Colchicine: A New Stopper for Postoperative Atrial Fibrillation?

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Objectives
1. Understand the epidemiology, pathophysiology, and impact of postoperative atrial fibrillation
2. Describe the possible mechanism of action of colchicine for prevention of postoperative atrial fibrillation
3. Summarize the literature regarding the use of colchicine for prevention of postoperative atrial fibrillation
I. **Atrial Fibrillation (AF)**
   a. **Background**
      i. Defined as an arrhythmia characterized by uncoordinated atrial activation and subsequent ineffective atrial contractions
      ii. Increases in prevalence with advanced age
         1. In 2010, the prevalence of AF amongst the Medicare population was 9% in patients who were 65 years or older compared to 2% in patients less than 65 years of age
   b. **Types**
      
      | Type                          | Definition                                                                 |
      |-------------------------------|---------------------------------------------------------------------------|
      | Paroxysmal AF                 | • AF that terminates spontaneously or with intervention within 7 days of onset |
      | Persistent AF                 | • Continuous AF that is sustained > 7 days                                 |
      | Long-standing persistent AF   | • Continuous AF > 12 months in duration                                    |
      | Permanent AF                  | • The term “permanent AF” is used when the patient and clinician to make a joint decision to stop further attempts to restore and/or maintain sinus rhythm |
      |                               | • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF |
      | Nonvalvular AF                | • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair |
      | Postoperative AF              | • No uniform definition                                                   |
      |                               | • Defined in clinical trials as AF that occurs postoperative and lasts more than 30 seconds |
   c. **Clinical presentation**
      i. Symptoms vary between patients
      ii. Encompasses fatigue, palpitations, dyspnea, hypotension, syncope, and reduced exercise tolerance
   d. **Complications**
      i. Strokes
         1. Associated with a five-fold increase in stroke risk
      ii. Heart failure
         1. Associated with a three-fold increase in heart failure risk
      iii. Hospitalizations
         1. Accounts for more than 467,000 hospitalizations
      iv. Mortality
         1. Associated with a two-fold increase in death
         2. Hospital mortality is 2.1% in patients with AF versus 0.1% in patients without AF
   e. **Goals of therapy**

i. Control ventricular rate response
ii. Restore and maintain sinus rhythm
iii. Prevent thromboembolic events

f. Management1
   i. Rate control
      1. Options to control the ventricular rate include beta blockers and non-dihydropyridine calcium channel blockers
   ii. Rhythm control
      1. Options to restore and maintain sinus rhythm include direct-current cardioversion (DCC), antiarrhythmic drugs, and cardiac ablation
   iii. Stroke prevention
      1. Antithrombotic therapy may be indicated based on a patient’s risk of thromboembolism using assessment tools such as CHA2DS2-VASc score

II. Postoperative Atrial Fibrillation (POAF)
   a. Epidemiology6,7
      i. Most common postoperative cardiac surgery complication that occurs in 10-50% of patients
         1. Majority of cases occur after valve surgery (up to 50%) and coronary artery bypass graft (CABG) surgery (up to 40%)
      ii. Advanced age is the most consistent risk factor
         1. Occurs most often in patients older than 70 years of age
         2. Incidence is expected to increase with an increased number of elderly patients undergoing cardiac operations

   b. Impact7,8,9
      i. Found to increase hospital stay by 4.9 days and create an additional $2 billion hospital costs annually
      ii. Found to be an independent predictor of mortality
         1. Increases both hospital mortality and 6-month mortality by two-fold

   c. Time course5,8,10
      i. Highest incidence of POAF occurs within 2 to 4 days after surgery
         1. Peak incidence on postoperative day 2
         2. 94% before the end of postoperative day 6
      ii. Majority of patients who are hemodynamically stable will convert spontaneously to sinus rhythm within 24 hours
      iii. Most cases will resolve within 4 to 6 weeks

   d. Proposed pathogenesis10
      i. Caused an interaction between a triggering factor and an electrophysiological substrate
         1. Triggering factors
            a. Atrial premature contraction, electrolyte imbalance, and adrenergic or vagal stimulation
         2. Electrophysiological substrate
            a. Interaction of multiple factors such as inflammation→ development of a vulnerable atrial structure→ dispersion of atrial electrical remodeling→ multiple re-entry wavelets→ development of atrial electrophysiological substrate

