Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial

Massimo Imazio, MD, FESC on behalf of the CORP-2 Investigators

Cardiology Dpt. Maria Vittoria Hospital, ASLTO2, Torino, Italy

A.S.L. TO2
Azienda Sanitaria Locale
Torino Nord

Conflicts of interest: None

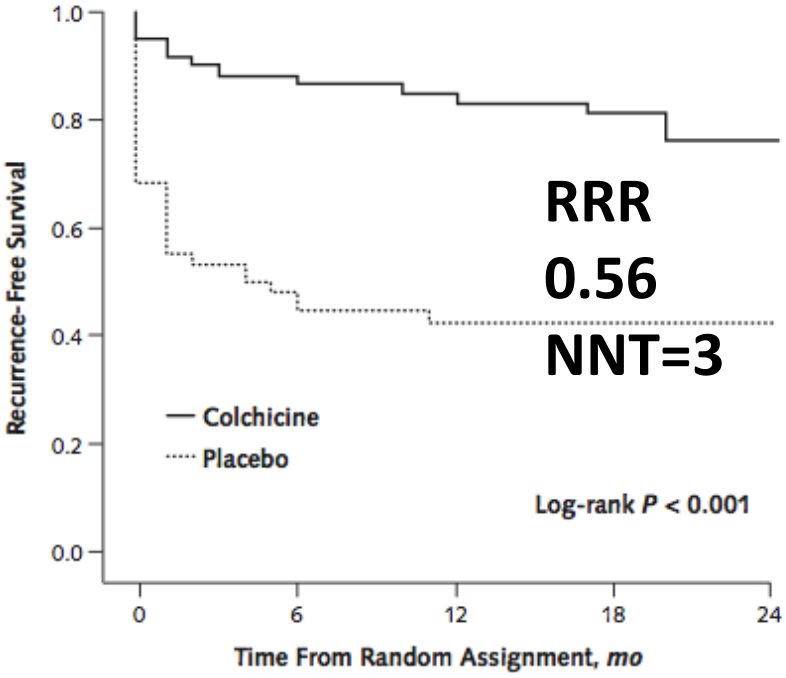
Funding: The CORP-2 trial was supported by the former Azienda Sanitaria 3 of Torino (now ASLTO2) within the Italian National Health Service. Acarpia (Madeira, Portugal) provided the study drug and placebo as an unrestricted grant.

Off-label use: colchicine for pericarditis but also all other therapies (i.e. NSAID) are off-label.

This trial is registered with ClinicalTrials.gov, number NCT00235079.

