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FASTTRACK
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COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial

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Aims No drug has been proven efficacious to prevent the post-pericardiotomy syndrome (PPS), but colchicine seems safe and effective for the treatment and prevention of pericarditis. The aim of the COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial is to test the efficacy and safety of colchicine for the primary prevention of the PPS.

Methods and results The COPPS study is a multicentre, double-blind, randomized trial. On the third post-operative day, 360 patients (mean age 65.7 $\pm$ 12.3 years, 66% males), 180 in each treatment arm, were randomized to receive placebo or colchicine (1.0 mg twice daily for the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients $\geq$70 kg, and halved doses for patients $<$70 kg or intolerant to the highest dose). The primary efficacy endpoint was the incidence of PPS at 12 months. Secondary endpoint was the combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses. Baseline characteristics were well balanced between the study groups. Colchicine significantly reduced the incidence of the PPS at 12 months compared with placebo (respectively, 8.9 vs. 21.1%; $P = 0.002$; number needed to treat = 8). Colchicine also reduced the secondary endpoint (respectively, 0.6 vs. 5.0%; $P = 0.024$). The rate of side effects (mainly related to gastrointestinal intolerance) was similar in the colchicine and placebo groups (respectively, 8.9 vs. 5.0%; $P = 0.212$).

Conclusion Colchicine is safe and efficacious in the prevention of the PPS and its related complications and may halve the risk of developing the syndrome following cardiac surgery.
ClinicalTrials.gov number, NCT00128427.

Keywords Colchicine • Post-pericardiotomy syndrome • Pericarditis • Prevention

Introduction

The post-pericardiotomy syndrome (PPS) is a relatively common and troublesome complication following cardiac surgery and occurring a few days to several weeks after the surgical operation in 10–40% of patients.[1–4] Treatment is empirical and based on aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids are considered in the case of contraindications or

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failure of NSAIDs. At present, no preventive pharmacological strategies (either NSAIDs or corticosteroids) have been proven to be efficacious in the prevention of the syndrome.[5,6]

Anecdotal reports have suggested that colchicine may be useful for the treatment of patients with the PPS.[7] On the basis of the efficacy of colchicine as an anti-inflammatory drug in acute gouty attacks,[8,9] familial Mediterranean fever,[10,11] and its efficacy in the treatment and secondary prevention of recurrent pericarditis,[12–24] colchicine has also been proposed for the primary prevention of the PPS in a preliminary report from Israel, where a statistically non-significant trend towards a reduction in the incidence of the syndrome was recorded in patients treated with colchicine.[4]

The PPS may have a troublesome course and complicate the post-operative period with even life-threatening events such as cardiac tamponade; moreover, it may prolong the hospital stay and increase management costs. Preventive measures may be valuable to reduce post-operative morbidity, improve the quality of life of patients, and reduce management costs.

The COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial is a prospective, randomized, double-blind, placebo-controlled, multicentre trial aimed at evaluating the efficacy and safety of colchicine for the primary prevention of the PPS following cardiac surgery. This is the first multicentre, double-blind, randomized trial to test this hypothesis with an intention-to-treat analysis.

Methods

Trial design

Prospective, randomized, double-blind, placebo-controlled, multicentre trial.

Participants and setting

The study population consisted of 360 patients enrolled at six hospitals in Italy (Maria Vittoria Hospital, Torino; Ospedali Riuniti, Bergamo; Mauriziano Hospital, Torino; Niguarda Hospital, Milano; San Maurizio Regional Hospital, Bolzano; and Ospedale degli Infermi, Rivoli).

Inclusion criteria

All consecutive patients undergoing cardiac surgery were recruited. Eligible patients had no contraindication to colchicine, were able to provide informed consent, and had no unfavourable short-term outlook. Inclusion criteria were: candidate for cardiac surgery, age ≥ 18 years, and informed consent. All patients have to be willing and able to give informed consent and to comply with the study procedures and follow-up.