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b. Refer to Appendix A for the list of possible factors involved in the development of a vulnerable atrial structure

e. Management\textsuperscript{1,5,10}
   i. Goals of therapy similar to AF
   ii. Guidelines
      1. 2014 AHA/ACC/HRS atrial fibrillation guideline
      2. 2010 ESC guideline for the management of atrial fibrillation
      3. Refer to Appendix B for summary of recommendations
   iii. Treatment\textsuperscript{1,5,10}
      1. Treatment is indicated in patients with any of the following characteristics
         a. Hemodynamic instability
         b. Development of cardiac ischemia or heart failure
         c. Lack of resolution of symptoms
      2. Rate control
         a. First line is beta blockers
         b. Second line is non-dihydropyridine calcium-channel blockers
         c. Preferred in patients who are hemodynamically stable
         d. Refer to Appendix C for treatment dosing, advantages, and side effects
      3. Rhythm control
         a. First line is DCC in both guidelines
         b. The AHA/ACC/HRS guideline also considers pharmacological conversion with ibutilide as a first line option
         c. Preferred in patients who are hemodynamically unstable
         d. Cardioversion should be considered in patients who remain symptomatic or rate control is difficult to achieve
         e. Refer to Appendix C for treatment dosing, advantages, and side effects
   4. Stroke prevention
      a. Anticoagulation is recommended in patients undergoing cardioversion
      b. Lack of strong recommendations in patients not undergoing cardioversion due to lack of robust evidence
         i. Antithrombotic/anticoagulation therapy may be reasonable patients with AF lasting more than 48 hours or multiple episodes
            1. Clinicians must weigh the benefit of preventing perioperative stroke with the increased risk of post-operative bleeding and the fact most cases of POAF are self-limiting and temporary
         ii. Agents most commonly used are vitamin K antagonists and heparin
   iv. Prevention\textsuperscript{1,5,10}
      1. Role in management
         a. Very limited number of strong recommendations
      2. First line
a. Beta-blocker unless contraindicated in all patients

3. Second-line
   a. Amiodarone in patients at high risk of POAF
      i. High risk is not defined

4. Other options
   a. Sotalol
   b. Colchicine (AHA/ACC/HRS guideline)
   c. Biaatrial pacing (ESC guideline)
   d. Corticosteroids (ESC guideline)
   e. Statins in coronary artery surgery (AHA/ACC/HRS guideline)

III. Review of Colchicine
   a. Indications\textsuperscript{11,12,13}
      i. FDA-approved
         1. Familial Mediterranean fever (FMF)
         2. Gout flare treatment and prophylaxis
      ii. Off-label
         1. Pericarditis
            a. Considered conventional therapy for acute and recurrent episodes
      iii. Multiple new indications being explored\textsuperscript{14,15}
         1. Postpericardiotomy syndrome (PPS)
            a. A postoperative complication that develops within days to several weeks after cardiac surgery with an incidence of 10 to 40%
            b. Complications include increased hospital stay, increased management cost, and rare but life-threatening conditions such as cardiac tamponade
            c. Management includes treatment with non-steroidal anti-inflammatory drugs and corticosteroids
               i. No established preventative measures
            d. Colchicine’s role in PPS is not as well-established as pericarditis and use is dependent on the clinician
      iv. Other cardiovascular indications being explored are acute coronary syndrome, stroke, and angioplasty
   b. Mechanism of action\textsuperscript{11,13,14,16}
      i. Not fully understood but may be due to the disruption of microtubule assembly in cells involved in the immune system
         1. Overall mechanism of action
            a. Binds to beta-tubulin (Figure 1) \(\rightarrow\) inhibits microtubule polymerization \(\rightarrow\) interferes with microtubules function in cells
               i. Microtubules are a main component of the cytoskeleton
                  1. Function includes determining cell structure and involvement in a variety of cell movements, including cell locomotion, transportation of organelles, and mitosis
2. Mechanism of action for anti-inflammatory effect (Figure 2)
   a. Colchicine concentrates in white blood cells → interfere with migration, degranulation, and phagocytosis → anti-inflammatory effects

![Figure 1. Colchicine binding site](image)

![Figure 2. Colchicine’s mechanism of action](image)

...
a. A meta-analysis found corticosteroid use was associated with a 26-45% reduction in POAF and shorter hospital stay
   i. Significant increase in hyperglycemia requiring insulin infusion
   ii. No difference in all-cause infection
   iii. Wound healing was not studied

b. Routine use is limited by concerns of poor wound healing and infection that can be caused by hyperglycemia

