COLCHICINE: ARRESTING POST-OP A FIB?

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Post-operative atrial fibrillation (POAF)

- Most common complication post cardiac surgery
  - 10-50% of patients in early post-op period
    - 30% post-CABG
    - 40% valve replacement/repair
    - 50% CABG + valve
- Peak incidence POD 2-4
  - 70% by end of POD 4
  - 94% by end of POD 6

Mitchell *et al. CJC* 2011; 91–7.

POAF - Etiology

- Atrial trauma/stretch/ischemia
- ? Other variables
  - Inflammation
  - Autonomic disturbance
    - ↑ catecholamines
  - Fluid + electrolyte disturbances

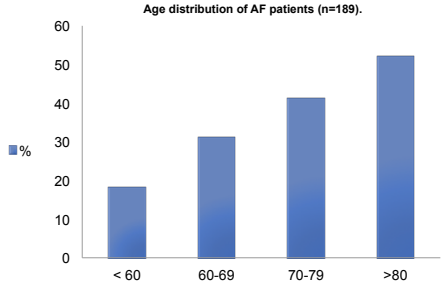
Mitchell *et al. CJC* 2011; 91–7.

POAF: Risk Factors

- ↑ Age
- Male sex
- Prior AF
- Hypertension
- Intra-operative variables
- Intra-aortic balloon-pump
- Ventilation > 24h
- Withdrawal of beta-blockers

Mitchell *et al. CJC* 2011; 91–7.

POAF: Risk Factors



Aranki S et al. Circulation 1996;94:390-397

POAF: Clinical Course

- If no prior AF, usually transient
  - Spontaneous conversion to NSR
    - 15-30% within 2 hours
- High recurrence
  - 43% > 1 episode
- Late POAF
  - Often asymptomatic, incidence likely underestimated
- Risk returns to baseline 6-12 weeks post-op

Mitchell *et al. CJC* 2011; 91–7.

POAF: Adverse Outcomes

- Discomfort/anxiety
- Hemodynamic instability
- Thromboembolic events
  - Stroke, cognitive impairment
- Prolonged hospitalization
- ↑ Mortality
- Anticoagulation ADRs
- ↑Health-care costs
- Late-onset POAF
  - Heart failure
  - Re-hospitalization

Mitchell *et al. CJC* 2011; 91–97

POAF: Prevention

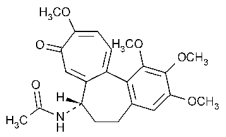
- **CCS GL:**
  - *"We recommend that patients who have **been receiving a beta-blocker before cardiac surgery** have that therapy **continued** through the operative procedure…"*
    (Strong Recommendation, High-Quality Evidence)
  - *"We suggest that patients who have not been receiving a beta-blocker before cardiac surgery **have beta-blocker therapy initiated just before or immediately after the operative procedure…"***
    (Conditional Recommendation, Low-Quality Evidence)
  - *"We recommend that patients who have a **contraindication to beta-blocker therapy** before or after cardiac surgery be considered for **prophylactic therapy with amiodarone** to prevent postoperative AF."*
    (Strong Recommendation, High-Quality Evidence)

Mitchell *et al. CJC* 2011; 91–97

POAF: Prevention

Colchicine

- Old drug, new indication?



http://commons.wikimedia.org

POAF: Colchicine

Micromedex® 2.0 | mobileMicromedex®

Actinic keratosis	Idiopathic pulmonary fibrosis
Amyloidosis	Intervertebral disc disorder
Aphthous ulcer of mouth	Malignant pericardial effusion
Asthma	Paget's disease
Behcet's syndrome	Pericarditis, Recurrent; Prophylaxis
Benign multirecurrent endothelioleukocytal meningitis	Peyronie's disease, Fibrosis and/or non-suppurative inflammation in
Bullous dermatosis	Porphyria
Cirrhosis of liver	Pseudogout
Condyloma acuminatum	Psoriasis
Constipation	Psoriatic arthritis
Contracture of palmar fascia	Pustular psoriasis of the palms AND/OR soles
Coronary angioplasty - Restenotic lesion of coronary artery; Prophylaxis	Relapsing polychondritis
Essential mixed cryoglobulinemia, Essential	Sarcoid arthritis
Familial Mediterranean fever	Sclerosing cholangitis
Gout	Sweet's syndrome
Gout; Prophylaxis	Systemic sclerosis
Gout; Treatment and Prophylaxis	Thrombocytopenic purpura, Immune or idiopathic
	Vasculitis

Micromedex 2.0

POAF: Colchicine

- Used for gout-associated arthritis for ~4000 years
- MOA in POAF prevention
  - Unknown
  - Concentrates in leukocytes (>10x plasma)
  - Suppresses release of chemotactic factors
    - Anti-inflammatory activity = ? antiarrhythmic effect