Background

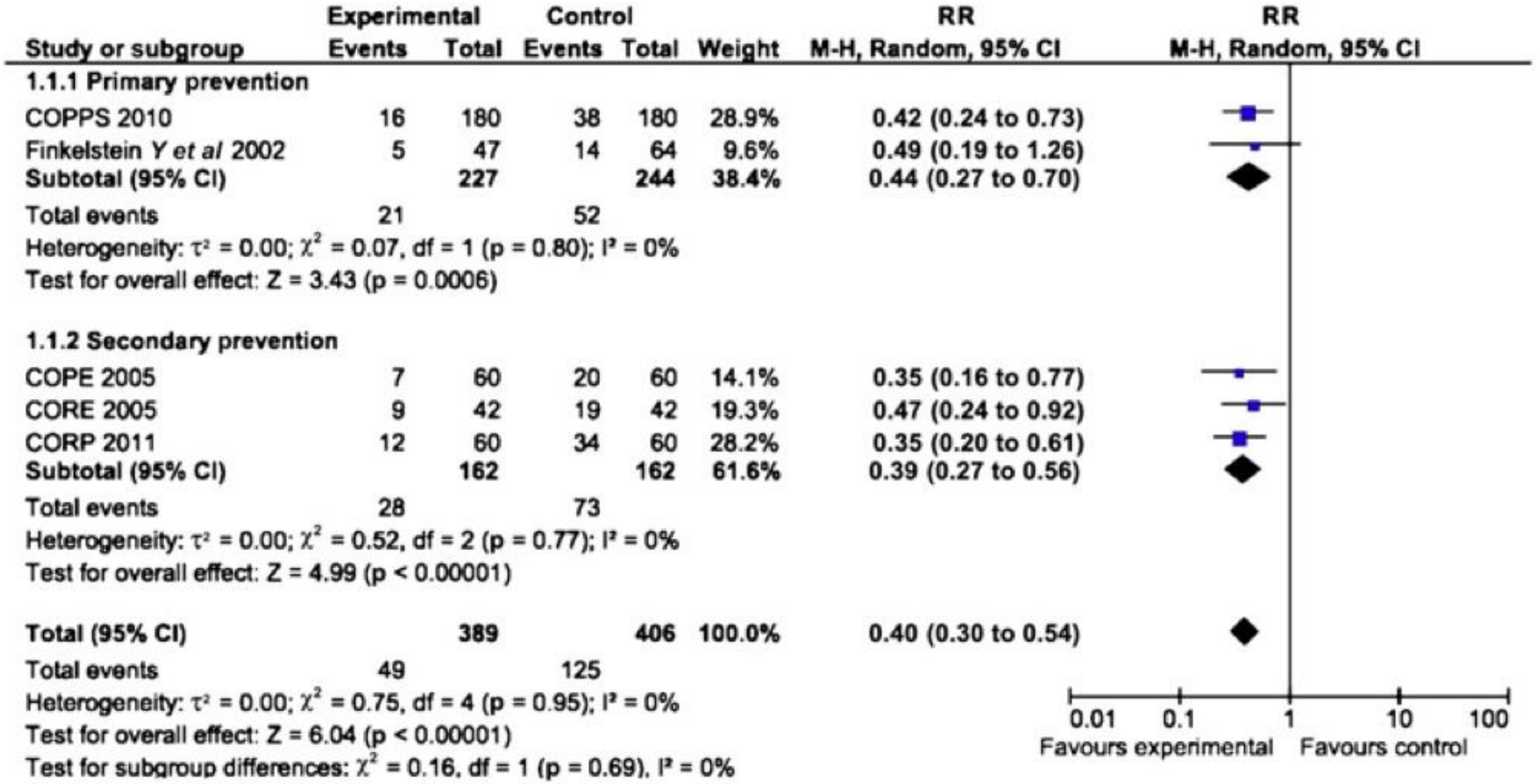
Clinical trials have shown that low-dose colchicine (0·5–1·0 mg daily) is efficacious and safe for treatment and prevention of acute pericarditis and first recurrences.