2. Statins
   a. Statin use was associated with 22-24% reduction in risk of POAF in retrospective and randomized controlled studies
   b. The ECS guideline suggests there are conflicting results from large, retrospective analysis but these studies are not discussed or referenced
   c. Routine statin use is not recommended due to insufficient evidence regarding optimal dose and administration time

b. Current recommendations regarding colchicine use
   i. The 2014 ACCF/AHA/HRS guideline states, “Administration of colchicine may be considered for patients postoperatively to reduce AF after cardiac surgery” (Class IIb, Level of evidence B)
      1. Class IIb: usefulness/efficacy is less well established by evidence/opinion
      2. Level of evidence B: data derived from a single randomized trial, or nonrandomized studies
   ii. Recommendation is in response to a single study, the COPP AF subset study
   iii. The ESC guideline does not address the role of colchicine

c. Proposed mechanism of action of colchicine in POAF
   i. Primary proposed mechanism is its anti-inflammatory effects
      1. May reduce the sympathetic response found in the postoperative stage by reducing neutrophil activation, endothelial cell adhesion, and migration to injured tissues
   ii. Speculation that there may be additional mechanisms of action
      1. In vitro and animal studies suggest colchicine may exert electrophysiological effects and directly affect microtubule assembly in cardiac myocytes

V. Clinical Question
   a. What is the efficacy and safety of colchicine in the prevention of POAF?

VI. Colchicine and Prevention of POAF: Literature Review

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Test the efficacy and safety of colchicine for the prevention of POAF after cardiac surgery</th>
</tr>
</thead>
</table>

### Study Design
- Prospective, randomized, double-blinded, placebo controlled, multicenter trial conducted in 6 hospitals in Italy

### Inclusion Criteria
- Adult patients undergoing cardiac surgery who were in sinus rhythm on day 3 of study
- No contraindication to colchicine

### Exclusion Criteria
- Current treatment with colchicine for any indication
- Chronic AF
- Persistent POAF on day 3 before starting colchicine
- Known severe liver disease or current transaminase > 1.5 times upper normal limit
- Known myopathy or elevated baseline preoperative creatinine kinase
- Current serum creatinine > 2.5 mg/dL
- 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

### Endpoints
- Primary outcome: incidence of POAF at one month
- Secondary outcomes: hospital stay (cardiac surgery, rehabilitation, overall stay), incidence of death and stroke, adverse effects

### Methods
- Randomized to placebo or colchicine on postoperative day 3
  - Colchicine dosing: 1.0 mg twice daily on first day, then maintenance dose of 0.5 mg twice daily for 1 month if \( \geq 70 \) kg and 0.25 mg twice daily if < 70 kg or intolerant to highest dose
  - All patients received standard care

### Statistics
- Intention-to-treat analysis
- \( N=125 \) per group to achieve 80% power to detect a difference in the POAF rate of 48% and 30%
- Mann-Whitney test, chi-squared analysis, Kaplan-Meier method, Cox proportional hazards model

### Study Population
- 366 patients, mean age 65.7 years, 69% male, 49% underwent CABG, 27% underwent valvular surgery

### Results (colchicine vs. placebo)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=167)</th>
<th>Colchicine (n=169)</th>
<th>P value</th>
<th>RRR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>POAF, %</td>
<td>22.0</td>
<td>12.0</td>
<td>0.021</td>
<td>45.5 (34-94)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery, d</td>
<td>10.3±4.3</td>
<td>9.4±3.7</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation stay, d</td>
<td>13.9±6.5</td>
<td>12.1±5.1</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Overall hospital stay, d</td>
<td>24.2±8.9</td>
<td>21.4±7.9</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Death or stroke, n (%)</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
<td>0.616</td>
<td></td>
</tr>
</tbody>
</table>

- Rate of side effects: 9.5% versus 4.8% (p=0.137)
  - GI intolerance was the only side effect in colchicine group
  - No severe side effects recorded
  - Rate of drug withdrawal: 11.8% versus 6.6% (p=0.131)

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<table>
<thead>
<tr>
<th>Results (continued)</th>
<th>• Independent clinic factor for POAF: dilated left atrium (HR 2.31, 95% CI: 1.15-4.63, p=0.0019)</th>
</tr>
</thead>
</table>
| Author’s Conclusions | • Colchicine seems safe and efficacious in reducing incidence of POAF after cardiac surgery  
  • Colchicine reduced rehabilitation stay and overall hospital stay  
  • Limitations: small sample size, need for further confirmation and validation in future studies, 43% of POAF events occurred before the onset of colchicine treatment |
| Commentary | • Strengths: independently funded by Italian National Healthcare System, landmark study  
  • Limitations: a post-hoc study in which POAF was not the primary outcome, cost-savings was not calculated but can be extrapolated from reduction in hospital stay, standard therapy was not defined, adherence was not assessed, effect of colchicine on inflammatory markers and white blood cell count not assessed |