Exclusion criteria

Patients meeting any of the following exclusion criteria were not eligible for the study: known severe liver disease or current transaminases >1.5 times the upper normal limit, current serum creatinine above 2.5 mg/dL, known myopathy or elevated baseline pre-operative creatine kinase, known blood dyscrasias or gastrointestinal disease, pregnant and lactating women or women of childbearing potential not protected by a contraception method, known hypersensitivity to colchicine, or current treatment with colchicine for any indications.

Table 1 Criteria for the diagnosis of the post-pericardiotomy syndrome

1. Fever lasting beyond the first post-operative week without evidence of systemic or focal infection
2. Pleuritic chest pain
3. Friction rub
4. Evidence of pleural effusion
5. Evidence of new or worsening pericardial effusion

The diagnosis of post-pericardiotomy syndrome was based on the presence of at least two criteria.

Interventions

Patients were randomized to receive placebo or colchicine on top of standard therapy. Treatment with placebo or colchicine started on the third post-operative day. Colchicine was given at the dosage of 1.0 mg twice daily for the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥70 kg, and halved doses for patients <70 kg or intolerant to the highest dose.

Endpoints

The primary study endpoint was the incidence of the PPS at 12 months. The secondary endpoint was the combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and recurrent pericarditis.

Criteria for the diagnosis of the PPS[4] are reported in *Table 1*. The diagnosis of PPS was based on the presence of at least two criteria.

Endpoint data were assessed by clinical records and regular clinical visits.

Randomization

Participants were randomly assigned to treatments by a central computer-based, automated sequence. Randomization was based on permuted blocks, with a block size of four. The random allocation sequence was implemented by sequentially numbered containers. All participants and trial investigators were blinded to randomized treatment. Tablets identical in colour, shape, and taste were provided in blister packs. Unblinded data were made available exclusively to an independent data and safety and monitoring board in the case of severe side effects. Data were collected using case report forms and clinical events adjudication forms. Data were managed blinded to treatment assignments. A blinded clinical endpoint committee adjudicated all events.

Safety

During follow-up, a monitoring and recording of all adverse events was performed. A severe adverse event was considered an untoward event which was fatal or life-threatening or required hospitalization or was significantly or permanently disabling or medically significant (may jeopardize the patient and may require medical or surgical intervention to prevent an adverse outcome). A safety monitoring committee did one interim analysis, masked to treatment assignment.

Statistical analysis and sample size

A total of 360 patients, 180 in each treatment arm, were needed to detect a difference in the PPS rate of 22.0 and 11.0% between the two treatment arms (placebo and colchicine) with a power of 80% using a two-sided $P = 0.05$ level test. The estimated rate of the PPS of 22.0% in the placebo group and 11.0% in the colchicine group

was based on the preliminary study from Israel.[4] Analyses were performed by intention to treat.

Data were expressed as mean ± standard deviation. Comparisons between patient arms were performed using the Mann–Whitney test for continuous variables and a χ^2 analysis for categorical variables. A *P*-value of <0.05 was considered to show statistical significance. Time-to-event distributions were estimated using the Kaplan–Meier method and compared using the log-rank test. Analyses were performed with the software package SPSS 13.0 (Chicago, IL, USA). The number of patients needed to treat (NNT) was estimated with its confidence interval (CI) using the GraphPad Software QuickCalcs (San Diego, CA, USA).

Results

Baseline characteristics

Baseline patient characteristics were similar between the two study groups and are reported in *Table 2*. A detailed flow diagram of the study is reported in *Figure 1*.

Main outcomes

Colchicine significantly reduced the incidence of the PPS at 12 months compared with placebo (respectively, 8.9 vs. 21.1%; $P = 0.002$; NNT 8, relative risk reduction—RRR 57.9%, 95% CI 27.3–75.6) and the secondary endpoint including disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses at 18 months (respectively, 0.6 vs. 5.0%; $P = 0.024$; NNT 22, RRR 88.9%, 95% CI 13.2–98.6) (*Table 3* and *Figure 2*).

Most PPS events occurred in the first 30 days (85% of all PPS events; *Figure 3*).

Safety and side effects

The rates of side effects and drug withdrawal were similar in the colchicine and placebo groups (respectively, 8.9 vs. 5.0%; $P = 0.212$ for side effects and 11.7 vs. 6.7%; $P = 0.145$ for drug withdrawal), although colchicine showed a trend towards an increased rate of both events. No severe side effects were recorded.