Patients at risk, *n*					
Colchicine	60	53	47	43	10
Placebo	60	28	22	19	10

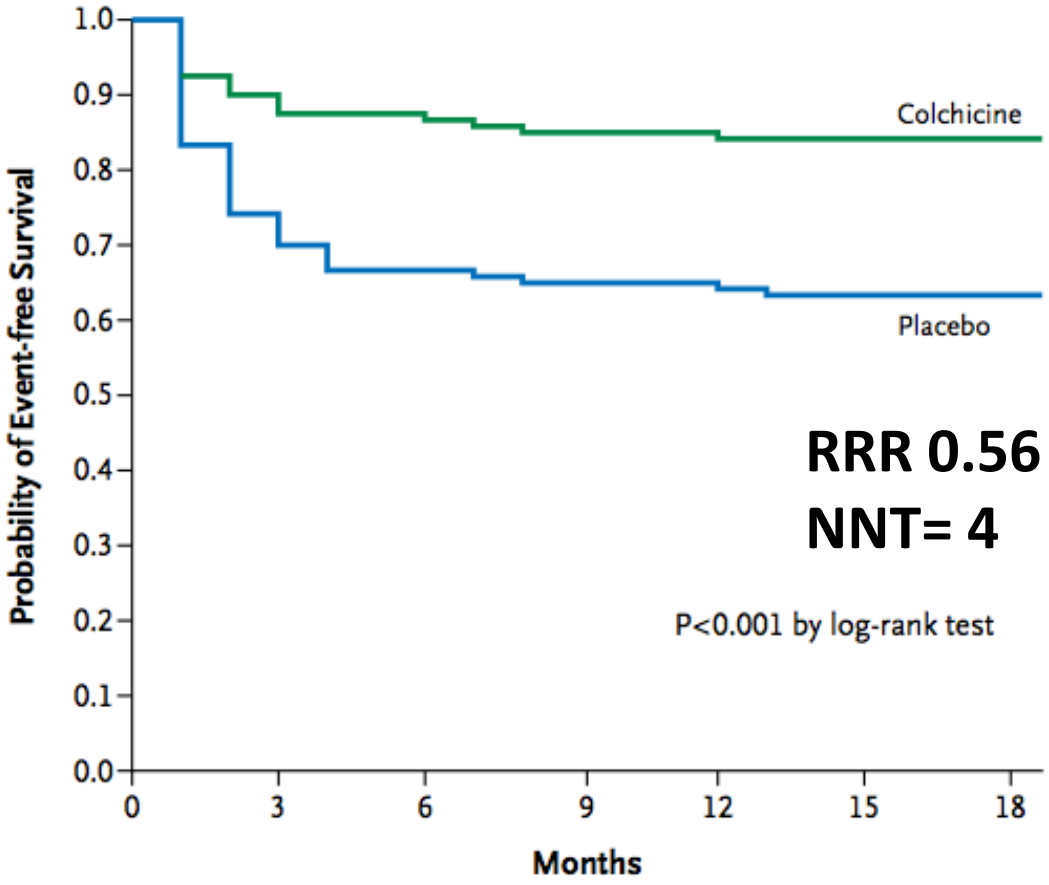
CORP trial

Ann Intern Med 2011; **155:** 409–14



Heart 2012;98:1078-1082

ICAP trial (Acute Pericarditis)



No. at Risk							
Colchicine	120	105	105	102	102	98	89
Placebo	120	87	80	78	78	75	69

N Engl J Med 2013; ***369:*** *1522–28*

CORP-2: Aim

To assess the efficacy and safety of colchicine to treat patients with multiple recurrences of pericarditis (≥2).

COlchicine for **R**ecurrent **P**ericarditis-**2**

J Cardiovasc Med (Hagerstown) 2007; **8:** 830–34

Diagnostic criteria

Disease	Criteria
Acute pericarditis	At least 2 out of 4: 1. Typical chest pain 2. Pericardial friction rub 3. Widespread ST segment elevation or PR depressions 4. New or worsening pericardial effusion
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

Methods

Feature	CORP-2 trial
Study design	Randomized, double-blind, placebo controlled
Eligibility	Second or subsequent recurrence
Primary outcome	Recurrence rate at 18 months
Secondary outcomes	Symptom persistence at 72 h, remission rate at 1 week, number of recurrences, time to recurrence, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis
Study treatment	Colchicine/placebo
Treatment length	6 months
Expected total enrollment	240