<table>
<thead>
<tr>
<th>Purpose</th>
<th>• To determine the efficacy and safety of perioperative administration of oral colchicine to reduce PPS, POAF, and postoperative pericardial/pleural effusions in patients undergoing cardiac surgery for any reason excluding cardiac transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>• Investigator-initiated, double-blind, placebo-controlled, randomized clinical trial conducted in 11 centers in Italy</td>
</tr>
</tbody>
</table>
| Inclusion Criteria | • Age > 18 years  
  • Candidate to cardiac surgery |
| Exclusion Criteria | • Treatment with colchicine for any indication  
  • Current AF  
  • Candidate for cardiac transplantation  
  • Severe liver disease or elevation of serum transaminases (> 1.5 times upper limit of normal)  
  • Hypersensitivity to colchicine  
  • Known chronic intestinal disease or blood dyscrasias  
  • Pregnancy, lactation, or women of childbearing potential not protected by a contraception method  
  • Serum creatinine > 2.5 mg/dL  
  • Preoperative elevated of CK or known myopathy |
| Endpoints | • Primary outcome: incidence of PPS within 3 months  
  • Secondary outcomes: POAF and postoperative effusions within 3 months after cardiac surgery, incidence of cardiac tamponade, need for pericardiocentesis or thoracentesis, recurrence of PPS, disease-related readmissions related to the 3 main outcomes, stroke incidence, and overall mortality |
| Methods | • Randomly assigned to placebo or colchicine 48 to 72 hours before surgery and continued for 1 month after surgery  
  • Colchicine dosing: 0.5 mg twice daily for 1 month if ≥ 70 kg and 0.25 mg twice daily if < 70 kg or intolerant to highest dose |
- Adherence was assessed through pill counts
- Current best practice guidelines were strongly recommended

**Statistics**
- Primary outcome: incidence of PPS within 3 months
  - Planned on-treatment analysis for patients who had at least 80% adherence
- N=180 per group to achieve 80% power to detect 11% reduction in primary outcome
  - Adequately powered to assess incidence of POAF and pericardial effusion
- Chi-squared test, Fischer’s exact tests, Kaplan-Meier method, logistic regression

**Study Population**
- 360 patients, mean age 67.5 years, 68.9% male, 36.4% had heart valve surgery, 33.9% had CABG

<table>
<thead>
<tr>
<th>Table 3a. Primary and Secondary Study Outcomes at 3-Month Follow-up</th>
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<tbody>
<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>Primary endpoint</td>
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<tr>
<td>PPS within 3 months</td>
</tr>
<tr>
<td>Secondary endpoints</td>
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<tr>
<td>POAF</td>
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<tr>
<td>Postoperative pericardial/pleural effusions</td>
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<tr>
<td>Cardiac tamponade</td>
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<tr>
<td>Pericardiocentesis or thoracentesis</td>
</tr>
<tr>
<td>PPS recurrence</td>
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<tr>
<td>Disease-related readmissions</td>
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<tr>
<td>Overall mortality</td>
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<tr>
<td>Stroke</td>
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</table>

- Pre-specified on-treatment analysis
  - POAF: 41.2% in placebo group vs 27.0% in colchicine group (absolute difference, 14.2%; 95% CI, 3.3%-24.7%)

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<thead>
<tr>
<th>Table 3b. Adverse Events in COPPS-2 at 3-Month Follow-up</th>
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<tr>
<td><strong>Adverse event</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>Any adverse events</td>
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<tr>
<td>Gastrointestinal intolerance</td>
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<tr>
<td>Hepatotoxicity</td>
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<tr>
<td>Drug Discontinuation</td>
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- No serious adverse events were observed

**Author’s Conclusions**
- Perioperative administration of colchicine significantly reduced the incidence of PPS after cardiac surgery but did not reduce the rate of POAF and postoperative pericardial/pleural effusion
- The relatively high discontinuation rate may have affected the overall drug efficacy, especially for POAF prevention
  - Likely due to significant vulnerability in the postoperative phase
- Limitations: limited sample size and follow-up may have prevented
**Authors’ Conclusions (continued)**  
Identification of rare adverse effects, highly selected study population which excluded patients at higher risk of complications and patients who had urgent cardiac surgery

**Commentary**  
- **Strengths:** Independently funded by Italian National Healthcare System, adherence was assessed  
- **Limitations:** POAF was a secondary outcome, cost-savings was not calculated, applicability is limited since the 0.5 mg tablets is not available in the United States, effect of colchicine on inflammatory markers and white blood cell count not assessed  
- High rate of drug discontinuation in this highly selected study population suggests patients who would be more at risk of side effects from colchicine would not benefit from postoperative administration of colchicine  
- Despite high drug discontinuation rate, colchicine was found to be effective in reducing PPS