Gastrointestinal intolerance was the only side effect recorded during the study, while one case of myotoxicity was recorded in the placebo group and related to concomitant use of a statin.

Colchicine was discontinued in 21 cases (11.7%). Patient or medical decision was the cause of drug withdrawal in 2.8% of cases for the colchicine group and 1.7% for the placebo group. A detailed list of side effects and drug withdrawal data is reported in *Table 4*.

Table 2 Baseline characteristics of the patients

Characteristic	Placebo (*n* = 180)	Colchicine (*n* = 180)
Age (mean ± SD)	67 ± 11	65 ± 14
Female sex (%)	65 (36.1)	56 (31.1)
Medical history (%)		
Hypertension	125 (69.4)	121 (67.2)
Diabetes mellitus	45 (25.0)	39 (21.7)
Tobacco use	54 (15.0)	41 (11.4)
Previous MI	37 (20.6)	37 (20.6)
Previous cardiac surgery	11 (6.1)	10 (5.6)
Previous pericarditis	2 (1.1)	2 (1.1)
Pre-operative pericardial effusion	2 (1.1)	3 (1.6)
Pre-operative data (%)		
Creatinine clearance <60 mL/min	22 (12.2)	33 (18.3)
Ejection fraction	54 ± 10	54 ± 12
NYHA class I–II	118 (65.6)	127 (70.5)
NYHA class III–IV	62 (34.4)	53 (29.5)
Surgery indication (%)		
Angina	66 (36.7)	66 (36.7)
Myocardial infarction	18 (10.0)	31 (17.2)
Mitral valve disease	37 (20.6)	36 (20.0)
Aortic valve disease	44 (24.4)	35 (19.4)
Aorta disease	5 (2.8)	5 (2.8)
Other	10 (5.5)	7 (3.9)
Cardiac surgery type (%)		
CABG	77 (42.8)	92 (51.1)
Valvular surgery	55 (30.6)	51 (28.3)
Aorta surgery	8 (4.4)	4 (2.2)
Combined surgery	37 (20.6)	30 (16.7)
Other	3 (1.6)	3 (1.6)

CABG, coronary artery bypass grafting; MI, myocardial infarction.

Discussion

The COPPS trial was designed to assess the efficacy and safety of colchicine for the primary prevention of the PPS. This possible indication was tested for the first time in a preliminary prospective, open-label, randomized trial of colchicine (1.5 mg/day) compared with placebo beginning on the third post-operative day in 163 patients who underwent cardiac surgery.[4] Fifty-two of the 163 (31.9%) initial patients were excluded because of post-operative complications, non-compliance, or gastrointestinal side effects. At 3 months, PPS was diagnosed in 19 of 111 patients (17.1%) who completed the study: 5 of 47 (10.6%) in the colchicine group and 14 of 64 (21.9%) in the placebo group. The difference showed a possible trend towards statistical significance ($P < 0.135$); however, these results can be considered only as preliminary, because of the limited sample size, the lack of an intention-to-treat analysis, and the short observation time.

The PPS is a common complication after cardiac surgery and can be often prolonged and disabling. Colchicine might represent a cheap, safe option not only for the treatment of the syndrome, but also for its primary prevention.

Colchicine is efficacious and safe in the treatment and prevention of pericarditis[12–23] and has been proposed as a first treatment option for recurrent pericarditis (class I indication) and optional for acute pericarditis (class IIa indication) in the 2004 European guidelines on the management of pericardial diseases.[25] At present, no pharmacological options have been shown efficacious in the prevention of the PPS.[5,6]

In the COPPS study, colchicine was safe and efficacious in the prevention of the PPS and its related complications. Colchicine halved the incidence of the PPS and its related complications