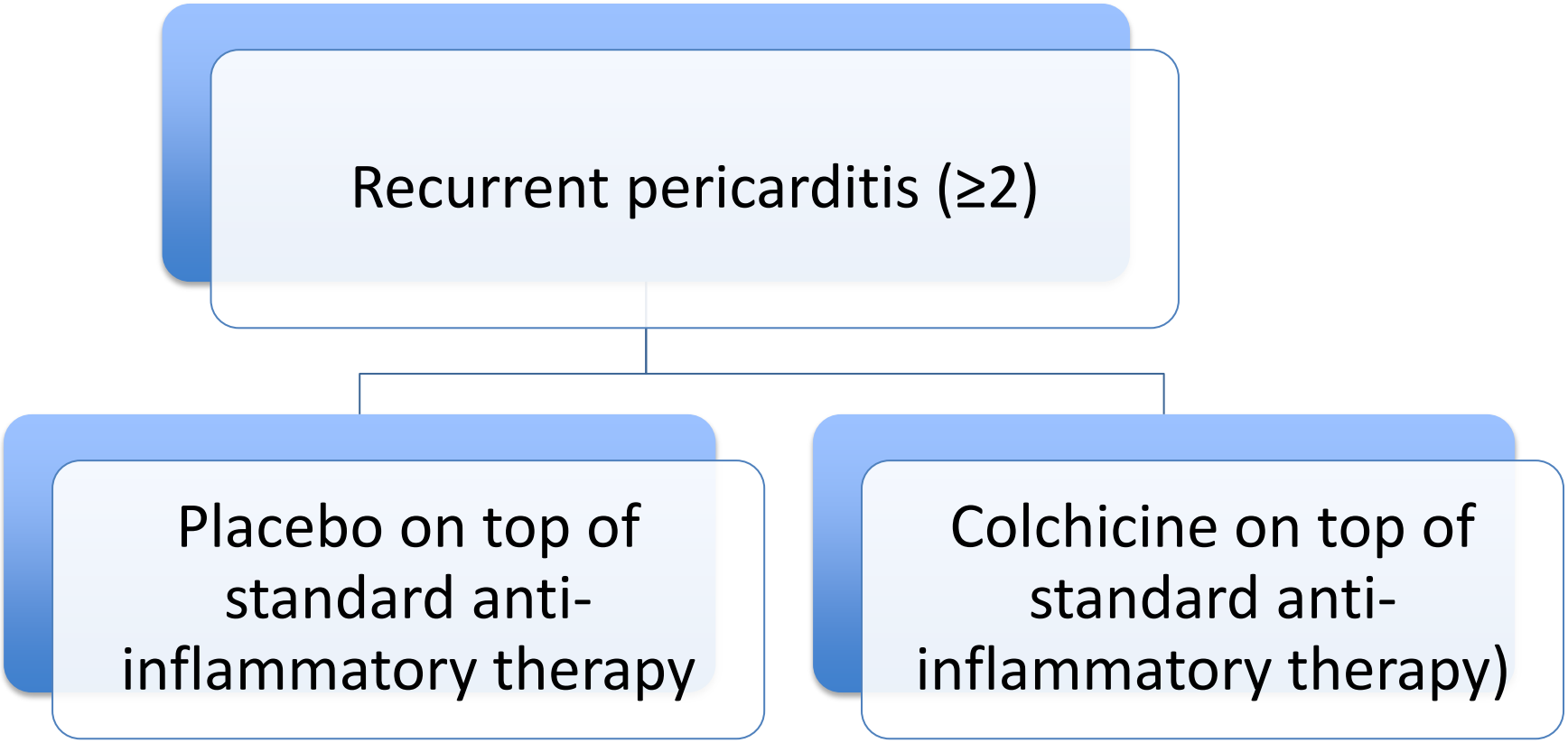
We assumed that 30% of patients would have recurrent pericarditis in the placebo group at 18 months and estimated that colchicine could reduce the proportion of patients with recurrent pericarditis by half. With a two-sided % level of 0·05, a total enrolment of 240 patients was needed to attain power of 0·80 to detect a 15% absolute reduction in the proportion of participants who had recurrent pericarditis in the colchicine group.

Inclusion criteria

- Consecutive patients aged 18 years or older with two or more recurrences of pericarditis (idiopathic, viral, post-cardiac injury, or caused by connective tissue disease).

