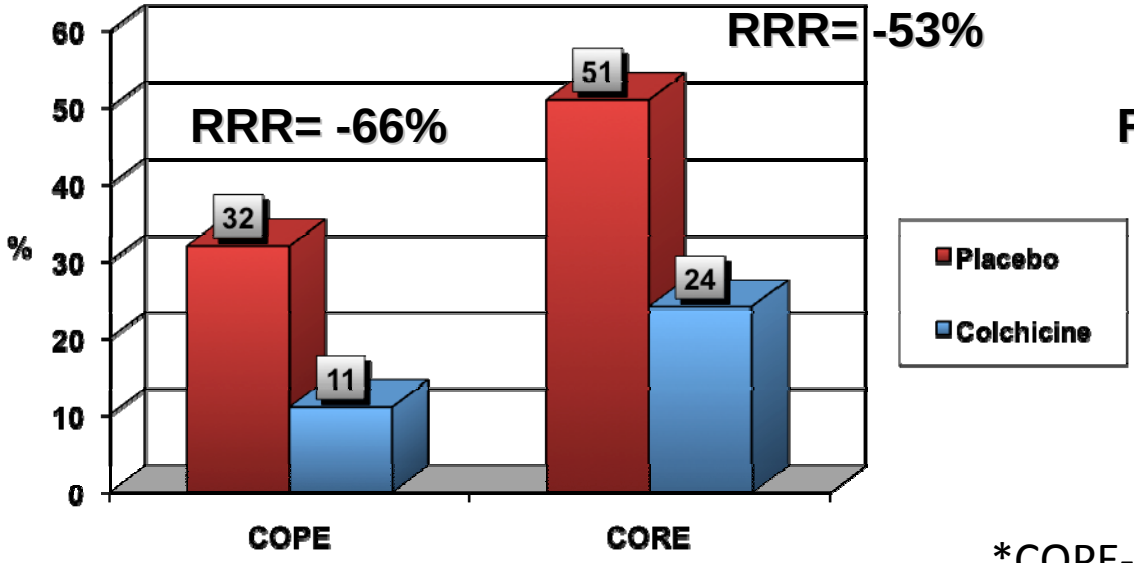
on behalf of the CORP Investigators

Cardiology Dpt. Maria Vittoria Hospital
ASLTO2, Torino, Italy

Background

I. Recurrences are reported in 30% of patients (range 10-50%) after pericarditis;

II. Colchicine is a promising drug for pericarditis treatment and prevention according to non-randomised studies, and COPE-CORE trials*.



RRR=Relative Risk Reduction

***= single-center, open-label RCTs**

*COPE- Circulation 2005;112:2012-6;
*CORE- Arch Int Med 2005;165:1987-91

Objective

- To evaluate the efficacy and safety of colchicine for the secondary prevention of pericarditis (recurrence prevention);
- Specific condition to test: first recurrence of pericarditis (reported recurrence rate: 50% according to CORE study).

Study design and setting

- Design: Prospective, randomized, double-blind, placebo-controlled, multicenter trial;
- Setting: 4 general hospital in North of Italy-urban areas (Torino, Bergamo, Bolzano, Savigliano-Cuneo);
- Patients: 120 patients with a first recurrence of pericarditis (*sample size to detect a difference 50 vs 25% in recurrence rate between placebo and colchicine with a power of 80% using a 2-sided p=0.05 level test*).

Inclusion criteria

1. Definite diagnosis of recurrent pericarditis (first recurrence);
2. Age ≥18 years;
3. Informed consent.

Criteria for recurrent pericarditis:

