Colchicine Reduces Postoperative Atrial Fibrillation

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

Massimo Imazio, MD; Antonio Brucato, MD; Paolo Ferrazzi, MD; Maria Elena Rovere, MD; Anna Gandino, MD; Roberto Cemin, MD; Stefania Ferrua, MD; Riccardo Belli, MD; Silvia Maestroni, MD; Caterina Simon, MD; Edoardo Zingarelli, MD; Alberto Barosi, MD; Fabrizio Sansone, MD; Davide Patrini, MD; Ettore Vitali, MD; Rita Trinchero, MD; David H. Spodick, MD; Yehuda Adler, MD; for the COPPS Investigators

Background—Inflammation and pericarditis may be contributing factors for postoperative atrial fibrillation (POAF), and both are potentially affected by antiinflammatory drugs and colchicine, which has been shown to be safe and efficacious for the prevention of pericarditis and the postpericardiotomy syndrome (PPS). The aim of the Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) POAF substudy was to test the efficacy and safety of colchicine for the prevention of POAF after cardiac surgery.

Methods and Results—The COPPS POAF substudy included 336 patients (mean age, 65.7±12.3 years; 69% male) of the COPPS trial, a multicenter, double-blind, randomized trial. Substudy patients were in sinus rhythm before starting the intervention (placebo/colchicine 1.0 mg twice daily starting on postoperative day 3 followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥70 kg, halved doses for patients <70 kg or intolerant to the highest dose). The substudy primary end point was the incidence of POAF on intervention at 1 month. Despite well-balanced baseline characteristics, patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P=0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4±3.7 versus 10.3±4.3 days; P=0.040) and rehabilitation stay (12.1±6.1 versus 13.9±6.5 days; P=0.009). Side effects were similar in the study groups.

Conclusion—Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00128427.

(Circulation. 2011;124:2290-2295.)

Key Words: atrial fibrillation • cardiac surgery • colchicine • postpericardiotomy syndrome • prevention

Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases, depending on the surgery type (coronary artery bypass graft surgery, valve surgery, or combined coronary artery bypass graft/valve surgery), patient features, definition of arrhythmia, and surveillance.1 Nowadays, POAF is becoming more common because of the increasing number of cardiac surgery operations and the aging of the population. This complication increases patient morbidity, length of hospital stay, and management costs.2

Editorial see p 2281

Clinical Perspective on p 2295

Prevention of POAF is an important management goal supported by American and European guidelines.3–5 Many different agents have been studied to fit this goal and may be grouped into 2 main categories: agents with antiarrhythmic properties and agents with antiinflammatory activity such as corticosteroids, statins, and free radical scavengers.6

The development of POAF is likely multifactorial. Pericardial inflammation, autonomic imbalance during the postoperative time, excessive production of catecholamines, and fluid shift may all contribute.7–8 Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are significantly decreased by corticosteroids.9 Thus, antiinflammatory therapy may be beneficial for the prevention of POAF. In the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) trial, colchicine was safe and efficacious in the prevention of the PPS and halved the risk of developing the syndrome after cardiac surgery.10 PPS may be relatively com-
mon and troublesome, affecting 10% to 40% of patients after cardiac surgery.11–14 Because of its antiinflammatory effect, colchicine may also reduce the risk of POAF. A substudy of the COPPS trial was designed to evaluate the efficacy of colchicine in preventing POAF. This is the first study to test the hypothesis that colchicine may prevent POAF.

**Methods**

**Trial Design and Participants**

This was a prospective, randomized, double-blind, placebo-controlled, multicenter trial. The overall study population consisted of 360 patients enrolled at 6 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 adult patients undergoing cardiac surgery and without contraindications to colchicine were recruited. Eligible patients had no unfavorable short-term outlook and were willing and able to give informed consent and to comply with the study procedures and follow-up. For the COPPS POAF substudy, all patients in sinus rhythm on day 3 were included for the analysis of colchicine effects (either stable sinus rhythm or intermittent POAF but in sinus rhythm on day 3 at the time of colchicine/placebo administration). Thus, the COPPS POAF substudy population included 336 patients (Figure 1).

**Exclusion Criteria**

The study exclusion criteria included (1) known severe liver disease or current transaminases >1.5 times the upper normal limit, (2) current serum creatinine >2.5 mg/dL, (3) known myopathy or elevated baseline preoperative creatine kinase, (4) known blood dyscrasias or gastrointestinal disease, (5) pregnant and lactating women or women of childbearing potential not protected by a contraception method, (6) known hypersensitivity to colchicine, and (7) current treatment with colchicine for any indications. 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.

**Interventions**

Patients were randomized to receive placebo or colchicine on top of standard therapy. Treatment with placebo or colchicine started on postoperative day 3. Colchicine was given at the dosage of 1.0 mg twice daily for the first day followed by a maintenance dosage of 0.5 mg twice daily for 1 month in patients >70 kg, and halved doses were given to patients <70 kg or intolerant to the highest dose. The rhythm was defined as AF when there were no consistent P waves before each QRS complex and the ventricular rate was irregular. AF episodes lasting >5 minutes were considered. Recognition of AF was performed by continuous ECG monitoring (3-channel ward monitor) and 12-lead ECG recordings.

**End Points**

The COPPS POAF substudy primary end point was the rate of POAF on placebo/colchicine treatment. Additional analyses included hospital stay (cardiac surgery, rehabilitation, overall stay) and the incidence of death and stroke.

**Randomization**

Participants were randomly assigned to treatments by a central computer-based, automated sequence based on permuted blocks with a block size of 4. The random allocation sequence was implemented by sequentially numbered containers. All participants and trial investigators were blinded to randomized treatment. Tablets identical in color, shape, and taste were provided in blister packs. Data were collected on case report forms and clinical events adjudication forms. Data were managed by investigators blinded to treatment assignments. A blinded clinical end point committee adjudicated all events.
Safety
During follow-up, monitoring and recording of all adverse events were performed. Potential side effects to be monitored included gastrointestinal effects (especially diarrhea), alopecia, anorexia, hepatotoxicity, myotoxicity, and bone marrow toxicity. An untoward event that was fatal or life-threatening, 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) was recorded as a severe adverse event.