**Background**  
- No published article, presented at the ESC Congress 365 conference  

**Purpose**  
- Determine if colchicine administered preoperatively to patients undergoing cardiac surgery and continued during hospitalization is effective in reducing incidence of POAF

**Study Design**  
- Multi-center, prospective, randomized, open-label study in Jordan

**Endpoints**  
- Primary outcome: incidence of POAF  
- Secondary outcome: side effects of colchicine

**Methods (continued)**  
- Colchicine dosing: 2 mg 12-24 hours before surgery, 1 mg day of surgery, and 0.5 mg twice daily from postoperative day one until discharge  
  - Dosing was reduced by 50% if patients were intolerant to full dose or weighed less than 70 kg

**Population**  
- 360 patients

**Results (colchicine vs. placebo)**  
- Primary endpoint: 14.5% versus 20.5% (p=0.140)  
  - Secondary endpoint  
  - Diarrhea: 24.6% versus 5.5% (p<0.001)  
  - Anorexia: 6.1% versus 2.2% (p=0.07)

**Author’s Conclusions**  
- Colchicine administered prior to cardiac surgery and continued until hospital discharge failed to reduce the incidence of early POAF  
- Colchicine was associated with significant GI side effects, which was severe enough leading to drug discontinuation in 52% of affected patients

**Commentary**  
- Efficacy may have been limited by side effects and shorter treatment duration  
- Confirmed findings from COPPS-2 trial that preoperative administration of colchicine is not effective in reducing incidence POAF

| Purpose | • Examine the potential of colchicine to reduce AF recurrence in a 3-month period after radiofrequency isolation of the pulmonary veins in patients with paroxysmal AF |
| Study Design | • Randomized, double-blind, controlled, 2-center study |
| Inclusion Criteria | • At least 2 documented episodes of paroxysmal AF within the last 12 months<br>• At least 1 documented episode of paroxysmal AF while on treatment with a class IC or III antiarrhythmic drug |
| Exclusion Criteria | • Older than 80 years<br>• Active inflammatory or infectious disease or malignancy<br>• Known autoimmune diseases<br>• Corticosteroid or other immunosuppressive or immunomodulatory therapy<br>• Moderate or severe hepatic impairment<br>• Severe renal failure (eGFR < 30 ml/min per 1.73 m²)<br>• Inability or unwilling to adhere to standard therapy or provide consent<br>• Did not appear for more than 1 follow-up visit or more than 1 follow-up electrocardiogram (ECG) |
| Endpoints | • Primary outcome: early AF recurrence, either symptomatic or evidence on ECG reading<br>• Secondary outcomes: median difference in inflammatory markers CRP and IL-6 between day 1 and day 4 |
| Methods (continued) | • All patients<br>• Had a run-in period (2 months) in which all antiarrhythmic medications were discontinued prior to AF ablation<br>• Underwent atrial pulmonary vein isolation<br>• Anticoagulated for 3 months after procedure<br>• Randomized to placebo or colchicine for 3 months with day of ablation as day 1<br>• Colchicine dosing: 0.5 mg twice daily<br>• No antiarrhythmic medications were allowed during study period<br>• Beta blockers were only continued if the indication was coronary heart disease or heart failure<br>• Follow up visits and ECG readings conducted every 2 weeks in outpatient antiarrhythmic clinic for 3 months |
| Statistics | • Intention–to-treat analysis<br>• N=80 per group to achieve 80% power to detect a 50% reduction of early AF<br>• Wilcoxon and Mann-Whitney tests, t test, chi-squared analysis, Kaplan-Meier method, Cox regression multivariate analysis |
| Study Population | • 170 patients, mean age 62 years, 71% male, 24% had heart failure, 34% had coronary artery disease, day 1 CRP level of 5.3 mg/l, day 1 IL-6 level of 3.1 pg/ml |
| Results (colchicine vs. placebo) | • Primary endpoint: 16% versus 33.5% (95% CI 0.18-0.80, NNT 5.6)<br>• Significant divergence in cumulative hazard curves for AF recurrence in 3 months (p=0.01)<br>• Secondary endpoints<br>• Median CRP reduction: -1.18 mg/l [-2.35 to -0.46 mg/l] versus -0.46 mg/l [-0.78 to 0.08 mg/l] (p < 0.01) |
| Results (colchicine vs. placebo) | • Median IL-6 level reduction: -0.50 pg/ml [-1.15 to -0.10 pg/ml] versus -0.10 mg/l [-0.30 to 0.10 pg/ml] (p < 0.01)  
• Diarrhea: 8.6% versus 1.3% (p = 0.03)  
• No serious adverse events reported and rates of nausea were similar  
• Treatment discontinuation: 12.3% versus 6.3% (p=0.18)  
  o Most patients still had treatment for at least 1 month  
• IL-6 level of day 4 was the most powerful univariate predictor of recurrence |
| Author’s Conclusions | • Colchicine is an effective and safe treatment for prevention of early AF recurrence after pulmonary vein isolation in the absence of antiarrhythmic agents  
• Positive effect of colchicine was strongly associated with a significant reduction in IL-6 and CRP levels  
• Limitation: unclear if 3 months is the appropriate length of time  
• Strength: Frequent follow-up was conducted to address concerns of inadequate detection of AF recurrences since many cases of asymptomatic |
| Commentary | • Strength: supports association between inflammation and AF recurrence and that colchicine’s efficacy is through its anti-inflammatory effects  
• Limitation: difficult to extrapolate results to POAF patients since early post-ablation AF recurrence does not necessarily have the same causes as POAF  
  • Compared to POAF, inflammation in AF ablation is localized versus systemic and these patients have AF at baseline, which puts them at higher risk of another episode of AF |