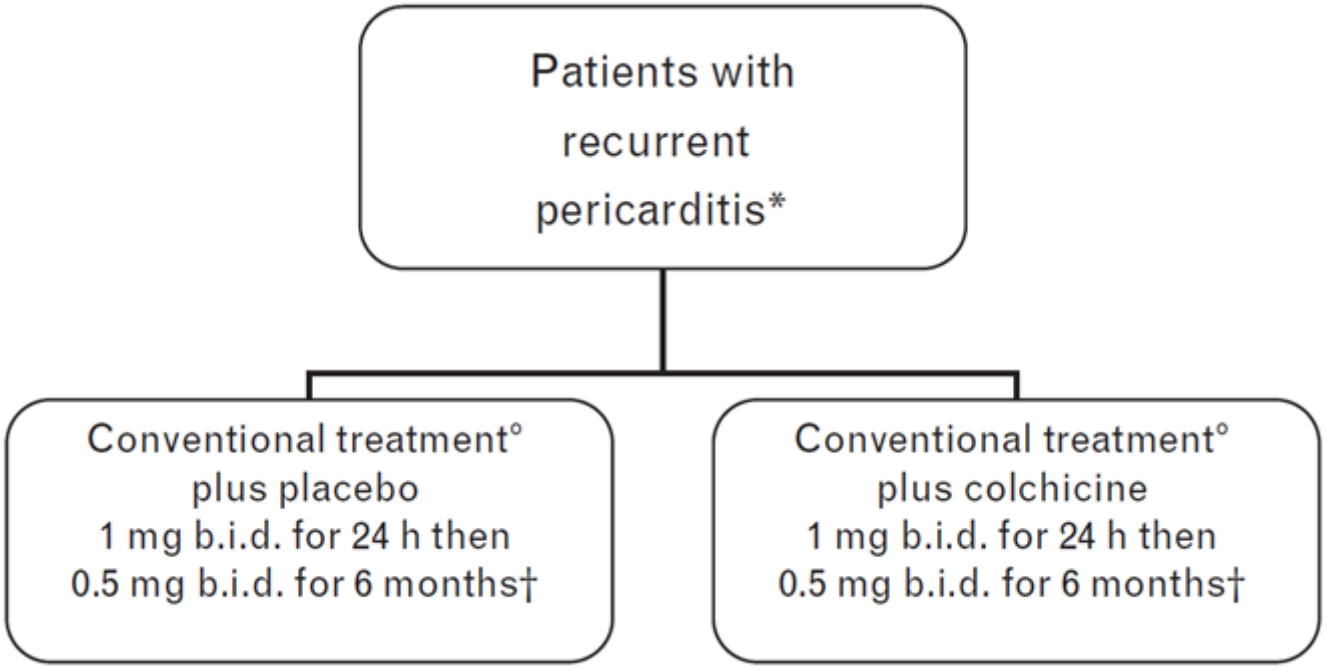
Recurrent pericarditis	Previous history of acute pericarditis (definite diagnosis) plus recurrent pain and at least one of the following criteria: 1. Fever 2. Pericardial friction rub 3. Electrocardiographic changes 4. New or worsening pericardial effusion 5. Elevations in the white blood cell count, erythrocyte sedimentation rate or C-reactive protein

J Cardiovasc Med 2007; 8: 830-4

Exclusion criteria

1. First attack of acute pericarditis or second or subsequent recurrence;
2. Tuberculous, neoplastic or purulent etiologies;
3. Known severe liver disease or current transaminases >1.5 times the upper normal limit;
4. Current serum creatinine above 221 µmol/L (2.5 mg/dl);
5. Known myopathy or current serum creatine kinase above the upper normal limit;
6. Known blood dyscrasias or gastrointestinal disease;
7. Pregnant and lactating women (in whom colchicine is considered contraindicated);
8. Women of childbearing potential not protected by a contraception method;
9. Known hypersensitivity to colchicine,
10. Current or previous treatment with colchicine for any indications.