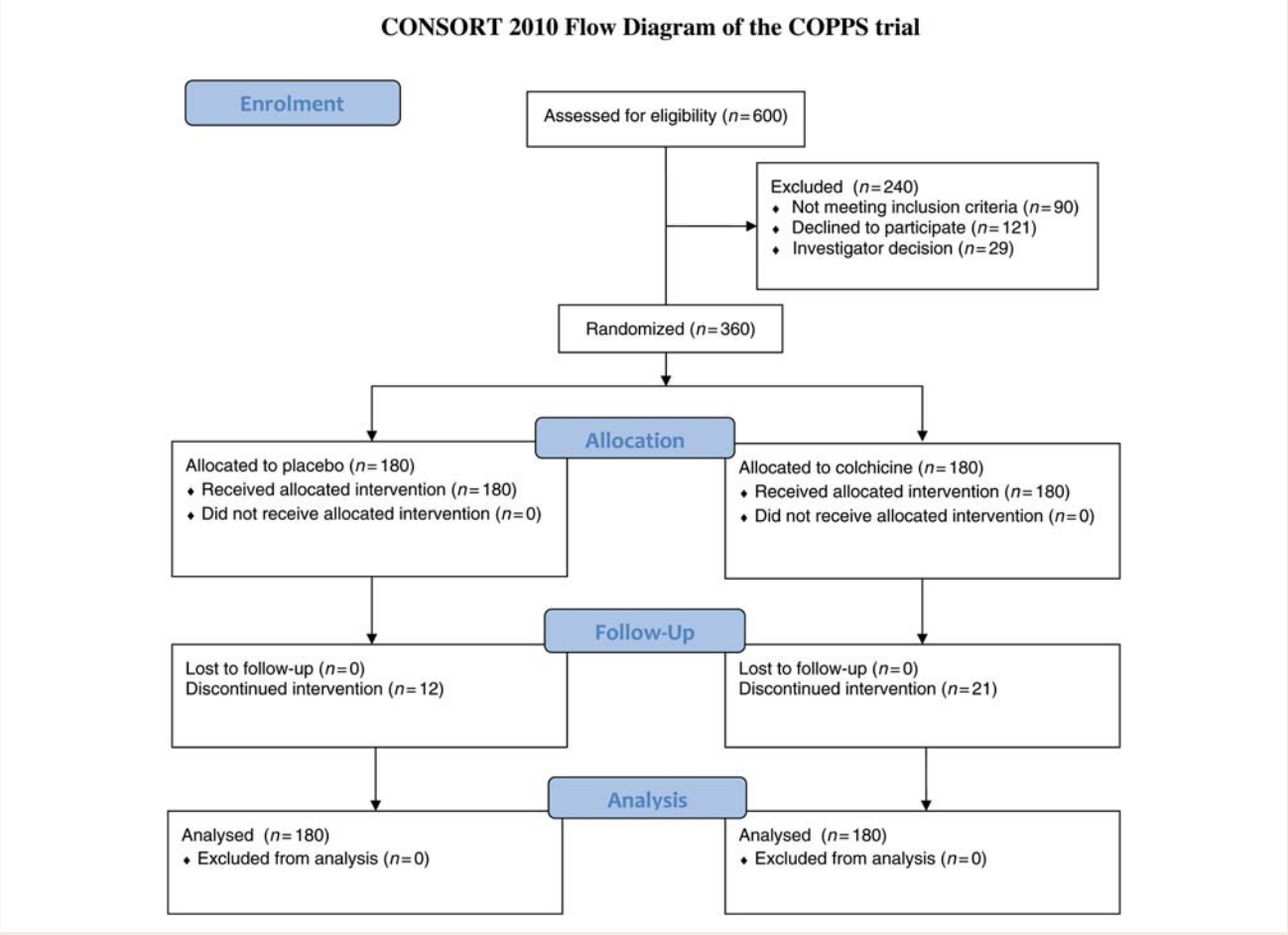

Figure 1 Study flow diagram.

providing evidence for the first time that pharmacological prevention of the PSS is possible and safe.

Most of the PPS events (85% of all PPS) occurred in the first month, and thus a preventive treatment with colchicine for the first 4 weeks following surgery seems appropriate.