a. Literature review summary\(^3,4,23,24\)  
i. Imazio et al., 2011 (COPPS atrial fibrillation substudy)  
  1. Post-hoc study that suggests that postoperative administration of colchicine was effective and safe in reducing the incidence of POAF by nearly half  
  2. Rehabilitation stay and hospital stay was also reduced in the colchicine group  
ii. Imazio et al., 2014 (COPP-2 study)  
  1. Another study in which incidence of POAF was not the primary outcome conducted by the same investigators in the COPPS study  
  2. Colchicine started preoperative was not effective in reducing incidence of POAF  
iii. Tabbalat et al., 2015 (END-AF study)  
  1. Incidence of POAF was the primary outcome  
  2. Results supported findings from COPPS-2 trial  
iv. Deftereos et al., 2012  
  1. Three months of colchicine safely reduced early AF recurrence after ablation  
  2. Colchicine also significantly reduced levels of CRP and IL-6  

b. Literature review discussion\(^3,4,23,24\)
i. Colchicine started preoperative is likely not effective in reducing incidence of POAF

ii. Limited evidence from a post-hoc study that postoperative administration of colchicine may be effective and safe in reducing the incidence of POAF, rehabilitation stay, and hospital stay

iii. Colchicine’s mechanism of action in reducing incidence of AF after a procedure is likely due to its anti-inflammatory effects

VII. Safety

a. No long-term safety data available for POAF
b. May be extrapolated from long-term safety data in patients with FMF
c. Data suggests colchicine is well-tolerated beyond its mild GI side effects
d. Treatment course for POAF is shorter than for FMF and gout so safety data for POAF should be similar or less severe

VIII. Conclusion

a. Similar to statins and corticosteroids, the benefits and optimal administration of colchicine for prevention of POAF are unclear and additional data is needed
b. Insufficient evidence to recommend use of colchicine in POAF
c. Colchicine appears to be a more favorable anti-inflammatory option compared to corticosteroids
   i. Colchicine does not affect glucose metabolism and potentially increase infection risk and delay wound healing
d. It is unclear whether statins or colchicine is preferred since both are not routinely used due to limited evidence
   i. Statin use has more clinical data
   ii. Colchicine associated with a higher reduction in incidence of POAF
e. Future topics for research
   i. Randomized studies with a larger sample size and first dose of colchicine given 2 to 3 days after surgery
      1. Available studies have small sample size and a larger sample may be needed to show efficacy
      2. Postoperative administration of colchicine had promising results
      3. Assess wound healing as an endpoint
         a. Confirm that colchicine does not have the concerning side effects of corticosteroids
     4. Assess safety and efficacy of 0.6 mg tablets
        a. Only 0.5 mg tablets has been used in clinical trials
        b. The United States only has the 0.6 mg tablets
     5. Calculate cost-savings due to reduction in POAF
     6. Assess effect of colchicine on inflammatory markers and white blood cell count
   ii. Trial in progress
      1. Canadian Institutes of Health Research is investigating the effects of colchicine on POAF in patients undergoing thoracic surgery
         a. The estimated completion is October 2015
References