Exclusion criteria

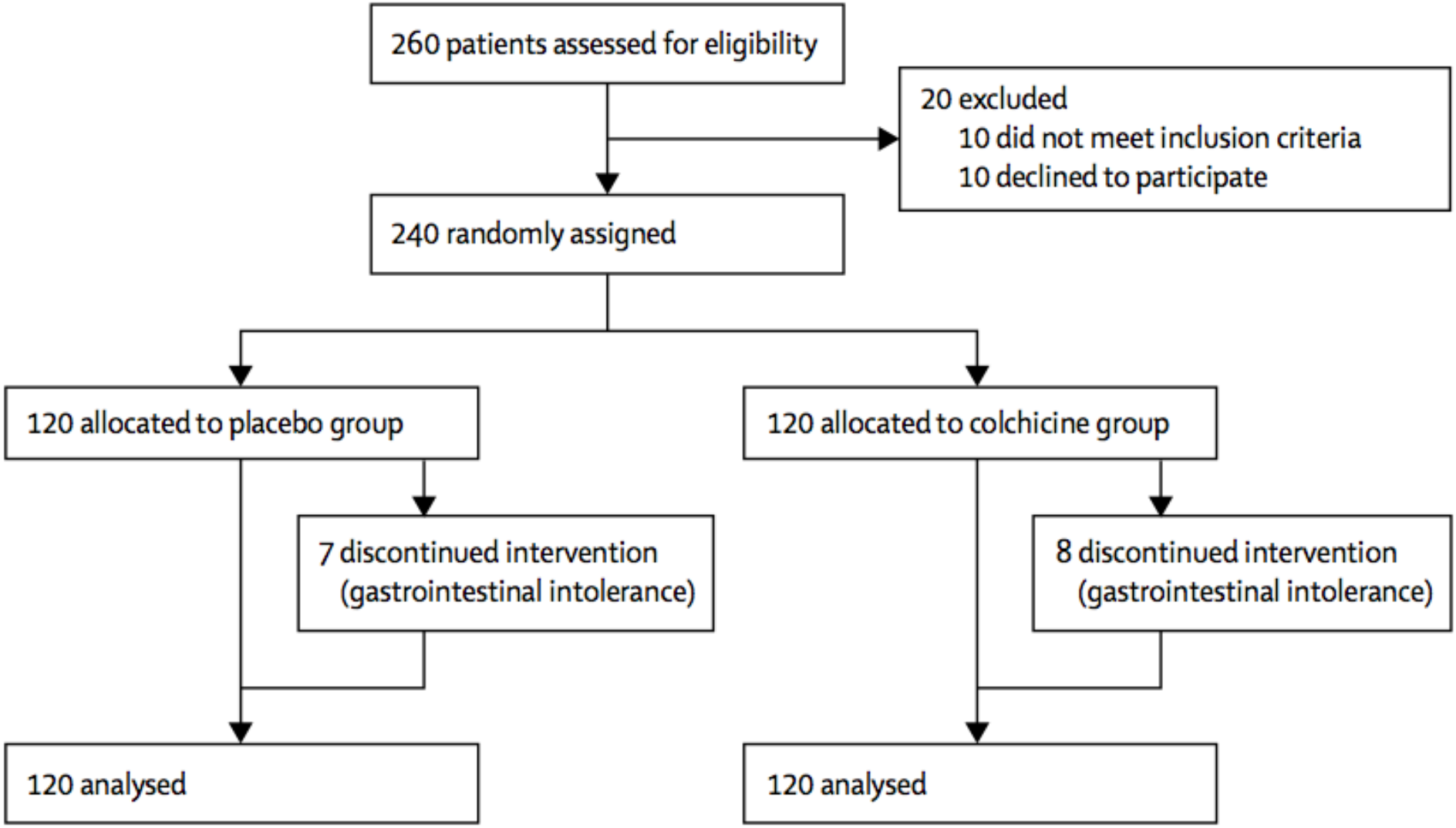
- Tuberculous, neoplastic, or purulent pericarditis etiology;
- Severe liver disease or current aminotransferase concentrations more than 1·5 times the upper limit of the normal;
- Serum creatinine concentration more than 221·00 μmol/L;
- Skeletal myopathy or serum creatine kinase concentration more than the upper limit of the normal;
- Blood dyscrasia;
- Inflammatory bowel disease;
- Hypersensitivity to colchicine or other contraindication to colchicine;
- Current treatment with colchicine;
- Life expectancy of 18 months or less;
- Pregnant or lactating women or women of childbearing potential not using contraception;
- Evidence of myopericarditis as indicated by any increase of serum troponin concentration.



(0·5 mg twice daily for 6 months for patients >70 kg or 0·5 mg once daily for patients ≤ 70 kg) in addition to conventional anti-inflammatory treatment with aspirin, ibuprofen, or indometacin.

Results

Trial profile



Lancet 2014; published today

	Placebo group (n=120)	Colchicine group (n=120)
Age (years)	48·9 (15·5)	48·6 (13·6)
Men	54 (45·0%)	66 (55·0%)
Previous cardiac surgery	5 (4·2%)	5 (4·2%)
Previous myocardial infarction	6 (5·0%)	11 (9·1%)
Time from first episode of pericarditis (months)*	17·1 (3–180)	14·2 (3–156)
Cause		
Idiopathic	102 (85·0%)	96 (80·0%)
Post-cardiac injury syndrome	8 (6·7%)	13 (10·8%)
Connective tissue diseases	8 (6·7%)	8 (6·7%)
Clinical findings		
Fever	43 (35·8%)	30 (25·0%)
Pericarditic chest pain	119 (99·2%)	120 (100·0%)
Pericardial rub	38 (31·7%)	44 (36·7%)
Pericardial effusion	68 (56·7%)	70 (58·3%)
High hs-CRP at presentation (>3 mg/L)	89 (74·2%)	85 (70·8%)
Ejection fraction (%)	58% (4·4)	58% (4·8)
Drug treatments		
Previous use of corticosteroids	24 (20·0%)	16 (13·3%)
Previous use of colchicine	79 (65·8%)	78 (65·0%)
Aspirin	96 (80·0%)	86 (71·7%)
Ibuprofen	18 (15·0%)	24 (20·0%)
Indometacin	10 (8·3%)	12 (10·0%)
Prednisone	6 (5·0%)	10 (7·5%)

Data are or mean (SD) or n (%) unless stated otherwise. hs-CRP=high-sensitivity C-reactive protein. *Mean (range).