No severe side effects were documented, and gastrointestinal side effects were equally distributed between the colchicine and placebo groups, although colchicine showed a trend towards an increased rate of such complications. Diarrhoea is relatively common, affecting up to 10% of patients on colchicine treatment for pericarditis. The use of weight-adjusted doses without a loading dose and especially lower doses (i.e. 0.5 mg/day to 0.5 mg b.i.d.) may be a way to reduce this side effect, improving drug compliance.[24,26,27]

The exact mechanism of colchicine action is not fully understood. Most of the pharmacological effects of colchicine on cells involved in inflammation appear to be related to its capacity to disrupt microtubules.[28] Colchicine inhibits the process of microtubule self-assembly by binding β-tubulin with the formation of tubulin–colchicine complexes. This action takes place either in the mitotic spindle or in the interphase stage, thus colchicine inhibits the movement of intercellular granules and the secretion of various substances.[7,8,12,18] By this mechanism, colchicine is able to inhibit various leucocytes functions, and this effect should be the most significant for the anti-inflammatory action. Moreover, colchicine shows a preferential concentration in leucocytes and its peak concentration may be more than 16 times the peak concentration in plasma. This seems to be related to its therapeutic effect.[28]

The major study limitation is related to the definition of the PPS because there is no general agreement on how to diagnose the syndrome. The diagnosis of PPS is challenging as there is no single finding that is pathognomonic for the condition. At present, the definition of the PPS is rather arbitrary. There are neither specific guidelines nor consensus documents. The only published criteria for the diagnosis have been proposed in the preliminary study from Israel,[4] which is the premise of the present multicentre, double-blind, randomized trial. We adopted the same diagnostic criteria for the PPS. They can be criticized and considered weak because they could lead to the diagnosis of PPS also for cases with mild pleuro-pericardial involvement following surgery, which may be considered trivial post-operative sequelae. Nevertheless, they represent the first attempt to have an objective approach to the diagnosis. Otherwise, the diagnosis would be based on a rather subjective 'clinical judgement', thus probably including only more severe cases. In the clinical arena, the PPS is not a single disease but rather a syndrome with different

Table 3 Study endpoints and diagnostic criteria for the post-pericardiotomy syndrome

Event	Placebo ($n = 180$)	Colchicine ($n = 180$)	*P*-value
Primary endpoint (%)			
PPS at 12 months	38 (21.1)	16 (8.9)	0.002
Fever beyond first post-operative week[a]	7 (3.9)	6 (3.3)	0.982
Pleuritic chest pain	23 (12.8)	7 (3.9)	0.004
Friction rub	15 (8.3)	5 (2.7)	0.036
Pleural effusion	46 (25.6)	22 (12.2)	0.002
New or worsening pericardial effusion[b]	41 (22.8)	23 (12.8)	0.019
Secondary endpoint[c] (%)	9 (5.0)	1 (0.6)	0.024
Recurrence	2 (1.1)	0 (0.0)	0.485
Cardiac tamponade	1 (0.6)	0 (0.0)	0.992
Constrictive pericarditis	0 (0.0)	0 (0.0)	0.982
PPS-related hospitalization	6 (3.3)	1 (0.6)	0.130
Mean follow-up (months)	18.5	20.2	0.252

PPS, post-pericardiotomy syndrome.
[a]Without evidence of systemic or focal infection.
[b]Pre-existing pre-operative pericardial effusions worsened in one case (0.6%) in the placebo group and two cases (1.2%) in the colchicine group ($P = 0.964$).
[c]Including combined rate of recurrence, cardiac tamponade, constrictive pericarditis, post-pericardiotomy syndrome-related hospitalization.

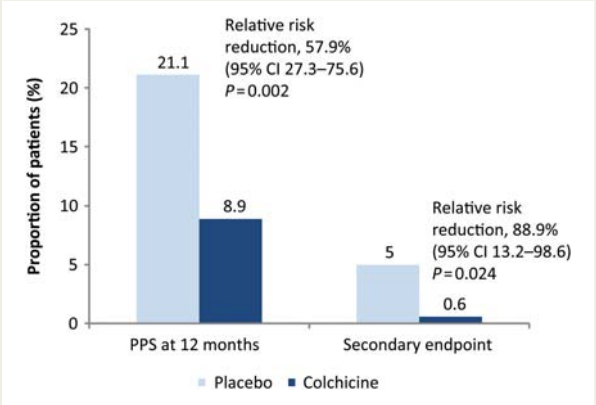

Figure 2 Proportion of patients developing the primary endpoint (post-pericardiotomy syndrome at 12 months; relative risk reduction 57.9%, 95% confidence interval 27.3–75.6; $P = 0.002$) and the secondary endpoint (recurrence, cardiac tamponade, constrictive pericarditis, and post-pericardiotomy syndrome-related hospitalization; relative risk reduction 88.9%, 95% confidence interval 13.2–98.6; $P = 0.024$).

