Colchicine for prevention of post-pericardiotomy syndrome and post-operative atrial fibrillation: the COPPS-2 randomized clinical trial.

Massimo Imazio, MD, FESC on behalf of the COPPS-2 Investigators
Cardiology Dpt. Maria Vittoria Hospital and University of Torino, Torino, Italy
massimo_imazio@yahoo.it
massimo.imazio@unito.it
Disclosures:

- The COPPS-2 trial was supported by former Azienda Sanitaria 3 of Torino (now ASLTO2) within the Italian National Health Service.
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Unlabeled use of drugs:

- Colchicine for PPS and POAF prevention
Background: COPPS Trial

Eur Heart J. 2010 Nov;31(22):2749-54
Am Heart J. 2011 Sep;162(3):527-32.e1
PPS and POAF

COPPS: PPS incidence

90% in 60 days

POAF incidence

70% POAF in ICU

Objective

- To determine the efficacy and safety of perioperative administration of oral colchicine to reduce:
  - post-pericardiotomy syndrome (PPS),
  - post-operative AF (POAF),
  - post-operative effusions (pleural and/or pericardial).
Design, Setting, Participants, Intervention

ClinicalTrials.gov Identifier: NCT01552187

Potential candidates identified

Eligibility Criteria met?

YES

Patient enrolled
Signed Informed Consent and Randomization

NO

Patient not eligible

180 patients on placebo
Placebo/Colchicine 0.5 mg BID or 0.5mg once daily (<70kg) till 1 months after surgery

Pre-discharge, 1 month, 3 months follow-up:
Primary study outcome
PPS within 3 months

Inclusion and exclusion criteria

Inclusion criteria
Age >18y
Candidate to cardiac surgery
Informed consent

Exclusion criteria
Current atrial fibrillation
Candidate to cardiac transplantation
Severe liver disease or elevation of serum transaminases (>1.5 times the upper reference limit)
Serum creatinine >2.5 mg/dL
Preoperative elevation of CK or known myopathy
Known chronic intestinal diseases or blood dyscrasias
Pregnancy, lactation, or women of childbearing potential not protected by a contraception method
Hypersensitivity to colchicine
Treatment with colchicine for any cause

Preoperative elevation of CK beyond upper limit of reference interval.
Main Outcome Measures

PPS within 3 month (primary end point):

At least 2 of these criteria should be present for the diagnosis

1. Fever without alternative causes
2. Pleuritic chest pain
3. Friction rub
4. Evidence of new or worsening pleural effusion
5. Evidence of new or worsening pericardial effusion

POAF within 3 months (secondary end point):
Post-operative AF was defined as AF lasting for more than 30 seconds. Continuous ECG monitoring at least 5 days post-surgery then daily ECG and symptoms-guided.

Post-operative eff. within 3 months (secondary end point):
Pericardial and/or Pleural by ultrasonography.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=180)</th>
<th>Colchicine (n=180)</th>
<th>Absolute differences (95% CI) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary End Point within 3 months Post-Pericardiotomy Syndrome</td>
<td>53 (29.4%)</td>
<td>35 (19.4%)</td>
<td>10.0 (1.1 to 18.7)</td>
</tr>
<tr>
<td>Main Secondary end points:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Operative Atrial Fibrillation</td>
<td>75 (41.7%)</td>
<td>61 (33.9%)</td>
<td>7.8 (-2.2 to 17.6)</td>
</tr>
<tr>
<td>POAF (on-treatment):</td>
<td>61 (41.2%)</td>
<td>38 (27.0%)</td>
<td>14.2 (3.3 to 24.7)</td>
</tr>
<tr>
<td>Post-operative effusions</td>
<td>106 (58.9%)</td>
<td>103 (57.2%)</td>
<td>1.7 (-8.5 to 11.7)</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>3 (1.7%)</td>
<td>1 (0.6%)</td>
<td>1.1 (-1.6 to 4.3)</td>
</tr>
<tr>
<td>Pericardiocentesis or thoracentesis</td>
<td>13 (7.2%)</td>
<td>13 (7.2%)</td>
<td>0.0 (-5.6 to 5.6)</td>
</tr>
<tr>
<td>PPS recurrence</td>
<td>3 (1.7%)</td>
<td>3 (1.7%)</td>
<td>0.0 (-3.3 to 3.3)</td>
</tr>
<tr>
<td>Disease-related readmissions</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
<td>0.0 (-2.7 to 2.7)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>2 (1.1%)</td>
<td>6 (3.3%)</td>
<td>2.2 (-1.6 to 6.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.6%)</td>
<td>2 (1.1%)</td>
<td>0.50 (-2.1 to 3.4)</td>
</tr>
</tbody>
</table>
Kaplan-Meier incidence of post-pericardiotomy syndrome according to treatment groups.

Log-rank p=0.046

Number at risk
Group: Placebo
180 143 131 128 128 128 128 127 126 126 125 81
Group: Colchicine
180 147 141 141 139 139 139 139 139 139 139 91
Safety

Reported data represent the number of affected individuals. No serious adverse events (any fatal or life-threatening event, requiring hospitalization, or significantly or permanently disabling or medically significant, that could have jeopardized the patient or required medical or surgical intervention to prevent an adverse outcome) were reported, as well as myotoxicity, alopecia or other side effects beyond those reported in the table.