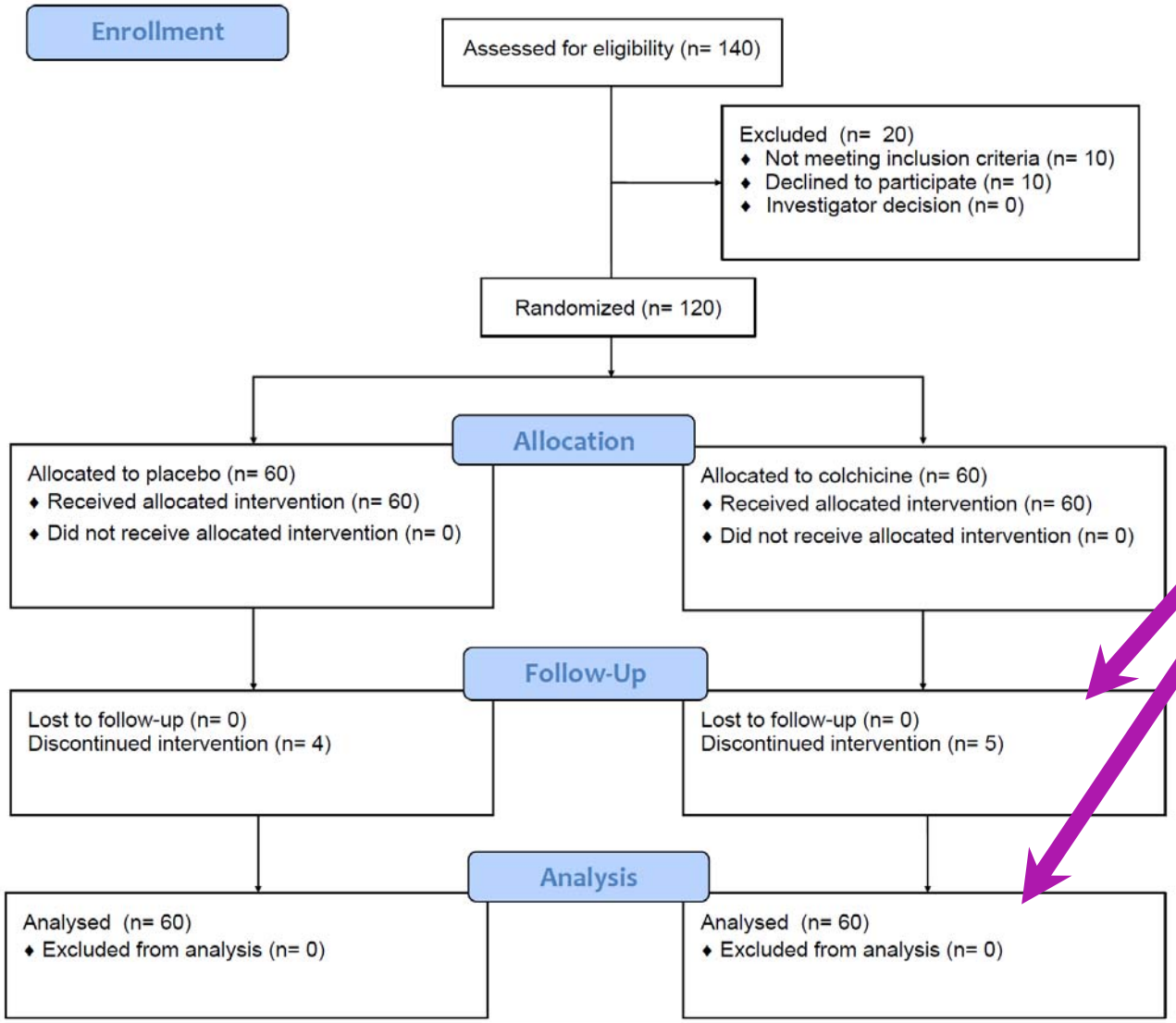
Intervention and End-points



Primary end-point: recurrence rate at 18 months
Secondary end-points: symptoms persistence at 72 h, remission rate at 1 month, number of recurrences, time to subsequent recurrence, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis

°aspirin, 800-1000mg (or ibuprofen, 600mg) orally every 8 hours for 7-10 days (1st choice); prednisone, 0.2-0.5 mg/kg/day for 4 weeks (2nd choice), for all gradual tapering;
†Colchicine/Placebo: 1.0 mg BID for 1 day then 0.5mg BID for 1 month (Pts >= 70Kg); 0.5 mg BID for 1 day then 0.5mg for 1 month (Pts<70Kg)