Statistical Analysis and Sample Size
For the COPPS POAF subgroup, a total of 250 patients, 125 in each treatment arm, were needed to detect a difference in the POAF rate of 48.0% and 30.0% between the 2 treatment arms (placebo and colchicine) with a power of 80% using a 2-sided \( P=0.05 \) level test. The estimated rates of POAF in the 2 study groups were based on the results of a randomized controlled trial in which the incidence of POAF was significantly lower in the hydrocortisone group (30%) than in the placebo group (48%; adjusted hazard ratio, 0.54; 95% confidence interval, 0.35–0.83; \( P=0.004 \)).13 Analyses were performed by intention to treat. For the COPPS POAF subgroup, intention-to-treat analysis was applied to patients enrolled in the study (336 patients) from the original overall study population of the COPPS trial (360 patients).

Data are expressed as mean±SD. Comparisons between patient groups were performed with the Mann-Whitney test for continuous variables and a \( \chi^2 \) analysis for categorical variables. A value of \( P<0.05 \) was considered to show statistical significance. Time-to-event distributions were estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards model was used to identify independent risk factors for recurrences. Stepwise selection procedure was adopted. A value of \( P<0.05 \) was considered significant for variable entry for stepwise selection. Analyses were performed with the SPSS 13.0 software package (SPSS, Inc, Chicago, IL).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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

Main Outcome
Chronic preoperative AF was recorded in 17 of 360 patients (4.7%). The overall incidence of POAF was 97 of 343 (28.3%): 42 of 97 (43.3%) on postoperative days 1 and 2 (before starting placebo/colchicine) and 55 of 97 (56.7%) from postoperative day 3 (on intervention). Persistent POAF starting on postoperative day 1 or 2 was recorded in 7 patients on postoperative day 3 before randomization to placebo/colchicine. These patients were excluded from subsequent analysis, including a total of 336 patients in sinus rhythm (Figure 1). For the assessment of the primary outcome (POAF on placebo or colchicine treatment), only AF events from postoperative day 3, ie, when placebo/colchicine was administered, were considered. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; \( P=0.021 \); relative risk reduction, 45%; number needed to treat, 11; Table 2 and Figure 2). The POAF events after the start of the intervention (placebo/colchicine) numbered 35 of 167 versus 20 of 169, respectively. The duration of POAF was shorter in the colchicine group compared with the placebo group (3.0±1.2 versus 7.7±2.5 days, respectively; \( P<0.001 \)).

| Table 1. Baseline Characteristics of the Patients in the Prevention of the Postpericardiotomy Syndrome (COPPS) Postoperative Atrial Fibrillation Substudy |
|-------------------------------------------------|-----------------|-----------------|-----|
| Characteristic | Placebo (n=167) | Colchicine (n=169) | \( P \) |
| 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 (68.9) | 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 |
| Preoperative data | | | |
| Creatinine clearance <60 mL/min (n=53), n (%) | 21 (12.6) | 32 (18.9) | 0.14 |
| Ejection fraction (%) | 54±10 | 54±12 | 0.74 |
| NYHA class I–II (n=257), n (%) | 123 (73.6) | 134 (79.3) | 0.27 |
| NYHA class III–IV (n=79), n (%) | 44 (26.4) | 35 (20.7) | 0.27 |
| 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 |

AF indicates atrial fibrillation; HF, heart failure; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; and CABG, coronary artery bypass grafting.

Patients treated with colchicine had a shorter in-hospital stay (9.4±3.7 versus 10.3±4.3 days; \( P=0.040 \)), rehabilitation stay (12.1±6.1 versus 13.9±6.5 days; \( P=0.009 \)), and overall hospital stay (cardiac surgery plus rehabilitation stay; 21 versus 24 days, respectively; \( P=0.030 \)). The incidence of death and stroke was similar in the study groups (Table 2).

The following clinical features were more commonly recorded in patients with POAF on placebo/colchicine treatment compared with those without POAF (Table 3): left atrium anteroposterior diameter >45 mm (32.7% versus...
15.3%; *P*=0.004), surgery other than coronary artery bypass graft (63.6% versus 47.7%; *P*=0.039), and the presence of pericardial effusion (27.3% versus 15.7%; *P*=0.051). On the contrary, a lower perioperative use of β-blockers (32.7% versus 55.5%; *P*=0.003) and colchicine (36.4% versus 53.0%; *P*=0.019) was recorded in patients with POAF compared with those without POAF. No significant differences were recorded in the periprosthetic use of amiodarone.

A dilated left atrium (hazard ratio 2.31; 95% confidence interval, 1.15–4.63; *P*=0.019) was identified as the only independent risk factor for POAF in multivariable analysis (Table 4).

### Safety and Side Effects

The rates of side effects and drug withdrawal were similar in the colchicine and placebo groups (9.5% versus 4.8%, respectively [*P*=0.137], for side effects, and 11.8% versus 6.6% [*P*=0.131] for drug withdrawal), although colchicine showed a trend toward an increased rate of both events. No severe side effects were recorded.

Gastrointestinal intolerance was the only side effect recorded during the study in colchicine-treated patients. One case of myotoxicity was recorded in the placebo group and was related to concomitant use of a statin.

Colchicine was discontinued in 20 patients (11.8%). Patient or medical decision was the cause of drug withdrawal in 2.4% in the colchicine group and 1.8% in the placebo group (Table 5).