Baseline data

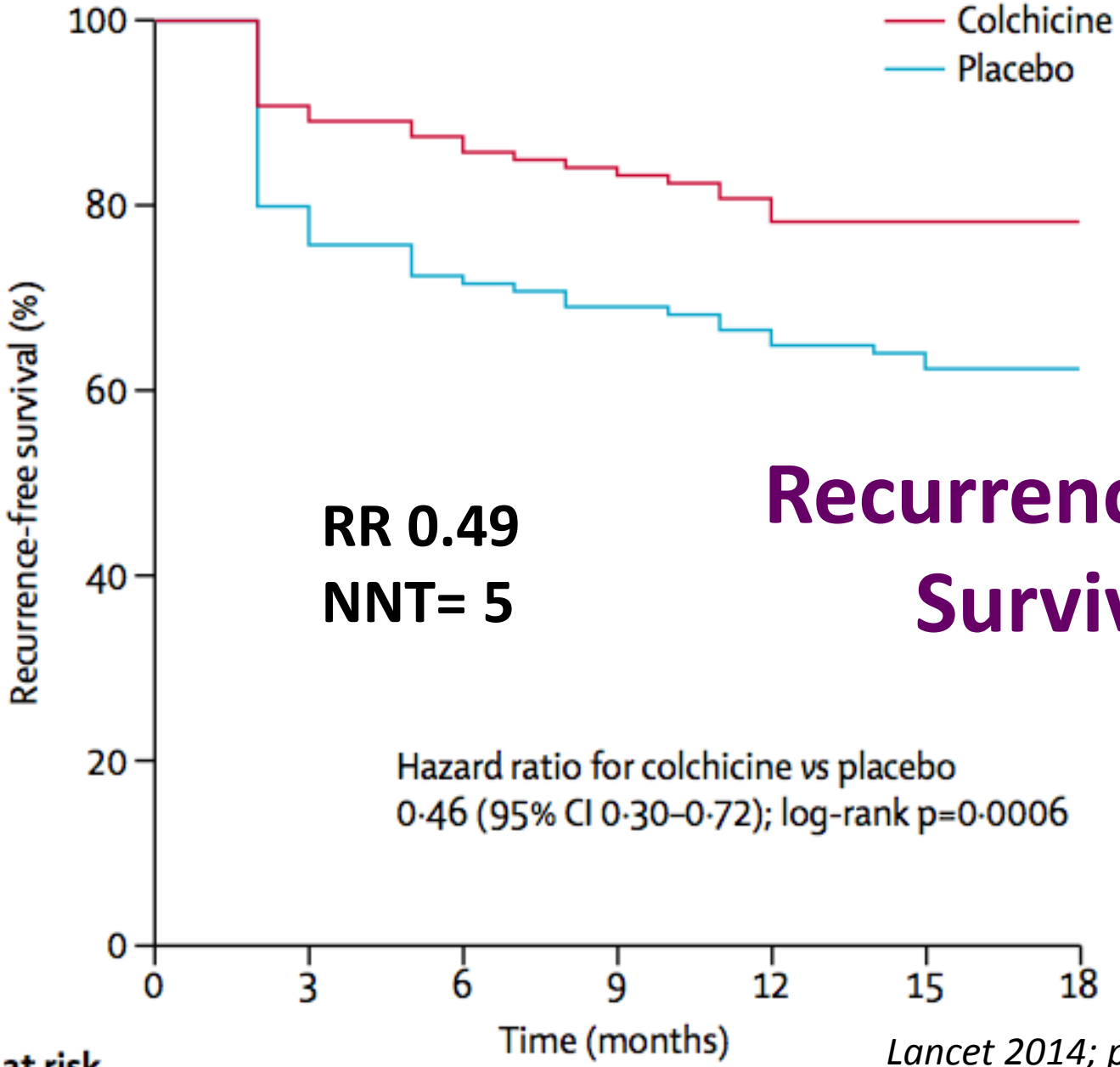
Lancet 2014; published today

Outcomes

	Placebo group (n=120)	Colchicine group (n=120)	p value
Recurrent pericarditis	51 (42·5%)	26 (21·6%)	0·0009*
Symptom persistence at 72 h	53 (44·2%)	23 (19·2%)	0·0001
Remission at 1 week	71 (59·2%)	100 (83·3%)	0·0001
Incessant course	32 (26·7%)	10 (8·3%)	0·0004
Number of recurrences per patient	0·63 (0·87)	0·28 (0·58)	0·0004
Time to subsequent recurrence (months)	5·3 (4·2)	8·1 (11·1)	0·220
Cardiac tamponade	2 (1·7%)	0 (0·0%)	0·478
Constrictive pericarditis	4 (3·3%)	0 (0·0%)	0·097
Pericarditis-related admission to hospital	12 (10·0%)	2 (1·7%)	0·013
Follow-up (months)	20·0 (4·4)	19·3 (3·1)	0·149

Data are n (%) or mean (SD). Similar proportions of recurrent pericarditis were recorded irrespective of the background anti-inflammatory treatment (49 of 182 [26·9%] patients taking aspirin, 12 of 42 [28·6%] patients taking ibuprofen, six of 22 [27·3%] patients taking indomethacin). *From log-rank test.

Lancet 2014; published today



RR 0.49
NNT= 5

Recurrence-free Survival

Lancet 2014; published today

Safety: side effects

	Placebo group (n=120)	Colchicine group (n=120)	p value
Overall	10 (8·3%)	14 (11·7%)	0·519
Gastrointestinal intolerance*	9 (7·5%)	9 (7·5%)	..
Hepatotoxicity†	1 (0·8%)	3 (2·5%)	..
Myotoxicity‡	0 (0·0%)	1 (0·8%)	..
Alopecia	0 (0·0%)	1 (0·8%)	..
Other	0 (0·0%)	0 (0·0%)	..
Serious adverse events§	0 (0·0%)	0 (0·0%)	..
Drug discontinuation	7 (5·8%)	8 (6·7%)	..

*Diarrhoea, nausea, cramping, abdominal pain, or vomiting. †Any increase of aminotransferase concentration above normal reference range. ‡Any increase of creatine kinase concentration above normal reference range. §Fatal or life-threatening, requiring admission to hospital, or significantly or permanently disabling or medically significant (could have jeopardised the patient or required medical or surgical intervention to prevent an adverse outcome).