CONSORT Flow Diagram of the CORP trial



No patients lost to follow-up

All patients analysed for outcomes

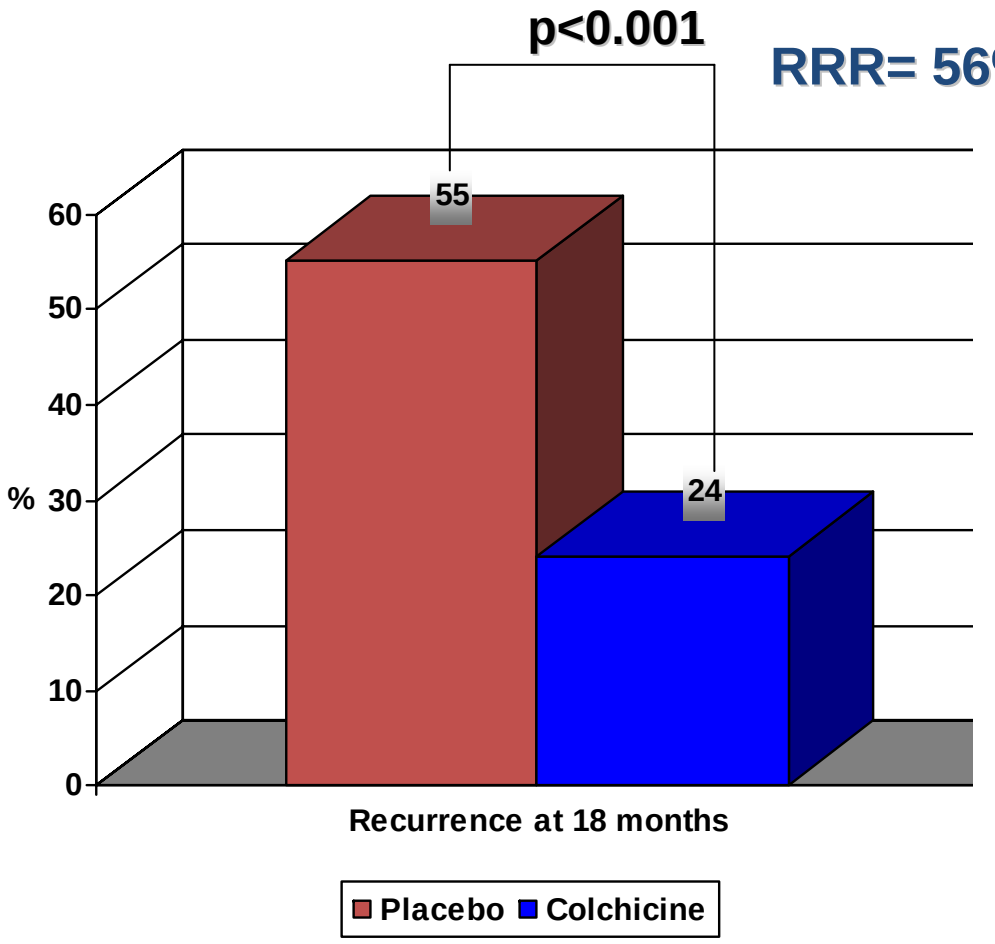
Baseline features

Characteristic	Placebo Group (n = 60)	Colchicine Group (n = 60)
Mean age (SD), *y*	47.3 (14.4)	47.9 (15.4)
Men, *n (%)*	29 (48)	34 (43)
Current smokers, *n (%)*	25 (42)	26 (56)
Hypertension, *n (%)*	15 (25)	12 (20)
Diabetes mellitus, *n (%)*	1 (2)	2 (3)
Chronic obstructive pulmonary disease, *n (%)*	2 (3)	2 (3)
Creatinine clearance <60 mL/min per 1.73 m^2, *n (%)**	2 (3)	4 (7)
Hypothyroidism, *n (%)*	1 (2)	2 (3)
Previous idiopathic cause, *n (%)*	48 (80)	50 (83)
Previous autoimmune cause, *n (%)*†	12 (20)	10 (17)
Previous use of corticosteroids, *n (%)*	6 (10)	5 (8)
Previous cardiac surgery, *n (%)*	4 (7)	3 (5)
Previous myocardial infarction, *n (%)*	6 (10)	7 (12)
Mean time from first attack (SD), *mo*	6.1 (4.9)	6.8 (4.0)

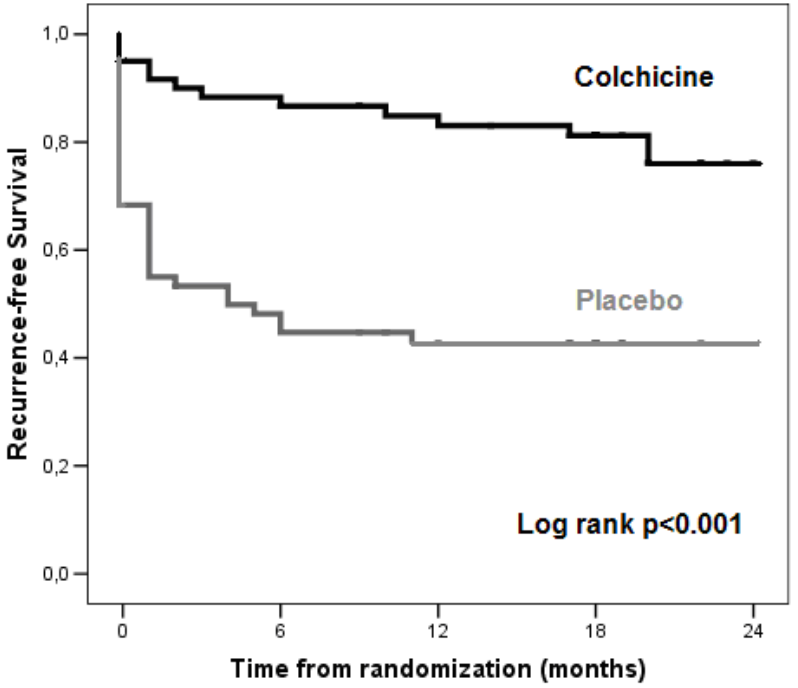
Concomitant therapies for recurrent pericarditis (adjunct to placebo/colchine)

Characteristic	Placebo Group (n = 60)	Colchicine Group (n = 60)
Fever, *n (%)*	19 (32)	18 (30)
Pericarditic chest pain, *n (%)*	60 (100)	60 (100)
Pericardial rub, *n (%)*	13 (22)	12 (20)
Pericardial effusion, *n (%)*	35 (58)	36 (60)
Mean ejection fraction (SD), %	58 (4.2)	58 (6.2)
Elevated C-reactive protein level, *n (%)*‡	54 (90)	57 (95)
Concomitant anti-inflammatory therapy, *n (%)*		
Aspirin or ibuprofen	55 (92)	56 (93)
Prednisone	5 (8)	4 (7)