Clinical Question

P	Adult patients undergoing cardiac surgery -CABG -Valve repair/replacement
I	Colchicine administered peri-operatively
C	Standard therapy, placebo
O	Occurrence of POAF Duration of POAF Length of hospitalization Stroke Mortality

Search Strategy

Search terms	Colchicine, atrial fibrillation, atrial flutter, supraventricular tachycardia, prophylaxis, post-operative, cardiac surgery, coronary artery bypass, valvular surgery
Databases	MEDLINE, EMBASE, Google, Google Scholar, IPA, Cochrane database of systematic reviews, CENTRAL, WHO ICTRP
Limits	Adults
Results	16 results: -No comparative trials **-1 RCT** -2 RCTs in progress

COlchicine for the Prevention of the Post-pericardiotomy Syndrome (The COPPS Trial)

Imazio *et al. Eur Heart J*. 2010

COPPS

- Post-pericardiotomy syndrome (PPS)
  - Mild pericarditis, low-grade fever, often with pericardial/ pleural effusion
  - 10-40% post cardiac surgery
    - Develops days to months post-op
  - Tx: ASA, NSAIDs, corticosteroids

Imazio *et al.* Eur Heart J. 2010.

COPPS

D	MC (Italy), DB, PC, RCT
P	Cardiac surgery patients
I	Colchicine
C	Placebo
O	1°: Incidence of PPS at 12 months 2°: PPS hospitalization/cardiac tamponade/constrictive pericarditis/ recurrent pericarditis

Imazio *et al.* Eur Heart J. 2010.

Colchicine Reduces Postoperative Atrial Fibrillation

Results of the COPPS Atrial Fibrillation Substudy

Imazio *et al. Circulation*. 2011

COPPS: POAF

D	MC (Italy), DB, PC, RCT Pre-specified sub-study of COPPS trial
P	Adult cardiac surgery patients NSR POD 3 Excluded: Severe liver disease, elevated SCr, myopathy, ↑CK, blood dyscrasias, GI disease, pregnancy, hypersensitivity, other indication for colchicine, chronic AF, persistent POAF on POD 3

Imazio *et al.* Circulation 2011.

COPPS: POAF

I	Colchicine 1 mg po BID POD 3 then, Colchicine 0.5 mg po BID POD 4-30 + standard care *(Colchicine dose halved if < 70 kg or intolerant)*
C	Placebo + standard care
O	1° Incidence of POAF (POD 3-30) Continuous ECG + 12 lead ECG > 5 min 2° Length of hospital stay Mortality/stroke

Imazio *et al.* Circulation 2011.

COPPS: POAF – Statistical Analysis

- Intention-to-treat
- Mann-Whitney test
  - Continuous variables
- Chi square test
  - Categorical variables
- Kaplan-Meier
  - Time to POAF occurrence
- Cox-proportional hazards
  - To identify independent risk factors for POAF recurrence

Imazio *et al.* Circulation 2011.

COPPS: POAF – Results

- n=336
- Average patient
  - 65 y.o
  - Male
  - Hypertensive
  - NYHA class I-II
  - CABG or valve surgery

Imazio *et al.* Circulation 2011.

COPPS: POAF – Results

	Colchicine (n=169)	Placebo (n=167)	ARR	P-value
POAF POD 3-30	12.0%	22.0%	10.0% NNT: 11	0.021
POAF Duration (days)	3.0 ± 1.2	7.7 ± 2.5	-	<0.001

Imazio *et al.* Circulation 2011.

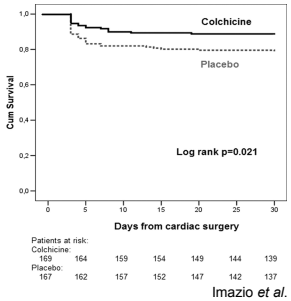
COPPS: POAF – Results 2° Outcomes

	Colchicine (n=169)	Placebo (n=167)	P-value
Overall length of stay (days)	21.4 ± 7.9	24.2 ± 8.9	0.030
Length of stay: Cardiac surgery Rehab	 9.4 ± 3.7 12.1 ± 6.1	 10.3 ± 4.3 13.9 ± 6.5	 0.040 0.009
Death/stroke	1.2%	1.2%	NSS

Imazio *et al.* Circulation 2011.

COPPS: POAF – Results 2° Outcomes

Kaplan-Meier POAF-free survival after postoperative day 3 according to treatment groups.



Imazio *et al.* Circulation 2011.