### Discussion

The COPPS POAF substudy was designed to assess the efficacy and safety of colchicine for the prevention of POAF. Colchicine has been shown to be safe and effective in the prevention of pericarditis.10,16–20

In the COPPS trial, colchicine halved the incidence of the PPS, providing evidence that pharmacological prevention of the PSS is possible and safe.10 In the COPPS POAF substudy, colchicine reduced the incidence of POAF (relative risk reduction, 45%; number needed to treat, 11) without significant side effects. Moreover, colchicine halved the mean duration of POAF; such an effect may be particularly important for reducing the subsequence rate of late AF (AF >30 days of surgery) because a longer duration of POAF is a strong and independent predictor of late AF.21

The mechanism of POAF is believed to be reentry. The electrophysiological substrate may be preexisting or may develop as a result of heterogeneity of refractoriness after surgery. Multiple perioperative factors have been proposed to contribute to the latter, including operative trauma, inflammation, eleva-

### Table 3. Comparison of Clinical Characteristics Between Patients With and Without Postoperative Atrial Fibrillation on Placebo/Colchicine Treatment

<table>
<thead>
<tr>
<th>Feature</th>
<th>No (n=281)</th>
<th>Yes (n=55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>66±11</td>
<td>67±13</td>
<td>0.677</td>
</tr>
<tr>
<td>Age &gt;65 y (n=196)</td>
<td>161 (57.3)</td>
<td>35 (63.6)</td>
<td>0.455</td>
</tr>
<tr>
<td>Male sex (n=230)</td>
<td>196 (69.8)</td>
<td>34 (61.8)</td>
<td>0.313</td>
</tr>
<tr>
<td>Previous history of AF (n=19)</td>
<td>14 (5.0)</td>
<td>5 (9.1)</td>
<td>0.213</td>
</tr>
<tr>
<td>Previous congestive HF (n=40)</td>
<td>31 (11.0)</td>
<td>9 (16.4)</td>
<td>0.260</td>
</tr>
<tr>
<td>Previous cardiac surgery (n=18)</td>
<td>13 (4.6)</td>
<td>5 (9.1)</td>
<td>0.303</td>
</tr>
<tr>
<td>Hypertension (n=231)</td>
<td>193 (68.7)</td>
<td>38 (69.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus (n=77)</td>
<td>65 (23.1)</td>
<td>12 (21.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>COPD (n=26)</td>
<td>23 (8.2)</td>
<td>3 (5.5)</td>
<td>0.781</td>
</tr>
<tr>
<td>LA anteroposterior diameter &gt;45 mm (n=61)</td>
<td>43 (15.3)</td>
<td>18 (32.7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**POAF** indicates postoperative atrial fibrillation; **AF**, atrial fibrillation; **HF**, heart failure; **COPD**, chronic obstructive pulmonary disease; **LA**, left atrial; **CABG**, coronary artery by-pass grafting; **ACEI**, angiotensin-converting enzyme inhibitor; and **ARB**, angiotensin II receptor blocker.

*Excluding pharmacological cardioversion of postoperative atrial fibrillation.

### Table 4. Hazard Ratios for Postoperative Atrial Fibrillation on Placebo/Colchicine Treatment in the Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA anteroposterior diameter &gt;45 mm</td>
<td>2.31</td>
<td>1.15–4.63</td>
<td>0.019</td>
</tr>
<tr>
<td>Perioperative β-blocker use</td>
<td>0.47</td>
<td>0.25–0.88</td>
<td>0.019</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.52</td>
<td>0.28–0.96</td>
<td>0.036</td>
</tr>
</tbody>
</table>

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.
Table 5. Side Effects and Drug Withdrawal

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

Drug withdrawal may be concentration in leukocytes, where its peak concentration may be >10 times the peak concentration in plasma.

Conclusions
Colchicine seems safe and efficacious in reducing the incidence of POAF after cardiac surgery. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both PPS and POAF, 2 common and troublesome complications of cardiac surgery that may increase management costs.

Acknowledgments
We thank all the participants of the study and the physicians, nurses, ethics committees, and administrative staff in hospitals who assisted with its conduct.

Sources of Funding
The trial is an independent study founded and performed within the Italian National Healthcare System. The research protocol was approved by the relevant institutional review boards or ethics committees, and all human participants gave written informed consent. The steering committee designed and oversaw the trial and had the final decision on the contents of the manuscript. All data were received, checked, and analyzed independently at the Coordinating Centre at the Cardiology Department, Maria Vittoria Hospital, Torino, Italy, after blinded adjudication of clinical events and side effects. Acarpia Lda supplied of drug/placebo as an unrestricted grant.

Study Limitations
Although the results are encouraging, important issues need to be considered. The relatively small sample size is the first study limitation. This study shows the first evidence of colchicine efficacy for the prevention of POAF, requiring further confirmation and validation in multicenter studies. Moreover, the highest incidence of POAF is generally seen in the first postoperative days. In the COPPS trial, colchicine was given starting on the postoperative day 3 following a preliminary positive experience from Israel. On this basis, the potential beneficial effect of the drug is limited from postoperative day 3, with the potential to miss early postoperative AF cases in the first 2 days. Further research should address whether alternative regimens providing the drug in the perioperative period (eg, starting the administration before the operation) may provide better prevention for either PPS or POAF. Both efficacy and safety should be evaluated in this setting.

Appendix

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, CA; David H. Spodick, MD, Worcester, MA.

COPPS Recruiting Centres and Investigators
Cardiology Department, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M. Imazio, A. Chiniaglia, B. Demichelis, D. Forno, S. Ierna); Ospedali Riuniti, Bergamo, Italy (investigators: A. Brucato, S. Maestroni, C. Simon, D. Curretti, P. Ferrazzi); Cardiac Surgery, Ospedale Mauriziano, Torino, Italy (investigators: M.E. Rovere, E. Zingarelli, F. Sansone); Ospedale Niguarda, Milano, Italy (investigators: A. Gandino, A. Barosi, D. Patrini, E. Vitali); Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin); Ospedale degli Infermi, Rivoli, Italy (S. Ferolla, M.R. Conte).

Appendix

Drug withdrawal may be concentration in leukocytes, where its peak concentration may be >10 times the peak concentration in plasma.

Conclusions
Colchicine seems safe and efficacious in reducing the incidence of POAF after cardiac surgery. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both PPS and POAF, 2 common and troublesome complications of cardiac surgery that may increase management costs.