* = Diarrhea, nausea, cramping, abdominal pain, or vomiting.
° = Any elevation of aminotransferase levels above the normal reference range.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo (n=180)</th>
<th>Colchicine (n=180)</th>
<th>Absolute differences (95% CI) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>21 (11.7%)</td>
<td>36 (20.0%)</td>
<td>8.3 (0.76 to 15.9)</td>
</tr>
<tr>
<td>Gastrointestinal intolerance*</td>
<td>12 (6.7%)</td>
<td>26 (14.4%)</td>
<td>7.7 (1.4 to 14.3)</td>
</tr>
<tr>
<td>Hepatotoxicity°</td>
<td>2 (1.1%)</td>
<td>1 (0.6%)</td>
<td>0.50 (-2.1 to 3.4)</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>32 (17.8%)</td>
<td>39 (21.7%)</td>
<td>3.9 (-4.4 to 12.5)</td>
</tr>
</tbody>
</table>
Conclusions

Among patients undergoing cardiac surgery, the perioperative use of colchicine compared with placebo reduced the incidence of post-pericardiotomy syndrome but not of postoperative AF or postoperative effusions.

The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.
Acknowledgment: COPPS-2 Investigators

Steering and Executive Committee: Massimo Imazio, MD (Chairman and Principal Investigator) (Ospedale Maria Vittoria and University of Torino, Torino, Italy), Riccardo Belli, MD (Co-chairman), (Ospedale Maria Vittoria, Torino, Italy), Antonio Brucato, MD (Ospedale Papa Giovanni XXIII, Bergamo, Italy), and Paolo Ferrazzi, MD, (Ospedale Papa Giovanni XXIII, Bergamo, Italy). Data and safety monitoring committee: Yaron Finkelstein, MD (Hospital for Sick Children, Toronto, Canada), Anna Leggieri, MD (Ospedale Maria Vittoria, Torino, Italy), Bernhard Maisch, MD (University of Marburg, Germany), Bongani Mayosi, MD (University of Cape Town, South Africa), Jae K. Oh, Rochester, MD (Mayo Clinic, Rochester, USA), Arsen D. Ristic, MD and Petar Seferovic, MD (University of Belgrade, Belgrade, Serbia). Clinical events committee: Yehuda Adler, MD (Cham Sheba Medical Center, Tel Hashomer and Sackler University, Tel Aviv, Israel), Brian Hoit, MD (Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, USA), David H. Spodick, MD (St Vincent Hospital, Worcester, USA) and Alberto Pullara, MD, (Ospedale Maria Vittoria and University of Torino, Torino, Italy).

Centers (Italy): Cardiac Surgery and Internal Medicine Department, Ospedale Papa Giovanni XXIII, Bergamo (103 patients enrolled): Antonio Brucato, MD (center principal investigator, PI), Paolo Ferrazzi, MD, Diego Cugola, MD, Davide Cumetti, MD, Silvia Maestroni MD, Francesco Innocente, MD, Anna Valenti, MD; Cardiac Surgery and Rehabilitation, Villa Maria Pia Hospital, Torino (56 patients enrolled): Chiara Comoglio, MD (center PI), Oleksandr Dyra, MD, Stefania Trimboli, MD, Elisabetta Lardone, MD, Paolo Sorrentino, MD, Ignignoli Biagio, MD, Roberto Valesio, MD, Annarita Zeoli, MD; Cardiology Department, Maria Vittoria Hospital, ASLTO2 Torino (54 patients enrolled): Massimo Imazio, MD (center PI), Riccardo Belli, MD, Alessandra Chinaglia, MD, Enrico Cecchi, MD, Luisella Coda, MD, Brunella Demichelis, MD, Silvia Ferro, MD, Davide Forno, MD; Cardiac Surgery, Ospedale Niguarda, Milano (34 patients enrolled): Alberto Barosi, MD (center PI), Anna Gandino, MD (center co-PI), Luigi Martinelli, MD, Gianna Attanasio, MD; Cardiac Surgery, ospedale Mauriziano, Torino (27 patients enrolled): Roberto Flocco, MD (center PI), Riccardo Casabona, MD; Cardiology and Cardiac Surgery Department, Ca’ Forcello Hospital, Treviso (26 patients enrolled): Fabio Chirillo, MD (center PI), Marcio Scorsin, MD, Zoran Olivari, MD, Elvio Polesel, MD; Cardiac Surgery, Ospedale San Camillo, Roma (24 patients enrolled): Vincenzo Polizzi, MD (center PI), Emanuela Belmonte, MD, Francesco Musumeci, MD, Amedeo Pergolini, MD; Cardiology Department, Ospedale Regionale San Maurizio, Bolzano and Cardiac Surgery, Ospedale Santa Chiara, Trento (15 patients enrolled): Roberto Cemin, MD (center PI), Angelo Graffigna, MD; Cardiology Department, Ospedale degli Infermi, Rivoli (9 patients enrolled): Stefania Ferrua, MD (center PI), Ferdinando Varbella, MD; Cardiology and Cardiac Surgery Dept of Cardiological Thoracic and Vascular Sciences, University of Padova (9 patients enrolled): Alida L Caforio (center PI), Vincenzo Tarzia (center co-PI), Sabino Iliceto, MD, Gino Gerosa, MD; Cardiology Department, San Giovanni Bosco Hospital, ASLTO2 Torino (3 patients enrolled): Piera Costanzo, MD (center PI), Massimo Minelli, MD.
Imazio M and coauthors

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