Primary end point:
Recurrence rate at 18 months

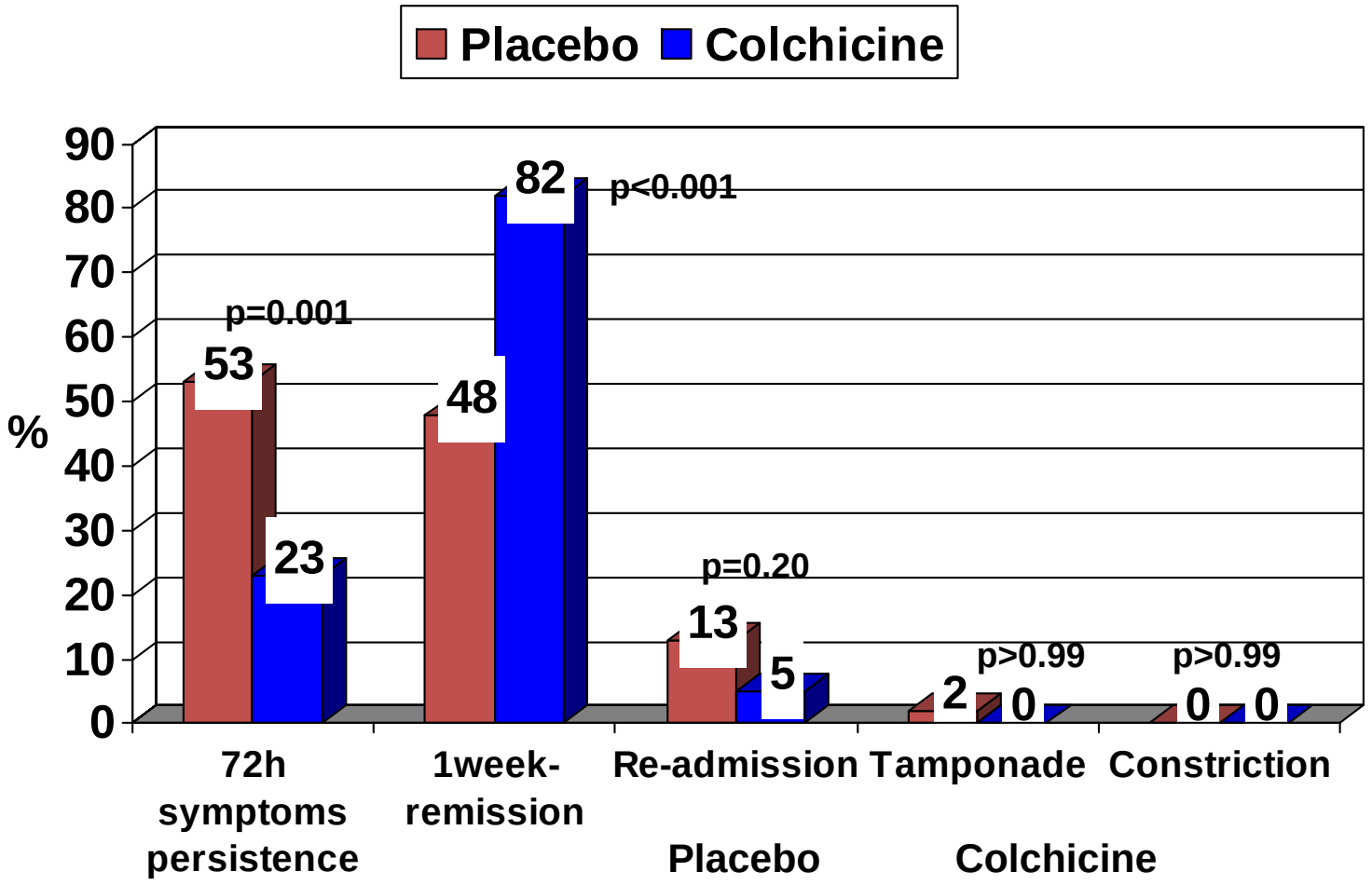


RRR= 56% 95% CI 27-73; NNT=3



Patients at risk:				
Colchicine:				
60	53	47	43	10
Placebo:				
60	28	22	19	10

Secondary end points



	Placebo	Colchicine	p
Number of recurrences†	1.0 (0.0-3.0)	0.1 (0.0-1.0)	<0.001
Time to first recurrence in months†	1.0 (0.0-5.5)	2.5 (0.0-19.1)	<0.001
Mean Follow-up in months (SD)	23.7 (12.6)	21.9 (9.4)	0.38

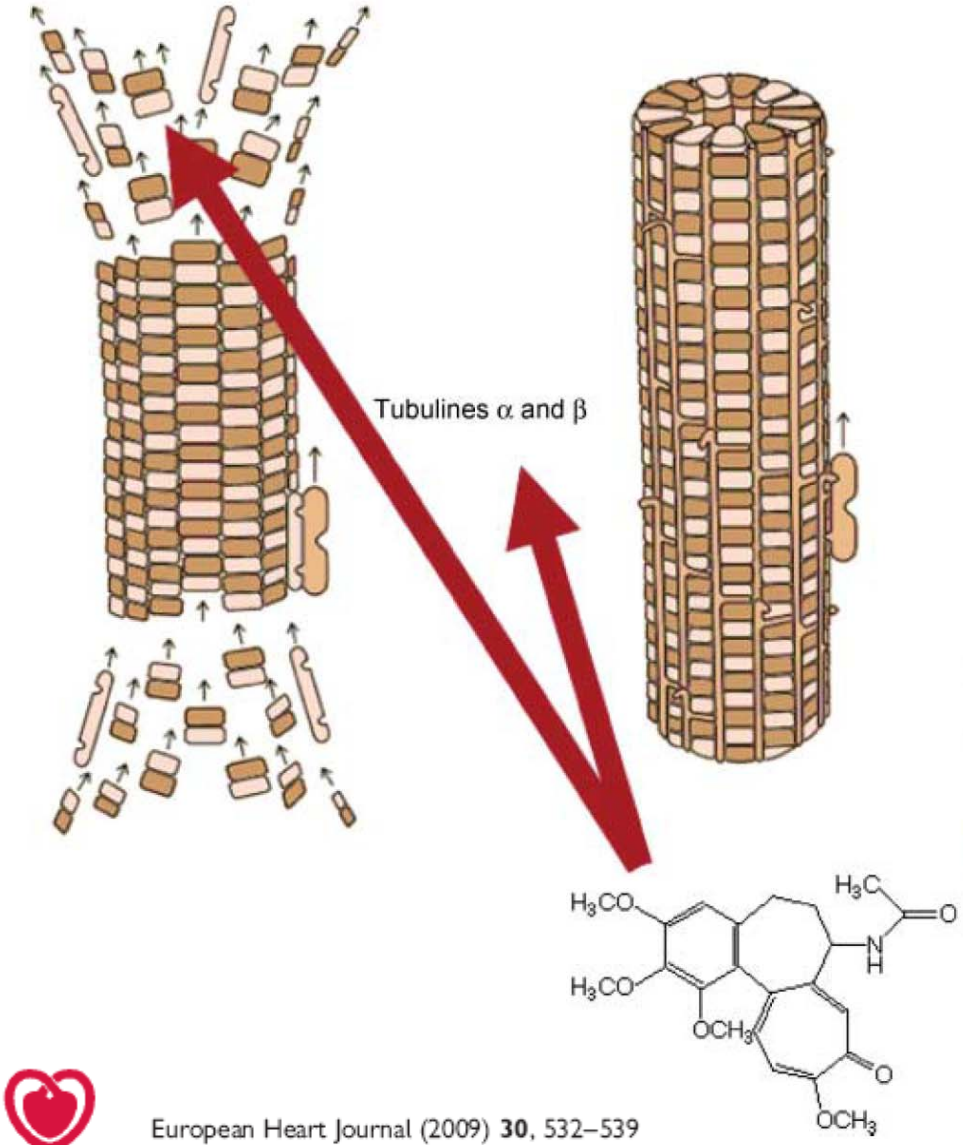
†= median (10th to 90th percentile)