Acknowledgments
We thank all the participants of the study and the physicians, nurses, ethics committees, and administrative staff in hospitals who assisted with its conduct.

Sources of Funding
The trial is an independent study founded and performed within the Italian National Healthcare System. The research protocol was approved by the relevant institutional review boards or ethics committees, and all human participants gave written informed consent. The steering committee designed and oversaw the trial and had the final decision on the contents of the manuscript. All data were received, checked, and analyzed independently at the Coordinating Centre at the Cardiology Department, Maria Vittoria Hospital, Torino, Italy, after blinded adjudication of clinical events and side effects. Acarpia Lda supplied of drug/placebo as an unrestricted grant.
Disclosures
None.

References

CLINICAL PERSPECTIVE
Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases. POAF increases patient morbidity, length of hospital stay, and management costs. Its prevention is an important management goal. Systemic and local inflammatory responses are believed to contribute to the pathogenesis of POAF. Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are decreased by corticosteroids. Because of its antiinflammatory effects for the treatment and prevention of pericarditis, colchicine has the potentiality to prevent POAF. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) POAF substudy is the first trial designed to assess the efficacy and safety of colchicine for POAF prevention. It is a substudy of the COPPS trial, in which colchicine halved the occurrence of the postpericardiotomy syndrome. On the third postoperative day, consecutive adult patients undergoing cardiac surgery and without contraindications to colchicine were randomized to receive placebo or colchicine on top of standard therapy. The substudy primary efficacy end point was the incidence of POAF on placebo/colchicine treatment at 1 month. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P = 0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4 ± 3.7 versus 10.3 ± 4.3 days; P = 0.040) and rehabilitation stay (12.1 ± 6.1 versus 13.9 ± 6.5 days; P = 0.009). Side effects were similar in the study groups. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both the postpericardiotomy syndrome and POAF, 2 common and troublesome complications of cardiac surgery.

Imazio et al Colchicine Reduces Postoperative AF 2295
Colchicine Reduces Postoperative Atrial Fibrillation: Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy

Massimo Imazio, Antonio Brucato, Paolo Ferrazzi, Maria Elena Rovere, Anna Gandino, Roberto Cemin, Stefania Ferrua, Riccardo Belli, Silvia Maestroni, Caterina Simon, Edoardo Zingarelli, Alberto Barosi, Fabrizio Sansone, Davide Patrini, Ettore Vitali, Rita Trinchero, David H. Spodick, Yehuda Adler and for the COPPS Investigators

_Circulation._ published online November 16, 2011;

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2011/11/15/CIRCULATIONAHA.111.026153

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2011/11/16/CIRCULATIONAHA.111.026153.DC1
http://circ.ahajournals.org/content/suppl/2013/10/14/CIRCULATIONAHA.111.026153.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Appendix

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.

COPPS recruiting centres and investigators:

Cardiology Dpt, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M. Imazio, A. Chinaglia, B. Demichelis, D. Forno, S. Ierna), Ospedali Riuniti, Bergamo, Italy (investigators: A. Brucato, S. Maestroni, C. Simon, D. Cumetti, P. Ferrazzi), Cardiac Surgery, Ospedale Mauriziano, Torino, Italy (investigators: M.E. Rovere, E. Zingarelli, F. Sansone), Ospedale Niguarda, Milano, Italy (investigators: A. Gandino, A. Barosi, D. Patrini, E. Vitali), Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin), Ospedale degli Infermi, Rivoli, Italy (S. Ferrua, M.R. Conte).
통풍 치료제로 심방세동 발생을 줄인다

오 세일 교수 서울대학교병원 순환기내과

Summary

배경
염증과 심외막염은 수술 후 심방세동(postoperative atrial fibrillation, POAF)의 기여인자일 수 있으며, 둘 다 항염증제 및 colchicine의 영향을 받는다. Colchicine은 심외막염과 심외막절개 후 증후군을 예방하는 데에 안전하고 효과적이며 COPPS(Cholicine for the Prevention of the Post-Pericardiotomy Syndrome) 연구를 통해 보여주었다. 본 연구의 목적은 심장 수술 후 POAF의 예방에 있어 colchicine의 효율과 안전성을 조사하는 것이다.

방법 및 결과
본 연구에서는 COPPS 연구에 모집된 336명의 환자(평균연령 65.7±12.3세; 남성 69%)를 분석하였다. 환자들은 투약(수술 후 3병일째에 위약/colchicine 1.0mg, 1일 2회 복용 시작, 이후 1개월간 유지 용량 0.5mg, 1일 2회 복용, 체중 70kg 미만 또는 이 용량에 적용하지 못하는 경우에는 절반 용량 복용) 전 모두 동일하였다. 연구의 일차 목표는 1개월 후 POAF의 발생이었다. Colchicine군에서 POAF의 발생이 낮았고(12.0% vs. 22.0%; P=0.021; 상대 위험도(relative risk) 감소, 45%; number needed to treat, 11명), 재원일(9.4±3.7 vs. 10.3±4.3일; P=0.040)과 재활일(12.1±6.1 vs. 13.9±6.5일; P=0.009)이 짧았다. 부작용은 양 군에서 유사하였다.

결론
Colchicine은 POAF의 발생을 줄여주는 데에 안전하고 효과적이며, 합병증을 반감시켜 재원 기간을 줄여줄 수 있을 것으로 보인다.
POAF의 발생은 심외막의 염증, 자율신경의 부조화, 순환 체액량 조절의 변화 등에 기인한다. 한편, 여러 가지 약제들이 POAF를 막기 위해 시도되었으나, 효과를 입증한 약제는 그리 많지 않다. 베타차단제, amiodarone, sotalol 정도가 인정받고 있다. 이들의 효과는 항부정맥제 본연의 작용으로 해석할 수 있겠지만, 모두 베타 차단 효과가 있는 약제들이므로 자율신경 활성도의 조절 역시 기여했을리라 판단된다. POAF에서 자율신경의 중요성을 시사하는 근거로, 다른 심장 수술에 비해 유독 심장 이식술을 받은 환자에서 POAF의 발병률이 우수하게 낮은데 이식된 심장은 완전 신경차단 상태이기 때문으로 이해된다.1, 2