COPPS: POAF – Results

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

Factor	Hazard Ratio	95% Confidence Interval	*P*
LA anteroposterior diameter >45 mm	2.31	1.15–4.63	0.019
Perioperative β-blocker use	0.47	0.25–0.88	0.019
Colchicine	0.52	0.28–0.96	0.036

Imazio *et al.* Circulation 2011.

COPPS: POAF – Safety

- More ADRs and discontinuations with colchicine
  - GI intolerance (diarrhea)
  - 1 case of myotoxicity in placebo group (on statin)
  - No statistically significant difference

	Colchicine	Placebo	P-value
ADR	9.5%	4.8%	0.137
Withdrawal	11.8%	6.6%	0.131

Imazio *et al.* Circulation 2011.

COPPS: POAF – Author's 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, two common and troublesome complications of cardiac surgery that may increase management costs."

Imazio *et al.* Circulation 2011.

COPPS: POAF - Strengths

- Randomization, allocation concealment, blinding well described
  - Selection bias minimized
- ITT analysis
  - All subjects accounted for, no loss to follow-up
- ? Appropriate duration of treatment

COPPS: POAF - Limitations

- Monitoring of outcomes post-discharge
  - Not reported
- Severity of POAF
  - Asymptomatic, clinical consequences?
- POAF prior to POD 3
  - 43% incidence POD 1-2
- Concomitant medications not reported
  - Benefit with beta-blocker use
- Small sample size

COPPS: POAF - Generalizability

- "Typical" cardiac surgery population
  - ~70% males
- Italian study
  - Lengthy hospital stay
  - Potential variations in managing POAF

POAF: Unanswered questions

- Optimal time to initiate therapy
- Duration of therapy
- ADRs
- ? Benefit in-addition to "standard therapy"
- Role as adjunctive therapy once POAF develops

Future Research

- COPPS-2
  - Imazio *et al.*
    - Recruitment phase
      - Sample size n=360
- COVER CABG
  - Pragiola *et al.*
  - Recruitment phase
    - Sample size n=320

POAF: Conclusions

- Promising preliminary results with colchicine
  - Cheap, generally considered "safe"
- Cannot discount ↑ GI events/discontinuations in colchicine group
  - ? Potential for: Bone marrow suppression, hepatotoxicity, myotoxicity
  - Drug interactions
- Larger, prospective studies required to clarify role

POAF: Conclusions

- Consider colchicine if…
  - Beta-blockers/amiodarone contraindicated AND
  - High risk of morbidity/mortality 2° to POAF
  - ? Added benefit of reduction in PPS

Supplementary Slides

POAF: Prevention

- Beta-blockers
- Sotalol
- Amiodarone
- Magnesium
- Corticosteroids
- Antioxidant vitamins
- Statins
- Atrial pacing

Mitchell *et al. CJC* 2011; 91–97

The JAMA Network

From: **A Multicenter Risk Index for Atrial Fibrillation After Cardiac Surgery**

JAMA. 2004;291(14):1720-1729. doi:10.1001/jama.291.14.1720

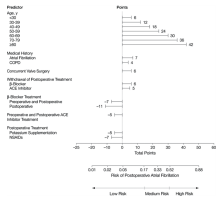


Figure Legend:

Risk is determined by assigning points from the points scale foreach of the predictors listed and then plotting the total points receivedagainst the risk score at the bottom of the nomogram. For example, 50 totalpoints predicts a risk of postoperative atrial fibrillation of 88%. ACE indicatesangiontensin-converting enzyme; COPD, chronic obstructive pulomonary disease;and NSAIDs, nonsteroidal anti-inflammatory drugs.

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POAF: Management

- Goals of therapy
- Correct risk-factors
  - Hypoxemia, lytes, hemodynamic instability
- Rate control
  - Beta blocker, diltiazem/verapamil, amiodarone
- Cardioversion
  - Difficult to control, highly symptomatic
- Anticoagulation
  - Sustained duration > 72h
- Continue rate control and OAC ≥ 6-12 weeks

Canadian Journal of Cardiology 27 (2011) 91–97

POAF: Non-Cardiac Surgery

- Am Heart J 2012 Bhave et al
  - POAF post non-cardiac major surgery
  - Retrospective review n=370,447
    - -33% = new POAF
    - Associated with increased mortality
      - OR: 1.72 (1.59-1.86, p<0.001)

COPPS-2

P	Cardiac surgery patients
I	Colchicine 0.5 mg BID x 30 days Initiated 48-72 h pre-op
C	Standard therapy, placebo
O	1°: PPS, effusion, POAF at 3 months 2°: Cardiac tamponade, pericardiocentesis/ thoracentesis, PPS recurrence, disease related admissions, stroke/mortality

Imazio *et al.*