**Table 6. Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>ACCF:</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>AF:</td>
<td>atrial fibrillation</td>
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<tr>
<td>AHA:</td>
<td>American Heart Association</td>
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<tr>
<td>AV:</td>
<td>atrioventricular</td>
</tr>
<tr>
<td>AVB:</td>
<td>atrioventricular block</td>
</tr>
<tr>
<td>CABG:</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CI:</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CRP:</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CYP:</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DCC:</td>
<td>direct-current cardioversion</td>
</tr>
<tr>
<td>ESC:</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ECG:</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FMF:</td>
<td>familial Mediterranean fever</td>
</tr>
<tr>
<td>GI:</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>HR:</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HRS:</td>
<td>Heart Rhythm Society</td>
</tr>
<tr>
<td>IL-6:</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>IV:</td>
<td>intravenous</td>
</tr>
<tr>
<td>OR:</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PO:</td>
<td>oral</td>
</tr>
<tr>
<td>POAF:</td>
<td>postoperative atrial fibrillation</td>
</tr>
<tr>
<td>PPS:</td>
<td>postpericardiotomy syndrome</td>
</tr>
<tr>
<td>RRR:</td>
<td>relative risk reduction</td>
</tr>
</tbody>
</table>
Figure 3. Pathogenesis and risk factors of POAF

Pre-disposing factors:
- Advanced age
- Hypertension
- Diabetes
- Obesity
- Metabolic syndrome
- Left atrial enlargement
- Diastolic dysfunction
- Left ventricular hypertrophy
- Genetic predisposition

Intraoperative factors:
- Surgical atrial injury
- Atrial ischemia
- Pulmonary vein vent
- Venous cannulation
- Acute volume changes

Post-operative factors:
- Volume overload
- Increased afterload
- Hypotension

Vulnerable atrial structure

Dispersion of atrial electrical remodeling

Multiple re-entry wavelets

Atrial electrophysiological substrate

POAF

Triggering factors:
- Atrial premature contraction
- Enhanced adrenergic or vagal stimulation
- Electrolyte imbalance (hypomagnesemia, hypokalemia)
### Table 2. Recommendations for Management of Postoperative Cardiac and Thoracic Surgery from 2014 ACCF/AHA/HRS guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A beta blocker is recommended to treat postoperative AF unless contraindicated.</td>
<td>a</td>
<td>A</td>
</tr>
<tr>
<td>A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for patients at high risk of postoperative AF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>It is reasonable to administer antithrombotic medications for postoperative AF.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>It is reasonable to manage new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow up.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Prophylactic sotalol may be considered for patient with AF risk after cardiac surgery.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Colchicine may be considered postoperatively to reduce AF after cardiac surgery.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

### Table 3. Recommendations for Management of POAF from 2010 ESC guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral beta-blocker are recommended to prevent post-operative AF for patients undergoing cardiac surgery in the absence of contraindications.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>If used, beta-blockers (or other antiarrhythmic drugs for AF management) are recommended to be continued until the day of surgery.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ventricular rate control is recommended in patients with AF without hemodynamic instability.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Restoration of sinus rhythm by DCC is recommended in patients who develop post-operative AF and are hemodynamic unstable.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Pre-operative administration of amiodarone should be considered as prophylactic therapy for patients at high risk for POAF.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Unless contraindicated, antithrombotic/anticoagulation medication for post-operative AF should be considered when the duration of AF is ≥ 48 h.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>If sinus rhythm is restored successfully, duration of anticoagulation should be a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Antiarrhythmic medication should be considered for recurrent or refractory postoperative AF in an attempt to maintain sinus rhythm.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Sotalol may be considered for prevention of AF after cardiac surgery, but is associated with risk of proarrhythmia.</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Biatrial pacing may be considered for prevention of AF after cardiac surgery.</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Corticosteroids may be considered in order to reduce incidence of AF after cardiac surgery, but they are associated with risk.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
### Table 4. Pharmacological Agents Used for Rate Control in POAF\(^1,5\)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Treatment Dosage</th>
<th>Advantages</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>0.25-1.0 mg IV, then 0.125-0.5 mg/day IV/PO</td>
<td>Can be used in heart failure</td>
<td>Nausea, atrioventricular block (AVB) moderate effect</td>
</tr>
<tr>
<td>Beta blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 μg/kg over 1 min, then 0.05-0.2 mg/kg/min</td>
<td>Short-acting effect and short duration</td>
<td>Might worsen heart failure, can cause bronchospasm, hypotension, AVB</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1-5 mg IV over 5 min, repeat after 10 min, then 50-100 mg twice daily PO</td>
<td>Rapid onset of rate control (IV)</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1-5 mg IV over 2 min, then 50-100 mg twice daily PO</td>
<td>Rapid onset of rate control (IV)</td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>2.5-10 mg IV over 2 min, then 80-120 mg/day twice daily PO</td>
<td>Short-acting effect</td>
<td>Might worsen heart failure, AVB</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg IV over 2 min, then 5-15 mg/h IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Pharmacological Agents Used for Rhythm Control in POAF\(^1,5\)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Treatment Dosage</th>
<th>Advantages</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>2.5-5 mg/kg IV over 20 min, then 15 mg/kg or 1.2 g over 24 hours</td>
<td>Can be used in patients with severe LV dysfunction</td>
<td>Thyroid and hepatic dysfunction, torsades de pointes, pulmonary fibrosis, photosensitivity, bradycardia</td>
</tr>
<tr>
<td>Procainamide</td>
<td>10-15 mg/kg IV up to 50 mg/min</td>
<td>Therapeutic levels quickly achieved</td>
<td>Hypotension, fever, accumulates in renal failure, can worsen heart failure, requires drug level monitoring</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg IV over 10 min, can repeat after 10 min if no effect</td>
<td>Easy to use</td>
<td>Torsades de pointes more frequently than amiodarone and procainamide</td>
</tr>
</tbody>
</table>
### Table. 6. Pharmacology of colchicine\textsuperscript{12,13,14,27}