한편, 항염증 효과로 POAF를 조절할 수 있으리라는 가설을 검증한 연구들 중의 하나가 colchicine을 사용한 본 연구이다. COPPS는 심장 수술을 받은 환자들 대상으로 colchicine의 투여가 심외막결개후 증후군을 줄여줄 수 있는지를 보는 연구였다.3 본 연구는 COPPS 연구에 모집된 환자들을 대상으로 분석한 하위 연구로 POAF의 발생에 대해 조사하였다. Colchicine는 역사적으로 매우 오래된 전통적인 항염증제로 약제가 갖는 독성에도 불구하고, 현대에도 통증 환자에게 사용되고 있다. 항염증 효과는 중성구의 활성화를 막아서 나타난다. 다른 약제의 주 작용기전은 tubulin에 결합하여 미세관(microtubule)의 중합체 형성을 방해하는 것으로, 이로 인해 세포의 유사분열을 정지시키는 효과를 나타낸다. 세포균은 세포가 증식을 할 수 있는 동안 특별히 칼슘 통로의 활성에 영향을 미친다. 따라서 colchicine이 POAF의 발생에 미치는 영향은 단순한 항염증작용뿐만 아니라, 전기생리학적인 요소도 관여할 수 있다.

본 연구의 문제점은 colchicine 투여의 시점에 있다. 일부로 POAF는 수술 후 2-3일에 가장 많이 발생하는 데, 본 연구에서는 colchicine을 수술 3병일째부터 투여했으므로 POAF에 대한 예방 효과를 평가하는 데에 제한이 있다. 연구 의자들이 처음부터 POAF에 조절을 둔 것이 아니라, COPPS의 하위 연구로 수행되었기 때문이 다. 따라서 향후 연구들에서는 약제의 투여가 수술 전, 수술 중 또는 수술 직후부터 이루어지는 의자인 것을 필요하며, colchicine 이외의 다양한 항염증제에 대한 검증도 필요할 것이다.

References
Colchicine Reduces Postoperative Atrial Fibrillation

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

Massimo Imazio, MD; Antonio Brucato, MD; Paolo Ferrazzi, MD; Maria Elena Rovere, MD; Anna Gandino, MD; Roberto Cemin, MD; Stefania Ferrua, MD; Riccardo Belli, MD; Silvia Maestroni, MD; Caterina Simon, MD; Edoardo Zingarelli, MD; Alberto Barosi, MD; Fabrizio Sansone, MD; Davide Patrini, MD; Ettore Vitali, MD; Rita Trinchero, MD; David H. Spodick, MD; Yehuda Adler, MD; for the COPPS Investigators

Background—Inflammation and pericarditis may be contributing factors for postoperative atrial fibrillation (POAF), and both are potentially affected by antiinflammatory drugs and colchicine, which has been shown to be safe and efficacious for the prevention of pericarditis and the postpericardiotomy syndrome (PPS). The aim of the Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) POAF substudy was to test the efficacy and safety of colchicine for the prevention of POAF after cardiac surgery.

Methods and Results—The COPPS POAF substudy included 336 patients (mean age, 65.7±12.3 years; 69% male) of the COPPS trial, a multicenter, double-blind, randomized trial. Substudy patients were in sinus rhythm before starting the intervention (placebo/colchicine 1.0 mg twice daily starting on postoperative day 3 followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥70 kg, halved doses for patients <70 kg or intolerant to the highest dose). The substudy primary end point was the incidence of POAF on intervention at 1 month. Despite well-balanced baseline characteristics, patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P=0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4±3.7 versus 10.3±4.3 days; P=0.040) and rehabilitation stay (12.1±6.1 versus 13.9±6.5 days; P=0.009). Side effects were similar in the study groups.

Conclusion—Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00128427.

(Circulation. 2011;124:2290-2295.)

Key Words: atrial fibrillation • cardiac surgery • colchicine • postpericardiotomy syndrome • prevention

Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases, depending on the surgery type (coronary artery bypass graft surgery, valve surgery, or combined coronary artery bypass graft/valve surgery), patient features, definition of arrhythmia, and surveillance.1 Nowadays, POAF is becoming more common because of the increasing number of cardiac surgery operations and the aging of the population. This complication increases patient morbidity, length of hospital stay, and management costs.2

Clinical Perspective on p 43

Prevention of POAF is an important management goal supported by American and European guidelines.3-5 Many different agents have been studied to fit this goal and may be grouped into 2 main categories: agents with antiarrhythmic properties and agents with antiinflammatory activity such as corticosteroids, statins, and free radical scavengers.6

The development of POAF is likely multifactorial. Pericardial inflammation, autonomic imbalance during the postoperative time, excessive production of catecholamines, and fluid shift may all contribute.7,8 Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are significantly decreased by corticosteroids.9 Thus, antiinflammatory therapy may be beneficial for the prevention of POAF. In the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) trial, colchicine was safe and efficacious in the prevention of the PPS and halved the risk of developing the syndrome after cardiac surgery.10 PPS may be relatively com-
mon and troublesome, affecting 10% to 40% of patients after cardiac surgery. Because of its antiinflammatory effect, colchicine may also reduce the risk of POAF. A substudy of the COPPS trial was designed to evaluate the efficacy of colchicine in preventing POAF. This is the first study to test the hypothesis that colchicine may prevent POAF.

Methods

Trial Design and Participants

This was a prospective, randomized, double-blind, placebo-controlled, multicenter trial. The overall study population consisted of 360 patients enrolled at 6 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 adult patients undergoing cardiac surgery and without contraindications to colchicine were recruited. Eligible patients had no unfavorable short-term outlook and were willing and able to give informed consent and to comply with the study procedures and follow-up. For the COPPS POAF substudy, all patients in sinus rhythm on day 3 were included for the analysis of colchicine effects (either stable sinus rhythm or intermittent POAF but in sinus rhythm on day 3 at the time of colchicine/placebo administration). Thus, the COPPS POAF substudy population included 336 patients (Figure 1).