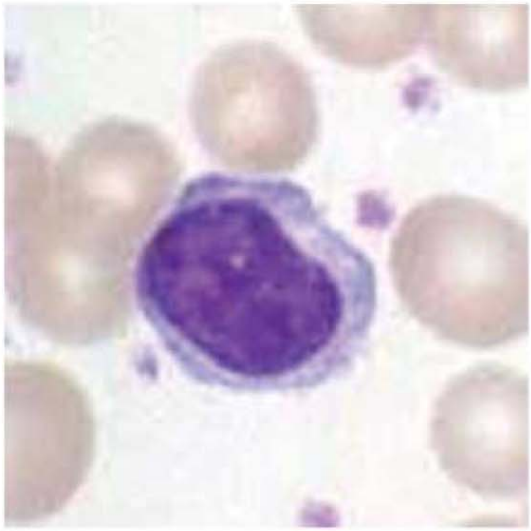
Safety and Drug Withdrawal

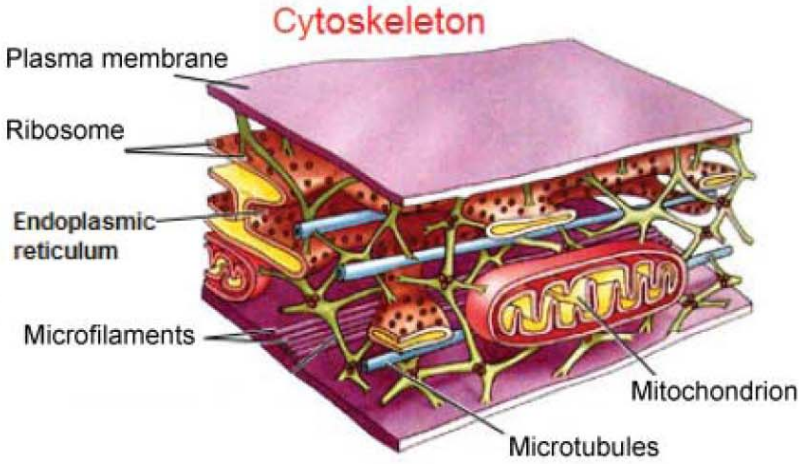
Adverse Effect	Placebo Group (n = 60), n (%)	Colchicine Group (n = 60), n (%)
Overall	4 (7)	4 (7)
Gastrointestinal intolerance*	3 (5)	4 (7)
Hepatoxicity†	1 (2)	0 (0)
Myotoxicity	0 (0)	0 (0)
Alopecia	0 (0)	0 (0)
Other	0 (0)	0 (0)
Severe side effects	0 (0)	0 (0)
Drug withdrawal	4 (7)	5 (8)
Physician decision	4 (7)	4 (7)
Patient decision	0 (0)	1 (2)

* Diarrhea, nausea, cramping, abdominal pain, or vomiting.
† Any elevation of transaminase levels above the normal reference interval.

Colchicine: How does it work?