<table>
<thead>
<tr>
<th>Feature</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing and Treatment Duration</strong></td>
<td>• FMF (lifelong)</td>
</tr>
<tr>
<td></td>
<td>o 1.2 to 2.4 mg daily in 1 to 2 divided doses</td>
</tr>
<tr>
<td></td>
<td>o Increase or decrease dose based on efficacy or adverse effects</td>
</tr>
<tr>
<td></td>
<td>• Gout flare treatment (acute)</td>
</tr>
<tr>
<td></td>
<td>o 1.2 mg at the first sign of flare, followed in 1 hour with a single dose of 0.6 mg; maximum: 1.8 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Gout prophylaxis (3-6 months)</td>
</tr>
<tr>
<td></td>
<td>o 0.6 mg once or twice daily</td>
</tr>
<tr>
<td></td>
<td>• Acute pericarditis (3 months)</td>
</tr>
<tr>
<td></td>
<td>o Patients &gt;70 kg: 0.5 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>o Patients ≤70 kg or unable to tolerate higher dosing regimen: 0.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Recurrent pericarditis (6 months)</td>
</tr>
<tr>
<td></td>
<td>o Regimens with loading dose</td>
</tr>
<tr>
<td></td>
<td>▪ Patients ≥70 kg: 0.5 to 1 mg every 12 hours for 1 day, followed by 0.25 to 0.5 mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>▪ Patients &lt;70 kg or unable to tolerate higher dosing regimen: 0.5 mg every 12 hours for 1 day followed by 0.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td>o Regimens without loading dose</td>
</tr>
<tr>
<td></td>
<td>▪ Patients ≥70 kg: 0.5 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>▪ Patients ≤70 kg or unable to tolerate higher dosing regimen: 0.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td>• POAF (1 month)</td>
</tr>
<tr>
<td></td>
<td>o Patients ≥70 kg: 1.0 mg every 12 hours for 1 day, followed by 0.5 mg every 12 hours for 1 month</td>
</tr>
<tr>
<td></td>
<td>o Patients &lt;70 kg or unable to tolerate higher dosing regimen: 1.0 mg every 12 hours for 1 day, followed 0.25 mg twice day</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
<td>• Elderly: Reduce daily dose by 50%</td>
</tr>
<tr>
<td></td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td>o CrCl 30-60 ml/min: Reduce dose by 50%</td>
</tr>
<tr>
<td></td>
<td>o CrCl 15-30 ml/min: Initial dose: 0.5 mg every 2 days</td>
</tr>
<tr>
<td></td>
<td>o Dialysis or CrCl &lt; 15 ml/min: Do not use</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>• Primarily metabolized by cytochrome (CYP) 3A4</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>• 27 to 31 hours (young, healthy volunteers)</td>
</tr>
<tr>
<td><strong>Major contraindications</strong></td>
<td>• Concomitant use of P-glycoprotein (P-gp) or strong CYP3A4 inhibitors in presence of renal or hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>• Severe renal impairment</td>
</tr>
<tr>
<td></td>
<td>• Severe liver disease</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
</tr>
<tr>
<td><strong>Major interactions</strong></td>
<td>• HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td>o May increase concentrations of HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td>• Strong CYP3A4 inhibitors (e.g. clarithromycin, intraconazole, ketoconazole, and cyclosporine) or P-gp inhibitors (e.g. cyclosporine and ranolazine)</td>
</tr>
<tr>
<td></td>
<td>o May increase concentration of colchicine</td>
</tr>
<tr>
<td></td>
<td>o In those with normal or hepatic function, reduce colchicine dose by 50%</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>• Commons side effects: abdominal pain, nausea, vomiting and diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Rare but serious side effects: bone marrow suppression and liver failure</td>
</tr>
</tbody>
</table>

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