Lancet 2014; published today

Study limitations

- Specific populations were excluded (children, pregnant or lactating women, and patients with potential contraindications or at high risk of complications after the administration of colchicine).
- Specific etiologies of pericarditis were also excluded (bacterial or neoplastic pericarditis).

➢ Thus, our results should only be applied to populations that were eligible for the study.

➢ At present, colchicine is not approved for treatment of recurrent pericarditis in North America or Europe, and its use as such is off-label.

- Study sample size and length of follow-up might have precluded identification of rare adverse effects or long-term effects of the drug.
- Arbitrary length of therapy for colchicine (6 months): further research is needed to identify the best duration of colchicine treatment for recurrences. A longer treatment duration (6–12 months) might further decrease recurrences.

Conclusions

- Colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences.
- Taken together with results from other randomised controlled trials, these findings suggest that colchicine should be probably regarded as a first-line treatment for either acute or recurrent pericarditis in the absence of contrandications.

Full paper published online today

13TL7274

Articles

SCN

Version 2

This version saved: 10:19, 17-Feb-14

THELANCET-D-13-07274

S0140-6736(13)62709-9

Embargo: [add date when known]

Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial

Massimo Imazio, Riccardo Belli, Antonio Brucato, Roberto Cemin, Stefania Ferrua, Federico Beqaraj, Daniela Demarie, Silvia Ferro, Davide Forno, Silvia Maestroni, Davide Cumetti, Ferdinando Varbella, Rita Trinchero, David H Spodick, Yehuda Adler