Exclusion Criteria

The study exclusion criteria included (1) known severe liver disease or current transaminases $>1.5$ times the upper normal limit, (2) current serum creatinine $>2.5$ mg/dL, (3) known myopathy or elevated baseline preoperative creatine kinase, (4) known blood dyscrasias or gastrointestinal disease, (5) pregnant and lactating women or women of childbearing potential not protected by a contraception method, (6) known hypersensitivity to colchicine, and (7) current treatment with colchicine for any indications. 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.

Interventions

Patients were randomized to receive placebo or colchicine on top of standard therapy. Treatment with placebo or colchicine started on postoperative day 3. Colchicine was given at the dosage of 1.0 mg twice daily for the first day followed by a maintenance dosage of 0.5 mg twice daily for 1 month in patients $\geq 70$ kg, and halved doses were given to patients $<70$ kg or intolerant to the highest dose. The rhythm was defined as AF when there were no consistent P waves before each QRS complex and the ventricular rate was irregular. AF episodes lasting $\geq 5$ minutes were considered. Recognition of AF was performed by continuous ECG monitoring (3-channel ward monitor) and 12-lead ECG recordings.

End Points

The COPPS POAF substudy primary end point was the rate of POAF on placebo/colchicine treatment. A didactical analyses included hospital stay (cardiac surgery, rehabilitation, overall stay) and the incidence of death and stroke.

Randomization

Participants were randomly assigned to treatments by a central computer-based, automated sequence based on permuted blocks with a block size of 4. The random allocation sequence was implemented by sequentially numbered containers. All participants and trial investigators were blinded to randomized treatment. Tablets identical in color, shape, and taste were provided in blister packs. Data were collected on case report forms and clinical events adjudication forms. Data were managed by investigators blinded to treatment assignments. A blinded clinical end point committee adjudicated all events.

Figure 1. Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) postoperative atrial fibrillation (POAF) substudy flow diagram. Preop AF indicates preoperative atrial fibrillation. *Including 17 patients with POAF on postoperative day 1 or 2 but in sinus rhythm on postoperative day 3; ° including 18 patients with POAF on postoperative day 1 or 2 but in sinus rhythm on postoperative day 3.
Safety
During follow-up, monitoring and recording of all adverse events were performed. Potential side effects to be monitored included gastrointestinal effects (especially diarrhea), alopecia, anorexia, hepatotoxicity, myotoxicity, and bone marrow toxicity. An untoward event that was fatal or life-threatening, 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) was recorded as a severe adverse event.

Statistical Analysis and Sample Size
For the COPPS POAF substudy, a total of 250 patients, 125 in each treatment arm, were needed to detect a difference in the POAF rate of 48.0% and 30.0% between the 2 treatment arms (placebo and colchicine) with a power of 80% using a 2-sided P=0.05 level test. The estimated rates of the POAF in the 2 study groups were based on the results of a randomized controlled trial in which the incidence of POAF was significantly lower in the hydrocortisone group (30%) than in the placebo group (48%); adjusted hazard ratio, 0.54; 95% confidence interval, 0.35-0.83; P=0.004.15 Analyses were performed by intention to treat. For the COPPS POAF substudy, intention-to-treat analysis was applied to patients enrolled in the substudy (336 patients) from the original overall study population of the COPPS trial (360 patients).

Data were expressed as mean±SD. Comparisons between patient groups were performed with the Mann-Whitney test for continuous variables and a χ2 analysis for categorical variables. A value of P<0.05 was considered to show statistical significance. Time-to-event distributions were estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards model was used to estimate the relative risk of recurrence. Stepwise selection procedure was adopted. A value of P<0.05 was considered significant for variable entry for stepwise selection. Analyses were performed with the SPSS 13.0 software package (SPSS, Inc, Chicago, IL).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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

Main Outcome
Chronic preoperative AF was recorded in 17 of 360 patients (4.7%). The overall incidence of POAF was 97 of 343 (28.3%): 42 of 97 (43.3%) on postoperative days 1 and 2 (before starting placebo/colchicine) and 55 of 97 (56.7%) from postoperative day 3 (on intervention). Persistent POAF starting on postoperative day 1 or 2 was recorded in 7 patients on postoperative day 3 before randomization to placebo/colchicine. These patients were excluded from subsequent analysis, including a total of 336 patients in sinus rhythm (Figure 1). For the assessment of the primary outcome (POAF on placebo or colchicine treatment), only AF events from postoperative day 3, ie, when placebo/colchicine was administered, were considered. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P=0.021; relative risk reduction, 45%; number needed to treat, 11; Table 2 and Figure 2). The POAF events after the start of the intervention (placebo/colchicine) numbered 35 of 167 versus 20 of 169, respectively. The duration of POAF was shorter in the colchicine group compared with the placebo group (3.0±1.2 versus 7.7±2.5 days, respectively; P<0.001).

Table 1. Baseline Characteristics of the Patients in the Prevention of the Postpericardiotomy Syndrome (COPPS) Postoperative Atrial Fibrillation Substudy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=167)</th>
<th>Colchicine (n=169)</th>
<th>P</th>
<th>RRR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>66.6±11.0</td>
<td>64.8±13.7</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 y (n=196), n (%)</td>
<td>102 (61.1)</td>
<td>94 (55.6)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Male sex (n=230), n (%)</td>
<td>112 (67.1)</td>
<td>118 (68.8)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous history of AF (n=19)</td>
<td>11 (6.6)</td>
<td>8 (4.7)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Previous congestive HF (n=40)</td>
<td>22 (13.2)</td>
<td>18 (10.7)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Previous cardiac surgery (n=18)</td>
<td>10 (6.0)</td>
<td>8 (4.7)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Hypertension (n=231)</td>
<td>116 (69.5)</td>
<td>115 (68.1)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (n=77)</td>
<td>43 (25.7)</td>
<td>34 (20.1)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>COPD (n=26)</td>
<td>15 (9.0)</td>
<td>11 (6.5)</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

Preoperative data
COPPS, Prevention of the Postpericardiotomy Syndrome; POAF, postoperative atrial fibrillation.