expressions of pleural and/or pericardial involvement with a wide spectrum of clinical severity ranging from mild isolated asymptomatic effusions to cardiac tamponade and/or massive pleural effusions. On this basis, if all cases are considered, the incidence of the

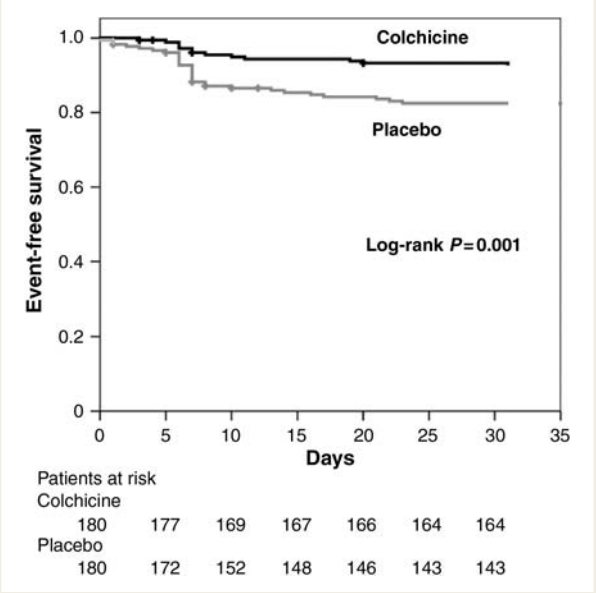

Figure 3 Kaplan–Meier event-free survival curves according to the treatment groups in the first 30 days (85% of all post-pericardiotomy syndrome events). Curves remained parallel after the first month.

Table 4 Side effects and drug withdrawal

Event	Placebo ($n = 180$)	Colchicine ($n = 180$)	*P*-value
Side effects (%)	9 (5.0)	16 (8.9)	0.212
Severe side effects	0 (0.0)	0 (0.0)	0.212
Other side effects	9 (5.0)	16 (8.9)	0.133
Gastrointestinal	8 (4.4)	16 (8.9)	0.939
Alopecia	0 (0.0)	0 (0.0)	
Anorexia	0 (0.0)	0 (0.0)	
Hepatoxicity	0 (0.0)	0 (0.0)	
Myotoxicity	1 (0.6)	0 (0.0)	
Bone marrow toxicity	0 (0.0)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	
Drug withdrawal (%)			
Overall	12 (6.7)	21 (11.7)	0.145
Related to side effects	9 (5.0)	16 (8.9)	0.212
Patient or medical decision	3 (1.7)	5 (2.8)	0.728

PPS may seem relatively high compared with what is encountered as 'significant disease' in most severe cases from daily practice. However, many cases of the PPS may not be diagnosed in the clinical setting, and delayed recognition and treatment may be responsible for complications and recurrences, often the cause of readmissions.

Nevertheless, in the COPPS study, colchicine showed to reduce all the major components of the PPS as reported in the adopted diagnostic criteria (pleuritic chest pain, friction rub, and pleural

and pericardial effusions), and thus showing a 'real' preventive effect even on several components of the pleuro-pericardial involvement following cardiac surgery.

In conclusion, colchicine is safe and efficacious in the primary prevention of the PPS and its related complications and may halve the risk of developing the syndrome following cardiac surgery. Such a finding is particularly important for clinical practice because the post-operative management may be complex, troublesome and empirical anti-inflammatory therapy may not be efficacious.[29,30]

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Conflict of interest: none declared.

Appendix

Steering committee

Chairman: R.T., MD, Torino, Italy.

Co-chairman and Principal Investigator: M.I., 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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