European Heart Journal (2009) **30**, 532–539
doi:10.1093/eurheartj/ehn608

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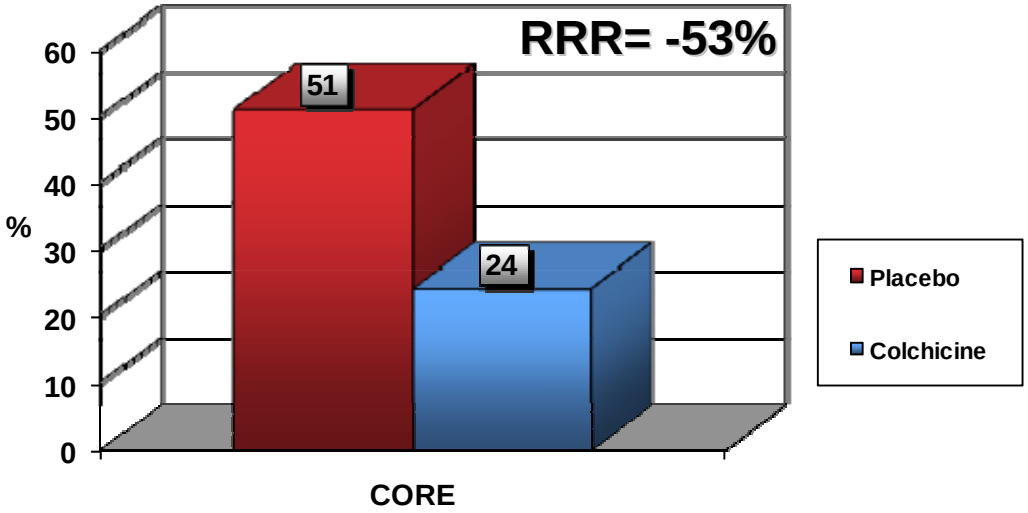
Comparison of study results with other published work

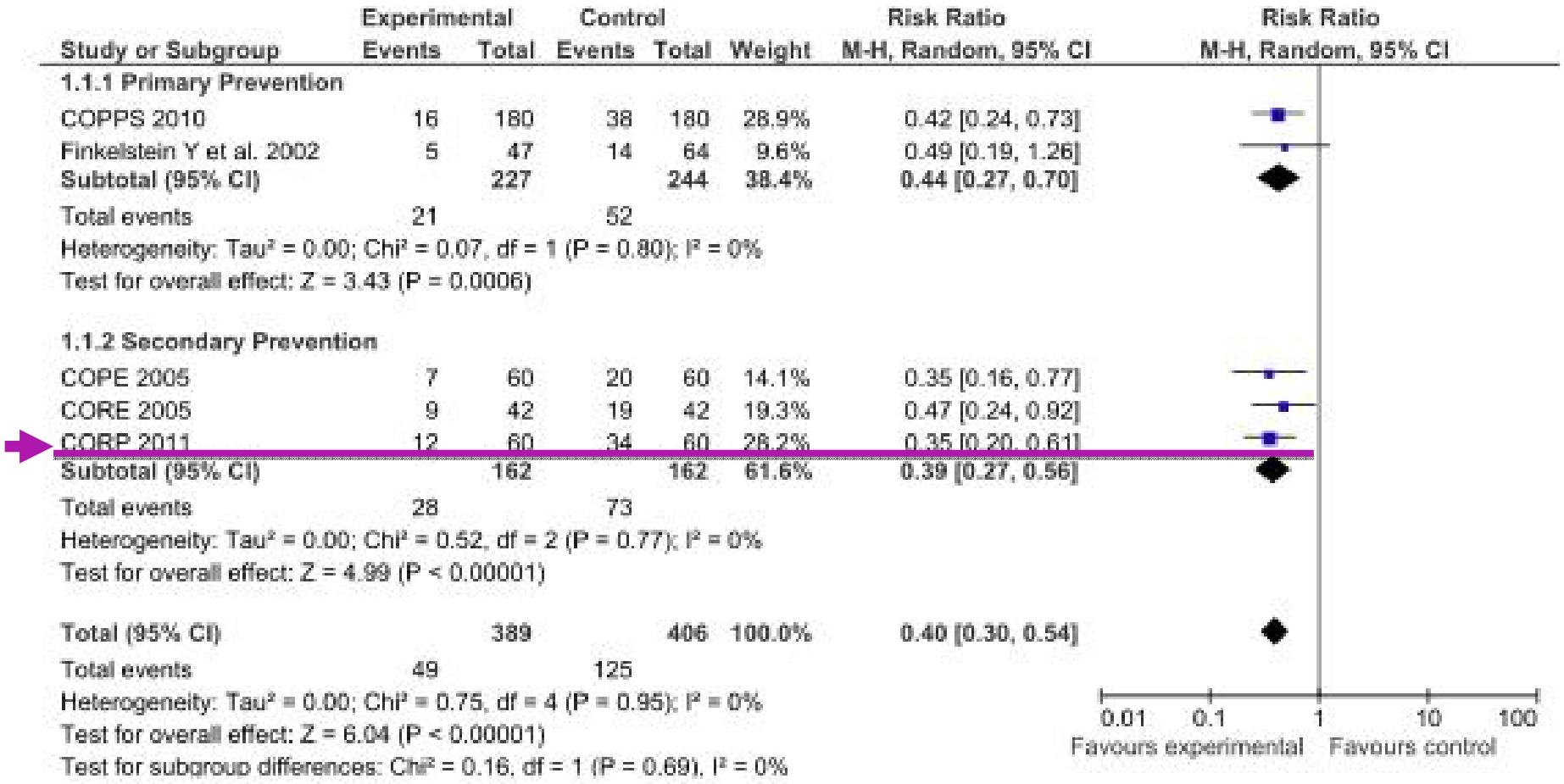
Study, Year (Reference)	Study Design	Patients, *n**	Maintenance Dosage, *mg/d*	Adjunct to Standard Therapy
Guindo et al, 1990 (5)	Nonrandomized, case series	9	1.0	Yes
Adler et al, 1994 (6)	Nonrandomized, case series	8	1.0	Yes
Millaire et al, 1994 (7)	Nonrandomized, case series	19	1.0	No
Adler et al, 1998 (2)	Nonrandomized, case series	51	1.0	Yes
Imazio et al, 2005 (13)	Nonrandomized, case series	35	1.0	Yes
Imazio et al, 2005 (4)	Randomized, open-label, single-center	84†	0.5–1.0	Yes