Results of a randomized controlled trial in which the incidence of POAF was significantly lower in the hydrocortisone group (30%) than in the placebo group (48%); adjusted hazard ratio, 0.54; 95% confidence interval, 0.35-0.83; P=0.004. Analyses were performed by intention to treat. For the COPPS POAF substudy, intention-to-treat analysis was applied to patients enrolled in the substudy (336 patients) from the original overall study population of the COPPS trial (360 patients).

Data were expressed as mean±SD. Comparisons between patient groups were performed with the Mann-Whitney test for continuous variables and a χ2 analysis for categorical variables. A value of P<0.05 was considered to show statistical significance. Time-to-event distributions were estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards model was used to identify independent risk factors for recurrences. Stepwise selection procedure was adopted. A value of P<0.05 was considered significant for variable entry for stepwise selection. Analyses were performed with the SPSS 13.0 software package (SPSS, Inc, Chicago, IL).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Patients treated with colchicine had a shorter in-hospital stay (9.4±3.7 versus 10.3±4.3 days; P=0.040), rehabilitation stay (12.1±6.1 versus 13.9±6.5 days; P=0.009), and overall hospital stay (cardiac surgery plus rehabilitation stay; 21 versus 24 days, respectively; P=0.030). The incidence of death and stroke was similar in the study groups (Table 2).

The following clinical features were more commonly recorded in patients with POAF on placebo/colchicine treatment compared with those without POAF (Table 3): left atrium anteroposterior diameter ≥45 mm (32.7% versus 3.0% in the placebo/colchicine group; P<0.001).
15.3%; P = 0.004), surgery other than coronary artery bypass graft (63.6% versus 47.7%; P = 0.039), and the presence of pericardial effusion (27.3% versus 15.7%; P = 0.051). On the contrary, a lower periperaoperative use of β-blockers (32.7% versus 55.5%; P = 0.003) and colchicine (36.4% versus 53.0%; P = 0.027) was recorded in patients with POAF compared with those without POAF. No significant differences were recorded in the periperaoperative use of amiodarone.

A dilated left atrium (hazard ratio 2.31; 95% confidence interval, 1.15–4.63; P = 0.019) was identified as the only independent risk factor for POAF in multivariable analysis (Table 4).

**Safety and Side Effects**

The rates of side effects and drug withdrawal were similar in the colchicine and placebo groups (5.9% versus 4.8%, respectively [P = 0.137], for side effects, and 11.8% versus 6.6% [P = 0.131] for drug withdrawal), although colchicine showed a trend toward an increased rate of both events. No severe side effects were recorded.

Gastrointestinal intolerance was the only side effect recorded during the study in colchicine-treated patients. One case of myotoxicity was recorded in the placebo group and was related to concomitant use of a statin.

Colchicine was discontinued in 20 patients (11.8%). Patient or medical decision was the cause of drug withdrawal in 2.4% in the colchicine group and 1.8% in the placebo group (Table 5).

**Discussion**

The COPPS POAF substudy was designed to assess the efficacy and safety of colchicine for the prevention of POAF. Colchicine has been shown to be safe and effective in the prevention of pericarditis.15–16, 20–21

In the COPPS trial, colchicine halved the incidence of the PPS, providing evidence that pharmacological prevention of the PSS is possible and safe.10 In the COPPS POAF substudy, colchicine reduced the incidence of POAF (relative risk reduction, 45%; number needed to treat, 11) without significant side effects. Moreover, colchicine halved the mean duration of POAF; such an effect may be particularly important for reducing the subsequent rate of late AF (AF >30 days of surgery) because a longer duration of POAF is a strong and independent predictor of late AF.21

The mechanism of POAF is believed to be reentry. The electrophysiological substrate may be preexisting or may develop as a result of heterogeneity of refractoriness after surgery. Multiple perioperative factors have been proposed to contribute to the latter, including operative trauma, inflammation, eleva-

**Table 3.** Comparison of Clinical Characteristics Between Patients With and Without Postoperative Atrial Fibrillation on Placebo/Colchicine Treatment

<table>
<thead>
<tr>
<th>Feature</th>
<th>No (n = 281)</th>
<th>Yes (n = 55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>66±11</td>
<td>67±13</td>
<td>0.677</td>
</tr>
<tr>
<td>Age &gt;65 y (n = 196)</td>
<td>161 (57.3)</td>
<td>35 (63.6)</td>
<td>0.455</td>
</tr>
<tr>
<td>Male sex (n = 230)</td>
<td>196 (69.8)</td>
<td>34 (61.8)</td>
<td>0.313</td>
</tr>
<tr>
<td>Previous history of AF (n = 19)</td>
<td>14 (5.0)</td>
<td>5 (9.1)</td>
<td>0.213</td>
</tr>
<tr>
<td>Previous congestive HF (n = 40)</td>
<td>31 (11.0)</td>
<td>9 (16.4)</td>
<td>0.260</td>
</tr>
<tr>
<td>Previous cardiac surgery (n = 18)</td>
<td>13 (4.6)</td>
<td>5 (9.1)</td>
<td>0.303</td>
</tr>
<tr>
<td>Hypertension (n = 231)</td>
<td>193 (68.7)</td>
<td>38 (69.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus (n = 77)</td>
<td>65 (23.1)</td>
<td>12 (21.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>COPD (n = 26)</td>
<td>23 (8.2)</td>
<td>3 (5.5)</td>
<td>0.781</td>
</tr>
<tr>
<td>LA anteroposterior diameter &gt;45 mm (n = 61)</td>
<td>43 (15.3)</td>
<td>18 (32.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ejection fraction &lt;40% (n = 42)</td>
<td>32 (11.4)</td>
<td>10 (18.2)</td>
<td>0.185</td>
</tr>
<tr>
<td>Surgery other than CABG (n = 169)</td>
<td>134 (47.7)</td>
<td>35 (63.6)</td>
<td>0.039</td>
</tr>
<tr>
<td>Postpericardiotomy syndrome (n = 50)</td>
<td>38 (13.5)</td>
<td>12 (21.8)</td>
<td>0.145</td>
</tr>
<tr>
<td>Pericardial effusion (n = 59)</td>
<td>44 (15.7)</td>
<td>15 (27.3)</td>
<td>0.051</td>
</tr>
<tr>
<td>Pleural effusion (n = 60)</td>
<td>47 (16.7)</td>
<td>13 (23.6)</td>
<td>0.248</td>
</tr>
<tr>
<td>Perioperative β-blocker use (n = 174)</td>
<td>156 (55.5)</td>
<td>18 (32.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Perioperative use of amiodarone* (n = 49)</td>
<td>42 (14.9)</td>
<td>7 (12.7)</td>
<td>0.830</td>
</tr>
<tr>
<td>Perioperative ACEI/ARB use (n = 126)</td>
<td>104 (37.0)</td>
<td>22 (40.0)</td>
<td>0.761</td>
</tr>
<tr>
<td>Colchicine (n = 169)</td>
<td>149 (53.0)</td>
<td>20 (36.4)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

POAF indicates postoperative atrial fibrillation; AF, atrial fibrillation; HF, heart failure; COPD, chronic obstructive pulmonary disease; LA, left atrial; CABG, coronary artery by-pass grafting; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

*Excluding pharmacological cardioversion of postoperative atrial fibrillation.

**Table 4.** Hazard Ratios for Postoperative Atrial Fibrillation on Placebo/Colchicine Treatment in the Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA anteroposterior diameter &gt;45 mm</td>
<td>2.31</td>
<td>1.15–4.63</td>
<td>0.019</td>
</tr>
<tr>
<td>Perioperative β-blocker use</td>
<td>0.47</td>
<td>0.25–0.88</td>
<td>0.019</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.52</td>
<td>0.28–0.96</td>
<td>0.036</td>
</tr>
</tbody>
</table>

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.
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. By this mechanism, colchicine is able to inhibit various leukocytes functions, and this effect should be the most significant for the antiinflammatory action.

It is especially relevant for the antiinflammatory effect and its capability to concentrate in leukocytes, where its peak concentration may be >10 times the peak concentration in plasma.19,23

Study Limitations

Although the results are encouraging, important issues need to be considered. The relatively small sample size is the first study limitation. This study shows the first evidence of colchicine efficacy for the prevention of POAF, requiring further confirmation and validation in multicenter studies. Moreover, the highest incidence of POAF is generally seen in the first postoperative days. In the COPPS trial, colchicine was given starting on the postoperative day 3 following a preliminary positive experience from Israel.14 On this basis, the potential beneficial effect of the drug is limited from postoperative day 3, with the potential to miss early postoperative AF cases in the first 2 days. Further research should address whether alternative regimens providing the drug in the perioperative period (eg, starting the administration before the operation) may provide better prevention for either PPS or POAF. Both efficacy and safety should be evaluated in this setting.

Conclusions

Colchicine seems safe and efficacious in reducing the incidence of POAF after cardiac surgery. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both PPS and POAF, 2 common and troublesome complications of cardiac surgery that may increase management costs.10,24,25

Appendix

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, CA; David H. Spodick, MD, Worcester, MA.

COPPS Recruiting Centres and Investigators

Cardiology Department, Maria Vittoria Hospital, Torino, Italy (Coordinator Centre; Investigators: M. Imazio, A. Chinaglia, B. Demichelis, D. Forno, S. Ierna); Ospedali Riuniti, Bergamo, Italy (Investigators: A. Brucato, S. Maestroni, C. Simon, D. Cunetti, P. Ferrazzi); Cardiac Surgery, Ospedale Mauriziano, Torino, Italy (Investigators: M.E. Rovere, E. Zingarelli, F. Sansone); Ospedale Niguarda, Milano, Italy (Investigators: A. Gandino, A. Barosi, D. Patrini, E. Vitali); Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin); Ospedale degli Infermi, Rivoli, Italy (S. Ferrua, M.R. Conte).

Acknowledgments

We thank all the participants of the study and the physicians, nurses, ethics committees, and administrative staff in hospitals who assisted with its conduct.

Sources of Funding

The trial is an independent study founded and performed within the Italian National Healthcare System. The research protocol was approved by the relevant institutional review boards or ethics committees, and all human participants gave written informed consent. The steering committee designed and oversaw the trial and had the final decision on the contents of the manuscript. All data were received, checked, and analyzed independently at the Coordinating Centre at the Cardiology Department, Maria Vittoria Hospital, Torino, Italy, after blinded adjudication of clinical events and side effects. A carpia Lda supplied of drug/placebo as an unrestricted grant.
Disclosures

None.

References


CLINICAL PERSPECTIVE

Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases. POAF increases patient morbidity, length of hospital stay, and management costs. Its prevention is an important management goal. Systemic and local inflammatory responses are believed to contribute to the pathogenesis of POAF. Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are decreased by corticosteroids. Because of its antiinflammatory effects for the treatment and prevention of pericarditis, colchicine has the potentiality to prevent POAF. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) POAF study is the first trial designed to assess the efficacy and safety of colchicine for POAF prevention. It is a substudy of the COPPS trial, in which colchicine halved the occurrence of the postpericardiotomy syndrome. On the third postoperative day, consecutive adult patients undergoing cardiac surgery and without contraindications to colchicine were randomized to receive placebo or colchicine on top of standard therapy. The substudy primary efficacy end point was the incidence of POAF on placebo/colchicine treatment at 1 month. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P = 0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4 ± 3.7 versus 10.3 ± 4.3 days; P = 0.040) and rehabilitation stay (12.1 ± 6.1 versus 13.9 ± 6.5 days; P = 0.009). Side effects were similar in the study groups. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both the postpericardiotomy syndrome and POAF, 2 common and troublesome complications of cardiac surgery.