Follow-up, *mo*	Recurrence Rate, *n/N (%)*
10–54	0/9 (0)
18–34	0/8 (0)
32–44	4/19 (21)
6–128	7/51 (14)
48–108	3/35 (9)
8–44	9/42 (21) vs. 19/42 (45)‡

NR= not randomised, ROL= randomised, open label; RRR-relative risk reduction

Meta-analysis of published trials



Imazio M et al. submitted

Limitations

Our findings might not be generalizable to other settings or other patient populations

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
Only first recurrence of pericarditis (not multiple)
Only adults (may not apply to paediatric populations)
Bacterial and neoplastic etiologies were excluded
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 an initial episode of recurrent pericarditis, colchicine, as adjunct to empiric anti-inflammatory therapy, appears to be an in-expensive and safe means

- to hasten symptoms resolution,
- improve remission rates by 1 week,
- reduce further recurrences during follow-up.

Acknowledgedments

The most important acknowledgement is to the participants in the study and to the physicians, nurses, ethical committees, and administrative staff in hospitals who assisted with its conduct.

- **Steering Committee:**
  - Chairman: Rita Trinchero, 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).
- **Safety and Clinical events Committee:**
  - Yehuda Adler, MD (Coordinator), Tel Hashomer, Israel, Ralph Shabetai, MD, San Diego, USA, David H Spodick, MD, Worcester, USA.
- **CORP recruiting centres and investigators:**

  Cardiology Dpt, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M. Imazio, D. Forno, S. Ferro, R. Belli), Ospedali Riuniti, Bergamo, Italy (investigators: A. Brucato, S. Maestroni, D. Cumetti), Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin), Ospedale SS Annunziata, Savigliano, Italy (S. Ferrua, A. Bassignana, B. Doronzo).

Annals of Internal Medicine | ORIGINAL RESEARCH

Colchicine for Recurrent Pericarditis (CORP)

A Randomized Trial

Massimo Imazio, MD; Antonio Brucato, MD; Roberto Cemin, MD; Stefania Ferrua, MD; Riccardo Belli, MD; Silvia Maestroni, MD; Rita Trinchero, MD; David H. Spodick, MD; and Yehuda Adler, MD on behalf of the CORP (COlchicine for Recurrent Pericarditis) Investigators*

Background: Recurrence is the most common complication of pericarditis, affecting 10% to 50% of patients.

Objective: To evaluate the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis.

Design: Prospective, randomized, double-blind, placebo-controlled multicenter trial. (ClinicalTrials.gov registration number: NCT00128414)

Setting: 4 general hospitals in urban areas of Italy.

Patients: 120 patients with a first recurrence of pericarditis.

Intervention: In addition to conventional treatment, patients were randomly assigned to receive either placebo or colchicine, 1.0 to 2.0 mg on the first day, followed by a maintenance dose of 0.5 to 1.0 mg/d, for 6 months.

Measurements: The primary study end point was the recurrence rate at 18 months. Secondary end points were symptom persistence at 72 hours, remission rate at 1 week, number of recurrences, time to first recurrence, disease-related hospitalization, cardiac tamponade, and rate of constrictive pericarditis.

Results: At 18 months, the recurrence rate was 24% in the colchicine group and 55% in the placebo group (absolute risk reduction, 0.31 [95% CI, 0.13 to 0.46]; relative risk reduction, 0.56 [CI, 0.27 to 0.73]; number needed to treat, 3 [CI, 2 to 7]). Colchicine reduced the persistence of symptoms at 72 hours (absolute risk reduction, 0.30 [CI, 0.13 to 0.45]; relative risk reduction, 0.56 [CI, 0.27 to 0.74]) and mean number of recurrences, increased the remission rate at 1 week, and prolonged the time to subsequent recurrence. The study groups had similar rates of side effects and drug withdrawal.

Limitation: Exclusion of multiple recurrences and neoplastic or bacterial causes.

Conclusion: Colchicine is safe and effective for the secondary prevention of recurrent pericarditis.

Primary Funding Source: Maria Vittoria Hospital, Torino, Italy.

Ann Intern Med. 2011;155:* * * FILL THIS IN * * *. www.annals.org

For author affiliations, see end of text.

* For a list of the CORP investigators, see the Appendix (available at www.annals.org).

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